First Construction of a Saricandin Analog Corresponding to Papulacandin D

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Abstract: The first total synthesis of a saricandin analog corresponding to papulacandin D has been achieved via a highly convergent synthetic strategy. A readily accessible chiral building block **3** was designed and prepared in large scale via an enantioselective reduction with pinanyl-9-BBN. The adaptability of compound **3** toward structural modifications and the highly convergent nature of the approach is illustrated in the construction of the side chain present in saricandin by Pd-catalyzed cross-coupling of **2** and **3** and sequences that include triple bond reduction of fragment C(5–16) and generation of the double bond (C4-C5) using Horner-Emmons reaction. The assembly of the spirocyclic monoglycoside with saricandin side chain is described. A practical technique for isolating the final product **1** after deprotection with TBAF is discussed. Compound **1** was evaluated for its antifungal activity in enzyme assay and cell based assays. However, in contrast the activity reported by Traxler for papulacandin D, the presence of the galactose moiety together with the short fatty acid in natural saricandin seem to be essential for the antifungal activity.

Key words: Saricandin, papulacandin, antifungal, enatioselective reduction

In 1977, Traxler and coworkers reported the isolation and characterization of a family of antifungal antibiotics named papulacandins A, B, C and D from *Papularia sphaerospema*.[1] The compounds displayed potent *in vitro* activity against *Candida albicans* and various other yeasts and have been shown to inhibit β-1,3-glucan synthase, an enzyme involved in fungal cell wall biosynthesis. However, little or no efficacy has been found in animal models. The papulacandins A, B and C contain a spirocyclic diglycoside and two unsaturated fatty acids, linked as esters to two hydroxyl groups of the diglycosides. Papulacandin D, a monosaccharide relative is the simplest member of the family. The antifungal properties of papulacandin D juxtaposed with lack of access to natural material and the synthetically challenging structural feature make this compound interesting synthetic target.[2] The first total synthesis and full stereochemical assignment of papulacandin D was reported by Barrett and coworkers[3] in 1996. Although there is no evidence for a biosynthetic pathway it is possible that papulacandin D, lacking the galactose residue and the short fatty acid chain (Figure 1), is formed as intermediate in the biosynthesis of papulacandins A, B and C.

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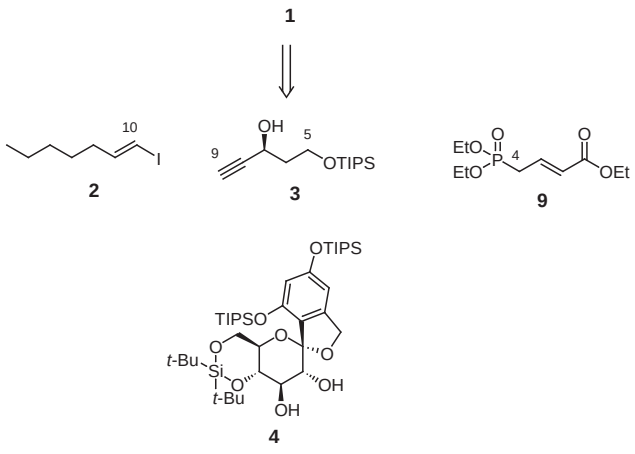
Recently, a new potent antifungal antibiotic produced by the fungal culture, AB 2202W-161, named saricandin was isolated and characterized.[4] Guided by the hypothesis that saricandin may be formed following an analogous biosynthetic pathway to the papulacandins, we postulated that compound 1 (Figure) may be an intermediate in the process.[5] Herein we wish to describe the first total synthesis of compound **1**. By analogy with the relationship between papulacandin D and A, compound **1** would address the question of how the biological profile of saricandin is affected by the absence of the galactose moiety together with the short fatty acid. Furthermore, the significance of such a synthesis is that it may provide a new starting point for the design of new antifungal agents.

Our retrosynthetic analysis of compound **1** is outlined in Scheme 1. We envisioned that disconnection of the ester would lead to the vinyl iodide **2**, the propargylic alcohol **3** along with the Horner-Emmons reagent and the spirocyclic glycoside **4**. Its ready accessibility and its adaptability toward structural modifications for possible structure activity relationship studies dictated the selection of the chiral building block **3**. The highly convergent nature of the approach is illustrated in the construction of the side chain via Pd-catalyzed cross-coupling of **2** and **3** and sequences that include triple bond reduction of fragment C(5–16) and generation of the double bond (C4-C5) via Horner-Emmons reaction.



Scheme 1

The asymmetric synthesis of the chiral building block **3** begins with the protection of propane-1,3-diol as the

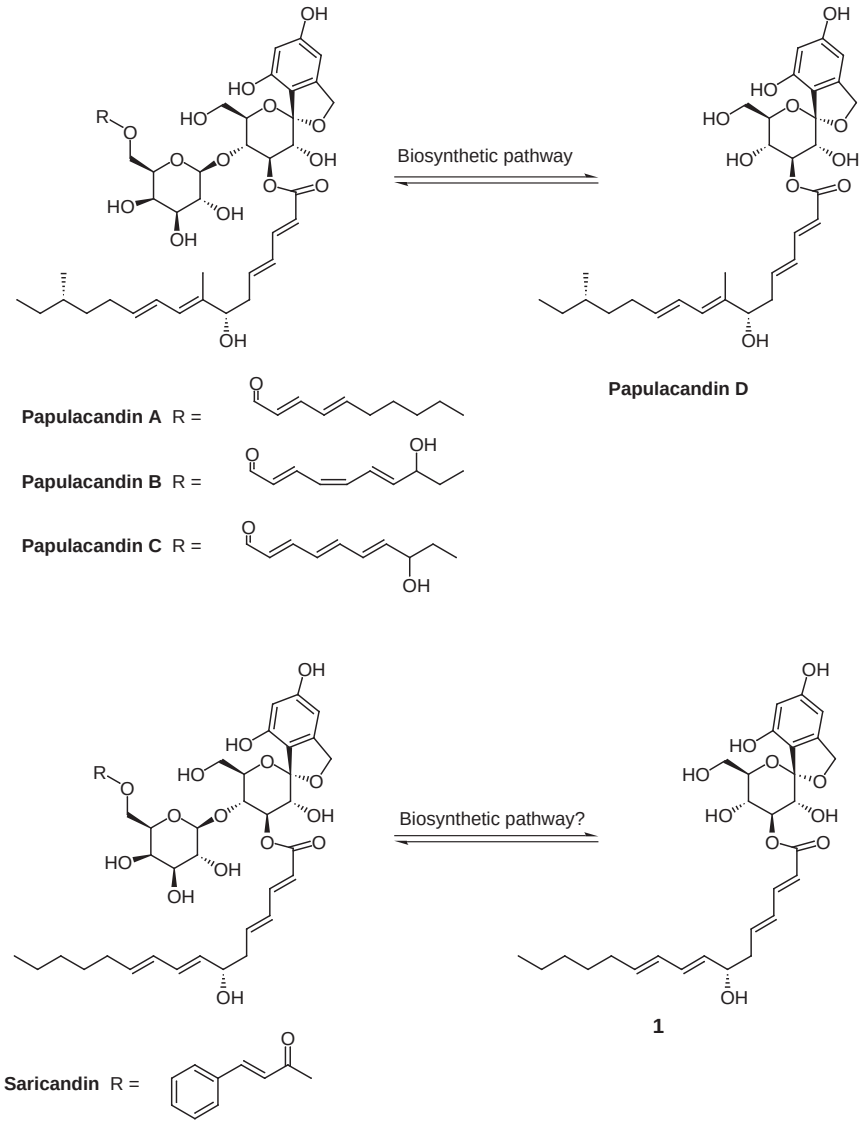
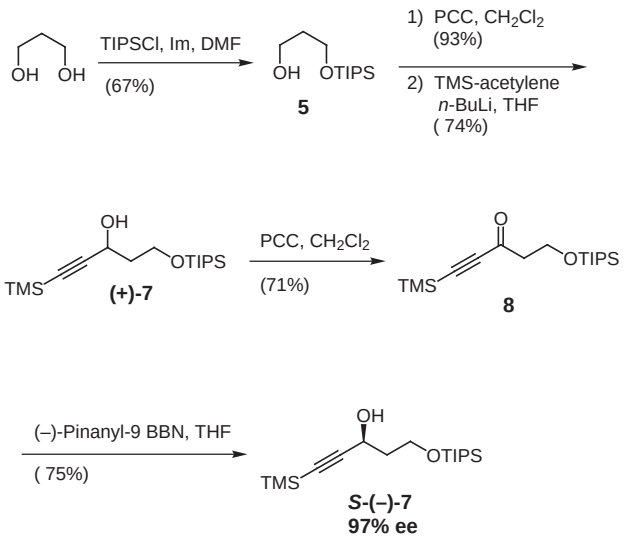


Figure Structures of papulacandin A-D, Saricandin and the related compound **1**

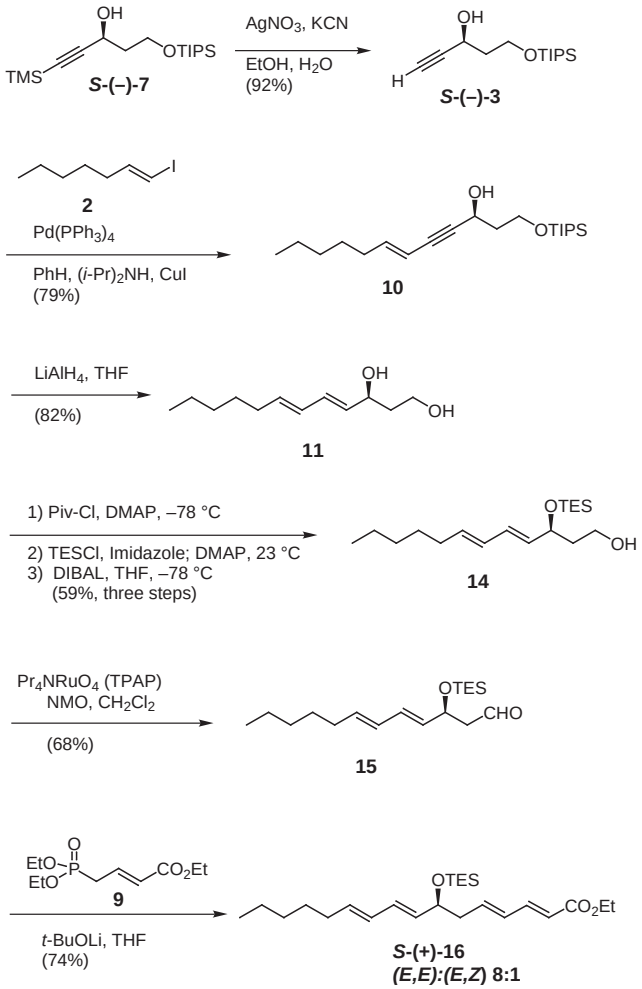
mono-TIPS ether **5**. Subsequent oxidation with PCC followed by condensation of the resulting aldehyde **6** (see experimental) with lithio(trimethylsilyl) acetylene furnished the racemic **7**[6] in 72% yield. Oxidation of the secondary alcohol using PCC produced the α,β-acetylenic ketone **8**, which was then subjected to an asymmetric reduction. Enantioselective reduction with pinanyl-9-BBN using Midland's conditions[7] proved to be very efficient and allowed the preparation of (*S*)-(−)-**7** on large scale in good yield and in 97% ee as determined from the Mosher esters.

The C-silyl group was removed from **7** under conditions that retained the TIPS group protecting the alcohol. Thus treatment of (*S*)-(−)-**7** with $AgNO_3$ in ethanol-water followed by quenching with a solution of KCN afforded **3** in 92% yield. The coupling of the propargylic alcohol **3** with vinyl iodide (*E*)-**2**[8] was performed with catalytic amount of palladium(0) under standard protocol[9] to afford the (*E*)-



Scheme 2

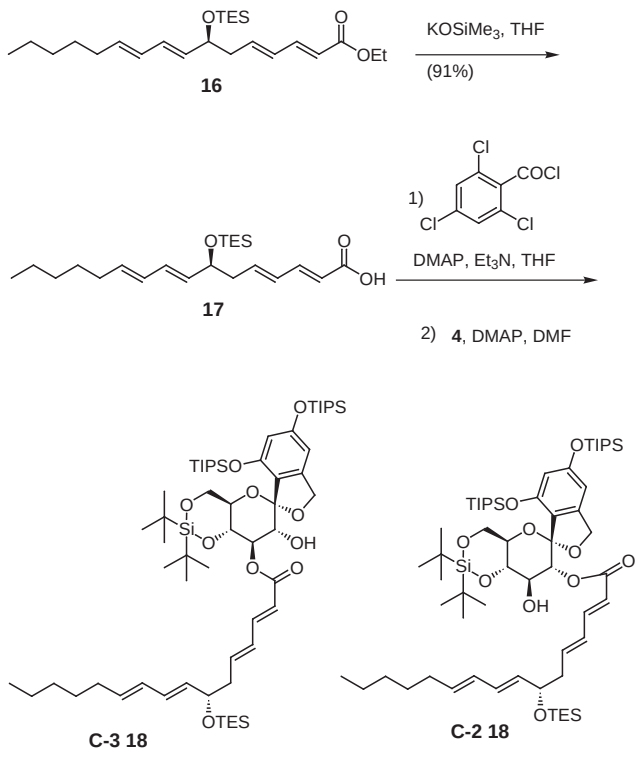
enyne alcohol **10** in 79% yield. When compound **10** was subjected to the conditions for the triple bond reduction with LAH,[10] we were pleased to find that in addition to generating the expected (*E*,*E*)-diene, removal of TIPS ether leading directly to the desired diene **11** in 82% yield also resulted. Similar *O*-silyl bond cleavage affected by LAH has been observed previously and attributed to a hydride transfer from the chelated *O*-aluminum hydride.[11]



Scheme 3

Selective protection of primary alcohol of **11** as its pivaloate at −78 ºC followed by silylation of the secondary alcohol as the silyl ether **13** (see experimental), then reduction of the pivaloate ester furnished the primary alcohol **14** in 59% overall yield. The oxidation of the primary alcohol to aldehyde **15** initially proved problematic. The use of PCC under variety of conditions was found to be sluggish and afforded a very low yield of **15**. Swern oxidation or Dess−Martin[12] oxidation provided mainly the product of elimination. Our efforts to circumvent this problem by applying the combination of Swern oxidation-Wittig condensation procedure reported by Ireland and coworkers[13] for highly unstable aldehyde was likewise unsuccessful. Ultimately, the use of tetrapropylammonium perruthenate (TPAP), introduced by Ley[14] for the oxidation of alcohols proved successful. Thus, treatment of the alcohol **14** with catalytic amount of TPAP in the presence of NMO furnished smoothly the aldehyde **15** in 68% yield. The reaction was performed on small and large scale and the desired aldehyde was isolated in pure form by simple filtration. With the aldehyde **15** in hand, the next step was the generation of the second (*E*,*E*)-diene and completion of the side chain. The aldehyde **15** was submitted to Horner−Emmons reaction using triethyl phosphonocrotonate (**9**). The Horner-Emmons reaction was studied using LiHMDS, KHMDS and NaH. The best result with regard to the stereoselectivity and the yield of the reaction was achieved using the *t*-BuOLi, conditions described recently by Posner. ^{1}H NMR analysis of the crude reaction mixture showed an 8:1 mixture of *E*,*E*- and *E*,*Z*-isomers. A simple column chromatography afforded the desired isomer (*S*)-(+)-**16** in 74% yield.

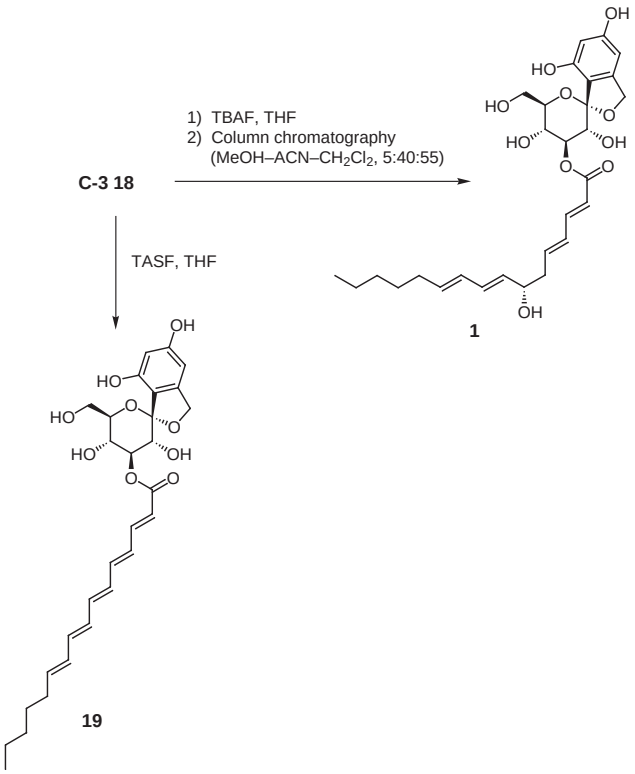
For the synthesis of the tricyclic spiroketal nucleus **4** we used reaction sequences similar to that described by Barrett[3] for the synthesis of papulacandin D. The process involved a condensation of aryllithium reagent with protected gluconolactone and subsequent acid-catalyzed spirocyclization.[15]



Scheme 4

Next, the unsaturated ester **16** was smoothly dealkylated to the corresponding acid using potassium trimethylsilanolate. The acid was then reacted with 2,4,6-trichlorobenzoyl chloride in the presence of DMAP. The resulting mixed anhydride was treated with the spiroketal

diol **4** in the presence of DMAP in DMF to afford a 3:1 mixture of the C-3 and C-2 esters. After separation and purification by column chromatography the desired C-3 ester **18** was isolated in 31% yield.



Scheme 5

The final deprotection step was next addressed. When using TBAF desilylation, Barrett et al.[3] reported difficulties separating tetraalkylammonium salts from papulacandin D. The authors then resolved to use tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF). In our hands the reaction of compound **18** with TASF afforded mainly pentaene **19** derived from elimination. We reasoned that TBAF could be employed if we could find the correct conditions for chromatographic separation of the product from the tetrabutylammonium salts. Thus after evaluating a variety of solvents we were pleased to find that column chromatography on silica gel under gravity using a mixture of 5:40:55 of MeOH-MeCN-CH_2Cl_2 furnished the final compound **1** in its pure form in 41% yield.[16]

Compound **1** was evaluated for its antifungal activity in enzyme assay and cell based assays. Unfortunately, no significant antifungal activity was found. This complete loss of antifungal activity is surprising and seems to indicate that the galactose moiety together with the short fatty acid in saricandin is essential for activity. This is in contrast to the observation in the papulacandin. This finding is now under further investigation in our laboratory.

In summary, we have described in this paper the first total synthesis of an analog of Saricandin corresponding to papulacandin D. We have demonstrated that in contrast to the papulacandin D originally isolated and tested by Traxler and found to be active, the presence of the galactose moiety together with the short fatty acid in natural saricandin are essential for the antifungal activity. The ready accessibility of the chiral building block used in this synthesis along with its adaptability toward structural modifications and the highly convergent nature of the approach promised its use in structure activity relationship studies.

All reagents were purchased from Aldrich and used without further purification. Solvents were purified by distillation: CH_2Cl_2 (CaH_2, N_2), THF and Et_2O (Na, benzophenone, N_2), CCl_4 ($CaCl_2$), benzene (Na, benzophenone, N_2), *i*-Pr_2NH (CaH_2, N_2) and DMF (24 h over 4 Å molecular sieves). Column chromatography was carried out on flash silica gel (Merck 230–400 mesh). TLC analysis was conducted on silica gel plates Whatman. ^1H and ^{13}C spectra were recorded on a 200 MHz Bruker AC-200P or a 300 MHz Bruker AMX, with CD_3OD or $CDCl_3$ as solvents (without internal reference). ^1H NMR data were assigned by irradiation experiments. ^{13}C NMR data were assigned by DEPT experiments. Mass spectra were recorded on VG-Autospec mass spectrometer. In the case of the FAB technique *m*-NBA was the matrix for low resolution and PEG for high resolution (HRMS). Optical rotations were measured with a Perkin Elmer 343 polarimeter.

(*E*)-1-Iodohept-1-ene (2)

A flame-dried 500 mL round-bottom flask equipped with a reflux condenser was purged with N_2. Hept-1-yne (19.23 g, 200 mmol) and anhyd pentane (40 mL) were introduced via syringe, then DIBAL-H (1 M in toluene, 200 mL) was added dropwise via cannula very slowly (1 h). After the addition was completed, the solution was heated at 100 °C for 3 h. The solvents were removed after cooling to r.t. and anhyd THF (80 mL) was added. The mixture was cooled to −50 °C and I_2 (50.76 g, 200 mmol) dissolved in anhyd THF (80 mL) was added dropwise under N_2. The reaction mixture turned brown and was allowed to warm to r.t. (outside the bath), then hydrolyzed very slowly with H_2SO_4 (10%, 160 mL) in an ice-bath. This mixture was poured into another mixture of H_2SO_4 (160 mL)-ice, and extracted with pentane (2 × 200 mL). The combined organic layers were washed with aq sat. $Na_2S_2O_3$ solution (50 mL), aq sat. $NaHCO_3$ solution and dried ($MgSO_4$). Solvents were removed and the product was distilled under reduced pressure (70 °C/8 Torr) in the presence of copper to give 24.7 g (5%) of a colorless liquid.[8]

^1H NMR (200 MHz, $CDCl_3$): δ = 6.51 (dt, 1 H, $J_{1,2}$ = 14.3 Hz, $J_{2,3}$ = 7.2 Hz, H-2), 5.95 (dt, 1 H, $J_{1,2}$ = 14.3 Hz, $J_{2,3}$ = 1.4 Hz, H-1), 2.04 (m, 2 H, H-3), 1.28 (m, 6 H, H-4,5,6), 1.28 (t, 3 H, *J* = 3.7, H-7).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 146.8 (C-2), 74.3 (C-1), 36.0 (CH_2), 31.1 (CH_2), 28.0 (CH_2), 22.4 (CH_2), 14.0 (CH_3).

3-[(Triisopropylsilyl)oxy]propan-1-ol (5)

A mixture of propane-1,3-diol (42.77 g, 0.562 mol), TIPSCl (54.09 g, 0.281 mol), imidazole (85.82 g, 0.70 mol) in anhyd DMF (90 mL) was stirred under N_2 for 24 h at r.t. Et_2O (600 mL) and aq sat. NH_4Cl solution (600 mL) were added. The layers were separated and the organic layer was washed with aq sat. NH_4Cl solution (3 × 300 mL) and brine (600 mL), dried ($MgSO_4$) and evaporated to give an oil. The residue was purified by distillation (65–75 °C/0.1–0.2 Torr) to give 43.6 g (67%) of **5**.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.92 (t, 2 H, *J* = 5.5, H-3), 3.87–3.79 (m, 2 H, H-1), 2.84–2.76 (m, 1 H, OH), 1.84–1.74 (m, 2 H, H-2), 1.23–1.05 [m, 21 H, $(CH_3)_2CHSi$).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 63.7 (CH_2OH), 62.8 (CH_2OTIPS), 34.1 (CH_2), 17.9 [$(CH_3)_2CHSi$], 11.8 [$(CH_3)_2CHSi$].

MS (EI$^+$): *m/z* (%) = 189.2 ($M^+ - C_3H_7$, 39.5), 157.2 (23.6), 131.1 (73.7), 119.1 (100.0), 103.1 (65), 75.0 (73.7).

Anal. calcd for $C_{12}H_{28}O_2Si$: C, 62.01; H, 12.14 ; found: C, 61.79; H, 12.01.

(*R,S*)-3-Hydroxy-5-[(triisopropylsilyl)oxy]-1-trimethylsilylpent-1-yne [(±)-7]

Step 1, 3-[(Triisopropylsilyl)oxy]propanal (**6**): A mixture of alcohol **5** (23.2 g, 0.01 mol) and PCC (32.3 g, 150 mmol) in anhyd CH_2Cl_2 (300 mL) was stirred under N_2 at r.t. for 5 h. The solvent was removed and Et_2O (400 mL) was added. The mixture was stirred for another 15 min and filtered through a pad of silica gel topped with florisil. The residue was washed with Et_2O. Removal of the solvent under vacuo gave 19.9 g (87%) of pure aldehyde **6** as an oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.82 (t, 1 H, *J* = 2.2 Hz, CHO), 4.08 (t, 2 H, *J* = 5.9 Hz, H-3), 2.61 (dt, 2 H, *J* = 5.9, 2.2 Hz, H-2), 1.29–0.98 [m, 21 H, $(CH_3)_2CHSi$].

^{13}C NMR (50 MHz, $CDCl_3$): δ = 202.2 (CHO), 57.8 (CH_2O), 46.7 (CH_2), 17.9 [$(CH_3)_2CHSi$], 11.8 [$(CH_3)_2CHSi$].

MS (EI$^+$): *m/z* (%) = 229 ($M^+ - 1$, 13.6), 187 (15.6), 145 (66.9), 119 (100.0), 103 (45.3,), 75 (55.7).

HRMS (EI$^+$): *m/z* calcd for $C_{12}H_{25}O_2Si$ (M^+- 1) 229.1624, found 229.1632.

Step 2, (*R,S*)-3-Hydroxy-5-[(triisopropylsilyl)oxy]-1-trimethylsilylpent-1-yne [(±)-**7**]: BuLi (1.98 M, 32.8 mL, 64.94 mmol) was added to a solution of trimethylsilylacetylene (9.2 mL, 65.10 mmol) in anhyd THF (50 mL) at 0 °C under N_2. After stirring for 30 min at the same temperature, the anion was transferred slowly via cannula to a solution of the aldehyde **6** (10g, 43.4 mmol) in anhyd THF (100 mL) at −78 °C, under N_2. The mixture was stirred at this temperature for 1 h and allowed to warm at r.t. The solvent was removed, and Et_2O (1 L) and aq sat. NH_4Cl solution (1 L) were added. The layers were separated and the organic layer was washed with aq sat. NH_4Cl solution (1L) and brine (1L), dried ($MgSO_4$) and evaporated to give an oil. The oil was purified by column chromatography (hexane−Et_2O, 9:1) to give 10.5 g (74%) of the desired propargylic alcohol **7** as a yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.64 (dt, 1 H, $J_{H,OH}$ = 5.0, 6.5 Hz, H-3), 4.21–4.13 (m, 1 H, H-5), 3.95–3.89 (m, 1 H, H-5), 3.64 (d, 1 H, *J* = 5.0 Hz, OH), 2.08–1.98 (m, 1 H, H-4), 1.91–1.81 (m, 1 H, H-4), 1.15–1.03 [m, 21 H, $(CH_3)_2CHSi$], 0.17 (s, 9 H, CH_3Si).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 106.3 (C½*C*CHO), 88.9 (Si*C*½C), 62.0 (CHOH), 61.3 (CH_2O), 38.5 (CH_2), 17.8 [$(CH_3)_2CHSi$], 11.6 [$(CH_3)_2CHSi$], -0.2 (CH_3Si).

Anal. cald for $C_{17}H_{36}O_2Si_2$: C, 62.13; H, 11.04 ; found: C, 62.06; H, 11.10.

5-[(Triisopropylsilyl)oxy]-1-trimethylsilylpent-1-yn-3-one (8)

To a solution of the alcohol **7** (26.3 g, 80.03 mmol) in anhyd CH_2Cl_2 (400 mL) was added PCC (25.9 g, 120.15 mmol) in small portions. The mixture was stirred under N_2 at r.t. for 20 h. Solvent was removed and Et_2O (700 mL) was added. The suspension was filtered through florisil and washed with Et_2O (2 × 200 mL). The solvent was removed under vacuo and the resulting oil was purified by column chromatography (hexane−Et_2O, 99:1) to give 18.6 g (71%) of the desired ketone **8**.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.07 (t, 2 H, *J* = 6.3 Hz, CH_2OSi), 2.77 (t, 2 H, *J* = 6.3 Hz, H-4), 1.05 (br s, 21 H, $[CH_3)_2CHSi]$, 0.23 (s, 9 H, CH_3Si).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 186.4 (CO), 101.9 (*C*½CCO), 98.0 (Si*C*½C), 59.0 (CH_2), 48.5 (CH_2), 17.9 [$(CH_3)_2CHSi$], 12.5 [$(CH_3)_2CHSi$], -0.2 (CH_3Si).

Anal. cald for $C_{17}H_{34}O_2Si_2$: C, 62.51; H, 10.49; found: C, 62.43; H, 10.56.

(*S*)-(-)-3-Hydroxy-5-[(triisopropylsilyl)oxy]-1-trimethylsilylpent-1-yne [(-)-7]

An oven-dried 250 mL round bottom-flask, equipped with a magnetic stirring bar, reflux condenser (with a septum) connected to a schlenk line was purged with N_2. 9-BBN (73.5 mL, 36.74 mmol, 0.5 M in THF) was added via cannula (through the condenser) followed by (−)-(α)-pinene (6.51 mL, 40.85 mmol, 9%, 97% ee). The solution was stirred at reflux for 3 h, then cooled to r.t. The ketone **8** (6.0 g, 18.37 mmol) dissolved in anhyd THF (15 mL) was tranferred to the flask via a syringe. The solution turned to yellow. The mixture was stirred at r.t. for 66 h. Acetaldehyde (1.9 mL) was added and mixture was stirred for 15 min. The flask was kept in a water bath and the solvent was removed by stirring under a stream of N_2 for 5 h. The operation was completed by stirring the residue at 40 °C under vacuum for an additional hour. The flask was filled with N_2 and anhyd Et_2O (50 mL) was added. The solution was cooled to 0 °C and ethanolamine (2.5 mL) was added. A white solid was formed. The mixture was stirred for 15 min at 0 °C. The flask was then opened to the air and the mixture was filtered and washed with cold, anhyd Et_2O (25 mL). The organic layer was washed with brine (300 mL), dried ($MgSO_4$) and evaporated. The mixture was purified by column chromatography (hexane−Et_2O, 98:2 to 95:5) to give 4.5 g (75%) of the alcohol as a colorless oil in 97% ee as determined from the Mosher esters; $[\alpha]_D^{23}$ –20.1 (*c* = 1.7, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.64 (dt, 1 H, $J_{H,OH}$ = 4.0, 6.0 Hz, H-3), 4.23–4.12 (m, 1 H, H-5), 4.00–3.87 (m, 1 H, H-5), 3.72 (d, 1 H, *J* = 6.0 Hz, OH), 2.11–1.78 (m, 2 H, H-4), 1.14–1.03 [m, 21 H, $(CH_3)_2CHSi$], 0.15 (s, 9 H, CH_3Si).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 106.1 (C½*C*CO), 89.2 (Si*C*½C), 62.6 (CHOH), 61.7 (CH_2O), 38.2 (CH_2), 17.9 [$(CH_3)_2CHSi$], 11.7 [$(CH_3)_2CHSi$], -0.1 (CH_3Si).

Anal. calcd for $C_{17}H_{36}O_2Si_20.1H_2O$: C, 61.45; H, 10.05; found: C, 61.40; H, 10.17.

The asymmetric reduction was repeated on 16 g scale and the yield was higher (82%).

(*S*)-(−)-3-Hydroxy-5-[(triisopropylsilyl)oxy]pent-1-yne [(−)-3]

The optically active alcohol (−)-**7** (5.87g, 17.86 mmol) was dissolved in EtOH (90 mL). The solution was cooled to 0 °C in an ice-bath. A solution of $AgNO_3$ (12.14 g, 71.44 mmol) in a mixture of EtOH−H_2O (390 mL v/v) was added dropwise through a funnel (45 min). A solid appeared immediately. After addition, the mixture was stirred at the same temperature for 30 min, and then 60 min outside the ice-bath. A solution of KCN (16.2 g, 248.8 mmol) in H_2O (50 mL) was added and the mixture was stirred until the solid had disappeared. More H_2O was added (50 mL) and the mixture was extracted with hexane (3 × 175 mL). The organic layer was washed with H_2O, dried ($MgSO_4$) and evaporated to give 4.18 g (92%) of pure (−)-**3** as an oil in 96% ee as determined from the Mosher esters; $[\alpha]_D^{23}$ –19.2 (*c* = 0.47, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.71–4.61 (m, 1 H, H-3), 4.23–4.12 (m, 1 H, H-5), 3.98–3.88 (m, 1 H, H-5), 3.82 (d, 1 H, *J* = 6.1 Hz, OH), 2.47 (d, 1 H, *J* = 2.2, H-1), 2.13–1.80 (m, 2 H, H-4), 1.17–1.00 [m, 21 H, $(CH_3)_2CHSi$].

^{13}C NMR (50 MHz, $CDCl_3$): δ = 84.4 (C-1), 72.8 (C-2), 62.1 (CHOH), 61.7 (CH_2O), 38.2 (CH_2), 17.9 [(CH_3)$_2$CHSi], 11.7 [(CH_3)$_2$CHSi].

Anal. calcd for $C_{14}H_{28}O_2Si$: C, 65.56; H, 11.00; found: C, 65.10; H, 10.88.

(6*E*,3*S*)-(−)-3-Hydroxy-1-[(triisopropylsilyl)oxy]dodeca-6-en-4-yne [(−)-(10)]

Anhyd *i*-Pr_2NH (4.32 mL, 30.8 mmol) and $Pd(Ph_3P)_4$ (0.42 g) were added sequentially under a N_2 stream to a stirred solution of the vinyl iodide **2** (3.4 g, 15.2 mmol) dissolved in anhyd and degassed benzene (62 mL) in 15 min. The reaction flask was protected against light and the mixture was allowed to stir at r.t. for 45 min and then a degassed solution of the terminal acetylene **3** (3.6 g, 14.04 mmol) in anhyd benzene was added, followed by CuI (0.411 g). The mixture was stirred in the dark at r.t. for 3.5 h. The reaction was transferred to a separating funnel and hexane (400 mL) and aq sat. NH_4Cl solution (400 mL) were added. The layers were separated and aqueous layer was extracted with more hexane (200 mL). The organic layers were combined and washed with aq sat. NH_4Cl solution and brine, dried ($MgSO_4$) and evaporated to give an oil. Purification by column chromatography (hexane−Et_2O, 9:1) gave 3.9 g (79%) of the coupling product **10** as an oil; $[\alpha]_D^{23}$ –19.6 (*c* = 0.48, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.12 (dt, 1 H, *J* = 7.0, 15.9 Hz, H-7), 5.47 (dq, 1 H, *J* = 1.6, 15.9 Hz, H-6), 4.79–4.69 (m, 1 H, H-3), 4.20–4.09 (m, 1 H, H-1), 3.96–3.86 (m, 1 H, H-1), 3.68 (d, 1 H, *J* = 6.0 Hz, OH), 2.16–1.79 (m, 4 H, H-2,8), 1.40–1.20 (m, 6 H, H-9,10,11), 1.35–0.89 [br s, 21 H, (CH_3)$_2$CHSi], 0.87 (t, 3 H, *J* = 6.7 Hz, H-12).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 145.2 (CH=), 108.9 (CH=), 87.9 (*C*½C), 86.3 (C½*C*), 62.6 (CHOH), 61.7 (CH_2O), 38.6 (CH_2), 33.0 (CH_2), 31.2 (CH_2), 28.3 (CH_2), 22.4 (CH_2), 17.9 [(CH_3)$_2$CHSi], 14.0 (*C*H_3CH_2), 11.7 [(CH_3)$_2$*C*HSi].

MS (FAB^+): *m/z* = 353.2 ([MH]$^+$).

HRMS (FAB): *m/z* calcd for $C_{21}H_{41}O_2Si$ (MH^+) 353.2876, found 353.2868.

Anal calcd for $C_{21}H_{40}O_2Si0.4H_2O$: C, 70.09; H, 11.43; found C, 70.16; H, 11.24.

(4*E*,6*E*,3*S*)-(−)-Dodeca-4,6-dien-1,3-diol [(−)-(11)]

$LiAlH_4$ (36.9 mL, 1 M in Et_2O) was added dropwise to a solution of **10** (4.34 g, 12.3 mmol) in anhyd THF (25 mL) at 0 °C under N_2. After addition, the ice-bath was removed and the mixture was stirred at r.t. for 5 h. Et_2O (25 mL) was added and the resulting solution was cooled to 0 °C (ice-bath) before the hydrolysis. H_2O (1.44 mL), NaOH (15%, 1.44 mL) and H_2O (4.32 mL) were added sequentially dropwise with vigorous stirring. The solid was filtered and washed with Et_2O. The solvent was removed and the oil was purified by column chromatography (hexane−EtOAc, 6:4) to afford 1.89 g (78%) of the desired diol **11**; $[\alpha]_D^{23}$ –11.3 (*c* = 0.31, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.23 (ddd, 1 H, $J_{4,5}$ = 15.0, $J_{5,6}$ = 10.3 Hz, $J_{5,3}$ = 1.1 Hz, H-5), 6.02 (ddt, 1 H, $J_{6,7}$ = 14.8, $J_{5,6}$ = 10.2, $J_{6,8}$ = 1.3 Hz, H-6), 5.71 (dt, 1 H, $J_{7,8}$ = 6.8, $J_{6,7}$ = 15.0 Hz, H-7), 5.62 (dd, 1 H, $J_{7,8}$ = 6.7, $J_{3,4}$ = 15.0 Hz, H-4), 4.46–4.36 (m, 1 H, H-3), 3.89–3.79 (m, 2 H, H-1), 2.24 (t, 1 H, *J* = 4.9 Hz, OH), 2.20 (d, 1 H, *J* = 3.4 Hz, OH), 2.12–2.02 (m, 2 H, H-8), 1.84–1.75 (m, 2 H, H-2), 1.45–1.19 (m, 6 H, H-9,10,11), 0.88 (t, 3 H, *J* = 6.6 Hz, H-12).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 135.6 (CH=), 132.7 (CH=), 130.6 (CH=), 129.2 (CH=), 71.6 (CHOH), 60.4 (CH_2OH), 38.5 (CH_2), 32.5 (CH_2), 31.3 (CH_2), 28.8 (CH_2), 22.4 (CH_2), 13.9 (*C*H_3CH_2).

Anal. calcd for $C_{12}H_{22}O_20.75H_2O$: C, 68.04; H, 11.19; found: C, 68.16; H, 10.35.

(4*E*,6*E*,3*S*)-(−)-3-[(Triethylsily)oxy]-1-pivaloyldodeca-4,6-diene [(−)-(13)]

A solution of **11** (1.94 g, 9.78 mmol) and DMAP (1.31g, 10.76 mmol) in anhyd CH_2Cl_2 (35 mL) was cooled to −78 °C. Pivaloyl chloride (1.19 mL, 9.70 mmol) was added via syringe very slowly (15 min). The bath was removed and the mixture was allowed to warm to r.t. for 3.5 h. DMAP (1.79 g, 16.67 mmol), imidazole (1.0 g, 14.67 mmol), and TESCl (2.48 mL, 14.67 mmol) were added sequentially and the mixture was stirred at the same temperature for another 2.5 h. A solution of aq sat. NH_4Cl (100 mL) was added and the mixture was extracted with EtOAc (2 × 150 mL). The organic layer was washed with brine and H_2O, dried ($MgSO_4$) and evaporated to give an oil that was purified by column chromatography (hexane−EtOAc, 95:5) to provide 3.04 g (75%) of compound **13**; $[\alpha]_D^{23}$ –4 (*c* = 0.7, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.15–5.91 (m, 2 H, H-5,6), 5.73–5.45 (m, 2 H, H-4,7), 4.28–4.19 (m, 1 H, H-3), 4.11 (t, 2 H, *J* = 6.3 Hz, H-1), 2.11–2.01 (m, 2 H, H-8), 1.85–1.74 (m, 2 H, H-2), 1.45–1.31 (m, 6 H, H-9,10,11), 1.19 (s, 9 H, *t*-C_4H_9), 0.94 (t, 9 H, *J* = 7.4 Hz, C*H*$_3$CH$_2$Si), 0.88 (t, 3 H, *J* = 6.8 Hz, H-12), 0.51 (m, 6 H, CH_3C*H*$_2$Si).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 178.3 (CO), 135.1 (CH=), 133.2 (CH=), 130.3 (CH=), 129.3 (CH=), 70.1 (CHOH), 61.0 (CH_2O), 38.6 [*C*(CH_3)$_3$], 37.3 (CH_2), 32.5 (CH_2), 31.3 (CH_2), 28.8 (CH_2), 27.1 [C(*C*H_3)$_3$], 22.5 (CH_2), 14.0 (*C*H_3CH_2), 6.7 (*C*H_3CH_2Si), 4.8 (CH_3*C*H_2Si).

MS (EI^+): *m/z* (%) = 396.3 (M^+, 0.8), 295.3 (11.3), 294.3 (35.2), 281.2 (17.8), 267.2 (37.4), 265.2 (19.8), 224.2 (27.7), 223.2 91.6), 57.1 (100.0).

Anal. calcd for $C_{23}H_{44}O_3Si$: C, 69.64; H, 11.18; found: C, 69.54; H, 11.02.

(4*E*,6*E*,3*S*)-(−)-3-[(Triethylsily)oxy]-1-hydroxydodeca-4,6-diene [(−)-14]

A stirred solution of the ester **13** (1.6 g, 4.03 mmol) in anhyd THF (25 mL) under N_2 was cooled to −78 °C. A solution of DIBAL (14.12 mL, 1 M in hexane) was added dropwise (30 min). The mixture was stirred for 2 h at the same temperature then quenched with MeOH (0.5 mL) and transferred to a decanting funnel. A saturated solution of sodium tartrate (150 mL) and EtOAc (600 mL) was added. After vigorous shaking the layers was separated and the organic layer was washed with more sodium tartrate, dried ($MgSO_4$) and evaporated to give an oil. The oil was purified by column chromatography (hexane−Et_2O, 97:3 to 90:10) to give 0.945 g (75%) of **14**; $[\alpha]_D^{23}$ –27 (*c* = 0.2, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.19–5.93 (m, 2 H, H-5,6), 5.68 (dt, 1 H, $J_{7,8}$ = 6.8, $J_{6,7}$ = 14.6 Hz, H-7), 5.56 (dd, 1 H, $J_{3,4}$ = 6.8, $J_{4,5}$ = 14.6 Hz, H-4), 4.47–4.38 (m, 1 H, H-3), 3.89–3.64 (m, 2 H, H-1), 2.66 (t, 1 H, *J* = 5.3 Hz, OH), 2.12–2.02 (m, 2 H, H-8), 1.90–1.66 (m, 2 H, H-2), 1.46–1.24 (m, 6 H, H-9,10,11), 1.00–0.91 (m, 9 H, C*H*$_3$CH$_2$Si), 0.88 (t, 3 H, *J* = 6.8 Hz, H-12), 0.66–0.54 (m, 6 H, CH_3C*H*$_2$Si).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 135.4 (CH=), 132.8 (CH=), 130.4 (CH=), 129.2 (CH=), 73.2 (CHO), 60.5 (CH_2OH), 39.6 (CH_2), 32.6 (CH_2), 31.4 (CH_2), 28.8 (CH_2), 22.5 (CH_2), 14.0 (*C*H_3CH_2), 6.7 (*C*H_3CH_2Si), 4.8 (CH_3*C*H_2Si).

Anal. calcd for $C_{18}H_{36}O_2Si$: C, 69.17; H, 11.61; found: C, 69.26; H, 11.57.

(4*E*,6*E*,3*S*)-(−)-3-[(Triethylsily)oxy]dodeca-4,6-dienal [(−)-15]

TPAP (5.1 mg, 0.0145 mmol, 5%) was added in one portion to a stirred mixture of the alcohol **14** (0.09 g, 0.29 mmol), NMO (0.051 g, 0.435 mmol) and freshly activated powered molecular sieves (150 mg) in anhyd CH_2Cl_2 (1.5 mL) under N_2. After 30 min, more CH_2Cl_2 was added and filtered trough a florisil-Celite pad. This pad

was washed with EtOAc (25 mL). Solvents were removed and the residue was purified by column chromatography (hexane-Et_2O, 95:5) to give 28 mg (76%) of **15**; $[\alpha]_D^{23}$ –19.1 (*c* = 1.15, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.77 (t, 1 H, *J* = 2.3 Hz, CHO), 6.17 (ddd,, 1 H, $J_{3,5}$ = 0.9, $J_{4,5}$ = 14.9, $J_{5,6}$ = 10.2 Hz, H-5), 6.00 (ddt, 1 H, $J_{6,8}$ = 1.2, $J_{5,6}$ = 10.3, $J_{6,7}$ = 14.7 Hz, H-6), 5.82 (dt, 1 H, $J_{7,8}$ = 7.3, $J_{6,7}$ = 14.7 Hz, H-7), 5.56 (dd, 1 H, $J_{3,4}$ = 6.7, $J_{4,5}$ = 14.9 Hz, H-4), 4.72–4.62 (m, 1 H, H-3), 2.70–2.45 (m, 2 H, H-2), 2.12–2.02 (m, 2 H, H-8), 1.54–1.23 (m, 6 H, H-9,10,11), 0.97–0.91 (m, 9 H, C*H*$_3$CH$_2$Si), 0.88 (t, 3 H, *J* = 6.8 Hz, H-12), 0.64–0.52 (m, 6 H, CH$_3$C*H*$_2$Si).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 201.8 (CHO), 136.1 (CH=), 132.0 (CH=), 130.7 (CH=), 129.0 (CH=), 68.9 (CHO), 51.7 (*C*H$_2$CHO), 32.6 (CH$_2$), 31.4 (CH$_2$), 28.8 (CH$_2$), 22.5 (CH$_2$), 14.0 (*C*H$_3$CH$_2$), 6.7 (*C*H$_3$CH$_2$Si), 4.8 (CH$_3$*C*H$_2$Si).

MS (FAB$^+$): *m*/*z* = 310.3 (M$^+$), 281.2 (M$^+$ – CHO).

Anal. calcd for $C_{18}H_{34}O_2Si$: C, 69.61; H, 11.03; found: C,69.27; H, 10.83.

Ethyl (2*E*,4*E*,8*E*,10*E*,7*S*)-(+)-7-[(Triethylsily)oxy]hexadeca-2,4,8,10-tetraenoate [(+)-16]

LiOBu-*t* (0.35 mmol, 0.35 mL, 1 M in THF) was added to a cooled (−78 °C) solution of triethyl phosphonocrotonate (**9**; 0.11 mL, 0.48 mmol) under N_2. The dry ice bath was removed and the brown solution was stirred for 15 min, then recooled to −78 °C. The solution was transferred via cannula to a cooled (−78 °C) solution, under N_2, of aldehyde **15** (50 mg, 0.16 mmol) in anhyd THF (3 mL). The resulting mixture was stirred at the same temperature for 30 min. The dry ice-bath was replaced by an ice-bath and the solution was stirred for another 2 h. Et_2O (40 mL) and aq sat. NH_4Cl solution−H_2O (v/v, 20 mL) were added. The layers were separated and the organic layer was washed with more H_2O, dried (Na_2SO_4) and evaporated to give a yellow oil. Purification by column chromatography (hexane−Et_2O, 95:5) gave 48 mg (74%) of **16**; $[\alpha]_D^{23}$ +6.1 (*c* = 0.64, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.25 (dd, 1 H, $J_{2,3}$ = 15.4, $J_{3,4}$ = 10.0 Hz, H-3), 6.26–5.91 (m, 4 H, H-4,5,9,10), 5.78 (d, 1 H, $J_{2,3}$ = 15.4 Hz, H-2), 5.66 (dt, 1 H, $J_{11,12}$ = 7.1, $J_{10,11}$ = 14.6 Hz, H-11), 5.50 (dd, 1 H, $J_{7\ 8}$ = 6.8, $J_{8\ 9}$ = 14.6 Hz, H-8), 4.26–4.13 (m, 1 H, H-7), 4.20 (q, 2 H, *J* = 7.1 Hz, CH$_3$C*H*$_2$O), 2.40–2.33 (m, 2 H, H-6), 2.12–2.01 (m, 2 H, H-12), 1.45–1.19 (m, 6 H, H-13,14,15), 1.29 (t, 3 H, *J* = 7.1, C*H*$_3$CH$_2$O), 0.97–0.89 (m, 9 H, C*H*$_3$CH$_2$Si), 0.88 (t, 3 H, *J* = 6.8 Hz, H-16), 0.63–0.50 (m, 6 H, C*H*$_3$CH$_2$Si).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.3 (CO), 144.8 (CH=), 140.3 (CH=), 133.5 (CH=), 133.1 (CH=), 130.5 (CH=), 130.4 (CH=), 129.3 (CH=), 119.7 (CH=), 72.6 (CHO), 60.2 (CH$_3$CH$_2$O), 42.2 (CH$_2$), 32.6 (CH$_2$), 31.4 (CH$_2$), 28.9 (CH$_2$), 22.5 (CH$_2$), 14.3 (CH$_3$*C*H$_2$O), 14.0 (*C*H$_3$CH$_2$), 6.8 (*C*H$_3$CH$_2$Si), 4.9 (CH$_3$*C*H$_2$Si).

Anal. calcd for $C_{24}H_{42}O_3Si$: C, 70.88; H, 10.41; found: C, 71.01; H, 10.48.

(2*E*,4*E*,8*E*,10*E*,7*S*)-7-[(Triethylsily)oxy]hexadeca-2,4,8,10-tetraenoic Acid (17)

$KOSiMe_3$ (205 mg, 1.6 mmol) was added in one portion to a solution of ester **16** (65 mg, 0.16 mmol) in anhyd THF (3.5 mL) at r.t. The mixture was stirred at the same temperature for 3.5 h. A solution of citric acid (3.4 mL, 0.327 g in H_2O) was added and the mixture was extracted with EtOAc (3 × 10 mL). The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to give **17** as a yellow solid in 91% yield that was used in the next step without purification. It should be noted that all attempts to purify the acid by column chromatography had led to decomposition. The compound should be used shortly after its preparation because of its instability.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.34 (dd, 1 H, $J_{2,3}$ = 15.4, $J_{3,4}$ = 10.0 Hz, H-3), 6.33–5.92 (m, 4 H, H-4,5,9,10), 5.80 (d, 1 H, $J_{2,3}$ = 15.4 Hz, H-2), 5.67 (dt, 1 H, $J_{11,12}$ = 6.9, $J_{10,11}$ = 14.4, H-11), 5.51 (dd, 1 H, $J_{7,8}$ = 6.8, $J_{8,9}$ = 14.4 Hz, H-8), 4.32–4.14 (m, 1 H, H-7), 2.42–2.36 (m, 2 H, H-6), 2.13–2.01 (m, 2 H, H-12), 1.41–1.25 (m, 6 H, H-13,14,15), 0.97–0.89 (m, 9 H, C*H*$_3$CH$_2$Si), 0.88 (t, 3 H, *J* = 6.8 Hz, H-16), 0.63–0.55 (m, 6 H, CH$_3$C*H*$_2$Si).

1,1-Anhydro-1-*C*-[6-(hydroxymethyl)-2,4-bis[(triisopropylsilyl)oxy]phenyl]-3-*O*-[(2*E*,4*E*,8*E*,10*E*,7*S*)-7-[(triethoxysilyl)oxy]hexadeca-2,4,8,10-tetraenoyl]-4,6-*O*-(di-*tert*-butylsilylene)-b-D-glucopyranose (C-3 18)

A mixture of acid **17** (60 mg, 0.16 mmol), Et_3N (40.1 μL, 0.288 mmol), 2,4,6-trichlorobenzoyl chloride (30.5 μL, 0.195 mmol) and DMAP (8.5 mg), under N_2, in anhyd THF (2 mL) was allowed to react at r.t. for 1 h in dark (aluminum foil). The solvent was removed under high vacuum and the remaining mixed anhydride was dissolved in anhyd DMF (1.7 mL) and transferred via cannula to a mixture of protected spiroketal **4** (0.18 g, 0.24 mmol) and DMAP (48.9 mg) in anhyd DMF (2.1 mL) at r.t. After 5 h, H_2O was added and the mixture was extracted with EtOAc (2 × 25 mL). The organic layer was washed with more H_2O (2 times), brine (2 times), dried ($MgSO_4$) and evaporated to give a 3:1 mixture of the C-3 and C-2 mixture. The mixture was purified by chromatography (hexane-EtOAc, 95:5) to afford 55 mg (31%) of **18** as a white solid; $[\alpha]_D^{23}$ –8.4 (*c* = 0.95, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.28 (dd, 1 H, $J_{3,4}$ = 10.3, $J_{2,3}$ = 15.3 Hz, H-3'), 6.31 (d, 1 H, *J* = 1.8, ArH), 6.23 (d, 1 H, *J* = 1.8, ArH), 6.29–5.97 (m, 4 H, H-4,' 5',9',10'), 5.89 (d, 1 H, *J* = 15.3 Hz, H-2'), 5.66 (dt, $J_{11,12}$ = 6.9, $J_{10,11}$ = 14.5 Hz, H-11'), 5.51 (dd, 1 H, $J_{7,8}$ = 6.8, $J_{8\ 9}$ = 14.5 Hz, H-8'), 5.30 (t, 1 H, *J* = 9.3 Hz, H-3), 5.16 (d, 1 H, *J* = 12.9 Hz, ABsystem), 5.02 (d, 1 H, *J* = 12.9 Hz, ABsystem), 4.40 (t, *J* = 10.3 Hz, H-2), 4.22–3.77 (m, 5 H, sugar + H-7'), 2.40–21.34 (m, 2 H, H-6'), 2.12–1.90 (m, 2 H, H-12'), 1.38–1.18 (m, 6 H, H-13',14',15'), 1.15–0.89 (m, 69 H, *t*-C$_4$H$_9$Si, C*H*$_3$CH$_2$Si, *i*-C$_3$H$_7$), 0.88 (t, 3 H, *J* = 6.4 Hz, H-16'), 0.63–0.50 (m, 6 H, C*H*$_3$CH$_2$Si).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.5, 158.7, 152.1, 144.9, 143.2, 140.1, 135.3, 133.2, 130.6, 130.3, 129.3, 119.8, 119.1, 111.0, 109.5, 104.8, 74.8, 73.3, 72.7, 71.5, 68.7, 66.8, 42.2, 32.6, 31.4, 29.7, 28.9, 27.3, 27.2, 22.7, 22.5, 19.9, 18.0, 17.8, 14.0, 13.2, 12.6, 6.8, 4.9.

Anal. calcd for $C_{61}H_{108}O_{10}Si_4$: C, 65.78; H, 9.77; found: C, 66.03; H, 9.86.

1,1-Anhydro-1-*C*-[6-(hydroxymethyl)-2,4-dihydroxyphenyl]-3-*O*-[hexadeca-2*E*,4*E*,8*E*,10*E*-tetraenoyl]-b-D-glucopyranose (1)

TBAF (115 μL, 0.115 mmol, 1 M in THF) was added in one portion to a solution of the ester **18** (20 mg, 0.018 mmol) in anhyd THF (1 mL) at r.t., under N_2, in dark (aluminum foil). The mixture was stirred at the same temperature for 3.5 h. A drop of MeOH was added and solvents were removed under vacuo. The resulting crude was immediately purified by column chromatography (MeOH−MeCN−CH_2Cl_2, 5:45:55). As it was pointed out in the text after an exhaustive study the mixture of MeOH−MeCN−CH_2Cl_2 was found to be effective for the purification of the final product **1** from the tetrabutylammonium salts. Additionally the column chromatography should be protected against light and performed without pressure. Following these conditions the desired compound **1** was isolated in its pure form; yield: 4 mg (41%); $[\alpha]_D^{23}$ +25 (*c* = 0.1, $CHCl_3$).

^{1}H NMR (200 MHz, CD_3OD): δ = 7.32 (dd, 1 H, $J_{3,4}$ = 10.3, $J_{2,3}$ = 15.3 Hz, H-3'), 6.39–5.85 (m, 5 H, H-2',4',5',9',10'), 6.18 (br s, 2 H, ArH), 5.68 (dt, 1 H, $J_{11,12}$ = 7.0, $J_{10,11}$ = 14.7 Hz, H-11'), 5.56 (dd, 1 H, $J_{7,8}$ = 6.7, $J_{8,9}$ = 14.5 Hz, H-8'), 5.34 (t, 1 H, *J* = 9.6 Hz, H-3), 5.07 (d, 1 H, *J* = 12.6 Hz, ABsystem), 4.98 (d, 1 H, *J* = 12.6 Hz, ABsystem), 4.33 (d, 1 H, *J* = 10.0 Hz, H-2), 4.21–4.11 (m, 1 H, H-7'), 3.92–3.63 (m, 4 H, sugar), 2.40 (m, 2 H, H-6'), 2.12–2.01 (m, 2

H, H-11'), 1.46–1.28 (m, 6 H, H-13',14'; 5'), 0.89 (t, 3 H, J = 6.9 Hz, H-16').

Anal. calcd for $C_{29}H_{38}O_{10}$: C, 63.72; H, 7.01; found: C, 63.60; H, 7.07.

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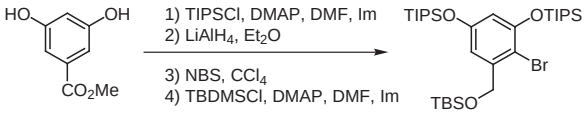
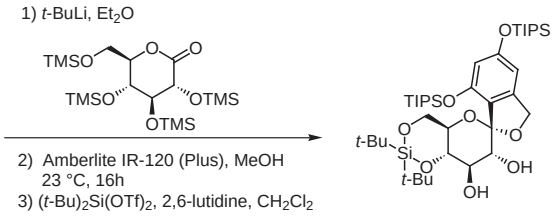
References and Notes

(1) (a) Traxler, P.; Gruner, J.; Auden, J. A. L. *J. Antibiot.* **1977**, *30*, 289. (b) Traxler, P.; Frittz, H.; Richter, W. J. *Helv. Chim. Acta* **1977**, *60*, 578. (c) Traxler, P.; Fritz, H.; Richter, W. J.; Fuhrer, H. *J. Antibiot.* **1980**, *33*, 967.
(2) (a) Danishefsky, S.; Phillips, G.; Ciufolini, M. *Carbohydr. Res.* **1987**, *171*, 317. (b) Friesen, R. W.; Sturino, C. F. *J. Org. Chem.* **1990**, *55*, 5808. (c) Dubois, E.; Beau, J. M. *Carbohydr. Res.* **1992**, *223*, 157. (d) Dubois, E.; Beau, J. M. *Tetrahedron Lett.* **1990**, *31*, 5165. (e) Czernecki, S.; Perlat, M. C. *J. Org. Chem.* **1991**, *56*, 6289. (f) Schmidt, R. R.; Frick, W. *Tetrahedron* **1988**, *44*, 7163. (g) Barrett, A. G. M.; Pena, M.; Willardsen, J. A. *J. Chem. Soc., Chem. Commun.* **1995**, 1147.
(3) Barett, A. G. M.; Pena, M.; Willardsen, J. A. *J. Org. Chem.* **1996**, *61*, 1082.
(4) Chen, R. H. *J. Antibiot.* **1996**, *49*, 596.
(5) The analogous papulacandin D is known as the least abundant of papulacandins family. Compound **1** has not been isolated, probably because of the extreme scarcity of the natural material.
(6) The racemic building block (±)-**7** was initially converted into a 1:1 mixture of **1** and its C-7 epimer following the same sequences employed for the preparation of **1** in enatiomrically pure form.
(7) Midlandess, M. M.; Mc Dowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Org. Chem.* **1980**, *102*, 867.
(8) The (*E*)-iodoheptene was prepared from the correspoding heptyne according to the procedure described by Zweifel and co-workers: Zweifel, G.; Whitney, C. C. *J. Am. Chem. Soc.* **1967**, *89*, 2753.
(9) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.
(10) Rossi, R.; Carpita, A. *Synthesis* **1977**, 561.
(11) Solladie, G.; Hamdouchi, C. *Synlett* **1989**, 66.
(12) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(13) Ireland, R. E.; Wardle, R. B. *J. Org. Chem.* **1987**, *52*, 1780.
(14) For an excellent review, see: Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, P. S. *Synthesis* **1994**, 639.
(15) The reason of this selection is supported by the fact that Barrett's approach is the only known efficient approach that delivers directly the spiroketal nucleus bearing the protecting group of choice for the generation of the correct monoester. On the other hand their study on protecting groups demonstrated that the protecting group of choice for this type of systems are *O*-4",*O*-6"-di-*tert*-butylsilylene, and phenol tris(triisopropylsilyl)





(16) The mixture of MeOH–CH_3CN–CH_2Cl_2 solvents turned out to be very useful and was applied successfully for the purification of other polar compounds from tetrabutylammonium salts and other salts that derived from Wittig or Horner-Emmons reactions.