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Approach to the Core Structure of 15-*epi*-Exiguolide

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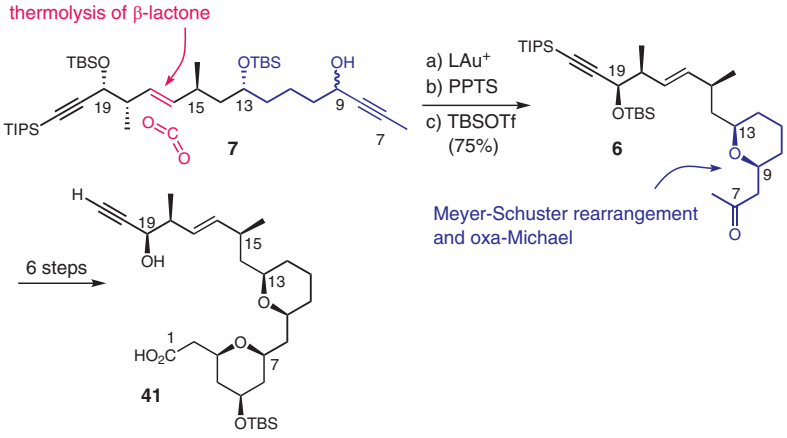

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Abstract The synthesis of seco acid **41** of the macrolactone part of 15-*epi*-exiguolide, containing a bis-pyran subunit and a *trans* double bond, is described. Key features of the synthetic strategy include a Feringa–Minnaard asymmetric organocuprate addition to unsaturated ester **17** to set the stereocenter at C15. The derived acid **8** (C9–C16 fragment) was ideally suited for combination with aldehyde **9** (C17–C21 fragment) via an aldol strategy leading to β-lactone **25** which upon thermal decarboxylation provided alkene **26**. Chain extension led to propargylic alcohol **7**. Treatment of **7** with a LAu^+ catalyst promoted a Meyer–Schuster rearrangement to enone **30** that led to *cis*-tetrahydropyran **31** via intramolecular oxa-Michael reaction. The second pyran ring was prepared from alkoxy ketone **5** by reductive cyclization. The further steps toward macrolactone **43** were hampered by the epimeric mixture at C5.

Key words exiguolide, β-lactone, Meyer–Schuster rearrangement, tetrahydropyrans, alkenes, Mulzer–Adam olefination

Polyketide-based macrolactones commonly feature substituents or transannular ether bridges to restrict the conformational freedom and to provide defined local conformations. Biosynthetic considerations make it understandable that tetrahydropyran rings are frequently seen in macrocyclic polyketides.[1] A few natural products, for example (–)-exiguolide (**1**) and the bryostatins (Figure 1), even contain two or more tetrahydropyran rings. Exiguolide (**1**) is a 20-membered macrolactone known since 2006.[2] It was isolated from the marine sponge *Geodia exigua*. Key structural features include two *cis*-2,6-disubstituted tetrahydropyran rings, one of them carrying an exocyclic enoate, one *trans* double bond within the macrocyclic ring, and a triene-containing side chain extending from C19. The C16–C17 double bond is flanked by two methyl-bearing stereocenters that might impede olefination reactions. Originally reported to inhibit the fertilization of sea urchin gametes, it was later shown that exiguolide has antiproliferative activity against some human cancer cell lines with IC_{50} values in the low micromolar range.[3,4]

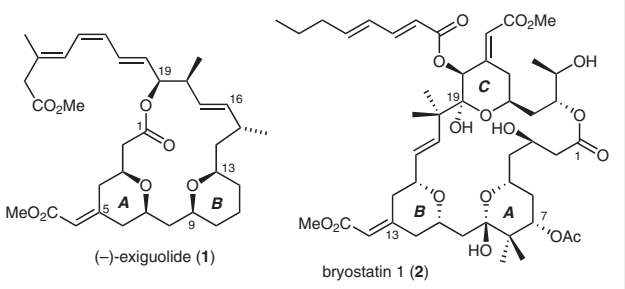


Figure 1 Structures of (–)-exiguolide (**1**) and bryostatin 1 (**2**)

In 2008 a paper by Cossy pointed out the structural similarity to the bryostatins.[5] These polyketides feature three tetrahydropyran rings, one double bond in the macrolactone and several stereocenters. They elicit a range of biological activities, but most important is their ability to modulate the activity of protein kinase C.[6] However, the total synthesis of bryostatins requires too many steps, making access to these compounds difficult.[7] Efforts by the Wender group generated much simpler bryostatin analogues, some of which show comparable activities as the natural lead compound.[8] If the Cossy hypothesis would be true, even more simple bryostatin analogues might be discovered. However, this seems questionable since the lower regions of these macrolides are quasi-enantiomeric so binding to the same protein targets seems unlikely.

So far, six total syntheses of exiguolide have been reported.[3,4,9] Three syntheses rely on a ring-closing metathesis (rcm) with formation of the C16–C17 double bond. In this context, the type of functional group extending from C19 seems to be crucial. Thus, the rcm on substrates with a vinyl iodide side chain gives low yields of the corresponding

macrolactone. In two of the total syntheses, macrolactonization strategies came into use. In the synthesis by the Scheidt group,[3] an intramolecular Prins cyclization led to the macrolactone. The shortest synthesis so far requires 19 steps in the longest linear sequence with an overall yield of 16.8%.[9b] Here, the two pyran rings were constructed by Prins cyclizations. Regarding the synthesis of exiguolide analogues, major contributions have come from the Fuwa group.[4,10] This work led to the SAR findings shown in Figure 2. Thus, the 15-CH_3 is not essential, whereas the exocyclic enoate seems to be crucial. The C20–C23 *E,Z*-diene, the correct length of the side chain and a heteroatom at C27 are also required for the antiproliferative activity. Tests on the A549 cell line showed that exiguolide arrests the cell cycle at the G1 phase. It seems that exiguolide inhibits phosphorylation and therefore activity of the retinoblastoma protein, a tumor suppressor protein.[11] However, it is still not known with certainty whether (–)-exiguolide really represents a simplified bryostatin. Accordingly, further analogues would be desirable.

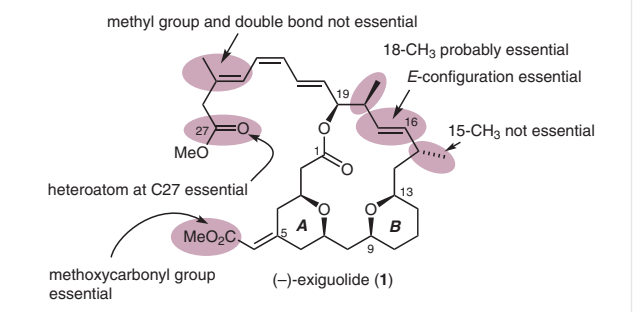
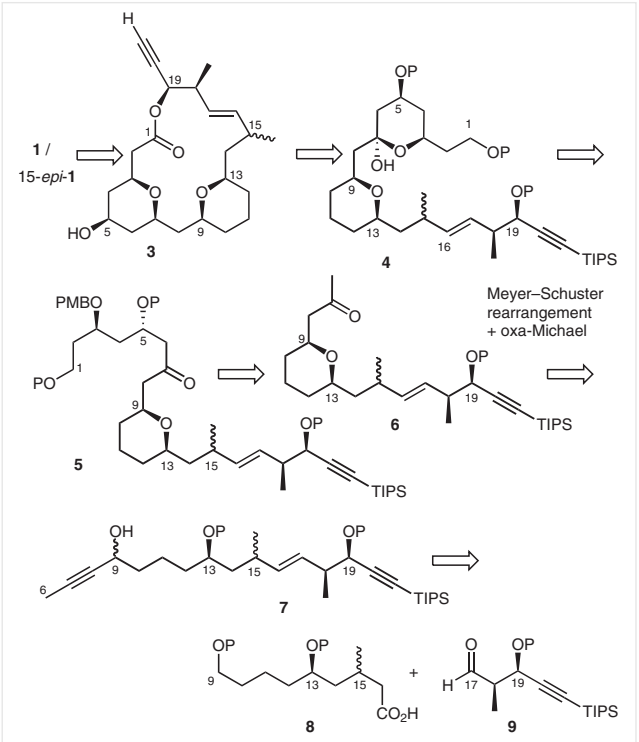


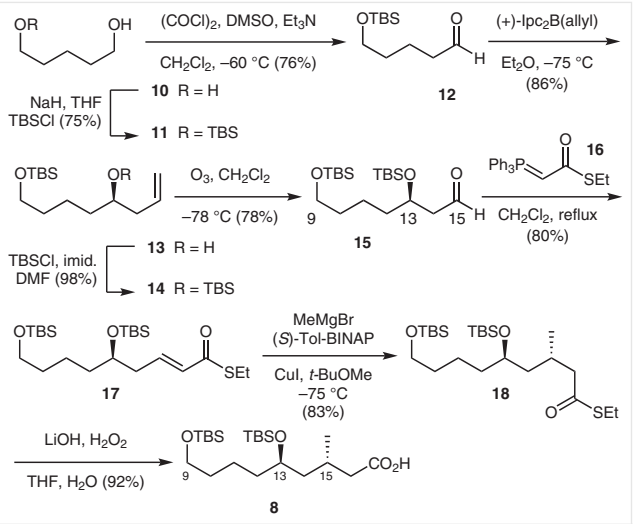
Figure 2 Key structure–activity findings by the Fuwa group[10]

Our interest in exiguolide was triggered by its appealing structure, its biology and the fact that we recently had found a method based on a Meyer–Schuster rearrangement for the synthesis of 2,6-*cis*-tetrahydropyrans.[12] In this transformation a substrate with a 6-heptyne-1,5-diol substructure (compound **7**) undergoes a gold(I)-catalyzed rearrangement to a 7-hydroxy enone that can cyclize to a tetrahydropyran (compound **6**) via an intramolecular oxa-Michael reaction. For the methyl-bearing stereocenter at C15, we opted for a Feringa–Minnaard asymmetric methyl cuprate addition to an enoate derivative, giving an acid of type **8**. We also hoped to utilize the 3-methyl carboxylic acid derivative for a subsequent olefination reaction (Scheme 1). The second tetrahydropyran ring would be constructed by chain extension of methyl ketone **6** and ionic reduction of a derived hemiacetal **4**. The exocyclic enoate extending from C5 would be installed by an asymmetric Horner–Wadsworth–Emmons reaction after macrolactonization. By chosing 15-*epi*-exiguolide as target, we hoped to modulate the activity or even redirect the analogue to another protein target.[13]



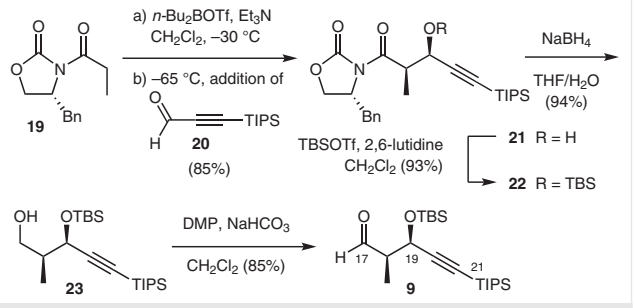
Scheme 1 Retrosynthetic plan for the synthesis of (–)-exiguolide and congeners; P = *tert*-butyldimethylsilyl (TBS)

We started the synthesis with the preparation of the C9–C16 fragment **8**, which carries two stereocenters. Thus, monoprotection of pentane-1,5-diol (**10**) with *tert*-butyldimethylsilyl chloride to alcohol **11** was followed by oxidation to pentanal derivative **12** using Swern conditions (Scheme 2).[12,14] Next, a Brown allylation[15] using (–)-Ipc_2BH[16] as the boron source established the stereocenter at C13, furnishing homoallyl alcohol[17] **13** in 86% yield and 95% ee. Subsequent protection of the alcohol function of **13** as *tert*-butyldimethylsilyl (TBS) ether **14** and ozonolysis of the double bond provided aldehyde **15** in good yield. Aldehyde **15** was used for chain extension with the stabilized ylide[18] **16** resulting in enethioate **17**. The methyl-bearing stereocenter at C15 was established using a Feringa–Minnaard asymmetric conjugate addition to unsaturated thioester **17**.[19,20] As we planned to prepare C15-*epi*-exiguolide, (*S*)-Tol-BINAP was used as a chiral ligand. Thus, enethioate **17** was reacted with MeMgBr (5 equiv) in the presence of (*S*)-Tol-BINAP (ca. 0.75 mol%) and CuI (1 mol%) in *t*-BuOMe at –75 °C to give thioester **18** in 83% yield (20 g scale). A final hydrolysis of the thioester function of **18** furnished carboxylic acid **8**.



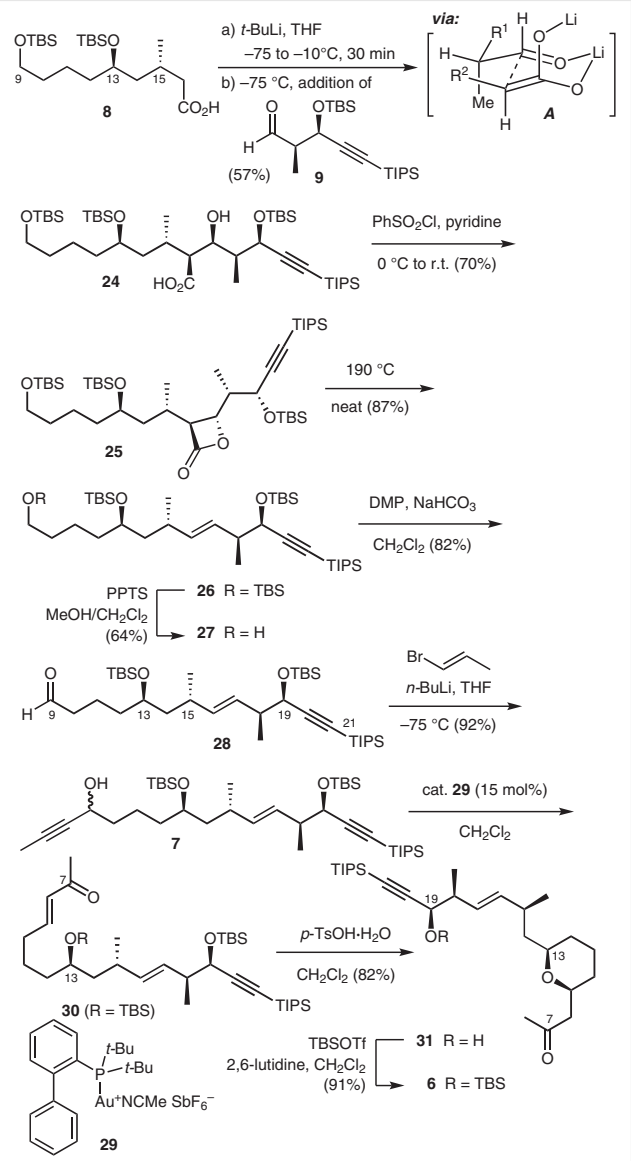
Scheme 2 Synthesis of carboxylic acid **8** (C9–C16 fragment). The allylborane reagent was prepared from (+)-α-pinene.

We next focused on the preparation of an aldehyde fragment **9** which would be combined with acid **8** in a Mulzer–Adam-type olefination reaction.[21] The synthesis of building block **9** began with an Evans aldol reaction between oxazolidinone[22] **19** and propynal derivative[23] **20** (Scheme 3). Classical conditions using the boron enolate of **19** and running the aldol reaction in CH_2Cl_2 at –65 °C provided an 85% yield of *syn*-aldol product **21**. Thereafter routine functional group manipulations, namely protection of the alcohol function as the TBS ether to give **22**, reductive removal of the chiral auxiliary and Dess–Martin periodinane (DMP) oxidation of alcohol **23**, furnished aldehyde **9**.



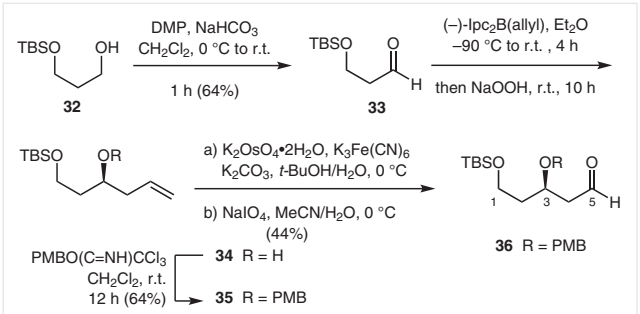
Scheme 3 Synthesis of pent-4-ynal derivative **9** (C17–C21 fragment) via an aldol strategy

With both fragments **8** and **9** in hand, we could then focus on their combination (Scheme 4). As far as we know, formation of an alkene of the size of **26**, with methine groups flanking the alkene, via an intermediate β-lactone has never been reported. The aldol reaction between acid **8** and aldehyde **9** turned out to be nontrivial. Thus, formation of the dilithium enolate of acid **8** with 2 equivalents of either *n*-BuLi, *N*-naphthalenide or $NaN(SiMe_3)_2$ in THF at –75 °C for 1 hour led to decomposition of the acid. This was detected after quenching of the enolate solution with pH 7 buffer solution. With LDA and *t*-BuLi at –75 to 0 °C for 1 hour, enolate formation was successful and did not lead to decomposition of the acid. In the aldol reaction, best results were obtained with *t*-BuLi, deprotonation at –75 to –10 °C, followed by addition of aldehyde **9** at –75 °C and stirring of the mixture at this temperature for 14 hours. Under these conditions, 57% of hydroxy acid **24** was obtained. Due to signal overlap in the ^{1}H NMR spectrum of **24**, we were not sure about the stereochemistry and the presence of isomers. The structure was tentatively assigned based on the chair-like transition state model ***A*** (Scheme 4) similar to attack of an *E*-enolate to an aldehyde with an α-methyl substituent.[24] Formation of the β-lactone was achieved by stirring hydroxy acid **24** with benzenesulfonyl chloride in pyridine. Lactone **25** essentially showed only one set of signals in the ^{13}C NMR spectrum indicating its isomeric purity. The thermal fragmentation of β-lactone **25** to alkene **26** was best performed neat at an oil bath temperature of 190 °C. This way, a 87% yield of *trans*-alkene **26** could be obtained. In the ^{1}H NMR spectrum of **26**, the coupling constant J = 15.4 Hz between the olefinic protons indicated formation of the *trans* double bond. We also tried to form β-lactone **25** from the corresponding 2-pyridyl thioester in a domino Mukaiyama aldol reaction/lactonization (LiTMP, THF, TESCl, –78 °C, 2 h, addition of $ZnCl_2$, r.t., 2 h, then addition of **9**, 50 °C, 3 d);[25] however, the expected **25** was not formed. Continuing with the synthesis, the primary alcohol function was deprotected by acid-catalyzed transetherification to give alcohol **27**. Its oxidation with Dess–Martin periodinane (DMP) led to aldehyde **28**. The propynyllithium species for addition to aldehyde **28** was generated from 1-bromoprop-1-ene using *n*-BuLi (1.5 equiv). This gave propargylic alcohol **7** as a nonsignificant mixture[26] of diastereomers. The key Meyer–Schuster rearrangement of **7** with the Echavarren catalyst[27] **29** was highly dependent on the catalyst loading. Here, the intermediate enone **30** typically was not isolated but rather treated in the same pot with *p*-TsOH to induce the intramolecular oxa-Michael addition to tetrahydropyran derivative **31**. Whereas 10 mol% of **29** gave methyl ketone **31** in 46% yield, 15 mol% of **29** led to ketone **31** in acceptable 82% yield. Reprotection of the 19-OH function as the TBS ether delivered key fragment **6**. In the NOESY spectrum, 9-H (δ = 3.68 ppm) and 13-H (δ = 3.28 ppm) showed a very strong cross-peak, indicating their *cis* configuration at the tetrahydropyran ring.



Scheme 4 Synthesis of alkene **26**, Meyer–Schuster rearrangement of alkynol **7** and formation of tetrahydropyran **6** (C6–C21 fragment)

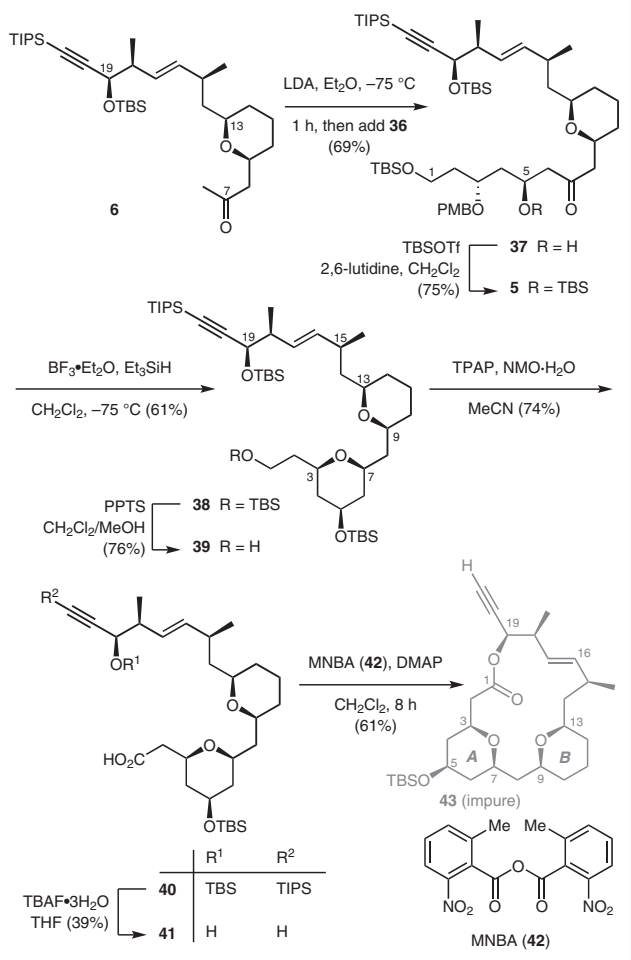
We then could turn to the synthesis of aldehyde **36** which corresponds to the C1–C5 fragment. The requirement for formation of the pyran ring ***A*** was a protected alcohol at C3 that could be liberated in a selective manner to form a hemiacetal with the keto function at C7. Therefore, we opted for a PMB protecting group for the 3-OH. Thus, known monoprotected propanediol[28] **32** was oxidized to aldehyde[29] **33** and then subjected to a Brown allylation[15] with (–)-*B*-allyldiisopinocampheylborane, prepared from (+)-α-pinene, leading to homoallyl alcohol **34** (Scheme 5). The enantiomeric excess was 91%, as determined by chiral GC. Since protection of alcohol **34** to give PMB ether **35** under basic conditions (NaH, PMBCl, DMF, 0 °C) proceeded only in a moderate yield of 40%, we used the PMB imidate[30] for this etherification (64%). For conversion of the terminal double bond into the aldehyde **36** we relied on a dihydroxylation reaction followed by oxidative cleavage of the intermediate diol.



Scheme 5 Synthesis of aldehyde **36** (C1–C5 fragment)

Next, we focused on the combination of aldehyde **36** with methyl ketone **6** to a C1–C21 fragment. Thus, reaction of the lithium enolate of **6**, prepared from ketone **6** and LDA, with aldehyde **36** gave hydroxy ketone **37** as a 3:1 mixture of diastereomers at C5 (Scheme 6).[31] Since this alcohol function would be oxidized at a later stage, the mixture was used as such for the further steps. After protection of the alcohol function as TBS ether **5**, the crucial pyran formation was investigated. Initial attempts at oxidative cleavage of the PMB ether using DDQ in MeOH/CH_2Cl_2 resulted in decomposition; using water instead of MeOH gave an intermediate hemiacetal in 48% yield. Ceric ammonium nitrate in acetone/H_2O led to decomposition as well. The best overall results were obtained with Et_3SiH in the presence of $BF_3{\cdot}Et_2O$. In this case, a one-step reductive removal of the PMB ether and ionic reduction of the hemiacetal took place, leading to bis-tetrahydropyran **38** in 61% yield. In the next step, selective cleavage of the silyl ether at C1 was performed using acid-catalyzed transetherification in a mixture of MeOH/CH_2Cl_2. The resulting primary alcohol **39** was then oxidized to acid **40** using Stark conditions,[32] where tetrapropylammonium perruthenate was used as catalyst together with *N*-methylmorpholine *N*-oxide (NMO) as oxidant. The NOESY spectrum of acid **40** showed the expected correlation for 3-H/7-H as well as 9-H/13-H indicating the *cis* configuration in the respective tetrahydropyran rings. In preparation for the crucial macrolactonization, acid **40** was treated with tetra-*n*-butylammonium fluoride hydrate which gave seco acid **41**. Surprisingly, the equatorial-positioned silyl ether at C5 was retained. We tried the macrolactonization with the Shiina method, which utilizes 2-methyl-6-nitrobenzoic anhydride (MNBA, **42**) to convert the acid function of ω-hydroxy acid **41** into a reactive mixed anhydride that undergoes the lactonization.[33] While the macrolactone formation could be realized (~60%), the compound was not 100% clean. Moreover, we were not able to cleave

the remaining silyl ether of lactone **43**, neither under acidic conditions (AcOH, CSA) nor under conditions that utilize fluoride (TBAF, HF·py).



Scheme 6 Combination of methyl ketone **6** with aldehyde **36** via aldol reaction to give the C1–C21 fragment **5**, subsequent formation of the second tetrahydropyran, and ring closure to macrolactone **43**. For C5, the stereochemistry of the major isomer is depicted.

In conclusion, we have described a novel strategy to the core structure of the macrolactone exiguolide, exemplified with the synthesis of seco acid **41** that would lead to 15-*epi*-exiguolide. For the construction of the C9–C21 building block **28** we used a Feringa–Minnaard asymmetric methyl cuprate addition to set the methyl-bearing stereocenter at C15. The C16–C17 *trans* double bond was created by combining carboxylic acid **8** with aldehyde **9**, leading to β-lactone **25**. Thermal decarboxylation of **25** provided the desired alkene **26**. This is probably the most complex compound prepared using this Mulzer–Adam olefination strategy. Another key transformation was a domino Meyer–Schuster rearrangement of propargylic alcohol **7** to an enone followed by an intramolecular oxa-Michael addition providing the *cis*-configured tetrahydropyran derivative **31**. Chain extension of the methyl ketone via aldol reaction eventually led to hydroxy ketone **5** which was cyclized through ionic reduction to deliver bis-tetrahydropyran **38**. Functional group manipulations gave seco acid **41** which was converted into macrolactone **43** (impure) using the Shiina method.

Reactions were generally run under nitrogen atmosphere in oven-dried glassware. Progress of the reactions was followed using POLYGRAM SIL G/UV254 TLC plates, and petroleum ether/Et_2O mixtures of them as an eluent. Anhydrous Et_2O and THF were distilled from sodium and benzophenone, whereas anhydrous CH_2Cl_2 and MeOH were distilled from CaH_2. Distilled petroleum ether with a boiling range of 40–60 °C was used. Ozonolysis: ozone generator Fischer OZ 502, applied oxygen pressure: 1.2 bar, operating pressure: 0.5 bar, flow: 50 L·h^{-1}, conversion was set to 100% which corresponds to 1.6 mol O_3/h. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker Avance 400 spectrometer using $CDCl_3$ as solvent at r.t. High-resolution mass spectra (HRMS) were recorded on a Bruker maXis 4G spectrometer with electrospray ionization (ESI). Optical rotations: Perkin Elmer polarimeter model 341, sodium D line (589 nm), *c* = g/100 mL. Chiral GC was performed with a 6-*tert*-butyl-2,3-di-*O*-ethyl-β-cyclodextrin column (Mega s.n.c., Italy; 25 m, 0.25 mm i.d.).

5-((*tert*-Butyldimethylsilyl)oxy)pentan-1-ol (11)[14]

To a suspension of NaH (5.04 g, 0.21 mol) in anhydrous THF (300 mL) was added pentane-1,5-diol (**10**; 20.83 g, 0.20 mol) at 0 °C in a dropwise fashion. After complete addition, stirring was continued at 0 °C for 15 min. The cooling bath was removed and the mixture stirred for an additional 1 h before a solution of TBSCl (30.14 g, 0.20 mol) in anhydrous THF (100 mL) was slowly added in a dropwise fashion. The yellow suspension was stirred for 12 h at r.t. and then carefully treated with H_2O (100 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with saturated NaCl solution, dried with $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/Et_2O, 2:3) to yield 32.9 g (75%) of silyl ether **11** as a colorless oil.

R_f = 0.61 (petroleum ether/Et_2O, 2:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01 (s, 6 H, $Si(CH_3)_2$), 0.86 (s, 9 H, $SiC(CH_3)_3$), 1.32–1.39 (m, 2 H, 3-H), 1.48–1.59 (m, 4 H, 2-H, 4-H), 3.56–3.61 (m, 4 H, 1-H, 5-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.4 ($Si(CH_3)_2$), 18.3 ($SiC(CH_3)_3$), 22.0 (C-3), 25.9 ($SiC(CH_3)_3$), 32.4 (C-2, C-4), 62.7 (C-1), 63.1 (C-5).

HRMS (ESI-TOF): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{26}O_2Si$: 219.177483; found: 219.177347.

5-((*tert*-Butyldimethylsilyl)oxy)pentanal (12)[14]

To a solution of DMSO (120 mL, 132 g, 1.69 mol) in CH_2Cl_2 (140 mL) at –75 °C, a solution of oxalyl chloride (75 mL, 111 g, 0.87 mol) in CH_2Cl_2 (550 mL) was slowly added dropwise while keeping the temperature of the solution below –60 °C. After complete addition, the mixture was stirred for 10 min at –75 °C, followed by dropwise addition of alcohol **11** (149.23 g, 0.683 mol). The reaction mixture was stirred for 1 h at this temperature, then treated dropwise with Et_3N (448 mL, 327 g, 3.23 mol), brought to r.t. and stirred for 1 h. The resulting white suspension was treated with H_2O (300 mL), the layers were separated and the aqueous phase was extracted with Et_2O (3 × 150 mL). The

combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/Et_2O, 4:1) giving 112.3 g (76%) of aldehyde **12** as a colorless oil.

R_f = 0.73 (petroleum ether/Et_2O, 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.04 (s, 6 H, $Si(CH_3)_2$), 0.81 (s, 9 H, $SiC(CH_3)_3$), 1.46 (q, *J* = 6.7 Hz, 2 H, 3-H), 1.62 (q, *J* = 7.3 Hz, 2 H, 4-H), 2.37 (td, *J* = 7.3, 1.8 Hz, 2 H, 2-H), 3.54 (t, *J* = 6.3 Hz, 2 H, 5-H), 9.68 (t, *J* = 1.6 Hz, 1 H, 1-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.5 ($Si(CH_3)_2$), 18.1 ($SiC(CH_3)_3$), 18.5 (C-3), 25.0 ($SiC(CH_3)_3$), 32.0 (C-4), 43.4 (C-2), 62.9 (C-5), 202.2 (C-1).

HRMS (ESI-TOF): *m*/*z* $[M + Na + MeOH]^+$ calcd for $C_{11}H_{24}O_2Si$: 271.169992; found: 271.169913.

(*R*)-8-((*tert*-Butyldimethylsilyl)oxy)oct-1-en-4-ol (13)

(–)-*B*-Methoxydiisopinocampheylborane[15]

To a solution of (–)-Ipc_2BH[16] (12.8 g, 44.7 mmol) in anhydrous THF (70 mL) at 0 °C was added anhydrous MeOH (4.0 mL, 3.16 g, 99 mmol) dropwise, which was accompanied by vigorous gas evolution. After complete addition, the reaction mixture was stirred at r.t. for 3 h and then concentrated for 10 h under reduced pressure (oil pump) at 40 °C using a cold trap. The product (10.9 g, 77%) was obtained as a white waxy solid.

(–)-*B*-Allyldiisopinocampheylborane[15]

To a solution of (–)-*B*-methoxydiisopinocampheylborane obtained as above (1.8 g, 5.70 mmol) in anhydrous Et_2O (10 mL) was added at –80 °C a freshly prepared solution of allylmagnesium bromide[34] (0.6 M in Et_2O, 9.6 mL, 5.75 mmol) dropwise followed by stirring of the mixture for 15 min. The suspension formed was allowed to warm to r.t. within 30 min and then stirred at r.t. for 1 h. The white suspension obtained was immediately used for the subsequent Brown allylation reaction.

(*R*)-8-((*tert*-Butyldimethylsilyl)oxy)oct-1-en-4-ol (13)

To a freshly prepared suspension of (–)-*B*-allyldiisopinocampheylborane (1.88 g, 5.70 mmol) in anhydrous Et_2O (20 mL) was added aldehyde **12** (1.0 g, 4.6 mmol), dissolved in Et_2O (10 mL), dropwise very slowly at –90 °C followed by stirring of the mixture at –75 °C for 1.5 h. Then, the reaction mixture was brought to r.t. within 1 h and stirred for 1 h at r.t., before it was cooled to 0 °C and slowly treated with 3 M NaOH (6 mL), H_2O_2 (30%, 2.5 mL) and saturated $NaHCO_3$ solution (8 mL). The reaction mixture was stirred at r.t. for 10 h and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude alcohol was purified by flash chromatography (petroleum ether/Et_2O, 2:1) resulting in 1.03 g (86%) of homoallyl alcohol **13** as a colorless oil; 95.3% ee.

$[\alpha]_D^{20}$ +3.75 (*c* 1.0, CH_2Cl_2) {Lit.[17a] $[\alpha]_D^{20}$ +4.6 (*c* 1.0, $CHCl_3$); Lit.[17b] $[\alpha]_D$ +4.5 (*c* 0.3, $CHCl_3$)}; R_f = 0.48 (petroleum ether/Et_2O, 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01 (s, 6 H, $Si(CH_3)_2$), 0.85 (s, 9 H, $SiC(CH_3)_3$), 1.31–1.53 (m, 6 H, 5-H, 6-H, 7-H), 2.07–2.14 (m, 1 H, 3-H), 2.22–2.28 (m, 1 H, 3-H), 3.58 (t, *J* = 6.3 Hz, 2 H, 8-H), 3.60–3.63 (m, 1 H, 4-H), 5.06 (s, 1 H, 1-H), 5.09 (d, *J* = 4.0 Hz, 1 H, 1-H), 5.74–5.84 (m, 1 H, 2-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.4 ($Si(CH_3)_2$), 18.3 ($SiC(CH_3)_3$), 21.9 (C-6), 25.9 ($SiC(CH_3)_3$), 32.7 (C-7), 36.4 (C-5), 41.9 (C-3), 63.0 (C-8), 70.5 (C-4), 117.8 (C-1), 134.8 (C-2).

HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{30}O_2Si$: 281.190728; found: 281.190740.

GC (75 kP; 80 °C, 3 min, 5 °C/min to 190 °C, 10 min): t_R = 18.38 (minor enantiomer), 18.55 (major enantiomer) min.

(*R*)-4,8-Bis((*tert*-butyldimethylsilyl)oxy)oct-1-ene (14)

A solution of alcohol **13** (500 mg, 1.93 mmol) in anhydrous DMF (23 mL) was treated with imidazole (1.3 g, 19.1 mmol) and DMAP (70 mg, 0.57 mmol). The reaction mixture was stirred for 20 min at r.t. before TBSCl (310 mg, 2.06 mmol) was added. Stirring was continued at r.t. for 12 h. Thereafter, the reaction was quenched with H_2O (50 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude silyl ether was purified by flash chromatography (petroleum ether/Et_2O, 20:1) resulting in 705 mg (98%) of ether **14** as a colorless oil.

$[\alpha]_D^{20}$ +4.92 (*c* 2.1, CH_2Cl_2); R_f = 0.72 (petroleum ether/Et_2O, 20:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 12 H, $Si(CH_3)_2$), 0.88 (s, 9 H, $SiC(CH_3)_3$), 0.89 (s, 9 H, $SiC(CH_3)_3$), 1.26–1.53 (m, 6 H, 5-H, 6-H, 7-H), 2.20 (m, 2 H, 3-H), 3.59 (t, *J* = 6.3 Hz, 2 H, 8-H), 3.68 (q, *J* = 5.6 Hz, 1 H, 4-H), 4.99 (s, 1 H, 1-H), 5.02 (d, *J* = 6.3 Hz, 1 H, 1-H), 5.75–5.85 (m, 1 H, 2-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3 ($Si(CH_3)_2$), –4.5 ($Si(CH_3)_2$), –4.4 ($Si(CH_3)_2$), 18.1 ($SiC(CH_3)_3$), 18.4 ($SiC(CH_3)_3$), 21.8 (C-6), 25.9 ($SiC(CH_3)_3$), 26.0 ($SiC(CH_3)_3$), 33.0 (C-7), 36.6 (C-5), 42.0 (C-3), 63.2 (C-8), 72.0 (C-4), 116.6 (C-1), 135.4 (C-2).

HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{44}O_2Si_2$: 395.277205; found: 395.277073.

(*R*)-3,7-Bis((*tert*-butyldimethylsilyl)oxy)heptanal (15)

Through a solution of alkene **14** (5.0 g, 13.41 mmol) in anhydrous CH_2Cl_2 (250 mL), cooled to –78 °C, was passed ozone via a glass tube until the starting material was consumed (TLC, about 60 min) and the color of the solution had changed to blue. Subsequently, the reaction mixture was purged with nitrogen for 20 min and then quenched by the dropwise addition of Me_2S (15 mL). The mixture was stirred for 12 h at r.t., then refluxed for 10 h before it was concentrated in vacuo. The oily residue was purified by flash chromatography (petroleum ether/Et_2O, 20:1) to give 3.9 g (78%) of aldehyde **15** as a colorless oil.

$[\alpha]_D^{20}$ +1.70 (*c* 1.0, CH_2Cl_2); R_f = 0.21 (petroleum ether/Et_2O, 20:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.01 (s, 6 H, $Si(CH_3)_2$), 0.02, 0.03 (2 s, 3 H each, $Si(CH_3)_2$), 0.82 (s, 9 H, $SiC(CH_3)_3$), 0.84 (s, 9 H, $SiC(CH_3)_3$), 1.32 (q, *J* = 7.1 Hz, 2 H, 5-H), 1.43–1.57 (m, 4 H, 4-H, 6-H), 2.45 (dd, *J* = 3.3, 2.5 Hz, 2 H, 2-H), 3.55 (t, *J* = 6.3 Hz, 2 H, 7-H), 4.14 (q, *J* = 5.8 Hz, 1 H, 3-H), 9.75 (t, *J* = 2.5 Hz, 1 H, 1-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.4 ($Si(CH_3)_2$), –4.8 ($Si(CH_3)_2$), –4.5 ($Si(CH_3)_2$), 17.9 ($SiC(CH_3)_3$), 18.2 ($SiC(CH_3)_3$), 21.5 (C-5), 25.7 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 32.7 (C-4), 37.6 (C-6), 50.8 (C-2), 62.8 (C-7), 68.1 (C-3), 202.0 (C-1).

HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{42}O_3Si_2$: 397.256469; found: 397.256703.

S-Ethyl (*R*,*E*)-5,9-Bis((*tert*-butyldimethylsilyl)oxy)non-2-enethioate (17)

To a solution of aldehyde **15** (6.90 g, 18.41 mmol) in anhydrous CH_2Cl_2 (350 mL) was added ylide[18] **16** (13.41 g, 36.80 mmol). Then, the reaction mixture was stirred for 12 h at reflux temperature. After being cooled to r.t., most of the volatiles were removed under reduced pres-

sure. The residue was washed with petroleum ether, the filtrate was concentrated in vacuo and the resulting crude product, obtained as a yellow oil, was purified by flash chromatography (petroleum ether/Et_2O, 20:1). The enethioate **17** (6.80 g, 80%) was obtained as a colorless oil.

$[\alpha]_D^{20}$ +4.39 (*c* 1.0, CH_2Cl_2); R_f = 0.31 (petroleum ether/Et_2O, 20:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01 (s, 12 H, $Si(CH_3)_2$), 0.85 (s, 9 H, $SiC(CH_3)_3$), 0.86 (s, 9 H, $SiC(CH_3)_3$), 1.24 (t, *J* = 7.6 Hz, 3 H, SCH_2CH_3), 1.27–1.50 (m, 6 H, 6-H, 7-H, 8-H), 2.23–2.36 (m, 2 H, 4-H), 2.90 (q, *J* = 7.3 Hz, 2 H, SCH_2CH_3), 3.57 (t, *J* = 6.5 Hz, 2 H, 9-H), 3.75 (q, *J* = 5.6 Hz, 1 H, 5-H), 6.06 (d, *J* = 15.4 Hz, 1 H, 2-H), 6.82–6.89 (m, 1 H, 3-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3 ($Si(CH_3)_2$), –4.6 ($Si(CH_3)_2$), 14.8 (SCH_2CH_3), 18.0 ($SiC(CH_3)_3$), 18.3 ($SiC(CH_3)_3$), 21.6 (SCH_2CH_3), 23.0 (C-7), 25.8 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 32.8 (C-8), 37.1 (C-6), 40.1 (C-4), 63.0 (C-9), 71.2 (C-5), 130.6 (C-2), 142.0 (C-3), 189.8 (C-1).

HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{48}O_3Si_2S$: 483.275490; found: 483.275363.

S-Ethyl (3*S*,5*R*)-5,9-Bis((*tert*-butyldimethylsilyl)oxy)-3-methylnonanethioate (18)

Under inert conditions, CuI (97.0 mg, 0.51 mmol) and (*S*)-Tol-BINAP (0.26 g, 0.383 mmol) were dissolved in *t*-BuOMe (400 mL) and the mixture was stirred for 1 h at r.t. Thereafter, it was cooled to –75 °C, and treated dropwise with MeMgBr (3 M in Et_2O, 85.8 mL, 257.4 mmol) and stirred for 15 min before enethioate **17** (23.72 g, 51.47 mmol), dissolved in *t*-BuOMe (118 mL), was added dropwise over a period of 2 h. The reaction mixture was stirred at –75 °C for another 2 h, then treated with MeOH (25 mL) and saturated NH_4Cl solution (50 mL). The mixture was brought to r.t., the layers were separated and the aqueous layer was extracted with Et_2O (3 × 40 mL). The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$ and concentrated in vacuo. The oily residue was purified by flash chromatography (petroleum ether/Et_2O, 20:1) to give thioester **18** (20.4 g, 83%) as a colorless oil.

$[\alpha]_D^{20}$ –11.92 (*c* 1.0, CH_2Cl_2); R_f = 0.42 (petroleum ether/Et_2O, 20:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 12 H, $Si(CH_3)_2$), 0.86 (s, 9 H, $SiC(CH_3)_3$), 0.87 (s, 9 H, $SiC(CH_3)_3$), 0.90 (d, *J* = 6.6 Hz, 3 H, 3-CH_3), 1.22 (t, *J* = 7.3 Hz, 3 H, SCH_2CH_3), 1.27–1.51 (m, 8 H, 4-H, 6-H, 7-H, 8-H), 2.12–2.21 (m, 1 H, 3-H), 2.32 (dd, *J* = 8.3, 6.1 Hz, 1 H, 2-H), 2.48 (dd, *J* = 8.3, 6.1 Hz, 1 H, 2-H), 2.83 (q, *J* = 7.3 Hz, 2 H, SCH_2CH_3), 3.57 (t, *J* = 6.6 Hz, 2 H, 9-H), 3.65–3.71 (m, 1 H, 5-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3 ($Si(CH_3)_2$), –4.5 ($Si(CH_3)_2$), –4.2 ($Si(CH_3)_2$), 14.8 (SCH_2CH_3), 18.1 ($SiC(CH_3)_3$), 18.3 ($SiC(CH_3)_3$), 19.7 (3-CH_3), 21.3 (SCH_2CH_3), 23.2 (C-7), 25.9 ($SiC(CH_3)_3$), 26.0 ($SiC(CH_3)_3$), 27.7 (C-3), 33.1 (C-8), 37.6 (C-6), 43.9 (C-4), 52.0 (C-2), 63.1 (C-9), 70.0 (C-5), 198.8 (C-1).

HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{52}O_3Si_2S$: 499.306790; found: 499.306575.

(3*S*,5*R*)-5,9-Bis((*tert*-butyldimethylsilyl)oxy)-3-methylnonanoic Acid (8)

To a solution of thioester **18** (130 mg, 0.27 mmol) in THF (4 mL), an aqueous solution of LiOH (2 mL, 27.2 mg, 1.136 mmol) and H_2O_2 (0.07 mL, 30% in H_2O) were dropped at r.t. The reaction mixture was stirred for 12 h at r.t., then adjusted to pH 3 with 1 N HCl. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The oily residue was purified by flash chromatography (petroleum ether/Et_2O, 2:1) to give acid **8** (108.5 mg, 92%) as a colorless oil.

$[\alpha]_D^{20}$ –4.06 (*c* 1.0, CH_2Cl_2); R_f = 0.36 (petroleum ether/Et_2O, 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 12 H, $Si(CH_3)_2$), 0.87 (s, 9 H, $SiC(CH_3)_3$), 0.88 (s, 9 H, $SiC(CH_3)_3$), 0.95 (d, *J* = 6.3 Hz, 3 H, 3-CH_3), 1.19–1.52 (m, 8 H, 4-H, 6-H, 7-H, 8-H), 2.07–2.14 (m, 1 H, 3-H), 2.16 (d, *J* = 7.8 Hz, 1 H, 2-H), 2.32 (m, 1 H, 2-H), 3.59 (t, *J* = 6.6 Hz, 2 H, 9-H), 3.67–3.73 (m, 1 H, 5-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3 ($Si(CH_3)_2$), –4.5 ($Si(CH_3)_2$), –4.2 ($Si(CH_3)_2$), 18.1 ($SiC(CH_3)_3$), 18.4 ($SiC(CH_3)_3$), 19.8 (3-CH_3), 21.3 (C-7), 25.9 ($SiC(CH_3)_3$), 26.0 ($SiC(CH_3)_3$), 26.8 (C-3), 33.0 (C-8), 37.6 (C-6), 42.2 (C-2), 43.9 (C-4), 63.2 (C-9), 70.2 (C-5), 179.2 (C-1).

HRMS (ESI-TOF): *m*/*z* $[M + H]^-$ calcd for $C_{22}H_{48}O_4Si_2$: 431.30184; found: 431.30268.

(*R*)-4-Benzyl-3-((2*R*,3*R*)-3-hydroxy-2-methyl-5-(triisopropylsilyl)pent-4-ynoyl)oxazolidin-2-one (21)

Under an inert atmosphere a solution of propionyloxazolidinone[22] **19** (100 mg, 0.43 mmol) in anhydrous CH_2Cl_2 (1 mL), that had been cooled to –30 °C, was treated dropwise with *n*-Bu_2BOTf (1 M in CH_2Cl_2, 0.5 mL, 0.50 mmol), and then with Et_3N (63 µL, 50 mg, 0.50 mmol). This solution was stirred for 30 min at 0 °C, then cooled to –65 °C before aldehyde[23] **20** (98.8 mg, 0.47 mmol), dissolved in CH_2Cl_2 (1 mL), was added dropwise. The reaction mixture was stirred for 30 min at –65 °C and for 1 h at 0 °C. It was quenched with pH 7 buffer (0.5 mL), MeOH (1.4 mL) and a MeOH/H_2O_2 (30% in H_2O) solution (2:1, 2.35 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 3 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The oily residue was purified by flash chromatography (petroleum ether/Et_2O, 3:2) resulting in aldol product **21** (161 mg, 85%) as a colorless oil.

$[\alpha]_D^{20}$ –42.21 (*c* 1.0, CH_2Cl_2); R_f = 0.73 (petroleum ether/Et_2O, 3:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (s, 21 H, $Si(CH(CH_3)_2)_3$), 1.35 (d, *J* = 6.8 Hz, 3 H, 2′-CH_3), 2.73 (dd, *J* = 13.4, 9.3 Hz, 1 H, CH_2Ph), 3.14 (dd, *J* = 13.4, 3.0 Hz, 1 H, CH_2Ph), 3.88–3.94 (m, 1 H, 2′-H), 4.09–4.16 (m, 2 H, 5-H), 4.58–4.64 (m, 1 H, 4-H), 4.65 (d, *J* = 5.1 Hz, 1 H, 3′-H), 7.11–7.28 (m, 5 H, H_{aromat}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.0 ($SiCH(CH_3)_2$), 12.4 (2′-CH_3), 18.5 ($SiCH(CH_3)_2$), 37.7 (CH_2Ph), 44.3 (C-2′), 55.0 (C-4), 63.7 (C-5), 66.2 (C-3′), 86.6 (C-5′), 105.9 (C-4′), 127.4, 128.9, 129.4, 134.9 (C_{aromat}), 152.8 (C-2), 175.1 (C-1′).

HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{25}H_{37}NO_4Si$: 466.238406; found: 466.238156.

(*R*)-4-Benzyl-3-((2*R*,3*R*)-3-((*tert*-butyldimethylsilyl)oxy)-2-methyl-5-(triisopropylsilyl)pent-4-ynoyl)oxazolidin-2-one (22)

A solution of alcohol **21** (1.0 g, 2.25 mmol) in anhydrous CH_2Cl_2 (30 mL) was treated at 0 °C dropwise with 2,6-lutidine (653 µL, 603 mg, 5.63 mmol). The reaction mixture was stirred for 10 min before TBSOTf[35] (0.778 mL, 895 mg, 3.38 mmol) was added dropwise. Stirring was continued for 1 h at r.t. before the mixture was treated with saturated NH_4Cl solution (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The oily residue was purified by flash chromatography (petroleum ether/Et_2O, 3:2) to give silyl ether **22** (1.167 g, 93%) as a colorless oil.

$[\alpha]_D^{20}$ –19.05 (*c* 1.0, CH_2Cl_2); R_f = 0.64 (petroleum ether/Et_2O, 3:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.00 (s, 3 H, $Si(CH_3)_2$), 0.04 (s, 3 H, $Si(CH_3)_2$), 0.78 (s, 9 H, $SiC(CH_3)_3$), 0.92 (s, 21 H, $Si(CH(CH_3)_2)_3$), 1.19 (d, *J* = 6.8 Hz, 3 H, 2′-CH_3), 2.67 (dd, *J* = 13.4, 9.3 Hz, 1 H, CH_2Ph), 3.12 (dd, *J* = 13.1, 2.8 Hz, 1 H, CH_2Ph), 3.95–4.06 (m, 3 H, 2′-H, 5-H), 4.44–4.48 (m, 1 H, 4-H), 4.51 (d, *J* = 7.8 Hz, 1 H, 3′-H), 7.07–7.22 (m, 5 H, H_{aromat}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.24 ($Si(CH_3)_2$), –4.66 ($Si(CH_3)_2$), 11.1 ($SiCH(CH_3)_2$), 13.8 (2′-CH_3), 18.1 ($SiC(CH_3)_3$), 18.5 ($SiCH(CH_3)_2$), 25.6 ($SiC(CH_3)_3$), 37.7 (CH_2Ph), 45.7 (C-2′), 55.4 (C-4), 64.5 (C-5), 66.0 (C-3′), 85.4 (C-5′), 107.7 (C-4′), 127.3, 128.9, 129.4, 135.2 (C_{aromat}), 152.8 (C-2), 173.9 (C-1′).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{31}H_{51}NO_4Si_2$: 580.324883; found: 580.324526.

(2*S*,3*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-methyl-5-(triisopropylsilyl)pent-4-yn-1-ol (23)

To a solution of acid derivative **22** (130 mg, 0.233 mmol) in THF (10 mL), a solution of $NaBH_4$ (53 mg, 1.40 mmol) in H_2O (2 mL) was added dropwise at 0 °C followed by stirring of the reaction mixture at r.t. overnight. Then, saturated NH_4Cl solution (2 mL) was added and the mixture stirred for 1 h. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The oily residue was purified by flash chromatography (petroleum ether/Et_2O, 3:2) providing alcohol **23** (84 mg, 94%) as a colorless oil.

$[\alpha]_D^{20}$ +41.00 (*c* 1.0, CH_2Cl_2); R_f = 0.51 (petroleum ether/Et_2O, 3:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.13 (s, 3 H, $Si(CH_3)_2$), 0.16 (s, 3 H, $Si(CH_3)_2$), 0.89 (s, 9 H, $SiC(CH_3)_3$), 0.91 (d, *J* = 7.1 Hz, 3 H, 2-CH_3), 1.06 (s, 21 H, $Si(CH(CH_3)_2)_3$), 2.01–2.10 (m, 1 H, 2-H), 3.54 (dd, *J* = 7.3, 3.8 Hz, 1 H, 1-H), 3.88 (dd, *J* = 11.1, 8.6 Hz, 1 H, 1-H), 4.51 (d, *J* = 4.3 Hz, 1 H, 3-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.4 ($Si(CH_3)_2$), –4.6 ($Si(CH_3)_2$), 11.2 ($SiCH(CH_3)_2$), 12.7 (2-CH_3), 18.1 ($SiC(CH_3)_3$), 18.6 ($SiCH(CH_3)_2$), 25.7 ($SiC(CH_3)_3$), 41.3 (C-2), 65.8 (C-1), 68.1 (C-3), 87.1 (C-5), 106.4 (C-4).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{44}O_2Si_2$: 407.277205; found: 407.277285.

(2*R*,3*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-methyl-5-(triisopropylsilyl)pent-4-ynal (9)

A solution of alcohol **23** (580 mg, 1.51 mmol) in anhydrous CH_2Cl_2 (12 mL) was treated at 0 °C with $NaHCO_3$ (421 mg, 5.0 mmol) and Dess–Martin periodinane (836 mg, 1.97 mmol). The reaction mixture was brought to r.t. and stirred for 2 h. The mixture was then washed with saturated $Na_2S_2O_3$ solution (3 mL) and saturated $NaHCO_3$ solution (2 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The oily residue was purified by flash chromatography (petroleum ether/Et_2O, 10:1) to give aldehyde **9** (492 mg, 85%) as a colorless oil.

$[\alpha]_D^{20}$ +36.3 (*c* 1.0, CH_2Cl_2); R_f = 0.61 (petroleum ether/Et_2O, 10:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.11 (s, 3 H, $Si(CH_3)_2$), 0.15 (s, 3 H, $Si(CH_3)_2$), 0.86 (s, 9 H, $SiC(CH_3)_3$), 1.05 (s, 21 H, $Si(CH(CH_3)_2)_3$), 1.18 (d, *J* = 7.1 Hz, 3 H, 2-CH_3), 2.51–2.57 (m, 1 H, 2-H), 4.70 (d, *J* = 4.6 Hz, 1 H, 3-H), 9.81 (d, *J* = 1.5 Hz, 1 H, 1-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3 ($Si(CH_3)_2$), –4.5 ($Si(CH_3)_2$), 9.3 (2-CH_3), 11.1 ($SiCH(CH_3)_2$), 18.1 ($SiC(CH_3)_3$), 18.5 ($SiCH(CH_3)_2$), 25.6 ($SiC(CH_3)_3$), 52.6 (C-2), 63.8 (C-3), 87.6 (C-5), 106.2 (C-4), 203.6 (C-1).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{42}O_2Si_2$: 405.261555; found: 405.261924.

(2*S*,3*S*,5*R*)-5,9-Bis((*tert*-butyldimethylsilyl)oxy)-2-((1*S*,2*S*,3*R*)-3-((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-2-methyl-5-(triisopropylsilyl)pent-4-yn-1-yl)-3-methylnonanoic Acid (24)

To a solution of acid **8** (100 mg, 0.231 mmol) in anhydrous Et_2O (2 mL) was added *t*-BuLi (1.7 M in hexane, 0.3 mL, 0.51 mmol) at –75 °C. The reaction mixture was stirred for 1 h at –75 °C and 1 h at –10 °C. Thereafter, the resulting yellow solution was cooled to –75 °C before aldehyde **9** (107.9 mg, 0.282 mmol), dissolved in anhydrous THF (5 mL), was added dropwise followed by stirring of the reaction mixture for 14 h at –75 °C. The reaction mixture was treated with pH 7 buffer (10 mL, KH_2PO_4/Na_2HPO_4). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The oily residue obtained was purified by flash chromatography (petroleum ether/Et_2O, 2:1) to give β-hydroxy acid **24** (87.3 mg, 57%) as a colorless oil.

$[\alpha]_D^{20}$ +4.8 (*c* 1.0, CH_2Cl_2); R_f = 0.21 (petroleum ether/Et_2O, 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 12 H, $Si(CH_3)_2$), 0.11 (s, 3 H, $Si(CH_3)_2$), 0.15 (s, 3 H, $Si(CH_3)_2$), 0.84 (s, 9 H, $SiC(CH_3)_3$), 0.87 (s, 18 H, $SiC(CH_3)_3$), 0.99 (d, *J* = 6.8 Hz, 3 H, 3-CH_3), 1.02 (d, *J* = 6.9 Hz, 3 H, 2′-CH_3), 1.04 (s, 21 H, $Si(CH(CH_3)_2)_3$), 1.23–1.30 (m, 3 H, 4-H, 7-H), 1.40–1.51 (m, 5 H, 4-H, 6-H, 8-H), 1.83–1.94 (m, 1 H, 2′-H), 2.01–2.12 (m, 1 H, 3-H), 2.48 (t, *J* = 6.1 Hz, 1 H, 2-H), 3.57 (t, *J* = 6.6 Hz, 2 H, 9-H), 3.63–3.70 (m, 1 H, 5-H), 4.33 (dd, *J* = 7.3, 3.3 Hz, 1 H, 1′-H), 4.43 (d, *J* = 5.6 Hz, 1 H, 3′-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3 ($Si(CH_3)_2$), –5.1 ($Si(CH_3)_2$), –4.6 ($Si(CH_3)_2$), –4.4 ($Si(CH_3)_2$), 9.1 (2′-CH_3), 11.2 ($SiCH(CH_3)_2$), 17.9 (3-CH_3), 18.0 ($SiC(CH_3)_3$), 18.1 ($SiC(CH_3)_3$), 18.3 ($SiC(CH_3)_3$), 18.6 ($SiCH(CH_3)_2$), 21.4 (C-7), 25.8 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 26.0 ($SiC(CH_3)_3$), 28.2 (C-3), 33.1 (C-6), 38.4 (C-8), 39.4 (C-4), 41.7 (C-2′), 55.0 (C-2), 63.1 (C-9), 66.7 (C-3′), 69.9 (C-5), 70.9 (C-1′), 87.2 (C-5′), 107.6 (C-4′), 179.2 (C-1).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{43}H_{90}O_6Si_4$: 837.57067; found: 837.57090.

(3*S*,4*S*)-3-((2*S*,4*R*)-4,8-Bis((*tert*-butyldimethylsilyl)oxy)octan-2-yl)-4-((2*S*,3*R*)-3-((*tert*-butyldimethylsilyl)oxy)-5-(triisopropylsilyl)pent-4-yn-2-yl)oxetan-2-one (25)

A solution of hydroxy acid **24** (100 mg, 0.122 mmol) in anhydrous pyridine (1 mL) was treated dropwise at 0 °C with benzenesulfonyl chloride (64.5 mg, 0.366 mmol), followed by stirring of the mixture at r.t. for 12 h. The reaction mixture was quenched with ice–water (2 mL) and diluted with Et_2O (3 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The oily residue was purified by flash chromatography (petroleum ether/Et_2O, 10:1) yielding β-lactone **25** (68 mg, 70%) as a colorless oil.

$[\alpha]_D^{20}$ +3.8 (*c* 1.0, CH_2Cl_2); R_f = 0.41 (petroleum ether/Et_2O, 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02, 0.03 (2 s, 12 H, $Si(CH_3)_2$), 0.12, 0.14 (2 s, 6 H, $Si(CH_3)_2$), 0.85 (s, 9 H, $SiC(CH_3)_3$), 0.88 (s, 9 H, $SiC(CH_3)_3$), 0.89 (s, 9 H, $SiC(CH_3)_3$), 1.03 (d, *J* = 6.8 Hz, 3 H, 1″-H), 1.06 (s, 21 H, $Si(CH(CH_3)_2)_3$), 1.11 (d, *J* = 6.8 Hz, 3 H, 1′-H), 1.18–1.33 (m, 3 H, 3′-H, 6′-H), 1.41–1.51 (m, 4 H, 5′-H, 7′-H), 1.83–1.94 (ddd, *J* = 9.4, 6.4, 3.8 Hz, 1 H, 3′-H), 1.96–2.04 (m, 1 H, 2″-H), 2.13–2.22 (m, 1 H, 2′-H), 3.37 (dd, *J* = 8.3, 3.8 Hz, 1 H, 3-H), 3.58 (t, *J* = 6.6 Hz, 2 H, 8′-H), 3.72–3.78 (m, 1 H, 4′-H), 4.42 (d, *J* = 5.1 Hz, 1 H, 3″-H), 4.48 (dd, *J* = 7.1, 3.8 Hz, 1 H, 4-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3 ($Si(CH_3)_2$), –5.2 ($Si(CH_3)_2$), –4.6 ($Si(CH_3)_2$), –4.4 ($Si(CH_3)_2$), –4.0 ($Si(CH_3)_2$), 11.2 ($SiCH(CH_3)_2$), 11.4 (C-1″), 17.5 (C-1′), 18.0 ($SiC(CH_3)_3$), 18.2 ($SiC(CH_3)_3$), 18.3 ($SiC(CH_3)_3$), 18.6 ($SiCH(CH_3)_2$), 21.3 (C-6′), 25.8 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 26.0 ($SiC(CH_3)_3$), 29.1 (C-2′), 33.1 (C-7′), 38.0 (C-5′), 40.6 (C-3′), 44.3 (C-2″), 60.9 (C-3), 63.1 (C-8′), 65.5 (C-3″), 69.6 (C-4′), 77.3 (C-4), 87.6 (C-5″), 106.1 (C-4″), 171.3 (C-2).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{43}H_{88}O_5Si_4$: 819.56010; found: 819.56112.

(5*R*,7*S*,10*S*,11*R*,*E*)-1,5,11-Tris((*tert*-butyldimethylsilyl)oxy)-7,10-dimethyl-13-(triisopropylsilyl)tridec-8-en-12-yne (26)

Lactone **25** (7.2 g, 9.03 mmol), kept neat in a round-bottom flask, was heated with an oil bath for 4 h at 190 °C. After the flask was cooled to r.t., the residue was purified by flash chromatography (petroleum ether/Et_2O, 10:1) to give alkene **26** (5.9 g, 87%) as a colorless oil.

$[\alpha]_D^{20}$ +21.5 (*c* 1.0, CH_2Cl_2); R_f = 0.73 (petroleum ether/Et_2O, 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 6 H, $(SiCH_3)_2$), 0.04 (s, 6 H, $(SiCH_3)_2$), 0.08 (s, 3 H, $(SiCH_3)_2$), 0.12 (s, 3 H, $(SiCH_3)_2$), 0.87 (s, 9 H, $SiC(CH_3)_3$), 0.89 (s, 18 H, $SiC(CH_3)_3$), 0.92 (d, *J* = 6.6 Hz, 3 H, 7-CH_3), 1.06 (s, 24 H, $Si(CH(CH_3)_2)_3$, 10-CH_3), 1.26–1.53 (m, 8 H, 2-H, 3-H, 4-H, 6-H), 2.17 (ddd, *J* = 13.6, 7.1, 6.8 Hz, 1 H, 7-H), 2.31 (dd, *J* = 6.8, 6.3 Hz, 1 H, 10-H), 3.59 (t, *J* = 6.6 Hz, 2 H, 1-H), 3.62–3.68 (m, 1 H, 5-H), 4.15 (d, *J* = 5.3 Hz, 1 H, 11-H), 5.32 (dd, *J* = 15.4, 7.3 Hz, 1 H, 8-H), 5.40 (dd, *J* = 15.7, 7.6 Hz, 1 H, 9-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3 ($Si(CH_3)_2$), –5.1 ($Si(CH_3)_2$), –4.5 ($Si(CH_3)_2$), –4.4 ($Si(CH_3)_2$), –4.3 ($Si(CH_3)_2$), 11.2 ($SiCH(CH_3)_2$), 16.0 (10-CH_3), 18.1 ($SiC(CH_3)_3$), 18.2 ($SiC(CH_3)_3$), 18.4 ($SiC(CH_3)_3$), 18.6 ($SiCH(CH_3)_2$), 20.6 (7-CH_3), 21.3 (C-3), 25.7 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 26.0 ($SiC(CH_3)_3$), 33.2 (C-2, C-7), 37.0 (C-4), 44.0 (C-10), 44.6 (C-6), 63.2 (C-1), 67.8 (C-11), 70.2 (C-5), 85.0 (C-13), 108.6 (C-12), 130.1 (C-9), 136.9 (C-8).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{42}H_{88}O_3Si_4$: 775.57027; found: 775.57091.

(5*R*,7*S*,10*S*,11*R*,*E*)-5,11-Bis((*tert*-butyldimethylsilyl)oxy)-7,10-dimethyl-13-(triisopropylsilyl)tridec-8-en-12-yn-1-ol (27)

A solution of silyl ether **26** (310 mg, 0.41 mmol) in anhydrous MeOH/CH_2Cl_2 (1:1, 8 mL) was treated at 0 °C with PPTS (10.3 mg, 0.041 mmol). The reaction mixture was stirred at r.t. for 5 h, then quenched with Et_3N (0.1 mL), and treated with H_2O (5 mL) and CH_2Cl_2 (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The oily residue was purified by flash chromatography (petroleum ether/Et_2O, 2:1) to give primary alcohol **27** (144 mg, 64%, brsm) as a colorless oil. In addition, some starting material (44 mg) was recovered.

$[\alpha]_D^{20}$ +27.1 (*c* 1.0, CH_2Cl_2); R_f = 0.45 (petroleum ether/Et_2O, 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 6 H, $Si(CH_3)_2$), 0.03, 0.04 (2 s, 3 H each, $Si(CH_3)_2$), 0.86 (s, 9 H, $SiC(CH_3)_3$), 0.88 (s, 9 H, $SiC(CH_3)_3$), 0.92 (d, *J* = 6.8 Hz, 3 H, 7-CH_3), 1.05 (s, 24 H, $Si(CH(CH_3)_2)_3$, 10-CH_3), 1.24–1.48 (m, 6 H, 3-H, 4-H, 6-H), 1.50–1.57 (m, 2 H, 2-H), 2.16 (ddd, *J* = 13.9, 7.1, 6.8 Hz, 1 H, 7-H), 2.30 (dd, *J* = 6.6, 6.3 Hz, 1 H, 10-H), 3.61 (t, *J* = 6.8 Hz, 2 H, 1-H), 3.63–3.69 (m, 1 H, 5-H), 4.14 (d, *J* = 5.6 Hz, 1 H, 11-H), 5.31 (dd, *J* = 15.7, 7.3 Hz, 1 H, 8-H), 5.40 (dd, *J* = 15.4, 7.6 Hz, 1 H, 9-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.1 ($Si(CH_3)_2$), –4.5 ($Si(CH_3)_2$), –4.4 ($Si(CH_3)_2$), –4.3 ($Si(CH_3)_2$), 11.2 ($SiCH(CH_3)_2$), 16.0 (10-CH_3), 18.1 ($SiC(CH_3)_3$), 18.2 ($SiC(CH_3)_3$), 18.6 ($SiCH(CH_3)_2$), 20.6 (7-CH_3), 21.1 (C-3), 25.7 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 33.0 (C-2), 33.2 (C-7), 36.7 (C-4), 44.0 (C-10), 44.5 (C-6), 62.9 (C-1), 67.7 (C-11), 70.0 (C-5), 85.0 (C-13), 108.6 (C-12), 130.1 (C-9), 136.8 (C-8).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{36}H_{74}O_3Si_3$: 661.483797; found: 661.484030.

(5*R*,7*S*,10*S*,11*R*,*E*)-5,11-Bis((*tert*-butyldimethylsilyl)oxy)-7,10-dimethyl-13-(triisopropylsilyl)tridec-8-en-12-ynal (28)

To a solution of alcohol **27** (160 mg, 0.25 mmol) in anhydrous CH_2Cl_2 (12 mL) were added at 0 °C $NaHCO_3$ (40 mg, 0.476 mmol) and Dess–Martin periodinane (150 mg, 0.353 mmol). The reaction mixture was stirred at r.t. for 2 h, then quenched with saturated $Na_2S_2O_3$ solution (2 mL) and saturated $NaHCO_3$ solution (2 mL), and stirred for 1 h. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The oily residue was purified by flash chromatography (petroleum ether/Et_2O, 10:1) to give aldehyde **28** (130 mg, 82%) as a colorless oil.

$[\alpha]_D^{20}$ +25.5 (*c* 1.0, CH_2Cl_2); R_f = 0.82 (petroleum ether/Et_2O, 6:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02, 0.02, 0.04, 0.05 (4 s, 3 H each, $Si(CH_3)_2$), 0.86 (s, 9 H, $SiC(CH_3)_3$), 0.88 (s, 9 H, $SiC(CH_3)_3$), 0.93 (d, *J* = 6.6 Hz, 3 H, 7-CH_3), 1.05 (s, 24 H, $Si(CH(CH_3)_2)_3$, 10-CH_3), 1.24–1.34 (m, 1 H, 6-H), 1.36–1.51 (m, 3 H, 4-H, 6-H), 1.58–1.73 (m, 2 H, 3-H), 2.14 (ddd, *J* = 14.1, 7.1, 6.8 Hz, 1 H, 7-H), 2.31 (dd, *J* = 6.8, 6.3 Hz, 1 H, 10-H), 2.39 (dd, *J* = 7.3, 1.8 Hz, 2 H, 2-H), 3.64–3.70 (m, 1 H, 5-H), 4.14 (d, *J* = 5.6 Hz, 1 H, 11-H), 5.30 (dd, *J* = 15.4, 7.6 Hz, 1 H, 8-H), 5.41 (dd, *J* = 15.4, 7.6 Hz, 1 H, 9-H), 9.74 (t, *J* = 1.8 Hz, 1 H, 1-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.1 ($Si(CH_3)_2$), –4.5 ($Si(CH_3)_2$), –4.4 ($Si(CH_3)_2$), –4.4 ($Si(CH_3)_2$), 11.2 ($SiCH(CH_3)_2$), 16.0 (10-CH_3), 17.6 (C-3), 18.1 ($SiC(CH_3)_3$), 18.2 ($SiC(CH_3)_3$), 18.6 ($SiCH(CH_3)_2$), 20.8 (7-CH_3), 25.7 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 33.3 (C-7), 36.2 (C-4), 44.0 (C-10), 44.0 (C-2), 44.4 (C-6), 67.7 (C-11), 69.9 (C-5), 85.0 (C-13), 108.6 (C-12), 130.3 (C-9), 136.6 (C-8), 202.4 (C-1).

HRMS (ESI-TOF): *m*/*z* [M + Na + MeOH]$^+$ calcd for $C_{36}H_{72}O_3Si_3$: 691.494362; found: 691.494713.

(8*R*,10*S*,13*S*,14*R*,*E*)-8,14-Bis((*tert*-butyldimethylsilyl)oxy)-10,13-dimethyl-16-(triisopropylsilyl)hexadeca-11-ene-2,15-diyn-4-ol (7)

To a solution of 1-bromoprop-1-ene (2.2 mL, 3.12 g, 25.7 mmol) in anhydrous THF (80 mL), cooled to –75 °C, was added dropwise *n*-BuLi (2.5 M in hexane, 15.2 mL, 38.02 mmol) followed by stirring of the mixture for 2 h at –75 °C. Subsequently, aldehyde **28** (10.46 g, 16.41 mmol), dissolved in anhydrous THF (20 mL), was added dropwise. After being stirred for 2 h at –75 °C, the mixture was slowly warmed to r.t., stirred for 1 h at r.t. and then treated with saturated NH_4Cl solution (40 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The oily residue was purified by flash chromatography (petroleum ether/Et_2O, 6:1) yielding propargylic alcohol **7** (10.24 g, 92%) as a colorless oil.

$[\alpha]_D^{20}$ +20.7 (*c* 1.0, CH_2Cl_2); R_f = 0.21 (petroleum ether/Et_2O, 6:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 6 H, $Si(CH_3)_2$), 0.07, 0.11 (2 s, 3 H each, $Si(CH_3)_2$), 0.87 (s, 9 H, $SiC(CH_3)_3$), 0.88 (s, 9 H, $SiC(CH_3)_3$), 0.92 (d, *J* = 6.6 Hz, 3 H, 10-CH_3), 1.05 (s, 24 H, $Si(CH(CH_3)_2)_3$, 13-CH_3), 1.24–1.33 (m, 1 H, 7-H), 1.38–1.50 (m, 5 H, 7-H, 6-H, 9-H), 1.58–1.65 (m, 2 H, 5-H), 1.82 (d, *J* = 2.0 Hz, 3 H, 1-H), 2.17 (ddd, *J* = 13.9, 7.1, 6.8 Hz, 1 H, 10-H), 2.31 (dd, *J* = 6.8, 6.1 Hz, 1 H, 13-H), 3.67–3.73 (m, 1 H, 8-H), 4.14 (d, *J* = 5.6 Hz, 1 H, 14-H), 4.27–4.35 (m, 1 H, 4-H), 5.32 (dd, *J* = 15.4, 7.3 Hz, 1 H, 11-H), 5.40 (dd, *J* = 15.4, 7.6 Hz, 1 H, 12-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.1 ($Si(CH_3)_2$), –4.5 ($Si(CH_3)_2$), –4.4 ($Si(CH_3)_2$), –4.3 ($Si(CH_3)_2$), 3.5 (C-1), 11.2 ($SiCH(CH_3)_2$), 16.0 (13-CH_3), 18.1 ($SiC(CH_3)_3$), 18.2 ($SiC(CH_3)_3$), 18.6 ($SiCH(CH_3)_2$), 20.6 (10-CH_3), 20.7 (C-6), 25.7 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 33.2 (C-10), 36.7 (C-7), 38.4 (C-5), 44.0 (C-13), 44.5 (C-9), 62.7 (C-4), 67.7 (C-14), 70.0 (C-8), 80.4 (C-2), 81.0 (C-3), 85.0 (C-16), 108.6 (C-15), 130.1 (C-12), 136.8 (C-11).

HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{39}H_{76}O_3Si_3$: 699.499447; found: 699.500080.

1-((2*S*,6*R*)-6-((2*S*,5*S*,6*R*,*E*)-6-Hydroxy-2,5-dimethyl-8-(triisopropylsilyl)oct-3-en-7-yn-1-yl)tetrahydro-2*H*-pyran-2-yl)propan-2-one (31)

To a solution of propargylic alcohol **7** (600 mg, 0.89 mmol) in CH_2Cl_2 (50 mL) was added gold catalyst **29** (103 mg, 0.133 mmol). The reaction mixture was warmed to r.t. and stirred for 3 h. After all the starting material had been converted into enone **30**, *p*-TsOH·H_2O (338 mg, 1.78 mmol) was added and the mixture stirred for another 8 h at r.t. Then, the mixture was washed with saturated $NaHCO_3$ solution (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The oily residue obtained was purified by flash chromatography (petroleum ether/Et_2O, 2:1) to give pyran derivative **31** (327 mg, 82%) as a colorless oil.

$[\alpha]_D^{20}$ +30.6 (*c* 1.0, CH_2Cl_2); R_f = 0.23 (petroleum ether/Et_2O, 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 6.6 Hz, 3 H, 2″-CH_3), 1.05 (s, 24 H, $Si(CH(CH_3)_2)_3$, 5″-CH_3), 1.10–1.29 (m, 3 H, 1″-H, 3′-H, 5′-H), 1.47–1.59 (m, 4 H, 1″-H, 3′-H, 4′-H, 5′-H), 1.78–1.84 (m, 1 H, 4′-H), 2.16 (s, 3 H, 3-H), 2.30 (dd, *J* = 7.1, 6.8 Hz, 1 H, 2″-H), 2.35 (m, 1 H, 5″-H), 2.39 (dd, *J* = 10.7, 4.8 Hz, 1 H, 1-H), 2.66 (dd, *J* = 8.1, 7.4 Hz, 1 H, 1-H), 3.30–3.36 (m, 1 H, 6′-H), 3.70–3.76 (m, 1 H, 2′-H), 4.20 (d, *J* = 4.6 Hz, 1 H, 6″-H), 5.39 (dd, *J* = 16.4, 8.3 Hz, 1 H, 4″-H), 5.53 (dd, *J* = 15.6, 7.1 Hz, 1 H, 3″-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.1 ($SiCH(CH_3)_2$), 16.7 (5″-CH_3), 18.6 ($SiCH(CH_3)_2$), 19.8 (2″-CH_3), 23.5 (C-4′), 31.0 (C-3), 31.5 (C-3′, C-5′), 32.5 (C-2″), 43.4 (C-5″, C-1″), 50.3 (C-1), 66.6 (C-6″), 74.4 (C-2′), 75.7 (C-6′), 86.2 (C-8″), 107.0 (C-7″), 127.7 (C-4″), 140.0 (C-3″), 207.7 (C-2).

HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{27}H_{48}O_3Si$: 471.326493; found: 471.326944.

NMR Data for Enone 30

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01, 0.02, 0.07, 0.11 (4 s, 3 H each, $Si(CH_3)_2$), 0.87, 0.87 (2 s, 9 H each, $SiC(CH_3)_3$), 0.93 (d, *J* = 6.8 Hz, 10-CH_3), 1.05 (s, 24 H, 13-CH_3, $Si(CH(CH_3)_2)_3$), 1.28 (ddd (app quin), *J* = 13.4, 6.8, 6.8 Hz, 1 H, 9-H), 1.35–1.52 (m, 5 H, 6-H, 7-H, 9-H), 2.11–2.22 (m, 3 H, 5-H, 10-H), 2.22 (s, 3 H, 1-H), 2.32 (q, *J* = 6.6 Hz, 1 H, 13-H), 3.63–3.70 (m, 1 H, 8-H), 4.15 (d, *J* = 5.3 Hz, 1 H, 14-H), 5.30 (dd, *J* = 15.7, 7.6 Hz, 1 H, 11-H), 5.41 (d, *J* = 15.4, 7.3 Hz, 1 H, 12-H), 6.05 (d, *J* = 15.9 Hz, 1 H, 3-H), 6.77 (dd, *J* = 15.9, 6.8 Hz, 1 H, 4-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.1, –4.5, –4.4, –4.3 ($Si(CH_3)_2$), 11.2 ($SiCH(CH_3)_2$), 16.0 (13-CH_3), 18.1, 18.2 ($SiC(CH_3)_3$), 18.6 ($SiCH(CH_3)_2$), 20.7 (10-CH_3), 23.5 (C-6), 32.7 (C-10), 33.3 (C-5), 36.5 (C-7), 43.9 (C-13), 44.5 (C-9), 67.7 (C-14), 69.8 (C-8), 85.0 (C-16), 108.5 (C-15), 130.3 (C-12), 131.4 (C-3), 136.6 (C-11), 148.3 (C-4), 198.6 (C-2).

1-((2*S*,6*R*)-6-((2*S*,5*S*,6*R*,*E*)-6-((*tert*-Butyldimethylsilyl)oxy)-2,5-dimethyl-8-(triisopropylsilyl)oct-3-en-7-yn-1-yl)tetrahydro-2*H*-pyran-2-yl)propan-2-one (6)

A solution of alcohol **31** (330 mg, 0.74 mmol) in anhydrous CH_2Cl_2 (10 mL) was treated dropwise with 2,6-lutidine (180 µL, 166.6 mg, 1.55 mmol) at 0 °C. The reaction mixture was stirred for 10 min at this temperature before TBSOTf (245 mg, 0.93 mmol) was added dropwise. The mixture was stirred for 1 h at r.t. and then treated with saturated NH_4Cl solution (3 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The oily residue was purified by flash chromatography (petroleum ether/Et_2O, 2:1) to give silyl ether **6** (377 mg, 91%) as a colorless oil.

$[\alpha]_D^{20}$ +25.3 (*c* 1.0, CH_2Cl_2); R_f = 0.71 (petroleum ether/Et_2O, 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.05, 0.09 (2 s, 3 H each, $Si(CH_3)_2$), 0.86 (s, 9 H, $SiC(CH_3)_3$), 0.90 (d, *J* = 6.8 Hz, 3 H, 2″-CH_3), 1.05 (s, 24 H, $Si(CH(CH_3)_2)_3$, 5″-CH_3), 1.09–1.23 (m, 3 H, 1″-H, 3′-H, 5′-H), 1.42–1.57 (m, 4 H, 1″-H, 3′-H, 4′-H, 5′-H), 1.74–1.82 (m, 1 H, 4′-H), 2.14 (s, 3 H, 3-H), 2.19–2.32 (m, 2 H, 2″-H, 5″-H), 2.37 (dd, *J* = 15.2, 4.8 Hz, 1 H, 1-H), 2.62 (dd, *J* = 14.9, 8.1 Hz, 1 H, 1-H), 3.26–3.32 (m, 1 H, 6′-H), 3.66–3.72 (m, 1 H, 2′-H), 4.20 (d, *J* = 4.6 Hz, 1 H, 6″-H), 5.33 (dd, *J* = 15.6, 6.6 Hz, 1 H, 4″-H), 5.38 (dd, *J* = 15.7, 6.8 Hz, 1 H, 3″-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.2 ($Si(CH_3)_2$), –4.5 ($Si(CH_3)_2$), 11.2 ($SiCH(CH_3)_2$), 15.8 (5″-CH_3), 18.2 ($SiC(CH_3)_3$), 18.6 ($SiCH(CH_3)_2$), 19.7 (2″-CH_3), 23.5 (C-4′), 25.7 ($SiC(CH_3)_3$), 31.1 (C-3), 31.3 (C-3′ or C-5′), 31.5 (C-3′ or C-5′), 32.4 (C-2″), 43.4 (C-1″), 43.9 (C-5″), 50.3 (C-1), 67.4 (C-6″), 74.5 (C-2′), 75.5 (C-6′), 84.9 (C-8″), 108.6 (C-7″), 129.7 (C-3″), 136.6 (C-4″), 207.8 (C-2).

HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{33}H_{62}O_3Si_2$: 585.41297; found: 585.41300.

3-((*tert*-Butyldimethylsilyl)oxy)propanal (33)[29]

To a solution of DMSO (33.2 mL, 36.52 g, 0.47 mol) in CH_2Cl_2 (40 mL) cooled to –75 °C was added dropwise a solution of oxalyl chloride (20.8 mL, 30.8 g, 0.24 mol) in CH_2Cl_2 (100 mL) keeping the temperature of the solution below –60 °C. After complete addition, the mixture was stirred for 10 min at –75 °C, followed by the dropwise addition of alcohol[28] **32** (38.6 g, 0.203 mol) in CH_2Cl_2 (40 mL). The reaction mixture was stirred for 1 h at –75 °C before Et_3N (66 mL, 48.18 g, 0.476 mol) was added dropwise. The mixture was brought to r.t. and stirred for 1 h. The resulting white suspension was treated with H_2O (100 mL), the layers were separated and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/Et_2O, 4:1) to give aldehyde **33** (24.3 g, 64%) as a colorless oil.

R_f = 0.67 (petroleum ether/Et_2O, 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.01 (s, 6 H, $Si(CH_3)_2$), 0.84 (s, 9 H, $SiC(CH_3)_3$), 2.51 (dt, *J* = 6.1, 2.0 Hz, 2 H, 2-H), 3.92 (t, *J* = 6.1 Hz, 2 H, 3-H), 9.72 (t, *J* = 2.0 Hz, 1 H, 1-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.6 ($Si(CH_3)_2$), 18.1 ($SiC(CH_3)_3$), 25.7 ($SiC(CH_3)_3$), 46.4 (C-2), 57.3 (C-3), 201.7 (C-1).

(*S*)-1-((*tert*-Butyldimethylsilyl)oxy)hex-5-en-3-ol (34)[36]

To a freshly prepared suspension of (–)-*B*-allyldiisopinocampheylborane (1.88 g, 5.75 mmol) (see procedure for compound **13**) in anhydrous Et_2O (20 mL) was added dropwise very slowly aldehyde **33** (1.0 g, 5.3 mmol), dissolved in anhydrous Et_2O (10 mL), at –90 °C. After

complete addition, the reaction mixture was stirred for 1.5 h at –75 °C. Then, it was brought to r.t. within 1 h, stirred for 1 h at r.t., then cooled to 0 °C, and slowly treated with aqueous 3 M NaOH (6 mL), then with H_2O_2 (30%, 2.5 mL), and finally with saturated $NaHCO_3$ (8 mL). The reaction mixture was stirred at r.t. for 10 h, then extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/Et_2O, 2:1) providing homoallyl alcohol **34** (860 mg, 70%) as a colorless oil; 91.3% ee.

$[\alpha]_D^{20}$ –6.3 (*c* 1.0, CH_2Cl_2) {Lit.[36b] $[\alpha]_D^{20}$ –5.95 (*c* 2.20, $CHCl_3$); Lit.[36c] $[\alpha]_D^{25}$ –4.2 (*c* 0.66, $CHCl_3$)}; R_f = 0.44 (petroleum ether/Et_2O, 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 6 H, $Si(CH_3)_2$), 0.87 (s, 9 H, $SiC(CH_3)_3$), 1.61–1.66 (m, 2 H, 2-H), 2.16–2.26 (m, 2 H, 4-H), 3.75–3.80 (m, 1 H, 3-H), 3.82–3.89 (m, 2 H, 1-H), 5.03–5.10 (m, 2 H, 6-H), 5.80 (dd, *J* = 10.1, 7.1 Hz, 1 H, 5-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.6 ($Si(CH_3)_2$), 18.1 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 37.7 (C-2), 41.9 (C-4), 62.5 (C-1), 71.1 (C-3), 117.2 (C-6), 135.0 (C-5).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{26}O_2Si$: 253.15943; found: 253.15963.

GC (75 kP; 80 °C, 3 min, 10 °C/min to 190 °C, 10 min): t_R = 9.14 (minor enantiomer), 9.26 (major enantiomer) min.

(*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)oxy)hex-5-ene (35)[36c,37]

A solution of alcohol **34** (100 mg, 0.43 mmol) and 4-methoxybenzyl-2,2,2-trichloroacetimidate[30] (182 mg, 0.645 mmol) in anhydrous CH_2Cl_2 (3 mL) was treated with CSA (1 mg, 0.0043 mmol). The reaction mixture was stirred at r.t. for 12 h and then quenched with H_2O (2 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 2 mL). The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude ether was purified by flash chromatography (petroleum ether/Et_2O, 2:1) to give pure **35** (98 mg, 64%) as a colorless oil.

$[\alpha]_D^{20}$ +8.5 (*c* 1.0, CH_2Cl_2); R_f = 0.81 (petroleum ether/Et_2O, 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.00 (s, 6 H, $Si(CH_3)_2$), 0.85 (s, 9 H, $SiC(CH_3)_3$), 1.60–1.76 (m, 2 H, 2-H), 2.13–2.22 (m, 1 H, 4-H), 2.28 (t, *J* = 5.9 Hz, 1 H, 4-H), 3.44–3.48 (m, 1 H, 3-H), 3.55–3.69 (m, 2 H, 1-H), 3.73 (s, 3 H, OCH_3), 4.38 (d, *J* = 10.9 Hz, 1 H, OCH_2Ar), 4.39 (d, *J* = 10.9 Hz, 1 H, OCH_2Ar), 4.96–5.06 (m, 2 H, 6-H), 5.71–5.85 (m, 1 H, 5-H), 6.81 (dd, *J* = 6.6, 2.3 Hz, 2 H, H_{aromat}), 7.20 (dd, *J* = 8.6, 3.3 Hz, 2 H, H_{aromat}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.4 ($Si(CH_3)_2$), 18.2 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 37.2 (C-2), 38.5 (C-4), 55.1 (OCH_3), 59.6 (C-1), 70.8 (OCH_2Ar), 75.1 (C-3), 113.7 (C_{aromat}), 116.9 (C-6), 129.2 (C_{aromat}), 130.9 (C_{aromat}), 134.9 (C-5), 159.0 (C_{aromat}).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{34}O_3Si$: 373.21694; found: 373.21735.

(*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)oxy)pentanal (36)

A solution of alkene **35** (543 mg, 1.55 mmol) in H_2O/*t*-BuOH (1:1, 27 mL) was treated at 0 °C with $K_3Fe(CN)_6$ (1.56 g, 4.74 mmol), K_2CO_3 (652 mg, 4.72 mmol) and K_2OsO_4·2 H_2O (6.8 mg, 0.018 mmol). The reaction mixture was stirred at r.t. for 8 h, then diluted with H_2O (4 mL) and Et_2O (5 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was immediately dissolved in MeCN/H_2O (3:2, 35 mL) and treated with $NaIO_4$ (644 mg, 3.01 mmol). This mixture was stirred for 1 h at 0 °C before it was diluted with H_2O (10 mL) and Et_2O (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated in vacuo. The product was purified by flash chromatography (petroleum ether/Et_2O, 20:1) providing aldehyde **36** (240 mg, 44%) as a colorless oil.

$[\alpha]_D^{20}$ +4.5 (*c* 1.0, CH_2Cl_2); R_f = 0.43 (petroleum ether/Et_2O, 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 6 H, $Si(CH_3)_2$), 0.87 (s, 9 H, $SiC(CH_3)_3$), 1.68–1.76 (m, 1 H, 4-H), 1.80–1.88 (m, 1 H, 4-H), 2.58–2.60 (m, 2 H, 2-H), 3.66–3.72 (m, 2 H, 5-H), 3.73 (s, 3 H, OCH_3), 4.07–4.14 (m, 1 H, 3-H), 4.47 (d, *J* = 2.5 Hz, 2 H, OCH_2Ar), 6.85 (d, *J* = 8.6 Hz, 2 H, H_{aromat}), 7.22 (d, *J* = 8.8 Hz, 2 H, H_{aromat}), 9.75 (t, *J* = 2.5 Hz, 1 H, 1-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.5 ($Si(CH_3)_2$), 18.2 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 37.3 (C-4), 48.6 (C-2), 55.2 (OCH_3), 59.1 (C-5), 71.1 (OCH_2Ar), 71.4 (C-3), 113.8, 129.3, 130.2, 159.2 (4 C_{aromat}), 201.6 (C-1).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{32}O_4Si$: 375.19621; found: 375.19632.

(6*R*)-8-((*tert*-Butyldimethylsilyl)oxy)-1-((2*S*,6*R*)-6-((2*S*,5*S*,6*R*,*E*)-6-((*tert*-butyldimethylsilyl)oxy)-2,5-dimethyl-8-(triisopropylsilyl)oct-3-en-7-yn-1-yl)tetrahydro-2*H*-pyran-2-yl)-4-hydroxy-6-((4-methoxybenzyl)oxy)octan-2-one (37)

Under an inert atmosphere, a solution of ketone **6** (347 mg, 0.62 mmol) in anhydrous Et_2O (2 mL) was added dropwise to a solution of LDA (1 M in THF, 0.65 mL, 0.65 mmol) at –75 °C. The mixture was stirred for 1 h at –75 °C before aldehyde **36** (239 mg, 0.68 mmol), dissolved in Et_2O (1 mL), was added dropwise. After complete addition, the reaction mixture was stirred for 1 h and then quenched with pH 7 buffer (2 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 2 mL). The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/Et_2O, 2:1) to provide aldol product **37** (391 mg, 69%) as a colorless oil (dr = 3:1).

$[\alpha]_D^{20}$ +14.1 (*c* 1.0, CH_2Cl_2); R_f = 0.19 (petroleum ether/Et_2O, 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02, 0.03, 0.06, 0.10 (4 s, 3 H each, $Si(CH_3)_2$), 0.87 (s, 18 H, $SiC(CH_3)_3$), 0.91 (d, *J* = 6.6 Hz, 3 H, 2″-CH_3), 1.04 (s, 24 H, $SiCH(CH_3)_2$, 5″-CH_3), 1.44–1.58 (m, 6 H, 1″-H, 5′-H, 4′-H), 1.61–1.86 (m, 6 H, 5-H, 7-H, 3′-H), 2.15–2.38 (m, 3 H, 5″-H, 2″-H, 1-H), 2.53–2.66 (m, 3 H, 3-H, 1-H), 3.23–3.32 (m, 1 H, 6′-H), 3.62–3.72 (m, 3 H, 6-H, 8-H), 3.74 (s, 3 H, OCH_3), 3.79–3.86 (m, 1 H, 2′-H), 4.14 (d, *J* = 5.6 Hz, 1 H, 6″-H), 4.26–4.34 (m, 1 H, 4-H), 4.34–4.54 (m, 2 H, OCH_2Ar), 5.32 (ddd, *J* = 8.6, 6.8, 2.8 Hz, 1 H, 4″-H), 5.38 (dd, *J* = 15.7, 7.1 Hz, 1 H, 3″-H), 6.80–6.83 (m, 2 H, H_{aromat}), 7.22 (t, *J* = 8.3 Hz, 2 H, H_{aromat}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.5 ($Si(CH_3)_2$), –5.2 ($Si(CH_3)_2$), –4.6 ($Si(CH_3)_2$), 11.1 ($SiCH(CH_3)_2$), 15.7 (5″-CH_3), 18.1 ($SiC(CH_3)_3$), 18.5 ($SiCH(CH_3)_2$), 19.8 ($SiC(CH_3)_3$), 19.9 (2″-CH_3), 23.3 (C-4′), 25.6 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 31.1, 31.4 (C-3′, C-5′), 32.3 (C-2″), 37.3 (C-7), 40.8 (C-5), 43.2 (C-1″), 43.8 (C-5″), 49.8 (C-1), 51.1 (C-3), 55.0 (OCH_3), 59.3 (C-8), 67.6 (C-6″), 70.4 (C-4), 71.3 (OCH_2Ar), 73.2 (C-4 isomer), 74.1, 74.2 (C-2′), 75.0 (C-6), 75.5, 75.6 (C-6′), 84.8 (C-8″), 108.5 (C-7″), 113.7 (C_{aromat}), 129.4 (C_{aromat}), 129.8 (C_{aromat}), 130.5 (C-3″), 136.3 (C-4″), 159.1 (C_{aromat}), 209.7 (C-2).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{52}H_{94}O_7Si_3$: 937.61996; found: 937.62065.

(6*R*)-4,8-Bis((*tert*-butyldimethylsilyl)oxy)-1-((2*S*,6*R*)-6-((2*S*,5*S*,6*R*,*E*)-6-((*tert*-butyldimethylsilyl)oxy)-2,5-dimethyl-8-(triisopropylsilyl)oct-3-en-7-yn-1-yl)tetrahydro-2*H*-pyran-2-yl)-6-((4-methoxybenzyl)oxy)octan-2-one (5)

To a solution of alcohol **37** (4.4 g, 4.8 mmol) in anhydrous CH_2Cl_2 (75 mL) was added dropwise 2,6-lutidine (1.4 mL, 1.29 g, 12.0 mmol) at 0 °C. The reaction mixture was stirred for 20 min before TBSOTf (2.5 g, 9.5 mmol) was added dropwise at 0 °C. The solution was brought to r.t. and stirred for 1 h. Thereafter, it was treated with saturated NH_4Cl solution (20 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/Et_2O, 2:1) providing silyl ether **5** (3.71 g, 75%) as a colorless oil.

$[\alpha]_D^{20}$ +11.6 (*c* 1.0, CH_2Cl_2); R_f = 0.77 (petroleum ether/Et_2O, 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01, 0.02, 0.03, 0.04, 0.05, 0.07, 0.12 (s, 18 H, Si(CH_3)$_2$), 0.85 (s, 9 H, SiC(CH_3)$_3$), 0.88 (s, 18 H, SiC(CH_3)$_3$), 0.93 (d, *J* = 6.1 Hz, 3 H, 2″-CH_3), 1.05 (s, 21 H, SiC*H*(CH_3)$_2$), 1.05 (d, *J* = 4.8 Hz, 3 H, 5″-CH_3), 1.10–1.25 (m, 3 H, 3′-H, 5′-H, 1″-H), 1.42–1.64 (m, 5 H, 5-H, 3′-H, 4′-H, 5′-H, 1″-H), 1.67–1.80 (m, 4 H, 5-H, 7-H, 4′-H), 2.23–2.38 (m, 3 H, 1-H, 2″-H, 5″-H), 2.54–2.66 (m, 3 H, 1-H, 3-H), 3.25–3.33 (m, 1 H, 6′-H), 3.60–3.73 (m, 4 H, 6-H, 8-H, 2′-H), 3.75 (s, 3 H, OCH_3), 4.15 (d, *J* = 4.3 Hz, 1 H, 6″-H), 4.28–4.35 (m, 1 H, 4-H), 4.37–4.48 (m, 2 H, OCH_2Ar), 5.34 (dd, *J* = 15.4, 6.6 Hz, 1 H, 4″-H), 5.40 (dd, *J* = 15.4, 6.6 Hz, 1 H, 3″-H), 6.84 (dd, *J* = 8.6, 2.8 Hz, 2 H, H_{aromat}), 7.24 (dd, *J* = 8.6, 3.5 Hz, 2 H, H_{aromat}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.4, –5.2, –4.6, –4.5, –4.5 (Si(CH_3)$_2$), 11.1 (Si*C*H(CH_3)$_2$), 15.8 (5″-CH_3), 17.8, 17.9, 18.1, 18.2 (Si*C*(CH_3)$_3$), 18.5 (SiCH(*C*H_3)$_2$), 19.9 (2″-CH_3), 23.4 (C-4′), 25.7, 25.8, 25.9 (SiC(*C*H_3)$_3$), 31.2, 31.5 (C-3′, C-5′), 32.3 (C-2″), 37.5, 37.7 (C-7), 43.1 (C-5), 43.4 (C-1″), 43.9 (C-5″), 50.8 (C-1), 52.1 (C-3), 55.0 (OCH_3), 59.4 (C-8), 66.3 (C-4), 67.7 (C-6″), 70.4 (OCH_2Ar), 72.4, 72.9 (C-6), 73.9 (C-2′), 75.5 (C-6′), 84.8 (C-8″), 108.6 (C-7″), 113.6 (C_{aromat}), 129.0 (C_{aromat}), 129.3 (C_{aromat}), 129.7 (C-3″), 136.3 (C-4″), 159.0 (C_{aromat}), 207.4, 207.7 (C-2).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{58}H_{108}O_7Si_4$: 1051.70643; found: 1051.70640.

Bis-tetrahydropyran 38

To a solution of ketone **5** (1.77 g, 1.72 mmol) in Et_3SiH/CH_2Cl_2 (1:3, 85 mL) was added slowly at –75 °C $BF_3{\cdot}Et_2O$ (1.02 mL, 1.173 g, 8.26 mmol). The stirred reaction mixture was allowed to warm to –20 °C within 1 h and stirred for 1 h at this temperature. The reaction was quenched with Et_3N (5 mL) and saturated $NaHCO_3$ solution (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/Et_2O, 4:1) to give bis-pyran **38** (937 mg, 61%) as a colorless oil.

$[\alpha]_D^{20}$ +20.3 (*c* 1.0, CH_2Cl_2); R_f = 0.82 (petroleum ether/Et_2O, 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02, 0.03, 0.04, 0.05, 0.08, 0.11 (6 s, 18 H, Si(CH_3)$_2$), 0.87 (s, 18 H, SiC(CH_3)$_3$), 0.88 (s, 9 H, SiC(CH_3)$_3$), 0.93 (d, *J* = 6.6 Hz, 3 H, 15-CH_3), 1.03 (d, *J* = 4.3 Hz, 3 H, 18-CH_3), 1.05 (s, 21 H, SiC*H*(CH_3)$_2$), 1.14–1.27 (m, 5 H, 6-H, 8-H, 10-H, 12-H, 14-H), 1.32–1.42 (m, 1 H, 4-H), 1.45–1.65 (m, 6 H, 2-H, 10-H, 11-H, 12-H, 14-H), 1.74–1.84 (m, 4 H, 4-H, 6-H, 8-H, 11-H), 2.20–2.35 (m, 2 H, 15-H, 18-H), 3.22–3.30 (m, 1 H, 13-H), 3.33–3.44 (m, 2 H, 5-H, 9-H), 3.64–3.77 (m, 3 H, 1-H, 7-H), 3.85–3.93 (m, 1 H, 3-H), 4.16 (d, *J* = 5.6 Hz, 1 H, 19-H), 5.35 (dd, *J* = 15.4, 6.8 Hz, 1 H, 17-H), 5.41 (dd, *J* = 15.4, 8.1 Hz, 1 H, 16-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3 (Si(CH_3)$_2$), –5.1 (Si(CH_3)$_2$), –4.5 (Si(CH_3)$_2$), –4.5 (Si(CH_3)$_2$), 11.2 (Si*C*H(CH_3)$_2$), 15.9 (18-CH_3), 18.1 (Si*C*(CH_3)$_3$), 18.2 (Si*C*(CH_3)$_3$), 18.3 (Si*C*(CH_3)$_3$), 18.6 (SiCH(*C*H_3)$_2$), 19.7 (15-CH_3), 23.8 (C-11), 25.8 (SiC(*C*H_3)$_3$), 25.9 (SiC(*C*H_3)$_3$), 26.0 (SiC(*C*H_3)$_3$), 31.5 (C-10, C-12), 33.7 (C-12), 32.3 (C-15), 39.3 (C-2), 41.4 (C-14), 42.0 (C-4), 42.6 (C-8), 43.6 (C-6), 44.0 (C-18), 59.7 (C-1), 67.8 (C-5), 69.0 (C-9), 72.1 (C-7), 72.2 (C-13), 74.3 (C-3), 75.3 (C-19), 84.9 (C-21), 108.7 (C-20), 129.7 (C-16), 136.8 (C-17).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{50}H_{100}O_5Si_4$: 915.65400; found: 915.65248.

Alcohol 39

A solution of bis-tetrahydropyran **38** (609 mg, 0.681 mmol) in anhydrous CH_2Cl_2/MeOH (1:1, 40 mL) was treated at 0 °C with PPTS (18.4 mg, 0.073 mmol). The reaction mixture was stirred at r.t. for 4 h and then treated with saturated $NaHCO_3$ solution (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/Et_2O, 2:1) providing primary alcohol **39** (406 mg, 76%) as a colorless oil.

$[\alpha]_D^{20}$ +31.2 (*c* 1.0, CH_2Cl_2); R_f = 0.38 (petroleum ether/Et_2O, 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 6 H, Si(CH_3)$_2$), 0.07 (d, *J* = 15.4 Hz, 6 H, Si(CH_3)$_2$), 0.86 (s, 9 H, SiC(CH_3)$_3$), 0.87 (s, 9 H, SiC(CH_3)$_3$), 0.92 (d, *J* = 6.6 Hz, 3 H, 15-CH_3), 1.05 (s, 24 H, SiC*H*(CH_3)$_2$, 18-CH_3), 1.13–1.26 (m, 4 H, 4-H, 11-H), 1.37–1.67 (m, 8 H, 6-H, 10-H, 12-H, 14-H), 1.70–1.89 (m, 4 H, 2-H, 8-H), 2.22–2.34 (m, 2 H, 15-H, 18-H), 3.21–3.29 (m, 1 H, 13-H), 3.29–3.39 (m, 1 H, 7-H), 3.48–3.56 (m, 1 H, 3-H), 3.69–3.81 (m, 3 H, 1-H, 5-H), 3.95–4.03 (m, 1 H, 9-H), 4.14 (d, *J* = 5.5 Hz, 1 H, 19-H), 5.29–5.38 (m, 1 H, 17-H), 5.41 (dd, *J* = 15.5, 6.6 Hz, 1 H, 16-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.1 (Si(CH_3)$_2$), –4.6 (Si(CH_3)$_2$), –4.5 (Si(CH_3)$_2$), 11.2 (Si*C*H(CH_3)$_2$), 15.8 (18-CH_3), 18.0 (Si*C*(CH_3)$_3$), 18.2 (Si*C*(CH_3)$_3$), 18.6 (SiCH(*C*H_3)$_2$), 19.5 (15-CH_3), 23.7 (C-11), 25.7 (SiC(*C*H_3)$_3$), 25.8 (SiC(*C*H_3)$_3$), 31.7 (C-15), 32.2 (C-12), 32.5 (C-10), 37.8 (C-2), 40.8 (C-14), 41.7 (C-4), 42.4 (C-8), 43.5 (C-6), 44.0 (C-18), 61.5 (C-1), 67.8 (C-5), 68.5 (C-9), 72.8 (C-7), 74.2 (C-13), 75.3 (C-3), 76.2 (C-19), 84.9 (C-21), 108.7 (C-20), 129.7 (C-16), 136.7 (C-17).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{44}H_{86}O_5Si_3$: 801.56753; found: 801.56785.

Carboxylic Acid 40

A solution of bis-tetrahydropyranyl alcohol **39** (320 mg, 0.411 mmol) in MeCN/petroleum ether (2:1, 15 mL) was treated at 0 °C with NMO·H_2O (576 mg, 4.26 mmol) and TPAP (13.8 mg, 0.039 mmol). The reaction mixture was stirred at r.t. for 3 h. After completion of the reaction (TLC), the volatiles were removed under reduced pressure and the residue was purified by flash chromatography (petroleum ether/Et_2O, 3:2). Acid **40** (240 mg, 74%) was obtained as a colorless oil.

$[\alpha]_D^{20}$ +10.5 (*c* 1.0, CH_2Cl_2); R_f = 0.78 (petroleum ether/Et_2O, 3:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03, 0.04, 0.07, 0.11 (4 s, 3 H each, $Si(CH_3)_2$), 0.87 (s, 9 H, $SiC(CH_3)_3$), 0.88 (s, 9 H, $SiC(CH_3)_3$), 0.93 (d, *J* = 6.7 Hz, 3 H, 15-CH_3), 1.03 (d, *J* = 6.7 Hz, 3 H, 18-CH_3), 1.05 (s, 21 H, $SiCH(CH_3)_2$), 1.13–1.28 (m, 5 H, 4-H, 6-H, 10-H, 12-H, 14-H), 1.37–1.67 (m, 6 H, 6-H, 8-H, 10-H, 11-H, 12-H, 14-H), 1.70–1.89 (m, 3 H, 4-H, 6-H, 8-H, 11-H), 2.22–2.35 (m, 2 H, 15-H, 18-H), 2.48 (dd, *J* = 11.3, 8.9 Hz, 1 H, 2-H), 2.56 (dd, *J* = 15.9, 8.1 Hz, 1 H, 2-H), 3.22–3.30 (m, 1 H, 13-H), 3.33–3.40 (m, 1 H, 9-H), 3.54–3.63 (m, 1 H, 7-H), 3.67–3.81 (m, 2 H, 3-H, 5-H), 4.14 (d, *J* = 5.5 Hz, 1 H, 19-H), 5.29–5.45 (m, 2 H, 16-H, 17-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.1 ($Si(CH_3)_2$), –4.6 ($Si(CH_3)_2$), –4.5 ($Si(CH_3)_2$), 11.2 ($SiCH(CH_3)_2$), 15.9 (18-CH_3), 18.0 ($SiC(CH_3)_3$), 18.2 ($SiC(CH_3)_3$), 18.6 ($SiCH(CH_3)_2$), 19.7 (15-CH_3), 23.6 (C-11), 25.8 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 31.7 (C-10, C-12), 32.3 (C-15), 40.7 (C-2), 41.1 (C-4), 42.1 (C-8), 43.4 (C-6, C-14), 44.0 (C-18), 67.8 (C-19), 68.2 (C-5), 71.8 (C-3), 73.2 (C-7), 74.2 (C-9), 75.4 (C-13), 84.9 (C-21), 108.7 (C-20), 129.8 (C-16), 136.7 (C-17), 173.9 (C-1).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{44}H_{84}O_6Si_3$: 815.54679; found: 815.54679.

Hydroxy Acid 41

To a solution of bis-tetrahydropyranyl carboxylic acid **40** (7.4 mg, 0.0093 mmol) in anhydrous THF (1 mL) was added at 0 °C TBAF·3 H_2O (17.6 mg, 0.056 mmol). The reaction mixture was stirred at r.t. for 4 h. After completion of the reaction (TLC), the volatiles were removed under reduced pressure and the residue was purified by flash chromatography (petroleum ether/Et_2O, 3:2). Seco acid **41** (1.9 mg, 39%) was obtained as a colorless oil.

$[\alpha]_D^{20}$ –9.8 (*c* 1.0, CH_2Cl_2); R_f = 0.19 (petroleum ether/Et_2O, 3:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 (d, *J* = 5.3 Hz, 6 H, $Si(CH_3)_2$), 0.87 (d, *J* = 5.6 Hz, 9 H, $SiC(CH_3)_3$), 0.97 (d, *J* = 6.7 Hz, 3 H, 15-CH_3), 1.07 (d, *J* = 7.0 Hz, 3 H, 18-CH_3), 1.21–1.31 (m, 4 H, 6-H, 11-H), 1.39–1.62 (m, 8 H, 4-H, 10-H, 12-H, 14-H), 1.79–1.88 (m, 2 H, 8-H), 2.28–2.40 (m, 2 H, 15-H, 18-H), 2.43 (t, *J* = 2.3 Hz, 1 H, 21-H), 2.45–2.50 (m, 1 H, 2-H), 2.56 (dd, *J* = 15.7, 8.4 Hz, 1 H, 2-H), 3.25–3.31 (m, 1 H, 13-H), 3.35–3.41 (m, 1 H, 7-H), 3.53–3.59 (m, 1 H, 9-H), 3.69–3.81 (m, 1 H, 5-H), 4.15–4.19 (m, 1 H, 3-H), 4.22 (d, *J* = 4.9 Hz, 1 H, 19-H), 5.39 (dd, *J* = 8.0, 3.7 Hz, 1 H, 17-H), 5.41 (dd, *J* = 15.4, 7.6 Hz, 1 H, 16-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.9 ($Si(CH_3)_2$), –4.6 ($Si(CH_3)_2$), 16.0 (18-CH_3), 18.0 ($SiC(CH_3)_3$), 20.1 (15-CH_3), 23.6 (C-11), 25.6 ($SiC(CH_3)_3$), 31.6 (C-10, C-12), 32.9 (C-15), 40.7 (C-2), 40.9 (C-4), 42.9 (C-18), 43.4 (C-6, C-14), 66.0 (C-19), 68.1 (C-5), 71.9 (C-3), 73.4 (C-7), 73.7 (C-21), 74.5 (C-9), 77.8 (C-21), 83.2 (C-20), 127.7 (C-16), 139.7 (C-17), 177.7 (C-1).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{29}H_{50}O_6Si$: 545.32689; found: 545.32701.

Macrolactone 43

To a solution of MNBA (**42**; 9.7 mg, 0.028 mmol) and DMAP (5.6 mg, 0.46 mmol) in anhydrous CH_2Cl_2 (2 mL) was added bis-tetrahydropyranyl hydroxy acid **41** (10 mg, 0.019 mmol), dissolved in anhydrous CH_2Cl_2 (20 mL), dropwise via syringe pump over a period of 7 h at r.t. The reaction mixture was stirred for an additional 1 h and quenched with saturated $NaHCO_3$ solution (5 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 3 mL). The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/Et_2O, 10:1) to give macrolactone **43** (5.9 mg, 61%) as a colorless oil.

$[\alpha]_D^{20}$ –17.4 (*c* 1.0, CH_2Cl_2); R_f = 0.17 (petroleum ether/Et_2O, 10:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 3 H, $Si(CH_3)_2$), 0.03 (s, 3 H, $Si(CH_3)_2$), 0.88 (s, 9 H, $SiC(CH_3)_3$), 1.07 (d, *J* = 7.1 Hz, 3 H, 15-CH_3), 1.19 (d, *J* = 6.8 Hz, 3 H, 18-CH_3), 1.21–1.31 (m, 5 H, 4-H, 6-H, 8-H, 10 H, 12 H), 1.39–1.62 (m, 9 H, 4-H, 6-H, 8 H, 10-H, 11-H (2 x), 12-H, 14-H (2 x)), 2.27–2.38 (m, 2 H, 15-H, 18-H), 2.42 (d, *J* = 2.1 Hz, 1 H, 21-H), 2.45–2.56 (m, 2 H, 2-H), 3.18–3.23 (m, 1 H, 13-H), 3.26–3.30 (m, 1 H, 9-H), 3.62–3.68 (m, 1 H, 7-H), 4.14–4.19 (m, 1 H, 5-H), 4.24–4.31 (m, 1 H, 3-H), 5.30 (t, *J* = 2.2 Hz, 1 H, 19-H), 5.46 (dd, *J* = 7.6, 6.7 Hz, 1 H, 17-H), 5.58 (dd, *J* = 15.8, 5.1 Hz, 1 H, 16-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.9 ($Si(CH_3)_2$), 14.6 (18-CH_3), 18.1 ($SiC(CH_3)_3$), 20.5 (15-CH_3), 23.6 (C-11), 25.6 ($SiC(CH_3)_3$), 31.6 (C-10, C-12) 32.9 (C-15), 40.6 (C-4, C-6), 40.8 (C-2), 41.5 (C-8), 42.2 (C-18), 43.9 (C-14), 65.1 (C-5), 68.1 (C-19), 68.7 (C-3), 69.8 (C-7), 72.2 (C-7, minor), 73.6 (C-21), 75.9 (C-9), 76.5 (C-13), 80.9 (C-20), 128.4 (C-16), 135.9 (C-17), 171.2 (C-1).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{29}H_{48}O_5Si$: 527.31632; found: 527.31672.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1609551.

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