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Towards the total synthesis of calyculin C: preparation of the C_9–C_{25} spiroketal-dipropionate unit†

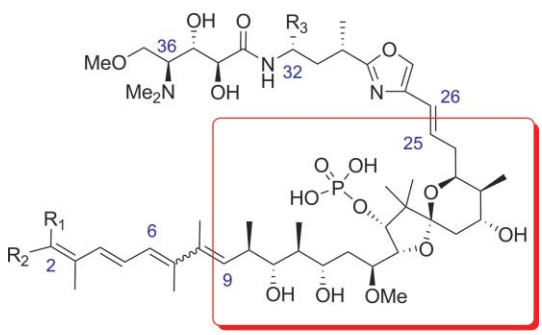
Damien Habrant and Ari M. P. Koskinen*

DOI: 10.1039/c0ob00092b

An asymmetric synthesis of the C_9–C_{25} spiroketal fragment of calyculin C is described. Key steps include two crotylation reactions using successively Brown's reagent and (*Z*)-crotyltrifluorosilane for the formation of the *anti*, *anti*, *anti* stereotetrad, ynone formation by a Pd-catalyzed coupling of a thiol ester with a terminal alkyne and a double intramolecular hetero-Michael addition for the stereoselective construction of the spiroketal framework.

Introduction

Calyculins are a class of highly cytotoxic metabolites originally isolated by Fusetani *et al.* from the marine sponge *Discodermia calyx*, collected in the Gulf of Sagami, near Tokyo Bay. Calyculin A was the first member of the family isolated, in 1986,[1] later followed by calyculins B–H.[2,3] The different calyculins vary by the substitution at C_{32} and the olefin geometry of the tetraene moiety (Fig. 1). *D. calyx* remains today the primary source of the natural products, the most abundant ones being calyculin A and C, but *Lamellomorpha strongylata* has also been shown to contain calyculins and structurally related calyculinamides.[4] Other natural products belonging to the calyculin family include calyculin J,[5] calyculinamides A, B and J,[4,5] des-*N*-methyl calyculin A,[5] dephosphocalyculin A,[6] clavosines A–C,[7] geometricin A[8] and swinhoeiamide A.[9]



Calyculins (R_1, R_2, R_3, C_6-C_7 geometry)
A (CN, H, H, *E*); **B** (H, CN, H, *E*); **C** (CN, H, Me, *E*);
D (H, CN, Me, *E*); **E** (CN, H, H, *Z*); **F** (H, CN, H, *Z*);
G (CN, H, Me, *Z*); **H** (H, CN, Me, *Z*)

Fig. 1 Structures of calyculins.

The calyculins display a wide variety of biological activities. The high cytotoxicity of calyculins relies on their ability to selectively and efficiently inhibit protein phosphatases 1 and 2A (PP1 and PP2A), two enzymes able to dephosphorylate serine/threonine residues of proteins in eukaryotic cells.[10,11] PP2A has been implied in several disease states, since a wide variety of cellular events are regulated by reversible protein phosphorylation.[12–14] Many observations support the role of PP2A in tumorigenesis; PP2A activity and expression are decreased in drug-resistant breast cancer cells and Alzheimer's disease, whereas targeted inhibition of PP1 is a potential strategy for minimizing the symptoms associated with Parkinson's disease.[15,16] Other naturally occurring toxins bind to inhibit more or less selectively PP, *i.e.* okadaic acid, microcystins, spirastrelloside or tautomycin.[17] Even if these compounds cover a wide structural diversity, it is interesting to observe that some of the most active compounds contain a spiroketal moiety in a conformationally flexible position. Our group has earlier postulated that the spiroketal moiety in calyculins plays a crucial role in binding to the phosphatase.[18]

The interesting biological profile coupled with their spellbinding structure has made calyculins very attractive targets for synthetic chemists. Massive efforts have been devoted to the synthesis of these natural products, leading to the total syntheses of (*ent*)-calyculin A by Evans,[19] Shioiri[20] and Barrett,[21] calyculin A by Masamune,[22] (*ent*)-calyculins A and B by Smith[23] and calyculin C by Armstrong.[24] In addition, the Trost group[25] and our group[26–29] have been involved in the synthesis of individual fragments. We have recently reviewed these different syntheses, along with some biological data.[30]

Results and discussion

Retrosynthetic analysis

The C_9–C_{25} spiroketal-dipropionate unit contains 11 of the total 16 chiral centres of calyculin C and therefore represents a very challenging target. Our strategy for the construction of fully protected spiroketal **1** relied on a double intramolecular hetero Michael addition (DIHMA) process on ynone **2** (Scheme 1). Ynone **2** was thought to arise from the coupling of the C_9–C_{20} alkyne fragment **3** with the C_{21}–C_{25} thiol ester moiety **4**. In turn, we planned to prepare alkyne **3** through a double crotylation sequence starting from the known lactone **5**.

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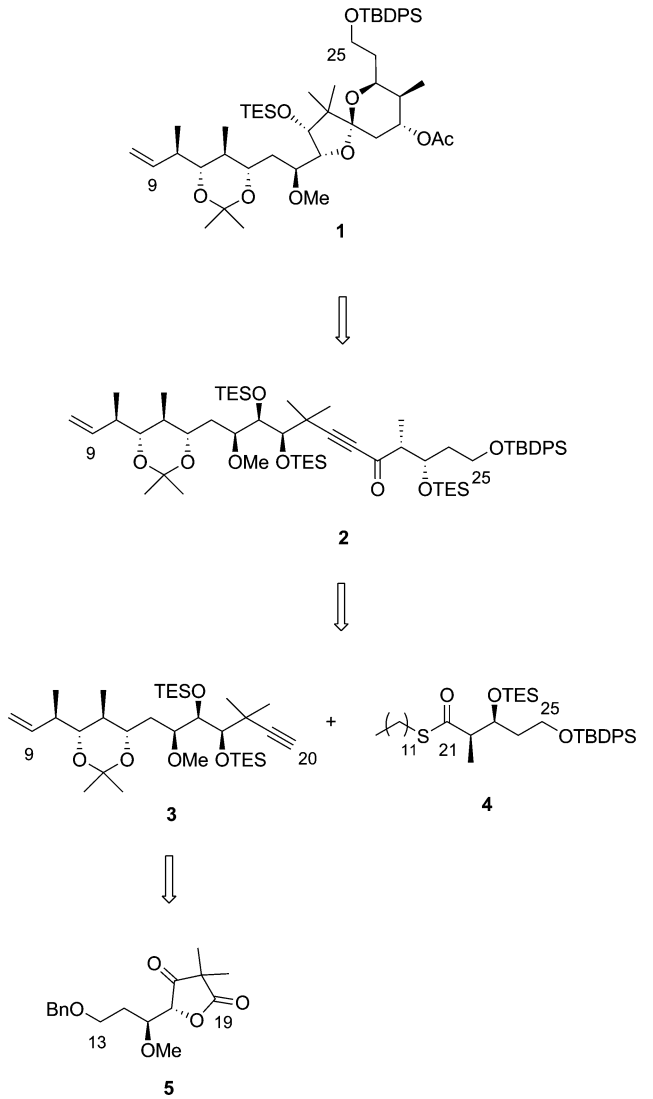
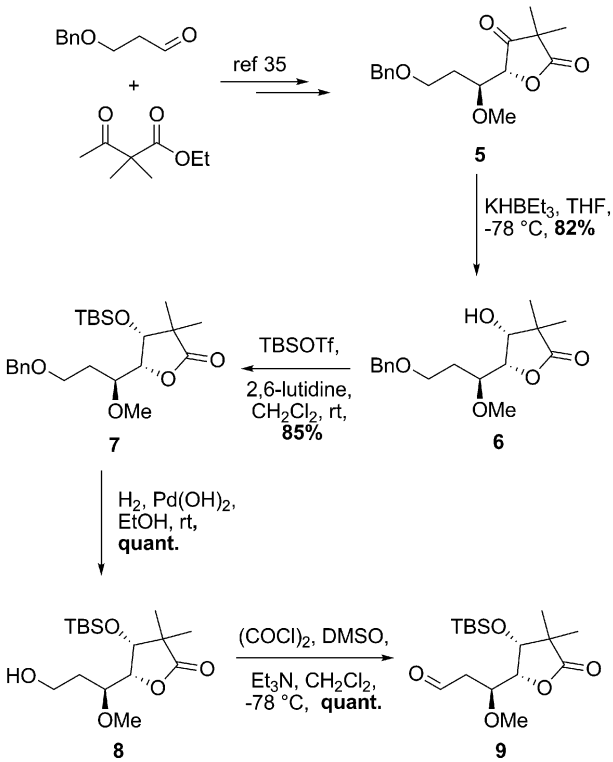
† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra of compounds **1**, **2**, **3**, **7**, **8**, **9**, **10a**, **14a**, **14b**, **16**, **17**, **19**, **20** and **21**. See DOI: 10.1039/c0ob00092b



Scheme 1 Retrosynthetic plan



Scheme 2 Preparation of aldehyde **9**

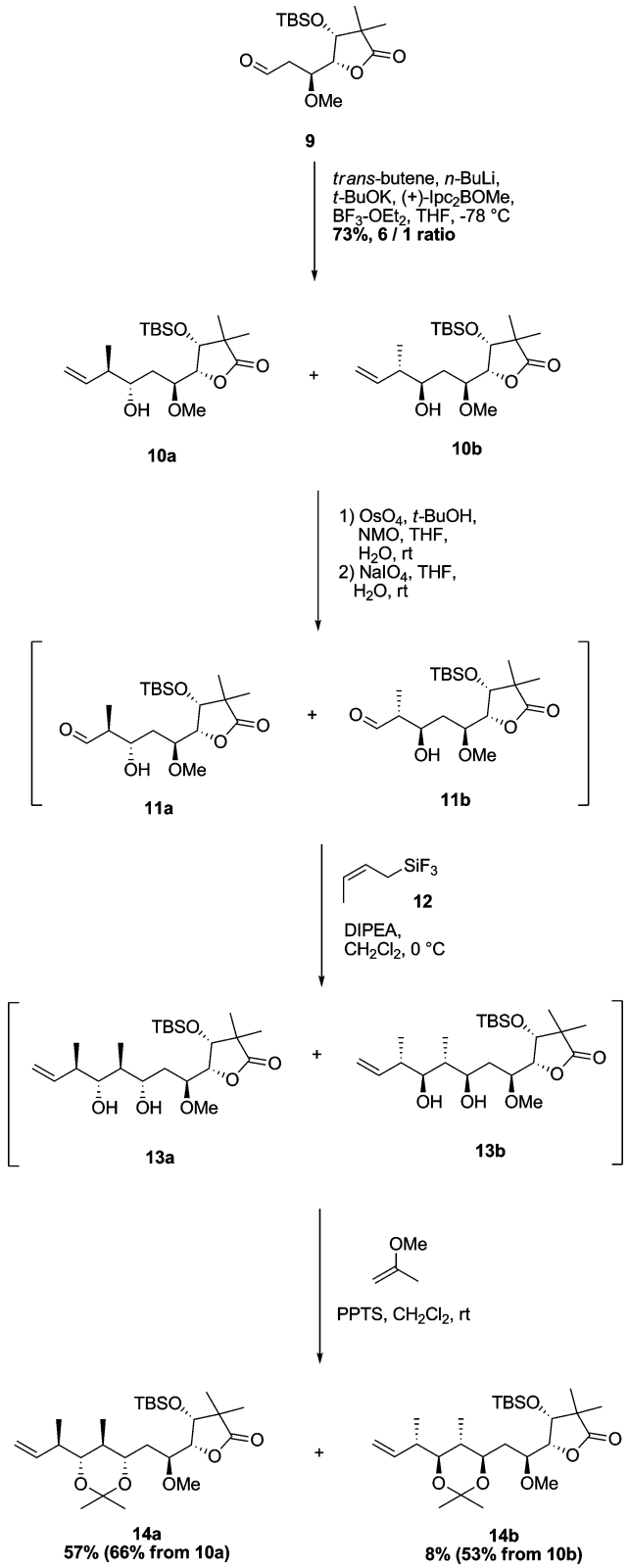
Double crotylation strategy

The preparation of the *anti*, *anti*, *anti* stereotetrad has proven to be challenging.[31] The use of crotylation reagents appeared to be the most common method, however, some selectivity issues have been observed. Barrett extensively used Brown's reagents in his formal synthesis of (*ent*)-calyculin A.[32] With a strategy similar to ours, Armstrong had described that the protecting group at the C_{19} hydroxyl played an unexpected but significant role in the asymmetric induction at C_{11}.[24,33] This property unfortunately led to a poor diastereomeric ratio in the crotylation. We have recently described a procedure on a model compound, using at first a classical Brown's crotylation followed by a second crotylation using (*Z*)-crotyltrifluorosilane to overcome this problem.[34]

The synthesis commenced with lactone **5** (Scheme 2).[35] Aldol reaction between 3-(benzyloxy)-propanal and ethyl 2,2-dimethyl-3-oxobutanoate, followed by dehydration, asymmetric dihydroxylation and *O*-methylation provided the expected lactone **5** in reasonable yields. Stereoselective reduction of **5** using potassium superhydride in THF was performed in good yield (82%) and selectivity (>7 : 1 by ^{1}H NMR) to yield **6**; superhydride gave better yields and reproducibility than the previously reported use of L-Selectride for this reduction.[29,35] TBS-protection of the newly-formed alcohol proceeded well under classical conditions[36] to yield **7**. Removal of the benzyl protecting group of **7** by hydrogenolysis furnished the primary alcohol **8**, which was then converted to the corresponding aldehyde **9** by Swern oxidation.

Compound **9** was then submitted to an asymmetric Brown's crotylation reaction, using *trans*-2-butene as the carbon input, giving rise to the two homoallylic alcohols **10a** and **10b**, in a 6 : 1 diastereomeric ratio by ^{1}H NMR (in favour of **10a** according to the Brown's algorithm and previous results by Armstrong[33]) and 73% overall yield (Scheme 3). The two isomers could not be separated at this stage by classical chromatographic techniques and the following reactions were carried out on the mixture of homoallylic alcohols. Alkenes **10a** and **10b** were converted to the corresponding aldehydes **11a** and **11b** by successive OsO_4-catalysed dihydroxylation and subsequent oxidative diol cleavage by $NaIO_4$. The mixture of **11a** and **11b** was then subjected to a second crotylation reaction. At this stage, we decided to use the methodology developed by Roush, using (*Z*)-crotyltrifluorosilane **12**.[37] This reaction has been shown to proceed *via* a bicyclic transition state in which the β-hydroxyl group is engaged in a chelate with the (*Z*)-crotylsilane, affording the *anti*, *anti* dipropionate, without any external source of chirality. However, the authors described that a sequential acidic (1 N HCl, 15 min) and basic (NaOH 1 N, 1 h) workup was required in order to hydrolyse the intermediate silylene ketals formed in the course of the reaction.

Applied to our substrate **11**, the crotylation reaction seemed to proceed smoothly, however, after such workup and purification, only a moderate amount (around 30%) of diols **13** could be obtained. We assumed that the workup procedure was too harsh



Scheme 3 The double crotylation strategy

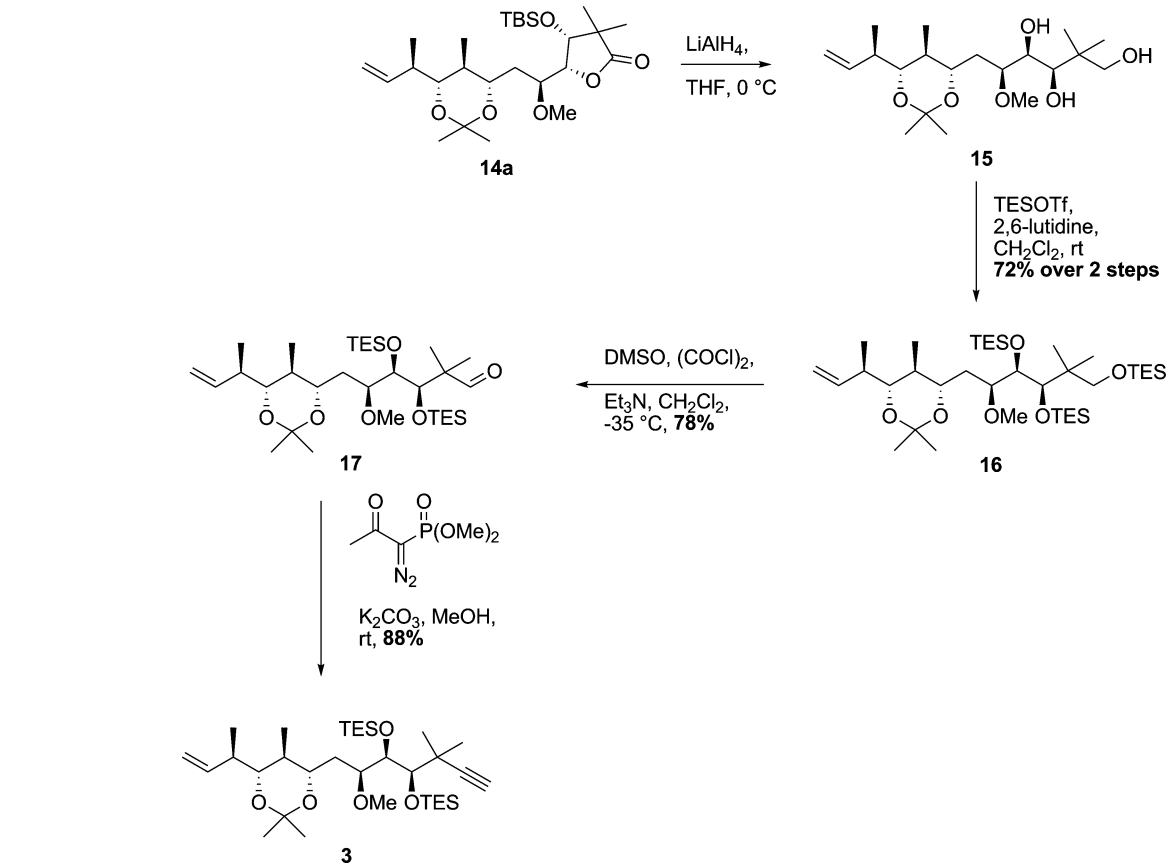
for our substrate. Pleasingly, we found out that, after treating a 0.08 M solution of **11** in CH_2Cl_2 with 320 mol% of **12** in the presence of 300 mol% of DIPEA for 36 h at 0 °C (as described in the original procedure), simply adding silica gel to the mixture was enough to hydrolyse the silylene ketals. Indeed, after stirring for 30 min at rt and simple filtration, the corresponding diols **13** were cleanly obtained. We therefore decided to run the 1,3-diol protection without any further purification. After acid-catalyzed reaction with 2-methoxypropene, the two diastereomer acetals **14a** and **14b** could be obtained and easily separated by simple column chromatography. Analysis of these products indicate that (1) the second crotylation occurred in a very selective manner, the amount of the undesired *syn* isomers being detected at around 5% by ^{1}H NMR and (2) both **14a** and **14b** proved to be the 1,3-*syn* acetonides according to the Rychnovsky's rules,[38] with ^{13}C signals of the acetonide at 19.6, 30.1 and 97.7 ppm for **14a** and 19.6, 30.2 and 97.9 for **14b**. Altogether, starting from the mixture of homoallylic alcohols **10**, this sequence allowed the synthesis of **14a** in 66% and **14b** in 53% yield, over 4 steps and involving a single chromatographic purification.

Conversion to the alkyne

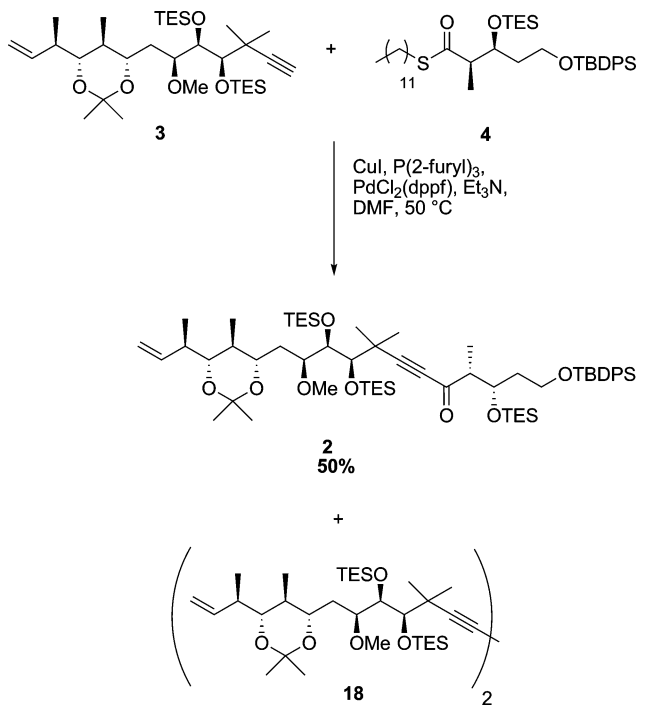
To convert **14a** to the acetylenic compound **3**, we decided to use a similar strategy as the one we previously reported for the construction of the C_{13}–C_{25} segment.[29] Lactone **14a** was reduced in the presence of an excess of $LiAlH_4$. Surprisingly, the TBS group was cleaved during the course of the reaction and triol **15** was obtained (Scheme 4). This unexpected result left us with a triol, whose two secondary hydroxyls could not be easily differentiated for selective protection. We therefore decided to protect all three free hydroxyl groups by TES, leading to compound **16**. This was then subjected to the conditions described by Spur for the selective oxidation of primary silyl ethers,[39] which appeared to be efficient in our case. Indeed, after addition of **16** to a DMSO/oxalyl chloride solution in CH_2Cl_2 at –78 °C, we observed that stirring the reaction mixture for 1 h at –35 °C before addition of Et_3N at –78 °C cleanly cleaved and oxidized the primary TES to give aldehyde **17** in a good isolated yield of 78%. Finally, homologation of aldehyde **17** to the corresponding terminal alkyne **3** was performed using the Ohira–Bestmann method;[40] the reaction required 48 h at rt to reach completion and alkyne **3** was obtained in a good yield of 88%.

Coupling and spirocyclisation

Compound **4** was prepared according to our previously reported procedure.[29] For coupling of the two key intermediates **3** and **4**, we decided to use the method developed by Fukayama (CuI, $PdCl_2$(dppf), P-(2-furyl)$_3$ in a DMF/Et_3N (5 : 1) mixture at 50 °C).[41] As already reported by us[29] and Kuwahara in his total synthesis of pteridic acids A and B,[42] this reaction only gave a moderate yield of the expected ynone. In this case ynone **2** was obtained in an acceptable 50% yield (Scheme 5). The relatively low yield is due to the oxidative homocoupling of the acetylenic compound **3**, leading to the formation of the corresponding Glaser-type diyne **18**. This side reaction precluded the reaction to go to completion and unreacted thiol ester **4** could be recovered (in our case, dimer **18** and **4** co-eluted during the purification by flash chromatography and therefore could not be separated). However, based on our previous studies on a model substrate, this method proved to be the only one allowing the preparation of the expected ynone.[29]

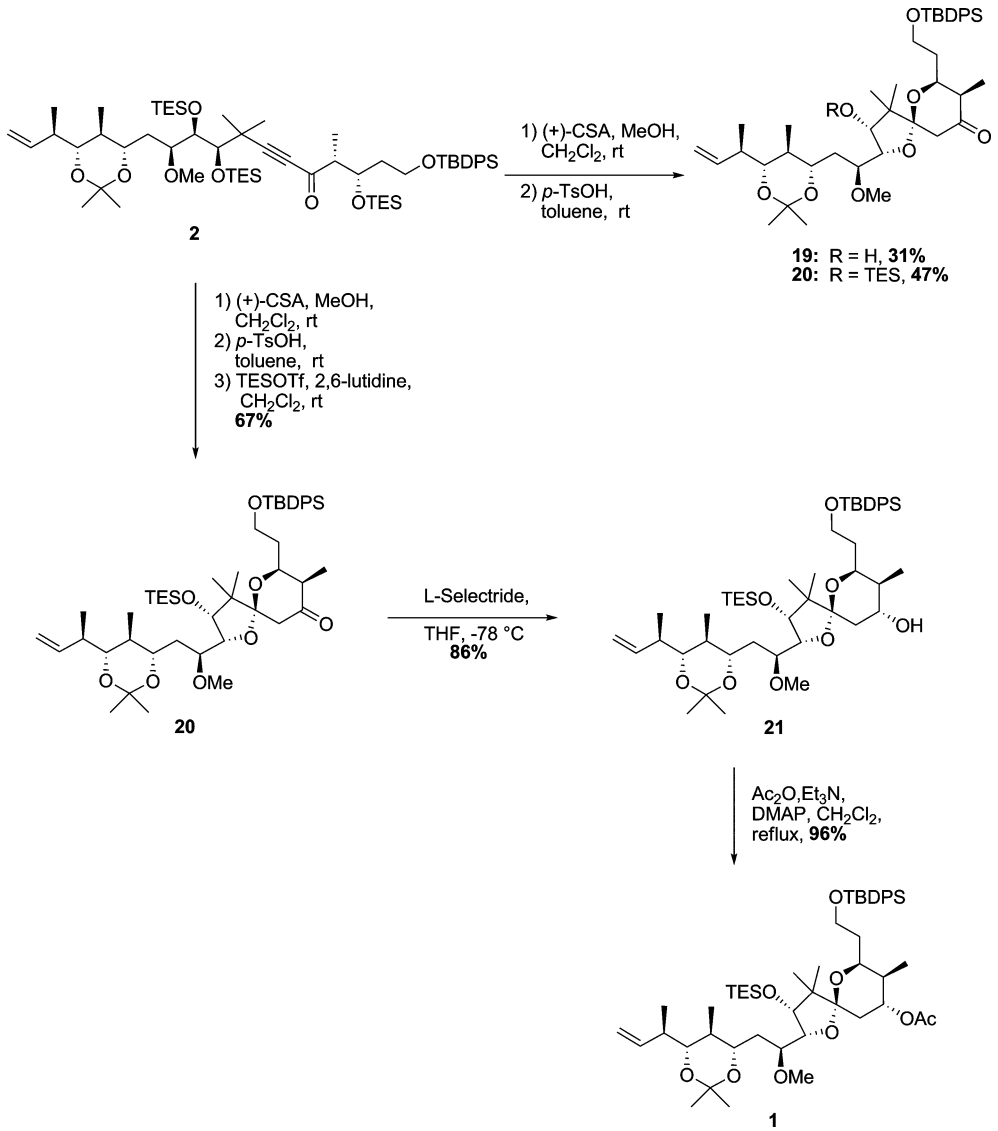


Scheme 4 Synthesis of alkyne **3**



Scheme 5 Pd-catalyzed coupling of **3** and **4**

With ynone **2** in hand, we then focused our attention on the key spirocyclisation step. The DIHMA protocol was first introduced by Crimmins in 1990,[43] and later elegantly used by Forsyth in a number of total syntheses.[44] In his 2009 preparation of the C_3–C_{14} domain of 7-deoxyokadaic acid, Forsyth used the DIHMA protocol to efficiently convert a di-TES protected ynone to the corresponding spiroketal, by simply treating the ynone with 120 mol% of *p*-TsOH in toluene for 24 h.[45] We also applied these conditions for the preparation of the C_{13}–C_{35} fragment with an acceptable yield.[29] Unfortunately, applied to our substrate ynone **2**, the same conditions (with a slightly larger excess of *p*-TsOH, 180 mol%, due to the presence of a third TES group) only furnished the expected spiroketal **19** in a poor 33% yield. After an optimization study on this reaction and some unsuccessful attempts (TMSOTf in CH_3CN–CH_2Cl_2, TBAF in THF, PPTS in CH_2Cl_2, (+)-CSA in MeOH), we were pleased to find out that the treatment of **2** with (+)-CSA (15 mol%) in a 4 : 1 mixture of CH_2Cl_2–MeOH for 1 h at rt, followed by evaporation of the solvent and subsequent treatment of the residue with *p*-TsOH (20 mol%) in toluene for 4 h furnished a mixture of two spiroketals, **19** and its TES-protected analog **20**, with a combined yield of 78% (Scheme 6). This protocol turned up to be very efficient for the spiroketal formation. After separation, **19** could be easily converted to **20** under classical conditions (TESOTf, 2,6-luditine in CH_2Cl_2, 85% yield). We then set up a 3-step sequence where ynone **2** was successively treated with (+)-CSA and *p*-TsOH as described above and, after simple filtration and concentration, the mixture of spiroketals **19** and **20** was directly treated with TESOTf. This allowed the efficient preparation of **20** from **2** in a single operation, with a very satisfying 67% yield. Ketone **20** was



Scheme 6 Last steps to **1**

then stereoselectively reduced with L-Selectride[46] to yield **21**, as a single axial diastereomer (the axial configuration was confirmed by examination of the IR spectra and a narrow O–H bond stretch at 3542 cm^{-1}, confirming the hydrogen bond between the hydrogen of the newly-formed hydroxyl with the oxygen of the 5-membered ring of the spiroketal). Finally, **21** was protected as its acetate ester, by refluxing for two days in the presence of an excess of Ac_2O and Et_3N in CH_2Cl_2, to complete the synthesis of **1** in an excellent yield.

Conclusions

In conclusion, we have achieved the synthesis of the fully protected C_9–C_{25} spiroketal dipropionate fragment **1** of calyculin C in 4% yield over 19 steps based on the longest linear sequence starting from lactone **5**. We were able to build the key *anti*, *anti*, *anti* stereotetrad *via* a highly selective double crotylation strategy. The key spirocyclisation step proved the efficiency of the DIHMA method and validated our planned strategy. We believe that this orthogonally protected fragment should prove amenable for the total synthesis of diverse members of the calyculin family. Moreover, spiroketals **19**, **20**, **21** and **1** can be directly used to study the binding to the phosphatase and therefore provide useful information on the mode of action of calyculins and related inhibitors of PP1 and 2A, since the spirocyclic part of the calyculins is thought to play a crucial role in the binding.

Experimental section

General methods

All moisture sensitive reactions were carried out under an argon atmosphere in flame-dried glassware. Dry oxygen free THF, CH_2Cl_2 and toluene were obtained by passing deoxygenated solvents through activated alumina columns. MeOH was obtained by distillation over magnesium methoxide, DMF by distillation over 4 Å molecular sieves and ninhydrin, Et_3N and DMSO by distillation over CaH_2 and storage over 4 Å molecular sieves. Oxalyl chloride

was freshly distilled prior to use. CuI was purified using a standard method.[47] Other solvents and reagents were used as obtained from supplier. Analytical TLC were performed using 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. Flash chromatography was carried out on silica gel 60 (230–400 mesh) and p.a. grade solvents. The ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ (^{1}H 399.98 MHz; ^{13}C 100.59 MHz) spectrometer. The chemical shifts are reported in ppm relative to $CHCl_3$ (δ 7.26) for ^{1}H NMR and (δ 77.16) for ^{13}C NMR. Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet), br (broad). Coupling constants, *J*, are reported in Hertz. Melting points are uncorrected.

(4*R*,5*S*)-5-((*S*)-3-(benzyloxy)-1-methoxypropyl)-4-hydroxy-3,3-dimethyldihydrofuran-2(3H)-one 6. Lactone **5** (3.5 g, 11.42 mmol, 100 mol%) was dissolved in THF (50 mL). The solution was cooled to –78 °C and $KHBEt_3$ (1 M in THF, 12.6 mL, 12.6 mmol, 110 mol%) was added. After 1 h 30 min, the reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (20 mL). After separation of phases, the aqueous phase was extracted with EtOAc (30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (Hex/AcOEt: 80 : 20 to 50 : 50) afforded compound **6** (2.88 g, 82%) as a colourless oil. Spectral data were in agreement with those previously reported.[35]

(4*R*,5*R*)-5-((*S*)-3-(benzyloxy)-1-methoxypropyl)-4-(*tert*-butyldimethylsilyloxy)-3,3-dimethyldihydrofuran-2(3H)-one 7. Lactone **6** (2 g, 6.5 mmol, 100 mol%) was dissolved in CH_2Cl_2 (30 mL). The solution was cooled to 0 °C and 2,6-lutidine (3.03 mL, 26 mmol, 400 mol%) and TBSOTf (3 mL, 13 mmol, 200 mol%) were successively added. The mixture was stirred overnight at rt. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (20 mL). After separation of phases, the aqueous phase was extracted with CH_2Cl_2 (15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (Hex/EtOAc: 95 : 5 to 80 : 20) afforded protected compound **7** (2.34 g, 85%), as a colourless oil. R_f: 0.57 (Hex/EtOAc: 70 : 30); $[\alpha]^D_{20}$ = –13.3 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.09 (s, 3H), 0.11 (s, 3H), 0.91 (s, 9H), 1.18 (s, 3H), 1.19 (s, 3H), 1.79-1.95 (m, 2H), 3.41 (s, 3H), 3.57-3.71 (m, 3H), 4.15 (d, *J* = 5.5 Hz, 1H), 4.43 (t, *J* = 5.5 Hz, 1H), 4.45-4.52 (m, 2H), 7.26-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$): δ -3.9, -3.4, 18.4, 19.4, 24.9, 26.1, 31.1, 44.6, 58.7, 66.3, 73.2, 75.3, 77.4, 82.9, 127.7, 127.8, 128.4, 138.4, 180.9; IR (ν_{max}, thin film): 2983, 2930, 2858, 1777, 1463, 1389, 1259, 1134, 1101; HRMS: *calculated for* $C_{23}H_{38}O_5NaSi$ $[M+Na]^+$: 445.2386, *found*: 445.2388.

(4*R*,5*R*)-4-(*tert*-butyldimethylsilyloxy)-5-((*S*)-3-hydroxy-1-methoxypropyl)-3,3-dimethyldihydrofuran-2(3H)-one 8. Benzyl protected lactone **7** (1.54 g, 3.64 mmol, 100 mol%) was dissolved in EtOH (60 mL). $Pd(OH)_2$ (20% on carbon, 0.307 g, 0.44 mmol, 10 mol%) was added. The mixture was flushed first by 3 cycles vacuum/argon then 3 cycles vacuum/H_2. After 1 h, the mixture was filtered through a pad of Celite, washed with EtOH (30 mL) and concentrated to yield alcohol **8** (1.21 g, quant.) as a white solid. R_f: 0.26 (Hex/EtOAc: 50 : 50); Mp: 57 °C; $[\alpha]^D_{20}$ = –17.4 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.09 (s, 3H), 0.10 (s, 3H), 0.93 (s, 9H), 1.20 (s, 3H), 1.24 (s, 3H), 1.69-1.78 (m, 1H), 1.84-1.92 (m, 1H), 2.17 (bs, 1H), 3.48 (s, 3H), 3.70-3.75 (m, 1H), 3.79-3.83 (m, 2H), 4.14 (d, *J* = 5.2 Hz, 1H), 4.43 (t, *J* = 5.5 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ -3.9, -3.4, 18.4, 19.4, 24.6, 26.1, 33.1, 44.8, 59.1, 59.8, 76.9, 77.4, 83.0, 180.6; IR (ν_{max}, thin film): 3436, 2954, 2931, 2859, 1775, 1472, 1464, 1390, 1132, 1100 cm^{-1}; HRMS: *calculated for* $C_{16}H_{32}O_5NaSi$ $[M+Na]^+$: 355.1917, *found*: 355.1922.

(*S*)-3-((2*R*,3*R*)-3-(*tert*-butyldimethylsilyloxy)-4,4-dimethyl-5-oxotetrahydrofuran-2-yl)-3-methoxypropanal 9. DMSO (0.3 mL, 3.5 mmol, 120 mol%) was added at –78 °C to a solution of oxalyl chloride (0.3 mL, 3.8 mmol, 130 mol%) in CH_2Cl_2 (20 mL); gas evolution was observed. After 15 min at –78 °C, a solution of alcohol **8** (0.97 g, 2.9 mmol, 100 mol%) in CH_2Cl_2 (10 mL) was added. The reaction mixture was stirred for 1 h at –78 °C before addition of Et_3N (1.2 mL, 8.7 mmol, 300 mol%). The solution was allowed to warm to rt and CH_2Cl_2 was evaporated. The residue was taken up with Et_2O (30 mL) and a saturated aqueous solution of NH_4Cl (20 mL). After separation of phases, the organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give aldehyde **9** (0.96 g, quant.), as a colourless oil. R_f: 0.59 (Hex/EtOAc: 50 : 50); $[\alpha]^D_{20}$ = –20.7 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.11 (s, 3H), 0.12 (s, 3H), 0.95 (s, 9H), 1.21 (s, 3H), 1.26 (s, 3H), 2.76 (ddd, *J* = 17.7, 6.0, 1.4 Hz, 1H), 2.82 (ddd, *J* = 17.7, 6.1, 1.1 Hz, 1H), 3.41 (s, 3H), 4.04 (dt, *J* = 6.1, 4.0 Hz, 1H), 4.22 (d, *J* = 6.5 Hz, 1H), 4.42 (dd, *J* = 6.4, 3.9 Hz, 1H), 9.84 (t, *J* = 1.1 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ -4.1, -3.9, 18.4, 19.4, 26.0, 26.1, 43.8, 45.0, 58.2, 72.8, 77.1, 81.7, 108.8, 200.4; IR (ν_{max}, thin film): 2955, 2932, 2589, 1777, 1724, 1472, 1390, 1257, 1132, 1098 cm^{-1}; HRMS: *calculated for* $C_{16}H_{30}O_5NaSi$ $[M+Na]^+$: 353.1760, *found*: 353.1756.

(4*R*,5*R*)-4-(*tert*-butyldimethylsilyloxy)-5-((1*S*,3*S*,4*R*)-3-hydroxy-1-methoxy-4-methylhex-5-enyl)-3,3-dimethyl dihydrofuran-2(3H)-one 10a and (4*R*,5*R*)-4-((*tert*-butyl dimethylsilyl)oxy)-5-((1*S*,3*R*, 4*S*)-3-hydroxy-1-methoxy-4-methylhex-5-en-1-yl)-3,3-dimethyldihydrofuran-2(3H)-one 10b. To a solution of *t*-BuOK (0.76 g, 6.7 mmol, 200 mol%) in THF (5 mL) were successively added *E*-butene (3 mL) and *n*-BuLi (2.3 M in hexanes, 2.9 mL, 6.7 mmol, 200 mol%) at –78 °C. The yellow solution was stirred for 30 min at –45 °C. A solution of (+)-IpcBOMe (2.13 g, 6.7 mmol, 200 mol%) in THF (5 mL) was then added at –78 °C. After 30 min, $BF_3{\cdot}OEt_2$ (0.85 mL, 6.7 mmol, 200 mol%) was added, followed by a solution of aldehyde **9** (1.11 g, 3.4 mmol, 100 mol%) in THF (5 mL). The mixture was stirred for 2 h at –78 °C, then MeOH (5 mL) was added and the mixture was allowed to warm to rt. Solvents were evaporated and the residue taken up in THF (20 mL) and H_2O (10 mL). After cooling to 0 °C sodium perborate (1 g) was added and the mixture was stirred overnight at rt. More water was added (20 mL) and, after extraction with EtOAc (40 mL), the organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (Hex/EtOAc: 95 : 5 to 75 : 25) afforded the homoallylic alcohols **10** (0.95 g, 73%) as a 6 : 1 mixture of diastereomers. Data for major isomer **10a** (obtained from the mixture): R_f: 0.44 (Hex/EtOAc: 80 : 20); ^{1}H NMR ($CDCl_3$): δ 0.09 (s, 3H), 0.10 (s, 3H), 0.93 (s, 9H), 1.06 (d, *J* = 6.8 Hz, 3H), 1.21 (s, 3H), 1.24 (s, 3H), 1.54-1.62 (m, 1H), 1.75 (ddd, *J* = 14.4, 6.0, 1.9 Hz, 1H), 2.15-2.22 (m, 1H), 2.72 (d, *J* = 2.2 Hz, 1H), 3.46 (s, 3H), 3.64-3.68 (m, 1H), 3.77 (q, *J* = 6.1 Hz, 1H), 4.17 (d, *J* = 5.2 Hz, 1H), 4.50 (t, *J* = 5.5 Hz, 1H), 5.06-5.12 (m, 2H), 5.78 (ddd, *J* = 17.0, 10.5, 8.2 Hz, 1H); ^{13}C

NMR ($CDCl_3$): δ -3.8, -3.4, 16.3, 18.5, 19.5, 24.8, 26.1, 34.2, 44.8, 45.2, 58.6, 72.3, 77.3, 77.5, 82.4, 116.4, 140.1, 180.8; IR (ν_{max}, thin film): 3501, 2958, 2931, 2859, 1773, 1472, 1390, 1132, 1101 cm^{-1}; HRMS: *calculated for* $C_{20}H_{38}O_5NaSi$ $[M+Na]^+$: 409.2386, *found*: 409.2394.

(4*R*,5*R*)-5-((*S*)-2-((4*S*,5*S*,6*R*)-6-((*R*)-but-3-en-2-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-1-methoxy ethyl)-4-(*tert*-butyl dimethylsilyloxy)-3,3-dimethyldihydrofuran-2(3H)-one 14a and (4*R*,5*R*)-5-((*S*)-2-((4*R*,5*R*,6*S*)-6-((*S*)-but-3-en-2-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-1-methoxyethyl)-4-(*tert*-butyl dimethylsilyloxy)-3,3-dimethyldihydrofuran-2(3H)-one 14b. To a solution of homoallylic alcohols **10a** and **10b** (0.99 g, 2.6 mmol, 100 mol%) in a 10 : 3 : 1 mixture of *t*-BuOH/THF/H_2O (14 mL) were successively added OsO_4 (2.5% in *t*-BuOH, 0.37 mL, 0.03 mmol, 5 mol%) and NMO (83 mg, 0.7 mmol, 120 mol%). After stirring overnight at rt, the reaction was quenched by addition of a saturated aqueous solution of $NaHSO_3$ (5 mL) and the mixture was stirred for 1 h at rt. After extraction with EtOAc (10 mL), the organic layers were dried over $MgSO_4$ and concentrated *in vacuo*.

The residue was taken up in THF (23.5 mL) and H_2O (2.5 mL) and treated with $NaIO_4$ (1.64 g, 7.65 mmol, 300 mol%). After 1 h, Et_2O (20 mL) and H_2O (20 mL) were added. After separation of phases, the organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give a mixture of aldehydes **11**.

To a solution of aldehydes **11** in CH_2Cl_2 (32 mL) 4 Å molecular sieves (1 g) were added. After 30 min, the mixture was cooled to 0 °C. (*Z*)-crotyltrifluorosilane **12** (1.1 mL, 8.2 mmol, 320 mol%) and DIPEA (1.3 mL, 7.7 mmol, 300 mol%) were successively added. After 36 h at 0 °C, 1 g of silica was added to the mixture and, after 30 min, the mixture was filtered through a short pad of silica.

After concentration, the residue was dissolved in CH_2Cl_2 (40 mL). 2-methoxypropene (1.2 mL, 12.8 mmol, 500 mol%) and PPTS (31 mg, 0.13 mmol, 5 mol%) were added. After 30 min, the reaction was stopped by addition of a saturated aqueous solution of $NaHCO_3$ (10 mL). After extraction with CH_2Cl_2 (20 mL), the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (Hex/EtOAc: 95 : 5 to 90 : 10) afforded compounds **14** (0.795 g, 65% global yield), as a separable mixture of **14a** (0.701 g, 66% over 4 steps from **10a**) as a white solid and **14b** (0.094 g, 53% over 4 steps from **10b**) as a colourless oil. Data for **14a**: R_f: 0.35 (Hex/EtOAc: 90 : 10); Mp: 89 °C; $[\alpha]^D_{20}$ = -52.0 (*c* 0.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.09 (s, 3H), 0.11 (s, 3H), 0.74 (d, *J* = 6.6 Hz, 3H), 0.92 (s, 9H), 1.03 (d, *J* = 7.0 Hz, 3H), 1.19 (s, 3H), 1.23 (s, 3H), 1.23-1.29 (m, 1H), 1.31 (s, 3H), 1.36 (s, 3H), 1.64 (ddd, *J* = 14.2, 9.8, 3.3 Hz, 1H), 2.00 (ddd, *J* = 14.3, 8.7, 2.3 Hz, 1H), 2.36-2.44 (m, 1H), 3.32 (s, 3H), 3.33-3.37 (m, 1H), 3.58 (dt, *J* = 9.9, 2.2 Hz, 1H), 3.64 (dt, *J* = 8.7, 3.6 Hz, 1H), 4.28 (d, *J* = 6.4 Hz, 1H), 4.51 (dd, *J* = 6.4, 3.9 Hz, 1H), 4.95-5.00 (m, 2H), 5.82 (ddd, *J* = 17.2, 10.4, 9.1 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ -4.0, -3.7, 11.8, 18.2, 18.4, 19.5, 19.6, 26.0, 26.1, 30.1, 32.6, 36.5, 39.6, 43.8, 56.8, 70.5, 74.5, 77.4, 77.5, 80.8, 97.7, 115.1, 139.6, 181.3; IR (ν_{max}, thin film): 2961, 2932, 2859, 1778, 1471, 1463, 1388, 1380, 1259, 1131 cm^{-1}; HRMS: *calculated for* $C_{26}H_{48}O_6NaSi$ $[M+Na]^+$: 507.3118, *found*: 507.3112. Data for **14b**: R_f: 0.20 (Hex/EtOAc: 90 : 10); $[\alpha]^D_{20}$ = −8.6 (*c* 0.5, $CHCl_3$); NMR ^{1}H ($CDCl_3$): δ 0.09 (s, 3H), 0.15 (s, 3H), 0.74 (d, *J* = 6.6 Hz, 3H), 0.94 (s, 9H), 1.05 (d, *J* = 6.9 Hz, 3H), 1.20 (s, 3H), 1.33 (s, 3H), 1.41 (s, 3H), 1.41-1.44 (m, 1H), 1.86 (ddd, *J* = 13.7, 11.1, 2.5 Hz, 1H), 2.37-2.46 (m, 1H), 3.38 (dd, *J* = 10.2, 2.2 Hz, 1H), 3.45 (s, 3H), 3.48-3.53 (m, 1H), 3.71 (dt, *J* = 10.3, 2.5 Hz, 1H), 3.64 (ddd, *J* = 10.1, 5.1, 2.7 Hz, 1H), 4.12 (d, *J* = 5.7 Hz, 1H), 4.28 (t, *J* = 5.4 Hz, 1H), 4.94-5.00 (m, 2H), 5.83 (ddd, *J* = 17.1, 10.4, 9.0 Hz, 1H); NMR ^{13}C ($CDCl_3$): δ -3.7, -3.6, 11.7, 18.2, 18.4, 19.4, 19.6, 25.1, 26.1, 30.2, 36.7, 36.8, 39.7, 44.5, 59.6, 70.2, 73.8, 77.3, 77.4, 84.7, 97.9, 115.0, 139.9, 181.0; IR (ν_{max}, thin film): 2961, 2931, 2859, 1778, 1472, 1380, 1256, 1202 cm^{-1}; HRMS: *calculated for* $C_{26}H_{48}O_6NaSi$ $[M+Na]^+$: 507.3118, *found*: 507.3105.

(5*R*,6*R*)-5-((*S*)-2-((4*S*,5*S*,6*R*)-6-((*R*)-but-3-en-2-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-1-methoxyethyl)-3,3,10,10-tetraethyl-7,7-dimethyl-6-(triethylsilyloxy)-4,9-dioxa-3,10-disiladodecane 16. To a suspension of $LiAlH_4$ (0.171 g, 4.52 mmol, 200 mol%) in THF (25 mL) was added a solution of **14a** (1.09 g, 2.26 mmol, 100 mol%) in THF (15 mL) at 0 °C. The mixture was stirred 1 h at 0 °C and then quenched by successive addition of H_2O (0.2 mL), 15% NaOH (0.2 mL) and H_2O (0.6 mL). After 30 min, the precipitate was filtered and washed with EtOAc (20 mL). The combined organic solution was dried over $MgSO_4$ and concentrated *in vacuo* to afford crude triol **15**.

Triol **15** was then dissolved in CH_2Cl_2 (50 mL). 2,6-Lutidine (3.58 mL, 30.7 mmol, 1200 mol%) and TESOTf (2.8 mL, 13.6 mmol, 600 mol%) were successively added at 0 °C. After 12 h at rt, a saturated aqueous solution of NH_4Cl (20 mL) was added to the mixture. After separation of phases, 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 (Hex/EtOAc: 100 : 0 to 95 : 5) afforded the triprotected compound **16** (1.16 g, 72% over 2 steps) as a colourless oil. R_f: 0.66 (Hex/EtOAc: 95 : 5); $[\alpha]^D_{20}$ = −31.3 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.55-0.66 (m, 18H), 0.75 (d, *J* = 6.6 Hz, 3H), 0.87 (s, 3H), 0.91 (s, 3H), 0.94-0.99 (m, 27H), 1.05 (d, *J* = 6.9 Hz, 3H), 1.09-1.25 (m, 1H), 1.33 (s, 3H), 1.39 (s, 3H), 1.41-1.44 (m, 1H), 2.05-2.10 (m, 1H), 2.38-2.45 (m, 1H), 3.21-3.25 (m, 2H), 3.28 (s, 3H), 3.36 (dd, *J* = 10.3, 2.1 Hz, 1H), 3.44 (d, *J* = 9.4 Hz, 1H), 3.58-3.63 (m, 1H), 3.69 (d, *J* = 2.0 Hz, 1H), 3.84 (dd, *J* = 8.2, 1.9 Hz, 1H), 4.95-5.01 (m, 2H), 5.86 (ddd, *J* = 17.1, 10.4, 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 4.6, 5.9, 6.0, 7.0, 7.3, 7.4, 12.1, 18.3, 19.5, 20.6, 22.4, 26.2, 30.3, 32.9, 36.3, 39.8, 41.1, 57.5, 69.9, 71.4, 75.4, 77.6, 81.0, 97.7, 114.8, 140.1; IR (ν_{max}, thin film): 2956, 2912, 2877, 1461, 1416, 1379, 1238, 1201, 1095 cm^{-1}; HRMS: *calculated for* $C_{38}H_{80}O_6NaSi_3$ $[M+Na]^+$: 739.5160, *found*: 739.5158.

(3*R*,4*R*,5*S*)-6-((4*S*,5*S*,6*R*)-6-((*R*)-but-3-en-2-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-5-methoxy-2,2-dimethyl-3,4-bis(triethylsilyloxy)hexanal 17. A solution of DMSO (98 µL, 1.4 mmol, 880 mol%) in CH_2Cl_2 (1 mL) was cooled to −78 °C. Oxalyl chloride (59 µL, 0.7 mmol, 440 mol%) was added to the solution (gas evolution was observed). TES-protected compound **16** (0.112 g, 0.16 mmol, 100 mol%) in CH_2Cl_2 (1 mL) was added. The solution was stirred 20 min at −78 °C and then warmed to −35 °C and stirred for 1 h at this temperature. The solution was then cooled down to −78 °C and Et_3N (0.33 mL, 2.35 mmol, 1500 mol%) was added. The mixture was allowed to warm to rt and after 1 h, a saturated aqueous solution of NH_4Cl (2 mL) was added. After separation of phases, the aqueous phase was extracted with EtOAc (10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (Hex/EtOAc: 100 : 0 to 95 : 5) afforded aldehyde **17** (74 mg, 78%)

as a colourless oil. R_f: 0.53 (Hex/EtOAc: 95 : 5); $[\alpha]^{D}_{20} = -46.7$ (*c* 1, $CHCl_3$) ^{1}H NMR ($CDCl_3$): δ 0.57 (q, *J* = 7.9 Hz, 6H), 0.65 (q, *J* = 7.7 Hz, 6H), 0.77 (d, *J* = 6.6 Hz, 3H), 0.93 (t, *J* = 7.9 Hz, 9H), 0.97 (t, *J* = 7.7 Hz, 9H), 1.03 (s, 3H), 1.04 (d, *J* = 7.2 Hz, 3H), 1.06 (s, 3H), 1.19-1.23 (m, 1H), 1.31 (s, 3H), 1.37 (s, 3H), 1.40-1.42 (m, 1H), 2.07-2.12 (m, 1H), 2.39-2.46 (m, 1H), 3.23 (s, 3H), 3.31-3.35 (m, 1H), 3.37 (dd, *J* = 10.2, 2.1 Hz, 1H), 3.67 (t, *J* = 9.1 Hz, 1H), 3.93-3.95 (m, 2H), 4.96-5.03 (m, 2H), 5.85 (ddd, *J* = 16.9, 10.3, 9.0 Hz, 1H), 9.83 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 5.5, 6.0, 7.2, 7.3, 12.2, 18.2, 19.5, 19.9, 23.2, 30.3, 31.5, 36.1, 39.8, 49.5, 56.3, 70.0, 74.2, 77.6, 79.5, 80.2, 97.7, 115.0, 139.9, 206.5; IR (ν_{max}, thin film): 2956, 2937, 2876, 1717, 1458, 1379, 1257, 1201, 1094 cm^{-1}; HRMS: *calculated for* $C_{32}H_{64}O_6NaSi_2$ $[M+Na]^+$: 623.4158, *found*: 623.4139.

(5*R*,6*R*)-5-((*S*)-2-((4*S*,5*S*,6*R*)-6-((*R*)-but-3-en-2-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-1-methoxyethyl)-3,3,8,8-tetraethyl-6-(2-methylbut-3-yn-2-yl)-4,7-dioxa-3,8-disiladecane 3. Aldehyde **17** (0.40 g, 0.66 mmol, 100 mol%) was dissolved in MeOH (15 mL). Ohira–Bestmann reagent (0.31 g, 1.65 mmol, 250 mol%) and K_2CO_3 (0.228 g, 1.65 mmol, 250 mol%) were then successively added and the mixture stirred at rt for 48 h. MeOH was evaporated and the residue taken up in EtOAc (20 mL) and H_2O (10 mL). After separation of phases, the aqueous phase was extracted with EtOAc (10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (Hex/EtOAc: 100 : 0 to 95 : 5) afforded alkyne **3** (0.345 g, 88%) as a colourless oil. R_f: 0.72 (Hex/EtOAc: 95 : 5); $[\alpha]^{D}_{20} = -43.6$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.61-0.70 (m, 12H), 0.76 (d, *J* = 6.5 Hz, 3H), 0.92-1.00 (m, 18 H), 1.05 (d, *J* = 6.9 Hz, 3H), 1.24 (s, 3H), 1.25 (s, 3H), 1.35 (s, 3H), 1.39 (s, 3H), 1.40-1.46 (m, 2H), 2.07 (s, 1H), 2.08-2.14 (m, 1H), 2.38-2.46 (m, 1H), 3.25-3.31 (m, 4H), 3.36 (dd, *J* = 10.3, 2.1 Hz, 1H), 3.59-3.64 (m, 1H), 3.74 (d, *J* = 2.0 Hz, 1H), 4.04 (dd, *J* = 7.7, 1.9 Hz, 1H), 4.95-5.01 (m, 2H), 5.86 (ddd, *J* = 17.5, 10.4, 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): 5.8, 5.9, 7.3, 7.4, 12.1, 18.2, 19.5, 25.4, 27.6, 30.2, 33.0, 36.2, 36.9, 39.7, 57.2, 69.5, 71.4, 74.5, 77.3, 77.7, 81.1, 92.3, 97.7, 114.8, 140.1; IR (ν_{max}, thin film): 3309, 2955, 2937, 2877, 2111, 1460, 1379, 1238, 1202, 1097; HRMS: *calculated for* $C_{33}H_{64}O_5NaSi_2$ $[M+Na]^+$: 619.4190, *found*: 619.4181.

(6*R*,7*R*,12*R*,13*R*)-13-((*S*)-2-((4*S*,5*S*,6*R*)-6-((*R*)-but-3-en-2-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-1-methoxyethyl)-15,15-diethyl-2,2,7,11,11-pentamethyl-3,3-diphenyl-6,12-bis(triethylsilyloxy)-4,14-dioxa-3,15-disilaheptadec-9-yn-8-one 2. To a solution of thiol ester **4** (49 mg, 71 µmol, 100 mol%) in DMF (0.15 mL) and Et_3N (45 µL) were successively added $PdCl_2$(dppf) (6 mg, 7 µmol, 10 mol%), CuI (26 mg, 0.135 mmol, 190 mol%), P(2-furyl)$_3$ (4 mg, 18 µmol, 25 mol%) and a solution of alkyne **3** (80 mg, 0.135 mmol, 190 mol%) in DMF (0.15 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 the pad was washed with EtOAc (10 mL). After separation of phases, the organic extracts were washed with H_2O (5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (Hex/EtOAc: 99 : 1 to 95 : 5) furnished ynone **2** (38 mg, 50%), as a colourless oil. R_f: 0.43 (Hex/EtOAc: 97 : 3); $[\alpha]^{D}_{20} = -27.7$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.54 (q, *J* = 7.9 Hz, 6H), 0.60-0.70 (m, 12H), 0.75 (d, *J* = 6.6 Hz, 3H), 0.90 (t, *J* = 7.9 Hz, 9H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.98 (t, *J* = 7.9 Hz, 9H), 1.05 (s, 9H), 1.05 (d, *J* = 6.6 Hz, 3H), 1.13 (d, *J* = 7.0 Hz, 3H), 1.29 (s, 6H), 1.33 (s, 3H), 1.39 (s, 3H), 1.42-1.44 (m, 1H), 1.77 (q, *J* = 6.4 Hz, 2H), 2.06-2.10 (m, 1H), 2.37-2.45 (m, 1H), 2.52-2.58 (m, 1H), 3.27 (s, 3H), 3.29-3.31 (m, 2H), 3.37 (dd, *J* = 10.2, 2.1 Hz, 1H), 3.61-3.64 (m, 1H), 3.68 (t, *J* = 6.4 Hz, 2H), 3.80 (d, *J* = 1.8 Hz, 1H), 3.97 (dd, *J* = 7.9, 1.7 Hz, 1H), 4.41-4.45 (m, 1H), 4.95-5.03 (m, 2H), 5.87 (ddd, *J* = 16.8, 10.0, 9.4 Hz, 1H), 7.35-7.44 (m, 6H), 7.64-7.68 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 5.3, 5.8, 5.9, 7.1, 7.3, 7.4, 10.1, 12.0, 18.2, 19.3, 19.5, 25.9, 27.0, 30.3, 32.6, 36.1, 37.8, 38.7, 39.8, 53.7, 57.2, 60.9, 69.9, 71.2, 77.4, 77.6, 80.6, 81.7, 97.7, 102.0, 114.8, 127.8, 129.7, 133.8, 133.9, 135.7, 140.1, 190.1; IR (ν_{max}, thin film): 2955, 2936, 2876, 2205, 1673, 1459, 1379, 1238, 1095 cm^{-1}; HRMS: *calculated for* $C_{61}H_{106}O_8NaSi_4$ $[M+Na]^+$: 1101.6863, *found*: 1101.6896.

(2*S*,3*R*,7*S*,8*R*)-2-((*S*)-2-((4*S*,5*S*,6*R*)-6-((*R*)-but-3-en-2-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-1-methoxyethyl)-7-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-3-hydroxy-4,4,8-trimethyl-1,6-dioxaspiro[4.5]decan-9-one 19. To a solution of ynone **2** (31 mg, 29 µmol, 100 mol%) in toluene (1 mL) was added *p*-TsOH (10 mg, 50 µmol, 180 mol%) 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, after separation of phases, the organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (Hex/EtOAc: 95 : 5 to 80 : 20) afforded spiroketal **19** (7 mg, 33%), as a colourless oil. R_f: 0.44 (Hex/EtOAc: 80 : 20); $[\alpha]^{D}_{20} = -64.3$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.61 (d, *J* = 6.5 Hz, 3H), 0.86 (s, 3H), 1.02-1.07 (m, 18H), 1.11 (s, 3H), 1.25 (s, 3H), 1.29-1.38 (m, 2H), 1.64-1.74 (m, 2H), 1.83-1.91 (m, 2H), 2.27-2.46 (m, 3H), 2.56 (d, *J* = 14.8 Hz, 1H), 3.19 (dd, *J* = 10.3, 2.1 Hz, 1H), 3.29 (s, 3H), 3.44-3.46 (m, 1H), 3.58-3.65 (m, 2H), 3.74 (dt, *J* = 9.4, 4.8 Hz, 1H), 3.79 (dd, *J* = 7.7, 3.7 Hz, 1H), 3.92 (ddd, *J* = 9.0, 4.3, 2.9 Hz, 1H), 4.05 (dd, *J* = 9.0, 8.1 Hz, 1H), 4.94-5.01 (m, 2H), 5.81 (ddd, *J* = 17.2, 10.2, 9.1 Hz, 1H), 7.36-7.45 (m, 6H), 7.63-7.66 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 10.8, 11.7, 17.2, 18.1, 19.3, 21.0, 27.0, 27.0, 30.0, 32.6, 34.9, 36.1, 39.6, 41.6, 48.3, 48.5, 56.3, 61.7, 68.4, 71.6, 76.4, 77.4, 77.4, 80.4, 97.8, 108.4, 115.2, 127.9, 129.9, 133.7, 135.6, 139.7, 210.0; IR (ν_{max}, thin film): 3469, 2959, 2930, 2857, 1720, 1472, 1462, 1428, 1379, 1203, 1111 cm^{-1}; HRMS: *calculated for* $C_{43}H_{65}O_8Si$ $[M+H]^+$: 737.4449, *found*: 737.4445.

(2*R*,3*R*,7*S*,8*R*)-2-((*S*)-2-((4*S*,5*S*,6*R*)-6-((*R*)-but-3-en-2-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-1-methoxyethyl)-7-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-4,4,8-trimethyl-3-((triethylsilyl)oxy)-1,6-dioxaspiro[4.5]decan-9-one 20. To a solution of ynone **2** (25.4 mg, 23.5 µmol, 100 mol%) in CH_2Cl_2 (0.60 mL) and MeOH (0.15 mL) (+)-CSA (1 mg, 4.3 µmol, 15 mol%) was added. After 1 h and total consumption of the starting material, the solvent was evaporated. The residue was taken up in toluene (1.5 mL) and *p*-TsOH·H_2O (1 mg, 5.2 µmol, 20 mol%) was added. After 4 h, the mixture was filtered and concentrated. The residue was dissolved in CH_2Cl_2 (3 mL). To this solution were successively added 2,6-lutidine (11 µL, 94.0 µmol, 400 mol%) and TESOTf (11 µL, 47.0 µmol, 200 mol%) at 0 °C. The reaction mixture was stirred at rt overnight and quenched by addition of a saturated aqueous solution of NH_4Cl (2 mL). After separation of phases, the aqueous phase was extracted with CH_2Cl_2 (5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*.

Purification by flash chromatography (Hex/EtOAc: 95 : 5 to 90 : 10) afforded spiroketal **20** (13.4 mg, 67% over 3 steps) as a colourless oil. R_f: 0.65 (Hex/EtOAc: 80 : 20); $[\alpha]^{D}_{20} = -47.7$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.53-0.59 (m, 9H), 0.88 (s, 3H), 0.94 (t, *J* = 7.9 Hz, 9H), 1.02 (s, 3H), 1.03-1.05 (m, 15H), 1.11 (s, 3H), 1.25 (s, 3H), 1.27-1.33 (m, 1H), 1.54 (dt, *J* = 13.8, 9.6 Hz, 1H), 1.61-1.67 (m, 1H), 1.83-1.97 (m, 2H), 2.24-2.29 (m, 1H), 2.33-2.37 (m, 2H), 2.49 (d, *J* = 15.4 Hz, 1H), 3.16-3.23 (m, 2H), 3.24 (s, 3H), 3.29-3.33 (m, 1H), 3.64 (dt, *J* = 9.7, 6.0 Hz, 1H), 3.68 (dd, *J* = 8.1, 1.7 Hz, 1H), 3.81 (dt, *J* = 9.9, 5.1 Hz, 1H), 3.95 (ddd, *J* = 9.5, 3.6, 2.9 Hz, 1H), 4.17 (d, *J* = 8.0 Hz, 1H), 4.94-5.00 (m, 2H), 5.81 (ddd, *J* = 17.2, 10.3, 9.1 Hz, 1H), 7.35-7.43 (m, 6H), 7.65-7.67 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 5.1, 7.1, 10.9, 11.8, 16.9, 18.2, 19.3, 21.3, 26.3, 27.0, 30.0, 34.8, 34.9, 36.5, 39.6, 41.0, 48.1, 48.4, 57.0, 61.9, 67.7, 71.5, 74.7, 77.4, 78.3, 79.8, 97.6, 108.4, 115.1, 127.9, 129.8, 133.8, 135.5, 139.8, 210.0; IR (ν_{max}, thin film): 2958, 2929, 2857, 1723, 1471, 1463, 1379, 1260, 1202, 1112 cm^{-1}; HRMS: *calculated for* $C_{49}H_{78}O_8NaSi_2$ $[M+Na]^+$: 873.5133, *found*: 873.5140.

(2*R*,3*R*,7*S*,8*S*,9*R*)-2-((*S*)-2-((4*S*,5*S*,6*R*)-6-((*R*)-but-3-en-2-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-1-methoxyethyl)-7-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-4,4,8-trimethyl-3-((triethylsilyl)oxy)-1,6-dioxaspiro[4.5]decan-9-ol 21. To a solution of spiroketal **20** (75.0 mg, 0.088 mmol, 100 mol%) in THF (4 mL) was added L-Selectride (1 M in THF, 0.26 mL, 0.26 mmol, 300 mol%) at −78 °C. After stirring for 1 h 30 at −78 °C, MeOH (1 mL), 1 M NaOH (1 mL), 30% H_2O_2 (0.5 mL) and THF (6 mL) were successively added. The reaction mixture was then allowed to warm to 0 °C, stirred for 30 min at 0 °C and finally 30 min at rt. Et_2O (10 mL) and brine (5 mL) were then added to the mixture. After extraction with Et_2O (10 mL), the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (Hex/EtOAc: 90 : 10 to 80 : 20) afforded alcohol **21** (65.0 mg, 86%) as a colourless oil. R_f: 0.37 (Hex/EtOAc: 80 : 20); $[\alpha]^{D}_{20} = -62.2$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.55 (q, *J* = 7.7 Hz, 6H), 0.64 (d, *J* = 6.4 Hz, 3H), 0.81 (d, *J* = 7.1 Hz, 3H), 0.87 (s, 3H), 0.92 (t, *J* = 7.9 Hz, 9H), 0.91 (s, 3H), 1.03 (s, 9H), 1.04 (d, *J* = 3.5 Hz, 3H), 1.09 (s, 3H), 1.24 (s, 3H), 1.29-1.35 (m, 1H), 1.57-1.69 (m, 4H), 1.74 (dd, *J* = 14.4, 2.8 Hz, 1H), 1.81-1.91 (m, 2H), 2.33-2.41 (m, 1H), 3.20 (dd, *J* = 10.4, 2.1 Hz,1H), 3.25 (s, 3H), 3.26-3.35 (m, 2H), 3.63 (dt, *J* = 9.9, 5.7 Hz, 1H), 3.71-3.78 (m, 3H), 3.81 (dt, *J* = 10.1, 5.0 Hz, 1H), 4.00 (ddd, *J* = 9.7, 3.0, 2.8 Hz, 1H), 4.13 (d, *J* = 8.0 Hz, 1H), 4.94-5.00 (m, 2H), 5.82 (ddd, *J* = 17.2, 10.3, 9.1 Hz, 1H), 7.35-7.43 (m, 6H), 7.65-7.68 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 5.1, 7.1, 10.9, 11.8, 16.8, 18.2, 19.2, 19.3, 21.3, 27.0, 28.4, 30.0, 34.9, 36.0, 36.5, 38.1, 39.6, 48.3, 57.1, 62.3, 64.1, 70.9, 71.6, 74.9, 77.4, 78.3, 79.8, 97.6, 107.8, 115.1, 127.8, 129.7, 134.0, 135.5, 139.8; IR (ν_{max}, thin film): 3542, 2959, 2932, 2913, 2877, 1472, 1463, 1379, 1259, 1112 cm^{-1}; HRMS: *calculated for* $C_{49}H_{80}O_8NaSi_2$ $[M+Na]^+$: 875.5289, *found*: 875.5299.

(2*R*,3*R*,7*S*,8*R*,9*R*)-2-((*S*)-2-((4*S*,5*S*,6*R*)-6-((*R*)-but-3-en-2-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-1-methoxyethyl)-7-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-4,4,8-trimethyl-3-((triethylsilyl)oxy)-1,6-dioxaspiro[4.5]decan-9-yl acetate 1. To a solution of alcohol **21** (28 mg, 33 µmol, 100 mol%) in CH_2Cl_2 (5 mL) were added Et_3N (0.15 mL, 1.1 mmol, 3300 mol%), Ac_2O (0.08 mL, 2500 mol%) and DMAP (1 mg, 8.2 µmol, 25 mol%). The mixture was heated to reflux for 48 h. After cooling to rt, the reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (4 mL). After separation of phases, the aqueous phase was extracted with CH_2Cl_2 (5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (Hex/EtOAc: 90 : 10) afforded spiroketal **1** (28 mg, 96%) as a colourless oil. R_f: 0.54 (Hex/EtOAc: 80 : 20); $[\alpha]^{D}_{20} = -67.7$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.55 (q, *J* = 7.5 Hz, 3H), 0.55 (q, *J* = 8.1 Hz, 3H), 0.65 (d, *J* = 6.6 Hz, 3H), 0.84 (s, 3H), 0.87 (d, *J* = 7.1 Hz, 3H), 0.92 (s, 3H), 0.93 (t, *J* = 7.9 Hz, 9H), 1.03 (s, 9H), 1.04 (d, *J* = 4.4 Hz, 3H), 1.12 (s, 3H), 1.25-1.27 (m, 4H), 1.30-1.37 (m, 1H), 1.53-1.62 (m, 3H), 1.70-1.71 (m, 2H), 1.77-1.84 (m, 1H), 1.99 (s, 3H), 2.33-2.38 (m, 1H), 3.20 (dd, *J* = 10.3, 2.1 Hz, 1H), 3.25 (s, 3H), 3.26-3.32 (m, 2H), 3.64 (dt, *J* = 9.6, 5.2 Hz, 1H), 3.68 (dd, *J* = 8.3, 1.3 Hz, 1H), 3.80 (dt, *J* = 9.7, 5.7 Hz, 1H), 4.05-4.09 (m, 1H), 4.17 (d, *J* = 8.3 Hz, 1H), 4.85 (dd, *J* = 5.7, 2.9 Hz, 1H), 4.94-5.01 (m, 2H), 5.83 (ddd, *J* = 17.2, 10.3, 9.1 Hz, 1H), 7.35-7.42 (m, 6H), 7.64-7.67 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 5.1, 7.1, 10.2, 11.8, 16.6, 18.2, 19.2, 19.3, 21.3, 21.8, 26.5, 27.0, 30.0, 35.0, 35.1, 35.9, 36.7, 39.7, 48.4, 57.0, 62.2, 64.0, 71.6, 72.4, 75.1, 77.4, 77.4, 79.9, 97.7, 105.8, 115.1, 127.8, 129.8, 134.0, 135.5, 139.9, 170.8; IR (ν_{max}, thin film): 2958, 2931, 2858, 1732, 1472, 1462, 1378, 1112 cm^{-1}; HRMS: *calculated for* $C_{51}H_{82}O_9NaSi_2$ $[M+Na]^+$: 917.5395, *found*: 917.5437.

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