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Towards the total synthesis of calyculin C: preparation of the C_9–C_25 spiroketal-dipropionate unit†

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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)-crotyl trifluorosilane 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, later followed by calyculins B–H. 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. Other natural products belonging to the calyculin family include calyculin J, calyculinamides A, B and J, des-N-methyl calyculin A, dephosphocalyculin A, clavosines A–C, geometricin A and swinhoeiamide A.†

![Fig. 1 Structures of calyculins.](image)

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. PP2A has been implied in several disease states, since a wide variety of cellular events are regulated by reversible protein phosphorylation. 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. Other naturally occurring toxins bind to inhibit more or less selectively PP, i.e. okadaic acid, microcystins, spirastrellolide or tautomycin. 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.

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, Shiouri and Barrett, calyculin A by Masamune, (ent)-calyculins A and B by Smith and calyculin C by Armstrong. In addition, the Trost group and our group have been involved in the synthesis of individual fragments. We have recently reviewed these different syntheses, along with some biological data.

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 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: ‘H and 13C NMR spectra of compounds 1, 2, 3, 7, 8, 9, 10a, 14a, 14b, 16, 17, 19, 20 and 21. See DOI: 10.1039/c0ob00092b
Double crotylation strategy

The preparation of the anti, anti, anti stereotetrad has proven to be challenging. 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. With a strategy similar to ours, Armstrong had described that the protecting group at the C19 hydroxyl played an unexpected but significant role in the asymmetric induction at C11. 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. The synthesis commenced with lactone 5 (Scheme 2). 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 1H NMR) to yield 6; superhydride gave better yields and reproducibility than the previously reported use of L-Selectride for this reduction. TBS-protection of the newly-formed alcohol proceeded well under classical conditions 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 1H NMR (in favour of 10a according to the Brown’s algorithm and previous results by Armstrong 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 OsO4-catalysed dihydroxylation and subsequent oxidative diol cleavage by NaIO4. 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. 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

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 1H NMR and (2) both 14a and 14b proved to be the 1,3-syn acetonides according to the Rychnovsky’s rules, with 13C 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 C13–C25 segment. Lactone 14a was reduced in the presence of an excess of LiAlH4. 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, which appeared to be efficient in our case. Indeed, after addition of 16 to a DMSO/oxalyl chloride solution in CH2Cl2 at −78 °C, we observed that stirring the reaction mixture for 1 h at −35 °C before addition of Et3N 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; 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. For coupling of the two key intermediates 3 and 4, we decided to use the method developed by Fukayama (CuI, PdCl2(dppf), P-(2-furyl)), in a DMF/Et3N (5:1) mixture at 50 °C. As already reported by us and Kuwahara in his total synthesis of pteridic acids A and B, 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.
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, and later elegantly used by Forsyth in a number of total syntheses. In his 2009 preparation of the C_{13}-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. We also applied these conditions for the preparation of the C_{13}-C_{15} fragment with an acceptable yield. 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$_3$CN–CH$_2$Cl$_2$, TBAF in THF, PPTS in CH$_2$Cl$_2$, (+)-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$_2$Cl$_2$–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 spiroketalts, 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-ludidine in CH$_2$Cl$_2$, 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 spiroketalts 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
then stereoselectively reduced with L-Selectride\(^\text{ac}\) 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\(_2\)O and Et\(_3\)N in CH\(_2\)Cl\(_2\), 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, spiroketalts 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\(_2\)Cl\(_2\) 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\(_3\)N and DMSO by distillation over CaH\(_2\) and storage over 4 Å molecular sieves. Oxaly chloride
was freshly distilled prior to use. CuI was purified using a standard method. 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 1H NMR and 13C NMR spectra were recorded in CDCl3 (1H 399.98 MHz; 13C 100.59 MHz) spectrometer. The chemical shifts are reported in ppm relative to CHCl3 (δ 7.26) for 1H NMR and (δ 77.16) for 13C NMR. Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Coupling constants, J, are reported in Hertz. Melting points are uncorrected.

(4R,5S)-5-((S)-3-benzoylxy)-1-methoxypropyl)-4-hydroxy-3,3-dimethylidihydrofuran-2(3H)-one 6. Lactone 5 (3.5 g, 11.42 mmol) was dissolved in THF (50 mL). The solution was cooled to −78 °C and KhBEt3 (1 M in THF, 12.6 mL, 12.6 mmol, 100 mol%) was added. After 1 h 30 min, the reaction was quenched by addition of a saturated aqueous solution of NH4Cl (20 mL). After separation of phases, the mixture was extracted with EtOAc (30 mL). The combined organic layers were dried over MgSO4 and concentrated in vacuo. Purification by flash chromatography (Hex:AcOEt: 80 : 20) afforded compound 6 (2.88 g, 82%) as a colourless oil. Spectral data were in agreement with those previously reported.

(4R,5R)-5-((S)-3-benzoylxy)-1-methoxypropyl)-4-(tert-butyldimethylsilyloxy)-3,3-dimethylidihydrofuran-2(3H)-one 7. Lactone 6 (2 g, 6.5 mmol, 100 mol%) was dissolved in CHCl3 (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 NH4Cl (20 mL). After separation of phases, the aqueous phase was extracted with EtOAc (30 mL). The combined organic layers were dried over MgSO4 and concentrated in vacuo. Purification by flash chromatography (Hex:AcOEt: 70 : 30) afforded compound 7 (2.34 g, 85%), as a colourless oil. Rf: 0.44 (Hex:EtOAc: 80 : 20); Mp: 57.8 °C [α]D20 = −17.4 (c 1, CHCl3); 1H NMR (CDCl3): 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, 3H), 3.79-3.83 (m, 2H), 4.14 (d, J = 5.2 Hz, 1H), 4.43 (t, J = 5.5 Hz, 1H); 13C NMR (CDCl3): 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 (v,max, thin film): 3436, 2954, 2931, 2859, 1777, 1724, 1472, 1390, 1257, 1132, 1098 cm−1; HRMS: calculated for C16H30O5NaSi [M+Na]+: 353.1760, found: 353.1756.

(4R,5R)-4-((tert-butyldimethylsilyloxy)-5-(((S),3R,4R)-3-hydroxy-1-methoxy-4-methylhex-5-yl)-3,3-dimethylidihydrofuran-2(3H)-one 10a and (4R,5R)-4-((tert-butyldimethylsilyloxy)-5-(((S),3R,4S)-3-hydroxy-1-methoxy-4-methylhex-5-en-1-yl)-3,3-dimethylidihydrofuran-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, BF3·OEt2 (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 H2O (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 MgSO4 and concentrated in vacuo. Purification by flash chromatography (Hex:EtOAc: 95:5 to 75:25) afforded the homooaldehyde 10 (0.95 g, 73%) as a 6:1 mixture of diastereomers. Data for major isomer 10a (obtained from the mixture): Rf: 0.44 (Hex:EtOAc: 80:20); 1H NMR (CDCl3): δ 0.09 (s, 3H), 0.10 (s, 3H), 0.93 (s, 9H), 1.06 (d, J = 6.8 Hz, 1H), 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 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); 13C
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The text also includes the synthesis of a diol compound and its characterization by NMR, IR, and HRMS. It mentions the use of NaBH₄ as a reducing agent and the isolation of a diol compound.
as a colourless oil. Rf: 0.53 (Hex/EtOAc: 95:5); [α]D20 = −46.7 (c 1, CHCl3) 1H NMR (CDCl3): 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 (dd, J = 16.9, 10.3, 9.0 Hz, 1H), 9.83 (s, 1H), 13C NMR (CDCl3): 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 (νmax, thin film): 2956, 2937, 2876, 1717, 1458, 1379, 1257, 1201, 1094 cm−1; HRMS: calculated for C15H25O4SiNa2[M+Na]+: 623.4158, found: 623.4139.

(5R,6R)-5-((S)-2-(((4S,5S,6R)-6-((R)-but-3-en-2-yl)2,5-trimethyl-1,3-dioxan-4-yl)-1-methoxymethyl)-3,3,8,8-tetraethyldicyclopenta-2,3,4,7a,8,8a,10,10a,10b,11a-decadiene 3. Alddehyde 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 K2CO3 (0.228 g, 1.65 mmol, 250 mol%) were then successively added. After 4 h, the mixture was filtered and concentrated. The residue was stirred at rt overnight and quenched by addition of a saturated aqueous solution of NaHCO3 (0.5 mL) and H2O (0.5 mL). The mixture was diluted with EtOAc (5 mL) and after separation of phases, the organic phase was washed with EtOAc (10 mL). The combined organic extracts were dried over MgSO4 and concentrated in vacuo. Purification by flash chromatography (Hex/EtOAc: 100:0 to 95:5) afforded two fractions: 17.5, 10.4, 9.0 Hz, 1H); 13CNMR(CDCl3): δ 5.8, 5.9, 7.3, 7.4, 10.1, 12.0, 18.2, 19.3, 19.5, 25.7, 27.0, 30.3, 36.2, 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, 137.9, 133.9, 135.7, 140.1, 190.1; IR (νmax, thin film): 2955, 2936, 2876, 1725, 1459, 1379, 1238, 1095 cm−1; HRMS: calculated for C31H51O4Si2Na[M+Na]+: 1101.6863, found: 1101.6896.

(2S,3R,7S,8R)-2-((S)-2-(((4S,5S,6R)-6-((R)-but-3-en-2-yl)-2,5-trimethyl-1,3-dioxan-4-yl)-1-methoxymethyl)-7-(2-((tert-butylidiphenylsilyloxy)ethyl)-3-hydroxy-4,4,8,8-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) and the mixture was stirred 24 h at rt. The reaction was quenched by addition of a saturated aqueous solution of NaHCO3 (0.5 mL) and H2O (0.5 mL). The mixture was diluted with EtOAc (5 mL) and after separation of phases, the organic phase was washed with MgSO4 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. Rf: 0.44 (Hex/EtOAc: 80:20); [α]D20 = −64.3 (c 1, CHCl3); 1H NMR (CDCl3): δ 0.55 (t, J = 6.5 Hz, 3H), 0.89 (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, 2H), 2.56 (d, J = 14.8 Hz, 1H), 2.88 (d, J = 10.3, 2.1 Hz, 1H), 2.89 (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 (dd, J = 9.0, 4.0 Hz, 1H), 4.13 (dd, J = 9.0, 8.1 Hz, 1H), 4.90-5.01 (m, 2H), 5.81 (dd, J = 17.2, 10.2, 9.1 Hz, 1H), 7.36-7.45 (m, 1H), 6.73-7.66 (m, 4H), 13C NMR (CDCl3): 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, 132.9, 133.7, 135.6, 139.7, 210.0; IR (νmax, thin film): 3469, 2959, 2930, 2887, 1720, 1472, 1462, 1428, 1379, 1203, 1111 cm−1; HRMS: calculated for C31H29O6Si4Na2[M+H]+: 737.4449, found: 737.4445.

(2R,3R,7S,8R)-2-((S)-2-(((4S,5S,6R)-6-((R)-but-3-en-2-yl)-2,5-trimethyl-1,3-dioxan-4-yl)-1-methoxymethyl)-7-(2-((tert-butylidiphenylsilyloxy)ethyl)-4,4,8,8-trimethyl-1,6-dioxaspiro[4.5]decan-9-one 20. To a solution of ynone 2 (25.4 mg, 23.5 µmol, 100 mol%) in CH2Cl2 (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·H2O (1 mg, 5.2 µmol, 20 mol%) was added. After 4 h, the mixture was filtered and concentrated. The residue was dissolved in CH2Cl2 (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 NH4Cl (2 mL). After separation of phases, the aqueous phase was extracted with CH2Cl2 (5 mL). The combined organic extracts were dried over MgSO4 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. Rf: 0.65 (Hex/EtOAc: 80:20); [α]D20 = -47.7 (c 1, CHCl3). 1H NMR (CDCl3): 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); 13C NMR (CDCl3): 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, 66.7, 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 (νmax, thin film): 2958, 2929, 2857, 1723, 1471, 1463, 1379, 1260, 1202, 1112 cm-1; HRMS: calculated for C49H78O8NaSi2 [M+Na]+: 873.5133, found: 873.5140.

Notes and references


