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Towards the total synthesis of Calyculin C: preparation of the C_{13}–C_{25} spirocyclic core

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ABSTRACT

A stereoselective synthesis of the C_{13}–C_{25} of Calyculin C is described. Key steps involve the coupling of a terminal acetylene with a thiol ester and subsequent spirocyclisation using a double intramolecular hetero-Michael addition.

1. Introduction

Originally isolated by Fusetani et al., from the marine sponge *Discodermia calyx*, the Calyculins comprise a family of structurally novel secondary metabolites that posses a remarkable range of biological properties.[1–3] The family is composed of 8 different members, which vary by substitution at C_{32} and the olefin geometry of the tetraene moiety (Calyculins A–H, see Fig. 1: Calyculin C). Of particular significance is the observation that most members of the family are potent inhibitors of protein phosphatases 1 and 2A[4,5] whilst calyculins A–D also display potent cytotoxicity against L1210 leukamia cells.[2]

This interesting biological profile combined with their complex structures made the Calyculins attractive from a synthetic point of view. Several synthetic approaches have been described,[6] leading amongst others to the total syntheses of (+)-Calyculin A by Evans[7] and Barrett,[6] (−)-Calyculin A by Masamune,[8] (−)-Calyculin B by Smith[9] and Calyculin C by Armstrong.[10] Efforts in our group have resulted in the preparation of the C_1–C_8,[11] C_{26}–C_{32},[12] C_{33}–C_{38}[13] fragments of Calyculin C. Herein we describe our latest results towards the construction of the C_{13}–C_{25} spirocyclic fragment.

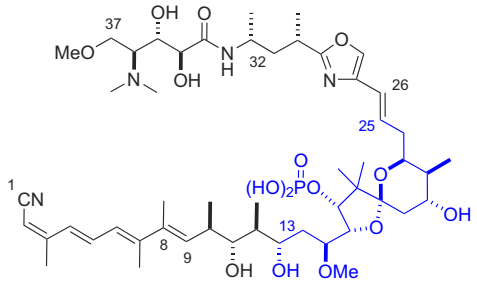

Figure 1. Structure of Calyculin C.

As shown in Scheme 1, our retrosynthetic strategy for the C_{13}–C_{25} fragment was based on a convergent approach. We have previously shown that the C_{21} carbonyl group of structures such as **2** can be selectively reduced using L-Selectride to deliver the axial diastereomer as found in the Calyculin family.[14] Furthermore, structurally and biologically related natural products such as Clavosines A–C[15] and Geometricin[16] differ from the Calyculins in the stereochemistry at this centre. It was assumed that the requisite equatorial isomer of these molecules could be accessed via K-Selectride-mediated reduction. With the synthesis of not only Calyculin C, but also the Clavosines and Geometricin in mind, we focused our efforts on the synthesis of common intermediate spiroketal **2**.

The DIHMA (double intramolecular hetero-Michael addition) process for the construction of spiroketal moieties was initially introduced by Crimmins[17] and further adapted by Forsyth in the total syntheses of natural products.[18] We proposed that utilisation of such DIHMA methodology would allow the formation of the key spiroketal **2** from the ynone **3**. Ynone **3** could, in principle, be obtained by coupling the terminal acetylene **4** with a carbonyl partner **5**. Finally, we proposed alkyne **4** to arise from the known lactone **6**.[19]

2. Results and discussion

We have recently studied and validated the mechanism of the spirocyclisation on a simplified model compound (Scheme 2).[14,20] Asymmetric dihydroxylation of enoate **7** followed by protection and reduction furnished lactol **8**, which was converted to alkyne **9** using Ohira-Bestmann reagent **10** and silyl protection.[21,22] This represented the first example of the use of a hindered lactol in a Seyferth–Gilbert-type homologation. Weinreb amide **12** was obtained from oxazolidinone **11** via an Evans aldol reaction.[23]

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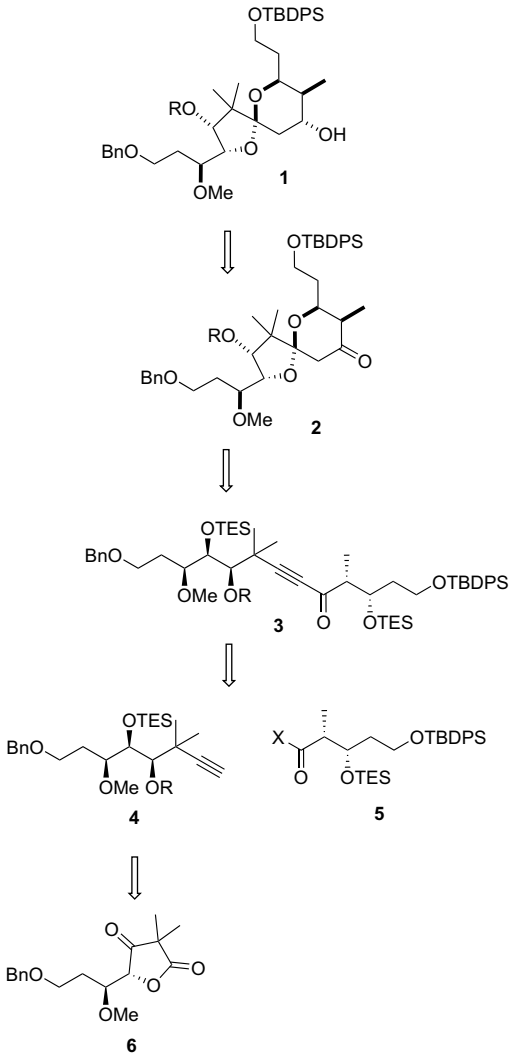
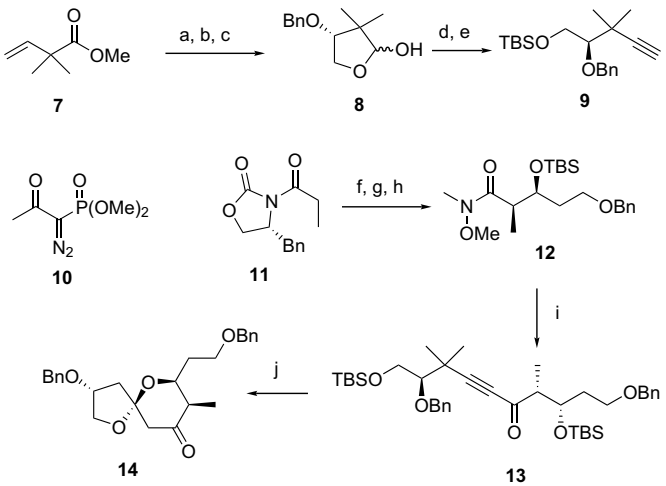


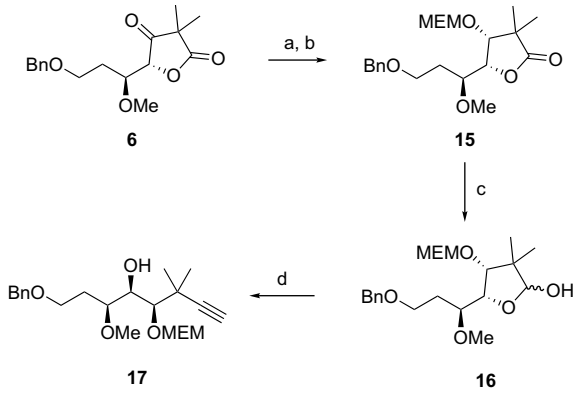
Scheme 1. Retrosynthetic analysis of spiroketal **1**.



Scheme 2. Reagents and conditions: (a) OsO_4, $(DHQ)_2PYR$, K_3FeCN_6, K_2CO_3, H_2O/*t*-BuOH (1:1), 0 °C, 82%; (b) $Cl_3CNHOBn$, CF_3SO_3H, CH_2Cl_2/*c*-C_6H_{12} (1:3), 35 °C, 91%; (c) DIBAL-H, PhMe, −78 °C, 90%; (d) **10**, K_2CO_3, MeOH, 36 °C, 61%; (e) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 89%; (f) Bu_2BOTf, Et_3N, CH_2Cl_2, 0 °C then $BnOCH_2CH_2CHO$, −78 °C, 80%; (g) MeO(Me)NH·HCl, $AlMe_3$, THF, 0 °C, 89%; (h) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 89%; (i) 9, *n*-BuLi, THF, −78 °C, 62%; (j) CSA, MeOH then *p*-TsOH, PhMe, rt, 86%.

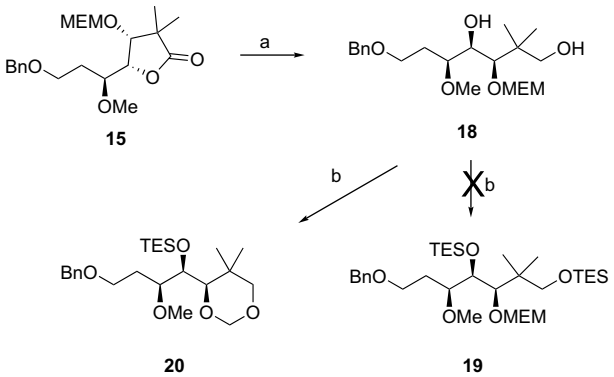
Weinreb–Nahm coupling[24] of alkyne **9** and amide **12** furnished alkynone **13**, which, upon successive treatment by CSA and *p*-TsOH underwent the spirocyclisation via the DIHMA pathway to yield spirocylcle **14** as a single enantiomer.

With this proof of concept in hand, we turned our attention towards the actual spirocyclic core of Calyculin C (Scheme 3). Our starting point was lactone **6**, the synthesis of which has previously been described by our group.[19] **15** was obtained in good yield and selectivity (>7:1 by ^1H NMR), by stereoselective reduction of ketone **6** using potassium superhydride.[8] MEM-protection of the resultant alcohol required a large excess of reagents and a prolonged reaction time but ultimately proceeded in 66% yield. DIBAL-H reduction of **15** efficiently furnished lactol **16**. Unfortunately, Ohira–Bestmann homologation of **16** gave only a low yield of alkyne **17**. Given that aldehydes adjacent to tertiary centres are well known to undergo homologation it was assumed that the issue lay in the position of the lactol–aldehyde equilibrium rather than steric factors. Attempts to force the equilibrium to favour the open-chain form (by performing the reaction at higher temperatures or in a microwave) only resulted in poorer yields.



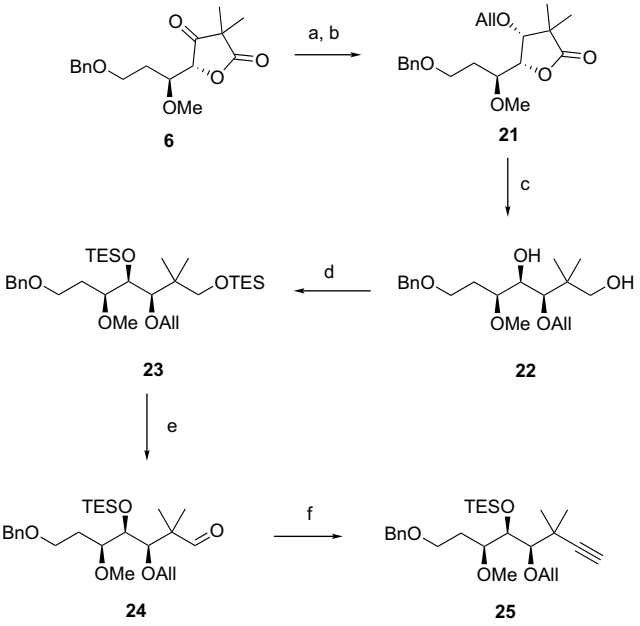
Scheme 3. Reagents and conditions: (a) $KHBEt_3$, THF, −78 °C, 76%; (b) MEMCl, $^iPr_2NEt$, CH_2Cl_2, reflux, 66%; (c) DIBAL-H, THF, −78 °C, 80%; (d) **10**, K_2CO_3, MeOH, 36 °C, 22%.

These disappointing results prompted us to devise an alternative strategy to access the key alkyne, which avoided reliance on the lactol–aldehyde equilibrium (Scheme 4). Reduction of lactone **15** with LAH cleanly furnished diol **18**, which was then subjected to classical TES-protection (TESOTf, 2,6-lutidine in CH_2Cl_2). Unfortunately, no bis-protected **19** was formed but instead dioxolane **20** was obtained. Such dioxolane formation has previously been reported by Boynton et al. upon treatment of a MEM-protected diol with $MgBr_2$ in EtOAc.[25] Attempts to obtain **19** using the weaker Lewis-acid TESCl were unsuccessful as, even when using a large excess of reagents and elevated temperatures, only mono-protected products were obtained.



Scheme 4. Reagents and conditions: (a) LAH, THF, 0 °C to rt; (b) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 60% over 2 steps.

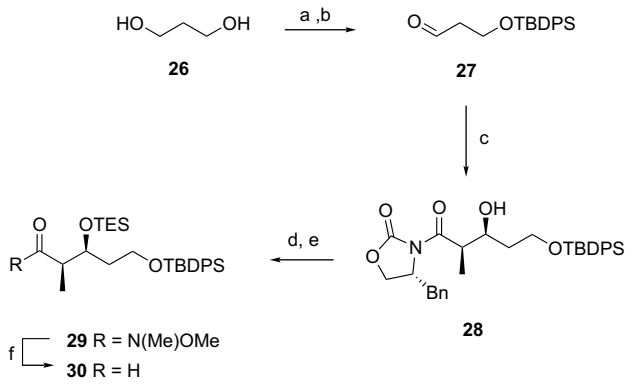
With the MEM ether proving problematic both in terms of its introduction and undesired reactivity, we were prompted to investigate an alternative protecting group for the C_{21} alcohol. An allyl group was selected for this purpose (Scheme 5). Lactone **6** was therefore protected, after reduction, to the corresponding allyl ether using classical conditions in an 86% yield. As observed previously, reduction of the lactone ring using LAH in THF proceeded cleanly to furnish diol **22**, which was used in the next step without purification. TES-protection of **22** yielded fully protected **23**, with a satisfactory yield of 88% for these two steps. The following step involved the selective deprotection of the primary TES in the presence of the secondary, in order to reach targeted aldehyde **24**.[26] Preliminary attempts to selectively deprotect the primary ether, either in the presence of TBAF or different acid sources were not satisfactory, leading to mixtures of starting material **23**, fully deprotected diol **22** and mono-deprotected compound. Pleasingly, using slightly modified conditions described by Spur et al.,[27] we found out that direct oxidation of the primary silyl ether could be achieved under Swern conditions. Indeed, after addition of **23** on a DMSO/oxalyl chloride solution in CH_2Cl_2 at −78 °C, we observed that stirring the reaction mixture for 1 h at −25 °C before addition of Et_3N at −78 °C cleanly cleaved and oxidized the primary TES to yield aldehyde **24** in a good isolated yield of 83%. Finally, Ohira–Bestmann homologation of **24** proceeded successfully, and the key alkyne **25** was obtained in excellent yield. This route proved to be of sufficient efficiency and reproducibility to consistently deliver acetylene **25** on gram scale.



Scheme 5. Reagents and conditions: (a) $KHBEt_3$, THF, −78 °C, 76%; (b) allyl bromide, *t*-BuOK, THF, rt, 86%; (c) LAH, THF, 0 °C to rt; (d) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 88% over 2 steps; (e) $(COCl)_2$, DMSO, −25 °C then Et_3N, −78 °C, 83%; (f) **10**, K_2CO_3, MeOH, rt, 92%.

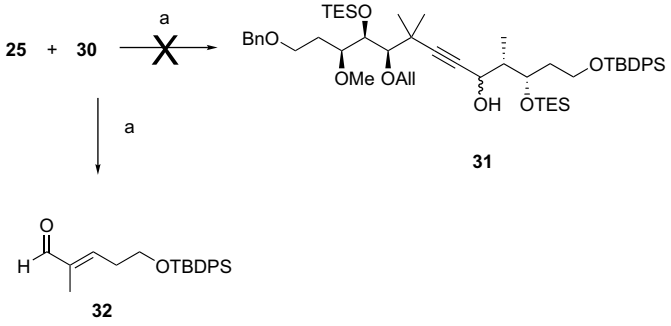
With key alkyne **25** in hand, we turned our attention to the synthesis of its coupling partner (Scheme 6). 1,3-Propanediol **26** was selectively mono-protected as its TBDPS ether and the resulting alcohol oxidized to aldehyde **27** using the Parikh–Doering protocol.[28] Evans aldol reaction with **11** gave **28**, which was reacted with *N*,*O*-dimethylhydroxylamine followed by TES-protection to furnish the Weinreb amide **29**.

With each coupling partner in hand the key-coupling reaction between alkyne **25** and Weinreb amide **29** was investigated. Unfortunately, under the conditions described for our model compound **9** (Scheme 2; *n*-BuLi, THF, −78 °C), only starting materials



Scheme 6. Reagents and conditions: (a) TBDPSCl, Et_3N, CH_2Cl_2, rt; (b) $SO_3{\cdot}Py$, Et_3N, DMSO, CH_2Cl_2, rt, 88% over 2 steps; (c) **11**, Bu_2BOTf, Et_3N, CH_2Cl_2, 0 °C then **27**, −78 °C, 83%; (d) MeO(Me)NH·HCl, $AlMe_3$, THF, 0 °C, 71%; (e) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 97%; (f) DIBAL-H, THF, −78 °C, 71%.

could be recovered. We then turned our attention to the synthesis of more reactive aldehyde coupling partner **30**, which was obtained by simple reduction of amide **29** (Scheme 6). It is well known that addition of lithium acetylides to readily enolizable aldehydes can be performed in the presence of anhydrous lithium bromide, as described by Carreira for the synthesis of (+)-Zaragozic acid C.[29] Unfortunately, in our case, application of these conditions led to the recovery of alkyne **25** and formation of elimination product **32**,[30] no trace of propargylic alcohol **31** being observed (Scheme 7). Changing the reaction conditions by varying the amount of reactants, the temperature or the solvent did not lead to any improvement for the reaction of acetylide anion of **25** with **29** or **30**. Quenching the acetylide anion of **25** with D_2O, however, resulted in quantitative insertion of deuterium and thus it was apparent that the lack of reactivity was not a matter of the acidity of **25** but instead its poor nucleophilicity.

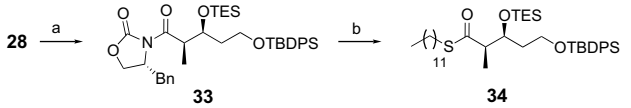


Scheme 7. Reagents and conditions: *n*-BuLi, LiBr, THF, −78 °C.

A range of alternative metallic species have been used for the construction of propargylic alcohols from the corresponding terminal acetylenes and aldehydes. Unfortunately, neither Carreira's ($Zn(OTf)_2$, Et_3N, (+)-*N*-methyl-ephedrine, toluene),[31] Cozzi's (Me_2Zn, toluene),[32] Pu's (Et_2Zn, Ti(O-^{i}Pr)$_4$, BINOL, toluene, ether),[33] Shibasaki's ($InBr_3$, BINOL, Cy_2NMe, CH_2Cl_2)[34] or Konakahara's ($InBr_3$, Et_3N, Et_2O)[35] conditions proved to be efficient in our case and only starting materials were recovered in all attempts performed.

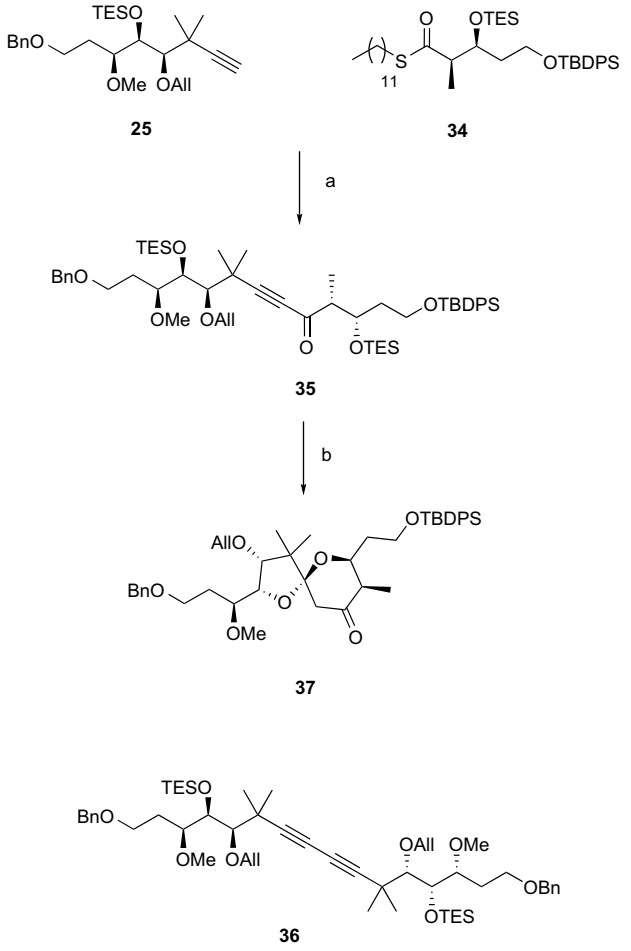
Among the numerous methodologies reported for the construction of α,β-acetylenic ketones, the palladium and/or copper coupling of terminal acetylenic derivatives with acid chlorides appeared to be the method of choice.[36] However, all attempts to form the acid chloride derivative of **29** failed. We then turned our attention to the method of Fukuyama in which dodecanethiol esters are reacted with terminal acetylenes in the presence of

$PdCl_2(dppf)_2$ and CuI.[37] To this end, thiol ester **34** was prepared in two steps from alcohol **28** by silyl ether formation followed by displacement of the oxazolidinone moiety with lithium dodecanethiolate (Scheme 8).[38]



Scheme 8. Reagents and conditions: (a) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 88%; (b) dodecanethiol, *n*-BuLi, THF, 0 °C, then **33**, −78 °C, 92%.

Pleasingly, using the above-described conditions, cross-coupling of terminal acetylene **25** and thiol ester **34** produced the desired ynone **35** in a moderate 55% yield (Scheme 9). The unreacted thiol ester **34** could be recovered almost quantitatively but alkyne **25** was completely consumed via its oxidative homocoupling to yield the corresponding Glaser-type diyne product **36**. Those observations are in close agreement with those reported by Kuwahara et al. in their synthesis of Pteridic acids A and B.[39] Finally, upon exposure to *p*-TsOH in toluene, ynone **35** underwent TES-deprotection followed by DIHMA to furnish the target spiroketal **37** as a single enantiomer in 57% yield.



Scheme 9. Reagents and conditions: (a) $PdCl_2(dppf)$, $P(2\text{-furyl})_3$, CuI, Et_3N, DMF, 50 °C, 55%; (b) *p*-TsOH, PhMe, rt, 57%.

3. Conclusion

In conclusion, we have achieved the synthesis of an orthogonally protected C_{13}–C_{25} spirocyclic unit, which should prove amenable to the convergent total synthesis of Calyculin C. The key-coupling step between alkyne **25** and thiol ester **34** furnished alkynone **35**, which upon acidic treatment underwent the pivotal spirocyclisation. This represents the first example of the use of the DIHMA process for the construction of this fragment. Application of the described methodology towards the total synthesis of Calyculin C and Geometricin are in progress and will be reported in due course.

4. Experimental section

4.1. General

All moisture sensitive reactions were carried out under an argon atmosphere in flame-dried glassware. THF, CH_2Cl_2 and toluene used were obtained by passing deoxygenated solvents through activated alumina columns (MBraun SPS-800 Series solvent purification system). MeOH was obtained by distillation over magnesium methoxide, DMF by distillation over 4Å molecular sieves and ninhydrin, Et_3N and DMSO by distillation over CaH_2 and storage over 4Å molecular sieves. Oxalyl chloride was freshly distilled prior to use. Allyl bromide was washed with a aqueous saturated solution of $NaHCO_3$ then water, dried over $MgSO_4$ and distilled prior to use. CuI was purified using standard method.[40] Other solvents and reagents were used as obtained from supplier. Analytical TLC was performed using Merck silica gel F254 (10–12 μm) plates and analyzed by UV light (254 or 366 nm) and by staining upon heating with standard permanganate or phosphomolybdic acid solutions. For silica gel chromatography, the flash chromatography technique was used, with Merck silica gel 60 (230–400 mesh) and p.a. grade solvents. The ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Avance 400 (^1H 399.98 MHz; ^{13}C 100.59 MHz) spectrometer. The chemical shifts are reported in ppm relative to $CHCl_3$ (δ 7.26) for ^1H NMR and (δ 77.16) for ^{13}C NMR. IR spectra were recorded on a Perkin–Elmer Spectrum One spectrometer. Optical rotations were obtained with a Perkin–Elmer 343 polarimeter. High resolution mass spectrometric data were measured using Micro-Mass LCT Premier Spectrometer.

4.2. (4*R*,5*R*)-5-((*S*)-3-(Benzyloxy)-1-methoxypropyl)-4-((2-methoxyethoxy)methoxy)-3,3-dimethyltetrahydrofuran-2-ol 16

To a solution of lactone **15** (1.775 g, 4.48 mmol, 1 equiv) in toluene (45 mL) was added DIBAL-H (1 M in toluene, 7.61 mL, 7.71 mmol, 1.7 equiv) at −78 °C. The mixture was stirred for 40 min at −78 °C, then quenched by addition of MeOH (20 mL) and allowed to warm to rt. 1 M HCl (50 mL) and EtOAc (50 mL) were then added and stirring was continued for 1 h. After separation, the aqueous phase was extracted with EtOAc (3×50 mL). The combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ (40 mL), brine (40 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (50% EtOAc/hexane) afforded lactol **16** (1.428 g, 80%), as a yellow oil, 1/1 mixture of diastereomers. R_f (50% EtOAc/hexane:) 0.11; ^1H NMR ($CDCl_3$, 2 diastereomers) δ: 1.03 (s, 3H), 1.06 (s, 3H), 1.08 (s, 3H), 1.12 (s, 3H), 1.66–1.75 (m, 2H), 1.88–1.95 (m, 2H), 3.34 (s, 3H), 3.35 (s, 3H), 3.38–3.52 (m, 9H), 3.55–3.68 (m, 9H), 3.75–3.82 (m, 3H), 3.85 (d, J=4.7 Hz, 1H), 4.17 (dd, J=4.6, 6.9 Hz, 1H), 4.24 (dd, J=4.7, 7.5 Hz, 1H), 4.59 (s, 1H), 4.72–4.78 (m, 5H), 5.11 (d, J=5.5 Hz, 1H), 7.27–7.33 (m, 10H); ^{13}C NMR ($CDCl_3$, 2 diastereomers) δ: 14.1, 18.3, 20.2, 22.6, 24.7, 29.3, 29.6, 31.0, 31.4, 31.9, 46.5, 47.1, 59.0, 59.2, 66.2, 66.3, 68.1, 68.4, 71.7, 73.0, 73.1, 77.6, 81.8, 84.2, 85.4, 86.3, 96.8, 97.0, 103.9, 105.1, 127.5, 127.6, 127.7, 128.2, 128.3, 138.4, 138.5; IR (υ_{max}, thin film) 3401, 2925, 2854, 1726, 1098 cm^{-1}; HRMS: calculated for $C_{21}H_{34}O_7Na$ $[M+Na]^+$: 421.2226, found: 421.2219.

4.3. (8*R*,9*R*,10*S*)-10-Methoxy-8-(2-methylbut-3-yn-2-yl)-14-phenyl-2,5,7,13-tetraoxatetradecan-9-ol 17

A solution of lactol **16** (0.155 g, 0.39 mmol, 1 equiv) in MeOH (8 mL) was treated with Ohira–Bestmann's reagent **10** (0.108 g, 0.78 mmol, 2 equiv) and K_2CO_3 (0.149 g, 0.78 mmol, 2 equiv). The mixture was heated to 35 °C and stirred for 24 h. More **10** and K_2CO_3 (1 equiv each) were added every 24 h during 6 days, after which the reaction was stopped. The reaction mixture was cooled to rt and MeOH was removed in vacuo. The residue was partitioned between EtOAc (20 mL) and H_2O (10 mL). The aqueous phase was further extracted with EtOAc (3×15 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (30–50% EtOAc/hexane) afforded expected alkyne **17** (0.034 g, 22%, 41% based on recovery of **16**) as a colourless oil and unreacted lactol **16** (0.071 g, 46%) as a yellow oil. R_f (50% EtOAc/hexane) 0.22; $[\alpha]_D^{20}$ +2.2 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 1.24 (s, 3H), 1.29 (s, 3H), 1.86–2.07 (m, 2H), 2.07 (s, 1H), 2.86 (d, *J*=6.4 Hz, 1H), 3.36 (s, 3H), 3.39–3.42 (m, 1H), 3.38 (s, 3H), 3.46 (d, *J*=2.3 Hz, 1H), 3.43 (s, 2H), 3.60–3.65 (m, 3H), 3.76–3.80 (m, 1H), 3.89–3.93 (m, 1H), 4.82 (s, 2H), 4.88 (d, *J*=6.6 Hz, 1H), 4.94 (d, *J*=6.6 Hz, 1H), 7.25–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ: 23.7, 26.8, 29.9, 36.2, 58.2, 59.0, 66.9, 68.4, 69.9, 71.3, 71.7, 73.0, 80.8, 82.8, 89.9, 97.8, 127.4, 127.7, 138.4; IR (υ_{max}, thin film) 3522, 3291, 2927, 1455, 1100, 1024 cm^{-1}; HRMS: calculated for $C_{22}H_{34}O_6Na$ $[M+Na]^+$: 417.2253, found: 417.2265.

4.4. (3*R*,4*R*,5*S*)-7-(Benzyloxy)-5-methoxy-3-((2-methoxy ethoxy)methoxy)-2,2-dimethylheptane-1,4-diol 18

Lithium aluminium hydride (0.44 g, 1.15 mmol, 2 equiv) was suspended in THF (2 mL). Compound **15** (0.228 g, 0.57 mmol, 1 equiv) in THF (1 mL) was then added dropwise at 0 °C; gas evolution was observed. The mixture was allowed to warm to rt and stirred for 2 h. The reaction was then quenched by successive addition of H_2O (0.05 mL), 15% NaOH (0.05 mL) and H_2O (0.15 mL). After 30 min, the precipitate formed was filtered and washed with EtOAc (20 mL). The organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated in vacuo to afford diol **18** as a yellow oil, which was used in the next step without further purification. R_f (5% MeOH/CH_2Cl_2) 0.67; ^{1}H NMR ($CDCl_3$) δ: 0.83 (s, 3H), 0.87 (s, 3H), 1.79–1.84 (m, 1H), 1.93–1.98 (m, 1H), 3.26–3.32 (m, 2H), 3.33 (s, 3H), 3.38 (s, 2H), 3.47–3.52 (m, 3H), 3.54–3.58 (m, 3H), 3.75–3.80 (m, 1H), 4.46 (s, 2H), 4.75 (d, *J*=6.9 Hz, 2H), 4.84 (d, *J*=6.9 Hz, 2H), 7.21–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$): 20.2, 23.2, 30.0, 40.2, 57.4, 58.3, 59.0, 66.6, 68.3, 70.2, 71.7, 73.2, 80.9, 82.8, 98.0, 127.7, 127.8, 128.4, 138.2; IR (υ_{max}, thin film) 3460, 2931, 2876, 1455, 1365, 1099, 1035 cm^{-1}; HRMS: calculated for $C_{21}H_{36}O_7Na$ $[M+Na]^+$: 423.2359, found: 423.2375.

4.5. ((1*R*,2*S*)-4-(Benzyloxy)-1-((*R*)-5,5-dimethyl-1,3-dioxan-4-yl)-2-methoxybutoxy)triethylsilane 20

Crude diol **18** was dissolved in CH_2Cl_2 (5 mL). 2,6-Lutidine (0.53 mL, 4.56 mmol, 8 equiv) and TESOTf (0.51 mL, 5.28 mmol, 4 equiv) were successively added at 0 °C. The mixture was stirred overnight and then quenched by addition of H_2O (5 mL). After separation, the aqueous phase was further extracted with CH_2Cl_2 (10 mL). Combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (5% EtOAc/hexane) furnished acetonide **20** (0.150 g, 60% over the 2 steps) as a colourless oil. R_f (10% EtOAc/hexane) 0.59; $[\alpha]_D^{20}$ −0.8 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 0.59 (q, *J*=7.4 Hz, 6H), 0.85 (s, 3H), 0.90 (s, 3H), 0.96 (t, *J*=7.4 Hz, 9H), 1.92–1.96 (m, 2H), 3.33–3.39 (m, 2H), 3.42 (s, 3H), 3.45 (d, *J*=9.5 Hz, 1H), 3.61–3.64 (m, 2H), 3.86–4.00 (m, 2H), 4.51 (s, 2H), 4.96 (d, *J*=11.1 Hz, 1H), 5.01 (d, *J*=9.5 Hz, 1H), 7.28–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ: 4.5, 6.9, 20.0, 20.6, 31.6, 38.5, 59.4, 66.9, 69.4, 73.2, 78.1, 78.9, 80.7, 95.9, 127.7, 127.8, 128.4, 138.4; IR (υ_{max}, thin film) 2955, 2876, 1456, 1363, 1239, 1099 cm^{-1}; HRMS: calculated for $C_{24}H_{42}O_5NaSi$ $[M+Na]^+$: 461.2699, found: 461.2760.

4.6. (4*R*,5*R*)-4-(Allyloxy)-5-((*S*)-3-(benzyloxy)-1-methoxy propyl)-3,3-dimethyldihydrofuran-2(3*H*)-one 21

Lactone **6** (0.257 g, 0.83 mmol, 1 equiv) was dissolved in THF (5 mL). Potassium *tert*-butoxide (1 M in THF, 1.25 mL, 1.25 mmol, 1.5 equiv) was then added at 0 °C and the reaction mixture was stirred 30 min at 0 °C, after which allyl bromide (0.10 mL, 1.25 mmol, 1.5 equiv) was added. The solution was stirred at rt overnight, then quenched by addition of a saturated aqueous solution of NH_4Cl (5 mL). After separation, the aqueous phase was further extracted with EtOAc (2×10 mL). Combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (20–30% EtOAc/hexane) afforded protected compound **21** (0.248 g, 86%) as a colourless oil. R_f (50% EtOAc/hexane) 0.64; $[\alpha]_D^{20}$ −7.1 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 1.11 (s, 3H), 1.26 (s, 3H), 1.64–1.72 (m, 1H), 1.84–1.92 (m, 1H), 3.46 (s, 3H), 3.58–3.63 (m, 1H), 3.67–3.77 (m, 3H), 3.92 (ddt, *J*=1.4, 5.5, 12.2 Hz, 1H), 4.09 (ddt, *J*=1.4, 5.5, 12.2 Hz, 1H), 4.46–4.49 (m, 3H), 5.13 (ddt, *J*=1.4, 1.4, 10.4 Hz, 1H), 5.24 (ddt, *J*=1.6, 1.6, 17.2 Hz, 1H), 5.85 (ddt *J*=5.3, 10.6, 17.2 Hz, 1H), 7.25–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ: 18.4, 23.1, 30.4, 45.8, 59.4, 65.8, 73.2, 73.6, 77.3, 83.5, 84.2, 117.4, 127.7, 127.8, 128.2, 133.6, 138.4, 180.5; IR (υ_{max}, thin film) 2973, 2934, 2869, 1771, 1455, 1139, 1096 cm^{-1}; HRMS: calculated for $C_{20}H_{28}O_5Na$ $[M+Na]^+$: 371.1834, found: 371.1836.

4.7. (3*R*,4*R*,5*S*)-3-(Allyloxy)-7-(benzyloxy)-5-methoxy-2,2-dimethylheptane-1,4-diol 22

Lithium aluminium hydride (0.100 g, 2.59 mmol, 2 equiv) was suspended in THF (7 mL). Compound **21** (0.452 g, 1.29 mmol, 1 equiv) in THF (3 mL) was then added dropwise at 0 °C, gas evolution was observed. The mixture was stirred for 1 h at 0 °C and then quenched by successive addition of H_2O (0.1 mL), 15% NaOH (0.1 mL) and H_2O (0.3 mL). After 30 min, the precipitate formed was filtered and washed with EtOAc (20 mL). The organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated in vacuo to afford diol **22** as a yellow oil, which was used in the next step without further purification. R_f (50% EtOAc/hexane) 0.45; ^{1}H NMR ($CDCl_3$) δ: 0.89 (s, 3H), 0.91 (s, 3H), 1.76–1.83 (m, 1H), 1.92–1.99 (m, 1H), 3.15 (br s, 1H), 3.20–3.24 (m, 2H), 3.41 (s, 3H), 3.58–3.63 (m, 1H), 3.55–3.61 (m, 3H), 3.74–3.76 (m, 2H), 4.08 (ddt, *J*=1.4, 5.5, 12.3 Hz, 1H), 4.19 (ddt, *J*=1.4, 5.5, 12.3 Hz, 1H), 4.49 (dd, *J*=0.7, 12.1 Hz, 2H), 5.13 (ddt, *J*=1.4, 1.4, 10.4 Hz, 1H), 5.25 (ddt, *J*=1.6, 1.6, 17.2 Hz, 1H), 5.90 (ddt, *J*=5.4, 10.6, 17.2 Hz, 1H), 7.25–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ: 21.3, 23.4, 30.3, 40.5, 58.4, 66.7, 68.1, 70.0, 73.2, 74.6, 80.9, 84.0, 116.7, 127.7, 127.8, 128.4, 134.6, 138.3; IR (υ_{max}, thin film) 3459, 2959, 2930, 2872, 1455, 1093 cm^{-1} HRMS: calculated for $C_{20}H_{32}O_5Na$ $[M+Na]^+$: 375.2147, found: 375.2149.

4.8. (5*R*,6*R*)-6-(Allyloxy)-5-((*S*)-3-(benzyloxy)-1-methoxy propyl)-3,3,10,10-tetraethyl-7,7-dimethyl-4,9-dioxa-3,10-disiladodecane 23

Crude diol **22** was dissolved in CH_2Cl_2 (15 mL). 2,6-Lutidine (1.23 mL, 10.57 mmol, 8 equiv) and TESOTf (1.19 mL, 5.28 mmol, 4 equiv) were successively added at 0 °C. After 2 h at 0 °C, a saturated aqueous solution of NH_4Cl (20 mL) was added to the mixture. After separation, the aqueous phase was extracted with CH_2Cl_2 (20 mL). Combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (0–2% EtOAc/hexane) afforded di-protected compound **23** (0.665 g, 88%

over 2 steps) as a yellow oil. R_f (5% EtOAc/hexane) 0.70; $[\alpha]_D^{20}$ −2.9 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 0.58 (q, *J*=8.2 Hz, 6H), 0.65 (q, *J*=8.1 Hz, 6H), 0.90 (s, 3H), 0.92 (s, 3H), 0.96 (t, *J*=8.1 Hz, 9H), 0.97 (t, *J*=8.2 Hz, 9H), 1.74–1.81 (m, 1H), 2.02–2.10 (m, 1H), 3.18 (d, *J*=9.4 Hz, 1H), 3.34–3.38 (m, 1H), 3.39 (s, 3H), 3.45 (d, *J*=4.3 Hz, 1H), 3.53 (d, *J*=9.4 Hz, 1H), 3.57–3.61 (m, 2H), 3.88 (dd, *J*=4.3, 5.3 Hz, 1H), 3.98 (ddt, *J*=1.6, 5.3, 13.1 Hz, 1H), 4.22 (ddt, *J*=1.6, 5.3, 13.1 Hz, 1H), 4.49 (d, *J*=12.0 Hz, 1H), 4.53 (d, *J*=12.0 Hz, 1H), 5.07 (ddt, *J*=1.7, 1.7, 10.5 Hz, 1H), 5.25 (ddt, *J*=1.9, 1.9, 17.2 Hz, 1H); 5.90 (ddt *J*=5.2, 10.5, 17.2 Hz, 1H); 7.27–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ: 4.5, 5.6, 7.0, 7.3, 20.1, 22.2, 40.7, 59.1, 67.3, 70.1, 73.0, 73.2, 73.3, 80.0, 80.6, 115.1, 127.5, 127.7, 128.4, 136.1, 138.8; IR (υ_{max}, thin film) 2956, 2933, 1732, 1456, 1097 cm^{-1}; HRMS: calculated for $C_{32}H_{60}O_5NaSi_2$ $[M+Na]^+$: 603.3877, found: 603.3882.

4.9. (3*R*,4*R*,5*S*)-3-(Allyloxy)-7-(benzyloxy)-5-methoxy-2,2-dimethyl-4-(triethylsilyloxy)heptanal 24

A solution of DMSO (1.49 mL, 20.94 mmol, 8.8 equiv) in CH_2Cl_2 (12 mL) was cooled to −78 °C. Oxalyl chloride (0.90 mL, 10.47 mmol, 4.4 equiv) was added to the solution (gas evolution was observed). TES-protected compound **23** (1.381 g, 2.38 mmol, 1 equiv) in CH_2Cl_2 (12 mL) was added. The solution was stirred for 20 min at −78 °C (solution turned pink) and then warmed to −25 °C and stirred for 1 h at this temperature (solution turned pale yellow). The solution was then cooled down to −78 °C and Et_3N (4.97 mL, 35.70 mmol, 15 equiv) was added. The mixture was allowed to warm to rt and after 45 min, the precipitate that had formed was filtered. H_2O (15 mL) was added to the filtrate. After separation, the aqueous phase was further extracted with EtOAc (2×15 mL). Combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (5–10% EtOAc/hexane) afforded aldehyde **24** (0.921 g, 83%) as a colourless oil. R_f (5% EtOAc/hexane) 0.28; $[\alpha]_D^{20}$ −0.9 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 0.61 (q, *J*=8.0 Hz, 6H), 0.94 (t, *J*=8.2 Hz, 9H), 1.06 (s, 3H), 1.09 (s, 3H), 1.68–1.77 (m, 1H), 2.06–2.12 (m, 1H), 3.30 (s, 3H), 3.36–3.41 (m, 1H), 3.50 (d, *J*=3.8 Hz, 1H), 3.53–3.57 (m, 2H), 3.92 (dd, *J*=3.8, 6.1 Hz, 1H), 4.01 (ddt, *J*=1.5, 5.3 Hz, 12.8 Hz, 1H), 4.21 (ddt, *J*=1.6, 4.9, 12.8 Hz, 1H), 4.48 (d, *J*=12.0 Hz, 1H), 4.51 (d, *J*=12.0 Hz, 1H), 5.13 (ddt, *J*=1, 1.6, 10.5 Hz, 1H), 5.27 (ddt, *J*=1.8, 1.6, 17.2 Hz, 1H), 5.87 (ddt, *J*=5.2, 10.5, 17.2 Hz, 1H), 7.27–7.34 (m, 5H), 9.64 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 5.3, 7.2, 20.0, 20.3, 29.8, 50.5, 28.1, 67.0, 72.6, 73.1, 74.0, 79.9, 83.7, 116.1, 127.6, 127.8, 128.4, 134.9, 138.6, 205.0; IR (υ_{max}, thin film) 2954, 2926, 1722, 1458, 1096 cm^{-1}; HRMS: calculated for $C_{26}H_{44}O_5NaSi$ $[M+Na]^+$: 487.2856, found: 487.2860.

4.10. ((3*S*,4*R*,5*R*)-5-(Allyloxy)-1-(benzyloxy)-3-methoxy-6,6-dimethyloct-7-yn-4-yloxy)triethylsilane 25

Aldehyde **24** (0.940 g, 2.02 mmol, 1 equiv) was dissolved in MeOH (20 mL). Ohira–Bestmann reagent **10** (0.972 g, 5.06 mmol, 2.5 equiv) and K_2CO_3 (0.700 g, 5.06 mmol, 2.5 equiv) were then successively added and the mixture was stirred at rt overnight. MeOH was then evaporated and the residue taken up in Et_2O (20 mL) and H_2O (15 mL). After separation, the aqueous phase was further extracted with EtOAc (2×20 mL). Combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (5% EtOAc/hexane) afforded alkyne **25** (0.856 g, 92%) as a colourless oil. R_f (5% EtOAc/hexane) 0.35; $[\alpha]_D^{20}$ −8.3 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 0.66 (q, *J*=7.6 Hz, 6H), 0.97 (t, *J*=7.6 Hz, 9H), 1.27 (s, 3H), 1.31 (s, 3H), 1.77–1.84 (m, 1H), 2.04–2.12 (m, 2H), 3.30 (d, *J*=4.2 Hz, 1H), 3.40 (s, 3H), 3.53–3.61 (m, 3H), 4.03–4.08 (m, 2H), 4.26 (ddt, *J*=1.6, 4.9, 13.0 Hz, 1H), 4.49 (d, *J*=11.8 Hz, 1H), 4.53 (d, *J*=11.8 Hz, 1H), 5.11 (ddt, *J*=1.7, 1.7, 10.5 Hz, 1H), 5.27 (ddt, *J*=1.8, 1.8, 17.2 Hz, 1H), 5.90 (dddd, *J*=17.2, 10.5, 5.6, 5.0 Hz), 7.27–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ: 5.6, 7.3, 25.2, 28.1, 30.9, 36.0, 58.8, 67.4, 70.0, 73.0, 73.5, 73.6, 80.5, 82.5, 91.3, 116.0, 127.6, 127.7, 128.4, 135.5, 138.8; IR (υ_{max}, thin film) 3306, 2953, 2875, 1458, 1097 cm^{-1}; HRMS: calculated for $C_{27}H_{44}O_4NaSi$ $[M+Na]^+$: 483.2907, found: 483.2917.

4.11. (*R*)-4-Benzyl-3-((2*R*,3*S*)-5-(*tert*-butyldiphenyl silyloxy)-3-hydroxy-2-methylpentanoyl)oxazolidin-2-one 28

Bu_2BOTf (1 M in CH_2Cl_2, 17.29 mL, 17.29 mmol, 1.2 equiv) was added to a solution of **11** (3.679 g, 15.85 mmol, 1.1 equiv) in CH_2Cl_2 (40 mL) at 0 °C. After 15 min, Et_3N (2.63 mL, 18.73 mmol, 1.3 equiv) was added. After 30 min at 0 °C, the mixture was cooled to −78 °C and a solution of aldehyde **27** (4.503 g, 14.41 mmol, 1 equiv) in CH_2Cl_2 (10 mL) was added. The reaction mixture was stirred for 2 h at −78 °C then allowed to warm to 0 °C and stirred for 2 h. Phosphate buffer (pH 7, 15 mL) and MeOH (15 mL) were then added, the mixture was stirred for 15 min and then a H_2O_2/MeOH solution (3/1, 20 mL) was added. The reaction was allowed to warm to rt and stirred for 1 h. Solvent was then evaporated and the residue was taken up by EtOAc (40 mL) and H_2O (30 mL). After separation, the organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (20–40% EtOAc/hexane) afforded alcohol **28** (6.52 g, 83%) as a waxy solid. R_f (20% EtOAc/hexane) 0.34; $[\alpha]_D^{20}$ −3.3 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 1.05 (s, 9H), 1.28 (d, *J*=7.0 Hz, 3H), 1.62–1.72 (m, 1H), 1.77–1.87 (m, 1H), 2.78–2.82 (m, 1H), 3.23–3.33 (m, 1H), 3.40 (br s, 1H), 3.80–3.91 (m, 2H), 4.15–4.27 (m, 3H), 4.65–4.72 (m, 1H), 7.20–7.45 (m, 11H), 7.65–7.69 (m, 4H); ^{13}C NMR ($CDCl_3$) δ: 11.3, 19.1, 26.9, 36.0, 37.8, 42.8, 55.2, 62.4, 66.2, 70.6, 127.3, 127.7, 128.9, 129.4, 129.8, 133.3, 135.2, 135.6, 153.1, 176.5; IR (υ_{max}, thin film) 3500, 2960, 2935, 1785, 1690, 1110 cm^{-1}; HRMS: calculated for $C_{32}H_{40}NO_5Si$ $[M+H]^+$: 546.2676, found 546.2701.

4.12. (2*R*,3*S*)-5-(*tert*-Butyldiphenylsilyloxy)-3-hydroxy-*N*-methoxy-*N*,2-dimethylpentanamide

N,*O*-dimethylhydroxylamine hydrochloride (2.50 g, 25.61 mmol, 2.2 equiv) was suspended in THF (20 mL) and cooled to 0 °C. Trimethylaluminium (2 M in hexanes, 12.8 mL, 25.61 mmol, 2.2 equiv) was added and the mixture was stirred for 15 min at 0 °C and 1 h at rt, where the solution became homogeneous. After cooling down to 0 °C, a solution of **28** (6.35 g, 11.64 mmol, 1 equiv) in THF (20 mL) and CH_2Cl_2 (15 mL) was added. The mixture was stirred for 3 h at 0 °C and 30 min at rt. The reaction mixture was then added at 0 °C to a CH_2Cl_2/HCl 0.5 M mixture (1/1, 150 mL). Gas evolution was observed and stirring was maintained for 2 h at 0 °C. After separation, the aqueous phase was further extracted with EtOAc (2×20 mL). Combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (20–50% EtOAc/hexane) afforded the Weinreb amide (3.54 g, 71%) as a yellow oil. R_f (50% EtOAc/hexane) 0.60; $[\alpha]_D^{20}$ −0.6 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 1.05 (s, 9H), 1.21 (d, *J*=6.8 Hz, 3H), 1.64–1.67 (m, 1H), 1.76–1.80 (m, 1H), 2.98 (br s, 1H), 3.19 (s, 3H), 3,67 (s, 3H), 3.83–3.86 (m, 2H), 3.98 (br s, 1H), 4.10–4.15 (m, 1H), 7.36–7.45 (m, 6H), 7.65–7.68 (m, 4H); ^{13}C NMR ($CDCl_3$) δ: 11.6, 19.2, 26.9, 32.0, 36.3, 39.7, 61.6, 62.4, 71.0, 127.8, 129.8, 133.4, 135.6, 177.7; IR (υ_{max}, thin film) 3436, 2931, 2857, 1638, 1427, 1111 cm^{-1}; HRMS: calculated for $C_{24}H_{35}NO_4NaSi$ $[M+Na]^+$: 452.2233; found: 452.2245.

4.13. (2*R*,3*S*)-5-(*tert*-Butyldiphenylsilyloxy)-*N*-methoxy-*N*,2-dimethyl-3-triethylsilyloxypentanamide 29

Weinreb amide (3.44 g, 8.00 mmol, 1 equiv) from the previous step was dissolved in CH_2Cl_2 (40 mL). 2,6-Lutidine (3.73 mL, 32.00 mmol, 4 equiv) and TESOTf (3.73 mL, 16.00 mmol, 2 equiv) were successively added at 0 °C. After 2 h at 0 °C, a saturated aqueous solution of NH_4Cl (20 mL) was added to the mixture. After separation,

the aqueous phase was extracted with CH_2Cl_2 (20 mL). Combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (10–30% EtOAc/hexane) afforded protected compound **29** (4.24 g, 97%) as a colourless oil. R_f (20% EtOAc/hexane) 0.57; $[\alpha]_D^{20}$ +0.3 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 0.58 (q, *J*=8.0 Hz, 6H), 0.94 (t, *J*=8.0 Hz, 9H), 1.04 (s, 9H), 1.13 (d, *J*=6.9 Hz, 3H), 1.68–1.85 (m, 2H), 2.90–2.93 (m, 1H), 3.13 (s, 3H), 3.55 (s, 3H), 3.70–3.79 (m, 2H), 4.06–4.10 (m, 1H), 7.34–7.44 (m, 6H), 7.65–7.67 (m, 4H); ^{13}C NMR ($CDCl_3$) δ: 5.1, 6.9, 13.9, 19.1, 26.8, 32.1, 38.8, 41.4, 60.7, 61.2, 71.2, 127.6, 129.5, 134.0, 135.6, 176.1; IR (υ_{max}, thin film) 3468, 2932, 2857, 1664, 1427, 1112 cm^{-1}; HRMS: calculated for $C_{30}H_{49}NO_4NaSi_2$ $[M+Na]^+$: 566.3098; found: 566.3110.

4.14. (2*R*,3*S*)-5-(*tert*-Butyldiphenylsilyloxy)-2-methyl-3-(triethylsilyloxy)pentanal 30

A solution of Weinreb amide **29** (0.909 g, 1.67 mmol, 1 equiv) in THF (10 mL) was cooled to −78 °C and treated with DIBAL-H (1 M in THF, 3.84 mL, 3.84 mmol, 2.3 equiv). After 3 h at −78 °C, a saturated aqueous solution of Rochelle's salt (10 mL) was added and the mixture was allowed to warm to rt. After separation, the aqueous phase was further extracted with EtOAc (10 mL). Combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (5% EtOAc/hexane) afforded aldehyde **30** (0.578 g, 71%) as a yellow oil. R_f (10% EtOAc/hexane) 0.75; $[\alpha]_D^{20}$ +0.3 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 0.57 (q, *J*=8.0 Hz, 6H), 0.92 (t, *J*=8.0 Hz, 9H), 1.02 (d, *J*=7.0 Hz, 3H), 1.06 (s, 9H), 1.70–1.76 (m, 2H), 2.42–2.45 (m, 1H), 3.64–3.77 (m, 2H), 4.39–4.43 (m, 1H), 7.35–7.44 (m, 6H), 7.64–7.67 (m, 4H), 9.75 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 5.3, 6.9, 7.7, 19.2, 26.9, 37.3, 51.5, 60.6, 69.2, 127.7, 129.8, 133.7, 135.7, 205.2; IR (υ_{max}, thin film) 3429, 2956, 2858, 1727, 1428, 1112 cm^{-1}; HRMS: calculated for $C_{28}H_{44}NO_3NaSi_2$ $[M+Na]^+$: 507.2727, found: 507.2724.

4.15. (*R*)-4-Benzyl-3-((2*R*,3*S*)-5-(*tert*-butyldiphenyl silyloxy)-2-methyl-3-(triethylsilyloxy)pentanoyl) oxazolidin-2-one 33

Alcohol **28** (1.014 g, 1.76 mmol, 1 equiv) was dissolved in CH_2Cl_2 (20 mL). 2,6-Lutidine (0.82 mL, 7.05 mmol, 4 equiv) and TESOTf (0.80 mL, 3.52 mmol, 2 equiv) were successively added at 0 °C. After 2 h at 0 °C, a saturated aqueous solution of NH_4Cl (10 mL) was added to the mixture. After separation, the aqueous phase was extracted with CH_2Cl_2 (20 mL). Combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (5–10% EtOAc/hexane) afforded TES-protected compound **33** (1.02 g, 88%) as a colourless oil. R_f (20% EtOAc/hexane) 0.65; $[\alpha]_D^{20}$ −38.6 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 0.58 (q, *J*=7.9 Hz, 6H), 0.94 (t, *J*=7.9 Hz, 9H), 1.08 (s, 9H), 1.23 (d, *J*=6.8 Hz, 3H), 1.75–1.83 (m, 1H), 1.86–1.94 (m, 1H), 2.79 (dd, *J*=9.6, 13.3 Hz, 2H), 3.30 (dd, *J*=3.1, 13.3 Hz, 2H), 3.76 (t, *J*=6.8 Hz, 2H), 3.91–3.98 (m, 1H), 4.08 (m, 1H), 4.16 (dd, *J*=2.1, 9.1 Hz, 1H), 4.19–4.23 (m, 1H), 4.56–4.61 (m, 1H), 7.23–7.43 (m, 11H), 7.67–7.71 (m, 4H); ^{13}C NMR ($CDCl_3$) δ: 5.1, 7.0, 12.5, 19.2, 27.0, 37.8, 38.3, 43.5, 55.9, 60.7, 66.0, 70.8, 127.4, 127.7, 129.0, 129.6, 129.7, 134.0, 135.5, 135.7, 153.1, 175.3; IR (υ_{max}, thin film) 2956, 2876, 1784, 1704, 1384, 1236, 1208, 1111 cm^{-1}; HRMS: calculated for $C_{38}H_{53}NO_5NaSi_2$ [M+Na]+: 682.3360, found: 682.3339.

4.16. (2*R*,3*S*)-*S*-Dodecyl 5-(*tert*-butyldiphenylsilyloxy)-2-methyl-3-(triethylsilyloxy)pentanethioate 34

To a solution of dodecanethiol (0.52 mL, 2.16 mmol, 4 equiv) in THF (7 mL) was added *n*-BuLi (2 M in hexanes, 0.81 mL, 1.62 mmol, 3 equiv) at 0 °C. A precipitate formed and the mixture was stirred 30 min at 0 °C, before being cooled down to −78 °C. A solution of compound **33** (0.356 g, 0.54 mmol, 1 equiv) in THF (3 mL) was added. The mixture was stirred for 1 h at −78 °C, allowed to warm to 0 °C and stirred 1 h at 0 °C. The reaction was quenched by addition of saturated aqueous solution of NH_4Cl (10 mL). After extraction with EtOAc (15 mL) and separation, organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (2–5% EtOAc/hexane) furnished thio-ester **34** (0.339 g, 92%) as a colourless oil. R_f (5% EtOAc/hexane) 0.82; $[\alpha]_D^{20}$ −14.7 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 0.60 (t, *J*=8.0 Hz, 6H), 0.91 (t, *J*=6.7 Hz, 3H), 0.95 (t, *J*=8.0 Hz, 9H), 1.09 (s, 9H), 1.18 (d, *J*=7.0 Hz, 3H), 1.29–1.42 (m, 18H), 1.56–1.63 (m, 2H), 1.70–1.84 (m, 2H), 2.75–2.80 (m, 1H), 2.88 (t, *J*=7.2 Hz, 2H), 3.71–3.75 (m, 2H), 4.31 (q, *J*=6.2 Hz, 1H), 7.37–7.45 (m, 6H), 7.68–7.72 (m, 4H); ^{13}C NMR ($CDCl_3$) δ: 5.2, 7.1, 12.1, 14.2, 19.2, 22.8, 26.9, 28.9, 29.1, 29.3, 29.5, 29.6, 29.7, 29.8, 32.0, 38.1, 54.0, 60.6, 71.0, 127.7, 129.7, 133.9, 135.7, 202.1 some C are overlapping; IR (υ_{max}, thin film) 2955, 2927, 2855, 1684, 1462, 1427, 1112 cm^{-1}; HRMS: calculated for $C_{40}H_{68}O_3NaSSi_2$ $[M+Na]^+$: 707.4328, found: 707.4318.

4.17. (7*S*,8*R*)-13-(Allyloxy)-14-(3-(benzyloxy)-1-methoxy propyl)-16,16-diethyl-2,2,8,12,12-pentamethyl-3,3-diphenyl-7-(triethylsilyloxy)-4,15-dioxa-3,16-disila octadec-10-yn-9-one 35

To a solution of thio-ester **34** (63 mg, 0.092 mmol, 1 equiv) in DMF (0.2 mL) and Et_3N (0.06 mL) were successively added $PdCl_2$ (dppf) (7 mg, 0.009 mmol, 0.1 equiv), CuI (34 mg, 0.18 mmol, 1.9 equiv), P(2-furyl)$_3$ (5 mg, 0.023 mmol, 0.25 equiv) and a solution of alkyne **25** (85 mg, 0.18 mmol, 2.4 equiv) in DMF (0.2 mL). The mixture was heated at 50 °C for 3 h and then cooled to rt. Celite (0.1 g), Et_2O (5 mL) and H_2O (2 mL) were added. After 10 min, the mixture was filtered through a pad of Celite and washed with EtOAc (10 mL). After separation, organic extracts were washed with H_2O (5 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (2–20% EtOAc/hexane) furnished unreacted **34** (27 mg, 43%), dimer **36** (29 mg, 36%) as a brownish oil and expected product **35** (48 mg, 55%) as a yellow oil. **35**: R_f (5% EtOAc/hexane) 0.35; $[\alpha]_D^{20}$ −2.1 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 0.55 (q, *J*=8.0 Hz, 6H), 0.64 (q, *J*=8.0 Hz, 6H), 0.90 (t, *J*=8 Hz, 9H), 0.96 (t, *J*=8 Hz, 9H), 1.05 (s, 9H), 1.11 (d, *J*=7.0 Hz, 3H), 1.29 (s, 3H), 1.32 (s, 3H), 1.70–1.79 (m, 3H), 2.02–2.11 (m, 1H), 2.55 (qd, *J*=3.7, 7.0 Hz, 1H), 3.35 (s, 3H), 3.36–3.38 (m, 1H), 3.42–3.46 (m, 1H), 3.55–3.59 (m, 2H), 3.67 (t, *J*=7.0 Hz, 2H), 4.01–4.09 (m, 2H), 4.20–4.26 (m, 1H), 4.44–4.53 (m, 3H), 5.09–5.12 (m, 1H), 5.24–5.30 (m, 1H), 5.83–5.92 (m, 1H), 7.27–7.43 (m, 11H), 7.64–7.68 (m, 4H); ^{13}C NMR ($CDCl_3$) δ: 5.3, 5.6, 7.1, 7.3, 9.8, 19.3, 24.7, 26.8, 27.0, 30.5, 36.8, 38.6, 53.6, 58.6, 60.8, 67.4, 69.8, 73.1, 73.2, 73.6, 80.4, 81.9, 82.2, 100.4, 116.0, 127.5, 127.7, 127.8, 128.4, 129.7, 133.8, 135.2, 135.7, 138.8, 190.1; IR (υ_{max}, thin film) 2654, 2876, 2205, 1673, 1457, 1095 cm^{-1}; HRMS: calculated for $C_{55}H_{86}O_7NaSi_3$ $[M+Na]^+$: 965.5579, found: 965.5603. **36**: R_f (5% EtOAc/hexane) 0.23; NMR ^{1}H ($CDCl_3$) δ: 0.66 (q, *J*=8.0 Hz, 12H), 0.97 (t, *J*=8.0 Hz, 18H), 1.25 (s, 6H), 1.27 (s, 6H), 1.74–1.80 (m, 2H), 2.05–2.10 (m, 2H), 3.28 (d, *J*=4.1 Hz, 2H), 3.37 (s, 3H), 3.41–3.45 (m, 2H), 3.59 (t, *J*=6.7 Hz, 4H), 4.02–4.07 (m, 4H), 4.20–4.25 (m, 2H), 4.50 (d, *J*=12.0 Hz, 2H), 4.53 (d, *J*=12.0 Hz, 2H), 5.08–5.11 (m, 2H), 5.23–5.28 (m, 2H), 5.83–5.92 (m, 2H), 7.27–7.34 (m, 10H); ^{13}C NMR ($CDCl_3$) δ: 5.5, 7.3, 25.3, 27.7, 29.8, 30.4, 36.9, 58.5, 67.2, 67.5, 73.1, 73.3, 73.5, 80.6, 82.6, 84.6, 116.0, 127.5, 127.8, 128.4, 132.2, 132.3, 135.5, 138.8; IR (υ_{max}, thin film) 3065, 2953, 2932, 2878, 1766, 1728, 1456, 1098 cm^{-1}; HRMS: calculated for $C_{54}H_{86}O_8NaSi_2$ $[M+Na]^+$: 918.5861, found: 918.5841.

4.18. (2*R*,3*R*,5*S*,7*S*,8*R*)-3-(Allyloxy)-2-((*S*)-3-(benzyloxy)-1-methoxypropyl)-7-(2-(*tert*-butyldiphenylsilyloxy) ethyl)-4,4,8-trimethyl-1,6-dioxaspiro[4.5]decan-9-one 37

To a solution of ynone **35** (22 mg, 0.023 mmol, 1 equiv) in toluene (1 mL) was added *p*-TsOH (5 mg, 0.025 mmol, 1.2 equiv) and the

mixture was stirred 24 h at rt. The reaction was quenched by addition of a saturated aqueous solution of $NaHCO_3$ (0.5 mL) and H_2O (0.5 mL). The mixture was diluted with EtOAc (5 mL) and the aqueous phase was separated. Organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (5–20% EtOAc/hexane) afforded spiroketal **37** (9.5 mg, 57%) as a colourless oil. R_f (20% EtOAc/hexane) 0.32; $[\alpha]_D^{20}$ −3.7 (*c* 1, $CHCl_3$); NMR ^1H ($CDCl_3$) δ: 0.94 (s, 3H), 0.97 (d, *J*=6.6 Hz, 3H), 1.03 (s, 3H), 1.05 (s, 9H), 1.58–1.65 (m, 2H), 1.72–1.79 (m, 2H), 1.91–1.99 (m, 1H), 2.39 (d, *J*=13.9 Hz, 1H), 2.52 (d, *J*=13.9 Hz, 1H), 3.34 (s, 3H), 3.42 (dt, *J*=2.9, 6.0 Hz, 1H), 3.50–3.60 (m, 2H), 3.68 (d, *J*=7.3 Hz, 1H), 3.70–3.86 (m, 4H), 3.86 (ddt, *J*=1.4, 5.4, 12.4 Hz, 1H), 4.01 (ddt, *J*=1.4, 5.4, 12.4 Hz, 1H), 4.43 (d, *J*=12.0 Hz, 1H), 4.48 (d, *J*=12.0 Hz, 1H), 5.11 (ddt, *J*=1.4, 1.4, 10.4 Hz, 1H), 5.23 (ddt, *J*=1.6, 1.6, 17.2 Hz, 1H), 5.86 (ddt, *J*=5.4, 10.6, 17.2 Hz, 1H), 7.27–7.40 (m, 11H), 7.63–7.67 (m, 4H); ^{13}C NMR ($CDCl_3$) δ: 10.9, 18.0, 19.3, 27.0, 29.8, 33.1, 33.6, 41.4, 48.4, 59.5, 61.2, 67.1, 67.5, 72.9, 73.4, 77.3, 80.3, 86.8, 108.5, 116.8, 127.5, 127.7, 127.8, 128.4, 129.8, 133.9, 134.7, 135.6, 135.7, 138.9, 210.1; IR (υ_{max}, thin film) 2926, 2855, 1721, 1463, 1428, 1112 cm^{-1}; HRMS: calculated for $C_{43}H_{58}O_7NaSi$ $[M+Na]^+$: 737.3850, found: 737.3862.

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