Total Synthesis and Bioactivity Mapping of Geodiamolide H
Veselin Nasufović, Florian Küllmer, Johanna Bößneck, Hans-Martin Dahse, Helmar Görls, Peter Bellstedt, Pierre Stallforth, and Hans-Dieter Arndt*
Table of contents

1. Additional Schemes, Figures, Tables ................................................................. 3
2. List of abbreviations ................................................................................................ 20
3. Synthesis ............................................................................................................... 21
   3.1. General information ......................................................................................... 21
      3.1.1. Reagents .................................................................................................. 21
      3.1.2. Reaction conditions ................................................................................. 21
      3.1.3. Thin Layer Chromatography .................................................................. 21
      3.1.4. Silica gel flash liquid chromatography (FCC) ......................................... 21
      3.1.5. NMR spectroscopy .................................................................................... 22
      3.1.6. Mass spectrometry .................................................................................. 22
      3.1.7. Analytical reversed-phase high-performance liquid chromatography (RP-HPLC).............................................................. 22
      3.1.8. Preparative reversed-phase HPLC (prep. HPLC) ...................................... 22
      3.1.9. Fourier transform infrared spectroscopy (FT-IR) ...................................... 22
      3.1.10. Melting points ........................................................................................ 23
      3.1.11. Specific optical rotation ......................................................................... 23
   3.3. Synthetic procedures ...................................................................................... 24
      3.3.1. General procedure geodiamolides 1: Loading of the 2-Cl-Trytil-chloride resin - Solid-phase supported synthesis (SPSS) .......................................................... 24
      3.3.2. General Procedure geodiamolides 2: Fmoc-Deprotection (SPPS) .............. 24
      3.3.3. General Procedure geodiamolides 3: Peptide-coupling on the solid support (SPPS) ............................................................................................................. 25
      3.3.4. General Procedure geodiamolides 4: Cleaving peptide from the solid support .... 25
      3.3.5. General Procedure geodiamolides 5: Esterification of tripeptide fragment .... 25
      3.3.6. General Procedure geodiamolides 6: Metathesis ...................................... 25
      3.3.7. General Procedure geodiamolides 7: Silyl deprotection .......................... 26
   3.4. Molecules synthesized by previously described procedures: ......................... 26
      3.4.1. Synthesis of (2S,4R)-4-methylhex-5-en-2-ol ........................................... 26
      3.4.2. Synthesis of N-Me-N-Fmoc-3’-I-O-TIPS-D-Tyrosine ................................ 33
      3.4.3. Synthesis of N-Me-N-Fmoc-O-TIPS-D-Tyrosine ..................................... 37
      3.4.4. Synthesis of esters .................................................................................. 41
      3.4.5. Metathesis products ............................................................................... 45
3.4.6. Natural products and analogs ........................................................................ 47
4. Crystal Structure Determination ...................................................................... 53
5. Evaluation of bioactivity .................................................................................. 53
6. In vitro actin polymerization assay ................................................................. 55
7. Computational investigations ........................................................................... 58
8. References ......................................................................................................... 59
9. NMR Spectra ................................................................................................. 61
1. Additional Schemes, Figures, Tables

| Geodiamolides, Seragamides, Neosiphoniamolide - Natural products |
|---------------------------------------------------------------|

| Geodiamolide A | Geodiamolide B | Geodiamolide C | Geodiamolide D | Geodiamolide E |
|----------------|----------------|----------------|----------------|----------------|
| ![Geodiamolide A](#) | ![Geodiamolide B](#) | ![Geodiamolide C](#) | ![Geodiamolide D](#) | ![Geodiamolide E](#) |

| Geodiamolide F | Geodiamolide G | Geodiamolide H | Geodiamolide I | Geodiamolide J |
|----------------|----------------|----------------|----------------|----------------|
| ![Geodiamolide F](#) | ![Geodiamolide G](#) | ![Geodiamolide H](#) | ![Geodiamolide I](#) | ![Geodiamolide J](#) |

| Geodiamolide K | Geodiamolide L | Geodiamolide M | Geodiamolide N | Geodiamolide O |
|----------------|----------------|----------------|----------------|----------------|
| ![Geodiamolide K](#) | ![Geodiamolide L](#) | ![Geodiamolide M](#) | ![Geodiamolide N](#) | ![Geodiamolide O](#) |

| Geodiamolide P | Geodiamolide Q | Geodiamolide R | Geodiamolide TA | Neosiphoniamolide A |
|----------------|----------------|----------------|-----------------|---------------------|
| ![Geodiamolide P](#) | ![Geodiamolide Q](#) | ![Geodiamolide R](#) | ![Geodiamolide TA](#) | ![Neosiphoniamolide A](#) |

| Seragamide A | Seragamide B | Seragamide C | Seragamide D | Seragamide E |
|--------------|--------------|--------------|--------------|--------------|
| ![Seragamide A](#) | ![Seragamide B](#) | ![Seragamide C](#) | ![Seragamide D](#) | ![Seragamide E](#) |

| Seragamide F |
|--------------|
| ![Seragamide F](#) |

**Figure S1.** Geodiamolide family of natural products structure compilation.[1-10] Variations are highlighted in red.
**Scheme S1.** Attempts toward diastereoselective alkylation of auxiliary enolates

\[ \text{propanoylated auxiliaries (S1)} \]

\[ \text{electrophiles (S2)} \]

| Entry | S1 | S2 | Product (S3) | Yield (%) |
|-------|----|----|--------------|-----------|
| 1     | a  | a  | S3a          | 17        |
| 2     | b  | b-d| S3b          | /         |
| 3     | b  | c  | S3c          | 42        |

*Reaction conditions:* (a) S1, LDA (1.5 equiv.), THF, -78 °C, 30 min then S2 (4.0 equiv.) in THF, -40 °C for 4 h let to warm to 25 °C over 16 h, reaction monitored by TLC and LC/MS. *No conversion to the desired product could be observed,* †In case of entry 2 for S2a-c NaHMDS gave no conversion, ‡Entry 2 for S2a-b) reactions in Et₂O gave no conversion to the desired product.
Scheme S2. Synthesis of (2S,4R)-4-methylhex-5-en-2-ol: 

\[ \text{Conditions and reagents:} \]

(a) Allylmagnesium bromide (1.3 equiv.), Et\(_2\)O, -78 °C, 2 h, 84%; (b) NaH (3.0 equiv.), TIPS-Cl (1.2 equiv.), THF, 0 °C to 25 °C, 16 h, 78%; (c) NMO (1.5 equiv.), 2,6-Lutidine (2 equiv.), OsO\(_4\) (3 mol%), acetone/water (\(c = 0.1\) M), 25 °C, 3 h, then PhI(OAc)\(_2\) (1.5 equiv.), 3 h, 83%; (d) N-Hydroxysuccinimide (1.05 equiv.), 0 °C then PhI(OAc)\(_2\) (1.05 equiv.), MeCN, -5 °C, 1 h, 73%; (e) Seebach’s oxazolidinone (1.1 equiv.), n-BuLi (1.1 equiv., 2.35 M), THF, -78 °C, 10 min, then active ester from d (1.0 equiv.) in THF added, -78 °C to 25 °C, 16 h, 82%; (f) LDA (1.5 equiv.), THF, -78 °C 1 h, then MeI (12 equiv.), -40 °C, 4 h, 89%; (g) LiBH\(_4\) (1.1 equiv.), H\(_2\)O (1.1 equiv.), THF, 0 °C, 3 h, 98%; (h) SO\(_3\)/Py (2.0 equiv.), DMSO (9 equiv.), DIPEA (4.0 equiv.), DCM, -30 °C to 25 °C, 5 h, 94%; (i) \(\text{i}i\). Ph\(_3\)PMeBr (2.2 equiv.), THF, -78 °C, BuLi (2.0 equiv.), 1 h then 30 min at 0 °C, \(\text{i}i\). aldehyde from h (2.0 equiv.), -78 °C, 1 h, 92%, (j) TBAF (2.2 equiv.), THF, 25 °C, 6 h, 96%.
Scheme S3. Synthesis of N-Me-N-Fmoc-3′-I-O-TIPS-D-Tyrosine:*

```
D-Tyr \rightarrow_{a}^{83\%} \text{D-Tyr-1} \rightarrow_{b}^{\text{quant.}} \text{D-Tyr-2} \rightarrow_{c}^{82\%} 18 \\
\text{8} \rightarrow_{f}^{72\% (2 \text{ steps})} \text{18-2} \rightarrow_{o}^{\text{18-1}}
```

*Conditions and reagents: (a) I$_2$ in aq. NH$_3$ 30% (1.0 equiv.), 0 °C, 3 h, 83%; (b) Boc$_2$O (1.1 equiv.), TEA (1.5 equiv.), 1,4-dioxane/H$_2$O (1:1), 0 °C, 8 h, quant; (c) Ic. DCE (1.05 equiv.) 0 °C, 30 min, DCM then TIPS-Cl (1.1 equiv.), 2 h, 2c. Imidazole (2.0 equiv.), DMAP (0.2 equiv.), TIPS-Cl (1.1 equiv.), 16 h, 25 °C; 3c. K$_2$CO$_3$ (2.0 equiv.), MeOH/THF/H$_2$O, 30 min, 25 °C, 82%; (d) NaH (2.1 equiv), MeI (8.0 equiv.), THF, 0 °C to 25 °C, 16 h, 67%; (e) 20% TFA/DCM, 0 °C, 4 h, (f) Fmoc-Osu, 1,4-dioxane/H$_2$O, NaHCO$_3$, 0 °C to 25 °C, 16 h, 72% (2 steps).
Scheme S4. Synthesis of N-Me-N-Fmoc-O-TIPS-D-Tyrosine:

*Conditions and reagents:* (b) Boc₂O (1.1 equiv.), TEA (1.5 equiv.), 1,4-dioxane/H₂O (1:1), 0 °C, 8 h, quant; (c) DCE (1.05 equiv.) 0 °C, 30 min, DCM then TIPS-Cl (1.1 equiv.), 2 h, 2c. Imidazole (2.0 equiv.), DMAP (0.2 equiv.), TIPS-Cl (1.1 equiv.), 16 h, 25 °C; 3c: K₂CO₃ (2.0 equiv.), MeOH/THF/H₂O, 30 min, 25 °C, 86%; (d) NaH (2.1 equiv), MeI (8.0 equiv.), THF, 0 °C to 25 °C, 16 h, 59%; (e) 20% TFA/DCM, 0 °C, 4 h, (f) Fmoc-OSu, 1,4-dioxane/H₂O, NaHCO₃, 0 °C to 25 °C, 16 h, 71% (2 steps).
Figure S2. Mechanistical observations in products formation during RCM: Product of isomerization during RCM 24 to 40 followed by $^1$H NMR. Specific residue assignments are highlighted.
**Figure S3.** Mechanistical observation.s in products formation during RCM: Product of isomerization during RCM 24 to 40 followed by HSQC-DEPT.
Figure S4. Attempts to isomerize 30 to 29 followed by $^1$H NMR. The characteristic vinylic proton is highlighted.
Table S1. NMR comparison of synthesized and isolated (literature data)\textsuperscript{[11]} geodiamolide H.

| Carbon | $\delta$H (measured in DMSO-$d_6$) | $\delta$H (literature - in Chloroform-$d$/DMSO-$d_6$) |
|--------|----------------------------------|--------------------------------------------------|
| 1      | /                                | /                                                |
| 2      | 2.70 – 2.52 (m)                  | 2.68 ($J = 15.5, 4.5$ Hz), 2.59 ($J = 15.5, 6.6$ Hz) |
| 3      | 5.13 (d, $J = 4.0$ Hz)           | 5.25 (m)                                         |
| 4      | /                                | /                                                |
| 5      | 5.30 (dd, $J = 10.7, 5.5$ Hz)    | 5.38 ($J = 9.8, 6.7$ Hz)                         |
| 6      | /                                | /                                                |
| 7      | 4.61 (dd, $J = 14.1, 7.3$ Hz)    | 4.75 (m)                                         |
| 8      | /                                | /                                                |
| 9      | 2.70 – 2.52 (m, 4H, 9C-1H)       | 2.55 (m)                                         |
| 10     | 1.82 – 1.73 (m)                  | 2.36 ($J = 15.2, 11.4$ Hz), 1.95 ($J = 15.2, 2.0$ Hz) |
| 11     | /                                | /                                                |
| 12     | 4.82 (d, $J = 8.5$ Hz)           | 4.82 ($J = 9.6$ Hz)                              |
| 13     | 2.29 (m)                         | 2.28 (m)                                         |
| 14     | 1.68 – 1.54 (m)                  | 1.39 ($J = 13.6, 11.1, 4.7$ Hz), 1.18 ($J = 13.5, 9.4, 4.5$ Hz) |
| 15     | 4.61 (dd, $J = 14.1, 7.3$ Hz, 2H, 15C-1H) | 4.64 (m)                                      |
| 16     | 2.94 (s)                         | 2.94 (s)                                         |
| 17     | 0.81 (d, $J = 6.8$ Hz)           | 1.08 ($J = 7.0$ Hz)                              |
| 18     | 1.06 (d, $J = 6.2$ Hz)           | 1.16 ($J = 7.0$ Hz)                              |
| 19     | 1.52 (s, 3H)                     | 1.60 ($J = 1.0$ Hz)                              |
| 20     | 0.84 (d, $J = 6.6$ Hz)           | 0.86 ($J = 7.0$ Hz)                              |
| 21     | 0.96 (d, $J = 6.8$ Hz)           | 1.09 ($J = 7.0$ Hz)                              |
| 22     | 2.79 (dd, $J = 21.3, 7.9$ Hz)    | 3.18 ($J = 14.5, 5.7$ Hz), 2.86 ($J = 14.5, 9.9$ Hz) |
| 23     | /                                | /                                                |
| 24     | 7.49 (d, $J = 2.0$ Hz)           | 7.48 ($J = 2.3$ Hz)                              |
| 25     | /                                | /                                                |
| 26     | /                                | /                                                |
| 27     | 6.72 (d, $J = 8.2$ Hz)           | 6.79 ($J = 8.5$ Hz)                              |
| 28     | 7.00 (dd, $J = 8.3, 2.0$ Hz)     | 6.96 ($J = 8.5, 2.3$ Hz)                         |
| 29     | /                                | /                                                |
| 30     | 7.06 (d, $J = 8.5$ Hz)           | 7.00 ($J = 8.5$ Hz)                              |
| 31     | 6.68 (d, $J = 8.5$ Hz)           | 6.77 ($J = 8.5$ Hz)                              |
| 32     | /                                | /                                                |
| NH1    | 8.24 (d, $J = 8.8$ Hz)           | 7.46 ($J = 8.3$ Hz)                              |
| NH2    | 7.72 (d, $J = 7.7$ Hz)           | 6.78 ($J = 8.5$ Hz)                              |
| OH1    | 10.08 (s)                        | 9.12 (s)                                         |
| OH2    | 9.31 (s)                         | 8.68 (s)                                         |
Figure S5. *In vitro* actin polymerization induced by cyclodepsipeptides. Geodiamolides and jaspplakinolide (each 20 µM) were incubated with pyrene-labeled actin (5 µM) under low salt non-polymerizing conditions. Induction of polymerization was followed by measuring of fluorescence enhancement at an emission wavelength of 410 nm, every 60 s over 4 h, at 37 °C (excitation at 360 nm). All measurements were performed in duplicates in 384-well plates.
**Figure S6a.** Molecular structure and numbering scheme of S3c. The ellipsoids represent a probability of 30%, H atoms of the chiral carbon atoms C2 and C20 are drawn with arbitrary radii, all other H atoms are omitted for clarity reasons. For details see chapter 4 (ESI).
Figure S6b. Molecular structure and numbering scheme of 16. The ellipsoids represent a probability of 30 %, H atoms of the chiral carbon atoms C2 and C20 are drawn with arbitrary radii, all other H atoms are omitted for clarity reasons. For details see chapter 4 (ESI).
Figure S7. Overlay of F-actin-bound jasplakinolide from Cryo-EM (PDB ID 6T23) and jasplakinolide Q (colored green) as obtained by in silico docking to ligand-depleted F-actin (PDB ID 6T23, ligand extracted). See methods section for details. Calculated RMSD: 0.91 Å.
Figure S8. Geodiamolide H orientation bound to F-actin (PDB ID 6T23, ligand extracted) as obtained from docking. See methods section for details.
Figure S9. Overlay of F-actin bound jasplakinolide from Cryo-EM (PDB ID 6T23) and geodiamolide H (colored green) as obtained by in silico docking to F-actin (PDB ID 6T23, ligand extracted). Calculated RMSD: 1.57 Å.
Figure S10. Interaction diagram of geodiamolide H docked to F-actin. Hydrophobic surface environment is indicated in green.
Table S2. Comparison of predicted binding energies to in vitro data for Geodiamolide H and analogs

| entry | compound | In vitro | In silico Prediction of Binding<sup>a</sup> |
|-------|----------|----------|------------------------------------------|
|       |          | K<sub>Kd</sub> | XP docking score | dG Binding Docking | dG Binding MD @ 0 ns | dG Binding MD @ 1 ns |
| 1     | 39 H E   | 1.59     | -7.12         | -56.02            | -70.28              | -68.14              |
| 2     | 36 H E   | 1.21     | -5.82         | -51.51            | -54.67              | -59.16              |
|       | geod. H (1) CH<sub>3</sub> E | 1.04 | -6.21         | -60.61            | -87.26              | -67.39              |
| 3     | JASP (3) | E        | -6.13         | -33.79            | -66.11              | -57.18              |
| 4     | 37 CH<sub>3</sub> H E | 0.71 | -5.50         | -43.27            | -68.87              | -65.80              |
| 5     | 38 CH<sub>3</sub> H Z | 0.12 | -5.20         | -49.91            | -68.25              | -50.14              |

<sup>a</sup>Comments: K<sub>Kd</sub>—relative change in fluorescence intensity of pyrene-labeled actin over time relative to the same change induced by jasplakinolide (both in the linear part of the curve after applying linear fit); Docking score and binding energies are given in kcal/mol; more negative values translate to stronger predicted binding, see section 7 (page 59) of this document for details on calculation methods and parameters employed.
### 2. List of abbreviations

| Abbreviation | Description |
|--------------|-------------|
| Boc          | tert-Butyloxycarbonyl |
| COMU         | (1-Cyano-2-ethoxy-2-oxoethylidnamino)dimethylamino-morpholino-carbenium hexafluorophosphate |
| cryo-EM      | Cryogenic electron microscopy |
| DMAP         | N,N-Dimethyl-4-aminopyridine |
| equiv.       | Equivalent |
| F-actin      | Filamentous actin |
| SPPS         | Solid-phase peptide synthesis |
| MNBA         | 2-Methyl-6-nitrobenzoic anhydride |
| FCC          | Flash column chromatography |
| Fmoc-OSu     | Fmoc-N-hydroxysuccinimide ester |
| HATU         | N-[(Dimethylamino)-IH-1,2,3-triazolo-[4,5-b]pyridin-1-ylmethylene]-N-methylmethanaminium hexafluorophosphate N-oxide |
| Hdn          | 8-hydroxy-2,4-dimethylnon-4-enoic acid |
| Htn          | 8-hydroxy-2,4,6-trimethylnon-4-enoic acid |
| HOAT         | 1-Hydroxy-7-azabenzotriazole |
| HPLC         | High-performance liquid chromatography |
| HUVEC        | Human umbilical vein endothelial cells |
| NOE(SY)      | Nuclear Overhauser effect (spectroscopy) |
| NRPS         | Nonribosomal peptide |
| O-Su         | N-Hydroxysuccinimide |
| Oxyma        | Ethyl cyanohydroxyiminoacetate |
| PE           | Petroleum ether (boiling range 40-60°C) |
| Pea          | 2,4-dimethylpent-4-enoic acid |
| PIDA         | (Diacetoxyiodo)benzene |
| PKS          | Polyketide synthase |
| RCM          | Ring-closing metathesis |
| SAR          | Structure-activity relationship |
| Tf           | Trifluoromethanesulfonyl (triflyl) |
| TFA          | Trifluoroacetic acid |
3. Synthesis

3.1. General information

3.1.1. Reagents

All reagents were obtained from Acros Chemicals, Alfa Aesar, Apollo Scientific, ABCR, Carbolution Chemicals, Carbosynth, Manchester Organics, Merck, Novabiochem, Sigma-Aldrich, TCI Europe, or VWR, and used without further purification. All solvents, if not purchased in purity or dryness suitable, were distilled using standard methods.\[12\] Tetrahydrofuran (THF) was distilled under an N\textsubscript{2} atmosphere from Na/benzophenone; dichloromethane (CH\textsubscript{2}Cl\textsubscript{2}) was distilled under an N\textsubscript{2} atmosphere from CaH\textsubscript{2} before use. Other solvents were passed through alumina columns (toluene) or molecular sieves columns (dimethylformamide - DMF) of a solvent purification system (Pure Solv, Innovative Technology, Inc., USA) by applying N\textsubscript{2} overpressure immediately before use.

All solvents for flash chromatography were distilled before use. All solvents used in reactions were anhydrous. Solvents were degassed by employing triple freeze-pump-thaw cycles when necessary or by purging with N\textsubscript{2} for a minimum of 15 minutes. Deionized water was used for all experiments.

3.1.2. Reaction conditions

All reactions were performed in heat-dried glassware under an atmosphere of N\textsubscript{2} if not stated otherwise.

3.1.3. Thin Layer Chromatography

TLC was carried out on Merck precoated silica gel plates (60F-254); compounds were visualized using ultraviolet light irradiation at 254 nm and 366 nm or by using the following staining agents (dip, dry & heat development):

- **Potassium Permanganate:** KMnO\textsubscript{4} (1 g), K\textsubscript{2}CO\textsubscript{3} (6.6 g), 5% NaOH (1.7 mL) in H\textsubscript{2}O (90 mL).
- **Ninhydrin:** Ninhydrin (0.3 g) dissolved in n-butanol (100 mL) and acetic acid (3 mL).
- **Ceric Ammonium Molybdate:** Ceric ammonium sulfate (0.5 g) and ammonium molybdate (12 g) are to be dissolved in H\textsubscript{2}O (235 mL) and conc. H\textsubscript{2}SO\textsubscript{4} (15 mL).

3.1.4. Silica gel flash liquid chromatography (FCC)

Purifications were performed using silica gel from Macherey & Nagel (particle size 40-60 \(\mu\)m) under approximately 0.2-0.6 bar pressure.\[13\]
3.1.5. NMR spectroscopy

$^1$H- and $^{13}$C-NMR spectra were recorded using a Bruker Avance I 250 system (250 MHz for $^1$H- and 63 MHz for $^{13}$C-NMR), a Bruker Fourier 300 system (300 MHz, $^1$H- and 75 MHz for $^{13}$C-NMR), a Bruker Avance I 400 system (400 MHz for $^1$H- and 101 MHz for $^{13}$C-NMR), Bruker Avance 600 system (600 MHz for $^1$H- and 151 MHz for $^{13}$C-NMR) or Avance III HD [500 MHz, probe: BBO (Prodigy)]. Spectra were calibrated to appropriate residual solvent peaks (chloroform-$d_1$, methanol-$d_4$, MeCN-$d_3$, DMSO-$d_6$).[14] Spectra were recorded at 298 K, if not stated otherwise. chloroform-$d$ was stored over molecular sieves at 5 °C. If mixtures of solvents were used, namely chloroform-$d$ and methanol-$d_4$, spectra were calibrated to chloroform-$d_1$.

3.1.6. Mass spectrometry

ESI-MS was performed on a Finnigan LCQ spectrometer for monitoring of reaction conditions. Calculated masses were obtained using the software ChemDraw Professional 16. High-resolution mass spectrometry (HR-MS) measurements were performed using LC-coupled MAXIS Impact ESI-TOF spectrometer (Bruker Daltronics, Bremen, Germany).

3.1.7. Analytical reversed-phase high-performance liquid chromatography (RP-HPLC)

Analyses were performed on a Varian Prostar system equipped with an autosampler Prostar 410 and a Varian Prostar 335 diode array detector using an EC250/4 Nucleodur C18 Gravity 5 μm (Macherey & Nagel, Düren, Germany) and a Phenomenex Luna 5 μm C8(2) 100 A (250 x 4 mm) column. Linear gradients were employed at 1 mL/min flow rate (A: water, B: acetonitrile).

3.1.8. Preparative reversed-phase HPLC (prep. HPLC)

A Varian Prostar system equipped with a fraction collector Prostar 701 and detection at 220 nm (UV/Vis Prostar 340) and a VP 250/21 Nucleodur C18 Gravity 5 μm column (Macherey & Nagel, Düren, Germany) was used. Fractions containing pure product were lyophilized using a Christ Alpha 1-2 LDplus freeze dryer. Linear gradients were employed with A: water, B: acetonitrile.

*Method used for preparative HPLC:* isocratic: 2 min (30% MeCN in H$_2$O), → gradient over 38 min (30-100% MeCN in H$_2$O) → 10 min 100% MeCN. Flow 25 mL/min.

3.1.9. Fourier transform infrared spectroscopy (FT-IR)

IR (ATR): spectra were measured by using a Thermo Nicolet Spectrometer FT-IR (ATR): Avatar 370 fitted with an ATR unit. Spectra were analyzed using Spectragryph v1.2.11. The following notations
indicate the normalized intensity of the absorption bands: s = strong (intensity > 67%), m = medium (intensity: 34%-66%), w = weak (intensity < 34%). Normalization was performed in Microsoft Excel.

3.1.10. Melting points

For melting point determination, a Büchi B-545 melting point apparatus and one-side open capillaries were used. All given values are an average of three measurements.

3.1.11. Specific optical rotation

Optical rotations were recorded in a Jasco P-2000 polarimeter at 589 nm and at a given temperature 22-24 °C. The path length of cuvettes was $d = 10 \text{ mm}$. Concentrations are given in g/100 mL solvent if not stated otherwise.
3.3. Synthetic procedures

3.3.1. General procedure geodiamolides 1: Loading of the 2-Cl-Trytil-chloride resin - Solid-phase supported synthesis (SPPS)

Solid-phase supported synthesis (SPPS) was done in 5-20 mL plastic syringes equipped with a blocking frit. Amounts of solvents and reagents are scaled to 1 g of resin (maximal loading: 1.4 mmol/g) and to 20 mL syringe size. The dry resin was washed with CH₂Cl₂ (2 x 10 mL for 1 min, 1 x 10 mL for 15 min). A solution of the first amino acid (1.4 mmol) and EtN(i-Pr)₂ (5.6 mmol) in CH₂Cl₂/DMF (10 mL, 1:1) was added to the resin, and the mixture was shaken at room temperature with approximately 300-400 rpm. After 4 h, the resin was drained, and washed with CH₂Cl₂ (3 x 10 mL). Capping solution (10 mL, CH₂Cl₂/MeOH/EtN(i-Pr)₂; 17:2:1) was introduced to the syringe and the mixture was shaken 3 x 1 min. After the final removal of the solvent, the resin was washed with CH₂Cl₂ (3 x 10 mL), DMF (3 x 10 mL), and CH₂Cl₂/MeOH (5 mL, 9:1) and dried for 4 h under a high vacuum in the dark. Long time storage was at -25 °C. The average loading was 0.5-0.7 mmol/g.

Determination of loading:

The resin-loading was determined by a quantitative Fmoc release. A Jasco V-630 UV-Vis-spectrometer was used to record the UV absorption. Approximately 10 mg of dry resin was weighed into a 2 mL Eppendorf tubes. The exact amount of the resin was noted. The tube was filled with 2 mL of piperidine solution (20 vol% piperidine/DMF). The contents were gently mixed for 20 min using an orbital shaker (300 rpm). 100 µL solution of the supernatant was introduced into a UV cuvette, and it was diluted with 900 µL piperidine solution (20 vol% Piperidine/DMF). A background UV absorbance of piperidine solution (20 vol% piperidine/DMF) was measured, followed by measurement of sample UV absorbance. The concentration of the solution was determined using the UV-extinction coefficient ε₃₀₁ = 7800 L/mmol/cm of the dibenzofulvene piperidine adduct at 301 nm. Resin loading was then calculated from the dibenzofulvene adduct concentration and the exact resin weight, as described in the equation below.

\[
\text{Loading (mmol/g)} = \frac{\text{Abs}_{301} \times 20000}{\varepsilon_{301} \times d_{kv} \times m_{\text{resin}}}
\]

\[m_{\text{resin}} = \text{mass of dry resin (mg)}\]

\[d_{kv} = \text{diameter of the quartz cuvette (cm)}\]

3.3.2. General Procedure geodiamolides 2: Fmoc-Deprotection (SPPS)

After swelling the resin in DMF (10 mL) for 20 min, the resin was washed with DMF (2 x 10 mL), drained, and treated with piperidine (10 mL, 20 vol% in DMF) for 5 min and washed with DMF (3 x 10 mL). After a second treatment with piperidine (5 mL, 20 vol% in DMF) for 15 min, the resin was washed with DMF (6 x 10 mL) and CH₂Cl₂ (3 x 10 mL).
3.3.3. General Procedure geodiamolides 3: Peptide-coupling on the solid support (SPPS)

A solution of the amino acid (indicated amount), COMU (1.0 equiv.), Oxyma (1.0 equiv. to indicated amount of amino acid), and EtN(i-Pr)₂ (2.0 equiv.) in DMF (10 mL) were mixed and preactivated by shaking for 3 min. The mixture was added to the resin after Fmoc deprotection, and the syringe was shaken at room temperature for the indicated period. The solvent was removed, and the resin was washed with DMF (4 x 10 mL). When needed, after evaporation of the solvents under reduced pressure and high vacuum, the resin was stored at -25 °C in the dark.

3.3.4. General Procedure geodiamolides 4: Cleaving peptide from the solid support

If dry resin was used, it was left to swollen in of CH₂Cl₂ (10 mL), without shaking, then it was washed with CH₂Cl₂ (1 x 10 mL). If swollen resin was used (immediately after SPPS couplings), additional washing was performed with CH₂Cl₂ (3 x 10 mL). The resin was shaken with of 20 vol% HFIP/CH₂Cl₂ (10 mL) in three cycles (5 min, 10 min, and 30 min), accompanied with red coloration. After the last cycle, the deprotected resin was washed with CH₂Cl₂ (3 x 10 mL), all fractions were combined, and the solvent was evaporated under reduced pressure. After trituration with toluene (3 x 20 mL) the solid rest was dried under a high vacuum for 16 h.

3.3.5. General Procedure geodiamolides 5: Esterification of tripeptide fragment

0.1 mmol (1 equiv.) of the respected peptide acid was mixed with 0.1 mmol (1 equiv.) of MNBA, 0.2 mmol (2 equiv.) of EtN(i-Pr)₂ in 7 mL of CH₂Cl₂ at 25 °C and stirred for 30 min. 0.1 mmol (1 equiv.) of DMAP was added, followed by the addition of 0.13 mmol (1.3 equiv.) of the corresponding alcohol. The reaction mixture was heated to reflux for 16 h, cooled to 25 °C, diluted with 30 mL of CH₂Cl₂, and washed with 10 mL of water. The organic layer was dehydrated (Na₂SO₄), the solvent evaporated under reduced pressure, and the product was purified by FCC.

3.3.6. General Procedure geodiamolides 6: Metathesis

Geodiamolides 6-1: For dienes with (S)-hex-5-en-2-ol moiety:

Toluene was added to a two-neck flask, and degassed by heating to reflux and active purging of argon for 30 min. The linear diene precursor 0.1 mmol (1 equiv.) for metathesis was dissolved in a small amount of degassed CH₂Cl₂ and added to a two-neck flask, previously filled with toluene, at a final concentration of 1.2 mM. The solution was refluxed with a continuous purge of argon for an additional 30 min, and 7.5 mol% of Grubbs 2nd generation catalyst were added. The reaction was carried for the indicated period (1-3 h) with a constant purge of argon. Reactions were followed by TLC. After completion, the solvent was evaporated under reduced pressure. Reaction products were purified using FCC.

Geodiamolides 6-2: For dienes with (2S,4R)-4-methylhex-5-en-2-ol moiety:

Toluene, in a two-neck flask, was degassed by heating to reflux and active purging of argon for 30 min. The linear diene precursor 0.1 mmol (1 equiv.) for metathesis was dissolved in a small amount of degassed CH₂Cl₂ and added to a two-neck flask, previously filled with toluene, at a final concentra-
tion of 1.2 mM. The solution was refluxed with a continuous purge of argon for an additional 30 min, and 35 mol% of Grubbs 2nd generation catalyst were added. The reaction was carried for the indicated period (1-3 h) with a constant purge of argon. Reactions were followed by TLC, and after completion, the solvent was evaporated under reduced pressure. The reaction products were purified using FCC.

3.3.7. General Procedure geodiamolides 7: Silyl deprotection

The silylated macrocycle (0.1 mmol) was transferred to a 15 mL size falcon tube. 700 µl of THF was added, followed by the addition of 70% HF/pyridine complex (50 µL), and stirred for 16 h at 25 °C under N₂. Volatiles were evaporated by blowing N₂ through the flask under the ventilated hood. The residue was dissolved in 5 mL of CH₂Cl₂ and passed through a pad of silica gel (1 cm), evaporated under reduced pressure, and purified using prep. HPLC.

3.4. Molecules synthesized by previously described procedures:

Fmoc-L-β-Tyr(TIPS)-OH (7),[15] (S)-2,4-dimethylpent-4-enoiic acid (10),[15] L-prolinol,[16] N-propionyl-L-prolinol (S1a),[16] Seebach’s auxiliary,[17] N-propionyl-Seebach’s auxiliary,[17] (S)-(1-iodopropan-2-yl)oxy triisopropylsilane (S2a),[18] (S)-tert-butyl ((1-iodopropan-2-yl)oxy) dimethylsilane (S2b), tert-butyl (2-iodoethoxy) dimethylsilane (S2c),[19] (S)-2-((tert-butyl(dimethyl)silyl)oxy) propyl-trifluoromethanesulfonate (S2e),[20] (S)-hex-5-en-2-ol (12),[21] Boc-D-Tyr(3'-I)-OH (D-Tyr-2),[22-23] Boc-D-Tyr-OH (D-Tyr-3).[24]

3.4.1. Synthesis of (2S,4R)-4-methylhex-5-en-2-ol

TIPS-(S)-hex-5-en-2-ol (12-1):

NaH (4.9 g, 123.9 mmol, 3 equiv., 60% NaH in oil) was suspended in THF (120 mL) and cooled down to 0 °C. Under N₂ atmosphere (S)-hex-5-en-2-ol (4.1 g, 41.3 mmol, 1 equiv.) was slowly added over 10 min. After 30 min of stirring at 0 °C, TIPS-Cl (10.8 mL, 50.7 mmol, 1.2 equiv.) was added, and the reaction mixture let warm up to 25 °C over 16 h. The reaction was again cooled down to 0 °C and water (50 mL) was added. The layers were separated, and the aqueous layer was extracted with E₂O (3 x 150 mL). The organic extracts were combined, dehydrated (Na₂SO₄), and concentrated under reduced pressure. FCC (PE 100%) provided 8.3 g of the product in 78% yield as a colorless oil.

TLC: \( R_f = 0.55 \) (PE 100%).

\([\alpha]_D^{20} = +8.1 \ (c = 1, \text{CHCl}_3)\).
IR (ATR): $\tilde{\nu} = 2962$ (m), 2942 (m), 2892 (m), 2866 (s), 2808 (w), 2709 (s), 1727 (s), 1461 (m), 1308 (m), 1290.3 (w), 1246 (w), 1219 (w), 1130 (m), 1057 (s), 1014 (m), 995 (s), 947 (m), 920 (m), 881 (m), 826 (m), 808 (m), 764 (s), 652 (m) cm$^{-1}$.

$^1$H NMR (300 MHz, chloroform-$d$, 298 K): $\delta = 5.83$ (dd, $J = 17.0, 10.3$ Hz, 1H), 5.09 – 4.87 (m, 2H), 3.97 (dd, $J = 11.8, 6.0$ Hz, 1H), 2.10 (dd, $J = 7.9, 6.8$ Hz, 2H), 1.57 (ddd, $J = 15.9, 13.8, 7.9$ Hz, 2H), 1.18 (d, $J = 6.1$ Hz, 3H), 1.07 (s, 21H) ppm.

$^{13}$C($^1$H) NMR (75 MHz, chloroform-$d$, 298 K): $\delta = 139.1, 114.3, 77.2, 68.2, 39.22, 29.8, 23.6, 18.3, 18.3, 12.7$ ppm.

HRMS (ESI−TOF) $m/Z$: $[M - (\text{CH}_3\text{CHCH}_3) + H]^+$, calculated for C$_9$H$_{19}$O$^+$ 171.1200; found 171.1197.

Spectral data corresponded to previously published data where the compound was synthesized by another synthetic route.$^{[25]}$

(S)-4-((triisopropylsilyl)oxy)pentanal (14):

Alkene 12-1 (6.9 g, 27.14 mmol, 1 equiv.) was dissolved in acetone/water (270 mL, 9/1) in a final concentration of 0.1 M followed by the addition of 2,6-Lutidine (6.5 mL, 54.2 mmol, 2 equiv.), 4-Methylmorpholine-$N$-oxide (4.75 g, 40.65 mmol, 1.5 equiv.) and OsO$_4$ (20.5 mL, 0.82 mmol, 3 mol%, 10 mg/ml solution in water). When the starting material was consumed (TLC controlled, 3 h), PhI(OAc)$_2$ (13 g, 40.65 mmol, 1.5 equiv.) was added in one portion, and the mixture was stirred for 6 h. The mixture was quenched with saturated sodium thiosulfate (100 mL) and extracted with EtOAc (3 x 300 mL). The combined organic extracts were washed with saturated aqueous CuSO$_4$ (3 x 150 mL), dehydrated (Na$_2$SO$_4$), and concentrated under reduced pressure. The crude residue was purified by FCC (PE/EtOAc 97:3) and provided 5.8 g of the product 14 in 83% yield, as a light-yellow oil.

TLC: $R_f = 0.65$ (PE/EtOAc = 95:5).

$[\alpha]_D^{20} = +17.0$ (c = 1, CHCl$_3$).

IR (ATR): $\tilde{\nu} = 2960$ (m), 2942 (m), 2892 (m), 2866 (m), 2715 (w, b), 1727 (s), 1687 (w), 1509 (w), 1462 (m), 1412 (m), 1246 (m), 1196 (m), 1040 (s), 1011 (s), 997 (s), 963 (m), 918 (m), 881 (s), 792 (m), 754 (m), 727 (m), 675 (s), 654 (s) cm$^{-1}$.

$^1$H NMR (300 MHz, chloroform-$d$, 298 K): $\delta = 9.77$ (dd, $J = 17.9, 0.8$ Hz, 1H), 4.10 – 3.25 (m, 1H), 2.60 – 2.05 (m, 2H), 1.90 – 1.50 (m, 2H), 1.11 (t, $J = 8.5$ Hz, 3H), 1.01 (d, $J = 0.5$ Hz, 18H) ppm.

$^{13}$C($^1$H) NMR (75 MHz, chloroform-$d$, 298 K): $\delta = 202.5, 77.2, 67.4, 39.6, 31.7, 23.3, 18.2, 18.1, 18.0, 12.6$ ppm.
HRMS (ESI−TOF) m/Z: [M − (CH₃CHCH₃)₂ + H]^+, calculated for C₈H₁₇O₂Si⁺ 173.0992; found 173.0990.

Spectral data corresponded to previously published data where the compound was synthesized by another synthetic route.[25]

2,5-Dioxopyrrolidin-1-yl (S)-4-((triisopropylsilyl)oxy)pentanoate (14-1):

![Chemical Structure]

Aldehyde 14 (5.7 g, 22.26 mmol, 1 equiv.) and N-hydroxysuccinimide (2.7 g, 23.35 mmol, 1.05 equiv.) were dissolved in acetonitrile (90 mL). After the reaction mixture was cooled to 0 °C, PhI(OAc)₂ (7.5 g, 23.35 mmol, 1.05 equiv.) was added in one portion. The temperature was maintained between 0 °C and 5 °C. After 1 h conversion was complete (TLC controlled). The mixture was diluted with EtOAc (200 mL), washed once with a saturated solution of NaHCO₃ (~30 mL), dehydrated (Na₂SO₄), and concentrated under reduced pressure. The crude residue was purified by FCC (PE/EtOAc 9:1) to obtain 6.1 g of active ester as colorless oil (73% yield).

TLC: RF = 0.45 (PE/EtOAc = 9:1).

[α]D₂₀ = +13.5 (c = 1, CHCl₃).

IR (ATR): ν = 2943 (m), 2891 (m), 2866 (m), 2813 (w), 1815 (m), 1781 (m), 1727 (s), 1585 (m), 1464 (m), 1435 (m), 1417 (m), 1295 (m), 1267 (m), 1251 (m), 1198 (s), 1133 (m), 1117 (m), 1063 (s), 998 (m), 965 (m), 785 (m), 748 (m), 714 (s), 681 (s), 643 (s) cm⁻¹.

¹H NMR (400 MHz, chloroform-d, 297 K): δ = 4.05 (dd, J = 11.5, 5.8 Hz, 1H), 2.80 (d, J = 13.9 Hz, 4H), 2.68 (t, J = 7.8 Hz, 2H), 1.94 – 1.74 (m, 2H), 1.16 (d, J = 6.1 Hz, 3H), 1.05 – 0.98 (m, 18H) ppm.

¹³C(¹H) NMR (101 MHz, chloroform-d, 297 K): δ = 169.3, 169.2, 77.2, 67.0, 34.2, 26.7, 25.7, 23.3, 18.2, 18.2, 18.1, 12.6 ppm.

HRMS (ESI−TOF) m/Z: [M + H]^+, calculated for C₁₈H₃₄O₅Si⁺ 372.2201; found 372.2205.

(R)-4-Isopropyl-5,5-diphenyl-3-((S)-4-((triisopropylsilyl)oxy)pentanoyl)oxazolidin-2-one (15):

![Chemical Structure]

Seebach’s auxiliary (5.8 g, 20.75 mmol, 1.1 equiv.) was dissolved in THF (120 mL). The solution was cooled to -78 °C, and n-BuLi (8.82 mL, 1.1 equiv., 2.35 M) was added dropwise over 10 min. After stirring at the same temperature for 30 min, active ester 14-1 (7 g, 18.86 mmol, 1 equiv., dissolved in
40 mL of THF) was added over 10 min. The reaction mixture was with stirring left to reach 25 °C over 16 h. A saturated solution of ammonium chloride (50 mL) was added, the reaction mixture was extracted with EtOAc (3 x 200 mL), dehydrated (Na₂SO₄), and concentrated under reduced pressure. The crude residue was purified by FCC (PE/EtOAc 95:5) to give 8.3 g of imide as a colorless oil (82% yield), that solidified amorphously when kept at 0 °C.

TLC: \( R_f = 0.65 \) (PE/EtOAc = 9:1).

\([\alpha]_{D}^{20} = +201.1 \) (c = 1, CHCl₃).

IR (ATR): \( \tilde{\nu} = 2865 \) (m), 2723 (m), 2559 (m), 2496 (m), 2470 (m), 2370 (m), 2324 (m), 2006 (m), 1884 (m), 1449 (m), 1363 (m), 1245 (m), 1207 (s), 1173 (s), 915 (s), 880 (s), 843 (s), 793 (s), 695 (s), 665 (s) cm⁻¹.

\( ^{1}H \) NMR (400 MHz, chloroform-d, 297 K): \( \delta = 7.48 \) (dd, \( J = 5.3, 3.3 \) Hz, 2H), 7.32 (ddt, \( J = 18.2, 5.8, 5.3 \) Hz, 7H), 5.44 – 5.26 (m, 1H), 4.02 – 3.86 (m, 1H), 3.24 – 2.56 (m, 2H), 2.05 – 1.89 (m, 1H), 1.82 – 1.59 (m, 2H), 1.55 (s, 1H), 1.27 (d, \( J = 11.4 \) Hz, 2H), 1.10 (t, \( J = 5.4 \) Hz, 3H), 1.07 – 0.99 (m, 18H), 0.88 (dd, \( J = 8.6, 4.7 \) Hz, 4H), 0.78 – 0.71 (m, 3H) ppm.

\( ^{13}C\)\( ^{1}H \) NMR (101 MHz, chloroform-d, 297 K): \( \delta = 173.8, 153.5, 142.9, 138.7, 129.3, 129.0, 128.8, 128.4, 126.4, 126.0, 89.8, 77.7, 68.0, 65.0, 34.6, 31.6, 30.3, 23.8, 22.2, 18.6, 18.6, 16.8, 12.9, 12.4 \) ppm.

HRMS (ESI−TOF) m/Z: \([M + Na]^+\), calculated for C\(_{32}\)H\(_{47}\)NNaO\(_4\)Si\(_5\) 560.3167; found 560.3174.

(R)-4-Isopropyl-3-((2R,4S)-2-methyl-4-((triisopropylsilyl)oxy)pentanoyl)-5,5-diphenyloxazolidin 2-one (16):

Diisopropylamine (3.3 mL, 23.17 mmol, 1.5 equiv.) was dissolved in THF (40 mL) and cooled to -78 °C. n-BuLi (9.3 mL, 23.17 mmol, 1.5 equiv., 2.5 M) was added in one portion, and the reaction was stirred for 30 min at -78 °C. Using a transfer needle, LDA solution was transferred to a cold (-78 °C) solution of 15 (8.3 g, 15.45 mmol, 1 equiv.) in THF (120 mL). After 30 min of stirring at the same temperature, precooled MeI (11.5 mL, 185 mmol, 12 equiv.) was added slowly over 10 min, along the cooled glass wall of the flask. The solution was let to warm to -40 °C by transferring the flask into a -40 °C cooling bath, and kept at this temperature for 8 hours. A saturated solution of ammonium chloride (50 mL) and additional water was added to redissolve, forming salts precipitate (~100 mL). After extraction with EtOAc (3 x 200 mL) combined, organic fractions were washed with saturated sodium thiosulfate (100 mL), dehydrated (Na₂SO₄), and concentrated under reduced pressure. FCC (PE/EtOAc 95:5) provided 7.4 g of the alkylated product was isolated (90% yield) as a col-
orless oil. The product solidifies over time in the freezer and/or crystalize from EtOH/water mixture (95:5).

**TLC:** $R_f = 0.70$ (PE/EtOAc = 9:1).

$[\alpha]_D^{20} = +123.3$ (c = 1, CHCl$_3$).

**IR (ATR):** $\tilde{\nu}$ = 3062.6 (w), 2944.4 (m), 2865.9 (m), 2727 (w), 2654.1 (w), 2571.8 (w), 2106 (w), 2044.3 (w), 1978.8 (w), 1772.8 (s), 1703.9 (s), 1451.3 (m), 1319.3 (m), 1176.9 (m), 1103.3 (s), 1052.2 (s), 986.66 (s), 883.44 (m), 758.61 (s), 700.8 (s) cm$^{-1}$.

**MP = 101 °C.**

**$^1$H NMR** (400 MHz, chloroform-$d$, 297 K): $\delta$ = 7.56 – 7.49 (m, 2H), 7.44 (d, $J = 7.3$ Hz, 2H), 7.40 – 7.25 (m, 7H), 5.39 (d, $J = 3.5$ Hz, 1H), 3.62 (d, $J = 6.3$ Hz, 2H), 2.09 – 1.89 (m, 2H), 1.29 (d, $J = 6.9$ Hz, 3H), 1.07 – 0.99 (m, 21H), 0.88 (d, $J = 7.0$ Hz, 3H), 0.79 (d, $J = 6.7$ Hz, 3H), 0.67 (d, $J = 6.1$ Hz, 3H) ppm.

**$^{13}$C{$_1^H$} NMR** (101 MHz, chloroform-$d$, 297 K): $\delta$ = 176.9, 152.7, 142.6, 138.2, 128.9, 128.6, 128.6, 128.1, 125.9, 125.5, 89.4, 77.2, 66.1, 64.8, 42.6, 33.9, 29.9, 23.0, 21.7, 19.6, 18.2, 16.5, 12.5 ppm.

**HRMS (ESI−TOF) m/Z:** $[M + Na]^+$, calculated for C$_{33}$H$_{49}$NNaO$_4$Si+ 574.3323; found 574.3328.

(2R,4S)-2-Methyl-4-((triisopropylsilyl)oxy)pentan-1-ol (17):

Imide 16 (7.4 g, 13.5 mmol, 1 equiv.) was dissolved in Et$_2$O (100 mL), and the solution was cooled to 0 °C. Water (270 µl, 14.85 mmol, 1.1 equiv.) was added, followed by the addition of a solution of LiBH$_4$ (327 mg, 14.85 mmol, 1.1 equiv.) in THF (5 mL). Evolution of gas was observed for 5 min, the reaction was stirred at the same temperature for 3 h. NaOH (20 mL of 1 M aqueous solution) was added, followed by additional Et$_2$O (160 mL). Layers were separated and Et$_2$O layer was and washed with brine (~50 mL), dehydrated (Na$_2$SO$_4$), and concentrated under reduced pressure. FCC (PE/EtOAc 9:1) provided 3.6 g of the alcohol 17 as a colorless oil (98% yield).

**TLC:** $R_f = 0.35$ (PE/EtOAc = 9:1).

$[\alpha]_D^{20} = +18.6$ (c = 1, CHCl$_3$).
1.25 (ddd, \( J = 7.1, 4.7, 2.9 \) Hz, 1H), 1.20 (d, \( J = 6.1 \) Hz, 3H), 1.06 (s, 21H), 0.94 (t, \( J = 6.0 \) Hz, 3H) ppm.

\( ^{13} \text{C} \{^{1} \text{H} \} \) NMR (75 MHz, chloroform-\( d \), 298 K): \( \delta = 72.2, 68.8, 67.3, 44.2, 32.8, 24.6, 18.3, 18.3, 17.6, 12.8 \) ppm.

HRMS (ESI−TOF) \( m/\text{Z} \): \([M + H]^+\), calculated for \( \text{C}_{15}\text{H}_{35}\text{O}_{2}\text{Si}\) 275.2401; found 275.2403.

(2R,4S)-2-Methyl-4-((triisopropylsilyloxy)oxy)pentanal (17-1):

Sulfur trioxide pyridine complex (8.8 g, 27.7 mmol, 2 equiv.) was suspended in CH\(_2\)Cl\(_2\) (150 mL) and cooled to -30 °C. DMSO (8.8 mL, 124.7 mmol, 9 equiv.) and alcohol 17 (3.8 g, 13.86 mmol, 1 equiv.) were added, followed by the addition of EtN(i-Pr)\(_2\) (9.64 mL, 55.44 mmol, 4 equiv.). The mixture was left to reach 25 °C over 5 h, with stirring. A saturated solution of ammonium chloride (50 mL) was added. The mixture was extracted with CH\(_2\)Cl\(_2\) (2 x 100 mL), dehydrated (Na\(_2\)SO\(_4\)), and concentrated under reduced pressure. FCC (PE/Et\(_2\)O 98:2) provided 3.54 g of the aldehyde 17 was obtained, as slightly yellow oil (94% yield).

TLC: \( R_f = 0.75 \) (PE/EtOAc = 9:1).

\([\alpha]_D^{20} = +2.9 \) (c = 1, CHCl\(_3\)).

IR (ATR): \( \tilde{\nu} = 2942.2 \) (m), 2866.6 (m), 2709.4 (w), 2040 (w), 1984.8 (w), 1727.7 (m), 1561.6 (w), 1461.3 (m), 1376.2 (w), 1246.8 (w), 1130.5 (m), 1057.5 (s), 995.21 (m), 881.49 (s), 674.45 (s) cm\(^{-1}\).

\(^1\text{H} \) NMR (300 MHz, chloroform-\( d \), 300 K): \( \delta = 9.63 \) (d, \( J = 1.9 \) Hz, 1H), 4.06 (ddd, \( J = 7.2, 6.1, 5.0 \) Hz, 1H), 2.68 – 2.45 (m, 1H), 1.97 (ddd, \( J = 13.8, 7.2, 6.5 \) Hz, 1H), 1.56 (s, 1H), 1.36 (ddd, \( J = 13.9, 7.1, 4.9 \) Hz, 1H), 1.20 (d, \( J = 6.1 \) Hz, 3H), 1.11 (t, \( J = 5.8 \) Hz, 3H), 1.06 (s, 21H) ppm.

\( ^{13} \text{C} \{^{1} \text{H} \} \) NMR (75 MHz, chloroform-\( d \), 300 K): \( \delta = 205.4, 77.2, 66.7, 43.7, 41.1, 24.5, 18.5, 18.5, 14.3, 12.9 \) ppm.

HRMS (ESI−TOF) \( m/\text{Z} \): \([M−(\text{CH}_3\text{CHCH}_3)_2 + \text{H}]^+\), calculated for \( \text{C}_9\text{H}_{19}\text{O}_2\text{Si}^+ \) 187.1149; found 187.1147.

TIPS-(2S,4R)-4-methylhex-5-en-2-ol (17-2):

Methyltriphenylphosphonium bromide (10.1 g, 28.2 mmol, 2.2 equiv.) was suspended in THF (100 mL). The solution was cooled to -78 °C, and \( n \)-BuLi (11 mL, 25.7 mmol, 2 equiv. 2.5 M) was
added over 5 min. After stirring at -78 °C for 30 min, the reaction was transferred to an ice bath and stirred an additional 30 min, at 0 °C. Aldehyde 17-1 (3.4 g, 12.83 mmol, 1 equiv.) was added to the solution of preformed ylide at 0 °C and kept stirring for an additional hour. The mixture was diluted with Et₂O (250 mL) and washed with water (2 x 50 mL). The organic layer was dehydrated (Na₂SO₄) and concentrated under reduced pressure. FCC (PE/Et₂O 95:5) provided 3.1 g of the alkene 17-2, as slightly yellow oil (92% yield).

**TLC:** $R_f = 0.90$ (PE/EtOAc = 95:5).

$[\alpha]_{D}^{20} = -6.4$ (c = 0.8, CHCl₃).

**IR (ATR):** $\tilde{\nu} = 2961$ (m), 2943 (m), 2926 (m), 2893 (m), 2866 (m), 1640 (w), 1461 (m), 1419 (w), 1128 (m), 1108 (m), 1056 (s), 1025 (m), 1012 (m), 994 (m), 935 (m), 911 (m), 881 (s), 852 (m), 808 (m), 750 (m), 717 (m), 674 (s), 652 (m) cm⁻¹.

**¹H NMR** (300 MHz, chloroform-d, 298 K): $\delta = 5.73 – 5.59$ (m, 1H), 4.92 (ddd, $J = 11.9$, 10.4, 1.4 Hz, 2H), 3.95 – 3.83 (m, 1H), 2.31 – 2.12 (m, 1H), 1.64 – 1.51 (m, 2H), 1.34 (ddd, $J = 13.5$, 7.9, 5.7 Hz, 1H), 1.16 (dd, $J = 6.0$, 2.4 Hz, 3H), 1.04 (d, $J = 7.0$ Hz, 21H), 1.00 (d, $J = 6.7$ Hz, 3H) ppm.

**¹³C{¹H} NMR** (75 MHz, chloroform-d, 298 K): $\delta = 144.6$, 112.7, 77.2, 66.9, 47.2, 35.1, 23.6, 21.2, 18.3, 18.3, 12.6 ppm.

**HRMS (ESI−TOF) m/z:** [M – (CH₃CHCH₃) + H]+, calculated for C₁₃H₂₇OSi+ 227.1826; found 227.1825.

**protected alcohol 17-2**: (2S,4R)-4-Methylhex-5-en-2-ol (11):

Protected alcohol 17-2 (2.5 g, 9.36 mmol, 1 equiv.) was dissolved in THF (80 mL), and TBAF (23.8 mL, 23.8 mmol, 2.5 equiv., 1 M in THF) was added at 25 °C. The mixture was stirred for 6 h until completion (TLC control). The reaction mixture was diluted with Et₂O (150 mL) and washed with water (80 mL). The layers were separated, the organic fraction was dehydrated (Na₂SO₄), and concentrated under reduced pressure. FCC (pentane/Et₂O 9:1) provided 1.1 g of the alcohol 11 as a colorless oil (96% yield).

**TLC:** $R_f = 0.22$ (PE/EtOAc = 8:2).

$[\alpha]_{D}^{21} = -6.4$ (c = 1.5, CHCl₃).

**IR (ATR):** $\tilde{\nu} = 2963$ (m), 2924 (m), 2872 (m), 1942 (w), 1824 (w), 1549 (m), 1457 (m), 1417 (m), 1373 (m), 1334 (m), 1301 (m), 1262 (m), 1225 (m), 1122 (m), 1036 (m), 994 (m), 953 (m), 908 (s), 840 (m), 806 (m), 728 (m), 682 (s), 648 (s) cm⁻¹.
1H NMR (250 MHz, chloroform-d, 297 K): \( \delta = 5.84 - 5.65 \) (m, 1H), \( 5.10 - 4.84 \) (m, 2H), 3.85 (dd, \( J = 12.9, 6.2 \) Hz, 1H), 2.28 (dt, \( J = 14.3, 7.2 \) Hz, 1H), 1.58 – 1.26 (m, 2H), 1.17 (d, \( J = 6.2 \) Hz, 3H), 1.01 (d, \( J = 6.7 \) Hz, 3H) ppm.

13C{1H} NMR (63 MHz, chloroform-d, 297 K): \( \delta = 145.0, 113.0, 77.2, 66.8, 46.3, 35.8, 23.8, 20.6 \) ppm.

Spectral data corresponded to previously published data where the compound was synthesized by another synthetic route.[15]

(R)-3-((S)-2-((tert-butyldimethylsilyl)oxy)propyl)-4-isopropyl-5,5-diphenyloxazolidin-2-one (S3c):

Unwanted product, obtained during exploratory alkylation of enolates (See Table S1).

1H NMR (500 MHz, Chloroform-d, 323 K) \( \delta = 7.62 \) (d, \( J = 7.8 \) Hz, 2H), 7.49 – 7.44 (m, 2H), 7.25 (t, \( J = 7.3 \) Hz, 1H), 4.45 (s, 1H), 3.91 – 3.82 (m, 1H), 3.78 – 3.70 (m, 1H), 3.60 (ddd, \( J = 18.2, 12.9, 6.7 \) Hz, 1H), 3.11 (dd, \( J = 14.2, 5.1 \) Hz, 1H), 2.02 (tt, \( J = 14.2, 7.3 \) Hz, 1H), 1.35 – 1.27 (m, 1H), 1.14 (d, \( J = 7.4 \) Hz, 3H), 0.87 (s, 9H), 0.74 (d, \( J = 6.0 \) Hz, 3H), 0.71 (d, \( J = 6.8 \) Hz, 3H), 0.03 (s, 3H), -0.03 (s, 3H) ppm.

13C{1H} NMR (125 MHz, Chloroform-d, 323 K) \( \delta = 157.1, 144.6, 139.2, 128.5, 128.1, 128.0, 127.5, 126.2, 125.2, 87.4, 68.6, 66.3, 51.5, 29.8, 25.8, 25.7, 22.7, 21.2, 17.9, 15.5, -4.5, -4.5, -4.7, -4.8 \) ppm.

3.4.2. Synthesis of N-Me-N-Fmoc-3′-I-O-TIPS-D-Tyrosine

(R)-2-amino-3-(4-hydroxy-3-iodophenyl)propanoic acid (D-Tyr-1):

In 1 L round bottom flask D-Tyrosine (8 g, 44.2 mmol, 1 equiv.) was dissolved in ammonium hydroxide solution (300 mL, 30%) and the solution was cooled to 0°C. Iodine (11.2 g, 44.2 mmol, 1 equiv.) was dissolved in EtOH (100 mL) and transferred to the addition funnel. A plastic funnel was placed on the top of the reaction flask, and an addition flask was clamped above in a way to allow dropping on the plastic sidewalls of the funnel. Keeping the reaction flask at constant temperature, the iodine solution was added slowly over 2 h, with additional stirring for 1 h at the same tem-
perature. The reaction mixture was concentrated under reduced pressure to ~100 mL, and the pH was adjusted to 4-5 by careful addition of 6 M HCl. After filtration, the obtained yellowish solid was washed 2 times with a minimal amount of acetone (approximately 2 x 30 mL) and dried in a drying oven at 70 ℃ for 4 h, with additional drying under high vacuum over 16 h. 11.2 g of off-white product D-Tyr-1 was obtained (83% yield).

Spectral properties corresponded to previously published data.[2]

Boc-D-Tyr(3'-I, TIPS)-OH (18):

To a cold (0 ℃) solution of phenol D-Tyr-2 (12.2 g, 30 mmol, 1 equiv.) in CH₂Cl₂ (125 mL) was added dicyclohexylamine (6.2 mL, 31.5 mmol, 1.05 equiv.), and the mixture was stirred for 30 min. TIPS-Cl (7.04 mL, 33 mmol, 1.1 equiv.) was then added and stirring was continued at the constant temperature for 2 h. Imidazole (4.08 g, 60 mmol, 2 equiv.), DMAP (0.73 g, 6 mmol, 0.2 equiv.), and additional TIPS-Cl (7.04 mL, 33 mmol, 1.1 equiv.) were added at 0 ℃ and stirring was continued for 16 h. When conversion to the bis-silylated compound was complete (TLC R_f = 0.95, PE/EE = 95:5), mixture was filtered through a pad of Celite, which was washed with additional CH₂Cl₂ (100 mL). The solvent was evaporated under reduced pressure, and the residue was dissolved in THF/MeOH/H₂O (2:1:1 mixture, 100 mL) at 25 ℃. K₂CO₃ (8.2 g, 60 mmol, 2 equiv.) was added, and the mixture was stirred for 30 min. The reaction was diluted with water (100 mL), and the pH was adjusted to 2-3 using aqueous 2 M HCl. After extraction with EtOAc (3 x 200 mL), the combined organic extracts were dehydrated (Na₂SO₄), the solvent was evaporated under reduced pressure. The product was purified by FCC (gradient of CH₂Cl₂ 100% to CH₂Cl₂/MeOH 9:1) to give 13.8 g of acid 18 as colorless amorphous solid (82% yield).

TLC: R_f = 0.45 (CH₂Cl₂/MeOH = 9:1).

[a]D₂₀ = +68 (c = 1, CHCl₃).

IR (ATR): ν = 2944 (m), 2892 (m), 2866 (m), 1712 (s), 1648 (m), 1508 (m), 1487 (m), 1479 (m), 1380 (m), 1367 (m), 1285 (s), 1254 (s), 1162 (s), 1103 (m), 1057 (m), 1038 (m), 1016 (m), 996 (m), 916 (s), 881 (s), 848 (m), 813 (m), 775 (m), 719 (m), 675 (s), 658 (s) cm⁻¹.

¹H NMR (400 MHz, DMSO-d₆, 323 K): δ = 12.45 (s, 1H), 8.01 – 7.48 (m, 1H), 7.12 (dd, J = 13.3, 8.3 Hz, 1H), 6.96 – 6.69 (m, 2H), 4.09 (s, 1H), 3.00 – 2.84 (m, 2H), 2.75 (d, J = 10.1 Hz, 2H), 1.32 (s, 12H), 1.07 (dd, J = 25.7, 8.1 Hz, 18H) ppm.

¹³C[¹H] NMR (101 MHz, DMSO-d₆, 323 K): δ = 173.0, 172.9, 171.5, 171.4, 162.0, 155.0, 154.9, 153.7, 153.2, 153.2, 139.5, 139.4, 138.9, 132.3, 132.1, 130.3, 130.1, 129.9, 129.9, 129.8, 118.9, 117.2,
114.6, 114.5, 89.5, 89.5, 83.9, 55.9, 54.9, 54.6, 35.5, 35.1, 30.6, 27.9, 17.7, 17.6, 17.5, 17.3, 12.3, 11.9, 11.9, 11.2 ppm.

**HRMS (ESI−TOF) m/Z**: [M + Na]+, calculated for C_{23}H_{38}INaO_{5}Si+ 586.1456; found 586.1448.

**Boc-N-Me-D-Tyr(3'-I, TIPS)-OH (18-1):**

Carbamate 18 (6.77 g, 12 mmol, 1 equiv.) was dissolved in THF (110 mL) and cooled to 0 °C. NaH (1.99 g, 25.2 mmol, 2.1 equiv. 60% in mineral oil) was added. After 10 min of stirring, MeI (5.9 mL, 96.1 mmol, 8 equiv.) was added and the mixture was stirred for 16 h, letting it reach 25 °C. Aqueous 0.1 M HCl (50 mL) was added and the mixture was extracted with EtOAc (3 x 120 mL). The combined organic extracts were dehydrated (Na_{2}SO_{4}) and the solvent was evaporated under reduced pressure. The product was purified by FCC (CH_{2}Cl_{2}/MeOH 95:5) to give 4.64 g of the methylated carbamate 18-1 as a colorless solid (67% yield).

**TLC**: R_{f} = 0.55 (CH_{2}Cl_{2}/MeOH = 9:1).

[α]_{D}^{20} = +60.1 (c = 1, CHCl_{3}).

**IR (ATR):** ν = 2943 (m), 2866 (m), 2727 (w), 2603 (w), 2563 (w), 2526 (w), 2365 (w), 2322 (w), 1991 (w), 1942 (w), 1869 (w), 1698 (m), 1558 (w), 1486 (m), 1445 (m), 1366 (m), 1259 (m), 1145 (m), 1073 (m), 1017 (m), 881 (m), 768 (m), 683 (m) cm^{-1}.

**Melting point** = 61 °C.

**^{1}H NMR** (400 MHz, DMSO-d_{6}, 324 K): δ = 12.62 (s, 1H), 7.66 (d, J = 11.8 Hz, 1H), 7.08 (dd, J = 12.2, 8.4 Hz, 1H), 6.78 (d, J = 8.8 Hz, 1H), 4.94 – 4.36 (m, 1H), 3.07 (ddq, J = 15.1, 10.5, 4.8 Hz, 1H), 2.88 (d, J = 10.5 Hz, 1H), 2.66 – 2.54 (m, 3H), 1.72 (s, 1H), 1.32 (dd, J = 17.8, 6.6 Hz, 10H), 1.07 (dd, J = 16.8, 7.4 Hz, 18H), ppm.

**^{13}C\left({^{1}H}\right) NMR** (101 MHz, DMSO-d_{6}, 324 K): δ = 172.7, 172.3, 155.5, 154.8, 154.3, 153.8, 141.0, 139.9, 130.3, 119.7, 117.9, 115.2, 89.7, 87.1, 79.4, 28.3, 18.5, 18.3, 18.1, 17.9, 15.0, 12.9, 12.6, 11.8 ppm.

**HRMS (ESI−TOF) m/Z**: [M + Na]+, calculated for C_{23}H_{38}INaO_{5}Si+ 600.1613; found 600.1613.
**N-Me-D-Tyr(3'-I, TIPS)-OH, trifluoroacetate (18-2):**

Carbamate 18-1 (4.64 g) was dissolved in CH$_2$Cl$_2$ (80 mL), and the solution cooled to 0 °C. Anhydrous CF$_3$COOH (20 mL, distilled prior to use) was added, and stirring was continued for 2 h keeping the temperature constant. Volatiles were removed under reduced pressure to give colorless solid used in the next step without further purification.

**Fmoc-N-Me-D-Tyr(3'-I, TIPS)-OH (8):**

Salt 18-2 was dissolved in 1,4-dioxane/water (1:1, 120 mL) and cooled to 0 °C. NaHCO$_3$ (2.6 g, 32 mmol, 4 equiv.) followed by Fmoc-OSu (2.96 g, 8.80 mmol, 1.1 equiv.) was added, and the mixture was stirred for 16 h, letting it reach 25 °C. The mixture was concentrated under reduced pressure to remove the rest of the 1,4-dioxane, washed once with EtOAc (30 mL) and acidified to pH 2 using aqueous 2 M HCl. The mixture was extracted with EtOAc (3 x 100 mL), the extracts were combined and dehydrated (Na$_2$SO$_4$). The solvent was evaporated under reduced pressure, and the residue was purified by FCC (CH$_2$Cl$_2$/MeOH 97:3 + 0.1% HCOOH) to give 4.02 g of the carbamate 8 as colorless solid (72% yield).

**TLC:** $R_f = 0.45$ (CH$_2$Cl$_2$/MeOH = 9:1).

$[\alpha]_{D}^{20} = +43.6$ (c = 1, CHCl$_3$).

**IR (ATR):** $\tilde{\nu} = 2865$ (w), 2729 (w), 2675 (w), 2615 (w), 2595 (w), 2548 (w), 2400 (w), 2375 (w), 1701 (m), 1596 (w), 1558 (w), 1486 (m), 1316 (m), 1284 (m), 1189 (m), 1144 (m), 1036 (m), 994 (m), 915 (m), 881 (m), 846 (m), 810 (m), 738 (m), 684 (m), 653 (m) cm$^{-1}$.

**MP** = 89-91 °C.

$^1$H NMR (300 MHz, DMSO-$d_6$, 298 K): (rotamers): $\delta = 12.93$ (s, 1H), 7.87 (d, J = 7.5 Hz, 2H), 7.77 – 7.22 (m, 7H), 7.21 – 6.82 (m, 1H), 6.69 (d, J = 8.3 Hz, 1H), 4.76 (dd, J = 11.4, 4.6 Hz, 1H), 4.35 – 3.95 (m, 3H), 3.33 (s, 1H), 3.18 – 2.77 (m, 2H), 2.71 (d, J = 20.1 Hz, 3H), 1.22 (dq, J = 22.0, 7.3 Hz, 3H), 1.10 – 0.91 (m, 17H) ppm.
$^{13}$C\{$^1$H\} NMR (125 MHz, DMSO-$d_6$, 324 K): (rotamers): $\delta = 171.5, 153.7, 153.2, 143.7, 143.6, 143.5, 140.5, 139.3, 139.2, 132.3, 129.9, 129.6, 127.4, 127.4, 126.9, 126.8, 124.7, 124.7, 119.8, 119.2, 117.4, 89.7, 66.8, 66.6, 59.9, 46.4, 32.4, 31.4, 17.8, 17.6, 17.4, 12.2, 11.8 ppm.

HRMS (ESI−TOF) $m/Z$: $[M + H]^*$, calculated for $C_{34}H_{43}INO_5Si^+$ 700.1950; found 700.1947.

3.4.3. Synthesis of N-Me-N-Fmoc-O-TIPS-D-Tyrosine

Boc-D-Tyr(TIPS)-OH (19):

![Boc-D-Tyr(TIPS)-OH structure]

Protected tyrosine analog 19 was synthesized from $N$-Boc-D-Tyr-OH (3.6 g, 12.8 mmol), using the procedure described for silylated 18 to give 4.8 g of silylated 19 (86% yield) as a colorless viscous oil, that solidified upon storage.

TLC: $R_f = 0.32$ (CH$_2$Cl$_2$/MeOH = 9:1).

$[\alpha]_{D}^{20} = -7.8$ (c = 1, CHCl$_3$).

IR (ATR): $\tilde{\nu} =$ 3059 (w), 3030 (w), 2944 (m), 2893 (m), 2867 (m), 1580 (w), 1510 (s), 1461 (m), 1326 (m), 1260 (s), 1144 (s), 1102 (m), 1072 (m), 1014 (m), 996 (m), 963 (m), 911 (s), 881 (s), 842 (m), 817 (m), 769 (m), 737 (m), 682 (s), 657 (s) cm$^{-1}$.

MP = 59 °C.

$^1$H NMR (400 MHz, DMSO, 323 K): $\delta =$ 7.09 (d, $J =$ 8.4 Hz, 2H), 6.74 (d, $J =$ 8.4 Hz, 2H), 4.04 (s, 1H), 3.22 – 2.66 (m, 3H), 1.34 – 1.17 (m, 12H), 1.09 – 0.98 (m, 18H) ppm.

$^{13}$C\{$^1$H\} NMR (101 MHz, DMSO, 323 K): $\delta =$ 174.0, 154.9, 153.6, 130.7, 130.0, 118.8, 77.6, 55.3, 36.0, 27.9, 17.6, 11.9 ppm.

HRMS (ESI−TOF) $m/Z$: $[M + Na]^*$, calculated for $C_{23}H_{39}NNaO_5Si^+$ 460.2490; found 460.2487.
Boc-N-Me-D-Tyr(TIPS)-OH (19-1):

\[
\begin{align*}
\text{TIPS} & \\
& \text{COOH} \\
& \text{N}\text{Boc}
\end{align*}
\]

\(N\)-methylated carbamate 19-1 was synthesized by the procedure described for 18-1 from carbamate 19 (4.7 g, 10.9 mmol), to give 2.9 g of a colorless viscous oil (59% yield), which solidified upon storage.

TLC: \(R_f = 0.45\) (CH\(_2\)Cl\(_2\)/MeOH = 9:1).

\([\alpha]_{D}^{20} = +52.6\) (c = 1, CHCl\(_3\)).

IR (ATR): \(\tilde{\nu} = 2943\) (m), 2893 (w), 2867 (m), 2623 (w), 2606 (w), 1510 (m), 1461 (m), 1406 (m), 1391 (m), 1367 (m), 1261 (m), 1167 (m), 1103 (w), 1015 (m), 996 (m), 913 (m), 882 (m), 832 (m), 774 (w), 754 (w), 684 (m), 602 (w) cm\(^{-1}\).

\(^1H\) NMR (400 MHz, DMSO-d\(_6\), 323 K): (rotamers): \(\delta = 12.56\) (s, 1H), 7.08 (d, \(J = 8.3\) Hz, 2H), 6.77 (d, \(J = 7.7\) Hz, 2H), 4.61 (d, \(J = 73.3\) Hz, 1H), 3.03 (ddd, \(J = 66.4, 19.7, 8.8\) Hz, 2H), 2.60 (s, 3H), 1.37 – 1.17 (m, 12H), 1.06 (d, \(J = 7.3\) Hz, 18H) ppm.

\(^{13}C\{^1H\}\) NMR (101 MHz, DMSO-d\(_6\), 323 K): (rotamers): \(\delta = 172.7, 155.4, 154.8, 154.3, 138.1, 131.2, 131.0, 130.4, 119.7, 79.3, 61.5, 59.8, 55.3, 34.5, 32.6, 28.4, 18.3, 18.2, 12.8, 12.6, 12.3\) ppm.

HRMS (ESI–TOF) \(m/Z: [M + Na]^+\), calculated for C\(_{24}\)H\(_{41}\)NNaO\(_5\)Si\(_4\) 474.2646; found 474.2646.

\(N\)-Me-D-Tyr(TIPS)-OH, trifluoroacetate (19-2):

\[
\begin{align*}
\text{TIPS} & \\
& \text{COOH} \\
& \text{CF}3\text{COO} \\
& \text{2H}_2
\end{align*}
\]

Salt 19-2 was obtained from carbamate 19-1 (2.1 g, 4.42 mmol) using the procedure described for 18-2. It was used in the next step without further purification.
Fmoc-N-Me-D-Tyr(TIPS)-OH (9):

Fmoc tyrosine analog 9 was synthesized by the procedure described for compound 8, from the salt 19-2 (4.42 mmol, theoretical amount) to give 1.8 g of the product as colorless amorphous solid (71% yield).

**TLC:** $R_f = 0.55$ (CH$_2$Cl$_2$/MeOH = 9:1).

**$[\alpha]_D^{20}$** = +41.7 (c = 1, CHCl$_3$).

**IR (ATR):** $\tilde{\nu} = 2200$ (w), 2013 (w), 1813 (w), 1783 (m), 1735 (m), 1676 (w), 1579 (w), 1477 (w), 1450 (w), 1432 (w), 1324 (w), 1230 (m), 1200 (m), 1049 (w), 1035 (w), 988 (w), 950 (m), 873 (w), 787 (m), 756 (m), 731 (m), 706 (w), 643 (m), 621 (m) cm$^{-1}$.

**MP** = 56 °C.

**$^1$H NMR** (400 MHz, DMSO-$d_6$, 323 K): $\delta = 12.81$ (s, 1H), 7.86 (d, $J = 7.5$ Hz, 2H), 7.64 – 7.48 (m, 2H), 7.35 (dt, $J = 37.0$, 7.3 Hz, 4H), 7.18 – 6.86 (m, 3H), 6.74 (dd, $J = 27.4$, 8.1 Hz, 3H), 4.98 (d, $J = 6.6$ Hz, 1H), 4.69 (d, $J = 10.7$ Hz, 1H), 4.40 – 3.97 (m, 3H), 3.35 – 2.82 (m, 4H), 2.71 (s, 3H), 1.26 – 1.11 (m, 3H), 1.06 – 0.96 (m, 18H) ppm.

**$^{13}$C{$^1$H} NMR** (101 MHz, DMSO-$d_6$, 323 K): $\delta = 171.6$, 169.9, 153.7, 143.6, 140.6, 130.3, 129.7, 127.4, 126.8, 124.7, 124.7, 119.8, 119.3, 119.1, 66.6, 60.7, 60.3, 46.4, 39.5, 33.0, 32.1, 31., 17.4, 11.8 ppm.

**HRMS (ESI–TOF) m/Z:** [M + H]$^+$, calculated for C$_{34}$H$_{44}$NO$_5$Si$^+$ 574.2983; found 574.2982.

### 3.4.3.1. Synthesis of peptide acids

L-Pea-L-Ala-D-N-Me-Tyr(3′-I, TIPS)-L-β-Tyr(TIPS)-OH (21):

Peptide acid 21 was synthesized according to **General procedure geodiamolides 1-4**, from Fmoc-L-β-Tyr-OH 7 (130 mg, 0.23 mmol, loaded on the 2-Cl-Trt-chloride resin). FCC (CH$_2$Cl$_2$/MeOH 97:3 +
0.1% HCOOH) provided 175 mg of the acylated tripeptide acid 21 as an amorphous colorless solid (77%, overall yield).

**TLC:** $R_f = 0.45$ (CH$_2$Cl$_2$/MeOH = 9:1).

$[\alpha]_D^{22} = +9.0$ (c = 2, CHCl$_3$).

**IR (ATR):** $\tilde{\nu} = 3035$ (w), 2942 (w), 2764 (w), 2638 (w), 2610 (w), 2576 (w), 2407 (w), 2339 (w), 2279 (w), 2159 (w), 2088 (w), 1719 (w), 1510 (m), 1411 (w), 1379 (w), 1264 (m), 1172 (w), 1096 (w), 997 (w), 914 (m), 882 (m), 836 (w), 735 (w), 683 (m) cm$^{-1}$.

**MP:** 97 °C.

**$^1$H NMR** (300 MHz, chloroform-$d$, 298 K): $\delta = 7.60$ (d, $J = 2.1$ Hz, 1H), 7.19 (t, $J = 13.7$ Hz, 2H), 7.05 (dt, $J = 20.9$, 9.1 Hz, 1H), 6.96 – 6.82 (m, 4H), 6.78 (d, $J = 8.3$ Hz, 1H), 6.32 (d, $J = 7.0$ Hz, 1H), 5.54 (dd, $J = 11.1$, 5.2 Hz, 1H), 5.42 – 5.40 (m, 1H), 4.79 (dd, $J = 18.0$, 10.9 Hz, 3H), 3.25 (dd, $J = 15.7$, 5.4 Hz, 1H), 3.06 – 2.99 (m, 4H), 2.89 (ddd, $J = 23.2$, 14.9, 6.8 Hz, 3H), 2.52 (ddd, $J = 20.7$, 14.4, 6.8 Hz, 2H), 2.13 (dd, $J = 14.3$, 7.7 Hz, 1H), 1.77 (d, $J = 6.5$ Hz, 3H), 1.46 – 1.25 (m, 8H), 1.24 – 1.12 (m, 43H), 1.08 (d, $J = 7.0$ Hz, 4H) ppm.

**$^{13}$C{$^1$H} NMR** (125 MHz, chloroform-$d$, 298 K): $\delta = 177.7$, 174.7, 172.4, 168.6, 155.5, 154.2, 142.6, 142.5, 139.3, 132.9, 131.0, 129.6, 127.3, 119.9, 119.7, 117.7, 112.8, 112.7, 90.1, 56.6, 49.5, 45.8, 45.8, 41.8, 41.6, 41.6, 40.6, 38.8, 38.8, 38.8, 37.9, 31.6, 30.5, 29.7, 22.2, 22.2, 18.1, 17.9, 17.1, 17.1, 16.9, 16.8, 13.1, 12.7 ppm.

**HRMS** (ESI−TOF) $m/z$: [M + H]$^+$, calculated for C$_{47}$H$_{77}$IN$_3$O$_7$Si$_2$: 978.4339; found 978.4338.

**L-Pea-L-Ala-D-N-Me-Tyr(TIPS)-L-β-Tyr(TIPS)-OH (22):**

Peptide acid 22 was synthesized according to **General procedure geodiamolides 1-4**, from Fmoc-L-β-Tyr-OH 7 (187 mg, 0.33 mmol, loaded on the 2-Cl-Trt-chloride resin). FCC (CH$_2$Cl$_2$/MeOH 97:3 + 0.1% HCOOH) provided 240 mg of the acylated tripeptide acid 22 as an amorphous colorless solid (84%, overall yield).

**TLC:** $R_f = 0.40$ (CH$_2$Cl$_2$/MeOH = 9:1).

$[\alpha]_D^{22} = +23.7$ (c = 2, CHCl$_3$).
IR (ATR): $\tilde{\nu} = 3309$ (w), 3171 (w), 3153 (w), 3031 (w), 2944 (m), 2867 (m), 2362 (w), 1736 (m), 1646 (m), 1609 (m), 1509 (m), 1459 (m), 1417 (m), 1374 (m), 1262 (m), 1172 (m), 1092 (w), 996 (w), 882 (m), 835 (m), 732 (m), 682 (m) cm$^{-1}$.

MP: 88 °C.

$^1$H NMR (500 MHz, chloroform-$d$, 297 K): $\delta = 7.23 - 7.02$ (m, 2H), 7.01 - 6.94 (m, 2H), 6.94 - 6.83 (m, 1H), 6.82 - 6.71 (m, 4H), 6.46 (d, $J = 6.8$ Hz, 1H), 5.56 - 5.13 (m, 1H), 4.80 - 4.72 (m, 1H), 4.72 - 4.59 (m, 1H), 3.28 - 3.16 (m, 1H), 3.08 - 2.90 (m, 3H), 2.88 - 2.73 (m, 2H), 2.48 - 2.31 (m, 1H), 2.03 (dd, $J = 14.3, 8.0$ Hz, 1H), 1.69 - 1.63 (m, 2H), 1.29 - 1.16 (m, 6H), 1.14 - 1.01 (m, 36H), 0.98 - 0.87 (m, 2H) ppm.

$^{13}$C{$^1$H} NMR (125 MHz, chloroform-$d$, 297 K): $\delta = 177.6, 174.4, 174.3, 172.6, 168.9, 167.8, 155.6, 155.4, 155.1, 154.7, 142.6, 133.0, 132.1, 129.7, 129.6, 129.1, 128.1, 127.4, 127.3, 120.2, 120.1, 119.9, 119.9, 119.7, 112.6, 59.3, 56.9, 49.5, 49.2, 45.7, 41.6, 40.6, 39.7, 38.8, 32.8, 32.3, 30.5, 22.2, 18.0, 17.9, 17.9, 17.8, 17.1, 16.9, 12.9, 12.6, 12.6, 12.4 ppm.

HRMS (ESI−TOF) m/Z: [M + H]$^+$, calculated for C$_{47}$H$_{77}$N$_3$O$_7$Si$_2$ $^+$ 852.5373; found 852.5384.

3.4.4. Synthesis of esters

(2S,4R)-2-[L-Pea-L-Ala-D-N-Me-Tyr(3'-I, TIPS)-L-β-Tyr(TIPS)-O-]-4-Me-hex-5-en (24):

Ester 24 was synthesized according to General procedure geodiamolides 5, from 40 mg of tripeptide acid 21 (0.04 mmol, 1 equiv.) and alcohol 11 (6 mg, 0.052 mmol, 1.3 equiv.). FCC (PE/EtOAc 8:2) provided 32 mg of the ester 24, as an amorphous colorless solid (74%, overall yield).

TLC: $R_f = 0.25$ (PE/EtOAc = 8:2).

$[\alpha]_{D}^{22} = +0.42$ (c = 1, CHCl$_3$).

IR (ATR): $\tilde{\nu} = 2893$ (w), 1732 (m), 1641 (m), 1610 (m), 1533 (m), 1461 (m), 1412 (m), 1376 (m), 1263 (m), 1172 (m), 1102 (m), 1060 (m), 1037 (m), 1014 (m), 996 (m), 970 (w), 913 (m), 883 (m), 837 (m), 815 (m), 740 (m), 682 (m), 661 (m) cm$^{-1}$.
$^1$H NMR (400 MHz, chloroform-$d$, 297 K): $\delta = 7.54$ (d, $J = 2.0$ Hz, 1H), 7.22 – 7.09 (m, 3H), 7.07 – 6.95 (m, 1H), 6.90 – 6.66 (m, 3H), 6.33 – 6.10 (m, 1H), 5.76 – 5.52 (m, 1H), 5.51 – 5.42 (m, 1H), 5.41 – 5.31 (m, 1H), 5.05 – 4.82 (m, 3H), 4.76 (d, $J = 28.0$ Hz, 2H), 4.58 (td, $J = 6.6$, 3.4 Hz, 1H), 3.41 – 3.27 (m, 1H), 2.94 (d, $J = 4.8$ Hz, 3H), 2.92 – 2.69 (m, 3H), 2.50 – 2.30 (m, 2H), 2.14 – 1.95 (m, 2H), 1.71 (d, $J = 7.7$ Hz, 4H), 1.67 – 1.50 (m, 1H), 1.39 – 1.19 (m, 9H), 1.19 – 1.06 (m, 39H), 1.01 (t, $J = 8.0$ Hz, 3H), 0.99 – 0.89 (m, 4H) ppm.

$^{13}$C($^1$H) NMR (101 MHz, chloroform-$d$, 297 K): $\delta = 176.4$, 174.2, 170.5, 168.6, 155.5, 154.3, 143.9, 143.4, 142.9, 139.5, 133.1, 131.4, 129.6, 127.7, 127.7, 119.9, 117.9, 113.6, 112.9, 112.6, 90.1, 77.2, 69.8, 69.6, 57.3, 49.7, 45.8, 42.9, 42.5, 41.9, 41.1, 32.2, 31.1, 22.4, 20.5, 18.2, 18.1, 17.3, 17.1, 13.2, 12.8 cm$^{-1}$.

HRMS (ESI−TOF) m/Z: [M + H]$^+$, calculated for C$_{54}$H$_{89}$IN$_3$O$_7$SI$_2$ $^{+}$ 1074.5278; found 1074.5280.

(2$S$)-2-[L-Pea-L-Ala-D-N-Me-Tyr(3′-I, TIPS)-L-β-Tyr(TIPS)-O-]-hex-5-en (25):

Ester 25 was synthesized according to General Procedure geodiamolides 5. Starting with 35 mg of 21 (0.035 mmol, 1 equiv.) and alcohol 12 (5 mg, 0.046 mmol, 1.3 equiv.). FCC (PE/EtOAc 7:3) provided 31 mg of the ester 25 as the amorphous colorless solid (82%, overall yield).

TLC: $R_f = 0.25$ (PE/EtOAc = 7:3).

[$\alpha$]$_D^{22} = -0.12$ (c = 1, CHCl$_3$).

IR (ATR): $\tilde{\nu} = 2892$ (w), 2866 (w), 1733 (w), 1639 (m), 1609 (w), 1533 (w), 1510 (m), 1487 (m), 1460 (m), 1411 (w), 1209 (w), 1171 (m), 1125 (w), 1102 (m), 1071 (w), 1060 (w), 1037 (m), 1014 (m), 995 (m), 913 (m), 882 (m), 837 (m), 814 (w), 741 (w), 682 (m), 660 (m) cm$^{-1}$.

$^1$H NMR (300 MHz, chloroform-$d$, 298 K): $\delta = 7.53$ (d, $J = 2.0$ Hz, 1H), 7.15 (d, $J = 8.5$ Hz, 3H), 6.99 (dd, $J = 8.3$, 2.1 Hz, 1H), 6.79 (d, $J = 8.5$ Hz, 2H), 6.71 (d, $J = 8.3$ Hz, 1H), 6.20 (d, $J = 5.8$ Hz, 1H), 5.73 (d, $J = 6.6$ Hz, 1H), 5.54 – 5.27 (m, 2H), 5.09 – 4.90 (m, 2H), 4.83 (dt, $J = 9.2$, 4.6 Hz, 1H), 4.78 (s, 1H), 4.72 (s, 1H), 3.85 (d, $J = 1.7$ Hz, 1H), 3.31 (d, $J = 5.4$ Hz, 1H), 3.00 – 2.67 (m, 6H), 2.39 (t, $J = 9.8$ Hz, 2H), 2.15 – 1.86 (m, 3H), 1.68 (d, $J = 8.7$ Hz, 3H), 1.60 (d, $J = 8.1$ Hz, 2H), 1.27 (d, $J = 6.7$ Hz, 8H), 1.16 – 1.05 (m, 38H), 1.01 (d, $J = 6.8$ Hz, 3H) ppm.

$^{13}$C($^1$H) NMR (75 MHz, chloroform-$d$, 298 K): $\delta = 176.4$, 174.2, 170.6, 168.6, 155.6, 154.3, 142.9, 139.5, 137.8, 133.1, 131.4, 129.6, 127.7, 119.9, 117.9, 115.0, 112.6, 90.1, 77.2, 71.2, 70.9, 60.2, 57.3,
49.7, 45.8, 41.9, 41.0, 38.8, 35.0, 32.5, 32.1, 31.1, 29.6, 22.4, 19.9, 18.2, 18.1, 17.3, 17.1, 13.2, 12.8 ppm.

HRMS (ESI–TOF) m/Z: [M + Na]+, calculated for C_{53}H_{86}N_{3}NaO_{7}Si_{2}+ 1082.4941; found 1082.4931.

(2S,4R)-2-[L-Pea-L-Ala-D-N-Me-Tyr(TIPS)-L-β-Tyr(TIPS)-O-]-4-Me-hex-5-en (26):

Ester 26 was synthesized according to General procedure geodiamolides 5, from 80 mg of 22 (0.094 mmol, 1 equiv.) and alcohol 11 (14 mg, 0.12 mmol, 1.3 equiv.). FCC (PE/EtOAc 8:2) provided 52 mg of the ester 26 as an amorphous colorless solid (58% overall yield).

TLC: \( R_f = 0.20 \) (PE/EtOAc = 8:2).

\([\alpha]_D^{22} = +7.8 \) (c = 0.4, CHCl₃).

IR (ATR): \( \tilde{\nu} = 3031 \) (w), 2943 (m), 2867 (m), 2572 (w), 2322 (w), 2257 (w), 2212 (w), 2160 (w), 1736 (m), 1639 (m), 1509 (m), 1458 (m), 1374 (m), 1263 (m), 1172 (m), 1104 (w), 995 (m), 912 (w), 836 (m), 739 (w), 681 (m) cm⁻¹.

¹H NMR (400 MHz, 1,4-dioxane-d₈, 297 K): \( \delta = 7.24 - 7.10 \) (m, 3H), 7.04 (t, \( J = 13.4 \) Hz, 3H), 6.94 – 6.66 (m, 4H), 5.79 – 5.53 (m, 1H), 5.50 – 5.36 (m, 1H), 5.31 (dd, \( J = 14.6, 8.3 \) Hz, 1H), 5.06 – 4.58 (m, 5H), 4.46 (p, \( J = 6.6 \) Hz, 1H), 3.36 – 3.20 (m, 1H), 2.93 – 2.88 (m, 3H), 2.88 – 2.65 (m, 3H), 2.44 (d, \( J = 14.2 \) Hz, 1H), 2.33 (tt, \( J = 15.6, 8.2 \) Hz, 2H), 2.18 – 2.03 (m, 1H), 2.03 – 1.89 (m, 1H), 1.68 – 1.63 (m, 3H), 1.63 – 1.47 (m, 1H), 1.35 – 1.18 (m, 9H), 1.08 (dd, \( J = 7.2, 2.6 \) Hz, 38H), 1.00 (dd, \( J = 13.1, 5.0 \) Hz, 4H), 0.94 – 0.84 (m, 6H) ppm.

¹³C{¹H} NMR (101 MHz, 1,4-dioxane-d₈, 297 K): \( \delta = 176.9, 174.4, 170.7, 170.6, 169.2, 155.8, 155.1, 145.1, 144.5, 144.2, 137.3, 135.4, 135.4, 131.7, 131.3, 130.6, 128.7, 128.6, 122.7, 120.2, 120.1, 113.9, 113.0, 112.5, 69.7, 69.4, 66.7, 57.7, 50.0, 46.2, 43.6, 43.2, 42.3, 41.6, 40.5, 38.9, 35.2, 34.9, 33.5, 31.0, 31.0, 30.4, 22.7, 20.9, 20.7, 20.4, 20.2, 18.4, 17.7, 16.8, 13.7, 13.4, 13.1 ppm.

HRMS (ESI–TOF) m/Z: [M + Na]+, calculated for C_{53}H_{86}N_{3}NaO_{7}Si_{2}+ 970.6131; found 970.6127.
(2S)-2-[L-Pea-L-Ala-D-N-Me-Tyr(TIPS)-L-β-Tyr(TIPS)-O-]-hex-5-en (27):

Ester 27 was synthesized according to General procedure geodiamolides 5. Starting with 40 mg of 22 (0.047 mmol, 1 equiv.) and alcohol 12 (6 mg, 0.061 mmol, 1.3 equiv.). FCC (PE/EtOAc 7:3) provided 33 mg of the ester 27 as an amorphous colorless solid (77%, overall yield).

**TLC:** \( R_f = 0.15 \) (PE/EtOAc = 8:2).

\[ [\alpha]_D^{22} = +12.1 \ \text{(c = 0.1, CHCl}_3) \].

**IR (ATR):** \( \tilde{\nu} = 2927 \) (m), 2861 (w), 2851 (m), 1624 (s), 1572 (s), 1536 (m), 1462 (w), 1450 (w), 1443 (w), 1412 (w), 1375 (w), 1266 (s), 1243 (s), 1171 (m), 1086 (m), 1046 (w), 1012 (w), 996 (w), 968 (w), 913 (m), 887 (m), 839 (w), 819 (w), 732 (s), 642 (s) cm\(^{-1}\).

**\(^1\)H NMR** (400 MHz, 1,4-dioxane-\(d_8\), 297 K): \( \delta = 7.16 \) (d, \( J = 8.5 \) Hz, 3H), 7.00 (s, 3H), 6.76 (d, \( J = 20.7 \) Hz, 4H), 5.75 (d, \( J = 6.7 \) Hz, 1H), 5.43 (dd, \( J = 11.2, 5.3 \) Hz, 1H), 5.31 (d, \( J = 6.4 \) Hz, 1H), 5.04 – 4.87 (m, 2H), 4.80 (s, 1H), 4.70 (d, \( J = 22.1 \) Hz, 2H), 4.52 – 4.40 (m, 1H), 3.27 (dd, \( J = 15.0, 5.2 \) Hz, 1H), 3.01 – 2.60 (m, 6H), 2.47 – 2.23 (m, 4H), 2.16 – 1.72 (m, 4H), 1.66 (d, \( J = 7.6 \) Hz, 3H), 1.52 (ddt, \( J = 19.8, 14.1, 6.2 \) Hz, 2H), 1.36 – 1.16 (m, 8H), 1.12 – 1.06 (m, 36H), 1.01 (d, \( J = 6.7 \) Hz, 3H), 0.94 – 0.79 (m, 5H) ppm.

**\(^{13}\)C\(^{1}\)H NMR** (101 MHz, 1,4-dioxane-\(d_8\), 297 K): \( \delta = 176.9, 174.4, 170.8, 169.2, 155.8, 155.1, 144.2, 139.1, 137.5, 135.4, 131.7, 130.6, 128.6, 120.3, 120.1, 115.2, 112.5, 70.8, 67.1, 66.8, 66.7, 57.7, 50.0, 46.2, 42.3, 41.6, 38.9, 35.7, 31.0, 30.3, 22.7, 20.1, 18.4, 17.7, 16.8, 13.4 ppm.

**HRMS** (ESI–TOF) \( m/Z \): \([M + H]^+\), calculated for \( \text{C}_{53}\text{H}_{88}\text{N}_3\text{O}_7\text{Si}_2^+ \) 934.6155; found 934.6147.
3.4.5. Metathesis products

cyclo-[(2S,4E/Z,6R,8S)Htn-L-Ala-D-N-Me-Tyr(3'-I, TIPS)-L-β-Tyr(TIPS)] (29)/(30):

Cyclodepsipeptides mixture $E$-29/Z-30 was obtained according to General procedure geodiamolides 6-2, starting with diene 24 (31 mg, 0.03 mmol). Products were isolated as a mixture of geometrical isomers by using FCC (PE/EtOAc 8:2), giving 16 mg of cyclodepsipeptide mixture as a brown solid (combined yield 53%).

**TLC:** $RF = 0.25$ (PE/EtOAc = 7:3) and for (Z) $0.30$ (PE/EtOAc = 7:3).

cyclo-[(2S,4E,8S)Hdn-L-Ala-D-N-Me-Tyr(3'-I, TIPS)-L-β-Tyr(TIPS)] (31):

Cyclodepsipeptide 31 was synthesized according to General procedure geodiamolides 6-1, starting with diene 25 (30 mg, 0.028 mmol). FCC (PE/EtOAc 8:2) gave 22 mg of the cyclodepsipeptide 31, as a colorless solid (74% yield).

**TLC:** $RF = 0.20$ (PE/EtOAc = 7:3).

$[\alpha]_D^{22} = +40.8$ (c = 0.25, CHCl$_3$).

**IR (ATR):** $\tilde{\nu} = 2928$ (w), 2866 (w), 2731 (w), 2278 (w), 2218 (w), 1988 (w), 1970 (w), 1892 (w), 1861 (w), 1638 (w), 1509 (m), 1410 (w), 1370 (w), 1131 (w), 1097 (w), 1057 (w), 1037 (m), 997 (m), 916 (m), 881 (m), 835 (w), 817 (w), 730 (w), 683 (m), 661 (m) cm$^{-1}$.

**$^1$H NMR** (300 MHz, chloroform-$d$, 298 K): $\delta = 7.57$ (d, $J = 2.0$ Hz, 1H), 7.06 (ddd, $J = 13.8$, 10.3, 5.2 Hz, 4H), 6.83 (t, $J = 5.8$ Hz, 2H), 6.76 – 6.57 (m, 2H), 5.58 – 5.35 (m, 1H), 5.29 – 5.14 (m, 1H), 5.05 (ddd, $J = 17.8$, 11.3 Hz, 1H), 4.90 – 4.63 (m, 2H), 3.28 – 2.72 (m, 6H), 2.58 (dt, $J = 22.2$, 7.3 Hz, 1H), 2.46 (d, $J = 10.1$ Hz, 2H), 1.88 (dd, $J = 23.7$, 11.1 Hz, 3H), 1.52 (d, $J = 8.4$ Hz, 3H), 1.40 – 1.20 (m, 10H), 1.14 (dt, $J = 14.0$, 5.5 Hz, 36H), 0.99 (t, $J = 6.6$ Hz, 3H), 0.91 – 0.80 (m, 3H) ppm.
$^{13}$C{H} NMR (75 MHz, chloroform-$d$, 298 K): $\delta = 175.4, 174.4, 170.6, 168.8, 155.6, 139.5, 134.2, 132.9, 131.0, 129.6, 127.2, 124.5, 120.1, 117.9, 90.4, 77.2, 69.9, 49.1, 46.2, 39.9, 35.7, 30.4, 20.4, 20.0, 18.5, 18.2, 18.1, 16.4, 13.2, 12.8 ppm.

HRMS (ESI–TOF) $m/z$: [M + H]$^+$, calculated for C$_{51}$H$_{83}$IN$_3$O$_7$Si$_2$ 1032.4809; found 1032.4811.

cyclo-[(2S,4E,Z,6R,8S)Htn-L-Ala-D-N-Me-Tyr(TIPS)-L-β-Tyr(TIPS)] (33):

Cyclodepsipeptide mixture 32/33 were synthesized according to General procedure geodiamolides 6-2, from diene 26 (39 mg, 0.04 mmol). The mixture of geometrical isomers (E-32/Z-33) using FCC (PE/EtOAc 7:3) to give 18 mg of slightly brown solid (49%, combined yield).

TLC: $R_f = 0.40$ (E-32), 0.50 (Z-33) (PE/EtOAc 6:4).

cyclo-[(2S,4E,8S)Hdn-L-Ala-D-N-Me-Tyr(TIPS)-L-β-Tyr(TIPS)] (34):

Cyclodepsipeptide 34 was synthesized according to General procedure geodiamolides 6-1, from diene 27 (16 mg, 0.017 mmol). The product was isolated using FCC (PE/EtOAc 7:3) to give 13 mg of amorphous colorless solid (82% yield).

TLC: $R_f = 0.45$ (PE/EtOAc = 1:1).

$[\alpha]_D^{22} = +22.7$ (c = 0.25, CHCl$_3$).

IR (ATR): $\tilde{\nu} = 3406$ (w), 3327 (w), 2944 (w), 2867 (w), 2728 (w), 2637 (w), 2592 (w), 2517 (w), 2361 (w), 2323 (w), 2240 (w), 1745 (w), 1680 (m), 1637 (w), 1510 (w), 1460 (m), 1366 (w), 1265 (w), 1179 (w), 1130 (w), 1081 (w), 915 (w), 837 (w), 754 (w), 686 (w) cm$^{-1}$.

$^1$H NMR (400 MHz, 1,4-dioxane-$d_4$, 323 K): $\delta = 7.16 – 6.94$ (m, 4H), 6.76 (ddd, $J = 14.1, 7.1, 4.9$ Hz, 4H), 5.42 (dd, $J = 10.2, 6.2$ Hz, 1H), 5.25 (d, $J = 3.5$ Hz, 1H), 5.02 (s, 1H), 4.85 – 4.62 (m, 2H), 2.92
(s, 6H), 2.66 – 2.51 (m, 1H), 2.48 – 2.36 (m, 1H), 2.32 (s, 3H), 1.83 (t, J = 11.7 Hz, 2H), 1.51 (s, 3H), 1.41 – 1.18 (m, 8H), 1.09 (t, J = 6.9 Hz, 36H), 0.88 (d, J = 6.7 Hz, 5H) ppm.

$^{13}$C{$^1$H} NMR (101 MHz, 1,4-dioxane-d$_8$, 323 K): δ = 175.0, 174.1, 171.0, 170.8, 169.4, 155.9, 155.4, 135.1, 134.9, 130.9, 130.6, 128.1, 128.1, 125.0, 124.2, 120.3, 120.3, 70.6, 66.7, 57.3, 57.0, 49.4, 46.3, 44.1, 40.4, 40.1, 36.4, 34.4, 33.4, 30.4, 23.9, 20.2, 19.9, 19.7, 18.8, 18.3, 17.2, 16.7, 16.5, 13.4 ppm.

HRMS (ESI–TOF) m/Z: [M + H]$^+$, calculated for C$_{51}$H$_{84}$N$_3$O$_7$Si$_2$ $^+$ 906.5842; found 906.5853.

3.4.6. Natural products and analogs

Geodiamolide H (1) and (Z)-Geodiamolide H (35):

Simultaneous silyl group deprotection was done according to General procedure geodiamolides 7 from the 16 mg mixture of cyclodepsipeptides E-29 and Z-30. 4.7 mg (42% yield) of natural products Geodiamolide H (1) and 3.9 mg (36% yield) of unnatural geometrical isomer Z-35 was obtained after prep. HPLC, both as colorless solids.

cyclo-[(2S,4E,6R,8S)Htn-L-Ala-D-N-Me-Tyr(3'-I)-L-β-Tyr] – Geodiamolide H (1):

\[
\text{TLC: } R_f = 0.18 \text{ (PE/EtOAc = 3:7).}
\]

$[\alpha]_D^{24} = +22.6$ (c = 0.1, CHCl$_3$; MeOH = 1:1), literature value: $[\alpha]_D^{24} +19.1$ (c = 0.17, CHCl$_3$).

IR (ATR): $\tilde{\nu} = 3014$ (w), 2970 (w), 2922 (w), 2717 (w), 2607 (w), 2375 (w), 2311 (w), 2161 (w), 2106 (w), 1944 (w), 1868 (w), 1736 (m), 1654 (w), 1508 (m), 1457 (w), 1419 (w), 1364 (m), 1216 (m), 1132 (w), 1097 (w), 1025 (w), 901 (w), 816 (w), 669 (w), 615 (w) cm$^{-1}$.

Melting point: 137 ℃.

$^1$H NMR (600 MHz, DMSO-d$_6$, 297 K): δ = 10.08 (s, 1H, OH-1), 9.31 (s, 1H, OH-2), 8.24 (d, J = 8.8 Hz, 1H, NH-1), 7.72 (d, J = 7.7 Hz, 1H, NH-2), 7.49 (d, J = 2.0 Hz, 1H, 24C-1H), 7.06 (d, J = 8.5 Hz, 2H, 30C-1H, 34C-1H), 7.00 (dd, J = 8.3, 2.0 Hz, 1H, 28C-1H), 6.72 (d, J = 8.2 Hz, 1H, 27C-1H), 6.68 (d, J = 8.5 Hz, 2H, 31C-1H, 33C-1H), 5.30 (dd, J = 10.7, 5.5 Hz, 1H, 5C-1H), 5.13 (d, J = 4.0 Hz, 1H, 3C-1H), 4.82 (d, J = 8.5 Hz, 1H, 12C-1H), 4.61 (dd, J = 14.1, 7.3 Hz, 2H, 15C-1H, 7C-1H), 2.94 (s, 3H, 16CH3), 2.79 (dd, J = 21.3, 7.9 Hz, 2H, 22C-2H), 2.70 – 2.52 (m, 4H, 9C-1H, 2C-
2H), 2.29 (m, 2H, 13C-1H), 2.14 (dd, J = 15.2, 10.5 Hz, 1H, 10C-1H), 1.82 – 1.73 (m, 1H, 10C-1H), 1.68 – 1.54 (m, 1H, 14C-1H), 1.52 (s, 3H, 9CH3), 1.27 (dd, J = 22.7, 15.6 Hz, 1H, 14C-1H), 1.06 (d, J = 6.2 Hz, 3H, 18CH3), 0.96 (d, J = 6.8 Hz, 3H, 21CH3), 0.84 (d, J = 6.6 Hz, 3H, 20CH3), 0.81 (d, J = 6.8 Hz, 3H, 17CH3) ppm.

13C{1H} NMR (125 MHz, DMSO-d6, 297 K): δ = 174.0, 173.0, 169.9, 169.1, 166.5, 158.6, 156.4, 156.3, 155.4, 138.3, 132.8, 132.2, 131.5, 130.4, 129.9, 129.2, 127.0, 125.8, 115.1, 114.5, 113.6, 74.8, 70.4, 70.1, 63.8, 62.9, 55.0, 48.5, 44.1, 43.6, 42.9, 41.6, 38.2, 37.2, 33.3, 30.6, 28.7, 22.7, 22.1, 21.2, 20.1, 19.6, 17.6, 16.5, 15.6, 13.7 ppm.

HRMS (ESI–TOF) m/Z: [M + H]+, calculated for C34H45IN3O7+ 734.2297; found 734.2295.

cyclo-[(2S,4Z,6R,8S)Htn-L-Ala-D-N-Me-Tyr(3'-I)-L-β-Tyr] – (Z)-Geodiamolide H (35):

TLC: Rf = 0.25 (PE/EtOAc = 3:7).

[α]D24 = +1.4 (c = 0.1, CHCl3/MeOH = 1:1).

IR (ATR): v = 3031 (w), 2970 (w), 2653 (w), 2421 (w), 2373 (w), 2347 (w), 2321 (w), 2259 (w), 2220 (w), 1986 (w), 1868 (w), 1734 (m), 1654 (m), 1541 (m), 1508 (m), 1457 (m), 1419 (m), 1374 (m), 1272 (w), 1025 (w), 830 (w), 800 (w), 763 (w), 720 (w), 669 (m) cm⁻¹.

MP: 132 °C.

1H NMR (600 MHz, DMSO-d6, 297 K): δ = 10.06 (s, 1H), 9.30 (s, 1H), 8.27 (d, J = 8.8 Hz, 1H), 7.98 (d, J = 7.4 Hz, 1H), 7.48 (d, J = 1.9 Hz, 1H), 7.10 – 6.95 (m, 4H), 6.76 – 6.62 (m, 4H), 5.24 (dd, J = 10.9, 5.1 Hz, 1H), 5.15 (d, J = 6.3 Hz, 1H), 5.02 (d, J = 9.1 Hz, 1H), 4.59 – 4.49 (m, 1H), 4.46 – 4.35 (m, 1H), 2.97 (s, 3H), 2.82 (d, J = 9.2 Hz, 4H), 2.63 – 2.54 (m, 1H), 2.42 – 2.26 (m, 3H), 1.88 (d, J = 7.1 Hz, 1H), 1.66 (s, 3H), 1.56 – 1.46 (m, 2H), 1.30 (dd, J = 33.3, 22.1 Hz, 3H), 1.13 – 1.04 (m, 1H), 1.01 (d, J = 6.2 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H), 0.83 (dd, J = 9.8, 6.9 Hz, 6H) ppm.

13C{1H} NMR (125 MHz, DMSO-d6, 297 K): δ = 174.8, 173.3, 170.4, 169.4, 161.2, 156.8, 155.5, 139.1, 133.4, 132.7, 131.2, 130.6, 130.5, 127.7, 115.4, 115.4, 114.9, 84.6, 71.8, 60.6, 58.9, 56.2, 54.2, 52.9, 48.6, 45.3, 44.8, 44.3, 41.7, 37.2, 36.3, 33.2, 30.9, 29.5, 23.1, 22.6, 22.4, 20.0, 17.9, 17.7 ppm.

HRMS (ESI–TOF) m/Z: [M + H]+, calculated for C34H45IN3O7+ 734.2297; found 734.2301.
cyclo-[(25,4E,8S)Hdn-L-Ala-D-N-Me-Tyr(3’-I)-L-β-Tyr] (36):

Simultaneous silyl group deprotection was done according to General procedure geodiamolides 7 from 18 mg of compound 31. Purification by using prep. HPLC gave 11 mg of geodiamolide analog 36 (74% yield).

TLC: \( R_f = 0.20 \) (PE/EtOAc = 3:7).

\([\alpha]_D^{24} = +22.4 \) (c = 0.1, CHCl\(_3\):
MeOH = 1:1).

\( \text{IR (ATR): } \tilde{\nu} = 2930.4 \) (w), 2581.3 (w), 2453.5 (w), 2376.8 (w), 2313 (w), 2028.6 (w), 1920 (w), 1869.1 (w), 1718.7 (m), 1635.6 (m), 1508.7 (m), 1416.8 (m), 1373.8 (m), 1216.8 (m), 1096 (m), 1036.2 (m), 954.48 (w), 828.95 (m), 731.79 (w), 668.48 (m) cm\(^{-1}\).

\( ^1H \text{ NMR (400 MHz, DMSO-}d_6, 297 \text{ K): } \delta = 9.26 \) (d, \( J = 59.9 \) Hz, 2H), 8.56 (d, \( J = 8.9 \) Hz, 1H), 7.79 (d, \( J = 8.2 \) Hz, 1H), 7.10 (dd, \( J = 8.7, 2.2 \) Hz, 2H), 6.99 (d, \( J = 8.4 \) Hz, 2H), 6.69 (d, \( J = 8.5 \) Hz, 2H), 6.64 – 6.56 (m, 2H), 5.41 (dd, \( J = 11.6, 4.9 \) Hz, 1H), 5.15 (d, \( J = 8.5 \) Hz, 1H), 4.94 (t, \( J = 6.3 \) Hz, 1H), 4.78 – 4.53 (m, 2H), 2.98 (d, \( J = 4.9 \) Hz, 3H), 2.92 – 2.54 (m, 5H), 2.25 – 2.08 (m, 1H), 1.82 (dd, \( J = 20.4, 13.4 \) Hz, 3H), 1.56 – 1.48 (m, 4H), 1.46 – 1.31 (m, 1H), 1.17 (d, \( J = 6.3 \) Hz, 3H), 0.94 (d, \( J = 6.8 \) Hz, 3H), 0.60 (dd, \( J = 11.6, 4.4 \) Hz, 3H) ppm.

\( ^{13}C\{^1H\} \text{ NMR (101 MHz, DMSO-}d_6, 297 \text{ K): } \delta = 174.5, 173.7, 170.7, 170.0, 170.0, 156.8, 155.5, 138.8, 133.4, 130.5, 130.2, 127.5, 127.4, 123.6, 115.6, 114.8, 84.7, 71.4, 55.5, 55.4, 49.6, 49.1, 44.1, 43.2, 42.4, 37.9, 35.3, 34.1, 31.2, 24.2, 19.9, 19.9, 19.7, 17.9, 17.4 ppm.

HRMS (ESI–TOF) \( m/Z: [M + H]^+, \) calculated for C\(_{33}\)H\(_{43}\)N\(_3\)O\(_7\): 720.2140; found 720.2139.

Des-iodo analogs of Geodiamolide H (37 and 38):

Simultaneous silyl group deprotection was done according to General procedure geodiamolides 7 from the 18 mg mixture of cyclodepsipeptides \( E\)-32/Z-33. Purification by using prep. HPLC gave 4.9 mg (39% yield) of \( E\)-geodiamolide analog 37 and 4.0 mg (32% yield) of \( Z\)-geodiamolide analog 38 as colorless solids.
cyclo-[(2S,4E,6R,8S)Htn-L-Ala-D-N-Me-Tyr-L-β-Tyr] (37):

TLC: \( R_f = 0.20 \) (PE/EtOAc = 2:8).

\([\alpha]_D^{24} = +25.8 \) (c = 0.1, CHCl₃/MeOH = 1:1).

IR (ATR): \( \tilde{\nu} = 2931.6 \) (w), 2629 (w), 2572.3 (w), 2503.9 (w), 2191.5 (w), 2160.4 (w), 2015.7 (w), 1915.8 (m), 1643.3 (m), 1509.2 (m), 1457.4 (m), 1364.7 (m), 957.19 (w), 826.52 (w), 721.07 (w), 669.81 (w), 617.15 (w) cm⁻¹.

\(^1\)H NMR (500 MHz, DMSO-\( d_{6} \), 297 K): \( \delta = 9.37 – 9.25 \) (m, 1H), 9.24 – 9.08 (m, 1H), 8.49 – 7.40 (m, 2H), 7.14 – 7.03 (m, 1H), 7.03 – 6.91 (m, 2H), 6.68 (dd, \( J = 11.3, 4.7 \) Hz, 2H), 6.64 – 6.57 (m, 2H), 5.35 (ddd, \( J = 24.2, 10.8, 5.5 \) Hz, 1H), 5.24 – 5.07 (m, 1H), 4.81 – 4.44 (m, 3H), 3.01 (s, 3H), 2.96 – 2.54 (m, 6H), 2.43 – 2.11 (m, 3H), 1.80 (t, \( J = 18.4 \) Hz, 1H), 1.59 – 1.39 (m, 5H), 1.32 – 1.16 (m, 2H), 1.14 – 1.04 (m, 3H), 1.04 – 0.92 (m, 4H), 0.86 (t, \( J = 16.1 \) Hz, 3H), 0.80 – 0.66 (m, 3H) ppm.

\(^{13}\)C\(^{(1)}\)H NMR (125 MHz, DMSO-\( d_{6} \), 297 K): \( \delta = 173.9, 172.9, 169.9, 169.2, 156.2, 155.7, 132.9, 132.1, 131.5, 129.6, 129.6, 127.2, 127.1, 115.0, 114.9, 114.8, 114.7, 70.0, 69.7, 55.8, 55.1, 48.5, 44.1, 43.5, 42.9, 41.5, 38.2, 33.9, 33.3, 30.5, 28.7, 21.6, 21.1, 20.1, 19.5, 19.4, 17.8, 17.7, 17.6, 17.5, 15.6 ppm.

HRMS (ESI–TOF) \( m/Z \): [M + H]+, calculated for C\(_{34}\)H\(_{46}\)N\(_{3}\)O\(_{7}\) + 608.3330; found 608.3328.

cyclo-[(2S,4Z,6R,8S)Htn-L-Ala-D-N-Me-Tyr-L-β-Tyr] (38):

TLC: \( R_f = 0.25 \) (PE/EtOAc = 2:8).

\([\alpha]_D^{24} = +38.0 \) (c = 0.1, CHCl₃/MeOH = 1:1).
IR (ATR): ᵦ = 3081 (w), 2970 (w), 2927 (w), 2853 (w), 2629 (w), 2368 (w), 2323 (w), 2256 (w), 2196 (w), 2114 (w), 2082 (w), 1943 (w), 1869 (w), 1735 (m), 1652 (m), 1508 (m), 1457 (m), 1374 (m), 1217 (m), 1099 (w), 956 (w), 910 (w), 832 (w), 729 (w), 669 (w), 617 (w) cm⁻¹.

¹H NMR (500 MHz, chloroform-ɗ, 297 K): ropdown δ = 8.10 – 7.40 (m, 3H), 6.98 (dd, ɗ = 23.3, 8.4 Hz, 4H), 6.64 (dd, ɗ = 42.3, 8.5 Hz, 4H), 6.33 (d, ɗ = 4.9 Hz, 1H), 5.53 (dd, ɗ = 9.5, 7.0 Hz, 1H), 5.18 (dd, ɗ = 6.9, 2.9 Hz, 1H), 5.07 (dd, ɗ = 9.4 Hz, 1H), 4.91 – 4.77 (m, 1H), 4.64 – 4.46 (m, 1H), 3.39 (dd, ɗ = 14.8, 6.7 Hz, 1H), 3.01 (d, ɗ = 22.4 Hz, 3H), 2.84 (dd, ɗ = 44.1, 34.1 Hz, 4H), 2.53 (ddd, ɗ = 25.6, 17.4, 10.6 Hz, 2H), 2.37 (s, 1H), 2.33 – 2.19 (m, 1H), 1.67 (d, ɗ = 0.8 Hz, 3H), 1.54 – 1.38 (m, 2H), 1.38 – 1.24 (m, 2H), 1.19 (d, ɗ = 7.0 Hz, 3H), 1.06 (dd, ɗ = 16.9, 6.6 Hz, 5H), 0.86 (d, ɗ = 6.6 Hz, 3H) ppm.

¹³C{¹H} NMR (125 MHz, chloroform-ɗ, 297 K): δ = 176.1, 175.0, 170.3, 168.9, 162.6, 155.5, 154.9, 134.4, 132.6, 130.4, 129.7, 128.3, 127.9, 126.1, 128.3, 115.5, 69.9, 57.6, 49.7, 45.8, 44.3, 44.2, 40.5, 39.3, 36.5, 35.2, 32.4, 31.5, 31.1, 28.9, 24.4, 20.9, 20.7, 17.2, 16.7 ppm.

HRMS (ESI−TOF) m/Z: [M + H]+, calculated for C₃₄H₄₆N₃O₇+ 608.3330; found 608.3327.

cyclo-[(2S,4E,8S)Hdn-L-Ala-D-N-Me-Tyr-L-β-Tyr] (39):

Simultaneous silyl group deprotection was done according to General procedure geodiamolides 7 from the 10 mg of bis-silylated macrocycle 34 and provided 5.8 mg of bis-phenol cyclodepsipeptide 39 after prep. HPLC, as a colorless solid (89% yield).

TLC: Rₛ = 0.15 (PE/EtOAc = 2:8).

[α]D²⁴ = +18.3 (c = 0.1, CHCl₃:MeOH = 1:1).

IR (ATR): ᵦ = 3326 (w), 3081 (w), 2970 (m), 2929 (m), 2725 (w), 2628 (w), 2571 (w), 2494 (w), 2347 (w), 2322 (w), 2254 (w), 1734 (m), 1437 (m), 1372 (m), 1266 (m), 1217 (m), 1172 (m), 1094 (m), 1058 (m), 984 (w), 956 (w), 909 (m), 830 (m), 729 (m), 647 (m), 614 (m) cm⁻¹.

¹H NMR (400 MHz, DMSO-ᵈ₆, 297 K): (rotamers): δ = 10.11 (s, 1H), 9.33 (s, 1H), 8.59 (d, ɗ = 9.9 Hz, 1H), 7.85 (d, ɗ = 8.2 Hz, 1H), 7.52 (d, ɗ = 1.9 Hz, 1H), 7.18 – 6.92 (m, 3H), 6.71 (dd, ɗ = 11.3, 8.4 Hz, 3H), 5.38 (dd, ɗ = 10.5, 6.0 Hz, 1H), 5.13 (d, ɗ = 3.0 Hz, 1H), 4.94 (s, 1H), 4.76 – 4.54 (m, 2H), 2.99 (d, ɗ = 6.2 Hz, 3H), 2.78 (s, 2H), 2.63 (d, ɗ = 34.8 Hz, 3H), 2.34 (dd, ɗ = 3.6, 1.8 Hz, 2H), 2.17 (d, ɗ = 11.6 Hz, 1H), 1.93 – 1.70 (m, 3H), 1.52 (s, 3H), 1.49 (s, 2H), 1.24 (s, 1H), 1.17 (d, ɗ = 11.3 Hz, 3H), 0.94 (d, ɗ = 6.8 Hz, 4H), 0.67 (t, ɗ = 7.3 Hz, 3H), 0.59 (d, ɗ = 6.0 Hz, 1H) ppm.
$^{13}$C{H} NMR (125 MHz, chloroform-$d$ + 5% methanol-$d_4$, 297 K): $\delta = 175.1, 174.4, 174.0, 170.8, 170.4, 168.7, 168.6, 155.9, 155.3, 134.3, 133.8, 131.8, 131.7, 129.7, 127.3, 127.1, 127.1, 124.5, 123.7, 115.4, 115.2, 70.1, 67.9, 57.1, 57.1, 45.8, 45.8, 44.3, 43.6, 43.2, 40.3, 40.1, 40.0, 40.0, 39.9, 35.3, 33.4, 32.9, 32.6, 31.1, 30.4, 30.3, 23.1, 22.7, 19.9, 19.3, 19.1, 18.0, 17.9, 16.8, 16.2, 16.0 ppm.

HRMS (ESI−TOF) m/Z: [M + H]$^+$, calculated for C$_{33}$H$_{44}$N$_3$O$_7$ $^+$ 594.3174; found 594.3175.
4. Crystal Structure Determination

The intensity data were collected on a Nonius KappaCCD diffractometer using graphite-monochromated Mo-Kα radiation. Data were corrected for Lorentz and polarization effects; absorption was taken into account on a semi-empirical basis using multiple-scans.\[26-28\]

The structures were solved by direct methods (SHELXS[29]) and refined by full-matrix least-squares techniques against Fo\(^2\) (SHELXL-97[29]). The hydrogen atoms bonded to the chiral carbon atoms C2 and C20 of 16-3 were located by difference Fourier synthesis and refined isotropically. All other hydrogen atoms were included at calculated positions with fixed thermal parameters. All non-hydrogen atoms were refined anisotropically.\[29\]

MERCURY[30] and XP[31] were used for structure representations.

**Crystal Data for S3c**: C\(_{27}\)H\(_{39}\)NO\(_3\)Si, Mr = 453.68 gmol\(^{-1}\), colourless prism, size 0.122 x 0.062 x 0.060 mm\(^3\), orthorhombic, space group P 2\(_1\) 2\(_1\) 2\(_1\), a = 6.3202(2), b = 14.6292(4), c = 29.4989(6) Å, V = 2727.45(13) Å\(^3\), T= -140 °C, Z = 4, ρ\(_{\text{calc}}\) = 1.105 gcm\(^{-3}\), μ (Mo-Kα) = 1.12 cm\(^{-1}\), multi-scan, transmission: 0.6937, transmax: 0.7456, F(000) = 984, 16337 reflections in h(-8/8), k(-18/18), l(-38/38), measured in the range 1.96° ≤ Θ ≤ 27.45°, completeness Θ\(_{\text{max}}\) = 99.3%, 6139 independent reflections, R\(_{\text{int}}\) = 0.0657, 5228 reflections with F\(_\text{o}\) > 4σ(F\(_\text{o}\)), 309 parameters, 0 restraints, R1\(_{\text{obs}}\) = 0.0502, wR\(_2\)\(_{\text{obs}}\) = 0.0967, R1\(_{\text{all}}\) = 0.0665, wR\(_2\)\(_{\text{all}}\) = 0.1037, GOOF = 1.102, Flack parameter 0.03(14), largest difference peak and hole: 0.248 / -0.229 e Å\(^{-3}\).

**Crystal Data for 16**: C\(_{33}\)H\(_{49}\)NO\(_4\)Si, Mr = 551.82 gmol\(^{-1}\), colourless prism, size 0.120 x 0.110 x 0.090 mm\(^3\), monoclinic, space group P 2\(_1\), a = 6.9814(6), b = 26.816(3), c = 9.1091(9) Å, β = 107.633(6)°, V = 1625.2(3) Å\(^3\), T= -140 °C, Z = 2, ρ\(_{\text{calc}}\) = 1.128 gcm\(^{-3}\), μ (Mo-Kα) = 1.07 cm\(^{-1}\), multi-scan, transmission: 0.6158, transmax: 0.7456, F(000) = 600, 10921 reflections in h(-5/9), k(-34/34), l(-11/10), measured in the range 2.80° ≤ Θ ≤ 27.48°, completeness Θ\(_{\text{max}}\) = 99.3%, 6999 independent reflections, R\(_{\text{int}}\) = 0.0484, 4816 reflections with F\(_\text{o}\) > 4σ(F\(_\text{o}\)), 362 parameters, 1 restraint, R1\(_{\text{obs}}\) = 0.0756, wR\(_2\)\(_{\text{obs}}\) = 0.1530, R1\(_{\text{all}}\) = 0.1212, wR\(_2\)\(_{\text{all}}\) = 0.1764, GOOF = 1.040, Flack parameter 0.1(2), largest difference peak and hole: 0.451 / -0.429 e Å\(^{-3}\).

**Supporting Information Available**: Crystallographic data deposited at the Cambridge Crystallographic Data Centre under CCDC-1938340 for S3c, and CCDC-1938341 for 16 contain the supplementary crystallographic data excluding structure factors; this data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

5. Evaluation of bioactivity
Compounds were assayed for their antiproliferative effects (GI\(_{50}\)) using human umbilical vein endothelial cells HUVEC (ATCC CRL-1730) and human chronic myeloid leukemia cells K-562 (DSM ACC 10) and for their cytotoxic effects (CC\(_{50}\)) using human cervix carcinoma cells HeLa (DSM ACC 57) as previously described.\([32]\). The test compounds were dissolved in DMSO (10 mg/mL or appropriately diluted). Mean values of four independent determinations are given with their standard deviations. Concentrations in supplementary information are given in µg/mL with standard deviations and for clarity and comparisons recalculated to µM concentrations.

| Code | HUVEC GI\(_{50}\) \(|\mu g/ml|\) | K-562 GI\(_{50}\) \(|\mu g/ml|\) | HeLa CC\(_{50}\) \(|\mu g/ml|\) |
|------|--------------------------------------|--------------------------------------|--------------------------------------|
| 1    | jasplakinolide 7x10^-3 (±1.5x10^-3) (µg/ml) | 1.7 (±0.7) (µg/ml) | 5.8x10^-2 (±6.2x10^-3) (µg/ml) |
|      | 0.0098 µM | 2.39 µM | 0.081 µM |
| 2    | geodiamolide H (1) 0.2 (±6x10^-5) (µg/ml) | 6.0 (±2.3) (µg/ml) | 0.3 (±8.2x10^-5) (µg/ml) |
|      | 0.27 µM | 8.17 µM | 0.41 µM |
| 3    | 35 3.5 (±0.6) (µg/ml) | 10.6 (±1.5) (µg/ml) | 4.8 (±0.2) (µg/ml) |
|      | 4.77 µM | 14 µM | 6.54 µM |
| 4    | 36 5.4x10^-3 (±1x10^-3) (µg/ml) | 4.0 (±0.8) (µg/ml) | 0.1 (±7.5x10^-2) (µg/ml) |
|      | 0.0075 µM | 5.56 µM | 0.13 µM |
| 5    | 37 0.6 (±6.4x10^-5) (µg/ml) | > 50 (µg/ml) | 0.6 (±7x10^-2) (µg/ml) |
|      | 0.98 µM | > 82 µM | 0.98 µM |
| 6    | 38 35.0 (±1.7) (µg/ml) | 29.5 (±2.9) (µg/ml) | 48.0 (±2.3) (µg/ml) |
|      | 57 µM | 48 µM | 78 µM |
| 7    | 39 1.0 (±0.2) (µg/ml) | > 50 (µg/ml) | 1.4 (±0.1) (µg/ml) |
|      | 1.68 µM | >84 µM | 2.35 µM |
6. *In vitro* actin polymerization assay

For the *in vitro* actin polymerization assay, fluorescence-based pyrene labeled muscle actin assay from Cytoskeleton, Inc was used, and supplier’s protocols were followed with modifications specific to our needs (Actin Polymerization Biochem Kit™, Cat. # BK003) https://www.cytoskeleton.com/pdf-storage/datasheets/bk003.pdf. The dye to protein (G-actin) ratio in the used kit is 0.6.

G-actin was diluted according to manufacturer’s protocol to a concentration of 5 µM in G-buffer, and secondary stocks of compounds were pipetted to give a final concentration of 20 µM, keeping the final concentration of DMSO at 2%. After shaking for 10 seconds using excitation at 360 nm and detection at 410 nm, fluorescence intensity was measured every 60 seconds over 4 h, at 37 °C. Experiments were done in duplicates and normalized to fluorescence emission of G-actin in a non-polymerizing buffer, followed throughout the experiment. Slopes were calculated in the linear range of plots and compared in relative to jasplakinolide.

**Detailed protocol information:**

Test compounds were dissolved in a non-polymerizing buffer provided by the supplier as “G-Buffer” (5 mM Tris-HCl pH 8.0, 0.2 mM CaCl₂, 0.2 mM ATP) by pipetting DMSO primary stock solutions of test compounds giving secondary stock solutions. Black, 384-well plates were used for measurement (Well plate reader: Tecan, The Infinite 200 PRO).

**G-Buffer preparation:**

1. An aliquot of ATP (# BSA04, Cytoskeleton, Inc.) was kept on ice until it liquified. (Previously stored at -80 °C). After thawing, it was centrifuged for 5 s in a microcentrifuge to collect the liquid at the bottom of the tube.

2. G buffer was prepared by adding 2.0 µL ATP (# BSA04, Cytoskeleton, Inc.) per 1.0 mL of “General Actin Buffer” (# BSA01, Cytoskeleton, Inc.).

**Pyrene-G-actin solution preparation:**

1. 1 mL of cold water was added to 1 mg of pyrene labeled G-actin (# AP05 Cytoskeleton, Inc.), and the suspension was divided into aliquots of 5 µL. Aliquots were frozen in liquid nitrogen and stored at -80 °C.

2. G-actin stock solution was prepared by dissolving an aliquot of pyrene actin (5 µL) in 356 µL of cooled G buffer (concentration of actin is 0.25 mg/mL). The solution was mixed by pipetting up and down and placed on ice for one hour (to depolymerize actin oligomers). If several aliquots of actin were used, they were transferred to a common vial after diluting.

3. G-actin stock solution was centrifuged at 4 °C and 14000 rpm/min for 30 minutes.

4. The supernatant was transferred to a new vial and kept on ice. (**pyrene-G-actin solution**)

```
Sample preparation:

1. 1.0 mM stock solutions of the geodiamolide(s) and jasplakinolide were prepared in DMSO as well (positive control) – **MainStock(s)**.

2. DMSO primary stock is made by pipetting of DMSO to G buffer in ratio 2:15. This can also be used to dilute the concentrations of the PrimaryStocks for concentration series. - **DMSO-PS**.

3. MainStocks of the geodiamolides and jasplakinolide were diluted with G buffer to obtain 118 µM solution (primary stock). (20 µL of the MainStock was dissolved in 150 µL G buffer) – **Test-PS (jasplakinolide-PS or geodiamolide-PS)**.

Carrying out the assay:

All experiments were carried out as duplicate determinations. A blank value and a reference value for jasplakinolide (positive control and for referencing) were recorded.

16 wells were used for the actin polymerization assay:

**Well 1 + 2**: pyrene-G-actin + DMSO-PS ("baseline reference")

**Well 3 + 4**: pyrene-G-actin + **jasplakinolide-PS** ("positive control reference")

**Well 5 + 6**: pyrene-G-actin + **geodiamolide H-PS** ("test")

**Well 7 + 8**: pyrene-G-actin + **geodiamolide-35-PS** ("test")

**Well 9 + 10**: pyrene-G-actin + **geodiamolide-36-PS** ("test")

**Well 11 + 12**: pyrene-G-actin + **geodiamolide-37-PS** ("test")

**Well 13 + 14**: pyrene-G-actin + **geodiamolide-38-PS** ("test")

**Well 15 + 16**: pyrene-G-actin + **geodiamolide-39-PS** ("test")

50 µL pyrene G actin solution was pipetted into each well (1-16). To keep final concentrations and dilutions constant, 10 µL of DMSO-PS was added to wells 1 - 2. To wells 3 - 16, each was added 10 µL of **Test-PS** solutions.

The 384 well plate prepared in this way was placed in the plate reader, and the measurement was initiated.
Well plate reader measurement parameters:

| Parameter                  | Value                      |
|----------------------------|----------------------------|
| Measurement type           | Kinetic                    |
| Fluorescence reading from  | Top-Mode                   |
| Fluorescence wavelengths   | Excitation 350 nm ± 20 nm  |
|                            | Emission 410 nm ± 20 nm    |
| Temperature                | 37 °C                      |
| Gain                       | 50                         |
| Number of Flashes          | 3                          |
| Integration Time           | 40 µs                      |
| Lag Time                   | 0 µs                       |
| Settle Time                | 0 ms                       |
| Mirror                     | 50%                        |
| Shaking                    | 5 s (orbital) Amplitude: 1 mm |

To evaluate the data, the values of the double determinations were averaged. The intensity of emitted enhanced fluorescence of the reference wells was subtracted from the intensity of emitted fluorescence of tested compounds. The slope k was determined from the data obtained in the range of the first 60 minutes. For this purpose, a linear regression according to y = kx + c (c = 0) was carried out (Using Origin(Pro), Version 2019b, OriginLab Corporation, Northampton, MA, USA).
7. Computational investigations

Workflow for docking, binding energy prediction and calculation of ADME properties:

The cryo-EM structure of jasplakinolide-stabilized F-actin (PDB code: 6T23)\textsuperscript{[33]} was downloaded from the PDB (ID: 6T23)\textsuperscript{[34]} reduced to 3 consecutive actin subunits and prepared using Maestro (Schroedinger Inc) and the OPLS3e force field.\textsuperscript{[35]} After removing ions and adenosine monophosphate, the docking grid was generated around the jasplakinolide binding site (25Å box size). Within the grid box all OH/SH groups of amino acid side chains were allowed to rotate. Jasplakinolide, geodiamolide H and analogs were imported from sdf files, prepared using the Ligprep Tool of Maestro using standard parameters and pH7±2 for ionization using Epik.\textsuperscript{[36]} Docking of the prepared ligands to the ligand-depleted F-actin was carried out with Glide (Schroedinger Inc) employing the generated grid box, extra-precision (XP) mode, flexible ligand sampling and macrocycle sampling powered by Prime.\textsuperscript{[37]} The output was limited to one pose only. In addition to the automatically calculated docking score (referred to as “XP docking score” in Table S2) the relative free binding energy of the docked ligands were calculated using the MM-GBSA method implemented in Prime and by extracting the resulting ‘MMGBSA dG Bind’ value (referred to as “dG Binding Docking”). For calculation of ADME properties (e.g. cell permeability), the docked ligands were extracted from the docking pose, minimized (PRCG method, 5000 iterations, OPLS3e force field) and subjected to the QikProp module. The docking poses obtained via Glide XP docking were furthermore subjected to a short 1 ns Molecular Dynamics (MD) Simulation using the Desmond module (D.E. Shaw Research) integrated in Schrödinger's Drug Discovery Suite. During the MD simulation a constant temperature of 300 K and a constant pressure of 1.01325 bar were maintained (NPT mode). For system building, the complex was solvated employing the TIP4P rigid water model and adjusted to a final concentration of 0.15M NaCl. The system was allowed to relax before the MD run using the integrated minimization/relaxation option of Desmond. After the MD the complex was extracted form first (start of MD after minimization) and last frame (equals 1 ns simulation time) and submitted to MM-GBSA runs to obtain relative binding energies referred to as dG Binding MD @ 0 ns and dG Binding MD @ 1 ns, respectively.
8. References

[1] W. R. Chan, W. F. Tinto, P. S. Manchand, L. J. Todaro, J. Org. Chem. 1987, 52, 3091-3093.
[2] J. D. White, J. C. Amedio, J. Org. Chem. 1989, 54, 736-738.
[3] Y. Hirai, K. Yokota, H. Sakai, T. Yamazaki, T. Momose, Heterocycles 1989, 29, 1865-1869.
[4] A. V. R. Rao, M. K. Gurjar, B. R. Rao Nallaganchu, A. Bhandari, Tetrahedron Lett. 1993, 34, 7085-7088.
[5] M. V. D’Auria, L. Gomez Paloma, L. Minale, A. Zampella, C. Debitus, J. Perez, J. Nat. Prod. 1995, 58, 121-123.
[6] J. H. Lang, T. Lindel, Beilstein J. Org. Chem. 2019, 15, 577-583.
[7] H. D. Arndt, S. Rizzo, C. Nocker, V. N. Wakchaure, L. G. Milroy, V. Bieker, A. Calderon, T. T. Tran, S. Brand, L. Dehmelt, H. Waldmann, Chem. Eur. J. 2015, 21, 5311-5316.
[8] C. Tanaka, J. Tanaka, R. F. Bolland, G. Marriott, T. Higa, Tetrahedron 2006, 62, 3536-3542.
[9] R. Talpir, Y. Benayahu, Y. Kashman, L. Pannell, M. Schleyer, Tetrahedron Lett. 1994, 35, 4453-4456.
[10] E. D. de Silva, R. J. Andersen, T. M. Allen, Tetrahedron Lett. 1990, 31, 489-492.
[11] W. F. Tinto, A. J. Lough, S. McLean, W. F. Reynolds, M. Yu, W. R. Chan, Tetrahedron 1998, 54, 4451-4458.
[12] W. L. Armarego, Purification of laboratory chemicals, Butterworth-Heinemann, Oxford, 2017.
[13] W. C. Still, M. Kahn, A. Mitra, J. Org. Chem. 1978, 43, 2923-2925.
[14] H. E. Gottlieb, V. Kotlyar, A. Nudelman, J. Org. Chem. 1997, 62, 7512-7515.
[15] R. Tannert, L. G. Milroy, B. Ellinger, T. S. Hu, H. D. Arndt, H. Waldmann, J. Am. Chem. Soc. 2010, 132, 3063-3077.
[16] V. Stepanenko, M. Ortiz-Marciales, C. L. Barnes, C. Garcia, Tetrahedron Lett. 2009, 50, 995-998.
[17] M. Brenner, L. La Vecchia, T. Leutert, D. Seebach, Org. Synth. 2003, 80, 57-65.
[18] H. M. Eng, D. C. Myles, Tetrahedron Lett. 1999, 40, 2275-2278.
[19] S. Yamashita, K. Iso, M. Hirma, Org. Lett. 2008, 10, 3413-3415.
[20] C. S. Gloo, F. Denes, P. Renaud, Angew. Chem., Int. Ed. 2017, 56, 13329-13332.
[21] A. P. Pulis, D. J. Blair, E. Torres, V. K. Aggarwal, J. Am. Chem. Soc. 2013, 135, 16054-16057.
[22] T. Chen, K. H. Altmann, Chem. Eur. J. 2015, 21, 8403-8407.
[23] J. Chiarello, M. M. Joullie, Synth. Commun. 1988, 18, 2211-2223.
[24] M. M. Neidhardt, M. Wolfrom, S. Beardsworth, T. Wohrle, W. Frey, A. Baro, C. Stubenrauch, F. Giesselmann, S. Laschat, Chem. Eur. J. 2016, 22, 16494-16504.
[25] C. Z. Rotsides, K. A. Woerpel, Dalton Trans. 2017, 46, 8763-8768.
[26] L. Krause, R. Herbst-Irmer, G. M. Sheldrick, D. Stalke, J. Appl. Crystallogr. 2015, 48, 3-10.
[27] R. Hooft, B. V. Nonius, BV Nonius, Delft, The Netherlands 1998.
[28] Z. Otwinowski, W. Minor, Meth. Enzymol. 1997, 276, 307-326.
[29] G. M. Sheldrick, Acta Cryst. C 2015, 71, 3-8.
[30] C. F. Macrae, P. R. Edgington, P. McCabe, E. Pidcock, G. P. Shields, R. Taylor, M. Towler, J. van De Streek, J. Appl. Crystallogr. 2006, 39, 453-457.
[31] V. SHELXTL, Inc.: Madison, WI 1994.
[32] F. Krauth, H. M. Dahse, H. H. Ruttinger, P. Frohberg, Bioorg. Med. Chem. 2010, 18, 1816-1821.
[33] S. Pospich, F. Merino, S. Raunser, Structure 2020, 28, 437-449.
[34] H. M. Berman, J. Westbrook, Z. Feng, G. Gilliland, T. N. Bhat, H. Weissig, I. N. Shindyalov, P. E. Bourne, *Nucleic Acids Res.* **2000**, *28*, 235-242.

[35] K. Roos, C. Wu, W. Damm, M. Reboul, J. M. Stevenson, C. Lu, M. K. Dahlgren, S. Mondal, W. Chen, L. Wang, R. Abel, R. A. Friesner, E. D. Harder, *J. Chem. Theory Comput.* **2019**, *15*, 1863-1874.

[36] J. C. Shelley, A. Cholleti, L. L. Frye, J. R. Greenwood, M. R. Timlin, M. Uchimaya, *J. Comput.-Aided Mol. Des.* **2007**, *21*, 681-691.

[37] D. Sindhikara, S. A. Spronk, T. Day, K. Borrelli, D. L. Cheney, S. L. Posy, *J. Chem. Inf. Model.* **2017**, *57*, 1881-1894.
9. NMR Spectra

$^1$H spectrum of compound 12-1: 300 MHz, Chloroform-$d$, 298 K

$^{13}$C$^1$H spectrum of compound 12-1: 75 MHz, Chloroform-$d$, 298 K
$^1$H spectrum of compound 14: 300 MHz, Chloroform-$d$, 298 K

$^{13}$C($^1$H) spectrum of compound 14: 75 MHz, Chloroform-$d$, 298 K
$^1$H spectrum of compound 14-1: 400 MHz, Chloroform-$d$, 297 K

$^{13}$C($^1$H) spectrum of compound 14-1: 101 MHz, Chloroform-$d$, 297 K
$^1$H spectrum of compound 15: 400 MHz, Chloroform-$d$, 297 K

$^{13}$C/$^1$H spectrum of compound 15: 101 MHz, Chloroform-$d$, 297 K
$^1$H spectrum of compound 16: 400 MHz, Chloroform-$d$, 297 K

$^{13}$C($^1$H) spectrum of compound 16: 101 MHz, Chloroform-$d$, 297 K
$^1$H spectrum of compound 17: 300 MHz, Chloroform-$d$, 298 K

$^{13}$C($^1$H) spectrum of compound 17: 75 MHz, Chloroform-$d$, 298 K
$^1$H spectrum of compound 17-1: 300 MHz, Chloroform-$d$, 300 K

$^{13}$C($^1$H) spectrum of compound 17-1: 75 MHz, Chloroform-$d$, 300 K
$^1$H spectrum of compound 17-2: 300 MHz, Chloroform-$d$, 298 K

$^{13}$C($^1$H) spectrum of compound 17-2: 75 MHz, Chloroform-$d$, 298 K
^1\text{H} \text{ spectrum of compound 11}: 250 \text{ MHz}, \text{ Chloroform-d}, 297 \text{ K}

^13\text{C}\{^1\text{H}\} \text{ spectrum of compound 11}: 63 \text{ MHz}, \text{ Chloroform-d}, 297 \text{ K}
$^1$H spectrum of compound S3c: 500 MHz, Chloroform-$d$, 323 K

$^{13}$C($^1$H) spectrum of compound S3c: 125 MHz, Chloroform-$d$, 323 K
$^1$H spectrum of compound 18: 400 MHz, DMSO-$d_6$, 323 K

$^{13}$C($^1$H) spectrum of compound 18: 101 MHz, DMSO-$d_6$, 323 K
$^1$H spectrum of compound 18-1: 400 MHz, DMSO-$d_6$, 324 K

$^{13}$C($^1$H) spectrum of compound 18-1: 101 MHz, DMSO-$d_6$, 324 K
$^1$H spectrum of compound 8: 300 MHz, DMSO-$d_6$, 298 K

$^{13}$C($^1$H) spectrum of compound 8: 125 MHz, DMSO-$d_6$, 324 K
$^1$H spectrum of compound 19: 400 MHz, DMSO-$d_6$, 323 K

$^{13}$C($^1$H) spectrum of compound 19: 101 MHz, DMSO-$d_6$, 323 K
$^1$H spectrum of compound 19-1: 400 MHz, DMSO-$d_6$, 323 K

$^{13}$C($^1$H) spectrum of compound 19-1: 101 MHz, DMSO-$d_6$, 323 K
$^1$H spectrum of compound 9: 400 MHz, DMSO-$d_6$, 323 K

$^{13}$C($^1$H) spectrum of compound 9: 101 MHz, DMSO-$d_6$, 323 K
$^1$H spectrum of compound 21: 300 MHz, Chloroform-$d$, 298 K

$^{13}$C($^1$H) spectrum of compound 21: 125 MHz, Chloroform-$d$, 298 K
\(^1\)H spectrum of compound 22: 500 MHz, Chloroform-\(d\), 297 K

\(^{13}\)C\(\{^1\)H\}\) spectrum of compound 22: 125 MHz, Chloroform-\(d\), 297 K
$^1$H spectrum of compound 24: 400 MHz, Chloroform-$d$, 297 K

$^{13}$C-$^1$H spectrum of compound 24: 101 MHz, Chloroform-$d$, 297 K
$^1$H spectrum of compound 25: 300 MHz, Chloroform-$d$, 298 K

$^{13}$C{$_{^1}$H} spectrum of compound 25: 75 MHz, Chloroform-$d$, 298 K
\(^1\)H spectrum of compound 26: 400 MHz, Dioxane-\(d_8\), 297 K

\(^{13}\)C\(^{1}\)H spectrum of compound 26: 101 MHz, Dioxane-\(d_8\), 297 K
$^1$H spectrum of compound 27: 400 MHz, Dioxane-$d_8$, 297 K

$^{13}$C$[^1]$H spectrum of compound 27: 101 MHz, Dioxane-$d_8$, 297 K
$^1$H spectrum of compound 31: 300 MHz, Chloroform-$d$, 298 K

$^{13}$C{$^1$H} spectrum of compound 31: 75 MHz, Chloroform-$d$, 298 K
$^1$H spectrum of compound 34: 400 MHz, Dioxane-$d_8$, 323 K

$^{13}$C-$^1$H spectrum of compound 34: 101 MHz, Dioxane-$d_8$, 323 K
$^1$H spectrum of Geodiamolide H (1): 600 MHz, DMSO-$d_6$, 297 K

$^{13}$C($^1$H) spectrum of Geodiamolide H (1): 125 MHz, DMSO-$d_6$, 297 K
HSQC-DEPT spectrum of Geodiamolide H (1):

Selective NOESY spectrum of Geodiamolide H (1): Irradiated signal at range 4.80-4.85 ppm
$^1$H spectrum of (Z)-Geodiamolide H (35): 600 MHz, DMSO-$d_6$, 297 K

$^{13}$C$\left(^1\text{H}\right)$ spectrum of (Z)-Geodiamolide H (35): 125 MHz, DMSO-$d_6$, 297 K
HSQC-DEPT spectrum of (Z)-Geodiamolide H (35):

Selective NOESY spectrum of (Z)-Geodiamolide H (35): Irradiated signal at range 5.00-5.05 ppm
$^1\text{H}$ spectrum of compound 36: 400 MHz, DMSO-$d_6$, 297 K

$^{13}\text{C}[^1\text{H}]$ spectrum of compound 36: 101 MHz, DMSO-$d_6$, 297 K
Selective NOESY spectrum of Des-Me-Geodiamolide H (36): Irradiated signal at range 4.90-5.00 ppm

Selective NOESY spectrum of Des-Me-Geodiamolide H (36): Irradiated signal at range 1.40-1.55 ppm
$^1$H spectrum of compound 37: 500 MHz, DMSO-$d_6$, 297 K

$^{13}$C($^1$H) spectrum of compound 37: 101 MHz, DMSO-$d_6$, 297 K
Selective NOESY spectrum of Des-iodo-Geodiamolide H (37): Irradiated signal at range 4.72-4.77 ppm

HSQC-DEPT spectrum of Des-iodo-Geodiamolide H (37):
$^1$H spectrum of compound 38: 500 MHz, Chloroform-$d$, 297 K

$^{13}$C($^1$H) spectrum of compound 38: 125 MHz, Chloroform-$d$, 297 K
135-DEPT spectrum of (Z)-des-iodo-Geodiamolide H (38):

Selective NOESY spectrum of (Z)-des-iodo-Geodiamolide H (38): Irradiated signal at range 5.00-5.05 ppm
$^1$H spectrum of compound 39: 400 MHz, DMSO-$d_6$, 297 K

$^{13}$C($^1$H) spectrum of compound 39: Chloroform-$d$ + 5% Methanol-$d_4$, 297 K
Selective NOESY spectrum of \((E)\)-des-iodo-des-Me-Geodiamolide H (39): Irradiated signal at range 4.90-5.00 ppm

No NOE correlation at 1.52 ppm

Selective NOESY spectrum of \((E)\)-des-iodo-des-Me-Geodiamolide H (39): Irradiated signal at range 1.40-1.60 ppm

No NOE correlation at 4.94 ppm
HSQC-DEPT spectrum of (E)-des-iodo-des-Me-Geodialolide H (39):