Formal Total Synthesis of Palmerolide A

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Abstract: A concise route to macrolactone **38**, an advanced intermediate of the Nicolaou/Chen synthesis of palmerolide A, is described. Key steps in our synthesis include a Noyori transfer hydrogenation of an alkynone, chain extension via Claisen rearrangement, and an ADH reaction on an enyne. After reduction of the triple bond, a selective silylation served to differentiate the hydroxy groups of the diol, which allowed for the preparation of aldehyde **30** containing already the carbamate function. A HWE reaction produced the substrate for an intramolecular Heck coupling. In contrast to the Stille cyclization, the Heck cyclization produced only the desired 14*E*,16*E*-diene. Elaboration of the C-19 side chain led to the key lactone **38**.

Key words: asymmetric synthesis, dihydroxylations, Heck reaction, macrocycles, natural products

The search for natural products that display potent cytotoxic activity represents a classical and proven strategy for identifying potential candidates for drug development in the field of cancer treatment. Thus, novel and fascinating structures like the enediynes, taxol, or the epothilones were discovered.[1] Moreover, natural products are instrumental in discovering novel biological pathways that might be suitable targets for interference with the drugs. In 2006, the structure of palmerolide A (**1**) along with its unique cytotoxicity profile was described (Figure 1).[2] This macrolide was isolated from the antarctic marine tunicate *Synoicum adareanum* by Baker et al.[2]

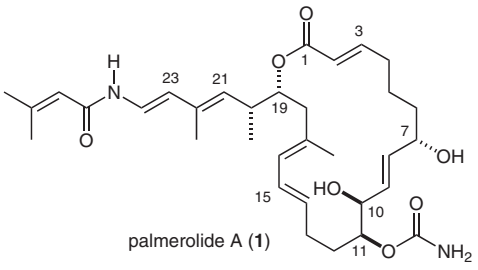

Figure 1 Revised structure of palmerolide A as determined by total synthesis and degradation studies

With the enamide-containing side chain it was not too surprising that palmerolide A turned out as a potent (2 nM) inhibitor of vacuolar V-ATPase (V-ATPase).[3] Among various cell lines tested, the melanoma cell line UACC-62 turned out to be rather sensitive (LC_{50} = 18 nM) to palmerolide A. Synthetic studies directed towards palmerolide A by Brabander et al. revealed that the originally assigned configuration had to be revised.[4,5] This work culminated in the synthesis of *ent*-**1**. In their synthesis, the macrolactone was closed via an intramolecular Wittig–Horner reaction forming the C8–C9 double bond. In the total synthesis by Nicolaou/Chen et al., a ring-closing metathesis, also formation of the C8–C9 bond, served as a key reaction.[6] Using this strategy a range of palmerolide A analogues was prepared and subjected to biological evaluation.[7] Without the carbamate a 5-fold decrease of activity was observed. Changing the stereochemistry at the various OH-bearing stereocenters resulted in significant loss of activity. Most of the analogues with a modified enamide were much less active, except for the phenyl- and the 3-methylbutanamide analogues. From other groups further studies towards the synthesis of palmerolide A have appeared in the literature.[8] Our group reported the synthesis of the C3–C23 fragment **2** of palmerolide A (Scheme 1).[9] While the stereochemistry of **2** at C7, C10, and C11 corresponded to the originally proposed wrong configurations, the lessons learned from this work eventually allowed us to move ahead with the total synthesis of **1**. Fragment **2** was assembled from two building blocks **3** and **4** via a cross-coupling reaction between C15 and C16 (Suzuki or Stille coupling). The vicinal stereocenters at C10 and C11 came from a Sharpless asymmetric dihydroxylation, whereas the C7 stereochemistry was controlled via a Noyori transfer hydrogenation. Macrolide formation was envisioned to occur by an intramolecular Horner–Wadsworth–Emmons (HWE) reaction. However, in compounds related to **2** we encountered problems in cleaving the C3-PMB ether in presence of the diene subunit.[10] This obstacle could eventually be by-passed by postponing the C15–C16 cross-coupling to a later stage of the synthesis. Thus, macrolactonization could eventually be realized by an intramolecular cross-coupling strategy forming the diene as described in this paper.

The known ester **5**, obtained form valerolactone,[9] was converted into alkynone **6** by reaction with lithium trimethylsilylacetylide (Scheme 2). A subsequent transfer hydrogenation according to Noyori[11] with the ruthenium catalyst **7**, containing the *S*,*S*-diamine furnished propargyl alcohol **8** in good yield and ee (98.2%). A sequence of six steps that we used previously led to chain extension and formation of an enyne subunit. Thus, liberation of the acetylene, protection of the hydroxy function, reaction of the acetylide with acrolein, and a Claisen rearrangement[12] furnished the unsaturated ester **12**. Reduction of the ester

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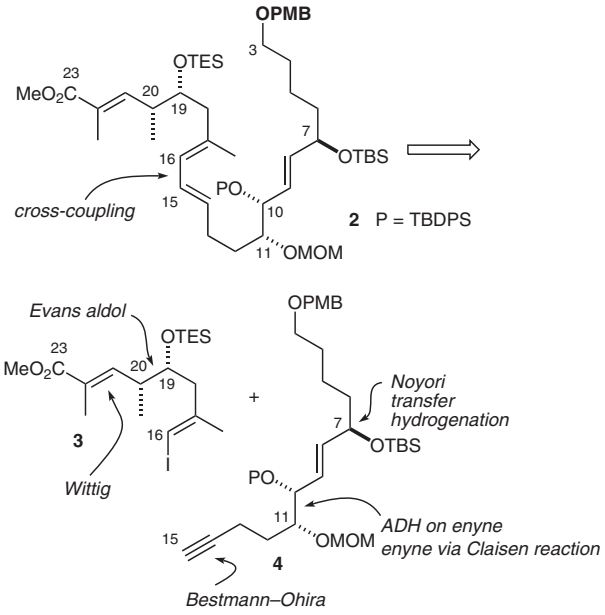
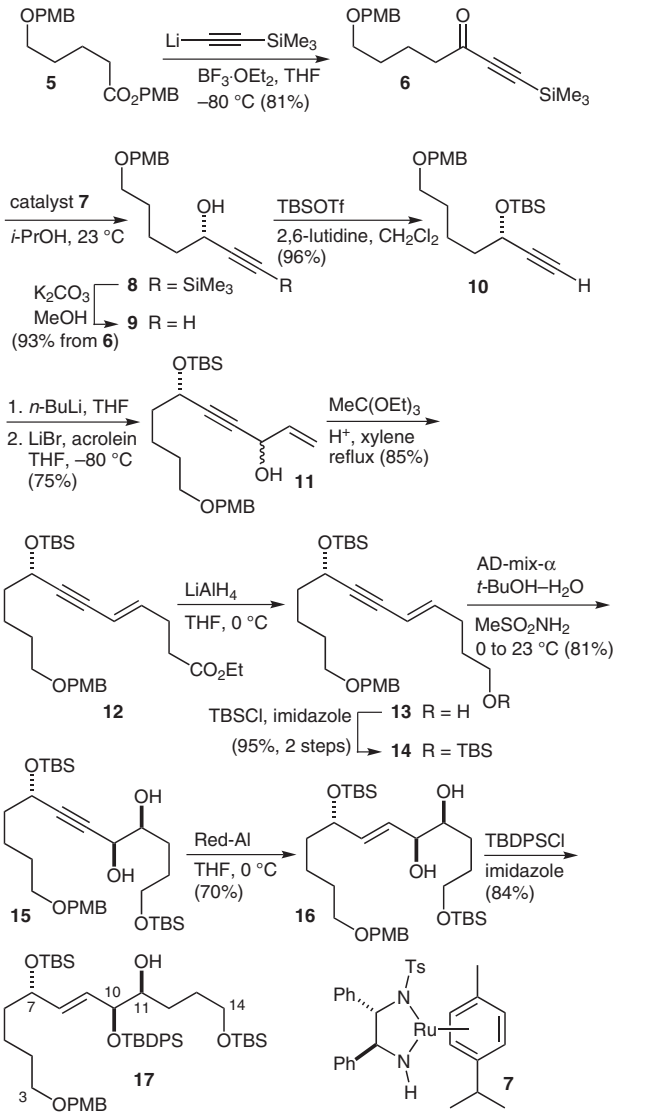


Scheme 1 Key step in our previous synthesis of the C3–C23 fragment **2** of palmerolide A in its original proposed configuration

and silylation of the alcohol function of **13** secured enyne **14**, the substrate for the ADH reaction.[13] The triple bond of diol **15** was reduced with Red-Al (3 equiv) in THF providing *E*-allylic alcohol **16** in reasonable yield. The differentiation of the two secondary hydroxy groups relied on the discovery that the propargylic or the allylic alcohol function reacts selectively with *tert*-butyldiphenylsilyl chloride.[9] Accordingly, diol **16** was converted to alcohol **17**, the C3–C14 fragment of palmerolide A.

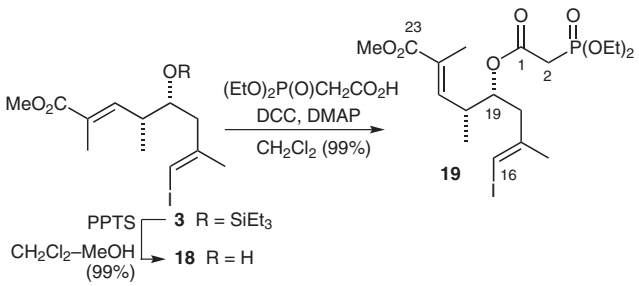
As another key building block we chose phosphonate **19**. This compound was intended to be employed in a HWE reaction either in an intramolecular or intermolecular fashion. Phosphonate **19** could easily be obtained from known ester[9] **3**. First, the triethylsilyl ether of **3** was cleaved under weakly acidic conditions giving hydroxy ester **18**. Subsequently, a condensation reaction between alcohol **18** and 2-(diethoxyphosphoryl)acetic acid under the action of DCC and DMAP furnished diester **19** in almost quantitative yield (Scheme 3).

With the key fragments **17** and **19** in hand, we could now move towards their unification. For reasons mentioned above, we planned to perform the HWE reaction prior to the cross-coupling. This would require aldehydes with a terminus suitable for subsequent coupling. In this regard we chose to prepare a (tributylstannyl)enal and an ynal (Scheme 4). To avoid additional protecting group measures in fragment **17**, the carbamate group was introduced next using the activated isocyanate $Cl_3C(CO)NCO$.[14] After selective cleavage of the primary silyl ether, alcohol **21** was oxidized to aldehyde **22** followed by alkyne formation with the Bestmann–Ohira ketodiazaphosphonate **23**.[15] Instead of extending now from C15 onwards leading to a diene, we first removed the PMB protecting group at

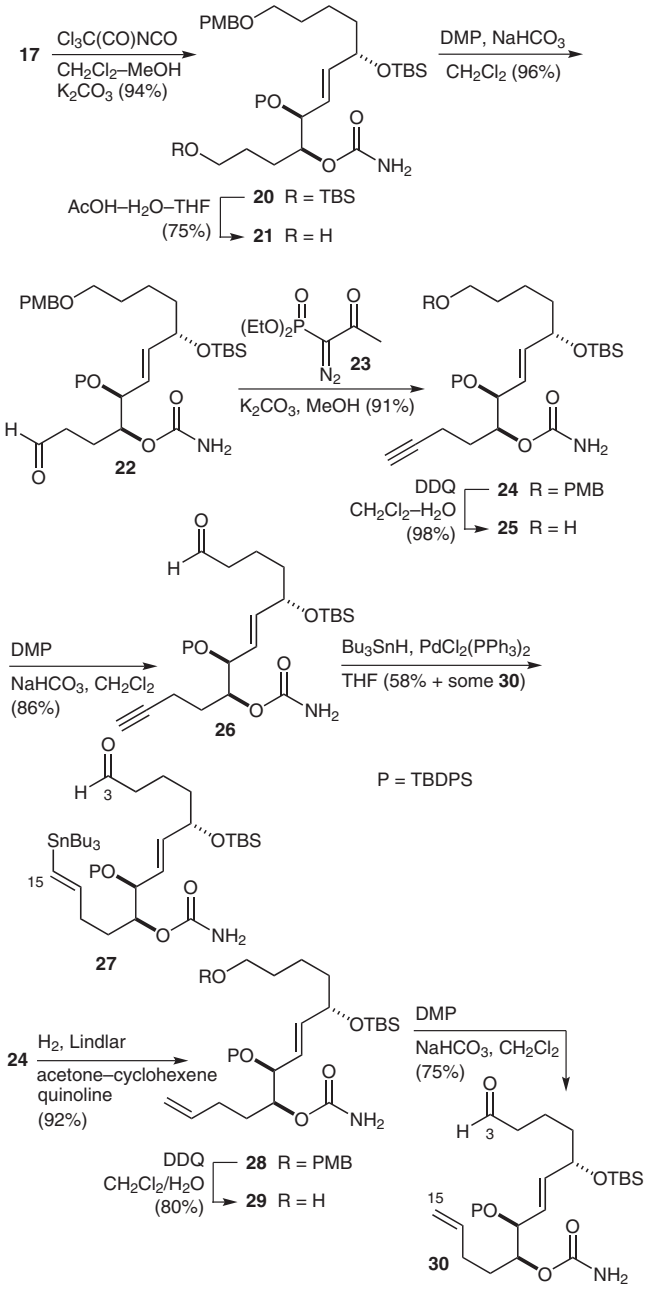


Scheme 2 Synthesis of C3–C14 fragment via enyne **12**

C3. A subsequent Dess–Martin oxidation of **25** to aldehyde **26** followed by palladium-catalyzed hydrostannylation[16,17] of the triple bond led to (tributylstannyl)enal **27**. With a view towards closing the macrocyclic ring by Heck reaction, the enal **30** was prepared as well. Thus, a Lindlar reduction on alkyne **24** generated alkene **28**, which was deprotected and oxidized at C3.

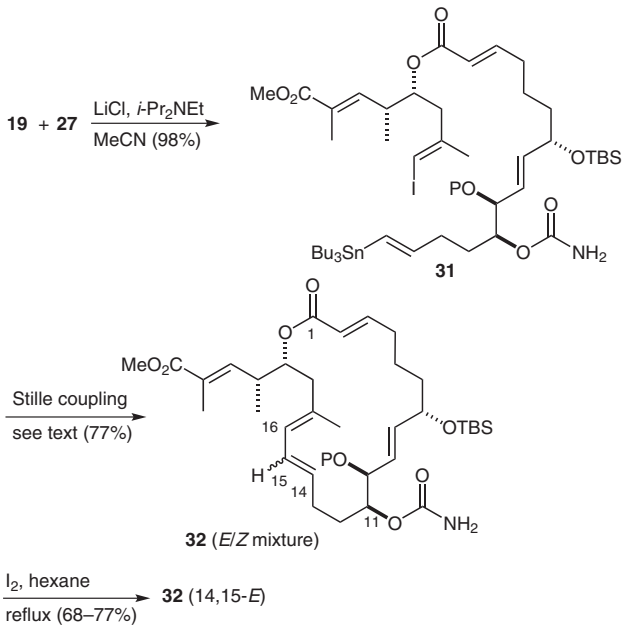


Scheme 3 Synthesis of phosphonate **19** from unsaturated ester **3**



Scheme 4 Synthesis of (tributylstannyl)enal **27** and the ynal **30** for coupling with phosphonate **19**

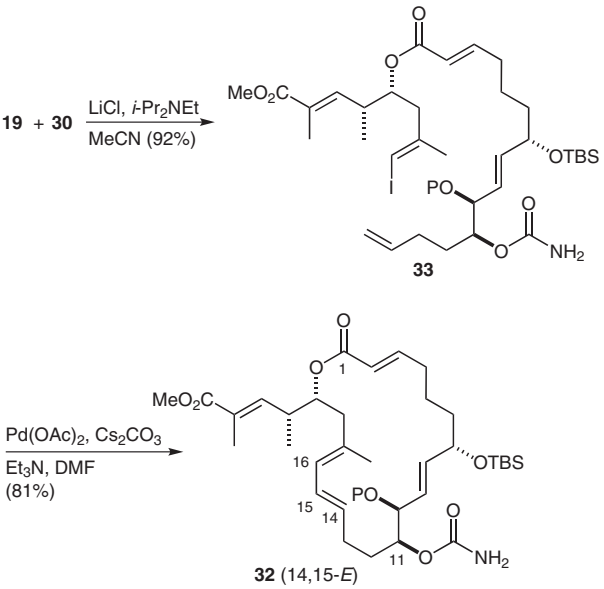
Macrolactone formation was initiated by a HWE reaction between (tributylstannyl)enal **27** with phosphonate **19** (Scheme 5). Under the influence of Hünig's base (*i*-Pr_2NEt) the desired unsaturated ester **31** was obtained in almost quantitative yield. No product of an intramolecular Michael addition of the phosphonate anion to its unsaturated ester was observed. Ester **31** was intended for an intramolecular Stille coupling reaction. Various conditions were tried, but in most cases the Stille cyclization produced an *E*/*Z* mixture of the C14–C15 double bond. The best conditions with regard to the chemical yield were obtained with $PdCl_2(Cl_3CN)_2$, (2-furyl)$_3$P (20 mol%) as ligand, and LiCl (0.4 equiv) plus *i*-Pr_2NEt as additives. Treatment of the 3:1 *E*/*Z* mixture of **32** with I_2 (cat.



Scheme 5 Macrolactone formation via intramolecular Stille coupling

amounts) in refluxing hexane resulted in complete isomerization to the (*E*,*E*)-diene **32**.

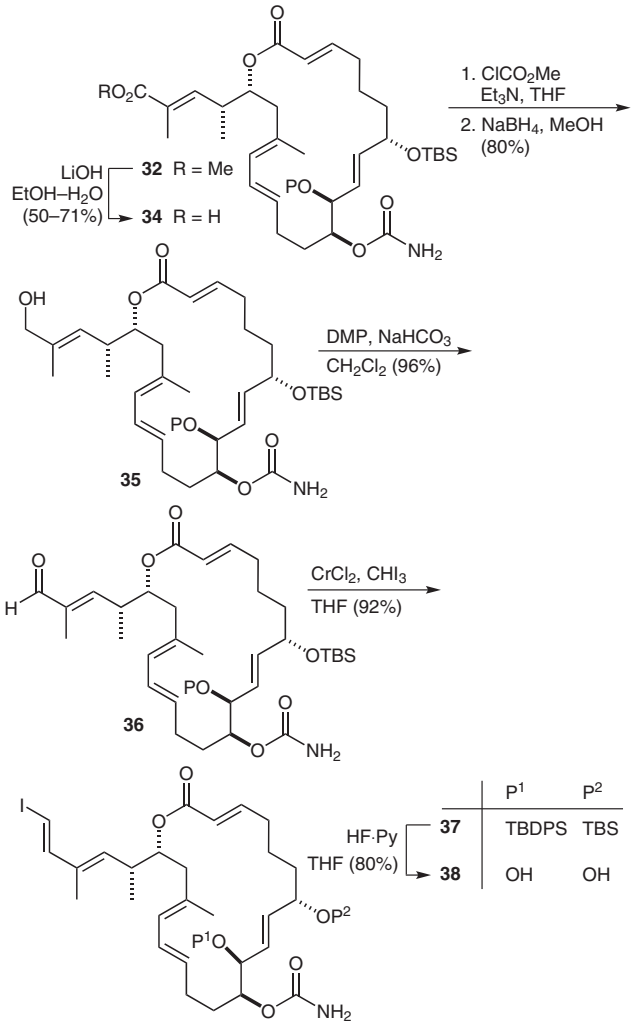
An even more efficient ring-closing reaction was found with the Heck cyclization[18,19] of ester **33**, obtained from aldehyde **30** and phosphonate **19**. In presence of $Pd(OAc)_2$ (1.3 equiv), Cs_2CO_3 (1.5 equiv), and Et_3N (1.1 equiv) in DMF at room temperature, an excellent yield of isomerically pure lactone **32** was obtained (Scheme 6).



Scheme 6 Macrolactone formation via intramolecular Heck coupling

The next challenge involved elaboration of the side chain to the unsaturated *N*-acyl dienamine. Accordingly, the methyl ester **32** was selectively hydrolyzed to acid **34**

using aqueous LiOH (Scheme 7). While the lactone remained untouched, a small amount of the decarbamated acid could be detected in the LC-MS. Reduction of the acid via the derived ethylcarbonic anhydride[20] produced allylic alcohol **35** that provided aldehyde **36** upon oxidation. At this point a Takai olefination[21] gave dienyl iodide **37**. Cleavage of the silyl protecting groups using the HF·pyridine complex[22] provided macrolactone **38**. Since this compound was an advanced intermediate in the Nicolaou/Chen synthesis,[6] the concise preparation of **38** represents a formal total synthesis of palmerolide A.



Scheme 7 Completion of the formal total synthesis of palmerolide A

To summarize, we have developed a novel route to an advanced intermediate of the Nicolaou/Chen synthesis of palmerolide A (**1**). The hydroxy group containing C3–C15 part **25** was created from an ynone via Noyori reduction, chain extension by Claisen rearrangement, and an ADH reaction. The triple bond was reduced to the double bond followed by differentiation of the vicinal diol by selective silylation. Thereafter, a HWE reaction on the C3 aldehyde furnished the open chain esters **31** and **33**. Macrocyclization was either achieved via a Stille coupling or a Heck reaction. The latter produced the diene in the desired *E*,*E* configuration. Key steps in the elaboration of the side chain were a selective ester saponification and a Takai olefination. This quite efficient strategy might allow the preparation of further analogues in order to probe the suitability of V-ATPases as target in cancer therapy.

Unless otherwise noted, all reactions were performed in oven-dried glassware. All solvents used in the reactions were purified before use. Dry diethyl ether, tetrahydrofuran, and toluene were distilled from sodium and benzophenone, whereas dry CH_2Cl_2, dimethylformamide, methanol, ethyl acetate, benzene, and triethylamine were distilled from CaH_2. Petroleum ether (PE) with a boiling range of 40–60 °C was used. Reactions were generally run under argon or nitrogen atmosphere. All commercially available compounds (Acros, Aldrich, Fluka, Merck) were used without purification. ^1H and ^{13}C NMR: Bruker Avance 400, spectra were recorded at 295 K in $CDCl_3$; chemical shifts are calibrated to the residual proton and carbon resonance of the solvent: $CDCl_3$ (δH 7.25, δC 77.0 ppm). HRMS (FT-ICR): Bruker Daltonic APEX 2 with electron spray ionization (ESI). Chiral GC (ee determination of alcohol **8**): HP 5890, fused silica column, 30% Lipodex E in PS255, 0.13 μm film, 80 °C, isothermal, carrier gas 50kPa H_2. Flash chromatography: J. T. Baker silica gel 43–60 μm. Thin-layer chromatography Machery-Nagel Polygram Sil G/UV254. Optical rotations: Perkin-Elmer 341 Polarimeter, Na-lamp, 589 nm, 1 dm cuvette, *c* = g per 100 mL.

7-[(4-Methoxybenzyl)oxy]-1-(trimethylsilyl)hept-1-yn-3-one (6)

To a stirred solution of trimethylsilylacetylene (8.0 mL, 56 mmol, 2 equiv) in THF (50 mL) at –80 °C was added *n*-BuLi (22.3 mL, 2.5 M in hexane, 56 mmol, 2 equiv) dropwise. After stirring at this temperature for 45 min, a vigorously stirred solution of pentanoate **5** (10.0 g, 28 mmol) and $BF_3{\cdot}OEt_2$ (3.4 mL) in THF (30 mL) was added slowly. After stirring for 12 h, the mixture was diluted with Et_2O (100 mL) and treated with aq sat. NH_4Cl (80 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with aq 1 M NaOH (50 mL), H_2O (50 mL), and brine (50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (PE–EtOAc, 10:1) to give 7.1 g (81%) of alkynone **6** as a light yellow oil; R_f = 0.54 (PE–EtOAc, 5:1); $[\alpha]_D^{20}$ –0.6 (*c* 1.00, CH_2Cl_2).

^1H NMR (400 MHz, $CDCl_3$): δ = 0.23 [s, 9 H, $Si(CH_3)_3$], 1.55–1.69 (m, 2 H, 6-H), 1.78–1.84 (m, 2 H, 5-H), 2.58 (t, *J* = 7.4 Hz, 2 H, 4-H), 3.45 (t, *J* = 6.2 Hz, 2 H, 7-H), 3.80 (s, 3 H, CH_3O), 4.42 (s, 2 H, PMB CH_2), 6.87 (d, *J* = 8.7 Hz, 2 H, CH_{arom}, *meta*), 7.25 (d, *J* = 7.6 Hz, 2 H, CH_{arom}, *ortho*).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –0.8 [$Si(CH_3)_3$)], 20.7 (C-5), 28.9 (C-6), 44.9 (C-4), 55.3 (CH_3O), 69.5 (C-7), 72.5 (PMB CH_2), 97.7 (C-1), 102.0 (C-2), 113.8 (CH_{arom}, *meta*), 129.2 (CH_{arom}, *ortho*), 130.6 (C_{arom}), 159.1 (C_{arom}, *para*), 187.6 (C-3).

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{38}O_3Si$ + Na $[M + Na]^+$: 341.15434; found: 341.15429.

(3*S*)-7-[(4-Methoxybenzyl)oxy]-1-(trimethylsilyl)hept-1-yn-3-ol (8)

To a stirred solution of alkynone **6** (5.0 g, 15.5 mmol) in *i*-PrOH (170 mL) the complex RuCl[(*S*,*S*)-NTsCH(Ph)CH(Ph)NH_2(η^6-cymene) (**7**; 125 mg, catalytic amount), dissolved in a minimal amount of CH_2Cl_2 (0.5 mL), was added. The mixture was stirred at r.t. for 5 h. The solvent was removed and the brown residue was used without further purification.

(3*S*)-7-[(4-Methoxybenzyl)oxy]hept-1-yn-3-ol (9)

To a stirred solution of propargylic alcohol **8** (crude, ca. 15.5 mmol) in MeOH (30 mL) was added K_2CO_3 (1.0 g, 7.2 mmol). After stir-

ring for 30 min at r.t., the reaction mixture was treated with H_2O (ca. 50 mL) and diluted with Et_2O (50 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 × 30 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (PE–EtOAc, 5:1) to give 3.36 g (93%) of alcohol **9** as a light yellow oil; R_f = 0.13 (PE–EtOAc, 5:1); $[\alpha]_D^{20}$ –2.9 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44–1.77 (m, 6 H, 4-H, 5-H, 6-H), 2.44 (d, *J* = 2.0 Hz, 1 H, 1-H), 3.44 (t, *J* = 6.4 Hz, 2 H, 7-H), 3.78 (s, 3 H, CH_3O), 4.23–4.37 (m, 1 H, 3-H), 4.42 (s, 2 H, PMB CH_2), 6.86 (d, *J* = 8.9 Hz, 2 H, CH_{arom}, *meta*), 7.24 (d, *J* = 8.7 Hz, 2 H, CH_{arom}, *ortho*).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7 (C-5), 29.2 (C-6), 37.3 (C-4), 55.2 (CH_3O), 62.0 (C-3), 69.7 (C-7), 72.5 (PMB CH_2), 72.7 (C-1), 85.0 (C-2), 113.7 (CH_{arom}, *meta*), 129.2 (CH_{arom}, *ortho*), 130.5 (C_{arom}), 159.0 (C_{arom}, *para*).

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{20}O_3$ + Na $[M + Na]^+$: 271.13047; found: 271.13058.

(3*S*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-7-[(4-methoxybenzyl)-oxy]hept-1-yne (10)

To a stirred solution of hept-1-yn-3-ol **9** (3.4 g, 13.5 mmol) in CH_2Cl_2 (85 mL) was added 2,6-lutidine (5.0 mL, 40.5 mmol, 3 equiv). After cooling to 0 °C, TBSOTf (3.5 mL, 14.9 mmol, 1.1 equiv) was added dropwise and the mixture was stirred for 20 min at this temperature. The mixture was diluted with CH_2Cl_2 (70 mL) and the organic layer was washed with H_2O (50 mL), aq 1 N HCl (50 mL), and aq sat. $NaHCO_3$ (50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (PE–EtOAc, 15:1) to give 4.7 g (96%) of silyl ether **10** as a colorless oil; R_f = 0.73 (PE–EtOAc, 6:1); $[\alpha]_D^{20}$ –28.2 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.09 [s, 3 H, $Si(CH_3)_2$], 0.11 [s, 3 H, $Si(CH_3)_2$], 0.88 [s, 9 H, $C(CH_3)_3$], 1.42–1.73 (m, 6 H, 4-H, 5-H, 6-H), 2.35 (d, *J* = 2.0 Hz, 1 H, 1-H), 3.43 (t, *J* = 6.5 Hz, 2 H, 7-H), 3.78 (s, 3 H, CH_3O), 4.28–4.35 (m, 1 H, 3-H), 4.41 (s, 2 H, PMB CH_2), 6.85 (d, *J* = 8.7 Hz, 2 H, CH_{arom}, *meta*), 7.24 (d, *J* = 8.7 Hz, 2 H, CH_{arom}, *ortho*).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.1 [$Si(CH_3)_2$], –4.6 [$Si(CH_3)_2$], 18.2 [$C(CH_3)_3$], 21.8 (C-5), 25.7 [$C(CH_3)_3$], 29.4 (C-6), 38.3 (C-4), 55.2 (CH_3O), 62.7 (C-3), 69.9 (C-7), 72.0 (C-1), 72.5 (PMB CH_2), 85.6 (C-2), 113.7 (CH_{arom}, *meta*), 129.2 (CH_{arom}, *ortho*), 130.7 (C_{arom}), 159.1 (C_{arom}, *para*).

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{34}O_3Si$ + Na $[M + Na]^+$: 385.21694; found: 385.21704.

(6*S*)-6-{[*tert*-Butyl(dimethyl)silyl]oxy}-10-[(4-methoxybenzyl)-oxy]dec-1-en-4-yne-3-ol (11)

A solution of alkyne **10** (5.4 g, 15 mmol) in THF (65 mL) was treated at –80 °C with *n*-BuLi (7.2 mL, 2.5 M in hexane, 18 mmol, 1.2 equiv). The mixture was stirred for 30 min, then warmed to r.t. Now, LiBr (920 mg, 11 mmol, 0.7 equiv) was added and the mixture stirred until the LiBr was dissolved. It was then cooled to –80 °C before acrolein (1.91 mL, 27 mmol, 1.8 equiv) in THF (30 mL) was slowly added over a period of 30 min. After additional stirring for 2 h at –80 °C, the reaction was quenched by the addition of aq NH_4Cl (100 mL) and the mixture warmed to r.t. The layers were separated and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (PE–EtOAc, 10:1) to give 7.8 g (75%) of allylic alcohol **11** as a light yellow oil; R_f = 0.30 (PE–EtOAc, 6:1); $[\alpha]_D^{20}$ –27.3 (*c* 1.00, CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.09, 0.11 [2 s, 3 H each, $Si(CH_3)_2$], 0.89 [s, 9 H, $C(CH_3)_3$], 1.38–1.75 (m, 6 H, 7-H, 8-H, 9-H), 2.06 (br s, 1 H, OH), 3.43 (t, *J* = 6.5 Hz, 2 H, 10-H), 3.79 (s, 3 H, CH_3O), 4.38 (td, *J* = 6.4 Hz, 1.4 Hz, 1 H, 6-H), 4.42 (s, 2 H, PMB CH_2), 4.82–4.90 (m, 1 H, 3-H), 5.19 (dd, *J* = 10.2, 1.3 Hz, 1 H, 1-H), 5.42 (dd, *J* = 17.0, 0.8 Hz, 1 H, 1-H), 5.85–6.01 (m, 1 H, 2-H), 6.86 (d, *J* = 8.6 Hz, 2 H, CH_{arom}, *meta*), 7.24 (d, *J* = 8.7 Hz, 2 H, CH_{arom}, *ortho*).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.0 [$Si(CH_3)_2$], –4.5 [$Si(CH_3)_2$], 18.2 [$C(CH_3)_3$], 21.9 (C-8), 25.8 [$C(CH_3)_3$], 29.3 (C-9), 38.2 (C-7), 55.2 (CH_3O), 62.8 (C-6), 63.1 (C-3), 69.8 (C-10), 72.5 (PMB CH_2), 82.7 (C-4), 88.1 (C-5), 113.7 (CH_{arom}, *meta*), 116.2 (C-1), 129.2 (CH_{arom}, *ortho*), 130.7 (C_{arom}), 137.0 (C-2), 159.1 (C_{arom}, *para*).

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{38}O_4Si$ + Na $[M + Na]^+$: 441.24316; found: 441.24332.

Ethyl (4*E*,8*S*)-8-{[*tert*-Butyl(dimethyl)silyl]oxy}-12-[(4-methoxybenzyl)oxy]dodec-4-en-6-ynoate (12)

A mixture of alcohol **11** (7.6 g, 18 mmol), triethyl orthoacetate (17.5 mL, 95 mmol, 5 equiv) and propionic acid (0.1 mL) in xylene (80 mL) was refluxed (150 °C) for 2 h. After cooling, the mixture was concentrated under reduced pressure and the residue purified by flash chromatography (PE–EtOAc, 15:1) to give 7.5 g (85%) of 1,4-unsaturated ester **12** as a light yellow oil; R_f = 0.55 (PE–EtOAc, 6:1); $[\alpha]_D^{20}$ –20.0 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.08, 0.10 [2 s, 3 H each, $Si(CH_3)_2$], 0.88 [s, 9 H, $C(CH_3)_3$], 1.24 (t, *J* = 7.3 Hz, 3 H, CH_3CH_2O), 1.40–1.74 (m, 6 H, 9-H, 10-H, 11-H), 2.33–2.44 (m, 4 H, 2-H, 3-H), 3.43 (t, *J* = 6.6 Hz, 2 H, 12-H), 3.79 (s, 3 H, CH_3O), 4.12 (q, *J* = 7.1 Hz, 2 H, CH_3CH_2O), 4.39–4.45 (m, 3 H, 8-H, PMB CH_2), 5.52 (d, *J* = 16.0 Hz, 1 H, 5-H), 5.99–6.11 (m, 1 H, 4-H), 6.86 (d, *J* = 8.7 Hz, 2 H, CH_{arom}, *meta*), 7.24 (d, *J* = 8.7 Hz, 2 H, CH_{arom}, *ortho*).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.0 [$Si(CH_3)_2$], –4.5 [$Si(CH_3)_2$], 14.2 (OCH_2CH_3), 18.2 [$C(CH_3)_3$], 22.0 (C-10), 25.8 [$C(CH_3)_3$], 28.2 (C-3), 29.4 (C-11), 33.3 (C-2), 38.4 (C-9), 55.2 (CH_3O), 60.4 (C-8), 63.3 (OCH_2CH_3), 70.0 (C-12), 72.5 (PMB CH_2), 82.4 (C-6), 90.2 (C-7), 110.6 (C-5), 113.7 (CH_{arom}, *meta*), 129.2 (CH_{arom}, *ortho*), 130.7 (C_{arom}), 141.7 (C-4), 159.1 (C_{arom}, *para*), 172.5 (C-1).

HRMS (ESI): *m*/*z* calcd for $C_{28}H_{44}O_5Si$ + Na $[M + Na]^+$: 511.28502; found: 511.28516.

(4*E*,8*S*)-8-{[*tert*-Butyl(dimethyl)silyl]oxy}-12-[(4-methoxybenzyl)oxy]dodec-4-en-6-yn-1-ol (13)

To a stirred suspension of $LiAlH_4$ (750 mg, 19.2 mmol, 1.2 equiv) in THF (50 mL) at 0 °C was added dropwise a solution of ester **12** (7.8 g, 16 mmol) in THF (100 mL). After stirring for 30 min, the reaction was quenched by the addition of H_2O (0.75 mL), aq 1 M NaOH (0.75 mL), and H_2O (2.25 mL). After filtration, the solvent was evaporated. The crude product was used without further purification. An analytical amount was purified by flash chromatography (PE–EtOAc, 3:1); R_f = 0.13 (PE–EtOAc, 6:1); $[\alpha]_D^{20}$ –21.3 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.09, 0.11 [2 s, 3 H each, $Si(CH_3)_2$], 0.89 [s, 9 H, $C(CH_3)_3$], 1.41–1.74 (m, 8 H, 2-H, 9-H, 10-H, 11-H), 2.13–2.23 (m, 2 H, 3-H), 3.43 (t, *J* = 6.6 Hz, 2 H, 12-H), 3.63 (t, *J* = 6.4 Hz, 2 H, 1-H), 3.79 (s, 3 H, CH_3O), 4.39–4.45 (m, 3 H, 8-H, PMB CH_2), 5.50 (dd, *J* = 15.9, 1.5 Hz, 1 H, 5-H), 6.02–6.13 (m, 1 H, 4-H), 6.86 (d, *J* = 8.8 Hz, 2 H, CH_{arom}, *meta*), 7.25 (d, *J* = 8.8 Hz, 2 H, CH_{arom}, *ortho*).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.0 [$Si(CH_3)_2$], –4.5 [$Si(CH_3)_2$], 18.2 [$C(CH_3)_3$], 22.0 (C-10), 25.8 [$C(CH_3)_3$], 29.3 (C-3), 29.4 (C-11), 31.6 (C-2), 38.5 (C-9), 55.3 (CH_3O), 62.1 (C-8), 63.3 (C-1), 70.0 (C-12), 72.5 (PMB CH_2), 82.7 (C-6), 89.8 (C-7), 109.9 (C-5),

113.7 (CH_{arom}, *meta*), 129.2 (CH_{arom}, *ortho*), 130.8 (C_{arom}), 143.4 (C-4), 159.1 (C_{arom}, *para*).

HRMS (ESI): *m/z* calcd for $C_{26}H_{42}O_4Si$ + Na $[M + Na]^+$: 469.27446; found: 469.27448.

(4*E*,8*S*)-1,8-Di-{[*tert*-butyl(dimethyl)silyl]oxy}-12-[(4-methoxybenzyl)oxy]dodec-4-en-6-yne (14)

To a stirred solution of alcohol **13** (crude, ca. 16 mmol) in DMF (100 mL) were added imidazole (1.6 g, 24 mmol, 1.5 equiv) and DMAP (cat.). At 0 °C, TBSCl (2.9 g, 19.2 mmol, 1.2 equiv) was added and the mixture was stirred for 12 h before it was diluted with Et_2O (100 mL). Then H_2O (100 mL) was added and after separation of the layers, the organic layer was washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (PE–EtOAc, 10:1) to give 8.5 g (95%, over 2 steps) of silyl ether **14** as a yellow oil; R_f = 0.70 (PE–EtOAc, 6:1); $[\alpha]_D^{20}$ –14.1 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 [s, 6 H, 1-OSi$(CH_3)_2$], 0.09, 0.11 [2 s, 3 H each, Si$(CH_3)_2$], 0.88 [s, 9 H, 1-OSi$(CH_3)_2$C(C$H_3)_3$], 0.89 [s, 9 H, 8-OSi$(CH_3)_2$C(C$H_3)_3$], 1.42–1.73 (m, 8 H, 2-H, 9-H, 10-H, 11-H), 2.10–2.20 (m, 2 H, 3-H), 3.43 (t, *J* = 6.6 Hz, 2 H, 12-H), 3.59 (t, *J* = 6.2 Hz, 2 H, 1-H), 3.79 (s, 3 H, CH_3O), 4.40–4.45 (m, 3 H, 8-H, PMB CH_2), 5.44–5.52 (m, 1 H, 5-H), 6.02–6.14 (m, 1 H, 4-H), 6.86 (d, *J* = 8.7 Hz, 2 H, CH_{arom}, *meta*), 7.25 (d, *J* = 8.7 Hz, 2 H, CH_{arom}, *ortho*).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3 [1-OSi$(CH_3)_2$], –5.3 [8-OSi$(CH_3)_2$], –4.5 [8-OSi$(CH_3)_2$], 18.3 [1-OSi$(CH_3)_2C(CH_3)_3$], 18.3 [8-OSi$(CH_3)_2C(CH_3)_3$], 22.0 (C-10), 25.8 [1-OSi$(CH_3)_2$C($CH_3)_3$], 25.9 [8-OSi$(CH_3)_2$C($CH_3)_3$], 29.4 (C-3), 29.4 (C-11), 31.7 (C-2), 38.5 (C-9), 55.2 (CH_3O), 62.2 (C-8), 63.3 (C-1), 70.0 (C-12), 72.5 (PMB CH_2), 82.9 (C-6), 89.5 (C-7), 109.6 (C-5), 113.7 (CH_{arom}, *meta*), 129.2 (CH_{arom}, *ortho*), 130.8 (C_{arom}), 143.9 (C-4), 159.1 (C_{arom}, *para*).

HRMS (ESI): *m/z* calcd for $C_{32}H_{56}O_4Si_2$ + Na $[M + Na]^+$: 583.36093; found: 583.36031.

(4*S*,5*S*,8*S*)-1,8-Di-{[*tert*-butyl(dimethyl)silyl]oxy}-12-[(4-methoxybenzyl)oxy]dodec-6-yne-4,5-diol (15)

$(DHQ)_2PHAL$ (83 mg, cat.), $K_3Fe(CN)_6$ (10.4 mg, 31 mmol, 3 equiv), K_2CO_3 (4.4 g, 31 mmol, 3 equiv), and $K_2OsO_2(OH)_4$ (20 mg, cat.) were dissolved in a 1:1 mixture of H_2O (56 mL) and *t*-BuOH (56 mL). $MeSO_2NH_2$ (1.04 g, 10.3 mmol, 1 equiv) was added and the vigorously stirred solution was cooled to 0 °C. At this point, the enyne **14** (5.8 g, 10.34 mmol) was added in one portion and the mixture was allowed to warm to r.t. within 4 h. Stirring was continued for 20 h before the reaction was quenched by the addition of solid Na_2SO_3 (13.6 g). The solution was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (PE–EtOAc, 6:1 – 1:1) to give 5.0 g (81%) of diol **15** as a light yellow oil; R_f = 0.25 (PE–EtOAc, 6:1); $[\alpha]_D^{20}$ –22.9 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.06 [s, 6 H, 1-OSi$(CH_3)_2$], 0.08, 0.10 82 s, 3 H each, Si$(CH_3)_2$], 0.88 [s, 9 H, 1-OSi$(CH_3)_2$C(C$H_3)_3$], 0.89 [s, 9 H, 8-OSi$(CH_3)_2$C(C$H_3)_3$], 1.37–1.91 (m, 10 H, 2-H, 3-H, 9-H, 10-H, 11-H), 3.42 (t, *J* = 6.5 Hz, 2 H, 12-H), 3.53–3.72 (m, 3 H, 4-H, 1-H), 3.79 (s, 3 H, CH_3O), 4.12–4.19 (m, 1 H, 5-H), 4.36 (t, *J* = 5.9 Hz, 1 H, 8-H), 4.41 (s, 2 H, PMB CH_2), 6.86 (d, *J* = 8.4 Hz, 2 H, CH_{arom}, *meta*), 7.24 (d, *J* = 8.1 Hz, 2 H, CH_{arom}, *ortho*).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.4 [1-OSi$(CH_3)_2$], –5.0 [8-OSi$(CH_3)_2$], –4.5 [8-OSi$(CH_3)_2$], 18.2 [1-OSi$(CH_3)_2C(CH_3)_3$], 18.3 [8-OSi$(CH_3)_2C(CH_3)_3$], 21.9 (C-10), 25.8 [8-OSi$(CH_3)_2$C($CH_3)_3$], 25.9 [1-OSi$(CH_3)_2$C($CH_3)_3$], 28.9 (C-11), 29.3 (C-2), 30.2 (C-3), 38.2 (C-9), 55.2 (CH_3O), 62.8 (C-8), 63.5 (C-1), 66.3 (C-5), 69.9 (C-12), 72.5 (PMB CH_2), 74.6 (C-4), 82.3 (C-6), 87.8 (C-7), 113.7 (CH_{arom}, *meta*), 129.2 (CH_{arom}, *ortho*), 130.7 (C_{arom}), 159.1 (C_{arom}, *para*).

HRMS (ESI): *m/z* calcd for $C_{32}H_{58}O_6Si_2$ + Na $[M + Na]^+$: 617.36641; found: 617.36645.

(4*S*,5*S*,6*E*,8*S*)-1,8-Di-{[*tert*-butyl(dimethyl)silyl]oxy}-12-[(4-methoxybenzyl)oxy]dodec-6-ene-4,5-diol (16)

To a stirred solution of diol **15** (2.0 g, 3.36 mmol) in THF (100 mL) was added at –10 °C a solution of Red-Al (4.0 mL, 65% in toluene, 10.0 mmol, 3 equiv). The mixture was allowed to warm to 0 °C and stirring was continued for 24 h. After quenching with aq 1 N HCl (50 mL), the mixture was extracted with EtOAc (3 × 70 mL). The combined organic layers were washed with brine (70 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (PE–EtOAc, 3:1) to give 1.4 g (70%) of diol **16** as a light yellow oil; R_f = 0.17 (PE–EtOAc, 3:1); $[\alpha]_D^{20}$ –9.4 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01, 0.03 [2 s, 3 H each, Si$(CH_3)_2$], 0.06 [s, 6 H, 1-OSi$(CH_3)_2$], 0.87 [s, 9 H, 1-OSi$(CH_3)_2$C(C$H_3)_3$], 0.89 [s, 9 H, 8-OSi$(CH_3)_2$C(C$H_3)_3$], 1.28–1.74 (m, 10 H, 2-H, 3-H, 9-H, 10-H, 11-H), 3.41 (t, *J* = 6.6 Hz, 3 H, 4-H, 12-H), 3.61–3.71 (m, 2 H, 1-H), 3.79 (s, 3 H, CH_3O), 3.84–3.91 (m, 1 H, 5-H), 4.06–4.14 (m, 1 H, 8-H), 4.41 (s, 2 H, PMB CH_2), 5.46–5.64 (m, 1 H, 6-H), 5.65–5.80 (m, 1 H, 7-H), 6.86 (d, *J* = 8.7 Hz, 2 H, CH_{arom}, *meta*), 7.24 (d, *J* = 8.7 Hz, 2 H, CH_{arom}, *ortho*).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.5 [1-OSi$(CH_3)_2$], –4.8 [8-OSi$(CH_3)_2$], –4.3 [8-OSi$(CH_3)_2$], 18.2 [1-OSi$(CH_3)_2C(CH_3)_3$], 18.3 [8-OSi$(CH_3)_2C(CH_3)_3$], 21.9 (C-10), 25.9 [8-OSi$(CH_3)_2$C($CH_3)_3$], 25.9 [1-OSi$(CH_3)_2$C($CH_3)_3$], 29.0 (C-11), 29.7 (C-2), 30.6 (C-3), 37.9 (C-9), 55.2 (CH_3O), 63.6 (C-1), 70.0 (C-12), 72.5 (C-8), 72.7 (PMB CH_2), 74.3 (C-4), 75.6 (C-5), 113.7 (CH_{arom}, *meta*), 128.6 (C-6), 129.2 (CH_{arom}, *ortho*), 130.7 (C_{arom}), 136.9 (C-7), 159.1 (C_{arom}, *para*).

HRMS (ESI): *m/z* calcd for $C_{32}H_{60}O_6Si_2$ + Na $[M + Na]^+$: 619.38206; found: 619.38204.

(4*S*,5*S*,6*E*,8*S*)-1,8-Di-{[*tert*-butyl(dimethyl)silyl]oxy}-5-{[*tert*-butyl(diphenyl)silyl]oxy}-12-[(4-methoxybenzyl)oxy]dodec-6-ene-4-ol (17)

To a stirred solution of diol **16** (1.54 g, 2.58 mmol) in CH_2Cl_2 (200 mL) was added imidazole (530 mg, 7.74 mmol, 3 equiv) and DMAP (cat.). After cooling to 0 °C, TBDPSCl (0.67 mL, 2.2 mmol, 1.1 equiv) was added and the mixture stirred for 5 h. This was followed by the addition of brine (100 mL) and separation of the layers. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (PE–EtOAc, 15:1) to give 1.8 g (84%) of alcohol **17** as a light yellow oil; R_f = 0.60 (PE–EtOAc, 6:1); $[\alpha]_D^{20}$ +6.3 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.08, –0.04 [2 s, 3 H each, 8-OSi$(CH_3)_2$], 0.01 [s, 6 H, 1-OSi$(CH_3)_2$], 0.82 [s, 9 H, 1-OSi$(CH_3)_2$C(C$H_3)_3$], 0.86 [s, 9 H, 8-OSi$(CH_3)_2$C(C$H_3)_3$], 1.03 [s, 9 H, OSi$(Ph)_2$C(C$H_3)_3$], 1.10–1.68 (m, 10 H, 2-H, 3-H, 9-H, 10-H, 11-H), 2.61 (d, *J* = 4.6 Hz, 1 H, OH), 3.33 (t, *J* = 6.7 Hz, 2 H, 12-H), 3.39–3.47 (m, 1 H, 4-H), 3.56 (t, *J* = 5.5 Hz, 2 H, 1-H), 3.77 (s, 3 H, CH_3O), 3.85–3.89 (m, 1 H, 8-H), 3.98–4.07 (m, 1 H, 5-H), 4.40 (s, 2 H, PMB CH_2), 5.22 (dd, *J* = 15.4, 6.2 Hz, 1 H, 7-H), 5.52 (dd, *J* = 15.5, 7.6 Hz, 1 H, 6-H), 6.85 (d, *J* = 8.7 Hz, 2 H, CH_{arom}, *meta*), 7.24 (d, *J* = 8.7 Hz, 2 H, CH_{arom}, *ortho*), 7.27–7.43 (m, 6 H, C_6H_5), 7.57–7.68 (m, 4 H, C_6H_5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3 [1-OSi$(CH_3)_2$], –4.8 [8-OSi$(CH_3)_2$], –4.3 [8-OSi$(CH_3)_2$], 18.1 [1-OSi$(CH_3)_2C(CH_3)_3$], 18.3 [8-OSi$(CH_3)_2C(CH_3)_3$], 19.4 [OSi$(Ph)_2C(CH_3)_3$], 21.7 (C-10), 25.8 [8-OSi$(CH_3)_2$C($CH_3)_3$], 25.9 [1-OSi$(CH_3)_2$C($CH_3)_3$], 27.0 [OSi$(Ph)_2$C($CH_3)_3$], 29.1 (C-11), 29.3 (C-2), 29.7 (C-3), 37.7 (C-9),

55.2 (CH_3O), 63.4 (C-1), 70.0 (C-12), 72.5 (PMB CH_2), 72.8 (C-8), 74.8 (C-4), 77.6 (C-5), 113.7 (CH_{arom}, *meta*), 127.4 (C_6H_5), 127.6 (C_6H_5), 128.2 (C-6), 129.1 (CH_{arom}, *ortho*), 129.6 (C_6H_5), 129.7 (C_6H_5), 130.7 (C_{arom}), 133.5 (C_6H_5), 133.7 (C_6H_5), 135.8 (C_6H_5), 135.9 (C_6H_5), 137.0 (C-7), 159.1 (C_{arom}, *para*).

HRMS (ESI): *m*/*z* calcd for $C_{48}H_{78}O_6Si_3$ + Na [M + Na]$^+$: 857.49984; found: 857.49946.

Methyl (2*E*,4*R*,5*R*,7*E*)-5-Hydroxy-8-iodo-2,4,7-trimethylocta-2,7-dienoate (18)

To a stirred solution of silyl ether **3** (0.5 g, 1.11 mmol) in a mixture of CH_2Cl_2–MeOH 6:1 (3.5 mL) was added PPTS (cat.) at r.t. After 4 h, the reaction mixture was quenched by the addition of aq sat. $NaHCO_3$ (2 mL), followed by separation of the layers. The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (PE–EtOAc, 5:1) to give 373 mg (99%) of hydroxy ester **18** as a light yellow oil; R_f = 0.80 (PE–EtOAc, 1:1); $[\alpha]_D^{20}$ +33.8 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.08 (d, *J* = 6.6 Hz, 3 H, 4-CH_3), 1.63 (d, *J* = 2.0 Hz, 1 H, OH), 1.85 (m, 6 H, 2-CH_3, 7-CH_3), 2.17–2.44 (m, 2 H, 6-H), 2.46–2.65 (m, 1 H, 4-H), 3.53–3.66 (m, 1 H, 5-H), 3.73 (s, 3 H, OCH_3), 6.02 (s, 1 H, 8-H), 6.59 (dd, *J* = 10.3, 1.4 Hz, 1 H, 3-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.8 (2-CH_3), 15.5 (4-CH_3), 24.0 (7-CH_3), 39.3 (C-4), 45.3 (C-6), 51.8 (OCH_3), 72.1 (C-5), 77.5 (C-8), 128.0 (C-2), 143.3 (C-3), 144.8 (C-7), 168.5 (C-1).

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{19}IO_3$ + Na [M + Na]$^+$: 361.02711; found: 361.02705.

Methyl (2*E*,4*R*,5*R*,7*E*)-5-{2-[(Diethoxy)phosphoryl]acetoxy}-8-iodo-2,4,7-trimethylocta-2,7-dienoate (19)

To a stirred mixture of alcohol **18** (360 mg, 1.10 mmol) and DMAP (cat.) in CH_2Cl_2 (50 mL) at r.t. was added a solution of $(EtO)_2POCH_2CO_2H$ (0.18 mL, 1.11 mmol, 1 equiv) in CH_2Cl_2 (2.5 mL), followed by DCC (334 mg,1.61 mmol, 1.5 equiv). After stirring for 40 min, the reaction mixture was concentrated in vacuo and the residue was purified by flash chromatography (PE–EtOAc, 3:1 → 1:2) to give 547 mg (99%) of phosphonate **19**; R_f = 0.27 (PE–EtOAc, 1:1); $[\alpha]_D^{20}$ +25.1 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05 (d, *J* = 6.9 Hz, 3 H, 4-CH_3), 1.33 [(t, *J* = 7.1 Hz, 6 H, ($CH_3CH_2O)_2$], 1.84 (m, 6 H, 2-CH_3, 7-CH_3), 2.32–2.46 (m, 2 H, 6-H), 2.64–2.80 (m, 1 H, 4-H), 2.92 (dd, *J* = 21.6, 1.5 Hz, 2 H, $COCH_2P$), 3.73 (s, 3 H, OCH_3), 4.05–4.25 [m, 4 H, ($CH_3CH_2O)_2$], 4.89–5.06 (m, 1 H, 5-H), 5.95 (s, 1 H, 8-H), 6.53 (dd, *J* = 10.3, 1.4 Hz, 1 H, 3-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.8 (2-CH_3), 15.7 (4-CH_3), 16.3, 16.4 [($OCH_2CH_3)_2$], 24.0 (7-CH_3), 33.6, 34.9 ($COCH_2P$), 37.1 (C-4), 42.3 (C-6), 51.9 (OCH_3), 62.6, 62.7 [($OCH_2CH_3)_2$], 75.2 (C-5), 78.0 (C-8), 128.7 (C-2), 141.7 (C-3), 143.5 (C-7), 165.1, 165.2 ($COCH_2P$), 168.2 (C-1).

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{30}IO_7P$ + Na [M + Na]$^+$: 539.06660; found: 539.06614.

Carbamic Acid (1*S*,2*S*,3*E*,5*S*)-5-{[*tert*-Butyl(dimethyl)silyl]-oxy}-1-{3-[*tert*-butyl(dimethyl)silyl]oxy}propyl]-2-{[*tert*-butyl-(diphenyl)silyl]oxy}-9-[(4-methoxybenzyl)oxy]non-3-enyl Ester (20)

To a stirred solution of alcohol **17** (1.5 g, 1.8 mmol) in CH_2Cl_2 (120 mL) was added trichloroacetyl isocyanate (0.45 mL, 3.8 mmol, 2.1 equiv) at r.t. After stirring for 30 min, MeOH (200 mL), followed by K_2CO_3 (1.15 g, 8.3 mmol, 4.6 equiv) were added and stirring was continued for additional 3 h. The reaction mixture was concentrated and the remaining solid was filtered off. After evaporation of the solvent, purification of the residue by flash chromatography (PE–EtOAc, 5:1) gave 1.49 g (94%) of carbamate **20** as a colorless oil; R_f = 0.29 (PE–EtOAc, 6:1); $[\alpha]_D^{20}$ +2.2 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.03, –0.01 [2 s, 3 H each, 5-$OSi(CH_3)_2$], 0.03 [s, 6 H, 3′-$OSi(CH_3)_2$], 0.86 [s, 9 H, 3′-$OSi(CH_3)_2C(CH_3)_3$], 0.88 [s, 9 H, 5-$OSi(CH_3)_2C(CH_3)_3$], 1.04 [s, 9 H, $OSi(Ph)_2C(CH_3)_3$], 1.13–1.92 (m, 10 H, 1′-H, 2′-H, 6-H, 7-H, 8-H), 3.37 (t, *J* = 6.1 Hz, 2 H, 9-H), 3.50–3.60 (m, 2 H, 3′-H), 3.79 (s, 3 H, CH_3O), 3.91–4.03 (m, 1 H, 5-H), 4.25–4.35 (m, 1 H, 2-H), 4.41 (s, 2 H, PMB CH_2), 4.46 (br s, 2 H, NH_2), 4.60–4.72 (m, 1 H, 1-H), 5.33 (dd, *J* = 15.5, 5.6 Hz, 1 H, 4-H), 5.55 (dd, *J* = 15.4, 7.3 Hz, 1 H, 3-H), 6.86 (d, *J* = 8.7 Hz, 2 H, CH_{arom}, *meta*), 7.24 (d, *J* = 8.4 Hz, 2 H, CH_{arom}, *ortho*), 7.28–7.45 (m, 6 H, C_6H_5), 7.58–7.71 (m, 4 H, C_6H_5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3 [3′-$OSi(CH_3)_2$], –4.9 [5-$OSi(CH_3)_2$], –4.5 [5-$OSi(CH_3)_2$], 18.2 [3′-$OSi(CH_3)_2C(CH_3)_3$], 18.3 [5-$OSi(CH_3)_2C(CH_3)_3$], 19.3 [$OSi(Ph)_2C(CH_3)_3$], 21.4 (C-7), 25.4 (C-2′), 25.8 [5-$OSi(CH_3)_2C(CH_3)_3$], 26.0 [3′-$OSi(CH_3)_2C(CH_3)_3$], 26.9 [$OSi(Ph)_2C(CH_3)_3$], 28.9 (C-8), 29.8 (C-1′), 37.7 (C-6), 55.2 (CH_3O), 63.0 (C-3′), 70.1 (C-9), 72.4 (PMB CH_2), 72.5 (C-5), 74.2 (C-1), buried under $CDCl_3$ (C-2), 113.7 (CH_{arom}, *meta*), 127.1 (C-3), 127.3 (C_6H_5), 127.5 (C_6H_5), 129.2 (CH_{arom}, *ortho*), 129.5 (C_6H_5), 129.6 (C_6H_5), 130.6 (C_{arom}), 133.8 (C_6H_5), 134.0 (C_6H_5), 135.9 (C_6H_5), 135.9 (C_6H_5), 136.7 (C-4), 156.4 ($CONH_2$), 159.1 (C_{arom}, *para*).

HRMS (ESI): *m*/*z* calcd for $C_{49}H_{79}NO_7Si_3$ + Na [M + Na]$^+$: 900.50565; found: 900.50528.

Carbamic Acid (1*S*,2*S*,3*E*,5*S*)-5-{[*tert*-Butyl(dimethyl)silyl]-oxy}-2-{[*tert*-butyl(diphenyl)silyl]oxy}-1-(3-hydroxypropyl)-9-[(4-methoxybenzyl)oxy]non-3-enyl Ester (21)

Carbamate **20** (0.93 g, 1.06 mmol) was dissolved in a mixture of AcOH–H_2O–THF (3:1:1, 15 mL) and stirred at r.t. for 12 h. The reaction mixture was diluted with EtOAc (15 mL). After separation of the layers, the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (PE–EtOAc, 4:1–1:1) to give 606 mg (75%) of alcohol **21** as a light yellow oil (160 mg of carbamate **20** could be recovered); R_f = 0.28 (PE–EtOAc, 1:1); $[\alpha]_D^{20}$ +3.1 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.03, 0.00 [2 s, 3 H each, $OSi(CH_3)_2$], 0.86 [s, 9 H, $OSi(CH_3)_2C(CH_3)_3$], 1.04 [s, 9 H, $OSi(Ph)_2C(CH_3)_3$], 1.17–1.85 (m, 10 H, 1′-H, 2′-H, 6-H, 7-H, 8-H), 2.04 (s, 1 H, OH), 3.37 (t, *J* = 6.6 Hz, 2 H, 9-H), 3.53 (t, *J* = 5.7 Hz, 2 H, 3′-H), 3.79 (s, 3 H, CH_3O), 3.96–4.06 (m, 1 H, 5-H), 4.26–4.34 (m, 1 H, 2-H), 4.40 (s, 2 H, PMB CH_2), 4.44 (br s, 2 H, NH_2), 4.63–4.73 (m, 1 H, 1-H), 5.37 (dd, *J* = 15.7, 5.6 Hz, 1 H, 4-H), 5.56 (dd, *J* = 15.4, 7.3 Hz, 1 H, 3-H), 6.86 (d, *J* = 8.6 Hz, 2 H, CH_{arom}, *meta*), 7.24 (d, *J* = 8.6 Hz, 2 H, CH_{arom}, *ortho*), 7.27–7.44 (m, 6 H, C_6H_5), 7.58–7.71 (m, 4 H, C_6H_5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.8 [$OSi(CH_3)_2$], –4.5 [$OSi(CH_3)_2$], 18.2 [$OSi(CH_3)_2C(CH_3)_3$], 19.3 [$OSi(Ph)_2C(CH_3)_3$], 21.4 (C-7), 25.6 (C-2′), 25.8 [$OSi(CH_3)_2C(CH_3)_3$], 26.9 [$OSi(Ph)_2C(CH_3)_3$], 28.5 (C-8), 29.8 (C-1′), 37.7 (C-6), 55.2 (CH_3O), 62.5 (C-3′), 70.1 (C-9), 72.3 (PMB CH_2), 72.5 (C-5), 74.3 (C-1), 76.5 (C-2), 113.7 (CH_{arom}, *meta*), 127.1 (C-3), 127.4 (C_6H_5), 127.5 (C_6H_5), 129.3 (CH_{arom}, *ortho*), 129.5 (C_6H_5), 129.7 (C_6H_5), 130.6 (C_{arom}), 133.9 (C_6H_5), 135.9 (C_6H_5), 135.9 (C_6H_5), 136.8 (C-4), 156.4 ($CONH_2$), 159.1 (C_{arom}, *para*).

HRMS (ESI): *m*/*z* calcd for $C_{43}H_{65}NO_7Si_2$ + Na [M + Na]$^+$: 786.41918; found: 786.41941.

Carbamic Acid (1*S*,2*S*,3*E*,5*S*)-5-{[*tert*-Butyl(dimethyl)silyl]-oxy}-2-{[*tert*-butyl(diphenyl)silyl]oxy}-9-[(4-methoxybenzyl)-oxy]-1-(3-oxopropyl)non-3-enyl Ester (22)

To a stirred solution of alcohol **21** (928 mg, 1.21 mmol) and $NaHCO_3$ (400 mg, 4.84 mmol, 4 equiv) in CH_2Cl_2 (40 mL) at r.t. was added Dess–Martin periodinane (DMP, 1.05 g, 2.48 mmol, 2 equiv) portionwise and stirring was continued for 3 h. The reaction was quenched by the addition of H_2O (20 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (PE–EtOAc, 3:1) to give 887 mg (96%) of aldehyde **22** as a colorless oil; R_f = 0.62 (PE–EtOAc, 1:1); $[\alpha]_D^{20}$ +0.6 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.03, 0.00 [2 s, 3 H each, $OSi(CH_3)_2$], 0.86 [s, 9 H, $OSi(CH_3)_2C(CH_3)_3$], 1.05 [s, 9 H, $OSi(Ph)_2C(CH_3)_3$], 1.17–2.15 (m, 8 H, 1′-H, 6-H, 7-H, 8-H), 2.40 (t, *J* = 7.1 Hz, 2 H, 2′-H), 3.37 (t, *J* = 5.9 Hz, 2 H, 9-H), 3.79 (s, 3 H, CH_3O), 3.96–4.06 (m, 1 H, 5-H), 4.29–4.36 (m, 1 H, 2-H), 4.40 (s, 2 H, PMB CH_2), 4.53 (br s, 2 H, NH_2), 4.60–4.70 (m, 1 H, 1-H), 5.38 (dd, *J* = 15.5, 5.4 Hz, 1 H, 4-H), 5.57 (dd, *J* = 15.4, 7.8 Hz, 1 H, 3-H), 6.86 (d, *J* = 8.6 Hz, 2 H, CH_{arom}, *meta*), 7.24 (d, *J* = 8.8 Hz, 2 H, CH_{arom}, *ortho*), 7.28–7.46 (m, 6 H, C_6H_5), 7.57–7.70 (m, 4 H, C_6H_5), 9.68 (s, 1 H, 3′-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.9 [$OSi(CH_3)_2$], –4.5 [$OSi(CH_3)_2$], 18.2 [$OSi(CH_3)_2C(CH_3)_3$], 19.3 [$OSi(Ph)_2C(CH_3)_3$], 21.3 (C-7), 21.8 (C-1′), 25.8 [$OSi(CH_3)_2C(CH_3)_3$], 26.9 [$OSi(Ph)_2C(CH_3)_3$], 29.8 (C-8), 37.7 (C-6), 40.1 (C-2′), 55.2 (CH_3O), 70.1 (C-9), 72.2 (PMB CH_2), 72.5 (C-5), 74.1 (C-1), 75.9 (C-2), 113.7 (CH_{arom}, *meta*), 126.6 (C-3), 127.4 (C_6H_5), 127.5 (C_6H_5), 129.2 (CH_{arom}, *ortho*), 129.6 (C_6H_5), 129.7 (C_6H_5), 130.6 (C_{arom}), 133.6 (C_6H_5), 133.7 (C_6H_5), 135.9 (C_6H_5), 135.9 (C_6H_5), 137.2 (C-4), 156.1 ($CONH_2$), 159.1 (C_{arom}, *para*), 201.5 (C-3′).

HRMS (ESI): *m*/*z* calcd for $C_{43}H_{63}NO_7Si_2$ +Na + MeOH [M + MeOH + Na]$^+$: 816.42974; found: 816.43045.

Carbamic Acid (1*S*,2*S*,3*E*,5*S*)-5-{[*tert*-Butyl(dimethyl)silyl]-oxy}-2-{[*tert*-butyl(diphenyl)silyl]oxy}-1-but-3-ynyl-9-[(4-methoxybenzyl)oxy]non-3-enyl Ester (24)

Diethyl 1-diazo-2-oxopropylphosphonate (**23**; 220 mg, 1.06 mmol, 1.5 equiv) was added to a stirred solution of aldehyde **22** (535 mg, 0.7 mmol) and K_2CO_3 (118 mg, 1.19 mmol, 1.7 equiv) in MeOH (9 mL) and stirring was continued at r.t. for 12 h. The reaction mixture was diluted with Et_2O (10 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 10 mL) and the combined organic layers were washed with brine (20 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (PE–EtOAc, 5:1) to give 485 mg (91%) of alkyne **24** as a light yellow oil; R_f = 0.50 (PE–EtOAc, 2:1); $[\alpha]_D^{20}$ –0.5 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.02, 0.00 [2 s, 3 H each, $OSi(CH_3)_2$], 0.86 [s, 9 H, $OSi(CH_3)_2C(CH_3)_3$], 1.05 [s, 9 H, $OSi(Ph)_2C(CH_3)_3$], 1.19–1.67 (m, 8 H, 1′-H, 6-H, 7-H, 8-H), 1.88–1.93 (m, 1 H, 4′-H), 2.01–2.21 (m, 2 H, 2′-H), 3.32–3.43 (m, 2 H, 9-H), 3.79 (s, 3 H, CH_3O), 3.96–4.06 (m, 1 H, 5-H), 4.30–4.38 (m, 1 H, 2-H), 4.40 (s, 2 H, PMB CH_2), 4.41 (s, 2 H, NH_2), 4.67–4.81 (m, 1 H, 1-H), 5.34 (dd, *J* = 15.4, 5.5 Hz, 1 H, 4-H), 5.55 (dd, *J* = 15.5, 7.4 Hz, 1 H, 3-H), 6.86 (d, *J* = 8.7 Hz, 2 H, CH_{arom}, *meta*), 7.24 (d, *J* = 10.2 Hz, 2 H, CH_{arom}, *ortho*), 7.29–7.47 (m, 6 H, C_6H_5), 7.55–7.74 (m, 4 H, C_6H_5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.8 [$OSi(CH_3)_2$], –4.5 [$OSi(CH_3)_2$], 15.0 (C-2′), 18.2 [$OSi(CH_3)_2C(CH_3)_3$], 19.3 [$OSi(Ph)_2C(CH_3)_3$], 21.3 (C-7), 25.8 [$OSi(CH_3)_2C(CH_3)_3$], 27.0 [$OSi(Ph)_2C(CH_3)_3$], 28.1 (C-8), 29.8 (C-1′), 37.7 (C-6), 55.3 (CH_3O), 68.5 (C-4′), 70.1 (C-9), 72.2 (C-5), 72.5 (PMB CH_2), 73.7 (C-2), 75.6 (C-1), 83.7 (C-3′), 113.7 (CH_{arom}, *meta*), 126.7 (C-3), 127.4 (C_6H_5), 127.5 (C_6H_5), 129.2 (CH_{arom}, *ortho*), 129.5 (C_6H_5), 129.7 (C_6H_5), 130.6 (C_{arom}), 133.7 (C_6H_5), 133.8 (C_6H_5), 135.9 (C_6H_5), 137.0 (C-4), 156.1 ($CONH_2$), 159.1 (C_{arom}, *para*).

HRMS (ESI): *m*/*z* calcd for $C_{44}H_{63}NO_6Si_2$ + Na [M + Na]$^+$: 780.40861; found: 780.40900.

Carbamic Acid (1*S*,2*S*,3*E*,5*S*)-5-{[*tert*-Butyl(dimethyl)silyl]-oxy}-2-{[*tert*-butyl(diphenyl)silyl]oxy}-1-but-3-ynyl-9-hydroxy-non-3-enyl Ester (25)

To a stirred solution of alkyne **24** (910 mg, 1.2 mmol) in CH_2Cl_2 (13 mL) was added H_2O (1 mL), followed by DDQ (300 mg, 1.32 mmol, 1.1 equiv). After 6 h, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2. (2 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (PE–EtOAc, 2:1) to give 750 mg (98%) of alkynol **25** as a light brown oil; R_f = 0.25 (PE–EtOAc, 2:1); $[\alpha]_D^{20}$ –1.0 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.02, 0.00 [2 s, 3 H each, $OSi(CH_3)_2$], 0.86 [s, 9 H, $OSi(CH_3)_2C(CH_3)_3$], 1.05 [s, 9 H, $OSi(Ph)_2C(CH_3)_3$], 1.16–2.28 (m, 10 H, 1′-H, 2′-H, 6-H, 7-H, 8-H), 1.88–1.94 (m, 1 H, 4′-H), 3.57 (t, *J* = 6.4 Hz, 2 H, 9-H), 3.99–4.08 (m, 1 H, 5-H), 4.31–4.39 (m, 1 H, 2-H), 4.51 (br s, 2 H, NH_2), 4.70–4.80 (m, 1 H, 1-H), 5.35 (dd, *J* = 15.5, 5.3 Hz, 1 H, 4-H), 5.56 (dd, *J* = 15.5, 7.1 Hz, 1 H, 3-H), 7.30–7.45 (m, 6 H, C_6H_5), 7.57–7.72 (m, 4 H, C_6H_5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.8 [$OSi(CH_3)_2$], –4.5 [$OSi(CH_3)_2$], 15.0 (C-2′), 18.2 [$OSi(CH_3)_2C(CH_3)_3$], 19.4 [$OSi(Ph)_2C(CH_3)_3$], 20.7 (C-7), 25.8 [$OSi(CH_3)_2C(CH_3)_3$], 27.0 [$OSi(Ph)_2C(CH_3)_3$], 28.3 (C-8), 32.7 (C-1′), 37.5 (C-6), 62.9 (C-9), 68.5 (C-4′), 72.2 (C-5), 73.8 (C-2), 75.8 (C-1), 83.7 (C-3′), 126.9 (C-3), 127.4 (C_6H_5), 127.5 (C_6H_5), 129.5 (C_6H_5), 129.7 (C_6H_5), 133.6 (C_6H_5), 135.9 (C_6H_5), 135.9 (C_6H_5), 136.9 (C-4), 156.1 ($CONH_2$).

HRMS (ESI): *m*/*z* calcd for $C_{36}H_{55}NO_5Si_2$ + Na [M + Na]$^+$: 660.35110; found: 660.35065.

Carbamic Acid (1*S*,2*S*,3*E*,5*S*)-5-{[*tert*-Butyl(dimethyl)silyl]-oxy}-2-{[*tert*-butyl(diphenyl)silyl]oxy}-1-but-3-ynyl-9-oxonon-3-enyl Ester (26)

To a stirred solution of alcohol **25** (260 mg, 0.41 mmol) and $NaHCO_3$ (135 mg, 1.61 mmol, 4 equiv) in CH_2Cl_2 (10 mL) at r.t. was added DMP (350 mg, 0.825 mmol, 2 equiv) portionwise and stirring was continued for 2.5 h. The reaction mixture was quenched by the addition of H_2O (5 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (PE–EtOAc, 2:1) to give 221 mg (86%) of aldehyde **26** as colorless oil; R_f = 0.45 (PE–EtOAc, 2:1); $[\alpha]_D^{20}$ –5.5 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.02, 0.00 [2 s, 3 H each, $OSi(CH_3)_2$], 0.86 [s, 9 H, $OSi(CH_3)_2C(CH_3)_3$], 1.05 [s, 9 H, $OSi(Ph)_2C(CH_3)_3$], 1.16–2.42 (m, 10 H, 1′-H, 2′-H, 6-H, 7-H, 8-H), 1.86–1.95 (m, 1 H, 4′-H), 3.96–4.09 (m, 1 H, 5-H), 4.28–4.42 (m, 1 H, 2-H), 4.51 (s, 2 H, NH_2), 4.70–4.84 (m, 1 H, 1-H), 5.33 (dd, *J* = 15.5, 5.6 Hz, 1 H, 4-H), 5.56 (dd, *J* = 15.5, 7.1 Hz, 1 H, 3-H), 7.28–7.48 (m, 6 H, C_6H_5), 7.54–7.73 (m, 4 H, C_6H_5), 9.69 (s, 1 H, 9-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.9 [$OSi(CH_3)_2$], –4.5 [$OSi(CH_3)_2$], 15.0 (C-2′), 17.2 (C-7), 18.2 [$OSi(CH_3)_2C(CH_3)_3$], 19.3 [$OSi(Ph)_2C(CH_3)_3$], 25.8 [$OSi(CH_3)_2C(CH_3)_3$], 26.9 [$OSi(Ph)_2C(CH_3)_3$], 28.2 (C-1′), 37.5 (C-6), 43.8 (C-8), 68.5 (C-4′), 71.9 (C-5), 73.7 (C-2), 75.7 (C-1), 83.6 (C-3′), 127.2 (C-3), 127.4 (C_6H_5), 127.6 (C_6H_5), 129.6 (C_6H_5), 129.8 (C_6H_5), 133.5 (C_6H_5),

133.9 (C_6H_5), 135.9 (C_6H_5), 135.9 (C_6H_5), 136.5 (C-4), 156.3 ($CONH_2$), 202.7 (C-9).

HRMS (ESI): *m/z* calcd for $C_{36}H_{53}NO_5Si_2$ + Na + MeOH [M + MeOH + Na]$^+$: 690.36166; found: 690.36101.

Carbamic Acid (1*S*,2*S*,3*E*,5*S*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-{[*tert*-butyl(diphenyl)silyl]oxy}-9-oxo-1-(4-tributylstannanylbut-3-enyl)non-3-enyl Ester (27)

To a stirred solution of aldehyde **26** (220 mg, 0.35 mmol) in THF (5 mL) was added $Pd(PPh_3)_2Cl_2$ (cat.). Bu_3SnH (0.1 mL, 0.37 mmol, 1.06 equiv) was added slowly and dropwise over a period of 20 min. After 30 min, additional Bu_3SnH (0.1 mL) was added. After 1 h, the reaction mixture was concentrated in vacuo and the residue was purified by flash chromatography (PE–EtOAc, 20:1 → 10:1) to give 188 mg (58%) of stannane **27** as a colorless oil (accompanied by the by-product **30**); R_f = 0.68 (PE–EtOAc, 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.04, –0.01 [2 s, 3 H each, $OSi(CH_3)_2$], 0.81–0.86 [m, 9 H, $OSi(CH_3)_2C(CH_3)_3$], 0.85–0.96 (m, 9 H, 3 × CH_3 tributyl),1.04 [s, 9 H, $OSi(Ph)_2C(CH_3)_3$], 1.14–2.40 (m, 28 H, 1′-H, 2′-H, 6-H, 7-H, 8-H, 3 × $CH_2CH_2CH_2$), 3.91–4.07 (m, 1 H, 5-H), 4.28–4.38 (m, 1 H, 2-H), 4.44 (br s, 2 H, NH_2), 4.63–4.77 (m, 1 H, 1-H), 5.05–5.13 (m, 1 H, 3′-H), 5.29 (dd, *J* = 15.4, 5.8 Hz, 1 H, 4-H), 5.56 (dd, *J* = 15.4, 7.3 Hz, 1 H, 3-H), 5.60–5.67 (m, 1 H, 4′-H), 7.27–7.46 (m, 6 H, C_6H_5), 7.55–7.72 (m, 4 H, C_6H_5), 9.67 (s, 1 H, 9-H).

HRMS (ESI): *m/z* calcd for $C_{48}H_{81}NO_5Si_2Sn$ [M + H]$^+$ (^{116}Sn): 924.47499; found: 924.47471.

Carbamic Acid (1*S*,2*S*,3*E*,5*S*)-1-But-3-enyl-5-{[*tert*-butyl(dimethyl)silyl]oxy}-2-{[*tert*-butyl(diphenyl)silyl]oxy}-9-[(4-methoxybenzyl)oxy]non-3-enyl Ester (28)

The alkyne **24** (695 mg, 0.92 mmol) was dissolved in a 1:1 mixture of acetone and cyclohexene (60 mL each). Quinoline (1 mL, 8.48 mmol, 9 equiv) and Lindlar's catalyst (340 mg, 5% Pd on $CaCO_3$ poisoned with lead, cat.) were added and the reaction mixture was stirred under a H_2 atmosphere for 8 h. The catalyst was filtered off and after concentration in vacuo the residue was purified by flash chromatography (PE–EtOAc, 20:1 → 4:1) to give 643 mg (92%) of alkene **28** as a light yellow oil; R_f = 0.60 (PE–EtOAc, 2:1); $[\alpha]_D^{20}$ –0.6 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.03, –0.01 [2 s, 3 H each, $OSi(CH_3)_2$], 0.85 [s, 9 H, $OSi(CH_3)_2C(CH_3)_3$], 1.04 [s, 9 H, $OSi(Ph)_2C(CH_3)_3$], 1.16–1.89 (m, 8 H, 1′-H, 6-H, 7-H, 8-H), 1.91–2.14 (m, 2 H, 2′-H), 3.26–3.46 (m, 2 H, 9-H), 3.79 (s, 3 H, CH_3O), 3.93–4.03 (m, 1 H, 5-H), 4.28–4.35 (m, 1 H, 2-H), 4.40 (s, 2 H, PMB CH_2), 4.41 (br s, 2 H, NH_2), 4.63–4.73 (m, 1 H, 1-H), 4.89–5.01 (m, 2 H, 4′-H), 5.34 (dd, *J* = 15.6, 5.5 Hz, 1 H, 4-H), 5.55 (dd, *J* = 15.5, 7.1 Hz, 1 H, 3-H), 5.66–5.81 (m, 1 H, 3′-H), 6.86 (d, *J* = 8.7 Hz, 2 H, CH_{arom}, *meta*), 7.24 (d, *J* = 8.7 Hz, 2 H, CH_{arom}, *ortho*), 7.28–7.44 (m, 6 H, C_6H_5), 7.51–7.75 (m, 4 H, C_6H_5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.8 [$OSi(CH_3)_2$], –4.5 [$OSi(CH_3)_2$], 18.2 [$OSi(CH_3)_2C(CH_3)_3$], 19.3 [$OSi(Ph)_2C(CH_3)_3$], 21.4 (C-7), 25.9 [$OSi(CH_3)_2C(CH_3)_3$], 26.9 [$OSi(Ph)_2C(CH_3)_3$], 28.4 (C-8), 29.6 (C-2′), 29.8 (C-1′), 37.7 (C-6), 55.3 (CH_3O), 70.1 (C-9), 72.4 (C-5), 72.5 (PMB CH_2), 74.2 (C-2), 76.3 (C-1), 113.8 (CH_{arom}, *meta*), 114.8 (C-4′), 127.2 (C-3), 127.4 (C_6H_5), 127.5 (C_6H_5), 129.2 (CH_{arom}, *ortho*), 129.5 (C_6H_5), 129.7 (C_6H_5), 130.7 (C_{arom}), 133.8 (C_6H_5), 133.9 (C_6H_5), 135.9 (C_6H_5), 136.8 (C-4), 138.0 (C-3′), 156.3 ($CONH_2$), 159.1 (C_{arom}, *para*).

HRMS (ESI): *m/z* calcd for $C_{44}H_{65}NO_6Si_2$ + Na [M + Na]$^+$: 782.42426; found: 782.424306.

Carbamic Acid (1*S*,2*S*,3*E*,5*S*)-1-But-3-enyl-5-{[*tert*-butyl(dimethyl)silyl]oxy}-2-{[*tert*-butyl(diphenyl)silyl]oxy}-9-hydroxynon-3-enyl Ester (29)

To a stirred solution of alkene **28** (608 mg, 0.8 mmol) in CH_2Cl_2 (6 mL) was added H_2O (1 mL), followed by DDQ (270 mg, 1.2 mmol, 1.5 equiv). After stirring for 12 h, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with H_2O (5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (PE–EtOAc, 1:1) to give 412 mg (80%) of alkenol **29** as a slightly brown oil; R_f = 0.22 (PE–EtOAc, 2:1); $[\alpha]_D^{20}$ –0.8 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.03, 0.00 [2 s, 3 H each, $OSi(CH_3)_2$], 0.85 [s, 9 H, $OSi(CH_3)_2C(CH_3)_3$], 1.04 [s, 9 H, $OSi(Ph)_2C(CH_3)_3$], 1.17–1.88 (m, 8 H, 1′-H, 6-H, 7-H, 8-H), 1.90–2.14 (m, 2 H, 2′-H), 3.56 (t, *J* = 6.6 Hz, 2 H, 9-H), 3.95–4.07 (m, 1 H, 5-H), 4.25–4.36 (m, 1 H, 2-H), 4.50 (br s, 2 H, NH_2), 4.64–4.74 (m, 1 H, 1-H), 4.86–5.02 (m, 2 H, 4′-H), 5.34 (dd, *J* = 15.5, 5.4 Hz, 1 H, 4-H), 5.56 (dd, *J* = 15.0, 6.7 Hz, 1 H, 3-H), 5.65–5.81 (m, 1 H, 3′-H), 7.28–7.45 (m, 6 H, C_6H_5), 7.57–7.70 (m, 4 H, C_6H_5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.9 [$OSi(CH_3)_2$], –4.5 [$OSi(CH_3)_2$], 18.2 [$OSi(CH_3)_2C(CH_3)_3$], 19.4 [$OSi(Ph)_2C(CH_3)_3$], 20.8 (C-7), 25.8 [$OSi(CH_3)_2C(CH_3)_3$], 26.9 [$OSi(Ph)_2C(CH_3)_3$], 28.5 (C-8), 29.6 (C-2′), 32.7 (C-1′), 37.5 (C-6), 62.8 (C-9), 72.3 (C-5), 74.2 (C-2), 76.4 (C-1), 114.8 (C-4′), 127.4 (C-3), 127.4 (C_6H_5), 127.5 (C_6H_5), 129.5 (C_6H_5), 129.7 (C_6H_5), 133.8 (C_6H_5), 134.0 (C_6H_5), 135.9 (C_6H_5), 136.6 (C-4), 138.0 (C-3′), 156.4 ($CONH_2$).

HRMS (ESI): *m/z* calcd for $C_{36}H_{57}NO_5Si_2$ + Na [M + Na]$^+$: 662.36675; found: 662.366327.

Carbamic Acid (1*S*,2*S*,3*E*,5*S*)-1-But-3-enyl-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-{[*tert*-butyl(diphenyl)silyl]oxy}-9-oxononon-3-enyl Ester (30)

To a stirred solution of alcohol **29** (220 mg, 0.34 mmol) and $NaHCO_3$ (115 mg, 1.37 mmol, 4 equiv) in CH_2Cl_2 (10 mL) at r.t. was added DMP (300 mg, 0.71 mmol, 2 equiv) portionwise and stirring was continued for 3 h. The reaction mixture was quenched by the addition of H_2O (5 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (PE–EtOAc, 5:1) to give 165 mg (75%) of aldehyde **30** as a colorless oil; R_f = 0.46 (PE–EtOAc, 2:1); $[\alpha]_D^{20}$ –1.4 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.03, 0.00 [2 s, 3 H each, $OSi(CH_3)_2$], 0.85 [s, 9 H, $OSi(CH_3)_2C(CH_3)_3$], 1.04 [s, 9 H, $OSi(Ph)_2C(CH_3)_3$], 1.15–1.88 (m, 6 H, 1′-H, 6-H, 7-H), 1.92–2.14 (m, 2 H, 2′-H), 2.21–2.41 (m, 2 H, 8-H), 3.92–4.10 (m, 1 H, 5-H), 4.22–4.37 (m, 1 H, 2-H), 4.49 (br s, 2 H, NH_2), 4.62–4.77 (m, 1 H, 1-H), 4.85–5.06 (m, 2 H, 4′-H), 5.32 (dd, *J* = 15.7, 5.6 Hz, 1 H, 4-H), 5.57 (dd, *J* = 15.5, 7.2 Hz, 1 H, 3-H), 5.65–5.85 (m, 1 H, 3′-H), 7.28–7.48 (m, 6 H, C_6H_5), 7.51–7.76 (m, 4 H, C_6H_5), 9.68 (s, 1 H, 9-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.9 [$OSi(CH_3)_2$], –4.5 [$OSi(CH_3)_2$], 17.3 [$OSi(CH_3)_2C(CH_3)_3$], 18.1 [$OSi(Ph)_2C(CH_3)_3$], 19.3 (C-7), 25.8 [$OSi(CH_3)_2C(CH_3)_3$], 26.9 [$OSi(Ph)_2C(CH_3)_3$], 28.5 (C-1′), 29.6 (C-2′), 37.0 (C-6), 43.8 (C-8), 72.1 (C-5), 74.1 (C-2), 76.3 (C-1), 114.8 (C-4′), 127.4 (C_6H_5), 127.5 (C_6H_5), 127.7 (C-3), 129.5 (C_6H_5), 129.7 (C_6H_5), 134.0 (C_6H_5), 135.9 (C_6H_5), 136.2 (C-4), 138.0 (C-3′), 156.3 ($CONH_2$), 202.7 (C-9).

HRMS (ESI): *m/z* calcd for $C_{36}H_{55}NO_5Si_2$ + Na + MeOH [M + MeOH + Na]$^+$: 692.37731; found: 692.378059.

(2*E*,7*S*,8*E*,10*S*,11*S*,14*E*)-7-{[*tert*-Butyl(dimethyl)silyl]oxy}-10-{[*tert*-butyl(diphenyl)silyl]oxy}-11-carbamoyloxy-15-tributylstannanylpentadeca-2,8,14-trienoic Acid 1′-(3″-Iodo-2″-methylallyl)-4′-methoxycarbonyl-2′-methylpent-3′-enyl Ester (31)

Aldehyde **27** (135 mg, 0.146 mmol) and phosphonate **19** (100 mg, 0.194 mmol, 1.3 equiv) were dissolved in MeCN (ca. 1 mL). To this stirred solution, LiCl (74 mg, 1.745 mmol, 12 equiv) and *i*-Pr_2NEt (0.3 mL, 1.764 mmol, 12 equiv) were added and the resulting mixture was stirred for 4 h at r.t. After evaporation of of the solvent, the residue was purified by flash chromatography (PE–EtOAc, 8:1) to give 185 mg (98%) of enoate **31** as a colorless oil; R_f = 0.53 (PE–EtOAc, 3:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.05, –0.01 [2 s, 3 H each, $OSi(CH_3)_2$], 0.84 [s, 9 H, $OSi(CH_3)_2C(CH_3)_3$], 0.87 (t, *J* = 7.5 Hz, 9 H, 3 × CH_3 tributyl), 1.01 (d, *J* = 6.9 Hz, 3 H, 2′-CH_3), 1.04 [s, 9 H, $OSi(Ph)_2C(CH_3)_3$], 1.16–1.60 (m, 22 H, 3 × $CH_2CH_2CH_2$, 5-H, 6-H), 1.83 (s, 6 H, 2″-CH_3, 5′-H), 1.96–2.30 (m, 6 H, 4-H, 12-H, 13-H), 2.40 (d, *J* = 6.4 Hz, 2 H, 1″-H), 2.68–2.82 (m, 1 H, 2′-H), 3.73 (s, 3 H, OCH_3), 3.91–4.02 (m, 1 H, 7-H), 4.26–4.34 (m, 1 H, 10-H), 4.35 (s, 2 H, NH_2), 4.65–4.76 (m, 1 H, 11-H), 4.96–5.05 (m, 1 H, 1′-H), 5.08, 5.63 (2 s, 0.5 H each, 15-H), 5.33 (m, 1 H, 8-H), 5.53 (dd, *J* = 15.5, 7.1 Hz, 1 H, 9-H), 5.70–5.79 (m, 1 H, 2-H), 5.85–5.88 (m, 1 H, 14-H) 5.91 (s, 1 H, 3″-H), 6.56 (d, *J* = 10.4 Hz, 1 H, 3′-H), 6.81–6.96 (m, 1 H, 3-H), 7.29–7.46 (m, 6 H, C_6H_5), 7.59–7.71 (m, 4 H, C_6H_5).

HRMS (ESI): *m*/*z* calcd for $C_{62}H_{100}INO_8Si_2Sn$ [M + H]$^+$(^{116}Sn): 1286.51304; found: 1286.51367.

Macrolactone 32 Formation via Stille Coupling (*E*/*Z* Mixture + 14,15-*E*)

To a stirred solution of stannane **31** (190 mg, 0.147 mmol) in DMF (1 mL) were added dried LiCl (2.4 mg, 0.057 mmol, 0.4 equiv), $PdCl_2(MeCN)_2$ (8 mg, 0.031 mmol, 0.2 equiv), (2-furyl)$_3$P (14.3 mg, 0.061 mmol, 0.4 equiv), and *i*-Pr_2NEt (0.1 mL, 0.588 mmol, 4 equiv) at r.t. After stirring for 6–8 h, the reaction was quenched by the addition of H_2O (5 mL) and EtOAc (8 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 8 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (PE–EtOAc, 10:1 → 5:1) to give 70 mg (54%) of lactone **32** (pure *E*,*E*-isomer) as light brown foam and a mixed fraction of *E*,*E*- and *E*,*Z*-isomers. The remaining mixture of *E*,*E*- and *E*,*Z*-isomers was dissolved in hexane (2 mL) and treated with I_2 (cat. amount, 2–3 crystals) under reflux for 30–45 min. After evaporation of the solvent, the residue was purified by flash chromatography (PE–EtOAc, 5:1) to give 30 mg (23%) of lactone **32** as pure *E*,*E*-isomer (total yield: 77%); *E*,*E*-isomer: R_f = 0.27 (PE–EtOAc, 3:1); *E*,*Z*-isomer: R_f = 0.28 (PE–EtOAc, 3:1); $[\alpha]_D^{20}$ –31.5 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01, 0.03 [2 s, 3 H each, $OSi(CH_3)_2$], 0.88 [s, 9 H, $OSi(CH_3)_2C(CH_3)_3$], 1.01 (d, *J* = 6.9 Hz, 3 H, 20-CH_3), 1.08 [s, 9 H, $OSi(Ph)_2C(CH_3)_3$], 1.17–1.58 (m, 8 H, 5-H, 6-H, 12-H, 13-H), 1.67 (s, 3 H, 17-CH_3), 1.85 (s, 3 H, 22-CH_3), 1.97–2.27 (m, 4 H, 4-H, 18-H), 2.64–2.78 (m, 1 H, 20-H), 3.74 (s, 3 H, OCH_3), 3.96–4.09 (m, 1 H, 7-H), 4.35–4.50 (m, 4 H, 10-H, 11-H, NH_2), 4.92–5.04 (m, 1 H, 19-H), 5.35–5.71 (m, 4 H, 8-H, 9-H, 14-H, 16-H), 5.75 (d, *J* = 15.5 Hz, 1 H, 2-H), 6.03 (dd, *J* = 15.0, 10.9 Hz, 1 H, 15-H), 6.57 (d, *J* = 11.7 Hz, 1 H, 21-H), 6.74–6.87 (m, 1 H, 3-H), 7.29–7.45 (m, 6 H, C_6H_5), 7.58–7.73 (m, 4 H, C_6H_5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.8 [$OSi(CH_3)_2$], –4.4 [$OSi(CH_3)_2$], 12.8 (C-22 CH_3), 16.3 (C-20 CH_3), 16.5 (C-17 CH_3), 18.2 [$OSi(CH_3)_2C(CH_3)_3$], 19.4 [$OSi(Ph)_2C(CH_3)_3$], 24.4 (C-5), 25.9 [$OSi(CH_3)_2C(CH_3)_3$], 27.1 [$OSi(Ph)_2C(CH_3)_3$], 29.4 (C-13), 29.5 (C-12), 33.0 (C-4), 38.0 (C-20), 38.3 (C-6), 43.7 (C-18), 51.9 (OCH_3), 72.4 (C-11), 73.6 (C-19), 73.6 (C-7), 76.3 (C-10), 121.0 (C-2), 126.5 (C-15), 127.5 (C_6H_5), 127.6 (C_6H_5), 127.9 (C-9), 128.4 (C-16), 129.6 (C_6H_5), 129.8 (C_6H_5), 131.3 (C-22), 132.5 (C-14), 133.3 (C-17), 134.1 (C_6H_5), 134.9 (C-8), 135.8 (C_6H_5), 135.9 (C_6H_5), 142.5 (C-21), 149.4 (C-3), 156.1 ($CONH_2$), 166.3 (C-1), 168.4 (C-23).

HRMS (ESI): *m*/*z* calcd for $C_{50}H_{73}NO_8Si_2$ + Na [M + Na]$^+$: 894.47669; found: 894.47683.

(2*E*,7*S*,8*E*,10*S*,11*S*)-7-{[*tert*-Butyl(dimethyl)silyl]oxy}-10-{[*tert*-butyl(diphenyl)silyl]oxy}-11-carbamoyloxypentadeca-2,8,14-trienoic Acid 1-(3″-iodo-2″-methylallyl)-4′-methoxycarbonyl-2′-methylpent-3′-enyl Ester (33)

Aldehyde **30** (150 mg, 0.235 mmol) and phosphonate **19** (143 mg, 0.277 mmol, 1.2 equiv) were dissolved in MeCN (ca. 3 mL). To this stirred solution LiCl (112.5 mg, 2.653 mmol, 11 equiv) and *i*-Pr_2NEt (0.45 mL, 2.65 mmol, 11 equiv) were added and the resulting mixture was stirred for 5 h at r.t. After evaporation of of the solvent, the residue was purified by flash chromatography (PE–EtOAc, 6:1) to give 210 mg (92%) of enoate **33** as a light yellow oil; R_f = 0.57 (PE–EtOAc, 2:1); $[\alpha]_D^{20}$ +16.9 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.04, 0.00 [2 s, 3 H each, $OSi(CH_3)_2$], 0.85 [s, 9 H, $OSi(CH_3)_2C(CH_3)_3$], 1.01 (d, *J* = 6.6 Hz, 3 H, 2′-CH_3), 1.04 [s, 9 H, $OSi(Ph)_2C(CH_3)_3$], 1.14–1.75 (m, 6 H, 5-H, 6-H, 13-H), 1.83 (s, 6 H, 2″-CH_3, 5′-H), 1.89–2.23 (m, 4 H, 4-H, 12-H), 2.40 (d, *J* = 6.3 Hz, 2 H, 1″-H), 2.65–2.84 (m, 1 H, 2′-H), 3.73 (s, 3 H, OCH_3), 3.91–4.05 (m, 1 H, 7-H), 4.27–4.36 (m, 1 H, 10-H), 4.38 (br s, 2 H, NH_2), 4.61–4.77 (m, 1 H, 11-H), 4.87–5.08 (m, 3 H, 1′-H, 15-H), 5.36 (dd, *J* = 15.7, 5.8 Hz, 1 H, 8-H), 5.54 (dd, *J* = 15.4, 6.8 Hz, 1 H, 9-H), 5.66–5.80 (m, 2 H, 2-H, 14-H), 5.90 (s, 1 H, 3″-H), 6.56 (d, *J* = 11.6 Hz, 1 H, 3′-H), 6.82–6.97 (m, 1 H, 3-H), 7.28–7.46 (m, 6 H, C_6H_5), 7.57–7.72 (m, 4 H, C_6H_5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.8 [$OSi(CH_3)_2$], –4.4 [$OSi(CH_3)_2$], 12.8 (C-5′), 15.9 (C-2′CH_3), 18.2 [$OSi(CH_3)_2C(CH_3)_3$], 19.3 [$OSi(Ph)_2C(CH_3)_3$], 23.3 (C-5), 24.1 (C-2″CH_3), 25.8 [$OSi(CH_3)_2C(CH_3)_3$], 26.9 [$OSi(Ph)_2C(CH_3)_3$], 29.6 (C-13), 29.7 (C-12), 32.2 (C-4), 37.2 (C-2′), 37.4 (C-6), 42.0 (C-1″), 51.9 (OCH_3), 72.4 (C-7), 73.7(C-1′), 74.1(C-10), 76.4 (C-11), 77.8 (C-3″), 114.8 (C-15), 120.8 (C-2), 127.4 (C_6H_5), 127.5 (C_6H_5), 127.6 (C-9), 128.6 (C-4′), 129.5 (C_6H_5), 129.7 (C_6H_5), 133.7 (C_6H_5), 134.0 (C_6H_5), 135.9 (C_6H_5), 136.5 (C-8), 137.9 (C-14), 142.0 (C-3′), 143.7 (C-2″), 150.0 (C-3), 156.2 ($CONH_2$), 166.0 (C-1), 168.3 (C-4′CO_2Me).

HRMS (ESI): m/z calcd for $C_{50}H_{74}INO_8Si_2$ + Na [M + Na]$^+$: 1022.38899; found: 1022.389415.

Macrolactone 32 Formation via Heck-Coupling (14,15-*E*)

To a stirred solution of vinyl iodide **33** (10 mg, 0.01 mmol) in DMF (1 mL) were added Cs_2CO_3 (5 mg, 0.015 mmol, 1.5 equiv), $Pd(AcO)_2$ (3 mg, 0.013 mmol, 1.3 equiv), and Et_3N (1.5 μL, 0.011 mmol, 1.1 equiv) at r.t. After stirring for 1–2 h, the reaction was quenched by the addition of H_2O (1 mL) and EtOAc (2 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (PE–EtOAc, 10:1 – 5:1) to give 6 mg (81%) of lactone **32** (*E*,*E*-isomer) as a light yellow foam.

Saponification of Ester 32 to Acid 34

To a stirred solution of lactone **32** (70 mg, 0.08 mmol) in EtOH (1 mL) were added H_2O (3–4 drops) and LiOH (cat.) at r.t. After 14 h, the reaction mixture was quenched by the addition of H_2O (4 mL) and EtOAc (8 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (PE–EtOAc, 3:1) to give 42 mg (62%) of acid **34** as a colorless, viscous oil, while 20 mg (29%) of the starting material were recovered back. If the reaction

time becomes too long (>24 h), some amount of decarbamated acid will form; R_f = 0.48 (PE–EtOAc, 1:1); $[\alpha]_D^{20}$ –35.6 (*c* 0.8, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01, 0.03 [2 s, 3 H each, $OSi(CH_3)_2$], 0.88 [s, 9 H, $OSi(CH_3)_2C(CH_3)_3$], 1.03 (d, *J* = 6.6 Hz, 3 H, 20-CH_3), 1.08 [s, 9 H, $OSi(Ph)_2C(CH_3)_3$], 1.19–1.57 (m, 8 H, 5-H, 6-H, 12-H, 13-H), 1.67 (s, 3 H, 17-CH_3), 1.86 (s, 3 H, 22-CH_3), 1.96–2.27 (m, 4 H, 4-H, 18-H), 2.65–2.85 (m, 1 H, 20-H), 3.97–4.09 (m, 1 H, 7-H), 4.37–4.51 (m, 2 H, 10-H, 11-H), 4.62 (br s, 2 H, NH_2), 4.94–5.06 (m, 1 H, 19-H), 5.35–5.71 (m, 4 H, 8-H, 9-H, 14-H, 16-H), 5.75 (d, *J* = 15.5, 1 H, 2-H), 6.04 (dd, *J* = 14.2, 11.2 Hz, 1 H, 15-H), 6.70 (d, *J* = 9.7 Hz, 1 H, 21-H), 6.75–6.88 (m, 1 H, 3-H), 7.29–7.46 (m, 6 H, C_6H_5), 7.58–7.72 (m, 4 H, C_6H_5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.8 [$OSi(CH_3)_2$], –4.4 [$OSi(CH_3)_2$], 12.5 (C-22 CH_3), 16.1 (C-20 CH_3), 16.5 (C-17 CH_3), 18.2 [$OSi(CH_3)_2C(CH_3)_3$], 19.4 [$OSi(Ph)_2C(CH_3)_3$], 24.4 (C-5), 25.9 [$OSi(CH_3)_2C(CH_3)_3$], 27.1 [$OSi(Ph)_2C(CH_3)_3$], 29.4 (C-13), 29.5 (C-12), 33.0 (C-4), 38.1 (C-20), 38.3 (C-6), 43.7 (C-18), 72.4 (C-11), 73.5 (C-19), 73.6 (C-7), 76.5 (C-10), 121.0 (C-2), 126.6 (C-15), 127.5 (C_6H_5), 127.6 (C_6H_5), 127.9 (C-9), 128.4 (C-16), 129.7 (C_6H_5), 129.8 (C_6H_5), 131.2 (C-22), 132.5 (C-14), 133.3 (C-17), 134.1 (C_6H_5), 134.9 (C-8), 135.9 (C_6H_5), 135.9 (C_6H_5), 144.6 (C-21), 149.5 (C-3), 156.5 ($CONH_2$), 166.3 (C-1), 172.1 (C-23).

HRMS (ESI): *m*/*z* calcd for $C_{49}H_{71}NO_8Si_2$ + Na $[M + Na]^+$: 880.46104; found: 880.45955.

Reduction of Acid 34 to Primary Alcohol 35

To a stirred solution of acid **34** (30 mg, 0.035 mmol) in THF (4 mL) was added Et_3N (5.3 μL, 0.039 mmol, 1.1 equiv). At 0 °C, methyl chloroformate (4 mL, 0.039 mmol, 1.1 equiv) was added. After 10 min, the white solid was filtered off and the residue was concentrated to approximately 1 mL. At 0 °C, a solution of $NaBH_4$ (5 mg, 0.13 mmol, 3–4 equiv) in MeOH (0.1 mL) was added. The mixture was allowed to warm to r.t. and after 1 h, the reaction was quenched by the addition of H_2O (5 mL) and EtOAc (8 mL) followed by separation of the layers. The aqueous layer was extracted with EtOAc (2 × 8 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (PE–EtOAc, 3:1 → 2:1) to give 23 mg (80%) of alcohol **35** as a white foam; R_f = 0.57 (PE–EtOAc, 1:1); $[\alpha]_D^{20}$ –46.3 (*c* 1.0, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01, 0.03 [2 s, 3 H each, $OSi(CH_3)_2$], 0.88 [s, 9 H, $OSi(CH_3)_2C(CH_3)_3$], 0.96 (d, *J* = 6.6 Hz, 3 H, 20-CH_3), 1.08 [s, 9 H, $OSi(Ph)_2C(CH_3)_3$], 1.17–1.60 (m, 8 H, 5-H, 6-H, 12-H, 13-H), 1.67 (s, 6 H, 17-CH_3, 22-CH_3), 1.78–2.26 (m, 4 H, 4-H, 18-H), 2.52–2.68 (m, 1 H, 20-H), 3.97–4.06 (m, 3 H, 7-H, 23-H), 4.29–4.54 (m, 4 H, 10-H, 11-H, NH_2), 4.84–4.96 (m, 1 H, 19-H), 5.24 (d, *J* = 9.7 Hz, 1 H, 21-H), 5.35–5.71 (m, 4 H, 8-H, 9-H, 14-H, 16-H), 5.75 (d, *J* = 15.5 Hz, 1 H, 2-H), 6.04 (dd, *J* = 14.8, 10.9 Hz, 1 H, 15-H), 6.71–6.86 (m, 1 H, 3-H), 7.30–7.45 (m, 6 H, C_6H_5), 7.58–7.70 (m, 4 H, C_6H_5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.8 [$OSi(CH_3)_2$], –4.4 [$OSi(CH_3)_2$], 14.1 (C-22 CH_3), 16.5 (C-20 CH_3), 17.0 (C-17 CH_3), 18.2 [$OSi(CH_3)_2C(CH_3)_3$], 19.4 [$OSi(Ph)_2C(CH_3)_3$], 24.4 (C-5), 25.9 [$OSi(CH_3)_2C(CH_3)_3$], 27.1 [$OSi(Ph)_2C(CH_3)_3$], 29.5 (C-13), 29.5 (C-12), 33.0 (C-4), 36.9 (C-20), 38.3 (C-6), 43.8 (C-18), 68.6 (C-23), 72.4 (C-11), 73.6 (C-7), 74.4 (C-19), 76.4 (C-10), 121.2 (C-2), 126.6 (C-15), 127.3 (C-21), 127.5 (C_6H_5), 127.6 (C_6H_5), 127.9 (C-9), 128.1 (C-16), 129.7 (C_6H_5), 129.8 (C_6H_5), 131.8 (C-22), 132.2 (C-14), 133.3 (C-17), 134.1 (C_6H_5), 134.9 (C-8), 135.9 (C_6H_5), 135.9 (C_6H_5), 149.0 (C-3), 156.0 ($CONH_2$), 166.5 (C-1).

HRMS (ESI): *m*/*z* calcd for $C_{49}H_{73}NO_7Si_2$ + Na $[M + Na]^+$: 866.48178; found: 866.48250.

Aldehyde 36

To a stirred solution of alcohol **35** (32 mg, 0.038 mmol) and $NaHCO_3$ (10 mg, 0.119 mmol, 3 equiv) in CH_2Cl_2 (2 mL) at r.t. was added DMP (33 mg, 0.078 mmol, 2 equiv) portionwise and stirring was continued for 1 h. The reaction was quenched by the addition of H_2O (6 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 8 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (PE–EtOAc, 6:1 – 3:1) to give 30 mg (96%) of aldehyde **36** as a colorless oil; R_f = 0.68 (PE–EtOAc, 1:1); $[\alpha]_D^{20}$ –46.2 (*c* 1.0, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01, 0.03 [2 s, 3 H each, $OSi(CH_3)_2$], 0.88 [s, 9 H, $OSi(CH_3)_2C(CH_3)_3$], 1.06 (d, *J* = 4.8 Hz, 3 H, 20-CH_3), 1.08 [s, 9 H, $OSi(Ph)_2C(CH_3)_3$], 1.18–1.64 (m, 8 H, 5-H, 6-H, 12-H, 13-H), 1.68 (s, 3 H, 17-CH_3), 1.76 (s, 3 H, 22-CH_3), 1.83–2.54 (m, 4 H, 4-H, 18-H), 2.83–3.02 (m, 1 H, 20-H), 3.93–4.11 (m, 1 H, 7-H), 4.35 (s, 1 H, NH_2), 4.39–4.54 (m, 4 H, 10-H, 11-H), 4.95–5.15 (m, 1 H, 19-H), 5.33–5.71 (m, 4 H, 8-H, 9-H, 14-H, 16-H), 5.76 (d, *J* = 15.7 Hz, 1 H, 2-H), 6.04 (dd, *J* = 14.9, 10.9 Hz, 1 H, 15-H), 6.29 (d, *J* = 8.8 Hz, 1 H, 21-H), 6.72–6.93 (m, 1 H, 3-H), 7.29–7.49 (m, 6 H, C_6H_5), 7.56–7.75 (m, 4 H, C_6H_5), 9.42 (s, 1 H, 23-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.8 [$OSi(CH_3)_2$], –4.4 [$OSi(CH_3)_2$], 9.7 (C-22 CH_3), 15.8 (C-20 CH_3), 16.5 (C-17 CH_3), 18.2 [$OSi(CH_3)_2C(CH_3)_3$], 19.4 [$OSi(Ph)_2C(CH_3)_3$], 24.4 (C-5), 25.9 [$OSi(CH_3)_2C(CH_3)_3$], 27.1 [$OSi(Ph)_2C(CH_3)_3$], 29.4 (C-13), 29.6 (C-12), 33.1 (C-4), 38.1 (C-20), 38.3 (C-6), 43.6 (C-18), 72.5 (C-11), 73.0 (C-19), 73.6 (C-7), 76.4 (C-10), 120.8 (C-2), 126.4 (C-15), 127.5 (C_6H_5), 127.6 (C_6H_5), 128.0 (C-9), 128.7 (C-16), 129.7 (C_6H_5), 129.8 (C_6H_5), 132.8 (C-14), 133.3 (C-17), 134.1 (C_6H_5), 134.9 (C-8), 135.9 (C_6H_5), 135.9 (C_6H_5), 139.7 (C-22), 149.7 (C-3), 154.1 (C-21), 156.0 ($CONH_2$), 166.2 (C-1), 195.1 (C-23).

HRMS (ESI): *m*/*z* calcd for $C_{49}H_{71}NO_7Si_2$ + Na $[M + Na]^+$: 864.46613; found: 864.46615.

Vinyl Iodide 37

To a stirred suspension of $CrCl_2$ (20 mg, 0.16 mmol, 8 equiv) in THF (0.2 mL) at 0 °C was added a solution of aldehyde **36** (18 mg, 0.02 mmol) and CHI_3 (40 mg, 0.10 mmol, 5 equiv) in THF (0.1 mL) dropwise. The reaction mixture was allowed to warm to r.t. and stirring was continued for 2 h. The reaction mixture was quenched by the addition of H_2O (2 mL) and diluted with EtOAc (6 mL). The layers were separated. The aqueous layer was extracted with EtOAc (2 × 6 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (PE–EtOAc, 10:1 → 7:1, + 0.05% Et_3N) to give 19 mg (92%) of vinyl iodide **37** as a colorless oil; R_f = 0.65 (PE–EtOAc, 2:1); $[\alpha]_D^{20}$ –7.5 (*c* 1.0, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01, 0.03 [2 s, 3 H each, $OSi(CH_3)_2$], 0.88 [s, 9 H, $OSi(CH_3)_2C(CH_3)_3$], 0.97 (d, *J* = 4.8 Hz, 3 H, 20-CH_3), 1.08 [s, 9 H, $OSi(Ph)_2C(CH_3)_3$], 1.38–1.62 (m, 6 H, 5-H, 6-H, 12-H), 1.66 (s, 3 H, 17-CH_3), 1.73 (s, 3 H, 22-CH_3), 1.80–2.27 (m, 6 H, 4-H, 13-H, 18-H), 2.60–2.74 (m, 1 H, 20-H), 3.98–4.08 (m, 1 H, 7-H), 4.36 (br s, 1 H, NH_2), 4.40–4.50 (m, 4 H, 10-H, 11-H), 4.84–4.97 (m, 1 H, 19-H), 5.28 (d, *J* = 10.6 Hz, 1 H, 21-H), 5.34–5.71 (m, 4 H, 8-H, 9-H, 14-H, 16-H), 5.74 (d, *J* = 15.4 Hz, 1 H, 2-H), 6.03 (dd, *J* = 15.2, 10.9 Hz, 1 H, 15-H), 6.21 (d, *J* = 14.7 Hz, 1 H, 24-H), 6.72–6.88 (m, 1 H, 3-H), 7.04 (d, *J* = 14.7 Hz, 1 H, 23-H), 7.29–7.45 (m, 6 H, C_6H_5), 7.58–7.71 (m, 4 H, C_6H_5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.8 [$OSi(CH_3)_2$], –4.4 [$OSi(CH_3)_2$], 12.4 (C-22 CH_3), 16.5 (C-17 CH_3), 16.9 (C-20 CH_3), 18.2 [$OSi(CH_3)_2C(CH_3)_3$], 19.4 [$OSi(Ph)_2C(CH_3)_3$], 24.4 (C-5), 25.9 [$OSi(CH_3)_2C(CH_3)_3$], 27.1 [$OSi(Ph)_2C(CH_3)_3$], 29.4 (C-13), 29.7 (C-12), 33.0 (C-4), 37.3 (C-20), 38.3 (C-6), 43.8 (C-18), 72.4 (C-10), 73.7 (C-7), 74.0 (C-19), 74.4 (C-24), 76.4 (C-11), 121.1 (C-

2), 126.6 (C-15), 127.5 (C_6H_5), 127.6 (C_6H_5), 127.9 (C-9), 128.3 (C-16), 129.7 (C_6H_5), 129.8 (C_6H_5), 131.5 (C-22), 132.4 (C-14), 133.3 (C-17), 134.9 (C_6H_5), 135.0 (C-8), 135.2 (C-21), 135.9 (C_6H_5), 135.9 (C_6H_5), 149.2 (C-23), 149.5 (C-3), 156.0 ($CONH_2$), 166.4 (C-1).

HRMS (ESI): *m/z* calcd for $C_{50}H_{72}INO_6Si_2$ + Na $[M + Na]^+$: 988.38351; found: 988.38302.

Macrolactone 38

To a stirred solution of vinyl iodide **37** (8 mg, 0.008 mmol) in THF (1.2 mL) was added HF·py complex (70% HF, 30% pyridine) (0.9 mL) at –30 °C. The reaction mixture was warmed to 0 °C and stirred for 24 h. After 24 h additional HF·py complex (0.3 mL) was added and stirring was continued for additional 24 h (ratio HF·py/THF = 3:4–1:1). The reaction mixture was quenched by the addition of solid K_2CO_3 until pH 8. The resulting precipitate was filtered off and the residue was concentrated in vacuo. After purification by flash chromatography (EtOAc + 0.05% Et_3N) 4 mg (80%) of diol **38** was obtained as a colorless oil; $R_f = 0.15$ (PE–EtOAc, 1:8); $[\alpha]_D^{20}$ –8.4 (*c* 0.2, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (d, *J* = 6.6 Hz, 3 H, 20-CH_3), 1.18–1.60 (m, 6 H, 5-H, 6-H, 12-H), 1.68 (s, 3 H, 17-CH_3), 1.73 (s, 3 H, 22-CH_3), 1.95–2.32 (m, 6 H, 4-H, 13-H, 18-H), 2.59–2.78 (m, 1 H, 20-H), 4.04–4.17 (m, 1 H, 7-H), 4.23–4.37 (m, 1 H, 10-H), 4.62–4.76 (m, 3 H, 11-H, NH_2), 4.87–4.99 (m, 1 H, 19-H), 5.28 (d, *J* = 9.4 Hz, 1 H, 21-H), 5.38–5.54 (m, 1 H, 14-H), 5.59–5.83 (m, 4 H, 2-H, 8-H, 9-H, 16-H), 6.11 (dd, *J* = 14.6, 10.8 Hz, 1 H, 15-H), 6.21 (d, *J* = 14.8 Hz, 1 H, 24-H), 6.82 (ddd, *J* = 15.3, 9.6, 5.1 Hz, 1 H, 3-H), 7.04 (d, *J* = 14.8 Hz, 1 H, 23-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.4 (C-22 CH_3), 16.4 (C-17 CH_3), 16.9 (C-20 CH_3), 24.7 (C-5), 28.9 (C-13), 30.3 (C-12), 32.7 (C-4), 36.8 (C-20), 37.3 (C-6), 43.7 (C-18), 72.3 (C-10), 73.0 (C-7), 74.0 (C-19), 74.4 (C-24), 77.1 (C-11), 121.3 (C-2), 127.2 (C-15), 128.0 (C-9), 129.6 (C-16), 131.2 (C-22), 132.0 (C-14), 134.2 (C-17), 135.0 (C-8), 135.2 (C-21), 148.8 (C-3), 149.5 (C-23), 156.9 ($CONH_2$), 166.3 (C-1).

HRMS (ESI): *m/z* calcd for $C_{28}H_{40}INO_6$ + Na $[M + Na]^+$: 636.17925; found: 636.17964.

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