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Approaches to the synthesis of the C1-C15 fragment of dolabelide C

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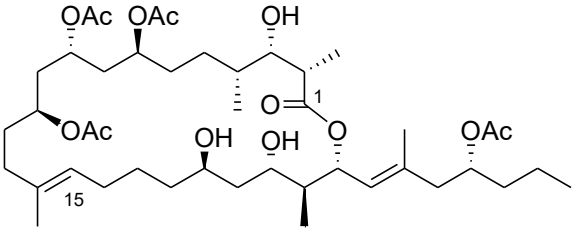
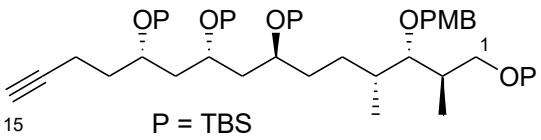
Abstract

Several approaches to the synthesis of the C1-C15 fragment of dolabelide C are presented, featuring cross-metathesis reactions as key steps. These approaches highlight the poor performance of the Negishi zirconium-catalyzed carboalumination of alkynes on substrates containing protected alcohols. A serendipitous deprotection of the benzylidene acetal moiety is described, using the reaction conditions to transform an ester into the corresponding Weinreb amide.



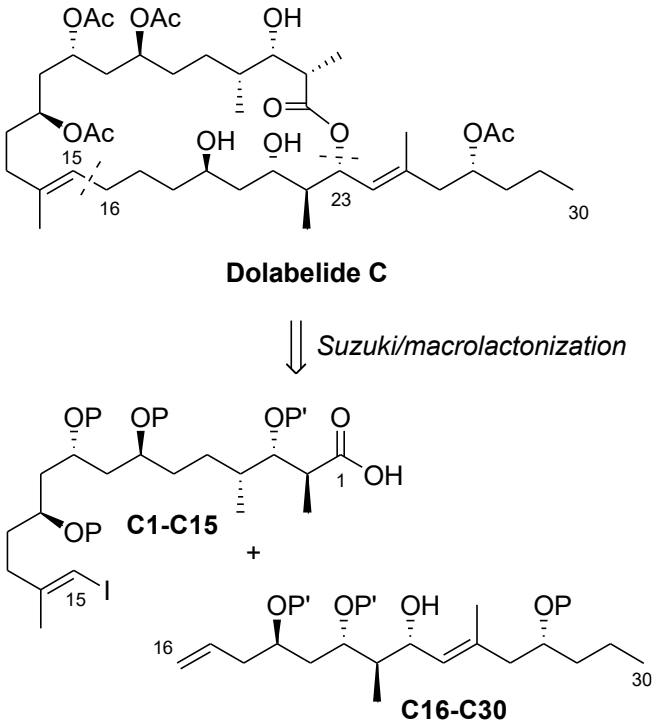
Dolabelide C



Keywords: Dolabelide C, multi-step synthesis, cross metathesis, benzylidene acetal deprotection, oxa-Michael

Introduction

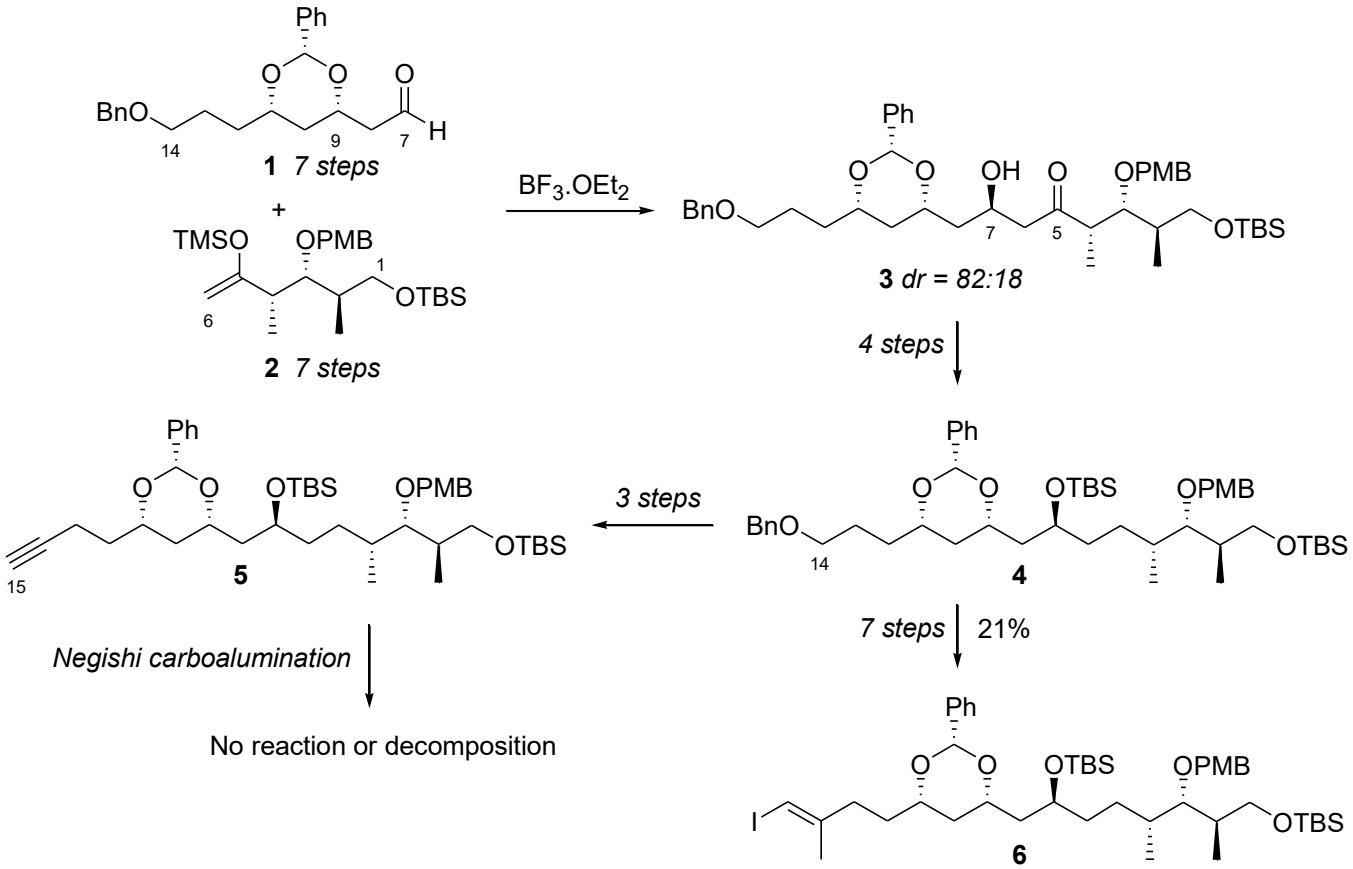
In 1995, Yamada and coworkers isolated the two 22-membered-ring lactones dolabelides A and B from the sea hare *Dolabella auricularia* (family Aplysiidae).[1] Two years later, dolabelides C and D, structurally related 24-membered-ring lactones, were extracted from the same marine organism by the same group.[2] All four polyketides are active against HeLa-S3 cell lines, with IC_{50} values of 6.3, 1.3, 1.9, and 1.5 μg/mL, respectively. The total synthesis of dolabelide D was accomplished by Leighton *et al.* in 2006,[3] and five years later the Hanson group reported the synthesis of dolabelide C.[4] In addition, several groups reported the preparation of diverse portions of dolabelides: Phansavath and Genêt,[5-7] Leighton,[8] Keck,[9] Hanson,[10,11] Yadav,[12] and we published the synthesis of the C1-C15[13] and C16-C30[14,15] fragments of dolabelide C. The retrosynthesis we envisaged is outlined in Scheme 1. The macrocycle would be formed by a lactonization reaction, and the two fragments assembled by a *B*-alkyl Suzuki coupling between the vinyl iodide at C15 and a borane derived from the alkene at C16.



Scheme 1. Retrosynthesis of dolabelide C.

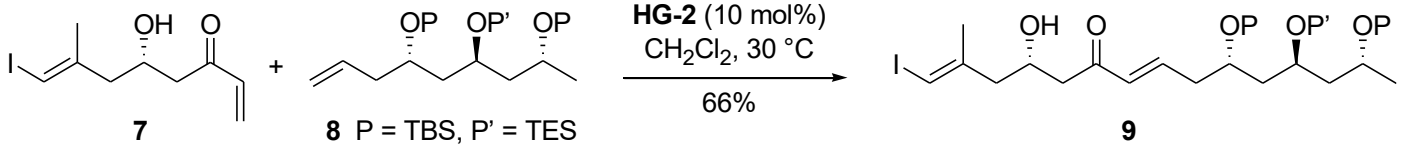
The construction of the C1-C15 fragment we previously reported[13] (Scheme 2) is efficient (10% overall yield) but long (19 steps for the longest linear sequence). The vinyl iodide moiety, which is a sensitive functional group, was installed towards the end from a benzyl alcohol at C14. We chose to form the C6-C7 bond and install the stereocenter at C7 by a diastereoselective aldol. The aldol reaction with the boron enolate controlling the stereoselectivity was very diastereoselective (not shown), but unfortunately gave the wrong epimer at C7.[16] The Mukaiyama aldol between the aldehyde **1** and the silyl enol ether **2**, where the stereochemistry is controlled by the C9 stereocenter of the aldehyde, was high yielding, but aldol **3** was obtained as an 82:18 mixture of epimers at C7. Furthermore, the ketone at C5 had to be removed, since it is not present in the natural product, adding 3 steps to the synthetic route. Finally, Negishi carboalumination of alkyne **5** failed to give the desired vinyl iodide: no reaction occurred at low temperature, and only decomposition was observed at 60°C. The benzylidene acetal moiety seems incompatible with the

carboalumination conditions. An alternative route involving a cross-metathesis reaction with a vinyl boronate was implemented, but compound **4** was transformed into the C1-C15 fragment **6** in only 21% yield over 7 steps. These results prompted us to modify our synthesis since the aldol strategy was not efficient.



Scheme 2. Previous synthesis of the C1-C15 fragment from our group.

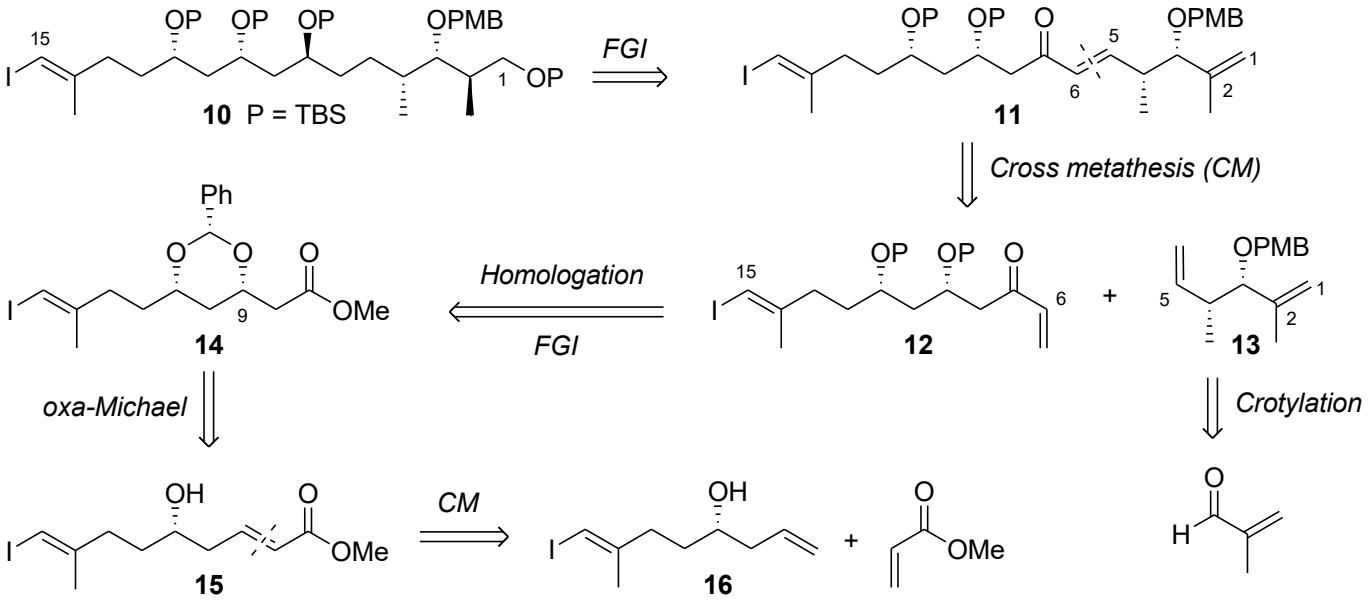
We decided to replace the key aldol reaction by a cross-metathesis reaction to form the C6-C7 bond. This reaction should be compatible with the vinyl iodide moiety at C15, as shown by the precedent described by Cossy *et al.* for their synthesis of marinomycin,[17] where enone **7** bearing a vinyl iodide and alkene **8** gave enone **9** in 66% yield (Scheme 3).



Scheme 3. Cross-metathesis rection en route to marinomycin.

Our revised synthesis of the C1-C15 fragment **10** is shown in Scheme 4. Functional group interconversions on **10** reveal enone **11**, which would be formed by cross metathesis between enone **12** and *bis* alkene **13**. We chose to install the hydroxyl group at C1 and the stereocenter at C2 by a diastereoselective hydroboration reaction, in order to shorten the synthesis of the C1-C5 fragment: two steps including an enantioselective crotylation[18] of methacrolein *vs* 7 steps in the previous route for the C1-C6 fragment. Enone **12** would be constructed from ester **14**, and the stereocenter at C9 would be installed by an intramolecular oxa-Michael

addition on conjugated ester **15**.[19] Ester **16** would be prepared by another cross-metathesis reaction, between homoallylic alcohol **16** and methyl acrylate.

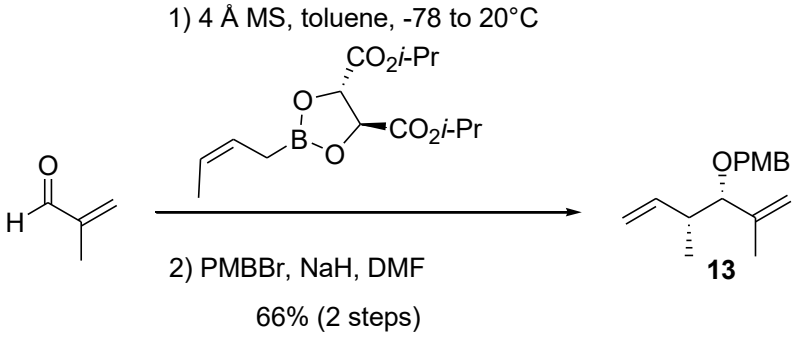


Scheme 4. New retrosynthesis of the C1-C15 fragment.

Herein we discuss the diverse attempts we made to improve the synthesis of the C1-C15 fragment of dolabelide C.

Results and Discussion

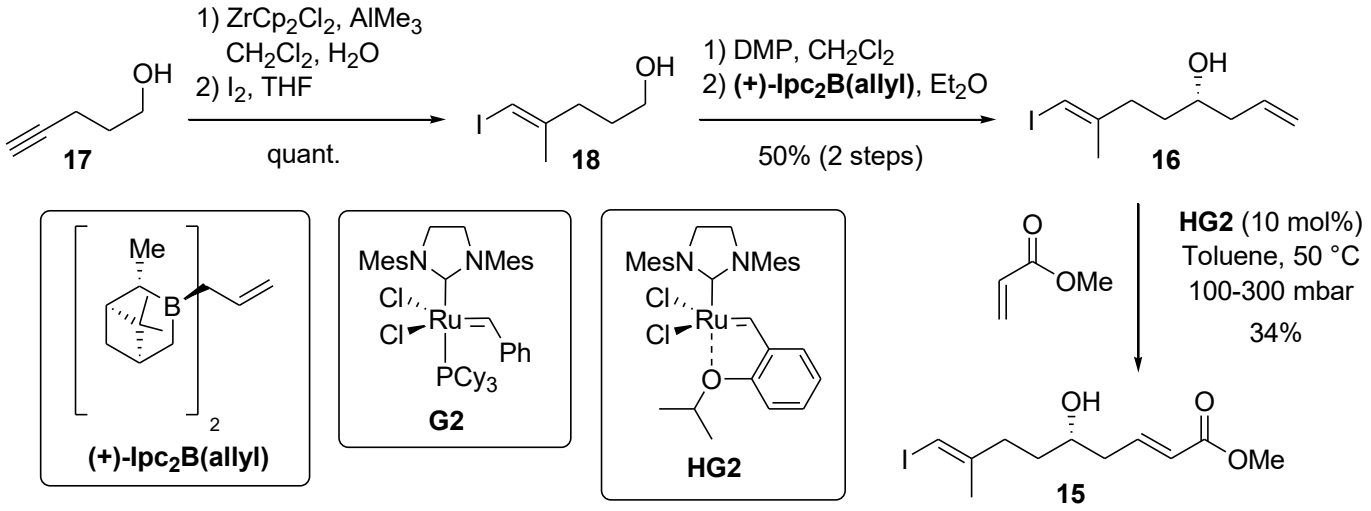
The construction of the C1-C5 fragment **13** is described in Scheme 5. Roush crotylation of methacrolein furnished the desired homoallylic alcohol (85:15 er), which was subsequently protected as its PMB ether **13** in 66% yield for the two steps.



Scheme 5. Synthesis of C1-C5 fragment **13**.

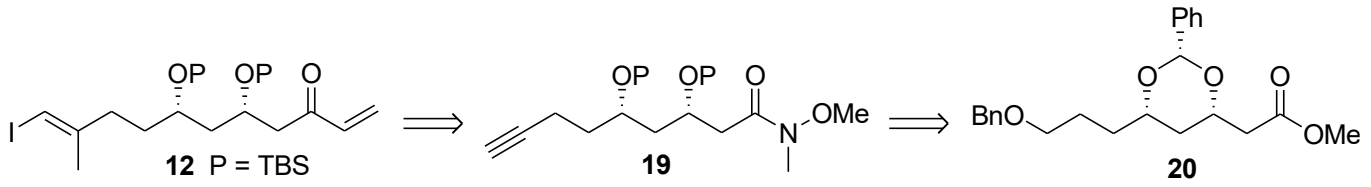
The synthesis of the C6-C15 fragment **12** started with a Negishi carboalumination of alkyne **17** under Wipf's conditions (Scheme 6), where the addition of one equivalent of water accelerates the reaction.[20] Alcohol **18**, obtained in quantitative yield, was oxidized with the Dess-Martin periodinane (DMP) and the

resulting aldehyde was submitted to a Brown allylation reaction[21] with (+)-Ipc$_2$B(allyl) in 50% yield for the 2 steps. The enantioselectivity of the allylation reaction was not determined at this stage, but was assumed to be on par with that observed with simple linear aldehydes. Cross metathesis with methyl acrylate in the presence of Grubbs second-generation catalyst (**G2**) in 1,2-dichlorethene at 50° C did not afford any of the desired product **15**. Switching to use of the Hoveyda-Grubbs second-generation catalyst (**G2**) in toluene at 50° C under reduced pressure gave compound **15** in 34% yield. The reaction was not optimized further, because exposure of conjugated ester **15** to benzaldehyde and catalytic potassium *tert*-butoxide did not give the desired benzylidene acetal **14** but only led to decomposition.



Scheme 6. Attempts at synthesizing alcohol **15**.

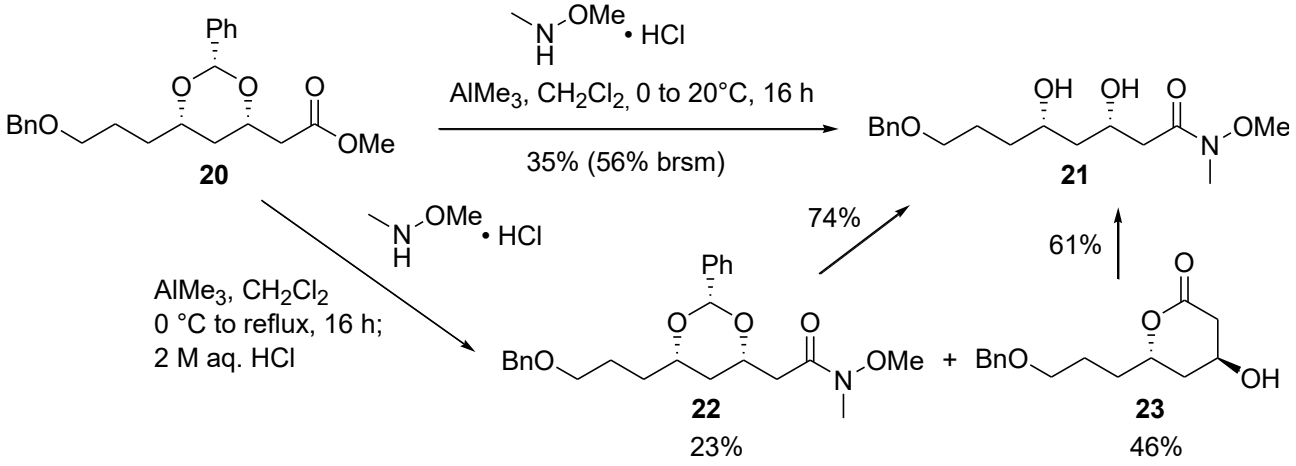
A modified retrosynthesis of enone **12** was thus devised, with the formation of the vinyl iodide taking place after the oxa-Michael reaction (Scheme 7). To that effect, the previously prepared benzylidene acetal **20** (precursor to aldehyde **1**) would need to be transformed into *bis* silyl ether Weinreb amide **19**.



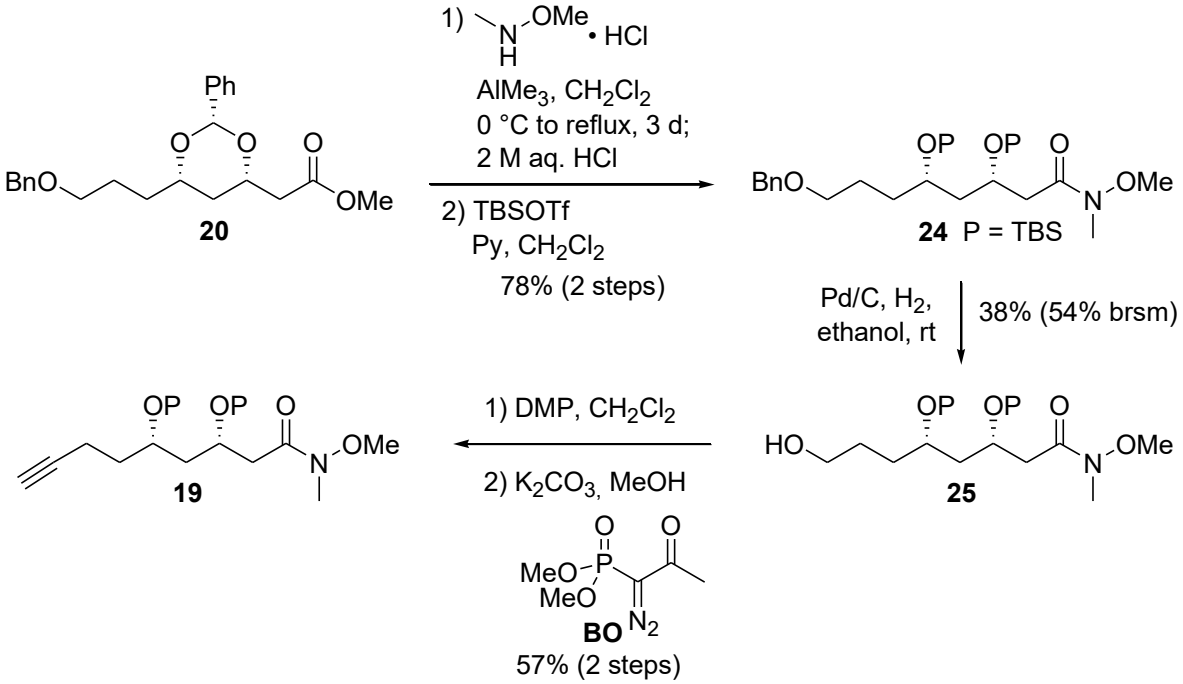
Scheme 7. Modified retrosynthesis of enone **12**.

We first attempted to convert ester **20** into the corresponding Weinreb amide; however, the standard conditions for this transformation (methoxyamine hydrochloride and trimethylaluminum) led to concomitant cleavage of the benzylidene acetal and diol **21** was formed in 35% yield, along with some recovered **20** (Scheme 8). This serendipitous discovery was fortuitous, since the benzylidene acetal is resistant to hydrogenation and its hydrolysis requires harsh acidic conditions, so we set out to optimize the formation of diol **21**. Under more forcing conditions (reflux of dichloromethane), benzylidene acetal-Weinreb amide **22** and lactone **23** were obtained in 23% and 46% yield, respectively, along with 13% of the starting material **20**, proving that cleavage of the benzylidene acetal and formation of the Weinreb amide occur at roughly the same rate. Both these intermediates could be converted into diol **21** by resubmission to the same reaction

conditions in 74% and 61% yield, respectively. Interestingly, when the amine was omitted from the reaction mixture, the benzylidene acetal remained intact, implying that the dimethylaluminum amide is necessary for its removal. This deprotection probably follows the same mechanistic pathway as the regioselective reduction of benzylidene acetals flanked by a sulfone group we observed with DIBAL-H:[22] complexation of the dimethylaluminum amide by the carbonyl of the ester and the proximal oxygen of the benzylidene acetal, opening of the benzylidene acetal to form the corresponding oxonium ion, which is attacked by the amido ligand to produce an aminocetal. This aminoacetal is then hydrolyzed during the acidic workup.



Scheme 8. Serendipitous hydrolysis of the benzylidene acetal.

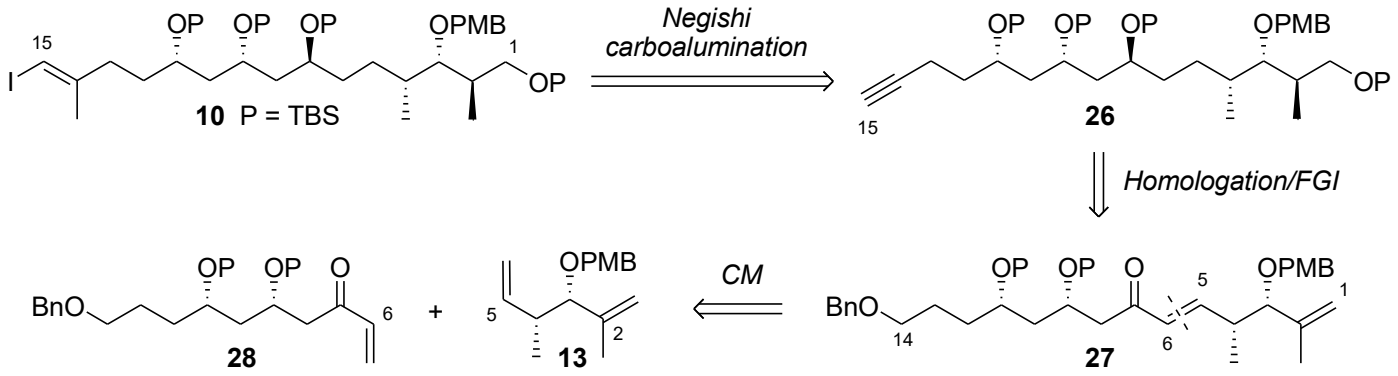


Scheme 9. Synthesis of terminal alkyne **19**.

Eventually, the best way forward was to let the reaction proceed for 3 days and perform the protection of the diol on the crude reaction mixture; in this fashion, *bis* silyl ether **24** was prepared in 78% yield for the 2 steps (Scheme 9). Hydrogenation of the benzyl ether produced the primary alcohol **25** in 38% unoptimized yield. This alcohol was oxidized with DMP to the corresponding aldehyde, which was converted into the

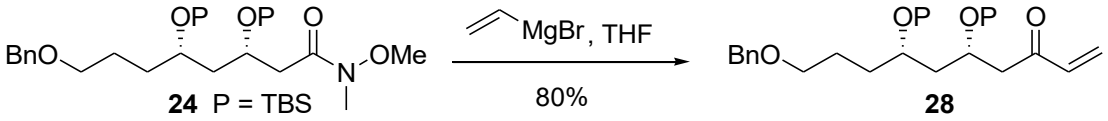
terminal alkyne **19** by treatment with the Bestmann-Ohira (**BO**) reagent. Unfortunately, the Negishi carboalumination failed on this substrate, only giving a complex mixture of products.

At this point, we decided to leave the formation of the vinyl iodide for the end of the synthesis, which would be installed on compound **26** (Scheme 10). Enone **27** would be formed by a cross metathesis between enone **28** and protected alcohol **13**.



Scheme 10. Revised retrosynthesis of vinyl iodide **10**.

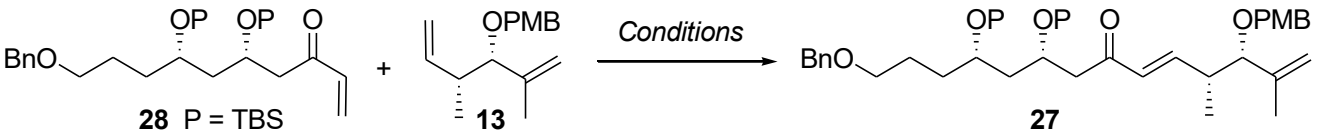
Enone **28** was formed by vinyl Grignard addition to the Weinreb amide **24** in good yield (Scheme 11).



Scheme 11. Synthesis of enone **28**.

The cross-metathesis reaction between enone **28** and protected alcohol **13** was then optimized. A slight excess of the more reactive but less precious olefin **13** was used. When heating the two compounds in the presence of the Grubbs 2 catalyst in dichloromethane at reflux for 3 days, only 39% yield of the desired product **27** was formed (Table 1, entry 1). This yield could be increased to 57% and 68% when using the Hoveyda-Grubbs 2 catalyst in 5 and 10 mol% loadings, respectively (entries 2 and 3). Running the reaction in toluene at 60 °C did not improve the yield any further (entry 4). The best conditions involved using an excess of enone **28** and decreasing the reaction time to 16 h (entry 5), the only drawback being that the excess of expensive **28** could not be recovered.

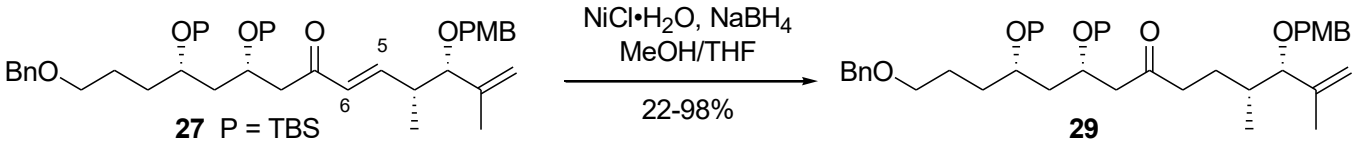
Table 1. Cross metathesis optimization of enone **28** with protected alcohol **13**.



Entry	Equivalents (28/13)	Catalyst (mol%)	Solvent	Time	Temp.	Yield
1	1:1.4	**G2** (10)	CH_2Cl_2	3 days	reflux	39%

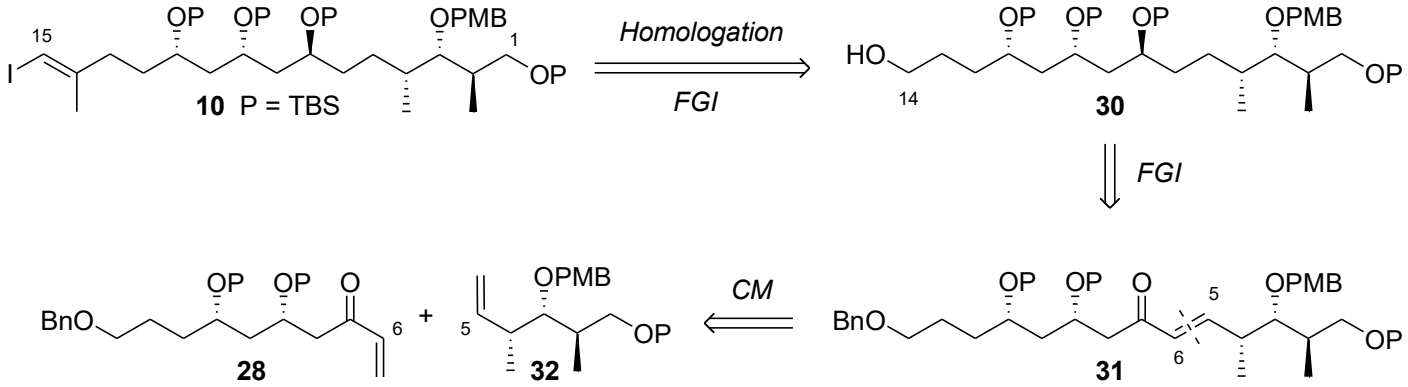
2	1:1.2	**HG2** (5)	CH_2Cl_2	3 days	reflux	57%
3	1:1.4	**HG2** (10)	CH_2Cl_2	3 days	reflux	68%
4	1:1.3	**HG2** (7.5)	Toluene	3 days	60 °C	64%
5	2:1	**HG2** (10)	CH_2Cl_2	16 h	reflux	86%

Chemoselective reduction of the C5-C6 alkene was performed with $NiCl_2{\cdot}H_2O/NaBH_4$ (Scheme 12). The reaction was high yielding on small scale, but unreproducible results were obtained on larger scale. Nevertheless, we attempted the key hydroboration step, but unfortunately, all attempts with 9-BBN only led to no reaction or decomposition under more forcing conditions. We have no explanation for the failure of this hydroboration reaction, which is well documented on similar substrates.[23] We also attempted the reduction of ketone **29** with the (*R*)-CBS catalyst and $BH_3{\cdot}THF$, but similar disappointing results were observed.[24] Once again, this lack of reactivity is surprising, since this reduction was successful on a very similar substrate (compound **31** in Scheme 15).



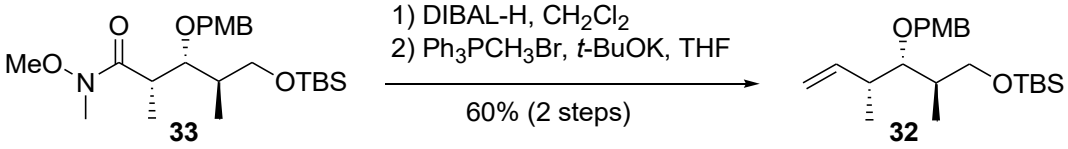
Scheme 12. Conjugate reduction of enone **27**.

The final retrosynthesis we envisioned still involved installing the vinyl iodide moiety at the end of the synthesis from the primary alcohol **30** (Scheme 13). The C5-C6 bond in compound **31** would be formed by a cross-metathesis reaction between enone **28** and the more functionalized C1-C5 fragment **32**.



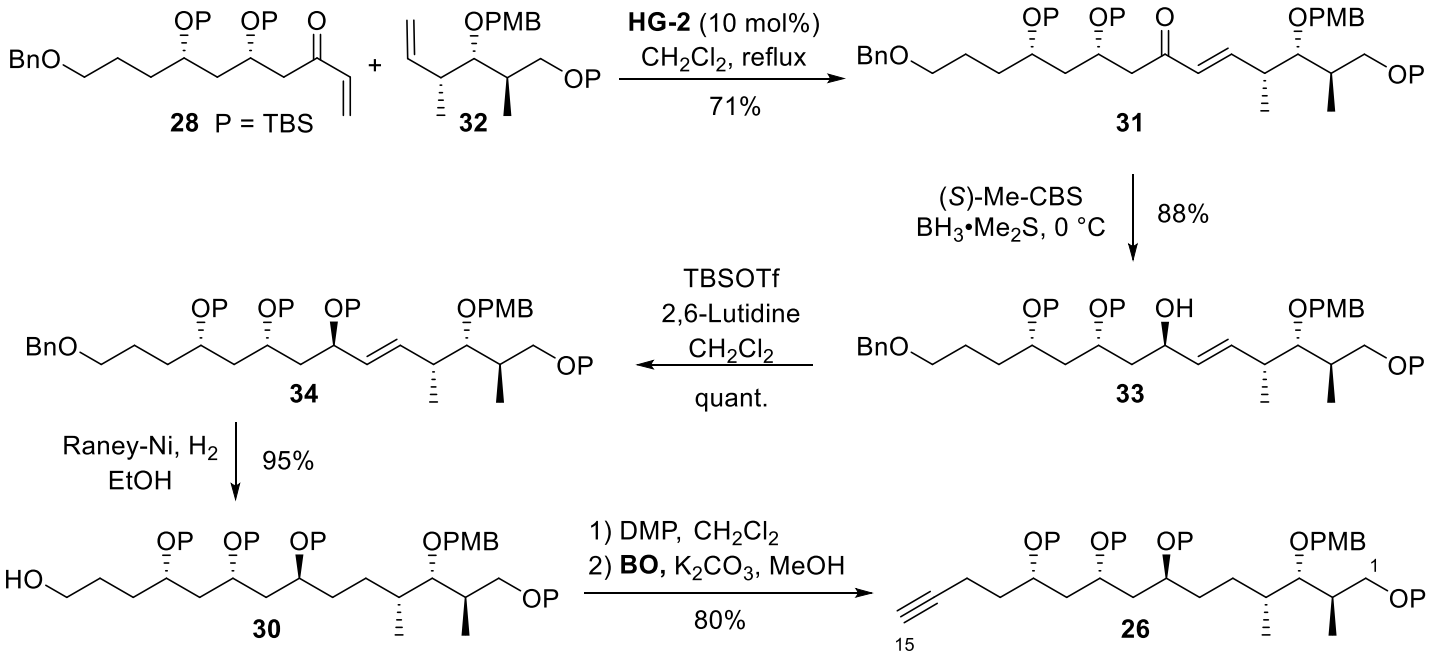
Scheme 13. Final retrosynthesis of the C1-C15 fragment of dolabelide C.

Alkene **32** was synthesized from the previously prepared Weinreb amide **33** (intermediate in the synthesis of silyl enol ether **2**) by DIBAL-H reduction and Wittig olefination of the resulting aldehyde (Scheme 14).



Scheme 14. Synthesis of enone **32**.

Cross metathesis of enone **28** and alkene **32** proceeded in 71% yield under the conditions previously optimized for the coupling of **28** and **13** (Table 1, entry 3), and the excess of alkene **32** could be entirely recovered (Scheme 15). Once again, when the less reactive enone **28** was used in excess (2:1 ratio of **28**/**32**), a better yield was obtained (89%), but only 14% of the excess enone was isolated. On this substrate, CBS reduction gave the expected alcohol in excellent yield, and **33** was obtained as a single diastereomer after purification. Protection of the secondary alcohol as a TBS ether was followed by hydrogenation of the alkene and cleavage of the benzyl ether to give primary alcohol **30** in excellent overall yield. Homologation of alcohol **30** into the terminal alkyne **26** was performed as described for alcohol **25**. However, not surprisingly, the Negishi carboalumination also failed on this substrate, only leading to the cleavage of the PMB and primary TBS ethers.

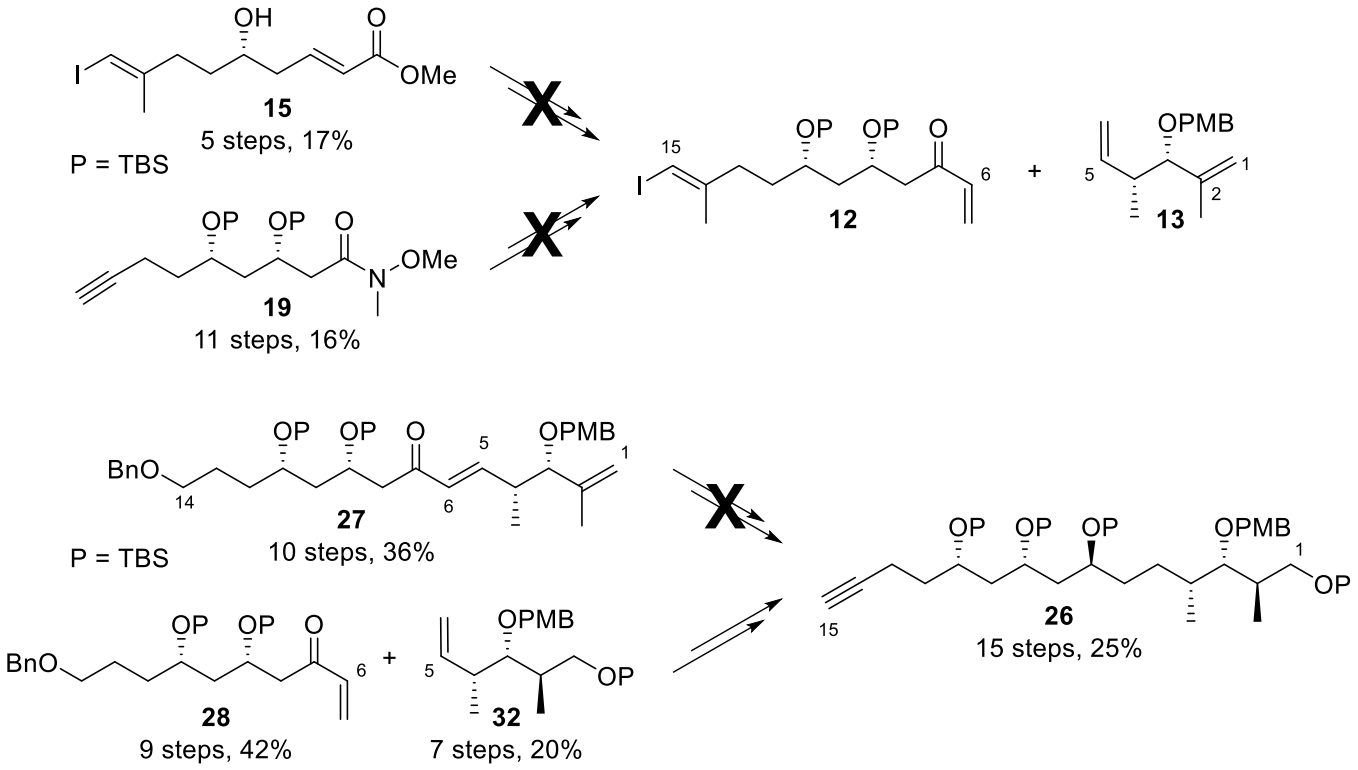


Scheme 15. Synthesis of an advanced precursor of the C1-C15 fragment of dolabelide C.

Conclusions

In summary, we have explored several synthetic approaches to the C1-C15 fragment of dolabelide C (Scheme 16). We had planned on introducing the trisubstituted vinyl iodide early in the synthesis, but the conjugate addition on compound **15** only led to decomposition. This conjugate addition could be performed on a precursor of the vinyl iodide to lead to alkyne **19**, but unfortunately the Negishi carboalumination failed on this substrate, so this route was abandoned. We then decided to introduce the vinyl iodide moiety at the end of the synthesis, from a benzyloxy group at C14. Compound **27** was prepared using an olefin cross-metathesis reaction to form the C5-C6 bond, but hydroboration of the C1-C2 alkene was unsuccessful. Finally, cross metathesis between enone **28** and alkene **32** afforded alkyne **26** after functional group transformations and homologation. This advanced precursor of the C1-C15 fragment of dolabelide C was synthesized from 4-

penten-1-ol in 25% yield over 15 steps. The Negishi carboalumination also failed on this compound. It is well known that propargylic alcohols are excellent substrates for this reaction,[25] so future work will involve attempting this carboalumination on diol and triol substrates, to install the vinyl iodide moiety either before or after the key cross-metathesis reaction.



Scheme 16. Summary of the synthetic approaches to the C1-C15 fragment of dolabelide C.

Experimental Section

General. Air or moisture sensitive reactions were carried out in pre-dried glassware by flame drying under vacuum and subsequently flushing with argon. Solvents were degassed using the freeze and thaw method. Dry solvents such as THF, CH_2Cl_2, Et_2O, MeCN and toluene were collected from an in-house Pure-SolvTM 500 Solvent Purification System. Dry ethanol, methanol, DMF, 1,2-dichoromethane were used from commercial bottles. All reagents were used directly from supplier, unless stated otherwise. Flash chromatography was executed under forced flow conditions, using HPLC graded solvents and silica gel 60 (Fluorochem silica gel 60, 40 - 63 or Merck silica gel 60, 40 – 63). Reactions were monitored by thin layer chromatography (TLC) using Merck silica gel 60 covered alumina plates F254. NMR spectra were recorded on either a Bruker AVI DPX-400 spectrometer, a Bruker AVIII DPX-400 spectrometer (^{1}H NMR: 400 MHz, ^{13}C NMR: 101 MHz) or on a Bruker DPX-500 spectrometer (^{1}H NMR: 500 MHz, ^{13}C NMR: 126 MHz). Deuterated chloroform ($CDCl_3$) was used as the solvent for both ^{1}H and ^{13}C NMR, with residual solvent peak δ 7.26 being used for calibration of ^{1}H NMR and $CDCl_3$ peak at δ 77.0 for ^{13}C. Signal splitting patterns are described as: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), sextet (sext), octet (oct), nonet (non), multiplet (m), broad singlet, or any combination of the above. Two-dimensional experiments (COSY, NOESY, HSQC, HMBC, and HMQC) were recorded, where necessary, for assignment. IR spectra were recorded using a Shimadzu FTIR-8400 Golden

Gate™ attachment, utilizing a type IIa diamond as a single reflection element, allowing for the direct reading of powder and oil samples. High resolution mass spectra were recorded under ESI and CI conditions by the University of Glasgow analytical service. Optical rotations were recorded on an Autopol V polarimeter.

1-((((3*S*,4*R*)-2,4-Dimethylhexa-1,5-dien-3-yl)oxy)methyl)-4-methoxybenzene 13. To a stirred suspension of 4 Å molecular sieves (1.0 g) and (*R,R*)-diisopropyl-(*Z*)-crotylboronate (0.5 M in toluene, 11.1 mL, 5.54 mmol, 1.75 equiv) at -78 °C was slowly added acrolein (222 mg, 3.17 mmol). The reaction mixture was stirred at -78 °C for 7 h and allowed to warm to 20 °C overnight. The reaction was then quenched with a 0.5 M aqueous solution of NaOH (20 mL) and extracted with ether (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The unpurified product was dissolved in DMF (13 mL) and cooled to 0 °C. Then PMBBr (1.15 g, 5.72 mmol, 1.80 equiv) was added followed by NaH (60% dispersion in mineral oil, 215 mg, 5.38 mmol, 1.70 equiv) and the resulting mixture was left to warm to 20 °C and stirred for a further 3 h after addition. The reaction was quenched using a saturated aqueous solution of NH_4Cl (15 mL), extracted with Et_2O (3 x 15 mL), washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel (petroleum ether: ether 95:5) to afford **13** (650 mg, 66% over 2 steps) as a clear liquid. $[\alpha]^{23}_D$ -38.7 (c 1.0, CH_2Cl_2), lit. -45.2 (c 1.0, CH_2Cl_2).[25] IR (neat, cm^{-1}) 2970, 1736, 1643, 1450, 1373, 1227, 1018. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.5 Hz, 2H, H-Ar), 6.87 (d, *J* = 8.6 Hz, 2H, H-Ar), 5.67-5.56 (m, 1H, CH-5), 5.04-4.95 (m, 2H, CH-1, CH-6), 4.92 (dd, *J* = 10.3, 1.4 Hz, 1H, CH-6_{cis}), 4.86 (s, 1H, CH-1), 4.45 (d, *J* = 11.4 Hz, 1H, CH_2-PMB), 4.16 (d, *J* = 11.4 Hz, 1H, CH_2-PMB), 3.81 (s, 3H, PMB-OCH_3), 3.39 (d, *J* = 8.8 Hz, 1H, CH-3), 2.43-2.33 (m, 1H, CH-4), 1.68 (s, 3H, CH-8), 1.09 (d, *J* = 6.6 Hz, 3H, CH-6). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0 (C-Ar), 143.5 (C-2), 140.7 (C-5), 130.9 (C-Ar), 129.4 (C-Ar), 114.9 (C-Ar), 113.7 (C-6 or C-1), 113.6 (C-6 or C-1), 87.1 (C-3), 69.7 (CH_2-PMB), 55.3 (OCH_3-PMB), 40.7 (C-4), 17.0 (C-8), 16.8 (C-7). HRMS (ESI, *m/z*) calcd for $(C_{16}H_{22}O_2Na)^+$ 269.1512, found 269.1500.
Spectroscopic data were in accordance with those reported in the literature.[26]

(*E*)-5-Iodo-4-methylpent-4-en-1-ol 18. Zirconocene dichloride (3.51 g, 12.0 mmol, 2.00 equiv) was weighed out into a flame dried, argon flushed 100 mL round bottom flask containing a magnetic stirrer bar in a glovebox. The flask was then sealed and subsequently removed. Degassed CH_2Cl_2 (2.0 mL) was added and the heterogenous mixture was cooled to -25 °C while stirring. Then $AlMe_3$ (2.0 M solution in toluene 14.4 mL, 28.8 mmol, 4.80 equiv) was added dropwise and the solution stirred for a further 20 min after the addition was complete. At this point the reaction mixture was homogenous with pale-yellow colouration and freshly distilled H_2O (216 µL, 12.0 mmol, 2.0 equiv) was then cautiously added. The mixture was then stirred for a further 30 min before the dropwise addition of a degassed solution of 1-pentenyn-4-ol (560 µL, 6.00 mmol) in CH_2Cl_2 (7.0 mL + 3.0 mL rinse) that had been pre-treated with $AlMe_3$ (2.0 M solution in toluene 3.6 mL, 7.2 mmol, 1.2 equiv). The mixture was then stirred for 6 h at -25 °C and 12 h at 20 °C before re-cooling back to -25 °C. A solution of iodine (7.61 g, 30.0 mmol, 5.00 equiv) in THF (18.0 mL) was then added and stirring continued for 1 h at -25 °C and 1 h at 0 °C. A saturated aqueous solution of K_2CO_3 (7.0 mL) was then slowly added followed by $MgSO_4$ while leaving the mixture to warm to 20 °C over 30 min. The resulting mixture was then filtered through a pad of celite and rinsed with CH_2Cl_2. The filtrate was then washed with a saturated aqueous solution of $Na_2S_2O_3$ (2 x 20 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography on silica gel (petroleum ether: ether 1:1) gave vinyl iodide **18** (1.36 g, quant.) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93-5.92 (m, 1H, CH-5), 3.66-3.61 (m, 2H, CH-1), 2.30 (t, J = 7.6 Hz, 2H, CH-3), 1.85 (s, 3H, CH-6), 1.71 (tt, J = 7.5, 6.4 Hz, 2H, CH-2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.4 (C-4), 74.9 (C-5), 62.0 (C-1), 35.7 (C-3), 30.5 (C-2), 23.8 (C-6).

Spectroscopic data were in accordance with those reported in the literature.[27]

(*E*)-5-Iodo-4-methylpent-4-enal. To a stirred solution of **18** (565 mg, 2.50 mmol) in CH_2Cl_2 (10.0 mL) was added Dess-Martin periodinane (1.27 g, 2.99 mmol, 1.20 equiv) at 20 °C. The resulting mixture was monitored by TLC until disappearance of the starting material, at which point ether (15 mL) and a saturated aqueous solution of $NaHCO_3$ (20 mL) were added. The mixture was then extracted with ether (3 x 10 mL) and the combined organic extracts were washed with a saturated aqueous solution of $Na_2S_2O_3$ (2 x 20 mL), brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude aldehyde as a colorless liquid that was immediately used in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.77 (s, 1H, CH-1), 5.98 (m, 1H, CH-5), 2.61-2.52 (m, 4H, CH-2, CH-3), 1.86 (s, 3H, CH-6); ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.8 (C-1), 145.8 (C-4), 76.0 (C-5), 41.8 (C-3), 31.4 (C-2), 24.0 (C-6).

(*R,E*)-8-Iodo-7-methylocta-1,7-dien-4-ol 16. The above unpurified aldehyde was dissolved in Et_2O (20.0 mL) and the stirred solution was cooled to -78 °C. Then (+)-*B*-allyldiisopinocampheylborane (1.0 M solution in pentane 5.0 mL, 5.0 mmol, 2.0 equiv) from a sealed ampule was added dropwise. The reaction mixture was stirred for 6 h at 20 °C and subsequently poured into a saturated aqueous solution of NH_4Cl (20 mL). The mixture was then separated, and the aqueous phase was extracted with Et_2O (3 x 15 mL), washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The product was purified by column chromatography on silica gel (petroleum ether: ether 2:1) to give homoallylic alcohol **16** (330 mg, 50% over 2 steps) as a colorless oil. IR (thin film, cm^{-1}) 3370, 2918, 1618, 1265, 1130, 1053, 1009. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93 (m, 1H, CH-8), 5.84-5.77 (m, 1H, CH-2), 5.16-5.13 (m, 2H, CH-1), 3.63-3.61 (m, 1H, CH-4), 2.42-2.36 (m, 1H, CH-3), 2.33-2.27 (m, 2H, CH-6), 2.19-2.13 (m, 1H, CH-3), 1.85 (s, 3H, CH-9), 1.63-1.58 (m, 2H, CH-5). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.7 (C-7), 134.4 (C-2), 118.6 (C-1), 74.9 (C-8), 69.8 (C-4), 42.1 (C-3), 35.7 (C-6), 34.7 (C-5), 23.9 (C-9). HRMS (ESI, *m/z*) calcd for $(C_9H_{15}IONa)^+$ 289.0060, found 289.0065.

Methyl (*R*,2*E*,8*E*)-5-hydroxy-9-iodo-8-methylnona-2,8-dienoate 15. Homoallylic alcohol **16** (120 mg, 0.45 mmol), methyl acrylate (120 µL, 1.35 mmol, 3 equiv) and toluene (5.0 mL) were dispensed in a Schlenk bomb and subsequently degassed using the freeze-pump-thaw method. **HG2** catalyst (28 mg, 0.045 mmol, 0.10 equiv) was then added, the bomb was evacuated (≈ 100 mbar), sealed and the resulting mixture was heated to 50 °C and stirred for 12 h. At this stage the reaction mixture was cooled to 20 °C and the pressure in the bomb measured (≈ 300 mbar) before filling with argon. The mixture was transferred to a round bottom flask (rinsed with toluene 3 x 2 mL) and concentrated *in vacuo.* Purification by column chromatography on silica gel (petroleum ether: ether 3:1) gave conjugated ester **15** (49.0 mg, 34%) as a colorless oil. IR (thin film, cm^{-1}) 3568, 2855, 1721, 1655, 1437, 1269, 1117, 1007. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (dt, *J* = 15.1, 7.4 Hz, 1H, CH-3), 5.93-5.89 (m, 2H, CH-2, CH-9), 3.74-3.69 (m, 1H, CH-5), 3.73 (s, 3H, OCH_3), 2.40-2.25 (m, 4H, CH-4, CH-7), 1.83 (s, 3H, CH-10), 1.65-1.58 (m, 2H, CH-6). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.6 (C-1), 147.3 (C-8), 144.9 (C-3), 123.7 (C-2), 75.2 (C-9), 69.7 (C-5), 51.5 (OCH_3), 40.3 (C-4), 35.6 (C-7), 34.9 (C-6), 23.9 (C-10). HRMS (ESI, *m/z*) calcd for $(C_{11}H_{17}IO_3Na)^+$ 347.0115, found 347.0114.

(3*S*,5*S*)-8-(Benzyloxy)-3,5-dihydroxy-*N*-methoxy-*N*-methyloctanamide 21. A stirred solution of *N,O*-dimethylhydroxylamine hydrochloride (1.53 g, 25.0 mmol, 5.34 equiv) in CH_2Cl_2 (18 mL) was cooled to 0 °C followed by the dropwise addition of $AlMe_3$ (2.0 M solution in toluene, 8.1 mL, 16.2 mmol, 3.5 equiv) (Caution! Exothermic reaction with release of methane). After the addition was complete the mixture was stirred at 20 °C for 2 h before adding a solution of ester **20** (1.80 g, 4.68 mmol) in CH_2Cl_2 (18 mL) dropwise. The reaction

mixture was heated to reflux and stirred for a further 3 days. Then the reaction mixture was cooled to 20 °C and was quenched by the careful addition of a 2 M aqueous solution of HCl (20 mL) and was extracted with EtOAc (5 x 20 mL). The combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ (50 mL), brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Crude **21** (contaminated with benzaldehyde) was obtained as a yellow oil and used in the next step without purification. For analysis a small sample was purified by column chromatography on silica gel (EtOAc) giving **21** as a clear oil. $[\alpha]^{23}_D$ +58.5 (c 0.5, $CHCl_3$). IR (neat, cm^{-1}) 2940, 1736, 1612, 1513, 1450, 1366, 1219, 1072, 1034. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.27 (m, 5H, H-Ar), 4.51 (s, 2H, CH-9), 4.38 (br s, 1H, C3-OH), 4.33-4.25 (m, 1H, CH-3), 4.00 (d, *J* = 1.4 Hz, 1H, C5-OH), 3.95-3.87 (m, 1H, CH-3), 3.68 (s, 3H, N-OMe), 3.52 (t, *J* = 6.1 Hz, 2H, CH-8), 3.19 (s, 3H, N-CH_3), 2.68-2.48 (m, 2H, CH-2), 1.81-1.67 (m, 2H, CH-4), 1.64-1.51 (m, 4H, CH-6, CH-7). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3 (C-1), 138.3 (C-Ar), 128.4 (C-Ar), 127.7 (C-Ar), 127.6 (C-Ar), 73.0 (C-9), 71.7 (C-5), 70.5 (C-8), 69.1 (C-3), 61.3 ($NOCH_3$), 42.5 (C-2), 38.6 (C-4), 34.8 (C-6), 31.8 (NCH_3), 25.9 (C-7). HRMS (ESI, *m/z*) calcd for $(C_{17}H_{27}NO_5Na)^+$ 348.1787, found 348.1789.

(3*S*,5*S*)-8-(Benzyloxy)-3,5-*bis*((*tert*-butyldimethylsilyl)oxy)-*N*-methoxy-*N*-methyloctanamide 24. Unpurified **21** obtained from the reaction described above was dissolved in CH_2Cl_2 (36 mL) and cooled to -78 °C. Then TBSOTf (2.60 mL, 15.2 mmol, 3.25 equiv) and pyridine (1.51 mL, 19.5 mmol, 4.16 equiv) were simultaneously added and the reaction was left to warm to 20 °C overnight. The reaction mixture was poured into a 250 mL separatory funnel containing an aqueous saturated solution of NH_4Cl (40 mL). The aqueous layer was then extracted with ether (3 x 40 mL) and the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography on silica gel (petroleum ether: ether 4:1) gave **24** (2.03 g, 78%) as a colorless oil. $[\alpha]^{23}_D$ +34.4 (*c* 0.5, $CHCl_3$). IR (neat, cm^{-1}) 2932, 2855, 1744, 1667, 1366, 1250, 1088, 1003. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.26 (m, 5H, H-Ar), 4.51 (s, 2H, CH-9), 4.35-4.29 (m, 1H, CH-3), 3.80-3.84 (m, 1H, CH-5), 3.68 (s, 3H, N-OMe), 3.48 (t, *J* = 6.0 Hz, 2H, CH-8), 3.17 (s, 3H, N-CH_3), 2.72-2.68 (m, 1H, CH-2), 2.47 (dd, *J* = 15.0, 5.0 Hz, 1H, CH-2), 1.78-1.60 (m, 5H, CH-4, CH-6, CH-7), 1.53-1.46 (m, 1H, CH-7) 0.91, 0.88 (2s, 18H,-SiC$(CH_3)_3$-), 0.10, 0.08, 0.06, 0.05 (4s, 12H, -SiC$(CH_3)_2$-). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.1 (C-1), 138.6 (C-Ar), 128.2 (C-Ar), 127.5 (C-Ar), 127.3 (C-Ar), 72.7 (C-9), 70.5 (C-8), 69.1 (C-3), 67.0 (C-5), 61.2 ($NOCH_3$), 45.5 (C-2), 39.9 (C-4), 33.4 (C-6), 31.8 (NCH_3), 25.9 (Si$C(CH_3)_3$), 25.8 (Si$C(CH_3)_3$), 25.3 (C-7), 17.9 (Si$C(CH_3)_3$), 17.9 (Si$C(CH_3)_3$), -4.4, -4.5, -4.6, -4.7 (Si$(CH_3)_2$). HRMS (ESI, *m/z*) calcd for $(C_{29}H_{55}NO_5Si_2Na)^+$ 576.3511, found 576.3487.

(3*S*,5*S*)-3,5-*bis*((*tert*-Butyldimethylsilyl)oxy)-8-hydroxy-*N*-methoxy-*N*-methyloctanamide 25. Palladium on carbon (214 mg, 32% w/w) was suspended into a 25 mL round-bottom flask that contained a stirred solution of Weinreb amide **24** (665 mg, 1.20 mmol) in ethanol (6.5 mL). A 3-way adaptor tap connected to a high vacuum pump and a balloon filled with H_2 was then fitted onto the flask and the vessel was flushed with H_2 10 times. The reaction mixture was then left to stir at 20 °C for 4 days before filtering through a pad of celite. The round-bottom flask was rinsed with Et_2O (3 x 10 mL) and the filtrate concentrated *in vacuo*. Purification by column chromatography on silica gel (petroleum ether: EtOAc 1:1) afforded the desired alcohol **25** (210 mg, 0.45 mmol, 39%) as a colorless oil as well as recovered starting material **24** (200 mg, 30%). $[\alpha]^{23}_D$ -6.0 (*c* 0.1, $CHCl_3$). IR (thin film, cm^{-1}) 2928, 2857, 1661, 1645, 1472, 1462, 1362, 1254, 1180, 1055. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.30-4.22 (m, 1H, CH-3), 3.95-3.85 (m, 1H, CH-5), 3.69 (s, 3H, N-OMe), 3.66-3.59 (m, 2H, CH-8), 3.17 (s, 3H, N-CH_3), 2.66 (dd, *J* = 14.7, 5.6 Hz, 1H, CH-2), 2.50 (dd, *J* = 15.1, 5.9 Hz, 1H, CH-2), 2.04 (t, *J* = 5.5 Hz, 1H, C8-OH), 1.72-1.55 (m, 6H, CH-4, CH-6, CH-7), 0.90, 0.87 (2s, 18H,-SiC$(CH_3)_3$-), 0.09, 0.07, 0.07, 0.04 (4s, 12H, -SiC$(CH_3)_2$-). ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.0 (C-1), 69.0 (C-3), 66.9 (C-5), 63.2 (C-8), 61.3 ($NOCH_3$), 44.8 (C-2),

40.2 (C-4), 32.9 (C-6), 30.3 (NCH_3), 27.9 (C-7), 25.9 ($Si(C(CH_3)_3$), 25.8 ($Si(C(CH_3)_3$), 18.0 ($Si(C(CH_3)_3$), 18.0 ($Si(C(CH_3)_3$), -4.5, -4.5, -4.5, -4.7 ($Si(CH_3)_2$). HRMS (ESI, *m*/*z*) calcd for $(C_{22}H_{49}O_5Si_2Na)^+$ 486.3041, found 486.3028.

(3*S*,5*S*)-3,5-*bis*((*tert*-Butyldimethylsilyl)oxy)-*N*-methoxy-*N*-methyl-8-oxooctanamide. The aldehyde was obtained from the corresponding alcohol **25** according to the procedure described for (*E*)-5-iodo-4-methylpent-4-enal, scale: 0.41 mmol, yield: 90%. The colorless oily product was used in the following step without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (t, *J* = 1.6 Hz, 1H, CH-8), 4.29-4.20 (m, 1H, CH-3), 3.90 (dt, *J* = 15.1, 4.7 Hz, 1H, CH-5), 3.69 (s, 3H, N-OMe), 3.17 (s, 3H, N-CH_3), 2.68 (dd, *J* = 15.0, 6.2 Hz, 1H, CH-2), 2.53-2.44 (m, 2H, CH-2, CH-7), 1.99-1.90 (m, 1H, CH-7), 1.78-1.61 (m, 4H, CH-4, CH-6), 0.88, 0.87 (2s, 18H,-$SiC(CH_3)_3$-), 0.07, 0.07, 0.04, 0.04 (4s, 12H, -$SiC(CH_3)_2$-). ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.6 (C-8), 181.0 (C-1), 68.1 (C-3), 66.8 (C-5), 61.3 ($NOCH_3$), 45.0 (C-2), 40.1 (C-4), 39.3 (C-7), 29.7 (NCH_3), 28.6 (C-6), 25.9 ($Si(C(CH_3)_3$), 25.8 ($Si(C(CH_3)_3$), 18.0 ($Si(C(CH_3)_3$), 17.9 ($Si(C(CH_3)_3$), -4.4, -4.5, -4.6, -4.7 ($Si(CH_3)_2$).

(3*S*,5*S*)-3,5-*bis*((*tert*-Butyldimethylsilyl)oxy)-*N*-methoxy-*N*-methylnon-8-ynamide 19. A stirred solution of the above unpurified aldehyde (189 mg, 0.410 mmol) in methanol (4.1 mL) was cooled to 0 °C. K_2CO_3 (227 mg, 1.64 mmol, 4.00 equiv) and dimethyl-1-diazo-2-oxopropylphosphonate (197 mg, 1.03 mmol, 2.50 equiv) were then added. The reaction mixture was left to warm to 20 °C and stirred overnight before it was diluted with Et_2O (15 mL), quenched with H_2O (15 mL) and a saturated aqueous solution of NH_4Cl (15 mL). The aqueous phase was extracted with Et_2O (3 x 15 mL) and the combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude was purified by column chromatography on silica gel (petroleum ether: ether 3:1) to afford alkyne **19** (107 mg, 57% over two steps) as a colorless oil. $[\alpha]^{23}_D$ -10.7 (c 0.1, $CHCl_3$). IR (thin film, cm^{-1}) 2953, 2857, 1661, 1472, 1385, 1256, 1090. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.33-4.24 (m, 1H, CH-3), 3.96-3.89 (m, 1H, CH-5), 3.69 (s, 3H, N-OMe), 3.17 (s, 3H, N-CH_3), 2.69 (dd, *J* = 14.2, 6.0 Hz, 1H, CH-2), 2.48 (dd, *J* = 14.7, 5.9 Hz, 1H, CH-2), 2.26 (td, *J* = 7.3, 2.4 Hz, 2H, CH-7), 1.92 (t, *J* = 2.6 Hz, 1H, CH-9), 1.85-1.59 (m, 4H, CH-4, CH-6,), 0.89, 0.87 (2s, 18H,-$SiC(CH_3)_3$-), 0.09, 0.07, 0.04 (3s, 12H, -$SiC(CH_3)_2$-). ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.1 (C-1), 84.6 (C-8), 68.4 (C-3), 67.9 (C-9), 66.8 (C-5), 61.3 ($NOCH_3$), 45.5 (C-2), 40.1 (C-4), 35.6 (C-6), 31.9 (NCH_3), 25.9 ($Si(C(CH_3)_3$), 25.9 ($Si(C(CH_3)_3$), 18.0 ($Si(C(CH_3)_3$), 17.9 ($Si(C(CH_3)_3$), 14.3 (C-7), -4.3, -4.5, -4.6 ($Si(CH_3)_2$). HRMS (ESI, *m*/*z*) calcd for $(C_{23}H_{47}O_4Si_2Na)^+$ 480.2936, found 480.2937.

(5*S*,7*S*)-10-(Benzyloxy)-5,7-*bis*((*tert*-butyldimethylsilyl)oxy)dec-1-en-3-one 28. To a stirred suspension of **24** (500 mg, 0.90 mmol) in THF (8 mL) at 0°C was added dropwise vinyl magnesium bromide (4.50 mL, 4.50 mmol, 5.00 equiv). The reaction mixture was then heated to reflux and monitored by TLC. When the complete consumption of staring material was observed, the reaction mixture was cooled to 20 °C and quenched by the addition of a saturated aqueous solution of NH_4Cl (10 mL). The aqueous layer was then extracted with ether (3 x 10 mL) and the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography on silica gel (petroleum ether: ether 9:1) gave **28** (373 mg, 80%) as a colorless oil. $[\alpha]^{23}_D$ +13.1 (c 1.0, $CHCl_3$). IR (neat, cm^{-1}) 2928, 2855, 1684, 1614, 1472, 1400, 1360, 1252, 1094, 1069. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.26 (m, 5H, H-Ar), 6.36 (dd, *J* = 17.6, 10.6 Hz, 1H, CH-2), 6.20 (dd, *J* = 17.6, 0.9 Hz, 1H, CH-1_{trans}), 5.81 (dd, *J* = 10.6, 0.9 Hz, 1H, CH-1_{cis}), 4.50 (s, 2H, CH-11), 4.33-4.28 (m, 1H, CH-5), 3.82-3.77 (m, 1H, CH-7), 3.47 (t, *J* = 6.5 Hz, 2H, CH-10), 2.76 (dd, *J* = 15.2, 7.0 Hz, 1H, CH-4), 2.66 (dd, *J* = 15.2, 4.9 Hz, 1H, CH-4), 1.72-1.55 (m, 5H, CH-6, CH-8, CH-9), 1.52-1.46 (m, 1H, CH-9) 0.89, 0.84 (2s, 18H,-$SiC(CH_3)_3$-), 0.06, 0.05, 0.04, 0.01 (4s, 12H, -$SiC(CH_3)_2$-). ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.4 (C-3),

138.6 (C-Ar), 137.5 (C-2), 128.3 (C-Ar), 128.3 (C-Ar), 127.6 (C-Ar), 127.5 (C-1), 72.8 (C-11), 70.6 (C-10), 69.1 (C-5), 67.8 (C-7), 47.3 (C-4), 45.3 (C-6), 33.6 (C-8), 25.9 (Si(C(CH_3)$_3$), 25.9 (Si(C(CH_3)$_3$), 25.3 (C-9), 18.0 (Si(C(CH_3)$_3$), 18.0 (Si(C(CH_3)$_3$), 4.3, 4.4, 4.5, 4.6 (Si(CH_3)$_2$). HRMS (ESI, *m/z*) calcd for ($C_{29}H_{52}O_4Si_2Na$)$^+$ 543.3296, found 576.3277.

(3*S*,4*R*,9*S*,11*S*,*E*)-14-(Benzyloxy)-9,11-*bis*((*tert*-butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)oxy)-2,4-dimethyltetradeca-1,5-dien-7-one 27. A solution of enone **28** (521 mg, 1.00 mmol) and diene **13** (345 mg, 1.40 mmol, 1.40 equiv) in CH_2Cl_2 (10 mL) was degassed using the freeze-pump-thaw method. Hoveyda-Grubbs 2 catalyst was then added in portions of 2.5 mol% (4 x 15.7 mg, 4 x 0.025 mmol) every 24 h. After 3 days, the reaction mixture was cooled to 20 °C and subsequently dry loaded on silica gel and purified by column chromatography (petroleum ether: ether 95:5) to afford **27** (503 mg, 68%) as a clear oil and as a 6:1 mixture of diastereomers. The major diastereomer is described below. IR (thin film, cm^{-1}) 2950, 2854, 1694, 1613, 1513, 1462, 1361, 1247, 1065, 1036. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.26 (m, 5H, H-Ar), 7.24 (d, *J* = 8.6 Hz, 2H, H-Ar(PMB)), 6.87 (d, *J* = 8.6 Hz, 2H, H-Ar(PMB)), 6.61 (dd, *J* = 15.9, 8.0 Hz, 1H, CH-5), 6.06 (dd, *J* = 15.9, 0.9 Hz, 1H, CH-6), 5.00 (s, 1H, CH-1), 4.90 (s, 1H, CH-1), 4.50 (s, 2H, CH-15), 4.46 (d, *J* = 11.5 Hz, 1H, CH_2-PMB), 4.29-4.24 (m, 1H, CH-9), 4.17 (d, *J* = 11.4 Hz, 1H, CH_2-PMB), 3.81-3.77 (m, 4H, PMB-OCH_3, CH-11), 3.50-3.45 (m, 3H, CH-3, CH-14), 2.66 (dd, *J* = 15.2, 6.9 Hz, 1H, CH-8), 2.62-2.50 (m, 2H, CH-4, CH-8), 1.71-1.53 (m, 9H, CH-10, CH-12, CH-13, CH-16), 1.12 (d, *J* = 6.6 Hz, 3H, CH-17) 0.88, 0.84 (2s, 18H, -SiC(CH_3)$_3$-), 0.05, 0.04, 0.04, 0.03 (4s, 12H, -SiC(CH_3)$_2$-). ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.9 (C-7), 159.1 (C-Ar), 148.6 (C-5), 142.7 (C-2), 138.7 (C-Ar), 130.4 (C-6), 130.4 (C-Ar), 129.4 (C-Ar), 128.3 (C-Ar), 127.6 (C-Ar), 127.4 (C-Ar), 115.6 (C-1), 113.7 (C-Ar), 86.0 (C-3), 72.8 (C-15), 70.6 (C-14), 69.7 (CH_2-PMB), 69.1 (C-9), 66.8 (C-11), 55.3 (OCH_3-PMB), 48.0 (C-8), 45.3 (C-10), 39.6 (C-4), 33.5 (C-12), 25.9 (Si(C(CH_3)$_3$), 25.9 (Si(C(CH_3)$_3$), 25.3 (C-13), 18.0 (Si(C(CH_3)$_3$), 17.9 (Si(C(CH_3)$_3$), 17.0 (C-17), 16.1 (C-16), -4.4 (Si(CH_3)$_2$), -4.6 (Si(CH_3)$_2$). HRMS (ESI, *m/z*) calcd for ($C_{43}H_{70}O_6Si_2Na$)$^+$ 761.4603, found 761.4578.

(3*S*,4*R*,9*S*,11*S*)-14-(Benzyloxy)-9,11-*bis*((*tert*-butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)oxy)-2,4-dimethyltetradec-1-en-7-one 29. Enone **27** (50.0 mg, 0.0680 mmol) was dissolved in a mixture of THF (0.4 mL) and MeOH (0.2 mL) and the resulting solution was cooled to 0 °C. Then $NiCl_2{\cdot}6H_2O$ (8.2 mg, 0.060 mmol 0.90 equiv) was added and the mixture was stirred for 15 min before adding $NaBH_4$ (5.1 mg, 0.13 mmol, 1.9 equiv) in two portions over 30 min. The reaction was then monitored by TLC and when indicated that the starting material was completely consumed (approx. 10 min after last addition of $NaBH_4$) it was concentrated *in vacuo.* The resulting mixture was dissolved in Et_2O, filtered through celite and concentrated *in vacuo* giving a clear oil that was further purified by column chromatography on silica gel (petroleum ether: ether 9:1) to afford **29** (49.0 mg, 98%) as a clear liquid and as 9:1 mixture of diastereomers. The major diastereomer is described below. IR (thin film, cm^{-1}) 2955, 2857, 1715, 1612, 1514, 1462, 1302, 1275, 1057. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.23 (m, 7H, H-Ar), 6.86 (d, *J* = 8.6 Hz, 2H, H-Ar(PMB)), 5.03 (s, 1H, CH-1), 4.91 (s, 1H, CH-1), 4.50 (s, 2H, CH-15), 4.45 (d, *J* = 11.4 Hz, 1H, CH_2-PMB), 4.24 (dt, *J* = 12.0, 6.0 Hz, 1H, CH-9), 4.15 (d, *J* = 11.4 Hz, 1H, CH_2-PMB), 3.79 (s, 3H, PMB-OCH_3), 3.77-3.73 (m, 2H, CH-11), 3.46 (t, *J* = 6.5 Hz, 2H, CH-14), 3.34 (d, *J* = 7.9 Hz, 1H, CH-3), 2.54-2.28 (m, 5H, CH-4, CH-6, CH-8), 1.67-1.48 (m, 10H, CH-5, CH-10, CH-12, CH-13, CH-16), 10.94 (d, *J* = 6.4 Hz, 3H, CH-17) 0.89, 0.85 (2s, 18H, -SiC(CH_3)$_3$-), 0.05, 0.05, 0.04, -0.01 (4s, 12H, -SiC(CH_3)$_2$-). ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.6 (C-7), 159.0 (C-Ar), 143.2 (C-2), 138.7 (C-Ar), 131.0 (C-Ar), 129.4 (C-Ar), 128.3 (C-Ar), 127.6 (C-Ar), 127.5 (C-Ar), 115.1 (C-1), 113.7 (C-Ar), 87.3 (C-3), 72.8 (C-15), 70.6 (C-14), 69.8 (CH_2-PMB), 69.1 (C-9), 66.8 (C-11), 55.3 (OCH_3-PMB), 50.2 (C-6), 45.0 (C-8),42.3 (C-10), 34.6 (C-4), 33.8 (C-12), 26.6 (C-5), 25.9 (Si(C(CH_3)$_3$), 25.9 (Si(C(CH_3)$_3$), 25.2 (C-13), 18.0 (Si(C(CH_3)$_3$), 17.9 (Si(C(CH_3)$_3$), 17.2 (C-17), 15.6 (C-16), -4.3

($Si(CH_3)_2$), -4.4 ($Si(CH_3)_2$), -4.5 ($Si(CH_3)_2$), -4.7 ($Si(CH_3)_2$). HRMS (ESI, *m/z*) calcd for $(C_{43}H_{72}O_6Si_2Na)^+$ 763.4760, found 763.4738.

***tert*-Butyl((2*R*,3*S*,4*R*)-3-(4-methoxybenzyloxy)-2,4-dimethylhex-5-enyloxy) dimethylsilane 32.** Weinreb amide **33** (250 mg, 0.57 mmol) was dissolved in CH_2Cl_2 (5 mL) and the stirred solution was cooled to -78 °C. Then DIBAL-H (1.0 M in hexanes 0.66 mL, 0.66 mmol, 1.2 equiv) was dropwise added and stirred until complete conversion judged by TLC. At that point EtOAc (5 mL), Et_2O (5 mL) and a saturated aqueous Rochelle's salt solution (7 mL) were added and the mixture was stirred for a further 1 h while allowing it to warm to 20 °C. Then the two phases were separated, and the aqueous phase was extracted with ether (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated in *vacuo*. The product obtained as a colorless liquid was used in the next step without purification. At 0 °C *t*-BuOK (717 mg, 2.01 mmol, 3.53 equiv) and methyltriphenylphosphonium bromide (226 mg, 2.01 mmol, 3.53 equiv) were dissolved in THF (2.7 mL) and stirred for 90 min. Then a solution of unpurified aldehyde in THF (3 mL) was added dropwise and the resulting stirred suspension was left to warm to 20 °C overnight. The reaction mixture was then poured into a 50 mL separatory funnel containing an aqueous saturated solution of NH_4Cl (6 mL). The aqueous layer was extracted with ether (3 x 40 mL) and the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography on silica gel (petroleum ether: ether 9:1) gave **32** (130 mg, 60% over 2 steps) as a colorless oil. $[\alpha]^{23}_D$ +20.1 (c 1.0, $CHCl_3$). IR (neat, cm^{-1}) 2955, 2929, 2857, 1611, 1513, 1460, 1247, 1085. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.7 Hz, 2H, H-Ar (PMB)), 6.86 (d, *J* = 8.7 Hz, 2H, H-Ar (PMB)), 5.93 (ddd, *J* = 17.5, 10.3, 7.5 Hz, 1H, CH-2), 5.07 (dt, 1H, *J* = 17.5, 1.6 Hz, CH-1_{trans}), 5.01-4.98 (m, 1H, CH-1_{cis}), 4.50 (d, 1H, *J* = 10.7 Hz, CH_2-PMB), 4.45 (d, 1H, *J* = 10.7 Hz, CH_2-PMB), 3.80 (s, 3H, CH_3-PMB), 3.68-3.61 (m, 2H, CH-6), 3.28 (dd, 1H, *J* = 7.4, 4.4 Hz, CH-4), 2.47-2.41 (m, 1H, CH-3), 1.89-1.81 (m, 1H, CH-5), 1.04 (d, 3H, *J* = 6.8 Hz, CH-7), 0.95 (d, 3H, *J* = 6.9 Hz, CH-8), 0.90 (s, 9H, -$SiC(CH_3)_3$-), 0.04, 0.03 (2s, 6H, -$Si(CH_3)_2$-). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0 (C-Ar), 143.1 (C-2), 131.4 (C-Ar), 129.2 (C-Ar), 113.7 (C-Ar), 113.6 (C-1), 84.1 (C-4), 74.3 (CH_2-PMB), 64.8 (C-6), 55.3 (CH_3-PMB), 40.1 (C-3), 38.6 (C-5), 26.0 (-$SiC(CH_3)_3$-), 18.3 (-$SiC(CH_3)_3$-), 14.6 (C-7), 14.0 (C-8), -5.3 (-$Si(CH_3)_2$-), -5.4 (-$Si(CH_3)_2$-). HRMS (ESI, *m/z*) calcd for $(C_{22}H_{38}O_3SiNa)^+$ 401.2482, found 401.2470.

(5*S*,7*S*,12*R*,13*S*,14*R*,*E*)-5-(3-(benzyloxy)propyl)-7-((*tert*-butyldimethylsilyl)oxy)-13-((4-methoxybenzyl)oxy)-2,2,3,3,12,14,17,17,18,18-decamethyl-4,16-dioxa-3,17-disilanonadec-10-en-9-one 31. A solution of enone **28** (521 mg, 1.00 mmol) and alkene **32** (606 mg, 1.60 mmol, 1.60 equiv) in CH_2Cl_2 was degassed using the freeze-pump-thaw method. Hoveyda-Grubbs 2 catalyst was then added in two portions of 5 mol% (2 x 31.0 mg, 2 x 0.050 mmol) every 24 h. After 2 days, the reaction mixture was cooled to 20 °C and subsequently dry loaded on silica gel and purified by column chromatography (petroleum ether: ether 95:5) to afford **31** (619 mg, 71%) as a clear oil. $[\alpha]^{23}_D$ -11.6 (*c* 0.336, $CHCl_3$). IR (thin film, cm^{-1}) 2953, 2855, 1612, 1514, 1462, 1362, 1302, 1250, 1173, 1059, 1007. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.26 (m, 5H, H-Ar), 7.22 (d, *J* = 8.6 Hz, 2H, H-Ar(PMB)), 6.93 (dd, *J* = 16.0, 7.5 Hz, 1H, CH-5), 6.85 (d, *J* = 8.6 Hz, 2H, H-Ar(PMB)), 6.16 (d, *J* = 15.9, 1H, CH-6), 4.50 (s, 2H, CH-15), 4.45 (d, *J* = 10.7 Hz, 1H, CH_2-PMB), 4.40 (d, *J* = 10.7 Hz, 1H, CH_2-PMB), 4.31 (m, 1H, CH-9), 3.81-3.77 (m, 4H, PMB-OCH_3, CH-11), 3.68 (dd, *J* = 9.7, 5.3 Hz, 1H, CH-1), 3.61 (dd, *J* = 9.7, 3.8 Hz, 1H, CH-1), 3.46 (t, *J* = 6.5 Hz, 2H, CH-14), 3.38 (dd, *J* = 7.9, 3.8 Hz, 1H, CH-3), 2.70 (dd, *J* = 15.2, 6.9 Hz, 1H, CH-8), 2.65-2.57 (m, 2H, CH-8, CH-4), 1.87-1.81 (m, 1H, CH-2), 1.73-1.54 (m, 6H, CH-10, CH-12, CH-13), 1.08 (d, *J* = 6.8 Hz, 3H, CH-17), 0.94 (d, *J* = 6.9 Hz, 3H, CH-16) 0.90, 0.88, 0.84 (3s, 27H, -$SiC(CH_3)_3$-), 0.06, 0.05, 0.04, 0.04, -0.01 (5s, 18H, -$SiC(CH_3)_2$-). HRMS (ESI, *m/z*) calcd for $(C_{49}H_{86}O_7Si_3Na)^+$ 893.5574, found 893.5533.

(5*S*,7*R*,9*R*,12*R*,13*S*,14*R*,*E*)-5-(3-(Benzyloxy)propyl)-7-((*tert*-butyldimethylsilyl)oxy)-13-((4-methoxybenzyl)oxy)-2,2,3,3,12,14,17,17,18,18-decamethyl-4,16-dioxa-3,17-disilanonadec-10-en-9-ol 33. (*S*)-(-)-2-Methyl-CBS-oxazaborolidine (1.0 M in toluene 0.36 mL, 0.36 mmol, 1.3 equiv) was cooled to 0 °C at which point $BH_3{\cdot}SMe_2$ (36 µL, 0. 38 mmol, 1.4 equiv) was added and the mixture was stirred for 3 h while keeping the temperature constant. Then a solution of enone **31** (240 mg, 0.275 mmol) in toluene (1.8 mL) was added dropwise over 5 min and the resulting suspension was left to stir for a further 4 h at 0 °C. The reaction was then quenched by the slow and cautious addition of methanol (2 mL) giving off H_2 evolution. Once bubbling had ceased, a saturated aqueous NH_4Cl solution (4 mL) was added and the mixture was extracted with ether (3 x 2 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (petroleum ether: ether 4:1) to give **33** (210 mg, 88%) as a colorless oil and as a single diastereomer. $[\alpha]^{23}_D$ -16.5 (c 0.20, $CHCl_3$). IR (thin film, cm^{-1}) 2953, 2928, 1612, 1514, 1362, 1250, 1055. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.24 (m, 7H, H-Ar, H-Ar(PMB)), 6.86 (d, *J* = 8.7 Hz, 2H, H-Ar(PMB)), 5.77 (dd, *J* = 15.5, 7.6 Hz, 1H, CH-6), 5.51 (dd, *J* = 15.5, 6.3 Hz, 1H, CH-5), 4.50-4.44 (m, 4H, CH-15, CH_2-PMB), 4.39-4.36 (m, 1H, CH-7), 4.12 (m, 1H, CH-9), 3.79 (s, 3H, PMB-OCH_3), 3.74-3.70 (m, 1H, CH-11), 3.67-3.62 (m, 2H, CH-1), 3.47 (t, *J* = 6.6 Hz, 2H, CH-14), 3.35 (br s, 1H, C7-OH), 3.28 (dd, *J* = 7.7, 4.2 Hz, 1H, CH-3), 2.47-2.41 (m, 1H, CH-4), 1.86-1.47 (m, 9H, CH-2, CH-8, CH-10, CH-12, CH-13), 1.03 (d, *J* = 6.8 Hz, 3H, CH-17), 0.94 (d, *J* = 6.9 Hz, 3H, CH-16) 0.91, 0.90, 0.88 (3s, 27H, -$SiC(CH_3)_3$-), 0.11, 0.09, 0.05, 0.04, 0.04, 0.03 (6s, 18H, -$SiC(CH_3)_2$-). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1 (C-Ar), 138.6 (C-Ar), 134.9 (C-6), 132.0 (C-5), 131.3 (C-Ar), 129.2 (C-Ar), 128.3 (C-Ar), 127.5 (C-Ar), 127.5 (C-Ar), 113.7 (C-Ar), 84.1 (C-3), 74.3 (CH_2-PMB), 72.8 (C-15), 70.5 (C-14), 69.4 (C-9), 69.2 (C-7), 68.7 (C-11), 64.8 (C-1), 55.2 (OCH_3-PMB), 43.3 (C-10), 42.0 (C-8), 38.7 (C-4), 38.6 (C-2), 34.1 (C-12), 26.0 ($Si(C(CH_3)_3$), 25.9 ($Si(C(CH_3)_3$), 25.8 ($Si(C(CH_3)_3$), 25.1 (C-13), 18.3 ($Si(C(CH_3)_3$), 18.0 ($Si(C(CH_3)_3$), 17.9 ($Si(C(CH_3)_3$), 14.6 (C-17), 14.1 (C-16), -4.2 ($Si(CH_3)_2$), -4.5 ($Si(CH_3)_2$), -4.6 ($Si(CH_3)_2$), -4.7 ($Si(CH_3)_2$), -5.3 ($Si(CH_3)_2$), -5.4 ($Si(CH_3)_2$). HRMS (ESI, *m/z*) calcd for $(C_{49}H_{88}O_7Si_3Na)^+$ 895.5730, found 895.5700.

(6*R*,7*S*,8*R*,11*R*,13*S*,15*S*,*E*)-15-(3-(Benzyloxy)propyl)-11,13-*bis*((*tert*-butyldimethylsilyl)oxy)-7-((4-methoxybenzyl)oxy)-2,2,3,3,6,8,17,17,18,18-decamethyl-4,16-dioxa-3,17-disilanonadec-9-ene 34. Protected alcohol **34** was obtained from alcohol **33** according to the procedure described for **24**. Purification by column chromatography on silica gel (petroleum ether: ether 95:5) gave **34** as a clear oil, scale: 0.18 mmol, yield: quant. $[\alpha]^{23}_D$ -11.0 (c 0.10, $CHCl_3$). IR (thin film, cm^{-1}) 2926, 2855, 1742, 1464, 1258, 1119. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (m, 3H, H-Ar), 7.27-7.26 (m, 2H, H-Ar), 7.24 (d, *J* = 8.7 Hz, 2H, H-Ar(PMB)), 6.86 (d, *J* = 8.7 Hz, 2H, H-Ar(PMB)), 5.63 (dd, *J* = 15.5, 8.1 Hz, 1H, CH-6), 5.43 (dd, *J* = 15.5, 7.5 Hz, 1H, CH-5), 4.50-4.43 (m, 4H, CH-15, CH_2-PMB), 4.15-4.11 (m, 1H, CH-7), 3.85-3.81 (m, 1H, CH-9), 3.79 (s, 3H, PMB-OCH_3), 3.76-3.71 (m, 1H, CH-11), 3.63 (m, 2H, CH-1), 3.47-3.40 (m, 2H, CH-14), 3.25 (dd, *J* = 7.6, 4.1 Hz, 1H, CH-3), 2.45-2.38 (m, 1H, CH-4), 1.85-1.80 (m, 1H, CH-2), 1.75-1.55 (m, 8H, CH-8, CH-10, CH-12, CH-13), 1.00 (d, *J* = 6.8 Hz, 3H, CH-17), 0.93 (d, *J* = 6.9 Hz, 3H, CH-16) 0.90, 0.89, 0.88, 0.87 (4s, 36H, -$SiC(CH_3)_3$-), 0.07, 0.06, 0.05, 0.04, 0.04, 0.03, 0.02, 0.02 (8s, 24H, -$SiC(CH_3)_2$-). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0 (C-Ar), 138.7 (C-Ar), 134.8 (C-6), 132.9 (C-5), 131.3 (C-Ar), 129.1 (C-Ar), 128.3 (C-Ar), 127.5 (C-Ar), 127.4 (C-Ar), 113.7 (C-Ar), 84.2 (C-3), 74.5 (CH_2-PMB), 72.7 (C-15), 71.5 (C-7), 70.7 (C-14), 69.3 (C-9), 67.1 (C-11), 64.7 (C-1), 55.3 (OCH_3-PMB), 47.6 (C-10 or C-8), 45.9 (C-10 or C-8), 39.1 (C-4), 38.6 (C-2), 33.1 (C-12), 26.0 ($Si(C(CH_3)_3$), 26.0 ($Si(C(CH_3)_3$), 26.0 ($Si(C(CH_3)_3$), 25.9 ($Si(C(CH_3)_3$), 25.7 (C-13), 18.3 ($Si(C(CH_3)_3$), 18.2 ($Si(C(CH_3)_3$), 18.1 ($Si(C(CH_3)_3$), 18.0 ($Si(C(CH_3)_3$), 14.8 (C-17), 14.5 (C-16), -3.8 ($Si(CH_3)_2$), -3.9 ($Si(CH_3)_2$), -4.1 ($Si(CH_3)_2$), -4.2 ($Si(CH_3)_2$), -4.3 ($Si(CH_3)_2$), -4.5 ($Si(CH_3)_2$), -5.4 ($Si(CH_3)_2$), -5.4 ($Si(CH_3)_2$). HRMS (ESI, *m/z*) calcd for $(C_{55}H_{102}O_7Si_4Na)^+$ 1009.6595, found 1009.6579.

(4*S*,6*R*,8*S*,11*R*,12*S*,13*R*)-4,6,8,14-tetrakis((*tert*-Butyldimethylsilyl)oxy)-12-((4-methoxybenzyl)oxy)-11,13-dimethyltetradecan-1-ol 30. Raney nickel (2.5 mL) (W.R. Grace and Co. Raney® 2800, ≈ 50% w/w slurry in H_2O) was transferred to a flame dried, argon flushed round bottom flask and the H_2O was removed. Freshly distilled H_2O (5 mL) was added and the mixture was stirred for 5 min before removing the water. This cycle of addition/stirring/removal was repeated 20 more times. Freshly distilled ethanol (10 mL) was then added and the mixture was stirred for 5 min before removing the ethanol. This cycle of addition/stirring/removal was repeated 5 more times. Then a solution of **34** (170 mg, 0.172 mmol) in ethanol (1.5 mL + 0.5 mL rinse) was added and a 3-way tap was fitted onto the flask that was connected to a high vacuum pump and a balloon of hydrogen. The round-bottom flask was then evacuated and subsequently filled with hydrogen several times. The reaction mixture was then left to stir at 20 °C for 5 days before filtering through a pad of celite and the round bottom flask was cautiously rinsed with Et_2O (3 x 15 mL). The filtrate was concentrated *in vacuo* and subsequently purified by column chromatography on silica gel (petroleum ether: ether 1:1) to give free alcohol **30** (148 mg, 95%) as a colorless oil. $[\alpha]^{23}_D$ -5.8 (c 0.10, $CHCl_3$). IR (thin film, cm^{-1}) 3381, 2953, 1626, 1614, 1248, 1126, 1053. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.7 Hz, 2H, H-Ar(PMB)), 6.86 (d, *J* = 8.6 Hz, 2H, H-Ar), 4.53-4.48 (m, 2H, CH_2-PMB), 3.97-3.90 (m, 1H, CH-9), 3.80 (s, 3H, PMB-OCH_3), 3.77-3.56 (m, 6H, CH-1, CH-7, CH-11, CH-14), 3.27 (dd, *J* = 8.7, 1.9 Hz, 1H, CH-3), 1.83-1.79 (m, 1H, CH-2), 1.68-1.50 (m, 10H, CH-4, CH-6, CH-8, CH-10, CH-12, CH-13), 1.41-1.33 (m, 2H, CH-5, CH-6), 1.25 (m, 1H, CH-5), 0.91-0.88 (m, 42 H, CH-16, CH-17, -$SiC(CH_3)_3$-), 0.08-0.04 (m, 24H, -$SiC(CH_3)_3$-). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0 (C-Ar), 131.6 (C-Ar), 129.0 (C-Ar), 113.7 (C-Ar), 83.9 (C-3), 74.6 (CH_2-PMB), 70.2 (C-7), 69.2 (C-9), 67.7 (C-11), 65.0 (C-1), 63.2 (C-14), 55.3 (OCH_3-PMB), 46.6 (C-10 or C-8), 45.1 (C-10 or C-8), 38.6 (C-2), 35.9 (C-6), 35.8 (C-4) 32.7 (C-13), 30.6 (C-5), 28.2 (C-12), 26.0 ($Si(C(CH_3)_3$), 26.0 ($Si(C(CH_3)_3$), 25.9 ($Si(C(CH_3)_3$), 18.3 ($Si(C(CH_3)_3$), 18.1 ($Si(C(CH_3)_3$), 18.1 ($Si(C(CH_3)_3$), 18.0 ($Si(C(CH_3)_3$), 14.8 (C-17), 13.4 (C-16), -3.7 ($Si(CH_3)_2$), -4.1 ($Si(CH_3)_2$), -4.3 ($Si(CH_3)_2$), -4.5 ($Si(CH_3)_2$), -5.3 ($Si(CH_3)_2$), -5.4 ($Si(CH_3)_2$). HRMS (ESI, *m/z*) calcd for $(C_{48}H_{98}O_7Si_4Na)^+$ 921.6282, found 921.6252.

(4*S*,6*R*,8*S*,11*R*,12*S*,13*R*)-4,6,8,14-tetrakis((*tert*-Butyldimethylsilyl)oxy)-12-((4-methoxybenzyl)oxy)-11,13-dimethyltetradecanal. Dichloromethane (5 mL) and distilled H_2O (5 mL) were mixed in a separatory funnel and the two layers were separated. Then CH_2Cl_2 (0.40 mL) was added to a mixture of alcohol **30** (18.8 mg, 20.0 µmol) and Dess-Martin periodinane (17.0 mg, 40.0 µmol, 2.00 equiv) and the resulting suspension was stirred for 2 h. The reaction mixture was then concentrated *in vacuo* and subsequently dissolved in Et_2O (1 mL), washed with a saturated aqueous solution of sodium thiosulfate (3 x 1 mL), a saturated aqueous solution of $NaHCO_3$ (1 mL), H_2O (1 mL) and brine (1 mL). The combined aqueous phases were then back extracted with Et_2O (1 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (pentane: ether 10:1) to give the aldehyde (16.7 mg, 93%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (s, 1H, CH-14), 7.25 (d, *J* = 8.0 Hz, 2H, H-Ar(PMB)), 6.85 (d, *J* = 8.4 Hz, 2H, H-Ar), 4.51 (s, 2H, CH_2-PMB), 3.92 (m, 1H, CH-9), 3.79 (s, 3H, PMB-OCH_3), 3.76-3.66 (m, 3H, CH-1, CH-7, CH-11), 3.62 (dd, *J* = 9.4, 2.4 Hz, 1H, CH-1), 3.28-3.26 (m, 1H, CH-3), 2.50-2.45 (m, 2H, CH-13), 1.92-1.91 (m, 1H, CH-2), 1.80 (m, 1H, CH-4), 1.68-1.57 (m, 8H, CH-6, CH-8, CH-10, CH-12), 1.36-1.29 (m, 2H, CH-5), 0.91-0.88 (m, 42H, CH-16, CH-17, -$SiC(CH_3)_3$-), 0.07-0.04 (m, 24H, -$SiC(CH_3)_3$-). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.4 (C-14), 159.0 (C-Ar), 131.6 (C-Ar), 129.0 (C-Ar), 113.7 (C-Ar), 83.8 (C-3), 74.5 (CH_2-PMB), 70.2 (C-7), 68.4 (C-9), 67.6 (C-11), 65.0 (C-1), 55.3 (OCH_3-PMB), 46.5 (C-10 or C-8), 45.5 (C-10 or C-8), 39.7 (C-13), 38.6 (C-2), 35.9 (C-6), 35.7 (C-4), 30.6 (C-5), 28.5 (C-12), 26.0 ($Si(C(CH_3)_3$), 25.9 ($Si(C(CH_3)_3$), 25.9 ($Si(C(CH_3)_3$), 25.8 ($Si(C(CH_3)_3$), 18.3 ($Si(C(CH_3)_3$), 18.1 ($Si(C(CH_3)_3$), 18.0 ($Si(C(CH_3)_3$), 14.8 (C-17), 13.4 (C-16), -3.8 ($Si(CH_3)_2$), -4.1 ($Si(CH_3)_2$), -4.1 ($Si(CH_3)_2$), -4.1 ($Si(CH_3)_2$), -4.2 ($Si(CH_3)_2$), -4.6 ($Si(CH_3)_2$). -5.3 ($Si(CH_3)_2$), -5.4 ($Si(CH_3)_2$).

(5*S*,7*R*,9*S*,12*R*,13*S*,14*R*)-5-(But-3-yn-1-yl)-7,9-*bis*((*tert*-butyldimethylsilyl)oxy)-13-((4-methoxybenzyl)oxy)-2,2,3,3,12,14,17,17,18,18-decamethyl-4,16-dioxa-3,17-disilanonadecane 26. Alkyne **26** was obtained from the above aldehyde according to the procedure described for **19**. Purification by column chromatography on silica gel (petroleum ether: ether 97:3) gave **26** as a clear oil, scale: 39 µmol, yield: 80% (over 2 steps). $[\alpha]^{23}_{D}$ -5.8 (c 0.50, $CHCl_3$). IR (thin film, cm^{-1}) 2928, 2857, 1462, 1383, 1250, 1142, 1072. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.5 Hz, 2H, H-Ar(PMB)), 6.85 (d, *J* = 8.6 Hz, 2H, H-Ar), 4.54-5.48 (s, 2H, CH_2-PMB), 3.97-3.91 (m, 1H, CH-9), 3.80 (s, 3H, PMB-OCH_3), 3.77-3.71-3.69 (m, 3H, CH-1, CH-7, CH-11), 3.63 (dd, *J* = 9.6, 3.0 Hz, 1H, CH-1), 3.27 (dd, *J* = 8.7, 1.3 Hz, 1H, CH-1), 2.28-2.23 (m, 2H, CH-13), 1.91 (t, *J* = 2.5 Hz, 1H, CH-15), 1.82-1.74 (m, 2H, CH-2, CH-4), 1.72-1.52 (m, 8H, CH-6, CH-8, CH-10, CH-12), 1.36-1.29 (m, 2H, CH-5), 0.91-0.88 (m, 42H, CH-16, CH-17, -$SiC(CH_3)_3$-), 0.08-0.04 (m, 24H, -$SiC(CH_3)_3$-). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0 (C-Ar), 131.6 (C-Ar), 129.0 (C-Ar), 113.7 (C-Ar), 84.6 (C-14), 83.9 (C-3), 74.6 (CH_2-PMB), 70.3 (C-7), 68.4 (C-9), 68.1 (C-15), 67.6 (C-11), 65.0 (C-1), 55.3 (OCH_3-PMB), 46.6 (C-10 or C-8), 45.9 (C-10 or C-8), 38.6 (C-2), 35.9 (C-6), 35.7 (C-4), 35.4 (C-12), 30.6 (C-5), 26.0 ($Si(C(CH_3)_3$), 26.0 ($Si(C(CH_3)_3$), 25.9 ($Si(C(CH_3)_3$), 18.3 ($Si(C(CH_3)_3$), 18.1 ($Si(C(CH_3)_3$), 18.0 ($Si(C(CH_3)_3$), 18.0 ($Si(C(CH_3)_3$), 14.8 (C-17), 14.4 (C-13), 13.4 (C-16), -3.8 ($Si(CH_3)_2$), -4.1 ($Si(CH_3)_2$), -4.1 ($Si(CH_3)_2$), -4.1 ($Si(CH_3)_2$), -4.2 ($Si(CH_3)_2$), -4.6 ($Si(CH_3)_2$). -5.3 ($Si(CH_3)_2$), -5.4 ($Si(CH_3)_2$). HRMS (ESI, *m/z*) calcd for $(C_{49}H_{96}O_6Si_4Na)^+$ 915.6176, found 915.6140.

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Supplementary Material

Copies of ^{1}H and ^{13}C NMR spectra are provided in the Supplementary Material associated with this paper.

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