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Graphical Abstract

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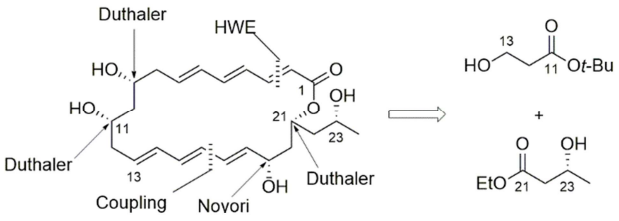

Synthesis of a stereoisomer of wortmannilactone C - Failure and success

Aurélia Dittoo, Damien Brandt, Véronique Bellosta and Janine Cossy∗

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Abstract: A diastereomer of wortmannilactone C was synthesized according to a versatile strategy from *tert*-butyl 3-hydroxypropanoate and ethyl (*R*)-3-hydroxybutanoate, by using versatile organometallic reagents to control four stereogenic centers out of five. The successful strategy consists of the construction of the C13-C17 triene by using a Liebeskind coupling and the construction of the C2-C7 triene by utilizing a Horner-Wadsworth-Emmons reaction to form the macrocycle.

Keywords: Macrolactone; Macrocyclization; Liebeskind coupling; Triene; Total synthesis.

1. Introduction

Using natural products to access leads is desirable, in particular, natural macrocycles that have potent biological activities. In general, as they have complex structures, their total synthesis plays a crucial role to confirm their structure and to develop derivatives that can modulate their biological activity or their pharmacokinetic properties. As we are embarked in a program to determine the structure of natural products[1] as well as in the synthesis of natural and/or biologically active compounds,[2] we became interested in the synthesis of wortmannilactones A-D which were isolated from *Talaromyces wortmanii*, a fungus collected from the soil in Xishuangbanna in the Yunnan province in China (Figure 1).[3] This fungus was then cultured in Erlenmeyer flasks and, after 14 days at 27 °C, the solid culture was extracted with ethyl acetate to furnish, after separation, wortmannilactones A-D in a ratio 71:9:13:7 (Figure 1).[3] We became particularly attracted by wortmannilactone C as this compound presents a cytotoxic activity against a panel of human cancer cell lines.[4] It is worth noting that, if the planar structure of wortmannilactone C was established by NMR (^{1}H, ^{13}C, COSY…), the absolute configuration of the five stereogenic centers at C9, C11, C19, C21 and C23, was not established. Thus, the challenge was to define a convergent and versatile strategy to access wortmannilactone C and/or one of its stereoisomers to progress in the establishment of its structure, and to have access to all the possible diastereomers. Arbitrarily, we decided to attribute the *R*, *S*, *S*, *R*, *R* configurations respectively to the C9, C11, C19, C21 and C23 stereogenic centers.

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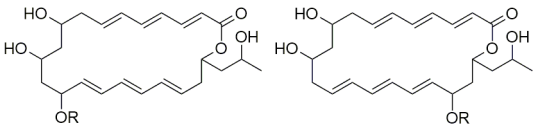


Figure 1. Structure of wortmannilactones A-D.

2. Results and discussion

After a first report towards the synthesis of wortmannilactone C,[5] we would like to report a full account on our efforts to access this natural product. Two convergent strategies have been examined and, in each case, versatile reagents have been utilized to control the stereogenic centers such as the Duthaler allyltitanation[6] of aldehydes and the Noyori reduction of acetylenic ketones.[7] In addition, the formation of the macrocycle was envisaged by using a Stille-type coupling to construct the C16-C17 bond and a Horner-Wadsworth-Emmons (HWE) reaction to form the C2-C3 bond (Figure 2).

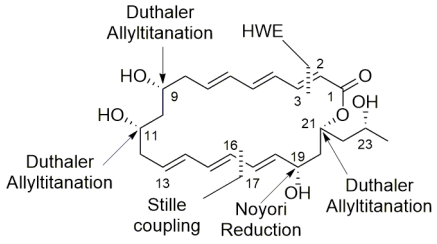
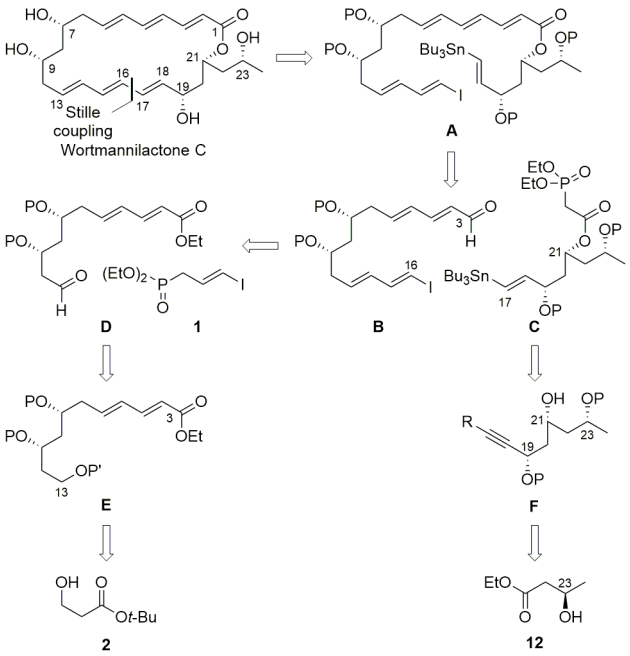


Figure 2. Synthetic strategy.

2.1. Formation of the macrocycle by construction of the C16-C17 bond using a Stille coupling

The construction of the macrocycle was envisaged from **A** using an intramolecular Stille coupling which would allow the construction of the C16-C17 bond and would permit, at the same time, the formation of the C13-C18 triene unit. Compound **A** would be synthesized by utilizing a Horner-Wadsworth-Emmons olefination (HWE) in between phosphonate **C** and the dienic aldehyde **B**, which would be accessible by olefination of aldehyde **D** by iodovinylphosphonate **1**. The precursor of aldehyde **D** would be the protected trihydroxy ester **E**, which could be prepared from *tert*-butyl 3–hydroxypropanoate **2**. By using two successive enantioselective allyltitanations, the C9 and C11 stereogenic centers should be controlled. Compound **C** would be synthesized by esterification of the hydroxyl group at C21 in **F**, which would be synthesized from the commercially available ethyl (*R*)-3-hydroxybutanoate **12**. The control of the stereogenic center at C19 would be realized by using an enantioselective Noyori reduction and the stereogenic center at C21 would be controlled by an enantioselective allyltitanation of an aldehyde. It is worth noting that in the synthesis of wortmannilactone C, only an orthogonal protection of the hydroxyl group at C21 is required relatively to the other

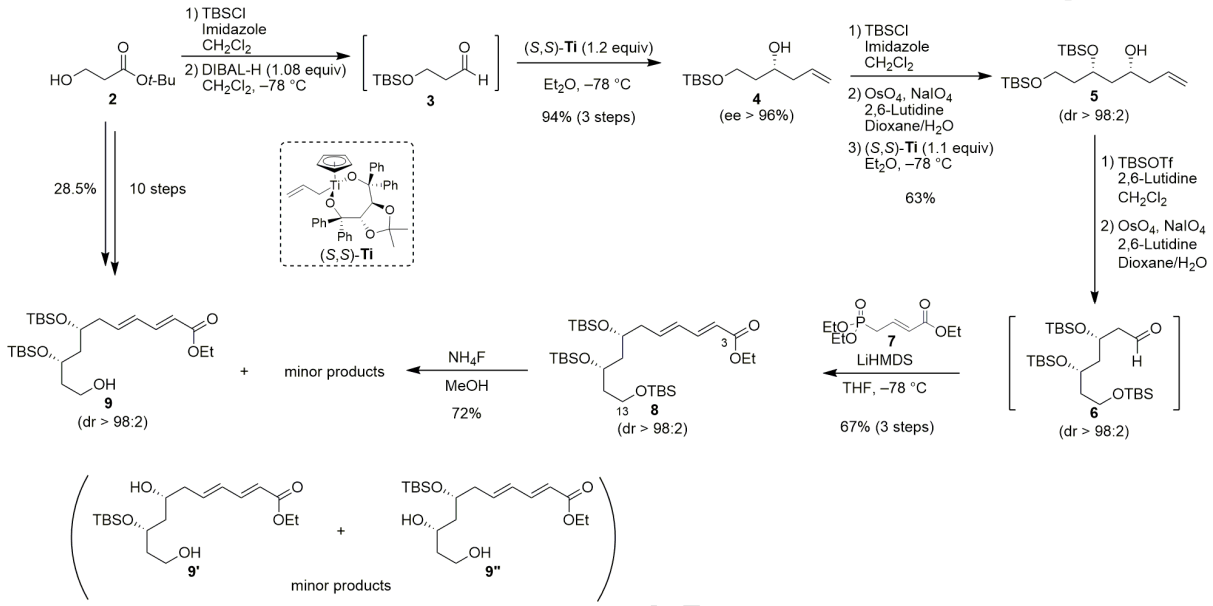
hydroxyl groups, as this hydroxyl has to be involved in an esterification. Thus, we chose to protect all the hydroxyl groups with a TBS group except the hydroxyl at C21 that will be protected by a TES group (Scheme 1).



Scheme 1. Retrosynthetic analysis of wortmannilactone C.

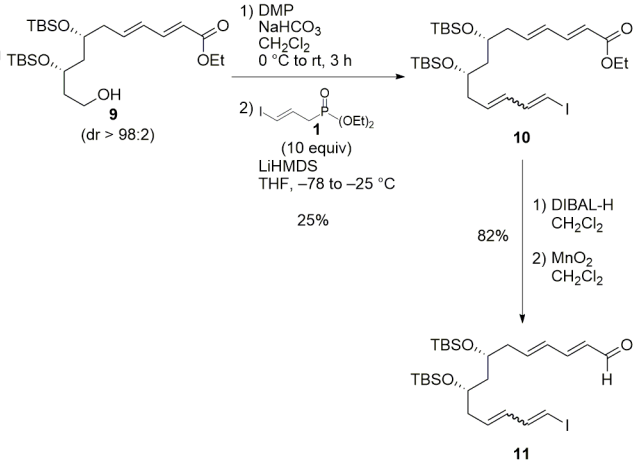
The synthesis of iodovinyl phosphonate **1** was achieved in four steps from the commercially available propynol according to the method developed by Smith *et al*.[8,9] The synthesis of the C3-C13 fragment, precursor of the C3-C16 fragment (compound **B**) was achieved from *tert*-butyl 3-hydroxypropanoate **2**. After protection of the hydroxy group [TBSCl (1.2 equiv), imidazole (2 equiv), CH_2Cl_2, 99%], the resulting protected hydroxyester was reduced by DIBAL-H (1.08 equiv; CH_2Cl_2, –78 °C, 2 h) to the unstable aldehyde **3**, which was directly involved in a highly enantioselective allytitanation using the (*S*,*S*)-**Ti** complex[6] (1.2 equiv; Et_2O, –78 °C, 12 h). Homoallylic alcohol **4** was isolated in 94% yield from **2** with an excellent enantioselectivity (ee > 96%).[10] The transformation of **4** to diol **5** was realized according to a three step sequence. After protection of **4** as a TBS ether and an oxidative cleavage of the olefin [OsO_4 (3 mol %), $NaIO_4$ (4 equiv), 2,6-lutidine (2 equiv), dioxane/H_2O, 3 h][11] followed by an enantioselective allyltitanation of the resulting aldehyde by using the highly face-selective (*S*,*S*)-**Ti** complex (1.2 equiv), the monoprotected *syn*-1,3-diol **5** was isolated in 85% yield with an excellent diastereoselectivity (dr > 98:2). To access the C3-C13 fragment, precursor of aldehyde **B** (fragment C3-C16), the unsaturated monoprotected 1,3-diol **5** was protected [TBSOTf (1.9 equiv), 2,6-lutidine (1.6 equiv), CH_2Cl_2, -78 °C, 2 h] and oxidatively cleaved [OsO_4 (3 mol %), $NaIO_4$ (4 equiv), 2,6-lutidine (2 equiv), dioxane/H_2O, 3 h] to produce the unstable aldehyde **6**. The latter was directly engaged in a HWE reaction with the lithium derivative of the unsaturated phosphonoester **7** leading to the dienic ester **8** [**7** (2 equiv), LiHMDS (1.9 equiv), THF, 2 h, 67% (over 3 steps)]. The selective deprotection of the primary alcohol at C13 was required to access alcohol **9**.

Different conditions were tested such as CSA,[12] PPTS,[13] oxone®,[14] $ZnBr_2$[15] and the best conditions to obtain **9** were *n*-Bu_4NF (10 equiv) in refluxing methanol as **9** was isolated in 72% yield.[16] It is worth noting that traces of compounds **9'** and **9"** were also formed but the bis-deprotected compounds could be separated from **9**. Thus, *tert*-butyl 3-hydroxypropanoate **2** was transformed to the highly functionalized alcohol **9** in 10 steps with an overall yield of 28.5% (Scheme 2).



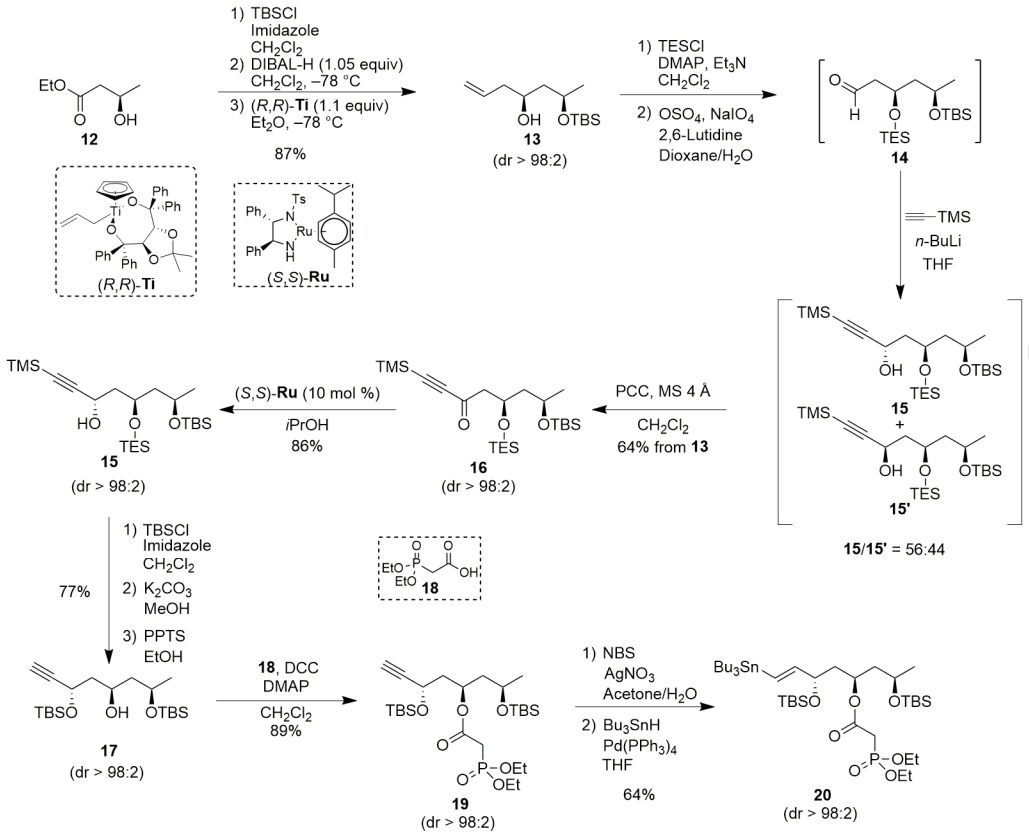
Scheme 2. Synthesis of alcohol **9**.

Having alcohol **9** in hand, this alcohol was oxidized to the corresponding aldehyde [DMP (2 equiv), $NaHCO_3$ (2.5 equiv), CH_2Cl_2], which was immediately treated with the lithium anion of the vinyl iodophosphonate **1**.[8] It is worth noting that if the conversion of the aldehyde was low when treated with 3.5 equiv of the lithium anion of **1**, its conversion was not complete even by utilizing 10 equiv of the lithium anion of **1** and, in addition, the iodo dienic ester **10** was isolated in only 25% yield as a mixture of *Z*- and *E*-isomers. This dienic ester was then transformed to aldehyde **11** after reduction with DIBAL-H and then oxidation by MnO_2 (82%) (Scheme 3).



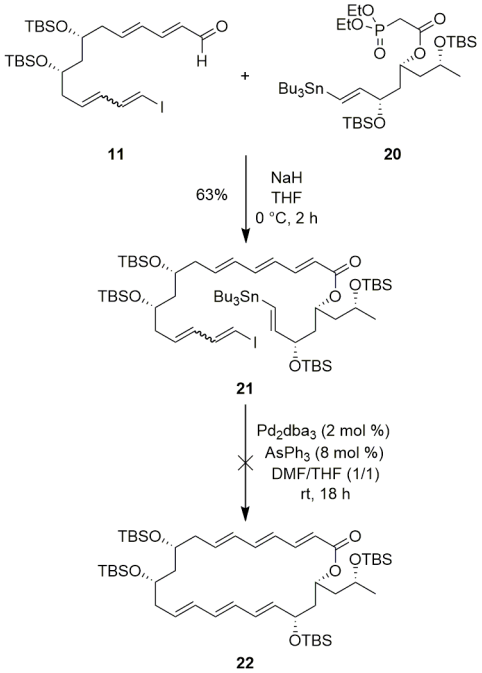
Scheme 3. Synthesis of iododiene **11**.

To transform **11** into a compound of type **A**, precursor of the macrocycle, phosphonate **20** (compound **C**) had to be synthesized (Scheme 4). The synthesis of **20** started with the protection of the commercially available ethyl (*R*)-3-hydroxybutanoate **12** as a TBS silyl ether [TBSCl (1.2 equiv), imidazole (2 equiv), CH_2Cl_2, 0 °C to rt, quant.] followed by a reduction step which produced an aldehyde [DIBAL-H (1.05 equiv), CH_2Cl_2]. After treatment of this aldehyde with the highly face-selective (*R*,*R*)-**Ti** complex (1.1 equiv), the homoallylic alcohol **13** was isolated in 87% yield and with an excellent diastereoselectivity (dr > 98:2).[6] The newly formed hydroxyl group at C21 was orthogonally protected by treatment with TESCl (1.5 equiv) [DMAP (0.1 equiv), Et_3N (2 equiv), CH_2Cl_2, 0 °C to rt] and, the obtained unsaturated protected 1,3-diol was then transformed to aldehyde **14** by oxidative cleavage of the double bond [OsO_4 (3 mol %), $NaIO_4$ (4 equiv), 2,6-lutidine (2 equiv), dioxane/H_2O, 3 h]. As the addition of the lithium derivative of trimethylsilylacetylene was not diastereoselective, **15** and **15'** were obtained in a ratio 56:44. To increase the **15**/**15'** ratio, an oxidation was performed [PCC (1.5 equiv), MS 4 Å, CH_2Cl_2, rt] producing the acetylenic ketone **16** in 64% yield (from **13**) which was reduced with the highly face-selective Noyori ruthenium complex (*S*,*S*)-**Ru** (10 mol %) in *i*PrOH at rt.[7] Thus, by using this oxidation/reduction sequence, **15** (85%) was obtained with an excellent diastereoselectivity (dr > 98:2). To couple **15** with the phosphono-carboxylic acid **18**, the hydroxy group at C19 has to be protected and the hydroxy group at C21 has to be deprotected. In consequence, the hydroxy group at C19 was protected as a TBS ether [TBSCl (2 equiv), imidazole (2.8 equiv), CH_2Cl_2, 0 °C to rt, 92%] and the deprotection of the acetylenic function was realized [K_2CO_3 (1.5 equiv), MeOH, 92%] followed by the deprotection of the hydroxy group at C21 using PPTS (10 mol %) in EtOH. The resulting di-protected triol **17**, obtained in 91% yield, was then treated with the carboxylic phosphonate **18**[17] (1.5 equiv) [DCC (2.25 equiv), DMAP (0.45 equiv), CH_2Cl_2, rt, 24 h][18] to furnish the corresponding phosphonoester **19** (89%). To transform **19** into the vinylstannane **20**, two steps were necessary i.e. a bromination of the acetylenic [NBS (1.2 equiv), $AgNO_3$ (10 mol %), acetone/H_2O] and a stereoselective palladium-catalyzed hydrostannation [$Pd(PPh_3)_4$ (5 mol %), Bu_3SnH (3 equiv), THF, -78 °C to rt, 2 h][19] which furnished the desired vinylstannane **20** with an overall yield of 64% for the two steps[20] (Scheme 4).



Scheme 4. Synthesis of vinylstannane **20**.

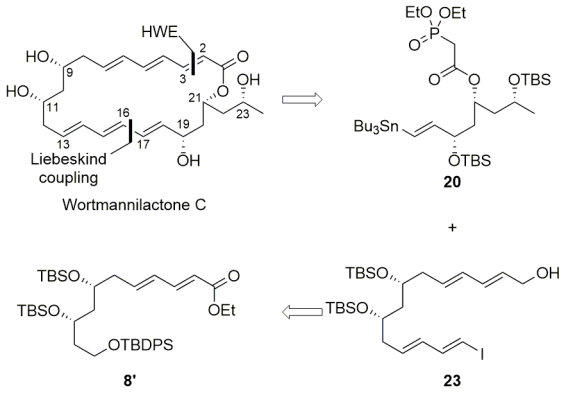
Having compounds **11** and **20** in hand, these two fragments were coupled using a HWE reaction (NaH, THF, 0 °C, 2 h) to produce the precursor of the macrocyclization, compound **21** which was isolated in 63% yield. Unfortunately a Stille coupling using Pd_2dba_3 (2 mol %), $AsPh_3$ (8 mol %) (DMF/THF = 1/1, rt, 18 h) did not lead to the desired macrocycle **22** and only degradation products were observed (Scheme 5).



Scheme 5. First attempt for the macrocyclization.

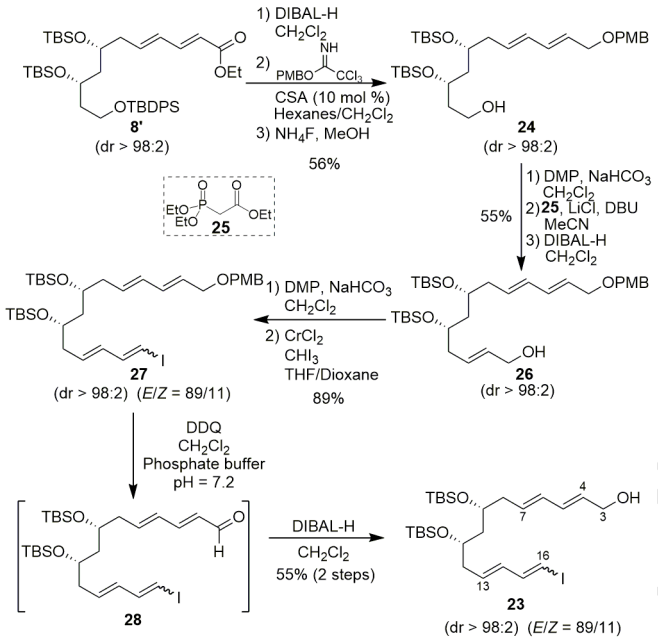
2.2. Formation of the macrocycle by construction of the C2-C3 bond using a HWE reaction

Due to the unsuccessful macrocyclization by forming the C2-C3 bond at first and then the C16-C17 bond, a second strategy with the reversal of the key steps was envisaged. Thus, the formation at first of the C16-C17 bond by a coupling reaction and, then a ring-closure using a HWE to form the C2-C3 bond, were envisaged. At the same time, we decided to modify the construction of the iododiene **23** to improve the stereoselectivity of the dienic moiety. It is worth noting that this new strategy involved intermediate **20** that had already been prepared, and compound **8'** which is similar to **8** and was prepared according to the same strategy from the *tert*-butyl 3-hydroxypropanoate in 10 steps. However, the primary alcohol was protected by a TBDPS group instead of a TBS group in order to facilitate its deprotection.[5] Furthermore, as the Stille coupling failed to form the C16-C17 bond, a Liebeskind coupling was envisaged to construct this bond (Scheme 6).



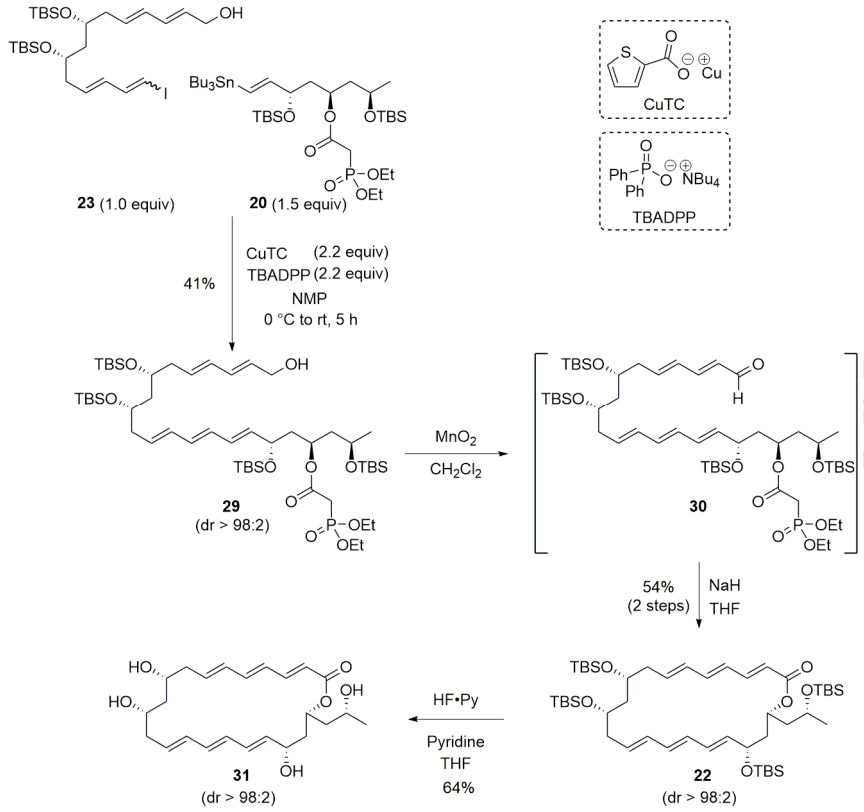
Scheme 6. New retrosynthetic analysis of wortmannilactone C.

The ester group in **8'** was reduced by DIBAL-H (3 equiv) in CH_2Cl_2 and the resulting alcohol was protected as a PMB ether [$PMBOC(NH)CCl_3$ (1.67 equiv), CSA (10 mol %), CH_2Cl_2, rt, 18 h, 90%]. After a selective deprotection of the primary alcohol, protected as a TBDPS ether [NH_4F (15 equiv), MeOH, reflux, 1.5 h], alcohol **24** was isolated and transformed into the allylic alcohol **26** after an oxidation, a HWE olefination with phosphonoester **25** [1.2 equiv; LiCl (1.3 equiv), DBU (1.2 equiv), MeCN, rt, 20 h][21] and a reduction (DIBAL-H, CH_2Cl_2, rt) (55% over the 3 steps). The obtained allylic alcohol **26** was then converted to iododiene **23** in four steps. After oxidation of **26**, the obtained aldehyde was submitted to the Takai conditions [$CrCl_2$ (20 equiv), CHI_3 (2 equiv), THF/dioxane, rt][22] to produce iododiene **27** in 89% yield (*E*/*Z* = 89:11) and after deprotection of the primary hydroxyl group in **27** followed by an oxidation with DDQ, the resulting aldehyde **28** was reduced by DIBAL-H. Thus, iododiene **23** was prepared in 9 steps from the advanced compound **8'** in 15% yield and with a good control of the configuration of the double bonds of diene **23** (Scheme 7).[5]



Scheme 7. Preparation of iododiene **23**.

Alcohol **23** was then involved in a Liebeskind coupling[23] with vinylstannane **20** using copper thiophencarboxylate (CuTC) (2.2 equiv) and tetrabutylammonium diphenylphosphinate (TBADPP) (2.2 equiv) in NMP (0 °C to rt, 5 h) to produce the (*E*,*E*,*E*)-triene **29** in a moderate yield of 41% with a good *E*/*E*/*E* stereoselectivity after purification.[24] To realize the intramolecular HWE reaction, the hydroxyl at C3 was oxidized (MnO_2, CH_2Cl_2, rt, 18 h) to the sensitive aldehyde **30**, which was directly treated with NaH (100 equiv) in THF to produce the macrocyclic lactone **22**, which, after treatment with HF•Py, led to the macrocyclic lactone **31** in 35% yield (from **29**) (Scheme 8). By comparison of the ^{1}H and ^{13}C NMR spectra and the $[\alpha]_D$ of the synthesized compound **31** with those reported for the natural product in the literature,[25] **31** revealed to be a diastereomer of wortmannilactone C. We have to point out that it is difficult to predict the absolute configuration of the stereogenic centers by comparing the ^{1}H and ^{13}C NMR spectra of the synthetic compound with those of the natural product as the stereogenic centers are too remote from each other. In addition, the use of the Kishi's method cannot be applied to the C19-C23 triol portion as the hydroxyl at C21 is embedded in a macrocyclic lactone.[26]



Scheme 8. Fragment coupling and end of the synthesis.

3. Conclusion

The success of the synthesis of one stereoisomer of wortmannilactone C was dependent on the order of construction of the two triene moieties. Triene C13-C18 has to be formed at first, and the macrocyclization has then to be performed, producing the C2-C7 triene.

Even if the natural product wortmannilactone C itself was not obtained, the strategy that we have designed can be used to access all the diastereomers of wortmannilactone C as the reagents involved in the synthesis, such as the allyltitanium complexes and the Noyori ruthenium complexes, are highly face-selective and can be utilized to control the *R* or *S* configuration of the stereogenic centers at will.

4. Experimental part

4.1. General experimental methods

All the reactions were carried out under anhydrous conditions and under argon. Flame-dried glassware was utilized. Infrared (IR) spectra were recorded on a Bruker TENSORTM 27 (IRFT) on an ATR plate, wavenumbers are indicated in cm^{-1}. NMR spectra were recorded on a Bruker Avance-1 400 instrument. ^{1}H NMR spectra were recorded at 400 MHz in $CDCl_3$ or deuterated benzene (C_6D_6) or DMSO-*d6* and data are reported as follows: chemical shift in ppm from tetramethylsilane as an internal standard, multiplicity (s = singlet, d = doublet, t = triplet, q = quadruplet, quint = quintuplet, m = multiplet or overlap of non-equivalent resonances, br = broad), integration. ^{13}C NMR spectra were recorded at 100 MHz in $CDCl_3$ or

deuterated benzene (C_6D_6) or DMSO-*d6* and data are reported as follows: chemical shift in ppm from tetramethylsilane with the solvent as an internal indicator ($CDCl_3$: 77.16 ppm or C_6D_6: 128.06 ppm), multiplicity and coupling constant, with respect to phosphorous. Mass spectra were obtained with a Shimadzu GCMS-QP20105 gas chromatograph-mass spectrometer. High resolution mass spectra (HRMS) were performed by the Groupe de Spectrométrie de Masse de l'Université Pierre et Marie Curie (Paris-France). Optical rotations were measured with a Perkin Elmer model 343 polarimeter with a 1 dm path length. TLC was performed on Merck 60F254 silica gel plates with UV and *p*-anisaldehyde stain visualization. Flash chromatography was performed on silica gel (230-400 mesh). CH_2Cl_2 was distilled from CaH_2, Et_2O and THF were distilled from Na/benzophenone.

*4.2. Synthesis of compound **4***

4.2.1. *tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)propanoate (**2'**): To a solution of *tert*-butyl 3-hydroxypropanoate **2** (3.03 mL, 20.5 mmol, 1.0 equiv) in CH_2Cl_2 (40 mL) at 0 °C was added imidazole (2.79 g, 41.0 mmol, 2.0 equiv) and, after 10 min, *tert*-butyldimethylsilyl chloride (3.71 g, 24.6 mmol, 1.2 equiv) was added. The mixture was slowly warmed up to rt. After 18 h, the reaction mixture was quenched with H_2O (30 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 99:1) to afford silyl ether **2'** (5.28 g, 20.3 mmol, 99%) as a colorless oil. **IR** (neat): 2929, 2857, 1732, 1472, 1392, 1366, 1254, 1156, 1097, 1061, 941 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.85 (t, *J* = 6.4 Hz, 2H), 2.42 (t, *J* = 6.4 Hz, 2H), 1.45 (s, 9H), 0.88 (s, 9H), 0.05 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.2, 80.3, 59.3, 39.3, 28.1 (3C), 25.8 (3C), 18.2, -5.4 (2C); **MS** (EI, 70 eV) *m/z* (abundance): 187 [(M-O*t*-Bu)$^+$, 8], 148 (10), 147 (100), 105 (77), 89 (14), 75 (42), 73 (18), 57 (42); **HRMS**: calculated for $C_{13}H_{28}O_3NaSi$ (M+Na^+): 283.1700. Found: 283.1700.

4.2.2 3-(*tert*-Butyldimethylsilyloxy)-propanal (**3**):[27] To a solution of ester **2'** (4.22 g, 16.2 mmol, 1.0 equiv) in CH_2Cl_2 (90 mL) at –78 °C was added DIBAL-H (17.5 mL, 1 M in toluene, 17.5 mmol, 1.08 equiv) dropwise and the reaction was stirred at –78 °C for 1 h. The reaction was quenched by slow addition of EtOAc (10 mL), poured onto a saturated aqueous solution of Rochelle's salt (90 mL) and the mixture was vigorously stirred for 2 h until the formation of two clear phases. The phases were separated and the aqueous phase was extracted with Et_2O (2 × 100 mL). The combined organic phases were washed with brine (80 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude instable aldehyde **3** which was used in the next step without any further purification. Spectroscopic and physical data matched the ones reported in the literature.[27] **IR** (neat): 2929, 2857, 1715, 1472, 1390, 1254, 1101, 1062, 939 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.79 (t, *J* = 2.1 Hz, 1H), 3.99 (t, *J* = 6.0 Hz, 2H), 2.58 (td, *J* = 6.0 and *J* = 2.3 Hz, 2H), 0.91 (s, 9H), 0.09 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 201.7, 57.4, 46.5, 25.8 (3C), 18.2, -5.5 (2C); **MS** (EI, 70 eV) *m/z* (abundance): 173 [(M-Me)$^+$, 1], 132 (9), 131 [(M-*t*-Bu)$^+$, 76], 117 (8), 103 (5), 102 (10), 101 (100), 75 (40), 73 (10), 59 (30).

4.2.3. (*R*)-1-(*tert*-Butyldimethylsilyloxy)-hex-5-en-3-ol (**4**):[28] To a suspension of cyclopentadienyl[(4*S*,*trans*)-2,2-dimethyl-*α*,*α*,*α'*,*α'*-tetraphenyl-1,3-dioxolane-4,5-dimethanolato-*O*,*O'*]titane (7.00 g, 11.5 mmol, 1.4 equiv) in Et_2O (120 mL) at 0 °C was added allylmagnesium chloride (4.90 mL, 2 M in THF, 9.80 mmol, 1.2 equiv) dropwise. After 2.5 h at 0 °C the red mixture containing (*S*,*S*)-**Ti** was cooled to –78 °C and a solution of the crude aldehyde **3** (8.2 mmol, 1 equiv) in Et_2O (20 mL) was added dropwise via a cannula. The mixture was stirred at –78 °C for 12 h, then quenched by the slow addition of H_2O (60 mL) at –78 °C, and warmed to rt and vigorously stirred for 24 h to precipitate the titanium salts. The white suspension was filtered through a pad of Celite®, the phases were separated and the aqueous phase was extracted with Et_2O (3 × 60 mL). The combined organic phases were washed with brine (60 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The thick yellow residue was stirred with pentane (20 mL) for 1 h to precipitate the (*S*,*S*)-TADDOL. The TADDOL was then filtered and the filtrate was concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/AcOEt = 95:5) to afford homoallylic alcohol **4** [1.80 g, 7.81 mmol, 95% (over two steps), ee > 96%]. Spectroscopic and physical data matched the ones reported in the literature.[28] $[\alpha]_D^{20}$ +8.7 (*c* 2.32, $CHCl_3$) {$[\alpha]_D^{23}$ lit.[28] +9.0 (*c* 0.95, $CHCl_3$)}; **IR** (neat): 3383, 2928, 2857, 1642, 1472, 1433, 1361, 1253, 1082 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.85 (m, 1H), 5.15-5.07 (m, 2H), 3.94-3.86 (m, 2H), 3.81 (m, 1H), 3.37 (br s, 1H, OH), 2.33-2.19 (m, 2H), 1.71-1.64 (m, 2H), 0.90 (s, 9H), 0.08 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 135.0, 117.3, 71.3, 62.6, 42.0, 37.8, 25.9 (3C), 18.1, -5.5, -5.6; **MS** (EI, 70 eV) *m/z* (abundance): 189 (10), 131 (12), 106 (5), 105 (59), 101 (16), 89 (29), 81 (85), 79 (17), 75 (100), 73 (34), 59 (17).

*4.3. Synthesis of compound **5***

4.3.1. (*R*)-4,6-Bis-(*tert*-butyldimethylsilyloxy)-hex-1-ene (**4'**):[28] To as solution of alcohol **4** (1.80 g, 7.81 mmol, 1.0 equiv) at 0 °C in CH_2Cl_2 (26 mL) was added imidazole (2.12 g, 31.2 mmol, 4.0 equiv) and, after 10 min, *tert*-butyldimethylsilylchloride (2.94 g, 19.5 mmol, 2.5 equiv) was added. The mixture was slowly warmed to rt. After 18 h, the reaction mixture was quenched with H_2O (20 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 99:1) to afford silyl ether **4'** (1.90 g, 5.51 mmol, 71%) as a colorless oil. Spectroscopic and physical data matched the ones reported in the literature.[28] $[\alpha]_D^{20}$ –16.2 (*c* 2.40, $CHCl_3$) {$[\alpha]_D^{28}$ lit.[28] –20.0 (*c* 1.10, $CHCl_3$)}; **IR** (neat): 2953, 2928, 2857, 1642, 1472, 1463, 1361, 1253, 1090, 1037, 1005, 911 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.82 (m, 1H), 5.08-5.01 (m, 2H), 3.88 ($quint_{app}$, *J* = 5.9 Hz, 1H), 3.67 (td, *J* = 6.6 and *J* = 1.5 Hz, 2H), 2.31-2.14 (m, 2H), 1.72-1.62 (m, 2H), 0.90 (s, 9H), 0.89 (s, 9H), 0.06 (s, 6H), 0.05 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 134.9, 116.5, 68.6, 59.5, 41.8, 39.5, 25.62 (3C), 25.56 (3C), 18.0, 17.8, -4.7, -5.0, -5.6 (2C); **MS** (EI, 70 eV) *m/z* (abundance): 344 ($M^{+\bullet}$, 1), 303 (12), 287 (11), 259 (23), 189 (27), 149 (11), 148 (14), 147 (93), 133 (21), 115 (11), 101 (18), 89 (54), 81 (69), 75 (26), 73 (100), 59 (22), 57 (11).

4.3.2. (4*R*,6*S*)-6,8-Bis-(*tert*-butyldimethylsilyloxy)-oct-1-en-4-ol (**5**): To a solution of alkene **4'** (1.90 g, 5.51 mmol, 1.0 equiv) in a 3:1 mixture of dioxane/H_2O (40 mL) at rt were successively added 2,6-lutidine (1.28 mL, 11.0 mmol, 2.0 equiv), OsO_4 (2.06 mL, 2.5 wt% in *tert*-butanol, 0.17 mmol, 3.0 mol %) and $NaIO_4$ (4.71 g, 22.0 mmol, 4 equiv). The thick mixture was stirred at rt and, after 3 h, the reaction mixture was quenched with a saturated aqueous solution of $Na_2S_2O_3$ (30 mL) and stirred for 3 h. The mixture was diluted with CH_2Cl_2 (80 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with brine (80 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting aldehyde **4"** was used in the next step without any further purification.

To a suspension of cyclopentadienyl[(4*S*,*trans*)-2,2-dimethyl-*α*,*α*,*α'*,*α'*-tetraphenyl-1,3-dioxolane-4,5-dimethanolato-*O*,*O'*]titane (4.70 g, 7.71 mmol, 1.4 equiv) in Et_2O (85 mL) at 0 °C was added allylmagnesium chloride (3.31 mL, 2 M in THF, 6.61 mmol, 1.2 equiv) dropwise. After 2.5 h at 0 °C, the red mixture containing (*S*,*S*)-**Ti** was cooled to –78 °C and a solution of the crude aldehyde **4"** (5.51 mmol, 1 equiv) in Et_2O (10 mL) was added dropwise via a cannula. The mixture was stirred at –78 °C for 12 h, then quenched by the slow addition of H_2O (40 mL) at –78 °C, and warmed to rt and vigorously stirred for 24 h to precipitate the titanium salts. The white suspension was filtered through a pad of Celite®, the phases were separated and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The thick yellow residue was stirred with pentane (18 mL) for 2 h to precipitate the (*S*,*S*)-TADDOL. The TADDOL was then filtered and the filtrate was concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/AcOEt = 95:5) to afford homoallylic alcohol **5** [1.90 g, 4.89 mmol, 89% (over two steps), dr > 98:2] as a yellow oil. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ +15.7 (*c* 2.13, $CHCl_3$); **IR** (neat): 3432, 3078, 2952, 2928, 2857, 1642, 1472, 1463, 1388, 1361, 1253, 1087, 1004, 913 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.84 (ddt, *J* = 17.2, *J* = 10.1 and *J* = 7.1 Hz, 1H), 5.15-5.07 (m, 2H), 4.07 (m, 1H), 3.83 (m, 1H), 3.66 (t, *J* = 6.3 Hz, 2H), 3.08 (br s, 1H, OH), 2.23 (t_{app}, *J* = 6.6 Hz, 2H), 1.85-1.64 (m, 3H), 1.55 (dt_{app}, *J* = 14.3 and *J* = 8.8 Hz, 1H), 0.90 (s, 9H), 0.89 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.04 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 134.9, 117.5, 70.4, 69.9, 59.5, 42.6, 42.2, 40.8, 25.9 (3C), 25.8 (3C), 18.2, 17.9, -4.2, -4.7, -5.36, -5.40; **MS** (EI, 70 eV) *m/z* (abundance): 373 [$(M\text{-}Me)^+$, 1], 199 (7), 189 (7), 171 (7), 149 (8), 147 (23), 145 (33), 133 (16), 131 (23), 129 (18), 115 (14), 107 (35), 105 (19), 101 (16), 89 (100), 83 (11), 79 (29), 75 (58), 73 (87), 59 (15), 57 (11), 55 (11); **HRMS**: calculated for $C_{20}H_{44}O_3NaSi_2$ ($M+Na^+$): 411.2721. Found: 411.2715.

*4.4. Synthesis of compound **8***

4.4.1. (4*R*,6*S*)-4,6,8-Tris-(*tert*-butyldimethylsilyloxy)oct-1-ene (**5'**): To a solution of alcohol **5** (293 mg, 0.754 mmol, 1 equiv) in CH_2Cl_2 (8.5 mL) at –78 °C was added 2,6-lutidine (0.142 mL, 1.22 mmol, 1.6 equiv) and 10 min later TBSOTf (0.336 mL, 1.46 mmol, 1.9 equiv) was added dropwise. The mixture was stirred at –78 °C for 2 h and then quenched with a saturated aqueous solution of NH_4Cl (5.0 mL), warmed up to rt and the organic phase was washed with a saturated aqueous solution of NH_4Cl (2 × 8 mL). The combined aqueous phases were extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic phases were

washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 98:2) to afford silyl ether **5'** (335 mg, 0.666 mmol, 88%, dr > 98:2) as a clear yellow oil. $[\alpha]_D^{20}$ –13.6 (*c* 1.12, $CHCl_3$); **IR** (neat): 2954, 2929, 2887, 2857, 1472, 1388, 1361, 1253, 1090, 1005, 913 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.82 (m, 1H), 5.08-5.01 (m, 2H), 3.90 ($quint_{app}$, *J* = 6.1 Hz, 1H), 3.82 ($quint_{app}$, *J* = 5.9 Hz, 1H), 3.72-3.61 (m, 2H), 2.28 (m, 1H), 2.17 (m, 1H), 1.78-1.56 (m, 4H), 0.90 (s, 9H), 0.89 (2s, 18H), 0.06 (2s, 12H), 0.05 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 135.0, 116.9, 69.1, 66.8, 59.9, 44.9, 42.0, 40.4, 26.0 (3C), 25.9 (3C), 25.7 (3C), 18.4, 18.05, 18.03, -4.3, -4.39, -4.42, -4.5, -5.29, -5.30; **MS** (EI, 70 eV) *m/z* (abundance): 446 [(M-*t*-Bu)$^+$, 1], 259 (17), 189 (12), 185 (42), 147 (35), 133 (13), 129 (15), 115 (16), 107 (26), 101 (11), 89 (57), 79 (14), 75 (18), 73 (100); **HRMS**: calculated for $C_{26}H_{58}O_3NaSi_3$ (M+Na$^+$): 525.3586. Found: 525.3580.

4.4.2. Ethyl (2*E*,4*E*,7*R*,9*S*)-7,9,11-tris-(*tert*-butyldimethylsilyloxy)undeca-2,4-dienoate (**8**): To a solution of alkene **5'** (537 mg, 1.07 mmol, 1.0 equiv) in a 3:1 mixture of dioxane/H_2O (8 mL) at rt were successively added 2,6-lutidine (249 µL, 2.14 mmol, 2.0 equiv), OsO_4 (402 µL, 2.5 wt % in *tert*-butanol, 0.03 mmol, 3.0 mol %) and $NaIO_4$ (917 mg, 4.28 mmol, 4.0 equiv). The thick mixture was stirred at rt for 3 h and then quenched with a saturated aqueous solution of $Na_2S_2O_3$ (50 mL) and stirred for 1.5 h. The mixture was diluted with CH_2Cl_2 (40 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude aldehyde **6** was engaged in the HWE olefination step without any further purification.

To a solution of the commercially available triethyl 4-phosphonocrotonate **7** (570 µL, 2.57 mmol, 2.4 equiv) in THF (15 mL), at –78 °C, was added LiHMDS (2.46 mL, 1 M in THF, 2.46 mmol, 2.3 equiv) dropwise. The mixture was stirred at –78 °C for 10 min and a solution of the crude aldehyde **6** (1.07 mmol, 1 equiv) in THF (20 mL) was slowly added via a cannula. After 5 min at –78 °C the mixture was warmed to –20 °C and stirred at this temperature for 2 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (12 mL) and warmed to rt. The two phases were separated and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 98:2) to afford conjugated ester **8** [489 mg, 0.814 mmol, 76%, dr > 98:2, (*E*,*E*)-**8**/(*E*,*Z*)-**8** = 90:10] as a slightly yellow oil. $[\alpha]_D^{20}$ –11.3 (*c* 1.78, $CHCl_3$); **IR** (neat): 2954, 2930, 2857, 1719, 1471, 1254, 1180, 1039, 834 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.26 (dd, *J* = 15.3 and *J* = 10.0 Hz, 1H), 6.25-6.07 (m, 2H), 5.80 (d, *J* = 15.3 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 3.88 (m, 2H), 3.66 (td, *J* = 6.7 and *J* = 1.6 Hz, 2H), 2.40 (dt_{app}, *J* = 13.8 and *J* = 5.5 Hz, 1H), 2.25 (dt_{app}, *J* = 13.8 and *J* = 6.3 Hz, 1H), 1.74-1.53 (m, 4H), 1.30 (t, *J* = 7.1 Hz, 3H), 0.09 (3s, 27H), 0.05 (s, 6H), 0.04 (s, 12H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 167.3, 144.7, 140.5, 130.7, 119.7, 68.8, 66.7, 60.2, 59.8, 45.1, 40.9, 40.5, 26.0 (3C), 25.88 (3C), 25.85 (3C), 18.3, 18.0 (2C), 14.3, -4.35, -4.39, -4.41 (2C), -5.30 (2C); **MS** (EI, 70 eV) *m/z* (abundance): 189 (14), 149 (7), 148 (15), 147 (100), 133 (8), 131 (7), 117 (11), 73 (29); **HRMS**: calculated for $C_{31}H_{64}O_5NaSi_3$ (M+Na$^+$): 623.3954. Found: 623.3949.

*4.5. Synthesis of compound **9***

Ethyl (2*E*,4*E*,7*R*,9*S*)-7,9-bis-(*tert*-butyldimethylsilyloxy)-11-hydroxyundeca-2,4-dienoate (**9**): To a solution of silyl ether **8** (682 mg, 1.13 mmol, 1.0 equiv) in MeOH (15 mL) at rt was added NH_4F (418 mg, 11.3 mmol, 10 equiv) and the mixture was refluxed for 4 h. The reaction mixture was allowed to cool to rt, quenched by addition of a saturated aqueous solution of $NaHCO_3$ (15 mL) and the mixture was extracted with Et_2O (2 × 20 mL) and EtOAc (2 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc: 85:15) to afford alcohol **9** (398 mg, 0.818 mmol, 72%) as a colorless oil. $[\alpha]_D^{20}$ –38.4 (*c* 1.04, $CHCl_3$); **IR** (neat): 3460, 2954, 2930, 2857, 1713, 1643, 1472, 1368, 1253, 1137, 1044, 1002, 834 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.26 (dd, *J* = 15.3 and *J* = 10.5 Hz, 1H), 6.20 (dd, *J* = 15.2 and *J* = 10.7 Hz, 1H), 6.10 (dt, *J* = 15.0 and *J* = 7.4 Hz, 1H), 5.81 (d, *J* = 15.3 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.06 (m, 1H), 3.86-3.77 (m, 2H), 3.72 (dt_{app}, *J* = 10.9 and *J* = 7.3 Hz, 1H), 2.39 (m, 1H), 2.29 (m, 1H), 1.88 (m, 1H), 1.73 (ddd, *J* = 13.6, *J* = 8.0 and *J* = 5.5 Hz, 1H), 1.69-1.58 (m, 2H), 1.44 (s, 1H, OH), 1.31 (t, *J* = 7.0 Hz, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H), 0.05 (2s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 167.2, 144.5, 139.7, 130.9, 120.0, 69.0, 68.8, 60.3, 60.1, 44.1, 41.3, 37.6, 25.83 (3C), 25.81 (3C), 18.0, 17.9, 14.3, -4.2, -4.4, -4.5, -4.7; **MS** (EI, 70 eV) *m/z* (abundance): 357 (1), 297 (10), 215 (20), 147 (16), 133 (19), 132 (12), 131 (93), 129 (11), 123 (19), 117 (10), 115 (10), 105 (17), 101 (20), 91 (11), 89 (38), 83 (67), 79 (10), 75 (82), 73 (100), 67 (10), 59 (15), 57 (13), 55 (11); **HRMS**: calculated for $C_{25}H_{50}O_5NaSi_2$ ($M+Na^+$): 509.3089. Found: 509.3083.

*4.6. Synthesis of compound **10***

Ethyl (2*E*,4*E*,7*R*,9*S*)-7,9-bis-(*tert*-butyldimethylsilyloxy)-14-iodotetradeca-2,4,11,13-tetraenoate (**10**): To a solution of alcohol **9** (107 mg, 0.220 mmol, 1.0 equiv) in CH_2Cl_2 (4.5 mL) at 0 °C were added $NaHCO_3$ (59 mg, 0.704 mmol, 3.2 equiv) and Dess-Martin periodinane (280 mg, 0.660 mmol, 3.0 equiv). The mixture was warmed to rt. After 12 h, the reaction mixture was diluted with hexanes (30 mL), filtered through a pad of Celite® and concentrated under reduced pressure. The crude aldehyde **9'** was used in the HWE olefination step without any further purification.

To a solution of phosphonate **1** (669 mg, 2.20 mmol, 10.0 equiv) in THF (4.5 mL) at –78 °C was added LiHMDS (2.19 mL, 1 M in THF, 2.19 mmol, 9.95 equiv) dropwise. After 30 min at –78 °C, a solution of crude aldehyde **9'** (0.220 mmol, 1.0 equiv) in THF (2.5 mL) was added via a cannula. The mixture was stirred at –78 °C for 1 h and at –25 °C for 2 h and then quenched by addition of a saturated aqueous solution of NH_4Cl (5 mL). The aqueous phase was extracted with Et_2O (3 × 10 mL) and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc: 98:2) to afford iododiene **10** [35 mg, 55.1 µmol, 25% (over 2 steps)] as a slightly yellow oil, as a mixture of 13*Z*/13*E* diastereomers (dr ~ 80:20). $[\alpha]_D^{20}$ +7.6 (*c* 0.29, $CHCl_3$); **IR** (neat): 3449,

2929, 2857, 1714, 1643, 1368, 1302, 1257, 1137, 1094, 1037, 1004 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) [major diastereomer (11*E*,13*Z*)]: δ 7.26 (dd, *J* = 15.3 and *J* = 10.3 Hz, 1H), 6.68 (dd, *J* = 9.7 and *J* = 7.6 Hz, 1H), 6.28-6.05 (m, 4H), 5.96 (dt_{app}, *J* = 15.2 and *J* = 7.6 Hz, 1H), 5.80 (d, *J* = 15.3 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.92-3.81 (m, 2H), 2.44-2.21 (m, 4H), 1.70-1.52 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 0.89 (br s, 18H), 0.07 (s, 3H), 0.05 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 167.3, 144.6, 140.2, 138.2, 135.7, 132.9, 130.8, 119.8, 80.2, 68.9, 68.8, 60.3, 44.5, 40.9, 40.8, 25.9 (6C), 18.0 (2C), 14.3, -4.3 (2C), -4.5 (2C); **HRMS**: calculated for $C_{28}H_{51}O_4INaSi_2$ ($M+Na^+$): 657.2263. Found: 657.2261.

*4.7. Synthesis of compound **13***

4.7.1. Ethyl (*R*)-3-(*tert*-butyldimethylsilyloxy)butanoate (**12'**):[29] To a solution of commercial ethyl (*R*)-3-hydroxybutyrate **12** (4.57 g, 34.6 mmol, 1.0 equiv) in CH_2Cl_2 (86 mL) at rt was added imidazole (4.71 g, 69.1 mmol, 2.0 equiv). The mixture was stirred at rt for 5 min, cooled to 0 °C and TBSCl (6.25 g, 41.5 mmol, 1.2 equiv) was added. The mixture was slowly warmed up to rt and stirred for 15 h. The reaction mixture was quenched with H_2O (60 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic phases were washed with brine (60 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 98:2) to afford silyl ether **12'** (8.53 g, 34.6 mmol, quant.) as a colorless oil. Spectroscopic and physical data matched the ones reported in the literature.[29] $[\alpha]_D^{20}$ −27.5 (*c* 1.02, $CHCl_3$) {$[\alpha]_D^{20}$ lit.[29b] –28.0 (*c* 1.10, $CHCl_3$)}; **IR** (neat): 2930, 2857, 1737, 1376, 1300, 1253, 1181, 1137, 1081, 1033, 1001 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.22 (m, 1H), 4.12-3.98 (m, 2H), 2.40 (dd, *J* = 14.5 and *J* = 7.6 Hz, 1H), 2.29 (dd, *J* = 14.5 and *J* = 5.3 Hz, 1H), 1.19 (t, *J* = 7.1 Hz, 3H), 1.13 (d, *J* = 6.1 Hz, 3H), 0.80 (s, 9H), 0.00 (s, 3H), -0.02 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.6, 65.8, 60.2, 44.9, 25.7 (3C), 23.9, 17.9, 14.2, -4.6, -5.1; **MS** (EI, 70 eV) *m/z* (abundance): 246 ($M^{+\bullet}$, 1), 190 (5), 189 (40), 161 (31), 159 (11), 147 (10), 119 (84), 115 (14), 103 (35), 75 (100), 73 (37), 59 (13); **HRMS**: calculated for $C_{12}H_{26}O_3NaSi$ ($M+Na^+$): 269.1543. Found: 269.1543.

4.7.2. (4*S*,6*R*)-6-(*tert*-Butyldimethylsilyloxy)hept-1-en-4-ol (**13**): To a solution of ester **12'** (3.71 g, 15.0 mmol, 1 equiv) in CH_2Cl_2 (100 mL) at –78 °C was added DIBAL-H (15.8 mL, 1 M in toluene, 15.8 mmol, 1.05 equiv) dropwise. The mixture was stirred at –78 °C for 1 h and the reaction was quenched with methanol (5 mL). The reaction mixture was poured onto a saturated aqueous solution of Rochelle's salts (150 mL) and diluted with Et_2O (100 mL). This mixture was vigorously stirred and after 2 h two clear phases were obtained and separated. The aqueous phase was extracted with Et_2O (3 × 100 mL) and the combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to obtain the crude aldehyde **12"** which was used in the next step without any further purification.

To a suspension of cyclopentadienyl[(4*R*,*trans*)-2,2-dimethyl-*α*,*α*,*α'*,*α'*-tetraphenyl-1,3-dioxolane-4,5-dimethanolato-*O*,*O'*]titane (11.9 g, 19.5 mmol, 1.3 equiv) in Et_2O (200 mL) at 0 °C was added allylmagnesium chloride (8.25 mL, 2 M in THF, 16.5 mmol, 1.1 equiv) dropwise. After 2.5 h at 0 °C, the red mixture containing (*R*,*R*)-**Ti** was cooled to –78 °C and a solution of the crude aldehyde **12"** (15 mmol, 1 equiv) in Et_2O (25 mL) was

added dropwise via a cannula. The mixture was stirred at –78 °C for 12 h, then quenched by the slow addition of H_2O (100 mL) at –78 °C, warmed to rt and vigorously stirred for 24 h to precipitate the titanium salts. The white suspension was filtered through a pad of Celite®, the phases were separated and the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The thick yellow residue was stirred with pentane (18 mL) for 2 h to precipitate the (*R*,*R*)-TADDOL. The TADDOL was then filtered and the filtrate was concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc gradient = 100:0 to 95:5) to afford homoallylic alcohol **13** (3.19 g, 13.1 mmol, 87%, dr > 98:2) as a slightly yellow oil. $[\alpha]_D^{20}$ – 33.0 (*c* 0.95, $CHCl_3$); **IR** (neat): 3457, 2930, 2857, 1472, 1463, 1255, 1078, 1002, 971, 910 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.83 (ddt, *J* = 17.2, *J* = 10.2 and *J* = 7.1 Hz, 1H), 5.13-5.05 (m, 2H), 4.07 (m, 1H), 3.82 (m, 1H), 3.47 (br d, *J* = 1.4 Hz, 1H, OH), 2.28-2.15 (m, 2H), 1.62-1.49 (m, 2H), 1.18 (d, *J* = 6.0 Hz, 3H), 0.89 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 134.9, 117.3, 70.6, 69.8, 45.2, 42.0, 25.8 (3C), 24.5, 17.9, -3.9, -4.8; **MS** (EI, 70 eV) *m/z* (abundance): 243 (1), 159 (20), 145 (16), 120 (7), 119 (75), 115 (10), 103 (9), 101 (18), 95 (53), 75 (100), 73 (38), 67 (18), 59 (17); **HRMS**: calculated for $C_{13}H_{28}O_2NaSi$ ($M+Na^+$): 267.1751. Found: 267.1753.

*4.8. Synthesis of compound **16***

4.8.1. (4*S*,6*R*)-6-(*tert*-Butyldimethylsilyloxy)-4-(triethylsilyloxy)hept-1-ene (**13'**): To a solution of alcohol **13** (3.70 g, 15.1 mmol, 1.0 equiv) and DMAP (185 mg, 1.51 mmol, 0.1 equiv) in CH_2Cl_2 (37 mL) at 0 °C were added Et_3N (4.21 mL, 30.3 mmol, 2.0 equiv) and triethylsilyl chloride (3.81 mL, 22.7 mmol, 1.5 equiv). The mixture was slowly warmed to rt over 2 h. The reaction mixture was quenched with H_2O (10 mL), acidified with 1M aqueous HCl (pH ~ 4) and the aqueous phase was extracted with Et_2O (3 × 25 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 99:1, dr > 98:2) to afford silyl ether **13'** (5.27 g, 14.7 mmol, 97%) as a colorless oil. $[\alpha]_D^{20}$ +1.6 (*c* 1.22, $CHCl_3$); **IR** (neat): 2954, 2878, 1462, 1374, 1361, 1254, 1051, 1004, 909 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.83 (m, 1H), 5.07-5.01 (m, 2H), 3.89 (m, 1H), 3.82 (m, 1H), 2.28 (m, 1H), 2.17 (m, 1H), 1.66 (ddd, *J* = 13.5, *J* = 7.2 and *J* = 6.2 Hz, 1H), 1.51 (ddd, *J* = 13.5, *J* = 6.8 and *J* = 5.8 Hz, 1H), 1.13 (d, *J* = 6.1 Hz, 3H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.88 (s, 9H), 0.59 (q, *J* = 7.9 Hz, 6H), 0.05 (s, 3H), 0.04 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 135.2, 116.7, 69.2, 65.9, 47.2, 41.7, 25.9 (3C), 24.0, 18.0, 6.9 (3C), 5.1 (3C), -4.3, -4.8; **MS** (EI, 70 eV) *m/z* (abundance): 343 [$(M-Me)^+$, 1], 287 (33), 259 (10), 233 (47), 190 (11), 189 (58), 162 (12), 161 (70), 160 (16), 159 (100), 147 (15), 143 (11), 133 (22), 119 (17), 115 (44), 105 (14), 103 (52), 102 (15), 101 (26), 99 (17), 95 (92), 88 (19), 87 (32), 75 (41), 73 (71), 67 (20), 59 (38), 57 (13), 55 (14); **HRMS**: calculated for $C_{19}H_{42}O_2NaSi_2$ ($M+Na^+$): 381.2616. Found: 381.2615.

4.8.2. (5*R*,7*R*)-7-(*tert*-Butyldimethylsilyloxy)-5-(triethylsilyloxy)-1-(trimethylsilyl) oct-1-yn-3-one (**16**): To a solution of alkene **13'** (4.20 g, 11.6 mmol, 1.0 equiv) in a 3/1

mixture of dioxane/H_2O (80 mL) at rt were successively added 2,6-lutidine (2.70 mL, 23.2 mmol, 2 equiv), OsO_4 (4.40 mL, 2.5 wt% in *tert*-butanol, 0.46 mmol, 4 mol %) and $NaIO_4$ (9.90 g, 46.4 mmol, 4.0 equiv). The thick mixture was stirred at rt for 3 h and then quenched with a saturated aqueous solution of $Na_2S_2O_3$ (60 mL) and stirred for an additional 2 h. The mixture was diluted with CH_2Cl_2 (150 mL), the two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude aldehyde **14**.

To a solution of trimethylsilylacetylene (9.60 mL, 69.6 mmol, 6.0 equiv) in THF (150 mL) at –25 °C was added *n*-BuLi (2.5 M in hexane, 26.9 mL, 2.5 M in hexane, 67.3 mmol, 5.8 equiv) dropwise. The mixture was stirred at –25 °C for 25 min and cooled to –78 °C. Crude aldehyde **14** in THF (25 mL) was added via a cannula, and the mixture was stirred at –78 °C for 30 min, at 0 °C for 40 min and at rt. After 1 h, the reaction was quenched by slow addition of a saturated aqueous solution of NH_4Cl (30 mL), the two phases were separated and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a crude mixture of alcohols **15** and **15'** in a 56/44 ratio.

The crude mixture of **15** and **15'** was diluted in CH_2Cl_2 (150 mL) and molecular sieves 4 Å (7.5 g) as well as PCC (3.74 g, 17.4 mmol, 1.5 equiv) were added. After 1.5 h at rt, Et_2O (500 mL) was added and the stirring was continued for 1 h. The mixture was then filtered through a pad of Celite®, the residue was concentrated under reduced pressure and the crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 99:1) to afford ketone **16** [3.5 g, 7.66 mmol, 66% (3 steps), dr > 98:2] as a yellow oil. $[\alpha]_D^{20}$ −13.2 (*c* 2.0, $CHCl_3$); **IR** (neat): 2955, 2878, 1678, 1462, 1375, 1252, 1134, 1066, 1005 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.42 (m, 1H), 3.88 (m, 1H), 2.76 (dd, *J* = 14.8 and *J* = 4.8 Hz, 1H), 2.68 (dd, *J* = 14.8 and *J* = 7.8 Hz, 1H), 1.75 (ddd, *J* = 13.7, *J* = 7.6 and *J* = 5.3 Hz, 1H), 1.55 (ddd, *J* = 13.7, *J* = 7.6 and *J* = 4.8 Hz, 1H), 1.16 (d, *J* = 6.0 Hz, 3H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.89 (s, 9H), 0.61 (q, *J* = 7.9 Hz, 6H), 0.24 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 186.8, 103.4, 98.5, 67.2, 66.4, 53.8, 48.6, 26.7 (3C), 24.9, 18.8, 7.7 (3C), 5.8 (3C), 0.0 (3C), -3.5, -3.8; **MS** (EI, 70 eV) *m/z* (abundance): 323 (1), 267 (19), 225 (17), 224 (16), 223 (68), 207 (35), 193 (23), 179 (12), 177 (53), 159 (60), 151 (11), 149 (27), 148 (10), 147 (64), 133 (18), 117 (12), 115 (17), 105 (22), 103 (16), 97 (12), 83 (12), 75 (77), 73 (100), 59 (12); **HRMS**: calculated for $C_{23}H_{48}O_3NaSi_3$ ($M+Na^+$): 479.2804. Found: 479.2804.

*4.9. Synthesis of compound **15***

(3*S*,5*S*,7*R*)-7-(*tert*-Butyldimethylsilyloxy)-5-(triethylsilyloxy)-1-(trimethylsilyl)oct-1-yn-3-ol (**15**): To a solution of ketone **16** (2.42 g, 5.30 mmol, 1.0 equiv) in freshly distillated *i*Pr-OH (53 mL) at rt was added (*S*,*S*)-**Ru** (0.318 g, 0.530 mmol, 0.1 equiv). The mixture was stirred at rt for 1 h and then concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 98:2) to afford alcohol **15** (2.1 g, 4.58 mmol, 86%, dr > 98:2) as a yellow oil. $[\alpha]_D^{20}$ −33.4 (*c* 1.45, $CHCl_3$); **IR** (neat): 3447, 2955, 2879, 2171, 1251, 1109, 1064, 1006 cm^{-1}; **^{1}H NMR** (400 MHz,

$CDCl_3$): δ 4.62 (m, 1H), 4.29 (m, 1H), 3.82 (m, 1H), 3.70 (br d, *J* = 4.9 Hz, 1H, OH), 1.98 (ddd, *J* = 14.3, *J* = 7.8 and *J* = 3.8 Hz, 1H), 1.81 (ddd, *J* = 14.3, *J* = 7.3 and *J* = 3.4 Hz, 1H), 1.75 (ddd, *J* = 13.5, *J* = 8.8 and *J* = 4.4 Hz, 1H), 1.60 (ddd, *J* = 13.6, *J* = 9.2 and *J* = 3.5 Hz, 1H), 1.14 (d, *J* = 6.1 Hz, 3H), 0.97 (t, *J* = 7.9 Hz, 9H), 0.88 (s, 9H), 0.65 (q, *J* = 7.9 Hz, 6H), 0.16 (s, 9H), 0.05 (s, 3H), 0.05 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 106.8, 88.9, 68.6, 65.6, 60.7, 47.2, 42.0, 26.0 (3C), 24.6, 18.0, 7.0 (3C), 5.1 (3C), 0.0 (3C), -4.1, -4.5; **MS** (EI, 70 eV) *m/z* (abundance): 297 (1), 233 (11), 189 (13), 161 (13), 160 (14), 159 (100), 145 (13), 119 (67), 115 (21), 103 (42), 101 (10), 87 (11), 83 (16), 75 (50), 73 (66), 59 (16); **HRMS**: calculated for $C_{23}H_{50}O_3NaSi_3$ ($M+Na^+$): 481.2960. Found: 481.2943.

*4.10. Synthesis of compound **17***

4.10.1. (3*S*,5*R*,7*R*)-3,7-bis(*tert*-Butyldimethylsilyloxy)-5-(triethylsilyloxy)-1-(trimethylsilyl)oct-1-yne (**15”**): To a solution of alcohol **15** (1.85 g, 4.03 mmol, 1 equiv) in CH_2Cl_2 (80 mL) at 0 °C were added imidazole (0.768 g, 11.3 mmol, 2.8 equiv) and after 10 min TBSCl (1.22 g, 8.06 mmol, 2 equiv). The reaction mixture was slowly warmed up to rt and stirred for 65 h. The reaction mixture was quenched with H_2O (30 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were washed with brine (60 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 99:1) to afford silyl ether **15”** (2.13 g, 3.71 mmol, 92%, dr > 98:2) as a colorless oil. $[\alpha]_D^{20}$ –16.9 (*c* 0.97, $CHCl_3$); **IR** (neat): 2957, 2930, 2881, 2858, 1472, 1463, 1377, 1362, 1251, 1074, 1006, 909 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.45 (t_{app}, *J* = 6.9 Hz, 1H), 4.00-3.89 (m, 2H), 1.91-1.79 (m, 2H), 1.68 (m, 1H), 1.57 (m, 1H), 1.13 (d, *J* = 6.0 Hz, 3H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.90 (s, 9H), 0.88 (s, 9H), 0.60 (q, *J* = 8.0 Hz, 6H), 0.14 (br s, 12H), 0.12 (s, 3H), 0.05 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 108.2, 89.3, 67.0, 66.0, 60.5, 47.8, 46.9, 26.2 (6C), 24.0, 18.5, 18.3, 7.2 (3C), 5.5 (3C), 0.0 (3C), -3.9, -4.1, -4.2, -4.3 (4C); **MS** (EI, 70 eV) *m/z* (abundance): 573 ($M^{+\bullet}$, 1), 343 (5), 317 (9), 316 (18), 315 (58), 242 (13), 241 (53), 234 (11), 233 (50), 189 (23), 161 (17), 160 (13), 159 (90), 147 (16), 133 (18), 115 (25), 103 (25), 87 (16), 75 (18), 73 (100), 59 (17); **HRMS**: calculated for $C_{29}H_{64}O_3NaSi_4$ ($M+Na^+$): 595.3825. Found: 595.3802.

4.10.2. (3*S*,5*R*,7*R*)-3,7-bis(*tert*-Butyldimethylsilyloxy)-5-(triethylsilyloxy)oct-1-yne (**15’”**): To a solution of alkyne **15”** (1.34 g, 2.34 mmol, 1.0 equiv) in MeOH (48 mL) at rt was added K_2CO_3 (485 mg, 3.51 mmol, 1.5 equiv) and the mixture was stirred for 5 h. The reaction mixture was quenched with H_2O (10 mL) and EtOAc (80 mL) and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine (80 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 99:1) to afford alkyne **15’”** (1.08 g, 2.16 mmol, 92%, dr > 98:2) as a colorless oil. $[\alpha]_D^{20}$ –24.2 (*c* 1.67, $CHCl_3$); **IR** (neat): 2957, 2931, 2879, 2858, 2360, 2340, 1472, 1463, 1376, 1362, 1254, 1111, 1005, 910 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.49 (t_{app}d, *J* = 6.7 and *J* = 2.1 Hz, 1H), 3.98-3.89 (m, 2H), 2.40 (d, *J* = 2.1 Hz, 1H), 1.95-1.80 (m, 2H), 1.71 (dt_{app}, *J* = 13.5 and *J* = 6.4 Hz, 1H), 1.57 (dt_{app}, *J* = 13.5 and *J* = 6.3 Hz, 1H), 1.13 (d, *J* = 6.1 Hz, 3H), 0.96 (t,

J = 7.9 Hz, 9H), 0.90 (s, 9H), 0.88 (s, 9H), 0.60 (q, *J* = 7.9 Hz, 6H), 0.15 (s, 3H), 0.12 (s, 3H), 0.05 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 86.0, 72.6, 66.6, 65.8, 59.6, 47.7, 46.7, 25.91 (3C), 25.87 (3C), 23.8, 18.2, 18.0, 6.9 (3C), 5.3 (3C), -4.3 (2C), -4.6, -4.7; **MS** (EI, 70 eV) *m/z* (abundance): 501 ($M^{+\bullet}$, 1), 243 (17), 233 (38), 189 (28), 169 (30), 161 (16), 160 (11), 159 (77), 147 (13), 133 (16), 115 (32), 113 (21), 105 (14), 103 (29), 87 (16), 75 (25), 73 (100), 59 (17); **HRMS**: calculated for $C_{26}H_{56}O_3NaSi_3$ ($M+Na^+$): 523.3430. Found: 523.3411.

4.10.3. (3*S*,5*R*,7*R*)-3,7-bis(*tert*-Butyldimethylsilyloxy)-5-hydroxyoct-1-yne (**17**): To a solution of silyl ether **15'"** (400 mg, 0.798 mmol, 1 equiv) in EtOH (8 mL) at rt was added PPTS (20 mg, 79.8 µmol, 10 mol %) and the mixture was stirred at rt for 3 h. The reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL), stirred for 1 h and the aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$ (30 mL), H_2O (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 95:5) to afford alcohol **17** (280 mg, 0.724 mmol, 91%, dr > 98:2) as a white solid. m.p. = 71 °C; $[\alpha]_D^{20}$ –55.4 (*c* 0.28, $CHCl_3$); **IR** (neat): 3293, 2954, 2930, 2858, 2115, 1462, 1377, 1254, 1088, 1005, 942 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.66 (td, *J* = 6.0 and *J* = 2.0 Hz, 1H), 4.13-4.00 (m, 2H), 3.63 (br s, 1H, OH), 2.38 (d, *J* = 2.0 Hz, 1H), 1.77 (t_{app}, *J* = 6.0 Hz, 2H), 1.62 (dt_{app}, *J* = 14.2 and *J* = 8.9 Hz, 1H), 1.51 (ddd, *J* = 14.1, *J* = 4.3 and *J* = 2.8 Hz, 1H), 1.18 (d, *J* = 6.1 Hz, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H), 0.10 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 85.5, 72.2, 69.3, 67.0, 60.0, 46.2, 45.7, 25.9 (6C), 24.3, 18.2, 17.9, -4.0, -4.7, -4.8, -5.2; **MS** (EI, 70 eV) *m/z* (abundance): 386 ($M^{+\bullet}$, 1), 197 (9), 189 (8), 169 (8), 159 (20), 155 (45), 147 (12), 146 (10), 145 (88), 133 (10), 129 (25), 119 (29), 115 (23), 105 (12), 103 (17), 101 (21), 75 (100), 74 (10), 73 (99), 59 (18); **HRMS**: calculated for $C_{20}H_{42}O_3NaSi_2$ ($M+Na^+$): 409.2565. Found: 409.2564.

*4.11. Synthesis of compound **19***

(2*R*,4*R*,6*S*)-2,6-bis(*tert*-Butyldimethylsilyloxy)oct-7-yn-4-yl 2-(diethoxyphosphoryl)acetate (**19**): To a solution of alcohol **17** (280 mg, 0.724 mmol, 1.0 equiv), 2-(diethoxyphosphoryl)acetic acid **18**[16] (213 mg, 1.09 mmol, 1.5 equiv) and DMAP (40 mg, 0.326 mmol, 0.45 equiv) in CH_2Cl_2 (36 mL) at rt was added DCC (336 mg, 1.63 mmol, 2.25 equiv) and the mixture was stirred for 24 h. The mixture was concentrated under reduced pressure and the crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 80:20 to 60:40) to afford ester **19** (362 mg, 0.641 mmol, 89%, dr > 98:2) as a colorless oil. $[\alpha]_D^{20}$ –17.5 (*c* 1.35, $CHCl_3$); **IR** (neat): 3311, 2955, 2930, 2857, 1735, 1463, 1391, 1252, 1100, 1051, 1023 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.14 (m, 1H), 4.39 (ddd, *J* = 9.1, *J* = 3.9 and *J* = 2.1 Hz, 1H), 4.15 (dq, *J* =8.1 and *J* = 7.1 Hz, 4H), 3.87 (m, 1H), 2.90 (d, *J* = 21.6 Hz, 2H), 2.38 (d, *J* = 2.1 Hz, 1H), 2.08-1.92 (m, 2H), 1.86 (ddd, *J* = 14.0, *J* = 6.7 and *J* = 5.7 Hz, 1H), 1.62 (dt_{app}, *J* = 14.0 and *J* = 6.3 Hz, 1H), 1.33 (td, *J* = 7.1 and *J* = 1.2 Hz, 6H), 1.15 (d, *J* = 6.2 Hz, 3H), 0.87 (s, 9H), 0.86 (s, 9H), 0.12 (s, 3H), 0.07 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 165.0 (d, *J* = 6.0 Hz), 85.2, 72.5, 70.2, 65.4, 62.6 (d, *J* = 6.0 Hz, 2C), 59.1, 44.3, 43.8, 34.5 (d, *J* = 133.8 Hz), 25.9 (3C), 25.7 (3C),

23.4, 18.0 (2C), 16.3 (d, *J* = 6.0 Hz, 2C), -4.4, -4.5, -4.7, -5.1; **MS** (EI, 70 eV) *m/z* (abundance): 565 ($M^{+\bullet}$, 1), 508 (11), 507 (32), 271 (58), 253 (60), 225 (23), 197 (18), 179 (31), 159 (16), 123 (12), 115 (23), 113 (16), 105 (23), 103 (20), 75 (40), 73 (100), 59 (10); **HRMS**: calculated for $C_{26}H_{53}O_7NaPSi_2$ ($M+Na^+$): 587.2960. Found: 587.2955.

*4.12. Synthesis of compound **20***

4.12.1. (2*R*,4*R*,6*S*)-8-Bromo-2,6-bis(*tert*-butyldimethylsilyloxy)oct-7-yn-4-yl 2-(diethoxyphosphoryl)acetate (**19'**): To a solution of alkyne **19** (264 mg, 467 µmol, 1 equiv), in acetone (2.2 mL) at rt, were successively added NBS (100 mg, 560 µmol, 1.2 equiv), $AgNO_3$ (7.94 mg, 46.7 µmol, 10 mol %) and a drop of water. The mixture was stirred at rt in the dark for 18 h, concentrated under reduced pressure and the residue was diluted in EtOAc (10 mL) and H_2O (5 mL). The two phases were separated, the aqueous phase was extracted with EtOAc (3 × 10 mL) and the combined organic phases were washed with brine (15 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 70:30) to afford bromoalkyne **19'** (243 mg, 377 µmol, 81%, dr > 98:2) as a colorless oil. $[\alpha]_D^{20}$ –19.8 (*c* 0.95, $CHCl_3$); **IR** (neat): 3364, 2954, 2930, 2856, 1733, 1250, 1098, 1022, 974 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.13 (m, 1H), 4.43 (dd, *J* = 9.0 and *J* = 4.0 Hz, 1H), 4.16 (dq, *J* = 8.1 and *J* = 7.1 Hz, 4H), 3.87 ($sext_{app}$, *J* = 6.1 Hz, 1H), 2.91 (d, *J* = 21.8 Hz, 2H), 2.07-1.91 (m, 2H), 1.86 (ddd, *J* = 14.0, *J* = 6.7 and *J* = 5.9 Hz, 1H), 1.62 (dt_{app}, *J* = 14.0 and *J* = 6.3 Hz, 1H), 1.34 (br t, *J* = 7.1 Hz, 6H), 1.15 (d, *J* = 6.1 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.12 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 165.0 (d, *J* = 7.0 Hz), 81.4, 70.1, 65.4, 62.64 (d, *J* = 6.3 Hz), 62.63 (d, *J* = 6.2 Hz), 60.3, 44.5, 44.3, 43.6, 34.5 (d, *J* = 133.8 Hz), 25.9 (3C), 25.8 (3C), 23.4, 18.1, 18.0, 16.4 (d, *J* = 2.6 Hz), 16.3 (d, *J* = 2.7 Hz), -4.3, -4.6, -4.7, -5.1; **HRMS**: calculated for $C_{26}H_{52}{}^{79}BrO_7NaPSi_2$ ($M+Na^+$): 665.2065. Found: 665.2061; calculated for $C_{26}H_{52}{}^{81}BrO_7NaPSi_2$ ($M+Na^+$): 667.2040. Found: 667.2044.

4.12.2. (2*R*,4*R*,6*S*,*E*)-2,6-bis(*tert*-butyldimethylsilyloxy)-8-(tributylstannyl)oct-7-en-4-yl 2-(diethoxyphosphoryl)acetate (**20**): To a solution of bromoalkyne **19'** (240 mg, 0.373 mmol, 1 equiv) in THF (13 mL) at rt was added $Pd(PPh_3)_4$ (21.5 mg, 18.6 µmol, 5 mol %). The mixture was cooled to –78 °C and Bu_3SnH (0.301 mL, 1.12 mmol, 3 equiv) was added. The mixture was stirred at –78 °C for 1 h, warmed up to rt and stirred for another 1 h. The mixture was concentrated under reduced pressure and the crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 85/15) to afford vinylstannane **20** (253 mg, 0.296 mmol, 79%, dr > 98:2) as a yellow oil. $[\alpha]_D^{20}$ –8.9 (*c* 0.75, $CHCl_3$); **IR** (neat): 2956, 2928, 2856, 1737, 1463, 1253, 1053, 1026, 962 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.05 (dd, *J* = 19.1 and *J* = 0.8 Hz, 1H), 5.90 (dd, *J* = 19.1 and *J* = 6.3 Hz, 1H), 5.08 (m, 1H), 4.21-4.12 (m, 4H), 4.09 (m, 1H), 3.89 (m, 1H), 2.93 (dd, *J* = 21.6 and *J* = 2.9 Hz, 2H), 1.87 (m, 1H), 1.80-1.72 (m, 2H), 1.64 (m, 1H), 1.54-1.42 (m, 6H), 1.39-1.24 (m, 12H), 1.15 (d, *J* = 6.0 Hz, 3H), 0.95-0.84 (m, 33H), 0.04 (s, 6H), 0.02 (s, 3H), -0.01 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 165.0 (d, *J* = 7.0 Hz), 151.6, 127.8, 73.5, 71.1, 65.6, 62.6 (d, *J* = 5.2 Hz), 62.5 (d, *J* = 6.0 Hz), 44.5, 43.3, 34.5 (d, *J* = 133.8 Hz), 29.1 (3C), 27.3 (3C), 25.9 (6C), 23.4, 18.1, 18.0, 16.4 (d, *J* = 6.2 Hz, 2C), 13.7 (3C), 9.4 (3C), -4.0, -4.4, -4.7, -4.8; **MS** (EI, 70 eV)

m/z (abundance): 317 (17), 315 (58), 314 (20), 313 (87), 312 (30), 311 (63), 310 (16), 309 (25), 259 (33), 258 (11), 257 (55), 256 (20), 255 (40), 254 (11), 253 (17), 201 (27), 199 (41), 198 (12), 197 (29), 195 (11), 177 (26), 175 (20), 173 (12), 121 (32), 120 (19), 119 (27), 118 (15), 117 (16), 57 (100), 55 (10); **HRMS**: calculated for $C_{38}H_{81}NaO_7PSi_2{}^{120}Sn$ ($M+Na^+$): 879.4173. Found: 879.4182.

*4.13. Synthesis of compound **21***

(*E*)-(1*R*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)-1-[(*R*)-2-(*tert*-butyldimethylsilyloxy)-propyl]-5-tributylstannanyl-pent-4-enyl (2*E*,4*E*,6*E*,9*R*,11*S*)-9,11-bis-(*tert*-butyldimethylsilyloxy)-16-iodohexadeca-2,4,6,13,15-pentaenoate (**21**): To a solution of ester **10** (34 mg, 53.6 µmol, 1.0 equiv) in CH_2Cl_2 (1.1 mL) at –78 °C was added DIBAL-H (150 µL, 1 M in CH_2Cl_2, 150 µmol, 3 equiv) dropwise and the mixture was slowly warmed up to –25 °C for a period of 2 h and then quenched by the addition of a saturated aqueous solution of Rochelle's salt (10 mL). The mixture was stirred at rt and after 1 h, two clear phases were obtained and separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (2.0 mL) and MnO_2 (46 mg, 0.536 mmol, 10 equiv) was added. After 12 h, a second portion of MnO_2 (46 mg, 0.536 mmol, 10 equiv) was added and the mixture was stirred for an additional 12 h, filtered through a pad of Celite® and concentrated under reduced pressure. The resulting crude aldehyde **11** (26 mg, 44.0 µmol, 82%) was involved in the next HWE step without any further purification.

To a suspension of NaH (0.9 mg, 60 wt% in mineral oil, 22.0 µmol, 1 equiv) in THF (220 µL) at 0 °C was added phosphonate **20** (18.8 mg, 22.0 µmol, 1.0 equiv) dropwise. After 30 min at 0 °C a solution of the crude aldehyde **11** (44.0 µmol, 2.0 equiv) in THF (200 µL) was canulated and the mixture was stirred at 0 °C for 2 h and quenched by the addition of a saturated aqueous solution of NH_4Cl (200 µL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 2 mL). The combined organic phases were washed with brine (2 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 98:2) to afford iododiene **21** (18 mg, 13.9 µmol, 63%). **^{1}H NMR** (400 MHz, $CDCl_3$) [major diastereomer (11*E*,13*Z*)]: δ 7.28 (dd, *J* = 15.3 and *J* = 11.2 Hz, 1H), 6.68 (dd, *J* = 9.8 and *J* = 7.8 Hz, 1H), 6.52 (dd, *J* = 14.9 and *J* = 10.7 Hz, 1H), 6.28-6.10 (m, 4H), 6.06 (d, *J* = 19.1 Hz, 1H), 6.02-5.88 (m, 3H), 5.85 (d, *J* = 15.3 Hz, 1H), 5.10 (m, 1H), 4.11 (m, 1H), 3.92-3.81 (m, 3H), 2.46-2.21 (m, 4H), 1.89 (m, 1H), 1.80 (m, 2H), 1.72-1.57 (m, 3H), 1.53-1.43 (m, 6H), 1.37-1.26 (m, 6H), 1.18 (d, *J* = 6.0 Hz, 3H), 0.93-0.85 (m, 51H), 0.09-0.02 (m, 24H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.4, 151.8, 144.4, 140.5, 138.3, 135.8 (d, 2C), 132.8, 132.3, 128.4, 127.4, 120.8, 80.0, 73.7, 69.4, 69.0, 68.9, 65.8, 45.1, 44.5, 43.6, 41.0, 40.8, 29.1 (3C), 27.3 (3C), 25.96 to 25.87 (12C), 23.5, 18.14, 18.10, 18.04 (2C), 13.7 (3C), 9.4 (3C), -4.06 to -4.84 (8C).[30]

*4.14. Synthesis of compound **24***

4.14.1. (2*E*,4*E*,7*R*,9*S*)-7,9-bis(*tert*-Butyldimethylsilyloxy)-11-(*tert*-butyldiphenylsilyloxy)undeca-2,4-dien-1-ol (**8"**): To a solution of ester **8'** (4.30 g, 5.93 mmol,

1 equiv) in CH_2Cl_2 (60 mL) at –78 °C was added DIBAL-H (17.8 mL, 1 M in toluene, 17.8 mmol, 3 equiv) dropwise. After 1 h at –78 °C, the reaction mixture was poured on a saturated aqueous solution of Rochelle salts (100 mL) and stirred for 3 h until obtaining two clear phases. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were washed with brine (150 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 95:5 to 90:10) to afford alcohol **8”** (3.89 g, 5.69 mmol, 96%, dr > 98:2) as a colorless oil. $[\alpha]_D^{20}$ –8.1 (*c* 1.19, $CHCl_3$); **IR** (neat): 3342, 2954, 2929, 2887, 2857, 1472, 1462, 1428, 1388, 1361, 1253, 1083, 988 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.69-7.64 (m, 4H), 7.45-7.35 (m, 6H), 6.20 (dd, *J* = 15.1 and *J* = 10.3 Hz, 1H), 6.04 (dd, *J* = 15.1 and *J* = 10.4 Hz, 1H), 5.75-5.64 (m, 2H), 4.16 (d, *J* = 6.3 Hz, 2H), 3.92 ($quint_{app}$, *J* = 6.2 Hz, 1H), 3.82 ($quint_{app}$, *J* = 5.9 Hz, 1H), 3.77-3.62 (m, 2H), 2.31 (m, 1H), 2.17 (m, 1H), 1.74 (m, 2H), 1.60 (t_{app}, *J* = 6.5 Hz, 2H), 1.05 (s, 9H), 0.88 (s, 9H), 0.84 (s, 9H), 0.04 (s, 3H), 0.03 (br s, 6H), -0.01 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 135.6 (4C), 133.9 (2C), 131.8, 131.7, 131.5, 129.9, 129.6 (2C), 127.6 (4C), 69.2, 66.9, 63.6, 60.9, 45.0, 40.5, 40.3, 26.9 (3C), 25.9 (6C), 19.2, 18.04, 18.00, -4.3, -4.40, -4.44 (2C); **HRMS**: calculated for $C_{39}H_{66}O_4NaSi_3$ ($M+Na^+$): 705.4161. Found: 705.4161.

4.14.2. (2*E*,4*E*,7*R*,9*S*)-7,9-bis(*tert*-Butyldimethylsilyloxy)-11-(*tert*-butyldiphenylsilyloxy)-1-(4-methoxybenzyloxy)undeca-2,4-diene (**8’”**): To a solution of 4-methoxybenzyltrichloroacetimidate (2.62 g, 9.26 mmol, 1.67 equiv) in hexane (46 mL) was added alcohol **8”** (3.79 g, 5.55 mmol, 1 equiv) in CH_2Cl_2 (23 mL) via a cannula. The mixture was cooled to 0 °C and (−)-CSA (128 mg, 554 μmol, 10 mol %) was added. After 5 min at 0 °C, the mixture was warmed to rt and stirred for 18 h. The white suspension was diluted with CH_2Cl_2 (50 mL) and filtered through a pad of Celite®. The filtrate was washed with a saturated aqueous solution of $NaHCO_3$ (50 mL), H_2O (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 98:2) to afford PMB ether **8’”** (3.99 g, 4.97 mmol, 90%, dr > 98:2) as a colorless oil. $[\alpha]_D^{20}$ –7.25 (*c* 0.95, $CHCl_3$); **IR** (neat): 2953, 2929, 2856, 1613, 1513, 1463, 1427, 1361, 1247, 1106, 1083, 1037, 990 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.68-7.63 (m, 4H), 7.44-7.34 (m, 6H), 7.27 (m, 2H), 6.88 (m, 2H), 6.20 (dd, *J* = 15.0 and *J* = 10.4 Hz, 1H), 6.04 (dd, *J* = 15.0 and *J* = 10.4 Hz, 1H), 5.71-5.62 (m, 2H), 4.44 (s, 2H), 4.01 (br d, *J* = 6.5 Hz, 2H), 3.91 ($quint_{app}$, *J* = 6.1 Hz, 1H), 3.81 (s, 3H), 3.80 (m, 1H), 3.75-3.64 (m, 2H), 2.30 (m, 1H), 2.15 (m, 1H), 1.73 (m, 2H), 1.59 (t_{app}d, *J* = 6.5 and *J* = 2.5 Hz, 2H), 1.04 (s, 9H), 0.87 (s, 9H), 0.83 (s, 9H), 0.03 (s, 3H), 0.02 (br s, 6H), -0.02 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 159.2, 135.6 (4C), 133.9 (2C), 133.2, 131.9, 131.3, 130.5, 129.6 (2C), 129.4 (2C), 127.63 (4C), 127.56, 113.8 (2C), 71.6, 70.3, 69.3, 66.9, 60.9, 55.3, 45.0, 40.6, 40.3, 26.9 (3C), 25.9 (6C), 19.2, 18.1, 18.0, -4.3, -4.38, -4.44 (2C); **HRMS**: calculated for $C_{47}H_{74}O_5NaSi_3$ ($M+Na^+$): 825.4736. Found: 825.4741.

4.14.3. (3*S*,5*R*,7*E*,9*E*)-3,5-bis(*tert*-Butyldimethylsilyloxy)-11-(4-methoxybenzyloxy)undeca-7,9-dien-1-ol (**24**): To a solution of silyl ether **8’”** (1.95 g, 2.43 mmol, 1 equiv) in MeOH (36 mL) was added NH_4F (1.35 mg, 36.5 mmol, 15 equiv) and the mixture was refluxed for 1.5 h. The reaction mixture was allowed to cool to rt, quenched by

the addition of a saturated aqueous solution of $NaHCO_3$ (60 mL) and the mixture was extracted with Et_2O (2 × 60 mL) and EtOAc (2 × 60 mL). The combined organic phases were washed with brine (120 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 90:10) to afford alcohol **24** (891 mg, 1.58 mmol, 65%, dr > 98:2) as a colorless oil. $[\alpha]_D^{20}$ –27.1 (*c* 0.99, $CHCl_3$); **IR** (neat): 3428, 2952, 2929, 2856, 1613, 1513, 1463, 1361, 1248, 1036, 990 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.28 (m, 2H), 6.89 (m, 2H), 6.23 (dd, *J* = 15.3 and *J* = 10.4 Hz, 1H), 6.08 (dd, *J* = 15.2 and *J* = 10.4 Hz, 1H), 5.75-5.61 (m, 2H), 4.45 (s, 2H), 4.08 (m, 1H), 4.03 (br d, *J* = 6.3 Hz, 2H), 3.82 (m, 1H), 3.81 (s, 3H), 3.77-3.67 (m, 2H), 2.60 (br s, 1H, OH), 2.41-2.18 (m, 2H), 1.88 (m, 1H), 1.75-1.58 (m, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 159.2, 132.9, 132.2, 130.4, 129.4 (2C), 128.6, 127.9, 113.8 (2C), 71.6, 70.2, 69.29, 69.28, 60.2, 55.3, 43.9, 41.2, 37.4, 25.9 (6C), 18.0, 17.9, -4.1, -4.4, -4.6, -4.7; **HRMS**: calculated for $C_{31}H_{56}O_5NaSi_2$ ($M+Na^+$): 587.3559. Found: 587.3555.

*4.15. Synthesis of compound **26***

4.15.1. (3*R*,5*R*,7*E*,9*E*)-3,5-bis(*tert*-Butyldimethylsilyloxy)-11-(4-methoxybenzyloxy)undeca-7,9-dienal (**24'**): To a solution of alcohol **24** (830 mg, 1.47 mmol, 1 equiv) in CH_2Cl_2 (29 mL) at 0 °C were added $NaHCO_3$ (308 mg, 3.67 mmol, 2.5 equiv) and Dess-Martin periodinane (1.25 g, 2.94 mmol, 2 equiv). After 10 min, the mixture was warmed up to rt. After 2 h, the mixture was diluted with hexanes (60 mL), filtered through a pad of Celite® (the cake was washed with hexanes 3 x 20 mL) and the filtrate was concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 95:5) to afford aldehyde **24'** (614 mg, 1.09 mmol, 74%, dr > 98:2) as a slightly yellow oil. $[\alpha]_D^{20}$ –13.1 (*c* 0.95, $CHCl_3$); **IR** (neat): 2953, 2928, 2855, 1726, 1613, 1513, 1463, 1361, 1249, 1090, 1037, 990 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.79 (dd, *J* = 3.0 and *J* = 2.0 Hz, 1H), 7.27 (m, 2H), 6.88 (m, 2H), 6.22 (dd, *J* = 15.1 and *J* = 10.5 Hz, 1H), 6.07 (dd, *J* = 15.0 and *J* = 10.5 Hz, 1H), 5.70 (dt, *J* = 15.5 and *J* = 6.3 Hz, 1H), 5.64 (dt, *J* = 15.1 and *J* = 7.3 Hz, 1H), 4.44 (s, 2H), 4.32 (m, 1H), 4.02 (d, *J* = 6.3 Hz, 2H), 3.80 (s, 3H), 3.77 (m, 1H), 2.58 (ddd, *J* = 15.7, *J* = 4.5 and *J* = 2.0 Hz, 1H), 2.48 (ddd, *J* = 15.7, *J* = 6.6 and *J* = 3.1 Hz, 1H), 2.39-2.18 (m, 2H), 1.79-1.58 (m, 2H), 0.88 (s, 9H), 0.86 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 202.2, 159.2, 132.9, 132.3, 130.4, 130.3, 129.4 (2C), 128.0, 113.8 (2C), 71.7, 70.2, 69.0, 65.6, 55.3, 50.7, 44.8, 40.8, 25.9 (3C), 25.8 (3C), 18.0, 17.9, -4.2, -4.3, -4.5, -4.7; **HRMS**: calculated for $C_{31}H_{54}O_5NaSi_2$ ($M+Na^+$): 585.3402. Found: 585.3409.

4.15.2. Ethyl (2*E*,5*S*,7*R*,9*E*,11*E*)-5,7-bis(*tert*-butyldimethylsilyloxy)-13-(4-methoxybenzyloxy)-trideca-2,9,11-trienoate (**24"**): LiCl (60 mg, 1.41 mmol, 1.3 equiv) was heated 1 min with a heatgun and slowly cooled to rt under argon. The flask was then cooled to 0 °C and aldehyde **24'** (612 mg, 1.09 mmol, 1 equiv) in MeCN (11 mL) was added. Triethyl phosphonoacetate **25** (259 µL, 1.31 mmol, 1.2 equiv) was added dropwise and the mixture was stirred for 5 min before adding DBU (195 µL, 1.31 mmol, 1.2 equiv). The orange mixture was warmed up to rt and stirred for 20 h. The mixture was diluted with Et_2O (50 mL) and

washed with a saturated aqueous solution of NH_4Cl (2 × 50 mL) and brine (50 mL). The organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 95:5) to afford ester **24"** (585 mg, 0.924 mmol, 85%, dr > 98:2) as a colorless oil. $[\alpha]_D^{20}$ –16.8 (*c* 1.10, $CHCl_3$); **IR** (neat): 2953, 2929, 2856, 1720, 1513, 1463, 1363, 1249, 1086, 1039, 989 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.27 (m, 2H), 6.94 (m, 1H), 6.88 (m, 2H), 6.21 (dd, *J* = 15.2 and *J* = 10.4 Hz, 1H), 6.05 (dd, *J* = 15.1 and *J* = 10.6 Hz, 1H), 5.82 (d, *J* = 15.7 Hz, 1H), 5.73-5.59 (m, 2H), 4.44 (s, 2H), 4.22-4.13 (m, 2H), 4.02 (d, *J* = 6.4 Hz, 2H), 3.90 (m, 1H), 3.80 (s, 3H), 3.78 (m, 1H), 2.45-2.15 (m, 4H), 1.70-1.51 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.88 (br s, 18H), 0.04 (br s, 12H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.3, 159.2, 145.7, 133.0, 132.1, 130.7, 130.4, 129.4 (2C), 127.8, 123.5, 113.8 (2C), 71.6, 70.2, 69.1, 68.5, 60.2, 55.3, 44.7, 40.8, 40.1, 25.9 (3C), 25.8 (3C), 18.0 (2C), 14.3, -4.2, -4.45, -4.49 (2C); **HRMS**: calculated for $C_{35}H_{60}O_6NaSi_2$ ($M+Na^+$): 655.3821. Found: 655.3822.

4.15.3 (2*E*,5*S*,7*R*,9*E*,11*E*)-5,7-bis(*tert*-Butyldimethylsilyloxy)-13-(4-methoxybenzyloxy)trideca-2,9,11-trien-1-ol (**26**): To a solution of ester **24"** (560 mg, 0.885 mmol, 1 equiv) in CH_2Cl_2 (44 mL) at –78 °C was added DIBAL-H (2.65 mL, 1 M in toluene, 2.65 mmol, 3 equiv) dropwise. The mixture was then stirred at –78 °C for 1 h. The reaction mixture was poured on a saturated aqueous solution of Rochelle's salts (75 mL) stirred for 2 h and the aqueous phase was extracted with CH_2Cl_2 (3 × 75 mL). The combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 85:15) to afford alcohol **26** (463 mg, 0.783 mmol, 88%, dr > 98:2) as a colorless oil. $[\alpha]_D^{20}$ –6.6 (*c* 0.50, $CHCl_3$); **IR** (neat): 3418, 2953, 2926, 2854, 1613, 1513, 1463, 1361, 1248, 1088, 1039 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.27 (m, 2H), 6.88 (m, 2H), 6.22 (dd, *J* = 15.0 and *J* = 10.4 Hz, 1H), 6.05 (dd, *J* = 15.1 and *J* = 10.6 Hz, 1H), 5.73-5.59 (m, 4H), 4.44 (s, 2H), 4.06 (br d, *J* = 3.8 Hz, 2H), 4.01 (d, *J* = 6.3 Hz, 2H), 3.86-3.75 (m, 2H), 3.80 (s, 3H), 2.38-2.10 (m, 4H), 1.64 (br s, 1H, OH), 1.59 (t_{app}, *J* = 6.4 Hz, 1H), 1.59 (t_{app}, *J* = 6.6 Hz, 1H), 0.89 (br s, 18H), 0.05 (br s, 12H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 159.2, 133.2, 132.0, 131.7, 131.1, 130.4, 129.5 (2C), 128.9, 127.6, 113.8 (2C), 71.7, 70.2, 69.2, 69.1, 63.6, 55.3, 44.1, 40.5, 40.2, 25.9 (6C), 18.1 (2C), -4.3 (2C), -4.47, -4.50; **HRMS**: calculated for $C_{33}H_{58}O_5NaSi_2$ ($M+Na^+$): 613.3715. Found: 613.3713.

*4.16. Synthesis of compound **27***

(1*E*,3*E*,6*S*,8*R*,10*E*,12*E*)-6,8-bis(*tert*-Butyldimethylsilyloxy)-1-iodo-14-(4-methoxybenzyloxy)tetradeca-1,3,10,12-tetraene (**27**): To a solution of alcohol **26** (430 mg, 0.728 mmol, 1 equiv) in CH_2Cl_2 (15 mL) at 0 °C was added $NaHCO_3$ (150 mg, 1.82 mmol, 2.5 equiv) and Dess-Martin periodinane (620 mg, 1.46 mmol, 2 equiv). The mixture was stirred at 0 °C for 15 min and warmed up to rt. After 2 h, the reaction mixture was diluted with hexanes (150 mL), stirred for 5 min, filtered through a pad of Celite® and concentrated under reduced pressure. The crude aldehyde **26'** was used without any further purification in the next step.

To a suspension of $CrCl_2$ (1.79 g, 14.6 mmol, 20 equiv) in THF (20 mL) at 0 °C was canulated a solution of crude aldehyde **26'** (0.728 mmol, 1 equiv) and CHI_3 (573 mg, 1.46 mmol, 2 equiv) in dioxane (50 mL). After 5 min at 0 °C the mixture was warmed up to rt, and stirred in the dark for 2 h. The reaction mixture was diluted with Et_2O (100 mL) and poured into H_2O (100 mL). The mixture was then stirred for 5 min and saturated with NaCl. The phases were separated and the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 95:5) to afford iododiene **27** (462 mg, 0.648 mmol, 89%) as a colorless oil. ^{1}H NMR analysis shows an 89:11 mixture of *E*/*Z* compounds; $[\alpha]_D^{20}$ –3.76 (*c* 1.25, $CHCl_3$); **IR** (neat): 2952, 2928, 2855, 1613, 1513, 1462, 1361, 1248, 1077, 1038 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) (major "all *E*" diastereomer): δ 7.27 (d, *J* = 8.7 Hz, 2H), 6.98 (dd, *J* = 14.3 and *J* = 10.6 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.21 (dd, *J* = 15.2 and *J* = 10.6 Hz, 1H), 6.18 (d, *J* = 14.4 Hz, 1H), 6.04 (dd, *J* = 15.1 and *J* = 10.3 Hz, 1H), 5.96 (dd, *J* = 15.2 and *J* = 10.4 Hz, 1H), 5.74-5.60 (m, 3H), 4.45 (s, 2H), 4.03 (d, *J* = 6.0 Hz, 2H), 3.88-3.73 (m, 2H), 3.80 (s, 3H), 2.40-2.07 (m, 4H), 1.59 (m, 2H), 0.88 (s, 9H), 0.87 (s, 9H), 0.06-0.02 (m, 12H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 159.2, 145.3, 133.1, 132.8, 132.1, 132.0, 130.9, 130.5, 129.4 (2C), 127.8, 113.8 (2C), 77.0, 71.7, 70.3, 69.2, 68.9, 55.3, 44.3, 40.7, 40.3, 25.9 (6C), 18.1 (2C), -4.2, -4.3, -4.47, -4.49; **HRMS**: calculated for $C_{34}H_{57}IO_4NaSi_2$ ($M+Na^+$): 735.2732. Found: 735.2734.

*4.17. Synthesis of compound **23***

(2*E*,4*E*,7*R*,9*S*,11*E*,13*E*)-7,9-bis(*tert*-Butyldimethylsilyloxy)-14-iodotetradeca-2,4,11,13-tetraen-1-ol (**23**): To a solution of PMB ether **27** (375 mg, 526 μmol, 1 equiv) in CH_2Cl_2 (45 mL) at 0 °C were added an aqueous phosphate buffer (pH = 7.2) (9 mL) and DDQ (179 mg, 789 μmol, 1.5 equiv) and the mixture was stirred at 0 °C for 4.5 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and quenched with a saturated aqueous solution of $NaHCO_3$ (50 mL). The two phases were separated and the organic phase was washed with a saturated aqueous solution of $NaHCO_3$ (50 mL), H_2O (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a non separable mixture of aldehyde **28** and *p*-anisaldehyde.

This crude mixture was diluted in CH_2Cl_2 (26 mL), cooled to –78 °C and DIBAL-H (1.05 mL, 1 M in DCM, 1.05 mmol, 2 equiv) was added dropwise. The mixture was stirred at –78 °C for 1 h, poured into a saturated aqueous solution of Rochelle salt (25 mL), diluted with CH_2Cl_2 (20 mL) and vigorously stirred for 3 h. The two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 90:10) to afford alcohol **23** (170 mg, 0.287 mmol, 55%, dr > 98:2) as a colorless oil. $[\alpha]_D^{20}$ –0.89 (*c* 1.69, $CHCl_3$); **IR** (neat): 3334, 2953, 2928, 2856, 1471, 1462, 1361, 1254, 1083 cm^{-1}; **^{1}H NMR** (400 MHz, C_6D_6): δ 6.89 (dd, *J* = 14.3 and *J* = 10.5 Hz, 1H), 6.16 (br dd, *J* = 15.1 and *J* = 10.5 Hz, 1H), 6.06 (dd, *J* = 15.0 and *J* = 10.6 Hz, 1H), 5.89 (d, *J* = 14.3 Hz, 1H), 5.77-5.65 (m, 2H), 5.64-5.50 (m, 2H), 3.90 (d, *J* = 5.6 Hz, 2H), 3.88-3.79 (m,

2H), 2.35-2.02 (m, 4H), 1.73 (m, 2H), 1.31 (m, 1H, OH), 1.00 (s, 9H), 0.98 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H), 0.06 (s, 3H); **^{13}C NMR** (100 MHz, C_6D_6): δ 145.5, 133.1, 132.9, 131.8, 131.6, 130.8, 130.2, 77.7, 69.7, 69.2, 63.1, 44.8, 41.0, 40.7, 26.10 (3C), 26.07 (3C), 18.3, 18.2, -4.1, -4.2, -4.3 (2C); **HRMS**: calculated for $C_{26}H_{49}IO_3NaSi_2$ ($M+Na^+$): 615.2157. Found: 615.2156.

*4.18. Synthesis of compound **29***

(2*R*,4*R*,6*S*,7*E*,9*E*,11*E*,14*S*,16*R*,18*E*,20*E*)-2,6,14,16-tetrakis(*tert*-Butyldimethylsilyloxy)-22-hydroxydocosa-7,9,11,18,20-pentaen-4-yl 2-(diethoxyphosphoryl)acetate (**29**): To a solution of iododiene **23** (90 mg, 152 μmol, 1 equiv) and vinylstannane **20** (195 mg, 228 μmol, 1.5 equiv) in NMP (1.0 mL) at 0 °C were added copper thiophencarboxylate (64 mg, 334 μmol, 2.2 equiv) and tetrabutylamonium diphenylphosphinate (154 mg, 334 μmol, 2.2 equiv) and the mixture was stirred at 0 °C for 3 h and 1 h at rt. The mixture was diluted with Et_2O (10 mL), washed with H_2O (2 × 15 mL) and brine (15 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (deactivated with petroleum ether/Et_3N = 99:1 and washed 3 times with petroleum ether/EtOAc = 75:25) (petroleum ether/EtOAc = 75:25) to afford triene **29** (64 mg, 62.0 μmol, 41%, dr > 98:2). $[\alpha]_D^{20}$ +4.75 (*c* 1.22, $CHCl_3$); **IR** (neat): 3424, 2954, 2929, 2857, 1737, 1472, 1463, 1387, 1361, 1253, 1054, 1027, 996 cm^{-1}; **^{1}H NMR** (400 MHz, C_6D_6): δ 6.54 (dd, *J* = 15.2 and *J* = 10.7 Hz, 1H), 6.37 (dd, *J* = 15.0 and *J* = 10.3 Hz, 1H), 6.28 (dd, *J* = 15.1 and *J* = 10.7 Hz, 1H), 6.19-6.04 (m, 3H), 5.81-5.64 (m, 4H), 5.51 (m, 1H), 4.59 (td, *J* = 8.3 and *J* = 3.3 Hz, 1H), 4.15 (m, 2H), 4.06-3.89 (m, 6H), 3.83 (m, 1H), 2.78 (d, *J* = 21.4 Hz, 2H), 2.40-2.21 (m, 4H), 2.06 (ddd, *J* = 13.9, *J* = 7.5 and *J* = 5.2 Hz, 1H), 1.99-1.84 (m, 3H), 1.79-1.65 (m, 2H), 1.29 (d, *J* = 6.0 Hz, 3H), 1.09-1.04 (m, 15H), 1.03-0.99 (m, 27H), 0.30 (s, 3H), 0.22 (s, 3H), 0.15 (s, 3H), 0.13 (s, 3H), 0.13-0.11 (m, 12H); **^{13}C NMR** (100 MHz, C_6D_6): δ 136.7, 134.0, 133.4, 133.3, 132.0, 131.3, 131.2, 130.90, 130.85, 129.7, 71.0, 70.9, 70.0, 69.6, 66.1, 63.0, 62.6 (d, *J* = 6.2 Hz, 2C), 45.6, 44.7, 44.1, 41.5, 40.5, 34.9 (d, *J* = 133.9 Hz), 26.3 (3C), 26.2 (3C), 26.12 (3C), 26.10 (3C), 23.7, 18.4, 18.30, 18.26 (2C), 16.4 (2C), -3.5 to -4.5 (8C).[31] **HRMS**: calculated for $C_{52}H_{103}O_{10}NaPSi_4$ ($M+Na^+$): 1053.6258. Found: 1053.6246.

*4.19. Synthesis of compound **22***

(3*E*,5*E*,7*E*,10*R*,12*S*,14*E*,16*E*,18*E*,20*S*,22*R*)-10,12,20-tris(*tert*-Butyldimethylsilyloxy)-22-[(*R*)-2-(*tert*-butyldimethylsilyloxy)propyl]oxacyclodocosa-3,5,7,14,16,18-hexaen-2-one (**22**): To a solution of alcohol **29** (61 mg, 59.1 μmol, 1 equiv) in CH_2Cl_2 (1.6 mL) at rt was added MnO_2 (154 mg, 1.77 mmol, 30 equiv) and the mixture was stirred at rt for 18 h. The reaction mixture was filtered through a pad of Celite® and concentrated under reduced pressure to afford crude aldehyde **30**.

To a solution of **30** (61 mg, 59.1 μmol, 1 equiv) in THF (75 mL) at 0 °C was added NaH (237 mg, 60%wt in mineral oil, 5.91 mmol, 100 equiv) and the mixture was stirred at 0 °C for 3 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (25 mL) and the aqueous phase was extracted with Et_2O (3 × 25 mL). The combined organic phases were washed with brine (75 mL), dried over $MgSO_4$, filtered and concentrated under

reduced pressure. The crude material was purified by flash chromatography on silica gel (deactivated with petroleum ether/Et_3N = 99:1 and washed 3 times with petroleum ether/EtOAc = 97:3) (petroleum ether/EtOAc: 97/3) to afford lactone **22** (28 mg, 32.0 µmol, 54%, dr > 98:2). $[\alpha]_D^{20}$ –65.1 (*c* 0.44, $CHCl_3$); **IR** (neat): 2955, 2928, 2856, 1709, 1620, 1471, 1463, 1379, 1361, 1254, 1083, 1001 cm^{-1}; **^{1}H NMR** (400 MHz, C_6D_6): δ 7.32 (dd, *J* = 15.2 and *J* = 11.3 Hz, 1H), 6.43 (br dd, *J* = 15.2 and *J* = 10.5 Hz, 1H), 6.16 (dd, *J* = 14.9 and *J* = 10.5 Hz, 1H), 6.10 (dd, *J* = 14.9 and *J* = 10.2 Hz, 1H), 5.97 (dd, *J* = 14.9 and *J* = 10.4 Hz, 1H), 5.95-5.82 (m, 4H), 5.81-5.59 (m, 3H), 5.53 (m, 1H), 4.40 (m, 1H), 3.94 (q_{app}, *J* = 6.2 Hz, 1H), 3.89 (m, 1H), 3.76 (m, 1H), 2.35-2.21 (m, 4H), 2.19-2.07 (m, 3H), 1.98 (m, 1H), 1.70-1.55 (m, 2H), 1.20 (d, *J* = 5.9 Hz, 3H), 1.04 (s, 9H), 1.04 (s, 9H), 1.02 (s, 18H), 0.15 (s, 3H), 0.14 (s, 3H), 0.13 (s, 6H), 0.12 (s, 6H), 0.11 (s, 3H), 0.09 (s, 3H); **^{13}C NMR** (100 MHz, C_6D_6): δ 165.8, 146.0, 141.7, 137.7, 135.7, 134.0, 132.72, 132.66, 131.7, 129.3, 128.6, 128.2, 120.9, 72.3, 70.7, 69.8, 69.2, 66.1, 45.9, 45.4, 42.5, 40.5, 40.3, 26.16 (3C), 26.15 (3C), 26.1 (3C), 26.0 (3C), 24.0, 18.4, 18.3 (2C), 18.2, -4.0, -4.2, -4.3 (2C), -4.49, -4.52, -4.6, -4.8; **HRMS**: calculated for $C_{48}H_{90}O_6NaSi_4$ ($M+Na^+$): 897.5707. Found: 897.5703.

*4.20. Synthesis of compound **31***

(3*E*,5*E*,7*E*,10*R*,12*S*,14*E*,16*E*,18*E*,20*S*,22*R*)-10,12,20-trihydroxy-22-[(*R*)-2-hydroxypropyl]oxacyclodocosa-3,5,7,14,16,18-hexaen-2-one (**31**): To a solution of silylated macrolactone **22** (25 mg, 28.6 µmol, 1 equiv) and pyridine (0.200 mL, 2.47 mmol, 87 equiv) in THF (2 mL) at 0 °C was added HF·Py (0.500 mL, 3.88 mmol, 136 equiv) and the mixture was stirred at rt for 3 h. The reaction mixture was quenched by careful addition of a saturated aqueous solution of $NaHCO_3$ (10 mL) and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by preparative thin layer chromatography on silica gel (deactivated with petroleum ether/Et_3N = 99:1 and washed twice with EtOAc) (EtOAc = 100%) to afford macrolactone **31** (7.7 mg, 18.4 µmol, 64%). $[\alpha]_D^{20}$ –42.1 (*c* 0.145, MeOH); **IR** (neat): 3383, 2361, 2341, 1653, 1024, 991 cm^{-1}; **^{1}H NMR** (400 MHz, DMSO-d6): δ 7.03 (dd, *J* = 15.0 and *J* = 11.2 Hz, 1H), 6.50 (dd, *J* = 14.9 and *J* = 10.5 Hz, 1H), 6.27 (dd, *J* = 14.9 and *J* = 11.1 Hz, 1H), 6.15 (dd, *J* = 15.2 and *J* = 10.6 Hz, 1H), 6.02-5.78 (m, 5H), 5.74 (d, *J* = 15.5 Hz, 1H), 5.57-5.46 (m, 2H), 5.09 (m, 1H), 4.82 (d, *J* = 4.0 Hz, 1H, OH), 4.74 (d, *J* = 4.1 Hz, 1H, OH), 4.61 (d, *J* = 4.1 Hz, 1H, OH), 4.50 (d, *J* = 4.9 Hz, 1H, OH), 3.96 (m, 1H), 3.67-3.52 (m, 3H), 2.36 (m, 1H), 2.24-2.07 (m, 2H), 2.06-1.91 (m, 2H), 1.79-1.63 (m, 2H), 1.59 (m, 1H), 1.49 (m, 1H), 1.17 (m, 1H), 1.06 (d, *J* = 6.0 Hz, 3H); **^{13}C NMR** (100 MHz, DMSO-d6): δ 165.5, 145.2, 141.4, 137.7, 136.2, 132.4, 132.3, 132.0, 130.6, 130.5, 128.3, 127.7, 120.0, 70.2, 69.8, 68.4, 67.9, 62.9, 44.6, 42.8, 41.0, 40.7, 40.3, 23.8; **HRMS**: calculated for $C_{24}H_{33}O_5$ ($M–H_2O+H^+$): 401.2328. Found: 401.2340.[32]

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6. References and notes

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4. Active on HCT-5 (colon cancer, IC_{50} = 56.3 µM), HCT-115 (colon cancer, IC_{50} = 52.4 µM), A549 (lung cancer, IC_{50} = 118.5 µM), MDA-MB-231 (breast cancer, IC_{50} = 120.4 µM) and K562 (leucocythemia, IC_{50} = 130.5 µM).
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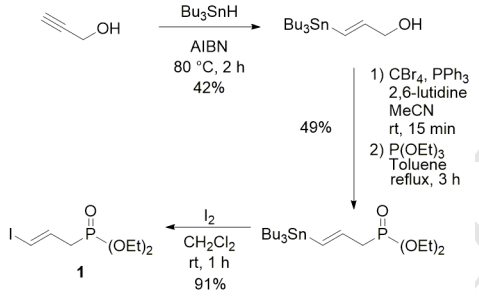
9. Propynol was transformed to iodovinyl phosphonate **1** in four steps as depicted in the following scheme according to reference 8:



10. The ee of **4** and its *R* absolute configuration were determined by ^{1}H NMR after derivatization with (*S*)- and (*R*)- methoxyphenylacetic acids. See: (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519. (b) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370–2374. (c) Seco, J. M.; Quiñoá, E.; Riguera, R. *Tetrahedron: Asymmetry* **2001**, *12*, 2915–2925.
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24. Starting from **27** as a 89:11 mixture of *E*/*Z* isomers, only the all-*E* coupling compound was isolated after purification by flash chromatography on silica gel (41% yield).
25. Macrolactone **31**: $[\alpha]_D^{20}$ –42.1 (*c* 0.145, MeOH); wortmannilactone C: $[\alpha]_D^{20}$ lit.[3] –9.2 (*c* 0.85, MeOH).
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30. A stored sample of compound **21** underwent decomposition before the HRMS could be recorded.
31. Due to the coupling with the phosphorus atom, the signal of the carbonyl was not visible on the ^{13}C NMR spectrum. However the carbonyl appears on the IR spectrum (1737 cm^{-1}) and is still present in the next compound, **22**.
32. Loss of one molecule of water was observed.