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Synthesis and Conformational Analysis of Geodiamolide Analogues

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Starting with the ω-hydroxy and ω-amino acid derivatives **13** and **21**, the two closely related geodiamolide analogs **32** and **35**, respectively, were prepared. Compared to the natural cyclodepsipeptide geodiamolide (**1**), the macrocycles **32** and **35** have a smaller ring size (17- vs. 18-membered). Conformational analysis by ROESY spectroscopy and molecular dynamics simulation revealed that the reduced ring size causes the polypropionate sector to flip with regard to the geodiamolide conformation.

Introduction

In general, peptide modifications are performed with the aim of finding more selective ligands to increase bioavailability and stability or to mimic certain folds.[1] Typical modifications are the replacement of peptide bonds with isosteric functional groups or the replacement of amino acids with side-chain-modified or other amino acid analogs.[2,3] For example, pseudopeptides in which cyclopropane rings rigidify the Cα, Cβ, and the NH group of an amino acid have been prepared. Also, pseudopeptides with trisubstituted (*E*)-alkene dipeptide isosteres were recently described.[4] Frequently, such modifications are incorporated into macrocyclic core structures.[5–8] Alternatively, small rings can be fused to the macrocycle,[9] or regions with small rings may be part of the macrocycle.[10,11] In nature, related strategies that influence the conformation of a macrocyclic ligand can be identified in cyclodepsipeptides. In these natural products, D-configured amino acids, β-amino acids, or *N*-methylated amino acids can be found that, in part, determine the conformation of the macrocycle. In addition, polypropionate-derived ω-hydroxy acids are typical fragments of cyclodepsipeptides. With several methyl groups in a 1,3-configuration, the polypropionate part can impose soft conformational constraints on the macrocycle conformation. Figure 1 depicts three representative cyclodepsipeptides. Geodiamolide (**1**), isolated from the marine sponge *Geodia* sp. shows activity against fungi.[12–14] The tripeptide fragment and the polypropionate form an 18-membered ring. The natural product jasplakinolide[15] (**2**), which is produced by the marine sponge *Jaspis* sp., contains the same ω-hydroxy acid. With one β-amino acid instead of an α-amino acid, jasplakinolide features a 19-membered ring. In the depsipeptide doliculide (**3**), isolated from the sea hare *Dolabella auricularea*,[16] the polypropionate is longer at the expense of an amino acid, resulting in a 16-membered macrocycle. Regarding the biological activity, jasplakinolide and doliculide are rather similar in that they arrest cells at the G_2/M phase of the cell cycle.[17] Both compounds enhance the assembly of actin into F-actin.

While hard conformational constraints such as rings may enhance the enthalpy of binding to a receptor, this may be offset by unfavorable binding entropies.[18] In contrast, soft constraints should allow for a smooth and movable fit between ligand and receptor. As indicated in Figure 2, the hydroxy acid of jasplakinolide and geodiamolide features two *syn*-pentane and one 1,3-allylic interaction.[19] With acid **4** and related hydroxy acids as lead structures we set out to design simpler or truncated versions giving novel ω-hydroxy or ω-amino acids.

These analogues might then be bridged with peptide fragments to give macrocycles.[20] By comparing related compounds it might then be possible to delineate the effect of these modifications on the conformation and the overall flexibility of the respective macrocycles. For example, we found that jasplakinolide analogs based on ω-amino acid **5** have a conformation comparable to jasplakinolide, but the macrocycles seem to be more rigid than the natural product.[21] In this paper we describe the synthesis of 7-hydroxy and 7-amino acids of type **6**, truncated versions of hydroxy acid **4**, and the synthesis of geodiamolide analogs **32** and **35**.

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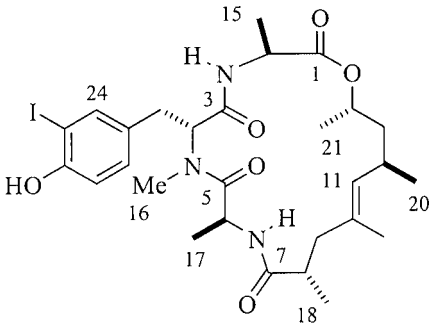
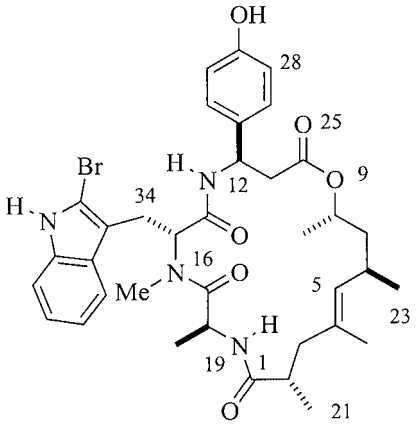
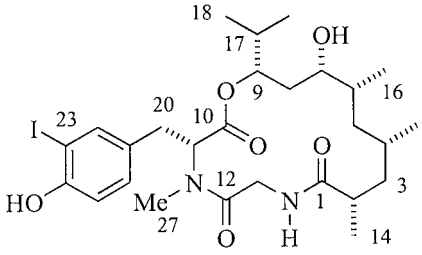


geodiamolide (**1**)



jasplakinolide (**2**)



doliculide (**3**)

Figure 1. Structures of three representative cyclodepsipeptides.

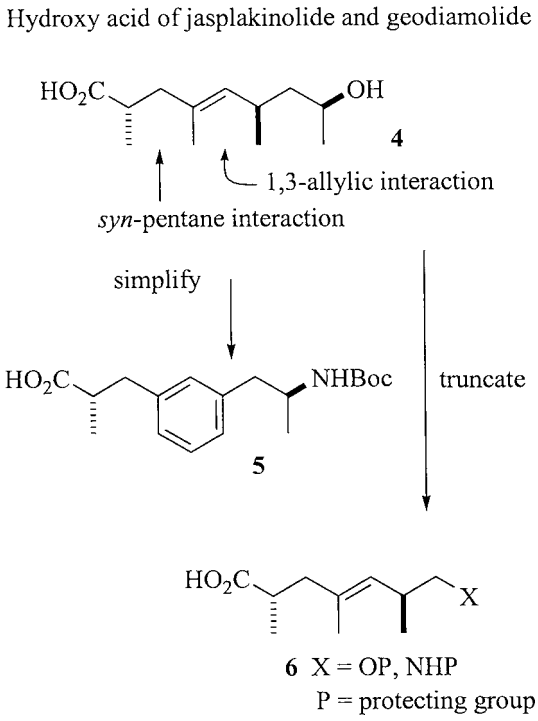


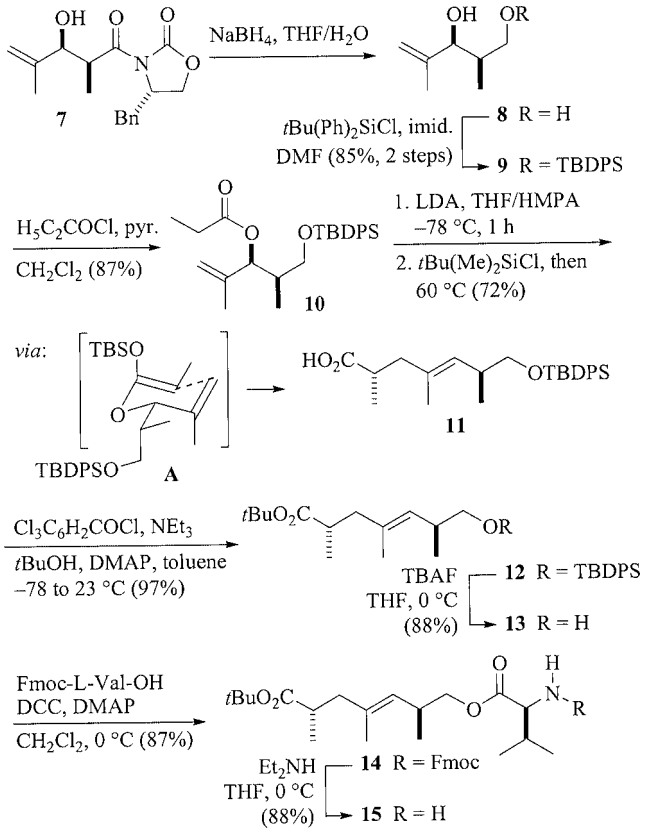
Figure 2. Design of conformationally constrained ω-amino and ω-hydroxy acids based on hydroxy acid **4**.

Results and Discussion

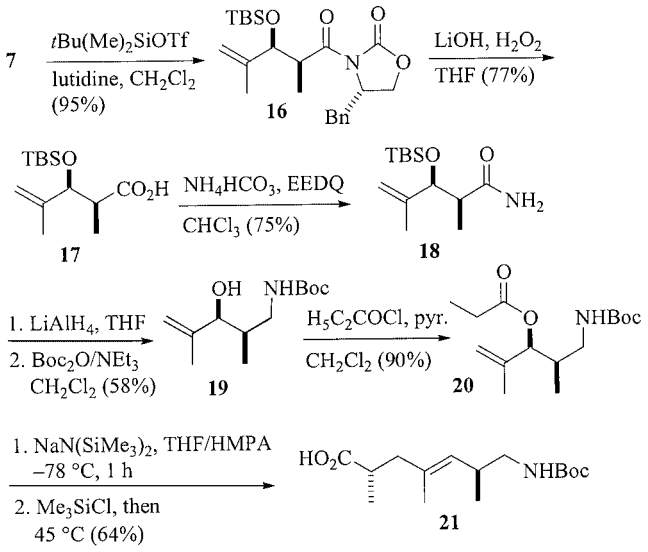
The silyl-protected hydroxy acid **11** was prepared from the known aldol adduct **7** (Scheme 1).[22] Reductive removal of the chiral auxiliary gave diol **8**. Selective protection of the primary alcohol afforded silyl ether **9**. Subsequent acylation of the secondary alcohol with propionyl chloride in the presence of pyridine gave ester **10** in good yield. As described by Heathcock et al.,[23] related esters can be rearranged to the 2,6-*anti* products by the application of the Ireland–Claisen rearrangement.[24] In order to reach the desired configuration at C-2, the corresponding (*Z*)-enolate of ester **10** was needed. The thermodynamically more stable (*Z*)-ester enolates can be generated in the presence of dipolar additives, which promote the desired equilibration. Adding ester **10** to an LDA solution in THF/HMPA (7:3) followed by trapping of the enolate after 10 min with *tert*-butyldimethylsilyl chloride and heating of the mixture brought about the desired Claisen rearrangement. However, the 1,4-unsaturated acid **11** was obtained as a 3:1 diastereomeric mixture at C-2. It was surmised that after 10 min, the enolate equilibrium was not yet reached. In fact, when the enolate solution was allowed to stir for 40 min prior to the addition of the silyl chloride, the subsequent Claisen rearrangement produced the desired acid **11** essentially as a single diastereomer (see transition state model **A**).

With a view to prepare a geodiamolide analog from hydroxy acid **11**, the carboxylic acid was converted into the corresponding *tert*-butyl ester **12** under Yamaguchi conditions.[25] Cleavage of the silyl ether then led to hydroxy ester **13**. The idea was to engage this hydroxy group with an *N*-protected amino acid. The resulting fragment could then be transformed by two amide-bond-forming reactions into geodiamolide analogs. In the event, *N*,*N*-dicyclohexylcarbodiimide (DCC) mediated esterification of Fmoc-L-valine with hydroxy ester **13** furnished the diester **14** in 88% yield. Finally, removal of the Fmoc protecting group with diethylamine in THF led to amine **15**.

The synthesis of the corresponding amino acid **21** started with the *syn*-aldol product **7** as well. Silylation of the secondary alcohol led to compound **16** (Scheme 2). Hydrolysis of the acylated oxazolidinone gave carboxylic acid **17**. This acid could be smoothly converted to amide **18** with 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ)



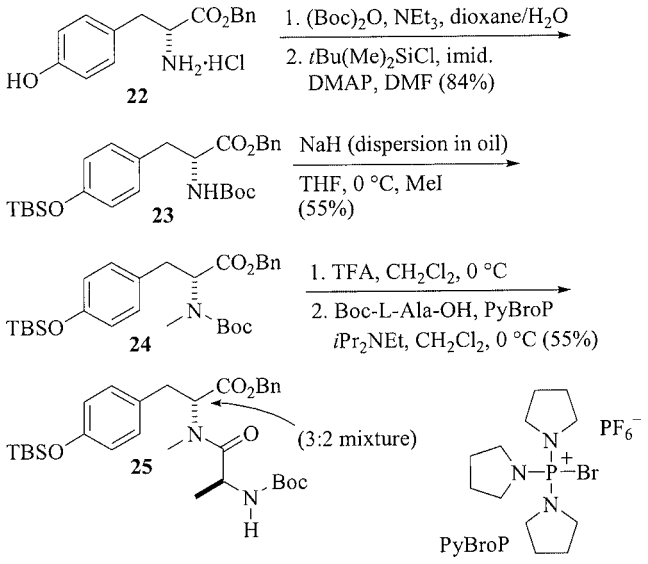
Scheme 1. Synthesis of ω-silyloxy acid **11** and its conversion to fragment **15**.



Scheme 2. Synthesis of the ω-amino acid derivative **21** by an aldol/Claisen strategy.

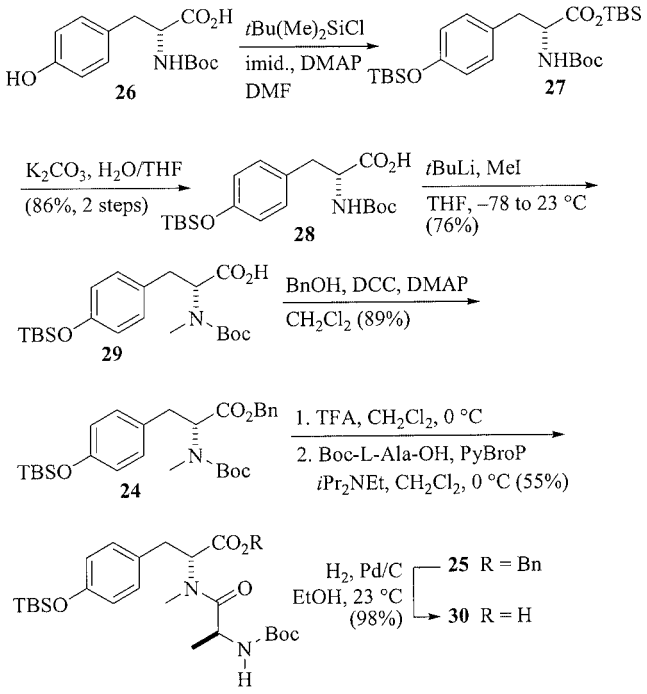
and ammonium hydrogen carbonate. Reduction of amide **18** with $LiAlH_4$ produced the corresponding amino alcohol, which was *N*-protected to give **19** with BOC anhydride in the presence of triethylamine. Acylation of alcohol **19** with propionyl chloride provided ester **20**, the required substrate for the Ireland–Claisen rearrangement. After some trials it was found that the use of $NaN(SiMe_3)_2$ (6 equiv.) in THF/HMPA (7:3) was suitable for enolate formation. Trapping of the enolate with Me_3SiCl, followed by heating of the intermediate ketene acetal delivered the desired amino acid **21** in 64% yield with excellent diastereoselectivity.

As a key building block in the assembly of the tripeptide sector of the geodiamolide analogs, we envisioned the *N*-protected dipeptide acid **30**. As described in the literature, D-tyrosine benzyl ester **22** was converted into the Boc-protected derivative, which was then silylated on the phenolic OH group. Subsequent *N*-methylation of **23** with a 60% dispersion of NaH in mineral oil as the base together with MeI provided the *N*-methyl-D-tyrosine derivative **24**.[13b] After cleavage of the *N*-Boc protecting group with TFA, the crude amine was coupled with *N*-Boc-L-alanine in the presence of PyBroP. However, the desired dipeptide **25** was obtained as a diastereomeric mixture (ratio 3:2). Since rotamers around the *N*-Boc group could be ruled out, we suspected that this problem might have occurred either in the *N*-methylation step or the peptide coupling. After careful examination of the NMR spectra of **25**, it turned out that racemization had occurred during the *N*-methylation step (Scheme 3).



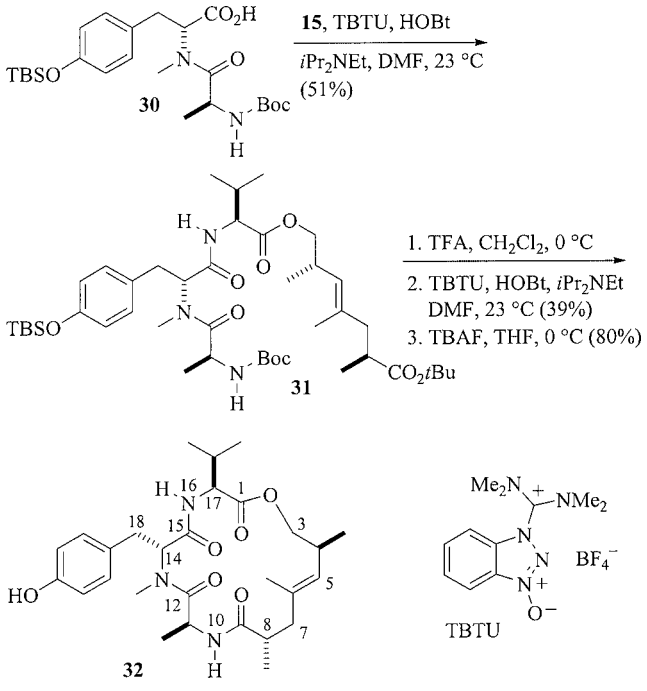
Scheme 3. Initial attempt at synthesizing the dipeptide fragment **25**.

Therefore, methylation was performed on the free acid **28**, which can be obtained from Boc-protected tyrosine (Scheme 4). Treatment of acid **28** with *t*-BuLi (2.5 equiv.) at –78 °C followed by the addition of MeI (4 equiv.) to the dianion provided the *N*-Boc-*N*-methyl tyrosine derivative **29**.[13a] After conversion of acid **29** to benzyl ester **30** and cleavage of the *N*-Boc protecting group, the resulting *N*-methylamine was condensed with *N*-Boc-L-alanine, leading to dipeptide **25**. The same sequence was performed with the L-tyrosine derivative, which proved that the earlier racemization had occurred during the *N*-methylation of ester **23**. Continuing with the synthesis, the benzyl ester of **25** was cleaved by hydrogenolysis, giving the pure acid **30**.



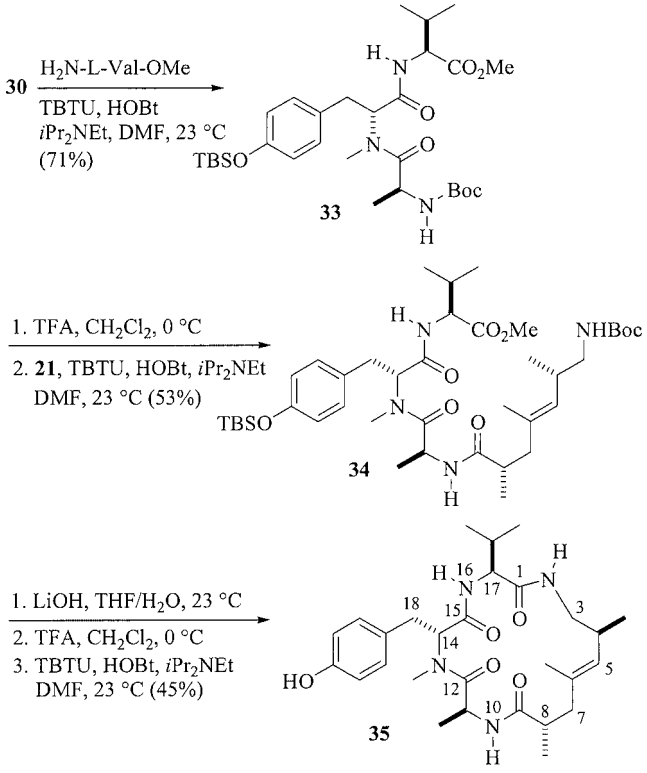
Scheme 4. Racemization-free synthesis of dipeptide fragment **30**.

To fashion a cyclodepsipeptide, featuring a tripeptide subunit and the hydroxy acid **11**, we planned to attach amine **15** to an *N*-protected dipeptide acid like the D-Tyr-L-Val derivative **30**. Accordingly, the coupling of acid **30** with amine **15** mediated by TBTU provided the linear depsipeptide **31** in 51% yield (Scheme 5). The two *tert*-butyl-based protecting groups could now be removed in one step with TFA. After concentration of the reaction mixture, macrolactam formation on the corresponding ammonium salt was carried out in DMF under high-dilution conditions (0.001 M) in the presence of TBTU/HOBt. In this way, the TBS-protected cyclic depsipeptide could be secured. A final deprotection step with TBAF furnished the desired cyclodepsipeptide **32**.



Scheme 5. Synthesis of the cyclodepsipeptide **32**.

In order to reach the amide analog (**35**) of cyclodepsipeptide **32**, we decided to assemble a tripeptide fragment and combine it with amino acid **30**. This strategy was attractive since ω-amino acid **21** was obtained in its *N*-Boc-protected form. The synthesis of geodiamolide analogue **35** started with dipeptide acid **30**, which was coupled with L-valine methyl ester to give tripeptide **33** (Scheme 6). At this point, the Boc protecting group at the N-terminus was removed with TFA. The resulting amine salt was condensed with amino acid **21** under the action of TBTU, leading to linear tetrapeptide **34**. The hydrolysis of **34** with LiOH in aqueous THF not only cleaved the ester group but the phenolic silyl ether as well. The deprotection of the Boc group produced the *seco* acid, which on macrolactamization with TBTU/HOBt, furnished the desired macrolactam **35**.



Scheme 6. Synthesis of cyclopeptide **35**.

Conformational Analysis

Both macrocyclic rings **32** and **35** exhibit single ^{1}H- and ^{13}C-NMR signal sets in [D$_6$]DMSO. Homo- and heteronuclear signal assignments were based on DQF-COSY, HSQC, and HMBC spectra. Rotating-frame NOESY (ROESY) and NOESY spectra corroborate these signal assignments. All amide bonds in **32** and **35** assume the *trans* configuration as indicated by the absence of NOE contacts expected

for *cis*-amide bonds. Coupling constants $^3J_{HH}$ and $^2J_{HH}$ were taken directly from the well-resolved ^{1}H NMR spectra after Lorentz–Gauss transformation. The temperature dependence of the N*H* chemical shifts yields information about the solvent accessibility of the amide protons.[26] Values between –5.8 and –7.6 ppb K^{-1} exclude relevant intramolecular hydrogen bonding for both molecules.

The NMR measurements yielded 57 ROEs for lactone **32** and 45 ROEs for lactam **35**. The volume integrals were translated into average proton-proton distances according to published methods.[27] The common Val-D-Tyr-Ala motif adopts a mainly extended conformation with interresidue CαH*i*–NH*i+1* average distances between 2.2 Å and 2.4 Å and intraresidue CαH*i*–NH*i* distances approaching 3 Å. The 1,3-allylic strain in the polypropionate moiety is documented by the strong 4H–6H$_3$ ROE contact in both molecules. $^3J_{HH}$ values and ROEs allowed the prochiral assignment of the *pro-R* and *pro-S* protons of the C-3 and C-7 methylene groups, which form the flexible joints between both termini of the polypropionate unit and the tripeptide unit. In both molecules, one of the $^3J_{H3,H4}$ and one of the $^3J_{H7,H8}$ values is small (Table 1), as expected if a single conformation around the C-2–C-4 and C-7–C-8 bonds predominates. Differences between **32** and **35** are detected only for the C-3 protons, which neighbors the lactone (**32**) or the amide (**35**) groups, respectively. The *gauche-anti* orientation dominates in lactam **35**, as does the *gauche-gauche* orientation in lactone **32**. The C-18 protons are well resolved in the case of the lactone but form a higher-order spin system in the case of the lactam. Chemical-shift differences between compounds **32** and **35** are restricted to the Northern half of the macrocyclic rings in the region of the Val residue.

Table 1. ^2J and ^3J values (given in Hz) for lactone **32** and lactam **35**.

Entry	Coupling	**32** (ester)	**35** (amide)
1	$^2J_{H3h,H3t}$	10.9	12.9
2	$^3J_{H3h,H4}$	2.5	9.1
3	$^3J_{H3t,H4}$	5.4	2.6
4	$^2J_{H7h,H7t}$	15.1	16.0
5	$^3J_{H7h,H8}$	<2	<2
6	$^3J_{H7t,H8}$	11.1	≈10 (COSY)

Molecular dynamics simulations were carried out with the MM+ force field, as implemented in HyperChem. NOEs and ^3J values were incorporated as additional distance or torsional restraints, respectively, in the empirical force field. Backbone NOEs are in agreement with one main conformation for each macrocycle. Fast conformational averaging is only of relevance for the amino acid side chains. The average structures represent minima on the potential energy surface, and the energy-minimized structures are shown in Figure 3. Structural differences are confined to the amino acid Val. The more folded structure of the lactone brings the 13-NMe and 6-Me groups into closer contact, which is documented by a particularly short NOE of 3.1 Å. The main difference between the ring-constrained analogs investigated here and the parent macrolide geodiamolide[12] is an approximately 180° rotation of the propionate relative to the tripeptide unit. As a consequence, the 6-Me group is oriented to the opposite side of the macrocyclic rings, which is documented by the intense transannular 13-NMe–6-Me NOE. The distance between these two groups is 7.7 Å in geodiamolide where they are positioned on opposite ring sides (Figure 3). Such a strong effect of a ring contraction from an 18-membered ring in geodiamolide to a 17-membered ring in **32** and **35** is completely unexpected but well documented by the solution-phase NMR spectroscopic data analyzed here.

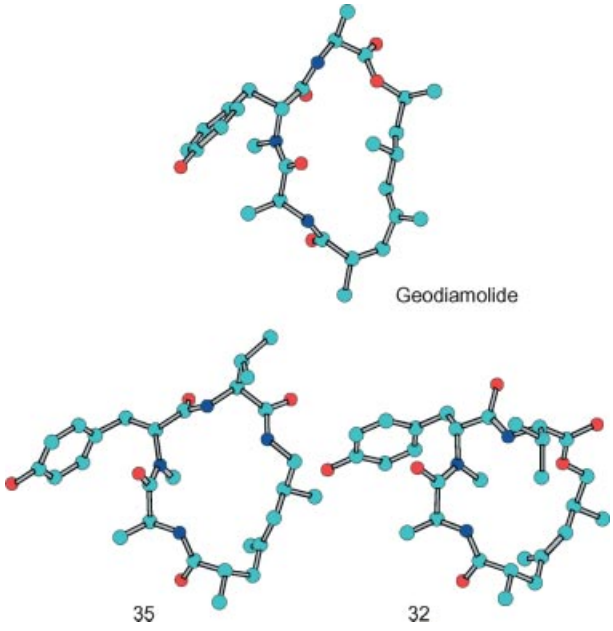


Figure 3. Energy-minimized structures for geodiamolide, lactam **35**, and lactone **32**.

Conclusions

Two ring-contracted geodiamolide analogs, the cyclodepsipeptide **32** and the cyclopeptide **35**, were prepared, and their solution conformations were studied by NMR spectroscopy. In contrast to the geodiamolides, the analogues contain simplified ω-hydroxy and ω-amino acids, respectively. Both of these building blocks could be easily synthesized from the aldol product **7**. After suitable functionalizations, an Ireland–Claisen rearrangement led to the polypropionate fragments **11** and **21**, respectively. With a *syn*-pentane and a 1,3-allylic interaction, these acids feature two non-bonded interactions that impose soft conformational constraints. Classical peptide chemistry was then used to fashion the analogs **32** and **35**. Conformational analysis by NMR spectroscopy and molecular dynamics simulation revealed that the reduced ring size causes the polypropionate sector to flip with regard to the geodiamolide conformation. A comparison between the ester and amide analogs shows that in lactone **32** the valine part is folded towards the macrocyclic ring. This study further

underscores the fact that small structural changes can have a profound effect on the conformation of a macrocyclic compound.

Experimental Section

General: ^{1}H and ^{13}C NMR: Bruker Avance 400 spectrometer; spectra were recorded at 295 K in $CDCl_3$; chemical shifts are calibrated to the residual proton and carbon resonance of the solvent: $CDCl_3$ (δ_H = 7.25 ppm, δ_C = 77.0 ppm), C_6D_6 (δ_H = 7.16 ppm, δ_C = 128.0 ppm), and [D$_6$]DMSO (δ_H = 2.49 ppm, δ_C = 39.5 ppm). Melting points: Büchi Melting Point B-540 apparatus, uncorrected. IR: Jasco FT/IR-430 apparatus [cm^{-1}]. MS: Finnigan Triple-Stage-Quadrupole TSQ-70 spectrometer (ionizing voltage of 70 eV). HRMS (FT-ICR): Bruker Daltonic APEX 2 spectrometer with electron spray ionization (ESI). The minimal resolution of this machine is 1 ppm ($\Delta m/m \times 10^6$). Flash chromatography: J. T. Baker silica gel, 43–60 μm. Thin-layer chromatography: Macherey–Nagel Polygram Sil G/UV254 plates. All solvents used in the reactions were distilled before use. Dry diethyl ether, tetrahydrofuran, and toluene were distilled from sodium and benzophenone, whereas dry CH_2Cl_2, dimethylformamide, pyridine, and triethylamine were distilled from CaH_2. Petroleum ether with a boiling range of 40–60 °C was used. Reactions were generally performed under an argon atmosphere. All commercially available compounds were used as received, unless stated otherwise.

(2*R*,3*S*)-2,4-Dimethylpent-4-ene-1,3-diol (8): To a solution of aldol product[22] **7** (1.0 g, 3.30 mmol) in THF (90 mL) was added $NaBH_4$ in H_2O (20 mL) at 0 °C. After complete addition, the mixture was warmed to room temperature and stirred for 7 h. The mixture was treated with saturated aqueous NH_4Cl (20 mL) and stirred for 1 h at room temperature. After separation of the layers, the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL) and saturated aqueous NaCl (50 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo to give the crude diol, which was purified by flash chromatography (ethyl acetate/CH_2Cl_2, 5:95), resulting in pure diol **8** as a colorless oil (365 mg, 85% yield). R_f = 0.23 (ethyl acetate/CH_2Cl_2, 5:95). $[\alpha]_D^{20}$ = –14.2 (c = 1.02, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3370, 2965, 2931, 1446, 1095 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (d, J = 6.8 Hz, 3 H, CH_3CH), 1.69 (s, 3 H, CH_3C=C), 1.84–1.89 (m, 1 H, CHCH$_2$O), 2.51 (br. s, 1 H, OH), 2.60 (br. s, 1 H, OH), 3.63–3.71 (m, 2 H, CH_2O), 4.22 (br. s, 1 H, CHO), 4.91 (s, 1 H, alkene H), 4.93 (s, 1 H, alkene H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.7 (*C*H$_3$CH), 19.3 (*C*H$_3$C=C), 37.1 (*C*HCH$_3$), 66.8 (CH$_2$OH), 76.9 (CHOH), 110.6 (alkene *C*H$_2$), 146.3 (alkene C) ppm.

(3*S*,4*R*)-5-{[*tert*-Butyl(diphenyl)silyl]oxy}-2,4-dimethylpent-1-en-3-ol (9): To a stirred solution of diol **8** (300 mg, 2.30 mmol) in dry DMF (10 mL) were added imidazole (392 mg, 5.75 mmol) and TBDPS-Cl (0.65 mL, 2.53 mmol) successively at room temperature. Stirring was continued for 12 h at room temperature. The mixture was diluted with H_2O (10 mL), stirred for 0.5 h, and then extracted with diethyl ether (3 × 15 mL). The combined organic layers were washed with 1 N HCl (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and saturated aqueous NaCl (15 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to provide the crude silyl ether, which was purified by flash chromatography (ethyl acetate/petroleum ether, 5:95), yielding the mono-protected alcohol **9** (870 mg, 97% yield) as a viscous oil. R_f = 0.24 (ethyl acetate/petroleum ether, 5:95). $[\alpha]_D^{20}$ = –6.5 (c = 1.0, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3370, 2965, 2931, 1446, 1095 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (d, J = 6.8 Hz, 3 H, CH_3CH), 1.06 (s, 9 H, *t*Bu), 1.66 (s, 3 H, CH_3C=CH), 1.83–1.90 (m, 1 H, CHCH$_2$O), 3.68 (dd, J = 10.1, 5.6 Hz, 1 H, CH_2O), 3.71–3.75 (m, 1 H, CH_2O), 4.33 (br. s, 1 H, CHO), 4.90 (s, 1 H, alkene H), 5.03 (s, 1 H, alkene H), 7.37–7.43 (m, 6 H, aromatic H), 7.66–7.72 (m, 4 H, aromatic H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.7 (*C*H$_3$CH), 19.2 [(CH$_3$)$_3$*C*Si], 19.4 (*C*H$_3$C=C), 26.5, 26.9 (3 C, *t*Bu), 37.3 (*C*HCH$_3$), 68.0 (*C*H$_2$OH), 76.3 (*C*HOH), 110.5 (alkene *C*H$_2$), 127.7, 129.7, 134.8, 135.6, 135.7 (aromatic), 145.7 (alkene) ppm. HRMS (ESI): calcd. for $C_{23}H_{22}O_2Si$ [M + Na]$^+$ 391.20638; found 391.20627 (Δm = 0.28 ppm).

(1*S*)-1-[(1*R*)-2-{[*tert*-Butyl(diphenyl)silyl]oxy}-1-methylethyl]-2-methylprop-2-enyl Propionate (10): To a solution of alcohol **9** (500 mg, 1.36 mmol) in dry CH_2Cl_2 (5 mL) were added pyridine (0.22 mL, 2.68 mmol) and n-propionyl chloride (0.18 mL, 2.00 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 12 h. It was then diluted with CH_2Cl_2 (4 mL), washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated in vacuo to give the crude ester, which was purified by flash chromatography (ethyl acetate/petroleum ether, 5:95), providing the propionate **10** (500 mg, 87% yield) as a gel. R_f = 0.55 (ethyl acetate/petroleum ether, 5:95). $[\alpha]_D^{20}$ = –11.0 (c = 1.02, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3066, 2938, 2865, 1739, 1519, 1461, 1095 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (d, J = 6.8 Hz, 3 H, CH_3CH), 1.05 (s, 9 H, *t*Bu), 1.12 (t, J = 7.6 Hz, 3 H, CH$_2$CH_3), 1.67 (s, 3 H, CH_3C=CH), 1.96–2.02 (m, 1 H, CHCH$_2$O), 2.31 (q, J = 7.6 Hz, 3 H, CH_2CH$_3$), 3.48–3.51 (m, 2 H, CH_2*O*), 4.84 (s, 1 H, alkene H), 4.87 (s, 1 H, alkene H), 5.34 (d, J = 5.1 Hz, 1 H, C*H*O), 7.35–7.42 (m, 6 H, aromatic H), 7.64 (t, J = 5.1 Hz, 4 H, aromatic H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.2 (CH$_2$*C*H$_3$), 11.2 (*C*H$_3$CH), 19.0 (*C*H$_3$C=C), 19.2 [(CH$_3$)$_3$*C*Si], 26.8 (3 C, *t*Bu), 27.7 (*C*H$_2$CH$_3$), 37.3 (*C*HCH$_3$), 65.4 (*C*H$_2$OH), 76.5 (*C*HOH), 112.0 (alkene CH$_2$), 127.6, 129.6, 133.6, 133.7, 135.6, 135.6 (aromatic), 142.3 (alkene), 173.4 (CO) ppm. HRMS (ESI): calcd. for $C_{26}H_{36}O_3Si$ [M + Na]$^+$ 447.23259; found 447.23264.

(2*S*,4*E*,6*S*)-7-{[*tert*-Butyl(diphenyl)silyl]oxy}-2,4,6-trimethylhept-4-enoic Acid (11): A solution of diisopropylamine (0.20 mL, 1.40 mmol) in dry THF (2 mL) was treated with *n*BuLi (2.5 M solution in hexane, 0.56 mL, 1.40 mmol) at 0 °C. Stirring was continued for 30 min at 0 °C before HMPA (0.5 mL) was added, and the mixture was cooled to –78 °C. Propionate **10** (500 mg, 1.17 mmol) in dry THF (0.3 mL) was added dropwise to the above solution. After stirring for 1 h at –78 °C, TBDMS-Cl (265 mg, 1.76 mmol) in THF (0.6 mL) was added dropwise. Stirring was continued for 30 min at –78 °C before the cooling bath was removed, and the reaction mixture was brought to room temperature. The mixture of the ketene acetal was stirred for 10 h at 60 °C. After cooling to room temperature, the mixture was treated with saturated aqueous NH_4Cl (5 mL), diluted with 1 N HCl (5 mL), and stirred for 5 min. The mixture was extracted with ethyl acetate (3 × 10 mL). The combined ethyl acetate layers were washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated in vacuo to give the crude acid, which was purified by flash chromatography (ethyl acetate/petroleum ether, 1:3), furnishing pure hydroxy acid **11** (360 mg, 72% yield) as a colorless gel; R_f = 0.45 (ethyl acetate/petroleum ether, 1:3). $[\alpha]_D^{20}$ = 4.3 (c = 1.13, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3448, 2966, 2879, 1718, 1629, 1439, 1377, 1195, 1159, 1103, 1053 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (d, J = 6.8 Hz, 3 H, CH_3CHCH$_2$O), 1.04 (s, 9 H, *t*Bu), 1.09 (d, J = 7.1 Hz, 3 H, CH_3CHCO), 1.56 (s, 3 H, CH_3), 2.02 (dd, J = 13.4, 8.1 Hz,

CH_2CO_2), 2.37 (dd, J = 13.3, 6.7 Hz, CH_2CO_2), 2.54–2.63 (m, 2 H, C*H*, C*H*), 3.41–3.49 (m, 2 H, CH_2OH), 4.99 (d, J = 9.1 Hz, 1 H, alkene H), 7.36–7.43 (m, 6 H, aromatic H), 7.82 (d, J = 6.8 Hz, 4 H, aromatic H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.8 (CH_3), 16.2 (CH_3CHCO), 17.3 (CH_3CHCH_2O), 19.2 [$(CH_3)_3CSi$], 26.8 (3 C, *t*Bu), 35.4 ($CHCO_2$), 37.8 ($CHCH_2O$), 43.8 (CH_2CO), 68.5 (CH_2O), 127.6, 129.5 (aromatic), 130.8 (C-5), 132.0 (aromatic), 134.0 (C-4), 135.6 (aromatic), 182.8 (CO_2H) ppm. HRMS (ESI): calcd. for $C_{26}H_{36}O_3Si$ [M + Na]$^+$ 447.23259; found 447.23264.

***tert*-Butyl (2*S*,4*E*,6*S*)-7-{[*tert*-Butyl(diphenyl)silyl]oxy}-2,4,6-trimethylhept-4-enoate (12):** To a stirred solution of acid **11** (300 mg, 0.71 mmol), DMAP (1.23 g, 10.61 mmol), Et_3N (1.0 mL, 7.10 mmol), and *t*BuOH (0.4 mL, 0.36 mmol) in dry toluene (70 mL) was added 2,4,6-trichlorobenzoyl chloride (1.1 mL, 7.10 mmol) at –78 °C. After stirring for 30 min at –78 °C, the cooling bath was removed, and the mixture was stirred for 12 h at room temperature. The mixture was treated with saturated aqueous $NaHCO_3$ (25 mL). After separation of the layers, the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with aqueous NaCl (25 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 5:95), resulting in pure ester **12** (330 mg, 97% yield). R_f = 0.22 (ethyl acetate/petroleum ether, 5:95). $[\alpha]_D^{20}$ = 7.7 (c = 0.71, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 3066, 2962, 2931, 2861, 1727, 1461, 1369, 1153, 1110 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (d, J = 6.8 Hz, 3 H, CH_3CH_2O), 1.03 (d, J = 8.1 Hz, 3 H, CH_3CO), 1.04 [s, 9 H, $(CH_3)_3CSi$], 1.41 (s, 9 H, *t*Bu), 1.54 (s, 3 H, CH_3C=C), 1.95 (dd, J = 13.6, 7.3 Hz, 1 H, CH_2CO), 2.30 (dd, J = 13.4, 7.3 Hz, 1 H, CH_2CO), 2.41–2.50 (m, 1 H, C*H*CO), 2.54–2.61 (m, 1 H, C*H*CH_2O), 3.39 (dd, J = 16.2, 6.8 Hz, 1 H, CH_2O), 3.45–3.49 (m, 1 H, CH_2O), 4.95 (d, J = 9.1 Hz, 1 H, alkene H), 7.35–7.41 (m, 6 H, aromatic H), 7.66 (d, J = 6.8 Hz, 4 H, aromatic H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.9 (CH_3C=CH), 16.9 (CH_3CH_2O), 17.4 (CH_3CHCO), 19.2 [$(CH_3)_3CSi$], 26.8 [3 C, $(CH_3)_3CSi$], 28.1 (3 C, *t*Bu), 35.4 ($CHCH_2O$), 38.7 (*C*HCO), 44.1 (CH_2C=CH), 68.6 (CH_2O), 79.7 (Boc quaternary), 127.5, 129.5 (aromatic), 129.8 (alkene CH), 132.8 (aromatic), 133.9 (alkene), 135.6 (aromatic), 175.9 (CO_2tBu) ppm. HRMS (ESI): calcd. for $C_{30}H_{44}O_3Si$ [M + Na]$^+$ 503.2952; found 503.2950.

***tert*-Butyl (2*S*,4*E*,6*S*)-7-Hydroxy-2,4,6-trimethylhept-4-enoate (13):** To a solution of ω-silyloxy ester **12** (300 mg, 0.63 mmol) in THF (5 mL) was added TBAF (1 M solution in THF containing 5% H_2O, 0.75 mL, 0.75 mmol) at 0 °C. Stirring was continued until TLC showed complete consumption of the reactant (4–5 h). The mixture was concentrated in vacuo, and the residue was purified by flash chromatography (ethyl acetate/petroleum ether, 1:3), providing pure hydroxy ester **13** (135 mg, 88% yield) as a colorless gel. R_f = 0.35 (ethyl acetate/petroleum ether, 1:3). $[\alpha]_D^{20}$ = –15.7 (c = 0.77, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3384, 2973, 2930, 2872, 1729, 1457, 1367, 1151 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (d, J = 6.6 Hz, 3 H, CH_3CH_2O), 1.06 (d, J = 7.1 Hz, 3 H, CH_3CHCO), 1.41 (s, 9 H, *t*Bu), 1.65 (s, 3 H, CH_3C=CH), 2.05–2.07 (m, 1 H, CH_2CHCO), 2.32 (dd, J = 13.3, 8.2 Hz, 1 H, CH_2CHCO), 2.46–2.55 (m, 1 H, C*H*CO), 2.56–2.65 (m, 1 H, C*H*CH_2O), 3.29 (dd, J = 10.2, 8.2 Hz, 1 H, CH_2O), 3.44 (dd, J = 10.4, 5.8 Hz, 1 H, CH_2O), 4.90 (d, J = 9.4 Hz, 1 H, alkene H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.6 (CH_3C=CH), 16.9 (CH_3CH_2O), 17.1 (CH_3CHCO), 28.1 (3 C, *t*Bu), 35.5 ($CHCH_2O$), 39.0 (*C*HCO), 43.8 (CH_2C=CH), 67.8 (CH_2O), 80.0 (Boc quaternary), 129.1 (alkene CH), 135.3 (alkene C), 175.8 (CO_2tBu) ppm. HRMS (ESI): calcd. for $C_{34}H_{45}NO_6$ [M + Na]$^+$ 265.1774; found 265.1775.

***tert*-Butyl (2*S*,4*E*,6*S*)-7-({*N*-[(9*H*-Fluoren-9-ylmethoxy) carbonyl]-L-valyl}oxy)-2,4,6-trimethylhept-4-enoate (14):** To a solution of hydroxy ester **13** (100 mg, 0.41 mmol), Fmoc-L-valine (140 mg, 0.41 mmol), and DMAP (25 mg, 0.20 mmol) in dry CH_2Cl_2 (4 mL) was added a solution of DCC (110 mg, 0.53 mmol) in dry CH_2Cl_2 (0.6 mL) dropwise at 0 °C. Stirring was continued for 0.5 h at 0 °C and for 10 h at room temperature. The reaction mixture was diluted with diethyl ether (10 mL), filtered to remove the cyclohexyl urea, and the precipitate was washed twice with diethyl ether (5 mL). After concentration of the filtrate in vacuo, the crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:4) to give the pure product **14** (205 mg, 87% yield) as a colorless gel. R_f = 0.30 (ethyl acetate/petroleum ether, 1:4). $[\alpha]_D^{20}$ = –5.86 (c = 0.87, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3351, 2969, 2904, 1724, 1677, 1454, 1369, 1153 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (d, J = 6.8 Hz, 3 H, CH_3CH_2O), 0.97 (d, J = 6.3 Hz, 6 H, Val CH_3), 1.03 (d, J = 6.8 Hz, 3 H, CH_3CHCO), 1.41 (s, 9 H, *t*Bu), 1.62 (s, 3 H, CH_3C=CH), 1.96 (dd, J = 13.6, 7.3 Hz, 1 H, CH_2CHCO), 2.13–2.20 (m, 1 H, C*H*NH), 2.32 (dd, J = 13.3, 8.2 Hz, 1 H, CH_2CHCO), 2.43–2.51 (m, 1 H, $CHCH_2O$), 2.71–2.79 (m, 1 H, CHCO), 3.88–3.98 (m, 2 H, Val CH, CH_2O), 4.11 (dd, J = 10.2, 8.2 Hz, 1 H, CH_2O), 4.22 (t, J = 7.0 Hz, 1 H, Fmoc CH), 4.30 (dd, J = 9.0, 4.7 Hz, 1 H, Fmoc CH_2), 4.34–4.43 (m, 1 H, Fmoc CH_2), 4.94 (d, J = 9.1 Hz, 1 H, alkene H), 5.34 (d, J = 9.1 Hz, 1 H, NH), 7.30 (t, J = 7.3 Hz, 2 H, Fmoc aromatic), 7.39 (t, J = 7.3 Hz, 2 H, Fmoc aromatic), 7.60 (d, J = 5.6 Hz, 2 H, Fmoc aromatic), 7.75 (d, J = 7.7 Hz, 2 H, Fmoc aromatic) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.0 (CH_3C=CH), 16.8 (CH_3CH_2O), 17.5 (2 C, Val CH_3), 18.9 (CH_3CHCO), 28.0 (3 C, *t*Bu), 31.4 ($CHCH_2O$), 32.0 (Val CH), 38.6 (*C*HCO), 43.8 (CH_2C=CH), 47.1 (Fmoc CH), 59.0 (*C*HNH), 67.0 (Fmoc CH_2), 69.5 (CH_2O), 79.8 (Boc quaternary), 119.9, 125.1, 127.0, 127.7 (Fmoc aromatic), 128.1 (alkene CH), 134.5 (alkene), 141.3, 143.7, 143.9 (Fmoc aromatic), 156.2 (NHCO), 172.1 (Val CO), 175.7 (CO_2tBu) ppm. HRMS (ESI): calcd. for $C_{34}H_{45}NO_6$ [M + Na]$^+$ 586.3139; found 586.3140.

***tert*-Butyl (2*S*,4*E*,6*S*)-2,4,6-Trimethyl-7-(L-valyloxy)hept-4-enoate (15):** Et_2NH (7 mL) was added to a precooled solution (0 °C) of Fmoc-protected valine ester **14** (150 mg, 0.27 mmol) in dry THF (7 mL). Stirring was continued for 15 min at 0 °C and then at room temperature for 3 h. The solution was concentrated in vacuo, and the resulting oil was purified by flash chromatography (MeOH/CH_2Cl_2, 5:95) to provide pure amine **15** (80 mg, 88% yield) as a slightly yellow oil. R_f = 0.25 (MeOH/CH_2Cl_2, 5:95). IR (film): $\tilde{\nu}$ = 3351, 2969, 2904, 1724, 1677, 1454, 1369, 1153 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (d, J = 6.8 Hz, 3 H, Val CH_3), 0.96 (d, J = 6.8 Hz, 6 H, Val CH_3, CH_3CH_2O), 1.03 (d, J = 7.1 Hz, 3 H, CH_3CHCO),1.41 (s, 9 H, *t*Bu), 1.62 (s, 3 H, CH_3C=CH), 1.93–2.03 (m, 2 H, CH_2CHCO, Val CH), 2.32 (dd, J = 13.3, 8.2 Hz, 1 H, CH_2CHCO), 2.41–2.50 (m, 1 H, $CHCH_2O$), 2.69–2.78 (m, 1 H, C*H*CO), 3.26 (d, J = 4.8 Hz, 1 H, C*H*NH_2), 3.89 (ddd, J = 18.1, 10.8, 6.9 Hz, 2 H, CH_2O), 4.94 (d, J = 8.8 Hz, 1 H, alkene H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.0 (CH_3C=CH), 16.8 (CH_3CH_2O), 17.1, 17.5 (2 C, Val CH_3), 19.3 (CH_3CHCO), 28.1 (3 C, *t*Bu), 32.0 (2 C, $CHCH_2O$, Val CH), 38.6 (CHCO), 43.9 (CH_2C=CH), 47.1 (Fmoc CH), 59.9 (*C*HNH), 69.1 (CH_2O), 79.9 (Boc quaternary), 128.4 (alkene CH), 134.2 (alkene C), 175.5 (Val CO), 175.7 (CO_2tBu) ppm. HRMS (ESI): calcd. for $C_{19}H_{35}NO_4$ [M + H]$^+$ 342.2639; found 342.2639.

(4*S*)-4-Benzyl-3-((2*S*,3*S*)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-2,4-dimethylpent-4-enoyl)-1,3-oxazolidin-2-one (16): To a solution of aldol product[22] **7** (1.06 g, 3.50 mmol) in dry CH_2Cl_2 (25 mL) was added 2,6-lutidine (1.02 mL, 8.75 mmol) at room temperature. The resulting solution was stirred for 5 min before TBDMSOTf

(1.05 mL, 4.54 mmol) was added. The reaction mixture was stirred for 5 h at room temperature. It was then diluted with H_2O (30 mL) and stirred for an additional 30 min. After separation of the layers, the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined CH_2Cl_2 layers were washed with saturated aqueous $NaHCO_3$ (30 mL), 1 N HCl (30 mL), and saturated aqueous NaCl (30 mL). After drying (Na_2SO_4) and filtration, the organic layer was concentrated in vacuo. The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:9) to provide the protected aldol product **16** (1.36 g, 95% yield) as a colorless solid. R_f = 0.32 (ethyl acetate/petroleum ether, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01, 0.03 [2 s, 6 H, Si(CH_3)$_2$], 0.93 [s, 9 H, (CH_3)$_3$-CSi], 1.23 (d, J = 6.6 Hz, 3 H, CH_3CH), 1.74 (s, 3 H, CH_3C=C), 2.78 (dd, J = 13.4, 9.9 Hz, 1 H, PhCH_2), 3.30 (dd, J = 13.3, 2.9 Hz, 1 H, PhCH_2), 4.01–4.08 (m, 1 H, CHCH$_3$), 4.13–4.21 (m, 2 H, OCH_2), 4.37 (d, J = 6.6 Hz, 1 H, CHOTBS), 4.59 (ddd, J = 12.9, 6.6, 3.0 Hz, 1 H, CHN), 4.86 (s, 1 H, alkene H), 4.96 (s, 1 H, alkene H), 7.23–7.37 (m, 5 H, aromatic) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.4, –4.8 [Si(CH_3)$_2$], 12.3 (CH_3CH), 17.8 (CH_3C=C), 18.2 [(CH_3)$_3$CSi], 25.8 [(CH_3)$_3$CSi], 37.7 (PhCH_2), 42.4 (CHCH$_3$), 55.7 (CHN), 66.0 (OCH_2), 76.9 (CHOH), 112.6 (alkene CH_2), 127.3, 128.9, 129.4, 135.1 (aromatic), 145.7 (alkene C), 153.1 (NCO), 174.8 (CO) ppm.

(2*S*,3*S*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-2,4-dimethylpent-4-enoic Acid (17): H_2O_2 (1.2 mL of a 30 wt-% solution, 9.6 mmol) was added at 0 °C to a solution of the protected aldol product **16** (1.00 g, 2.4 mmol) in THF (25 mL), and LiOH·H_2O (200 mg, 4.80 mmol), dissolved in H_2O (12 mL), was added. The solution was stirred at 0 °C for 5 h. Subsequently, saturated aqueous Na_2SO_3 (10 mL) and saturated aqueous $NaHCO_3$ (10 mL) were added at 0 °C. The whole mixture was partially concentrated in vacuo and diluted with H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL) to recover the auxiliary. The aqueous layer was then acidified at 0 °C to pH 3 by the addition of 1 N HCl and then extracted with ethyl acetate (4 × 25 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to give an oily residue. Purification of the residue by flash chromatography (ethyl acetate/petroleum ether, 1:3) gave the pure acid. Further acid could be obtained by flash chromatography of the concentrated CH_2Cl_2 layers. Yield 480 mg (77%) of a colorless oil. R_f = 0.35 (ethyl acetate/petroleum ether, 1:3). $[\alpha]_D^{20}$ = –11.4 (c = 1.10, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3100, 2938, 2892, 2618, 1708, 1461, 1079 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.01 [s, 3 H, (CH_3)$_2$Si], 0.02 [s, 3 H, (CH_3)$_2$Si], 0.87 (s, 9 H, tBu), 1.11 (d, J = 7.1 Hz, 3 H, CH_3CH), 1.69 (s, 3 H, CH_3C=C), 2.59–2.65 (m, 1 H, CHCO), 4.32 (d, J = 5.8 Hz, 1 H, CHO), 4.86 (s, 1 H, alkene H), 4.95 (s, 1 H, alkene H), 11.42 (br. s, CO_2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.4, –4.7 [(CH_3)$_2$Si], 11.3 (CH_3CH), 17.7 (CH_3C=C), 18.1 [(CH_3)$_3$CSi], 25.7 (tBu), 44.3 (CHCO), 77.3 (CHOTBS), 113.2 (alkene CH_2), 144.7 (alkene C), 180.8 (CO_2H) ppm. HRMS (ESI): for $C_{13}H_{26}O_3Si$ [M + Na]$^+$ 281.1543; found 281.1542.

(2*S*,3*S*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-2,4-dimethylpent-4-enamide (18): To a solution of acid **17** (400 mg, 1.54 mmol) in dry $CHCl_3$ (10 mL) were added NH_4HCO_3 (360 mg, 4.50 mmol) and EEDQ (410 mg, 1.66 mmol) at room temperature. The mixture was stirred for 48 h at room temperature and then diluted with CH_2Cl_2 (15 mL) and washed with H_2O (10 mL) and saturated aqueous NaCl (10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate/petroleum ether, 1:1) to furnish the pure amide **18** (300 mg, 75% yield) as a colorless gel; R_f = 0.40 (ethyl acetate/petroleum ether, 1:1). $[\alpha]_D^{20}$ = –4.5 (c = 1.18, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3340, 3193, 2935, 2892, 1662, 1461, 1072 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.03 [s, 3 H, (CH_3)$_2$Si], 0.02 [s, 3 H, (CH_3)$_2$Si], 0.86 (s, 9 H, tBu), 1.07 (d, J = 7.1 Hz, 3 H, CH_3CH), 1.66 (s, 3 H, CH_3C=C), 2.40–2.46 (m, 1 H, CHCO), 4.21 (d, J = 5.8 Hz, 1 H, CHOTBS), 4.84 (s, 1 H, alkene H), 4.91 (s, 1 H, alkene H), 5.91, 6.13 (2s, br. , 2 H, NH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.4, –4.8 [(CH_3)$_2$Si], 12.5 (CH_3CH), 18.0 (CH_3C=C), 18.1 [(CH_3)$_3$CSi], 25.8 (tBu), 45.4 (CHCO), 77.8 (CHOTBS), 113.2 (alkene CH_2), 144.7 (alkene C), 177.2 ($CONH_2$) ppm. HRMS (ESI): calcd. for $C_{13}H_{27}NO_2Si$ [M + Na]$^+$ 280.1703; found 280.1702.

***tert*-Butyl (2*R*,3*S*)-3-Hydroxy-2,4-dimethylpent-4-enylcarbamate (19):** To a solution of amide **18** (275 mg, 1.07 mmol) in dry THF (5 mL) was added $LiAlH_4$ (1 M solution in ether, 4.0 mL, 4.0 mmol) at 0 °C. The mixture was stirred for 0.5 h at 0 °C, brought to room temperature by removing the ice bath, and finally heated at reflux for 2 h. After cooling, the reaction was worked up by the dropwise and sequential addition of H_2O (0.15 mL), 15% aqueous NaOH (0.15 mL) and additional H_2O (0.5 mL, Fieser quench). The mixture was filtered through celite, and the celite bed was washed thoroughly with diethyl ether (6 × 10 mL). The combined filtrates were dried ($MgSO_4$), filtered, and concentrated in vacuo to give crude aminol, which was used for the next step (Boc protection) without any further purification.

To the foregoing crude aminol in dry CH_2Cl_2 (5 mL) were added NEt_3 (0.27 mL, 2.00 mmol) and Boc anhydride (270 mg, 1.25 mmol) at room temperature. After being stirring for 12 h, the reaction mixture was acidified to pH 3 with 5% aqueous $KHSO_4$ before it was extracted with CH_2Cl_2 (3 × 5 mL).The combined organic layers were washed with saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous NaCl (5 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate/petroleum ether, 1:3) to give pure alcohol **19** (145 mg, 58% yield over two steps) as a colorless gel; R_f = 0.35 (ethyl acetate/petroleum ether, 1:3). $[\alpha]_D^{20}$ = –4.9 (c = 1.00, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3363, 2973, 2931, 1689, 1523, 1072 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.76 (d, J = 6.8 Hz, 3 H, CH_3CH), 1.42 (s, 9 H, tBu), 1.67 (s, 3 H, CH_3C=C), 1.75–1.80 (m, 1 H, CHCH$_3$), 2.91–2.98 (m, 2 H, CH_2NH, *OH*), 3.24–3.31 (m, 1 H, CH_2NH), 4.02 (br. s, 1 H, CHOH), 4.90 (br. s, 2 H, NH, alkene H), 5.03 (s, 1 H, alkene H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.6 (CHCH_3), 19.5 (CH_3C=C), 28.4 (tBu), 36.3 (CHCH$_3$), 43.8 (CH_2NH), 74.1 (CHOH), 79.6 (Boc quaternary), 110.5 (alkene CH_2), 145.7 (alkene), 157.1 (C=O) ppm. HRMS (ESI): calcd. for $C_{12}H_{23}NO_3$ [M + Na]$^+$ 252.15701; found 252.15697.

(1*S*)-1-{(1*R*)-2-[(*tert*-Butoxycarbonyl)amino]-1-methylethyl}-2-methylprop-2-enyl Propionate (20): To a solution of alcohol **19** (130 mg, 0.57 mmol) in dry CH_2Cl_2 (5 mL) was added pyridine (0.09 mL, 1.14 mmol) and *n*-propionyl chloride (0.07 mL, 0.79 mmol) at 0 °C. The cooling bath was removed, and the mixture was stirred for 12 h at room temperature. The mixture was diluted with CH_2Cl_2 (4 mL), washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered and concentrated in vacuo. The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:9) to provide the propionate **20** (145 mg, 90% yield) as a colorless oil. R_f = 0.40 (ethyl acetate/petroleum ether, 1:9). $[\alpha]_D^{20}$ = –15.6 (c = 0.95, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3374, 2974, 2935, 1712, 1511, 1172 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84 (d, J = 6.8 Hz, 3 H, CH_3CH), 1.15 (t, J = 7.6 Hz, 3 H, CH_2CH_3), 1.42 (s, 9 H, tBu), 1.69 (s, 3 H, CH_3C=C), 2.01–2.04 (m, 1 H, CHCH$_3$), 2.37 (q, J = 7.6 Hz, 2 H, CH_2CH$_3$), 2.78–2.85 (m, 1 H, CH_2NH), 3.08–3.15 (m,

1 H, CH_2NH), 4.90 (br. s, 3 H, NH, alkene H), 5.19 (br. s, 1 H, CHOR) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.2 (CH_2CH_3), 11.8 (CH_3CH), 19.3 (CH_3C=C), 27.7 (CH_2CH_3), 28.4 (*t*Bu), 35.1 ($CHCH_3$), 43.2 (CH_2NH), 76.4 (CHOH), 79.2 (Boc quaternary), 112.1 (alkene CH_2), 141.9 (alkene), 156.0 (Boc C=O), 174.0 (CO_2R) ppm. HRMS (ESI): calcd. for $C_{15}H_{27}NO_4$ [M + Na]$^+$ 308.1832; found 308.1834.

(2*S*,4*E*,6*S*)-7-[(*tert*-Butoxycarbonyl)amino]-2,4,6-trimethylhept-4-enoic Acid (21): To solution of propionate **20** (140 mg, 0.49 mmol) in THF/HMPA (1.1 mL/0.4 mL) was added $NaN(SiMe_3)_2$ (2 M in THF, 1.5 mL, 3.0 mmol) at –78 °C. After being stirred for 45 min at –78 °C, TMS-Cl (0.5 mL, 4.00 mmol) and Et_3N (0.20 mL, 1.50 mmol) were added simultaneously. After an additional 15 min at –78 °C, the cooling bath was removed, and the reaction mixture was allowed to reach room temperature within 1 h. The mixture was then heated to 60 °C for 5 h. After the mixture was cooled, saturated aqueous NH_4Cl (2 mL) and 1 N HCl (2 mL) were added, and the mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with saturated aqueous NaCl (4 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate/petroleum ether, 1:1) to give the pure amino acid **21** (90 mg, 64% yield) as a slightly yellow oil. R_f = 0.45 (ethyl acetate/petroleum ether, 1:1). $[\alpha]_D^{20}$ = –34.6 (*c* = 0.62, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3361, 2974, 2930, 1735, 1712, 1511, 1172 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 6.6 Hz, 3 H, 6-CH_3), 1.12 (d, *J* = 6.8 Hz, 3 H, 2-CH_3), 1.42 (s, 9 H, *t*Bu), 1.62 (s, 3 H, CH_3C=C), 2.03–2.10 (m, 1 H, 3-H), 2.34–2.39 (m, 1 H, 3-H), 2.56–2.67 (m, 2 H, 2-H, 6-H), 2.76–2.78 (m, 1 H, 7-H), 3.11–3.14 (m, 1 H, 7-H), 4.55 (br. s, 1 H, NH), 4.91 (d, *J* = 9.4 Hz, 1 H, alkene H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.2 (CH_3C=C), 16.3 (2-CH_3), 18.2 (6-CH_3), 28.4 (*t*Bu), 33.0 (C-6), 37.9 (C-2), 43.6 (C-3), 46.4 (CH_2NH), 79.1 (Boc quaternary), 130.8 (alkene CH), 133.4 (alkene), 156.0 (Boc C=O), 181.7 (CO_2H) ppm. HRMS (ESI): calcd. for $C_{15}H_{27}NO_4$ [M + Na]$^+$ 308.18323; found 308.18317.

Benzyl *N*-(*tert*-Butoxycarbonyl)-*O*-[*tert*-butyl(dimethyl)silyl]-*N*-methyl-D-tyrosinate (24): To a solution of acid **29** (700 mg, 1.71 mmol), benzyl alcohol (0.53 mL, 5.13 mmol), and DMAP (104 mg, 0.86 mmol) in dry CH_2Cl_2 (15 mL) was added at 0 °C a solution of DCC (460 mg, 2.22 mmol) in CH_2Cl_2 (2.5 mL). The solution was stirred for 0.5 h at 0 °C and then for 12 h at room temperature. The dicyclohexyl urea was filtered off, and the precipitate was washed with diethyl ether (3 × 5 mL). The filtrate was concentrated in vacuo to provide the crude product, which was purified by flash chromatography (ethyl acetate/petroleum ether, 1:9) to furnish the benzyl ester **24** (760 mg, 89% yield) as a colorless oil. R_f = 0.52 (ethyl acetate/petroleum ether, 1:9). $[\alpha]_D^{20}$ = 71.8 (*c* = 1.70, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.16 [s, 6 H, Si(CH_3)$_2$], 0.96 [s, 9 H, (CH_3)$_3$CSi], 1.32, 1.37 (2s, 9 H, *t*Bu Boc), 2.65, 2.70 (2s, NCH_3), 2.93–3.00 (m, 1 H, Tyr CH_2), 3.19–3.28 (m, 1 H, Tyr CH_2), 4.51, 4.86 (2 dd, *J* = 10.6, 4.6 Hz, *J* = 10.5, 5.4 Hz, 1 H, Tyr CH), 5.11–5.20 (m, 2 H, OCH_2Ph), 6.74 (d, *J* = 8.1 Hz, 2 H, Tyr), 7.00–7.05 (m, 2 H, Tyr), 7.34 (s, 5 H, Bn aromatic) ppm.

Benzyl *N*-(*tert*-Butoxycarbonyl)-L-alanyl-*O*-[*tert*-butyl(dimethyl)silyl]-*N*-methyl-D-tyrosinate (25): To a solution of D-tyrosine benzyl ester derivative **24** (650 mg, 1.30 mmol) in CH_2Cl_2 (10 mL) was added TFA (1.0 mL, 13.0 mmol), and the mixture was stirred at room temperature for 1 h. The solvent was removed in vacuo, and the residue was dried by azeotropic removal of H_2O with toluene. The crude material was subjected to the next reaction without further purification. To a stirred solution of crude amine, *N*-Boc-L-alanine (240 mg, 1.30 mmol), and PyBroP (635 mg, 1.30 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added iPr$_2$NEt (0.8 mL, 4.70 mmol), and the mixture was allowed to stir for 3 h at room temperature. The solvent was removed in vacuo, and the residue was purified by flash chromatography (ethyl acetate/petroleum ether, 1:3) to give the dipeptide **25** (403 mg, 55% yield) as a colorless gel. R_f = 0.45 (ethyl acetate/petroleum ether, 1:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.13 [s, 6 H, (CH_3)$_2$Si], 0.84 (d, *J* = 6.8 Hz, 3 H, Ala CH_3), 0.94 [s, 9 H, (CH_3)$_3$CSi], 1.41 (s, 9 H, Boc *t*Bu), 2.80 (s, 3 H, NCH_3), 2.95 (dd, *J* = 14.5, 11.8 Hz, 1 H, Tyr CH_2), 3.33 (dd, *J* = 14.8, 4.9 Hz, 1 H, Tyr CH_2), 4.43–4.50 (m, 1 H, Ala CH), 5.12–5.20 (m, 2 H, CH_2Ph), 5.26–5.30 (m, 1 H, Tyr CH), 5.44 (d, *J* = 7.8 Hz, 1 H, Ala NH), 6.71 (d, *J* = 8.6 Hz, 2 H, aromatic H), 6.99 (d, *J* = 8.6 Hz, 2 H, aromatic H), 7.31–7.34 (5 H, aromatic CO_2Bn) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.5 [2 C, (CH_3)$_2$Si], 18.1 (Ala CH_3), 18.4 [(CH_3)$_3$CSi], 25.6 [(CH_3)$_3$CSi], 28.3 (Boc *t*Bu), 32.5 (NCH_3), 33.9 (Tyr CH_2), 46.4 (Ala CH), 58.4 (Tyr CH), 67.0 (OCH_2), 79.5 (Boc C), 120.1, 128.2, 128.6, 129.0, 129.6, 135.6 (aromatic), 154.5 (Boc CO), 155.0 (phenolic), 170.3 (Ala CO), 173.6 (Tyr CO) ppm.

***N*-(*tert*-Butoxycarbonyl)-*O*-[*tert*-butyl(dimethyl)silyl]-D-tyrosine (28):** To a solution of *N*-Boc-D-tyrosine **26** (1.00 g, 3.55 mmol) in dry DMF (15 mL), imidazole (725 mg, 10.66 mmol) and TBDMSCl (1.10 g, 7.80 mmol) were added successively at room temperature. The resulting solution was stirred overnight at room temperature. The reaction mixture was then treated with H_2O (15 mL) and stirred for 30 min. The mixture was extracted with diethyl ether (3 × 30 mL). The combined ether layers were successively washed with 1 N HCl (20 mL), saturated aqueous $NaHCO_3$ (20 mL), and saturated aqueous NaCl (20 mL). The dried (Na_2SO_4) organic layers were filtered and concentrated in vacuo to give the crude silyl ester **27** as a colorless oil.

The crude ester **27** was dissolved in THF (10 mL) and treated with K_2CO_3 solution (1 M, 10 mL), and the mixture was stirred at room temperature for 1 h. The mixture was acidified to pH 3 by adding 1 N HCl and then extracted with ethyl acetate (3 × 30 mL). The combined ethyl acetate layers were dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate/petroleum ether, 1:3) to provide the pure acid **28** (1.20 g, 86% yield) as a colorless oil. R_f = 0.44 (ethyl acetate/petroleum ether, 1:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.21 [s, 6 H, Si(CH_3)$_2$], 1.03 [s, 9 H, (CH_3)$_3$CSi], 1.34 (s, 9 H, Boc *t*Bu), 2.71–2.79 (m, 1 H, CH_2), 3.21 (br. s, 1 H, CH_2), 4.31 (br. s, 1 H, CH), 6.74 (d, *J* = 6.6 Hz, 2 H, aromatic H), 7.10 (d, *J* = 4.8 Hz, 2 H, Tyr) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.5 [s, (CH_3)$_2$Si], 18.1 [(CH_3)$_3$CSi], 25.6 [(CH_3)$_3$CSi], 28.2 (Boc *t*Bu), 37.0 (CH_2), 56.8 (CH), 79.1 (Boc quaternary), 119.6, 125.2, 130.2 (aromatic), 153.9 (phenolic), 156.4 (Boc CO), 179.1 (CO_2H) ppm.

***N*-(*tert*-Butoxycarbonyl)-*O*-[*tert*-butyl(dimethyl)silyl]-*N*-methyl-D-tyrosine (29):** To a solution of *N*-Boc amino acid **28** (1.04 g, 2.64 mmol) in dry THF (12 mL) was added *t*BuLi (1.5 M solution in pentane, 4.40 mL, 6.60 mmol) dropwise at –78 °C. The mixture was stirred for 10 min, and then methyl iodide (0.57 mL, 10.6 mmol) was added to the reaction mixture at –78 °C. Stirring was continued for 12 h with simultaneous warming of the reaction mixture to room temperature. The reaction mixture was diluted with saturated aqueous NH_4Cl (3 mL), and the resulting mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo to give the crude product, which was purified by flash chromatography (ethyl acetate/petroleum ether, 1:3) to afford the *N*-methylated acid **29** (820 mg, 76% yield) as a colorless solid. R_f = 0.52 (ethyl acetate/petroleum ether, 1:3). ^{1}H NMR (400 MHz,

$CDCl_3$): δ = 0.15 [s, 6 H, $Si(CH_3)_2$], 0.95 [s, 9 H, $(CH_3)_3CSi$], 1.34, 1.37 (2s, 9 H, Boc *t*Bu), 2.65, 2.71 (2s, NCH_3), 2.92–3.03 (m, 1 H, CH_2), 3.17–3.27 (m, 1 H, CH_2), 4.49, 4.79 (2 dd, *J* = 10.9, 4.1 Hz, *J* = 11.0, 4.9 Hz, 1 H, CH), 6.74 (d, *J* = 8.3 Hz, 2 H, aromatic), 7.01 (d, *J* = 8.3 Hz, 1 H, aromatic), 7.04 (d, *J* = 8.3 Hz, 2 H, aromatic) ppm.

***N*-(*tert*-Butoxycarbonyl)-L-alanyl-*O*-[*tert*-butyl(dimethyl)silyl]-*N*-methyl-D-tyrosine (30):** To a solution of dipeptide **25** (400 mg, 0.70 mmol) in ethanol (5 mL) was added 10% Pd/C (80 mg). The reaction mixture was connected to a hydrogenation machine (Parr apparatus) and shaken for 16 h under a hydrogen atmosphere of about 2 bar (30 psi) at room temperature. The reaction mixture was filtered through a bed of celite, and the celite bed was washed with ethyl acetate (2 × 5 mL). The filtrate was concentrated in vacuo to afford the crude acid **30** (98% yield), which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.13 [s, 6 H, $(CH_3)_2Si$], 0.86 (d, *J* = 7.6 Hz, 3 H, Ala CH_3), 0.94 [s, 9 H, $(CH_3)_3CSi$], 1.40, (s, 9 H, Boc *t*Bu), 2.85 (s, 3 H, NCH_3), 2.93–3.03 (m, 1 H, Tyr CH_2), 3.34 (dd, *J* = 14.7, 4.3 Hz, 1 H, Tyr CH_2), 4.47–4.53 (m, 1 H, Ala CH), 5.28 (dd, *J* = 11.2, 3.9 Hz, 1 H, Tyr CH), 5.56 (d, *J* = 8.1 Hz, 1 H, Ala NH), 6.72 (d, *J* = 8.3 Hz, 2 H, aromatic H) 7.00 (d, *J* = 8.3 Hz, 2 H, aromatic H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.5 [2 C, $(CH_3)_2Si$], 14.1, 18.2 (Ala CH_3), 18.2 [$(CH_3)_3CSi$], 25.6 [$(CH_3)_3CSi$], 28.3 (Boc *t*Bu), 32.6 (NCH_3), 33.7 (Tyr CH_2), 46.5 (Ala CH), 58.4 (Tyr CH), 79.8 (Boc quaternary C), 120.1, 129.1, 129.6 (aromatic), 154.5 (Boc C=O), 155.3 (phenolic), 173.6 (Ala CO), 174.2 (Tyr CO) ppm.

(2*S*,3*E*,6*S*)-7-*tert*-Butoxy-2,4,6-trimethyl-7-oxohept-3-enyl *N*-(*tert*-Butoxycarbonyl)-L-alanyl-*O*-[*tert*-butyl(dimethyl)silyl]-*N*-methyl-D-tyrosyl-L-valinate (31): To a solution of acid **30** (70 mg, 0.15 mmol), and amine **15** (50 mg, 0.15 mmol) in dry DMF (1.5 mL) were added iPr$_2$NEt (0.07 mL, 0.44 mmol), HOBt (20 mg, 0.15 mmol), and TBTU (47 mg, 0.15 mmol) at room temperature. The reaction mixture was stirred for 5 h at room temperature before it was treated with H_2O (2 mL) and stirred for a further 5 min and then extracted with ethyl acetate (3 × 4 mL). The combined ethyl acetate layers were washed with 1 N HCl (3 mL), saturated aqueous $NaHCO_3$ (3 mL), and saturated aqueous NaCl , dried (Na_2SO_4), filtered, and concentrated in vacuo to give the crude product, which was purified by flash chromatography (ethyl acetate/petroleum ether, 15:85), providing the linear depsipeptide **31** (60 mg, 51% yield) as a colorless oil. R_f = 0.37 (ethyl acetate/petroleum ether, 15:85). $[\alpha]_D^{20}$ = 28.0 (*c* = 0.50, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3361, 2974, 2930, 1735, 1712, 1511, 1172 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.12 [s, 6 H, $(CH_3)_2Si$], 0.85 (d, *J* = 6.1 Hz, 3 H, Val CH_3), 0.87 (d, *J* = 6.1 Hz, 3 H, Val CH_3), 0.89 (d, *J* = 6.8 Hz, 3 H, CH_3CHCH_2O), 0.93–0.95 [m, 12 H, $(CH_3)_3CSiBu$, CH_3CHCO], 1.02 (d, *J* = 6.8 Hz, 3 H, Ala CH_3), 1.38, 1.40 (2 s, 18 H, *t*Bu, Boc *t*Bu), 1.60 (s, 3 H, CH_3C=C), 1.91–1.97 (m, 1 H, Val CH), 2.10–2.18 (m, 1 H, CH_2CHCO), 2.28–2.34 (m, 1 H, CH_2CHCO), 2.42–2.48 (m, 1 H, CHCO), 2.70–2.75 (m, 1 H, $CHCH_2O$), 2.84–2.88 (m, 1 H, Tyr CH_2), 2.91 (s, 3 H, NCH_3), 3.29 (dd, *J* = 14.9, 5.8 Hz, 1 H, Tyr CH_2), 3.84–3.92 (m, 1 H, CH_2O), 4.39–4.45 (m, 1 H, Ala CH), 4.92 (d, *J* = 8.8 Hz, alkene H), 5.25 (d, *J* = 7.1 Hz, Val CH), 5.28 (br. s, 1 H, Ala NH), 5.49 (dd, *J* = 10.4, 5.8 Hz, 1 H, Tyr CH), 6.59 (d, *J* = 8.8 Hz, 1 H, Val NH), 6.69 (d, *J* = 8.1 Hz, 2 H, aromatic H), 7.01 (d, *J* = 8.3 Hz, 2 H, aromatic H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.5 [2 C, $(CH_3)_2Si$], 16.0 (CH_3C=C), 16.8 (CH_3CHCO), 17.5 (Val CH_3), 17.7 (Val CH_3, CH_3CH_2CHO), 18.2 [$(CH_3)_3CSiBu$], 19.1 (Ala CH_3), 25.6 [$(CH_3)_3CSiBu$], 28.1, 28.3 (6 C, *t*Bu, Boc *t*Bu), 30.6 ($CHCH_2O$), 30.8 (Val CH), 31.8 (NCH_3), 34.3 (Tyr CH_2), 38.6 (CHCO), 43.9 (CH_2CHO), 46.6 (Ala CH), 57.2 (Val CH), 57.4 (Tyr CH), 69.5 (CH_2O), 79.6, 79.9 (2 C, Boc, *t*Bu), 120.0, 128.1, 129.4 (aromatic), 129.7 (alkene CH), 134.4 (alkene), 154.4 (Boc C=O), 155.3 (phenolic), 170.1 (Tyr CO), 171.7 (Val CO), 174.5 (Ala CO), 175.7 (CO_2tBu) ppm. HRMS (ESI): calcd. for $C_{43}H_{73}N_3O_9Si$ $[M + Na]^+$ 826.50083; found 826.50078.

(3*S*,6*R*,9*S*,12*R*,16*R*)-6-(4-Hydroxybenzyl)-3-isopropyl-7,9,12,14,16-pentamethyl-1-oxa-4,7,10-triazacycloheptadec-14-ene-2,5,8,11-tetrone (32): To a solution of linear depsipeptide **31** (40 mg, 0.05 mmol) in CH_2Cl_2 (0.5 mL) was added TFA (0.08 mL, 0.99 mmol) at 0 °C. Stirring was continued for 2 h; at this time TLC showed the complete consumption of reactant **31**. The solvent was removed in vacuo, and the residue was dried by the azeotropic removal of H_2O with toluene. The crude material was used in the next step without further purification. To a solution of crude amine salt in dry DMF (50 mL) were added iPr$_2$NEt (0.04 mL, 0.20 mmol), HOBt (20 mg, 0.15 mmol), and TBTU (48 mg, 0.15 mmol) successively at room temperature. The solution was stirred at room temperature for 18 h and then partitioned between ethyl acetate and H_2O. The aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined ethyl acetate layers were washed successively with 5% aqueous $KHSO_4$, H_2O, 50% aqueous $NaHCO_3$, and saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated in vacuo to give the crude product, which was purified by flash chromatography (ethyl acetate/petroleum ether, 1:1), providing the pure cyclic depsipeptide (12 mg, 39% yield) as a colorless oil. To this TBS-protected cyclic depsipeptide (12 mg, 0.02 mmol) in THF (0.2 mL) was added TBAF containing 5% H_2O (1 M solution in THF, 0.04 mL, 0.04 mmol) at 0 °C, and stirring was continued for 3 h at 0 °C. The mixture was concentrated in vacuo, and the crude macrocycle was purified by flash chromatography (ethyl acetate/petroleum ether, 7:3), yielding the pure cyclic depsipeptide **32** (8 mg, 80% yield) as a colorless oil. R_f = 0.22 (ethyl acetate/petroleum ether, 7:3). $[\alpha]_D^{20}$ = +11.6 (*c* = 0.70, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3361, 2974, 2930, 1735, 1712, 1511, 1172 cm^{-1}. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 0.86 (CH_3CHCH_2O), 0.87 (Val CH_3), 0.93 (d, *J* = 6.7 Hz, 3 H, Val CH_3), 0.95 (d, *J* = 6.6 Hz, 3 H, Ala CH_3), 1.01 (d, *J* = 6.9 Hz, 3 H, CH_3CHCO), 1.56 (s, 3 H, CH_3C=C), 1.83 (d, *J* = 14.9 Hz, 1 H, CH_2^hCHCO), 2.02 (pseudo-sext, *J* = 6.7 Hz, 1 H, Val CH), 2.25 (dd, *J* = 15.1, 11.1 Hz, 1 H, CH_2^tCHCO), 2.36–2.43 (m, 1 H, CHCO), 2.56–2.63 (m, 1 H, $CHCH_2O$), 2.66 (dd, *J* = 14.3, 8.1 Hz, 1 H, Tyr CH_2^h), 2.79 (s, 3 H, NMe), 3.00 (dd, *J* = 14.3, 6.4 Hz, 1 H, Tyr CH_2^t), 3.70 (dd, *J* = 10.8, 2.5 Hz $CH^{2h}O$), 4.04 (pseudo-t, *J* = 7.7 Hz, Val CH), 4.18 (dd, *J* = 10.9, 5.4 Hz, 1 H, CH_2^tO), 4.52 (quint, *J* = 6.9 Hz, 1 H, Ala CH), 5.05 (d, *J* = 8.0 Hz, alkene), 5.24 (dd, *J* = 8.7, 6.5 Hz, 1 H, Tyr CH), 6.61 (d, *J* = 8.5 Hz, 2 H, $TyrArH_{meta}$), 6.98 (d, *J* = 8.5 Hz, 2 H, $TyrArH_{ortho}$), 7.43 (d, *J* = 7.7 Hz, 1 H, Val NH), 8.05 (d, *J* = 7.8 Hz, 1 H, Ala NH), 9.05 (s, Tyr-OH) ppm. ^{13}C NMR (600 MHz, [D$_6$]DMSO): δ = 16.9 (Ala CH_3), 17.8 (CH_3C=C), 18.8 (Val CH_3), 19.5 (CH_3CHCO), 29.1 (Val CH), 29.8 (NCH_3), 31.3 ($CHCH_2O$), 32.4 (Tyr CH_2), 38.5 (CHCO), 40.6 (CH_2CHCO), 44.0 (Ala CH), 56.3 (Tyr CH), 58.8 (Val CH), 68.1 (CH_2O), 114.4 ($TyrAr_{meta}$), 125.2 (alkene CH), 127.7 ($C_{ipso}Ar$), 129.5 ($TyrAr_{ortho}$), 133.8 (alkene C), 155.3 (C-OH Ar), 169.8 (Tyr CO), 170.2 (Val CO), 171.5 (Ala CO), 174.1 (CH_2CHCO) ppm. HRMS (ESI): calcd. for $C_{28}H_{41}N_3O_6Si$ $[M + Na]^+$ 538.2888; found 538.2891.

Methyl *N*-(*tert*-Butoxycarbonyl)-L-alanyl-*O*-[*tert*-butyl(dimethyl)-silyl]-*N*-methyl-D-tyrosyl-L-valinate (33): To a solution of dipeptide acid **30** (200 mg, 0.42 mmol) and L-valine methyl ester hydrochloride (70 mg, 0.42 mmol) in dry DMF (4 mL) were added iPr$_2$NEt (0.18 mL, 1.05 mmol), HOBt (58 mg, 0.42 mmol), and TBTU (135 mg, 0.42 mmol) at room temperature. The resulting mixture was stirred for 3 h at room temperature. Thereafter, it was treated with H_2O (5 mL), stirred for 5 min, and extracted with ethyl acetate

(3 × 10 mL). The combined ethyl acetate layers were washed with 1 N HCl (5 mL), saturated aqueous $NaHCO_3$ (5 mL), and saturated aqueous NaCl (5 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo to furnish the crude product, which was purified by flash chromatography (ethyl acetate/petroleum ether, 1:3), yielding the pure tripeptide **33** (177 mg, 71% yield) as a colorless gel. R_f = 0.44 (ethyl acetate/petroleum ether, 1:3). $[\alpha]_D^{20}$ = 45.4 (c = 1.01, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3336, 2962, 2930, 1739, 1685, 1511, 1172, 1052 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.11 [s, 6 H, $(CH_3)_2Si$], 0.85 (d, J = 6.1 Hz, 3 H, Val CH_3), 0.87 (d, J = 6.1 Hz, 3 H, Val CH_3), 0.89 (d, J = 7.6 Hz, 3 H, Ala CH_3), 0.92 [s, 9 H, $(CH_3)_3CSi$], 1.37 (s, 9 H, Boc tBu), 2.10–2.18 (m, 1 H, Val CH), 2.84–2.87 (m, 1 H, Tyr CH_2), 2.91 (s, 3 H, NCH_3), 3.28 (dd, J = 14.8, 5.4 Hz, 1 H, Tyr CH_2), 3.68 (s, 3 H, OCH_3), 4.39–4.42 (m, 2 H, Ala CH, Val CH), 5.26 (d, J = 6.3 Hz, 1 H, Ala NH), 5.49 (dd, J = 9.9, 5.9 Hz, 1 H, Tyr CH), 6.61 (d, J = 8.3 Hz, 1 H, Val NH), 6.69 (d, J = 7.8 Hz, 2 H, aromatic H), 7.00 (d, J = 7.6 Hz, 2 H, aromatic H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.6 [2 C, $(CH_3)_2Si$], 17.5 (Val CH_3), 17.8 (Val CH_3), 18.1 [$(CH_3)_3CSi$], 19.0 (Ala CH_3), 25.6 [$(CH_3)_3CSi$], 28.2 (Boc tBu), 30.4 (NCH_3), 30.8 (Val CH), 32.7 (Tyr CH_2), 46.6 (Ala CH), 52.0 (OCH_3), 57.1 (Val CH), 57.5 (Tyr CH), 79.6 (quaternary C), 120.0, 129.3, 129.7 (aromatic), 154.4 (Boc CO), 155.3 (phenolic), 170.2 (Tyr CO), 172.0 (Ala CO), 174.8 (Val CO) ppm. HRMS (ESI): calcd. for $C_{30}H_{51}N_3O_7Si$ $[M + Na]^+$ 616.3389; found 616.3396.

Methyl *N*-{(2*S*,4*E*,6*S*)-7-[(*tert*-Butoxycarbonyl)amino]-2,4,6-trimethylhept-4-enoyl}-L-alanyl-*O*-[*tert*-butyl(dimethyl)silyl]-*N*-methyl-D-tyrosyl-L-valinate (34): To solution of tripeptide **33** (30 mg, 0.05 mmol) in CH_2Cl_2 (0.5 mL) was added TFA (0.03 mL, 0.5 mmol) at 0 °C. The resulting mixture was stirred for 1 h at 0 °C. The solvent was removed in vacuo, and the residue was dried by the azeotropic removal of H_2O with toluene. The crude material was used in the next reaction without further purification. To a solution of crude amine salt and amino acid **21** (15 mg, 0.05 mmol) in dry DMF (1 mL) were added iPr$_2$NEt (0.02 mL, 0.25 mmol), HOBt (7 mg, 0.05 mmol), and TBTU (16 mg, 0.05 mmol) successively. The reaction mixture was stirred for 2 h before it was diluted with H_2O (2 mL), stirred for 5 min, and then extracted with ethyl acetate (3 × 4 mL). The combined organic layers were washed with 1 N HCl (2 mL), saturated aqueous $NaHCO_3$ (2 mL), and saturated aqueous NaCl (2 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1:1), producing pure tetrapeptide **34** (20 mg, 53% yield) as a colorless gel. R_f = 0.52 (ethyl acetate/petroleum ether, 1:1). $[\alpha]_D^{20}$ = 16.6 (c = 0.84, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3361, 2974, 2930, 1735, 1712, 1511, 1172 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.13 [s, 6 H, $(CH_3)_2Si$], 0.87 (d, J = 6.8 Hz, 3 H, Val CH_3), 0.88 (d, J = 6.8 Hz, 3 H, Val CH_3), 0.89 (d, J = 7.6 Hz, 3 H, CH_3CHCH$_2$O), 0.91–0.94 [m, 12 H, $(CH_3)_3CSi$, CH_3CHCO], 1.04 (d, J = 6.8 Hz, 3 H, Ala CH_3), 1.41 (s, 9 H, Boc tBu), 1.56 (s, 3 H, CH_3C=C), 1.97–2.03 (m, 1 H, Val CH), 2.13–2.21 (m, 1 H, CHCH$_2$NH), 2.27 (dd, J = 13.8, 6.7 Hz, 1 H, CH_2CHCO), 2.33–2.40 (m, 1 H, CH_2CHCO), 2.53–2.56 (m, 1 H, CHCO), 2.75–2.81 (m, 1 H, CH_2NH), 2.85–2.89 (m, 1 H, CH_2NH), 2.93 (s, 3 H, NCH_3), 3.08–3.12 (m, 1 H, Tyr CH_2), 3.29 (dd, J = 14.9, 6.1 Hz, 1 H, Tyr CH_2), 3.69 (s, 3 H, OCH_3), 4.41 (dd, J = 8.5, 5.8 Hz, 1 H, Val CH), 4.61–4.68 (m, 1 H, Ala CH), 4.75 (br. s, 1 H, NHBoc), 4.89 (d, J = 9.1 Hz, alkene H), 5.48 (dd, J = 10.6, 6.1 Hz, 1 H, Tyr CH), 6.37 (d, J = 5.8 Hz, 1 H, Val NH), 6.70 (d, J = 8.3 Hz, 2 H, aromatic), 7.02 (d, J = 8.3 Hz, 2 H, aromatic) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.5 [2 C, $(CH_3)_2Si$], 16.4 (CH_3C=C), 16.9 (CH_3CHCO), 17.4 (Ala CH_3), 17.9 (Val CH_3), 18.2 [$(CH_3)_3CSi$], 18.2 (Val CH_3), 19.0 (CH_3CHCH_2NH), 25.6 [$(CH_3)_3CSi$], 28.4 (Boc tBu), 30.4 (NCH_3), 30.8 ($CHCH_2NH$), 32.8 (Val CH), 33.0 (Tyr CH_2), 39.2 ($CHCO$) 43.8 (CH_2CHCO), 45.5 (CH_2NH), 46.5 (Ala CH), 52.1 (OCH_3), 57.1 (Tyr CH)), 57.7 (Val CH), 77.9 (quaternary C Boc), 120.1, 129.3 (aromatic), 129.7 (alkene CH), 130.5 (alkene C), 154.4 (phenolic), 156.1 (Boc C=O), 170.1 (Ala CO), 172.3 (Tyr CO), 174.3 (Val CO), 175.7 (CO_2Me) ppm. HRMS (ESI): calcd. for $C_{40}H_{68}N_4O_8Si$ $[M + Na]^+$ 783.4699; found 783.4704.

(3*S*,6*R*,9*S*,12*R*,16*R*)-6-(4-Hydroxybenzyl)-3-isopropyl-7,9,12,14,16-pentamethyl-1,4,7,10-tetraazacycloheptadec-14-ene-2,5,8,11-tetrone (35): An aqueous solution of LiOH·H_2O (0.4 N 0.08 mL, 0.03 mmol) was added dropwise to a stirred solution of linear tetrapeptide **34** (20 mg, 0027 mmol) in THF (0.5 mL). The reaction mixture was stirred for 2 h at room temperature before it was acidified to pH 3 with 1 N HCl and extracted with ethyl acetate (3 × 2 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo to furnish the TBS-deprotected free acid in quantitative yield. This acid was used in the next step without further purification. To a solution of the *N*-Boc-protected free acid (17 mg, 0.027 mmol) in CH_2Cl_2 (0.3 mL) was added TFA (0.02 mL, 0.99 mmol) at 0 °C, and the mixture was stirred for 2 h. The solvent was removed in vacuo, and the residue was dried by the azeotropic removal of H_2O with toluene. The crude material was used in the next reaction without further purification. To a solution of crude amine salt in dry DMF (20 mL) were added iPr$_2$NEt (0.01 mL, 0.08 mmol), HOBt (8 mg, 0.06 mmol), and TBTU (19 mg, 0.06 mmol) successively at room temperature. The solution was stirred at room temperature for 18 h and then partitioned between ethyl acetate and H_2O. The aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined ethyl acetate layers were washed successively with 5% aqueous $KHSO_4$, H_2O, 50% aqueous $NaHCO_3$, and saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated in vacuo to give the crude product, which was purified by flash chromatography (ethyl acetate) to deliver the macrolactam **35** (6 mg, 45% yield) as a colorless oil. R_f = 0.55 (ethyl acetate). $[\alpha]_D^{20}$ = –72.0 (c = 0.40, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3361, 2974, 2930, 1735, 1712, 1511, 1172 cm^{-1}. ^1H NMR (600 MHz, [D$_6$]-DMSO): δ = 0.66 (dd, J = 3.7, 3.6 Hz, 6 H, Val CH_3), 0.84 (d, J = 7.0 Hz, 3 H, CH_3CHCH$_2$NH), 0.98 (d, J = 6.9 Hz, 3 H, CH_3CHCO), 1.04 (d, J = 7.0 Hz, 3 H, Ala CH_3), 1.46 (s, 3 H, CH_3C=C), 1.76 (d, J = 15.9 Hz, 1 H, CH_2^hCHCO), 2.20 (m, 2 H, Val CH, CH_2^tCHCO), 2.53 (m, 1 H, CHCO), 2.54–2.58 (m, 1 H, CHCH$_2$NH), 2.83 (ddd, J = 12.9, 5.6, 2.6 Hz, 1 H, CH_2^tNH), 2.91 (d, J = 8.2 Hz, 2 H, Tyr CH_2), 3.06 (s, 3 H, NMe), 3.14 (ddd, J = 13.1, 9.1, 6.0 Hz, 1 H, CH_2^hNH), 4.06 (dd, J = 9.6, 4.9 Hz, Val CH), 4.59 (quint, J = 6.9 Hz, 1 H, Ala CH), 4.96 (d, J = 8.0 Hz, alkene H), 5.01 (t, J = 8.2 Hz, 1 H, Tyr CH), 6.64 (d, J = 8.5 Hz, 2 H, TyrArH_{meta}), 7.03 (d, J = 8.5 Hz, 2 H, TyrArH_{ortho}), 7.43 (t, J = 5.8 Hz, 1 H, CH$_2$NH), 7.87 (d, J = 9.7 Hz, 1 H, Val NH), 8.00 (d, J = 7.0 Hz, 1 H, Ala NH), 9.10 (s, Tyr-OH) ppm. ^{13}C NMR (600 MHz, [D$_6$]DMSO): δ = 16.7 (Val CH_3), 16.9 (Ala CH_3), 17.8 (CH_3C=C), 18.8 (CH_3CHCH_2NH), 18.9 (Val CH_3), 19.5 (CH_3CHCO), 28.1 (Val CH), 30.7 (NCH_3), 31.6 ($CHCH_2NH$), 32.9 (Tyr CH_2), 36.7 ($CHCO$), 41.1 (CH_2CHCO), 44.3 (Ala CH), 45.7 (CH_2NH), 56.7 (Val CH), 57.6 (Tyr CH), 114.6 (TyrAr$_{meta}$), 126.7 (alkene CH), 126.8 (C$_{ipso}$Ar), 129.2 (TyrAr$_{ortho}$), 133.6 (alkene C), 155.5 (C-OH Ar), 170.4 (Val CO), 170.9 (Tyr CO), 174.4 (CH_2CHCO), 174.8 (Ala CO) ppm. HRMS (ESI): calcd. for $C_{28}H_{42}N_4O_5Si$ $[M + Na]^+$ 537.3047; found 537.3044.

Supporting Information (see also the footnote on the first page of this article): Copies of ^1H and ^{13}C NMR spectra of the described compounds.

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