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Modular synthesis of polyene side chain analogues of the potent macrolide antibiotic etnangien by a flexible coupling strategy based on hetero-bis-metallated alkenes†

Mario Altendorfer,[a] Aruna Raja,[b] Florenz Sasse,[b] Herbert Irschik[c] and Dirk Menche*[a,d]

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An efficient procedure for the concise synthesis of hetero-bis-metallated alkenes as useful building blocks for the modular access to highly elaborate polyenes and stabilized analogues is reported. By applying these bifunctional olefins in convergent Stille/Suzuki–Miyaura couplings, novel, carefully selected side chain analogues of the potent RNA polymerase inhibitor etnangien were synthesized by a modular late stage coupling strategy and evaluated for antibacterial and antiproliferative activities.

Introduction

Enlivened nature produces a wide variety of natural products with impressive structural diversity and remarkable bioactive properties. The architecture of natural metabolites reaches from small molecules like salicylic acid, polycyclic compounds, peptides and polypeptides to highly unsaturated polyenes bearing conjugated or isolated olefin subunits.[1,2] Polyene structures, as exemplified by the myxobacterial antibiotic etnangien (**1**)[3–5] and its similarly potent methyl ester **2**,[6] often show powerful biological activities. These polyketide macrolides illustrate particularly efficient RNA polymerase inhibitors and are highly effective against a broad panel of Gram-positive bacteria. Importantly, they show no cross-resistance to the clinically used antibiotic rifampicine, which likewise targets RNA polymerase.[7,8] We have recently developed a first total synthesis of etnangien and etnangien methyl ester,[6] which also unequivocally confirmed the stereochemistry of these potent macrolides. However, the further advancement has been severely hampered by the extended conjugated alkene subunits, which renders the etnangiens extremely labile drugs. We have previously shown that the macrocyclic core of etnangien alone is essentially nonactive suggesting that at least part of the polyene side chain of etnangien is part of the pharmacophore.[6c] Therefore, in order to further develop these promising polyketides, an efficient access to more stable and readily available analogues presents an important research goal (Fig. 1).

As shown in Scheme 1 for the etnangien side chain, polyenes may be accessible in a rapid and modular fashion by using hetero-bis-metallated olefins of type **5**, which have been introduced by the groups of Coleman[9] and Carboni.[10] Herein, we report in full detail a concise and efficient synthetic route to these types of hetero-bis-metallated alkenes **5** as well as the partially saturated homologues thereof (**6**).[11] Furthermore, we demonstrate their effectiveness in convergent, standardized Stille/Suzuki–Miyaura reaction processes towards complex and highly unsaturated polyenes as well as stabilized derivatives.[12] Their synthesis was enabled by modular late stage assemblies of the authentic etnangien side chain and carefully selected simplified analogues thereof. Biological studies of these polyenes provide useful SAR data, which will be helpful for the further evaluation of these promising macrolide antibiotics.

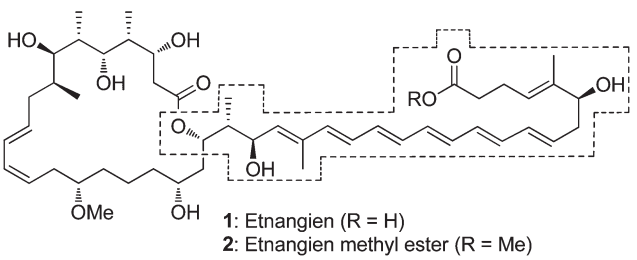

Fig. 1 Stereostructure for the polyene macrolide antibiotics etnangien (**1**) and etnangien methyl ester (**2**).

[a]*University of Heidelberg, Department of Organic Chemistry, INF 270, D-69120 Heidelberg, Germany, EU*
[b]*Helmholtz Centre for Infection Research, Department of Chemical Biology, Inhoffenstr. 7, 38124 Braunschweig, Germany, EU*
[c]*Helmholtz Centre for Infection Research, Research Group Microbial Drugs, Inhoffenstr. 7, 38124 Braunschweig, Germany, EU*
[d]*University of Bonn, Kekulé-Department of Organic Chemistry and Biochemistry, Gerhard-Domagk-Str. 1, D-53121 Bonn, Germany, EU.*
E-mail: dirk.menche@uni-bonn.de

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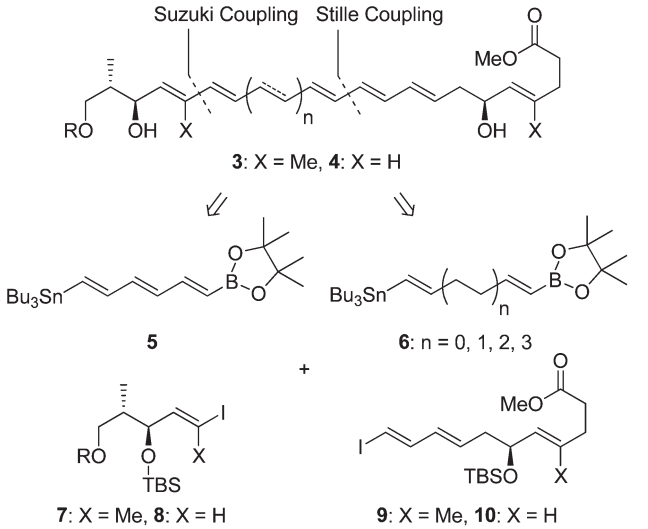
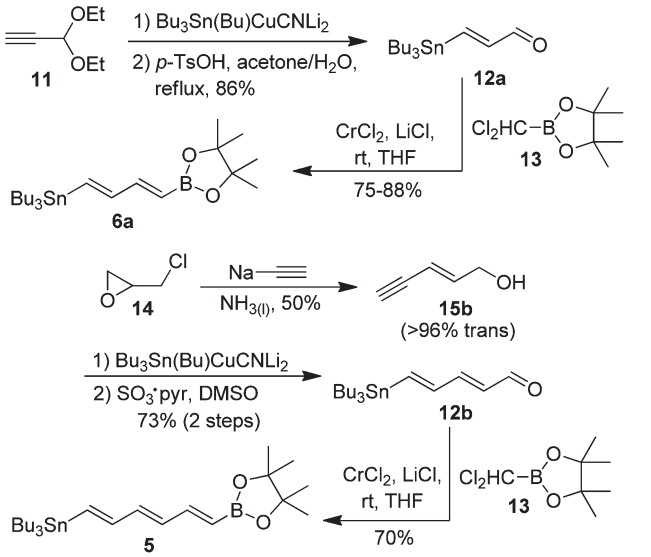
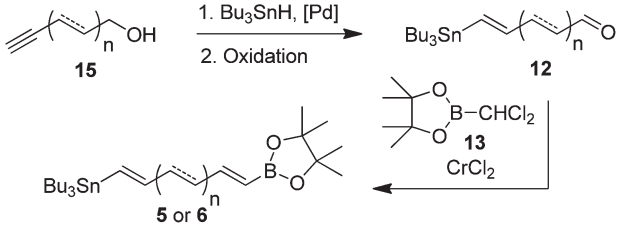


Scheme 1 Modular retrosynthetic approach towards the original etnangien side chain **3** and simplified analogues thereof (**4**).



Scheme 2 Coleman's procedure for the synthesis of bis-metallated alkenes **5** and **6**.[9]



Scheme 3 General sequence for the synthesis of hetero-bis-metallated reagents of type **5** and type **6**, reported herein.

Results and discussion

Synthetic strategy

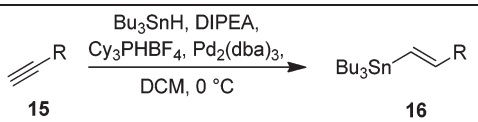
Our main focus in designing stable side chain analogues of etnangien was to develop a modular access to the authentic etnangien side chain **3** together with simplified analogues thereof by interrupting or shortening the labile hexaene subunit and displacement of selected vinylic methyl groups. As shown in Scheme 1, our concept relies on a modular late stage Stille/Suzuki–Miyaura cross-coupling sequence based on central building blocks **5** and **6** and the Western fragments **7**, **8**, and the Eastern parts **9** and **10**.

Synthesis of hetero-bis-metallated alkenes

Hetero-bis-metallated alkenes as bifunctional substrates in convergent Stille/Suzuki–Miyaura reactions enable a rapid and highly convergent construction of complex olefin systems. In the following we describe an advanced and generally useful synthesis of bis-metallated conjugated alkenes **5** and their partially saturated analogues **6**. Previous work of the Coleman group on the construction of diene **6a** started from the commercially available diethyl acetal **11** involving stannylcupration and acetal hydrolysis to obtain aldehyde **12a**. Subsequent Takai olefination provided the desired bis-metallated diene **6a** (Scheme 2).[9a] The synthesis of triene **5**, in turn, starts from epichlorohydrin **14** applying stannylcupration, Parikh–Doering oxidation and Takai olefination to afford the bifunctional triene **5**.[9e]

In order to improve the scalability, robustness and generality of these sequences, we decided to develop an alternative approach to these reagents. Our route towards these metallated alkenes (**5**) and partially saturated analogues thereof (**6**) relies on a three-step procedure. As illustrated in Scheme 3, this involves hydrostannylation of terminal alkynols **15**,[13] subsequent oxidation of the derived primary alcohols and final boryl-Takai olefination of aldehyde **12** to afford the desired bifunctional alkene systems **5** and **6**.

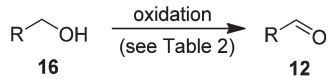
Table 1 Palladium catalyzed hydrostannylation of terminal alkynes **15**



Entry	Alkyne	R	Product	Yield (%)
1	**15a**	CH_2OH	**16a**	63
2	**15b**	$CH{=}CHCH_2OH$	**16b**	60
3	**15c**	$(CH_2)_2OH$	**16c**	72
4	**15d**	$(CH_2)_3OH$	**16d**	90
5	**15e**	$(CH_2)_5OH$	**16e**	73
6	**15f**	$(CH_2)_7OH$	**16f**	76

Best results for the initial hydrostannylation of terminal alkynes **15** were obtained by a palladium-catalyzed hydrostannylation procedure developed by the Chong group[14] (Table 1), which enabled a practicable access to the (*E*)-vinyl-stannanes **16** in reliable yields. High degrees of stereoselectivity, mild and cyanide-free reaction conditions and an easy work-up procedure are remarkable advantages of this protocol.

Table 2 Evaluation of methods for the oxidation of alcohol **16** to aldehyde **12**[a]



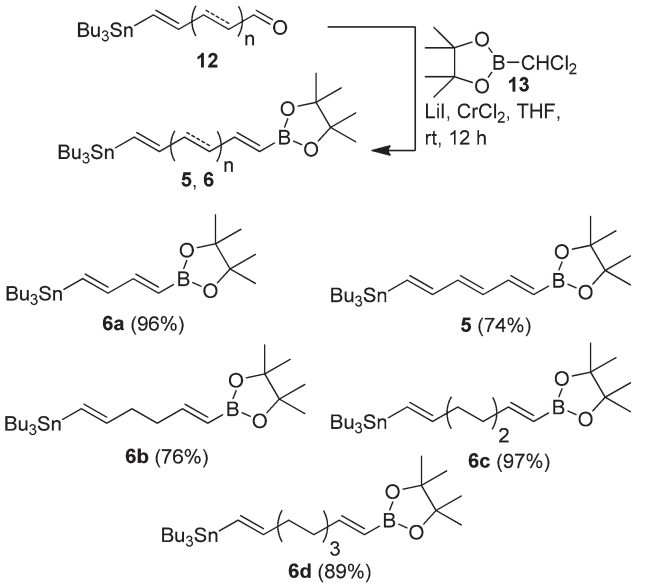
16 **12**

Entry	Alkyne	R	Conditions	Product	Yield (%)
1	**16a**	$Bu_3SnCH{=}CHCH_2$	A	**12a**	76
2	**16a**	$Bu_3SnCH{=}CHCH_2$	B	**12a**	88
3	**16b**	$Bu_3SnCH{=}(CH)_2{=}CHCH_2$	B	**12b**	86
4	**16c**	$Bu_3SnCH{=}CH(CH_2)_2$	A, C–F	**12c**	—
5	**16d**	$Bu_3SnCH{=}CH(CH_2)_3$	A	**12d**	—
6	**16d**	$Bu_3SnCH{=}CH(CH_2)_3$	C	**12d**	72
7	**16d**	$Bu_3SnCH{=}CH(CH_2)_3$	E	**12d**	80
8	**16e**	$Bu_3SnCH{=}CH(CH_2)_5$	A	**12e**	—
9	**16e**	$Bu_3SnCH{=}CH(CH_2)_5$	C	**12e**	29
10	**16e**	$Bu_3SnCH{=}CH(CH_2)_5$	D	**12e**	26
11	**16e**	$Bu_3SnCH{=}CH(CH_2)_5$	E	**12e**	81
12	**16f**	$Bu_3SnCH{=}CH(CH_2)_7$	A	**12f**	—
13	**16f**	$Bu_3SnCH{=}CH(CH_2)_7$	D	**12f**	26
14	**16f**	$Bu_3SnCH{=}CH(CH_2)_7$	E	**12f**	82

[a] Condition A: DMP, DCM, 0 °C – rt. Condition B: MnO_2, DCM, rt, 2 h. Condition C: SO_3·py, DMSO, NEt_3, DCM, −10 °C–0 °C. Condition D: oxalylchloride, DMSO, NEt_3, −78 °C – rt, 2 h. Condition E: TPAP, NMO, 4 Å Molecular sieve powder, DCM, 0 °C, 30 min. Condition F: PCC, CH_3COONa, DCM, rt, 2 h.

With these (*E*)-vinyl stannanes in hand, efforts were then directed towards subsequent oxidation of the primary alcohol function (Table 2). Allylic alcohol **16a** was initially oxidized to aldehyde **16a** by the Dess–Martin reagent in good yields (76%, entry 1). Subsequently, higher yields for the oxidation of **16a** and **16b** were obtained with activated MnO_2 (entries 2 and 3). The oxidation of non-allylic alcohols **16d–f** in turn was best performed using the Ley–Griffith protocol[15] to obtain the corresponding aldehydes routinely above 80%, (entries 7, 11, 14). Surprisingly, we were not able to transform compound **16c** into the derived aldehyde, despite considerable efforts with different reaction conditions (entry 4).

To complete the reaction sequence, the aldehyde function was then transformed selectively into (*E*)-olefins **5**/**6**. This was efficiently done by boryl-Takai olefinations.[16] The desired lynchpin hetero-bis-metallated alkenes were obtained in preparative useful yields (74–97%, Scheme 4).



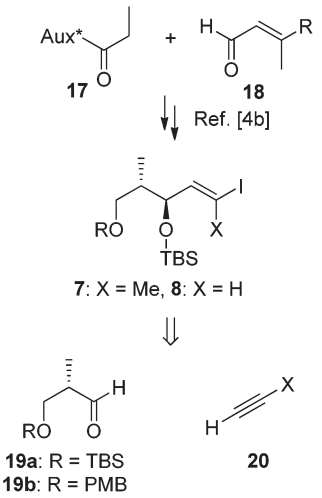
Scheme 4 Boryl-Takai olefination of aldehydes **12**.

Fragment synthesis

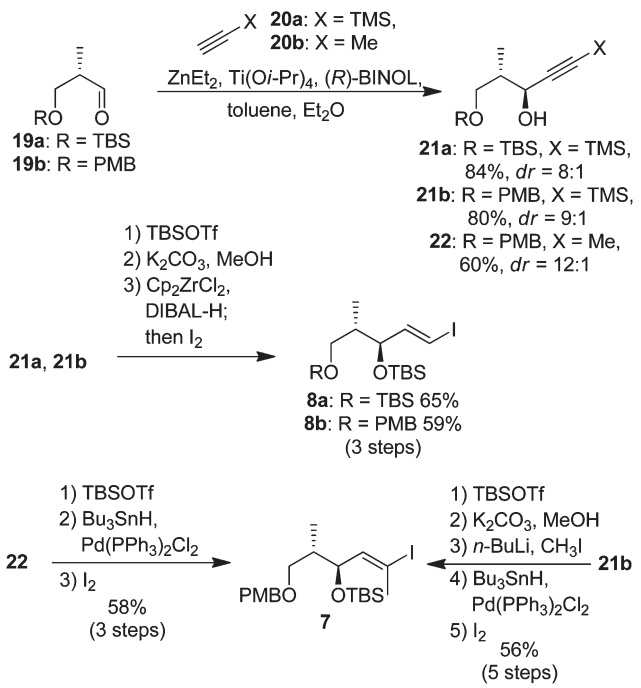
Western fragments

With an efficient synthesis of diverse hetero-bis-metallated reagents in hand, we then turned our attention to the synthesis of the required vinylic iodide coupling partners. As outlined in Scheme 5, construction of the Western fragment **7** has previously been accomplished in our group by an auxiliary mediated aldol coupling of **17** with aldehyde **18**.[6] In order to enable a more modular approach, an alternative, more economic sequence was evaluated within this study relying on an asymmetric alkyne addition of **20** to **19**.

As shown in Scheme 6, the synthesis of the authentic fragment **7** together with the desmethyl analogue **8** started from an asymmetric addition of TMS-acetylene to α-chiral aldehydes **19** using a method developed by the Marshall group.[17] Accordingly, treatment of aldehyde **19a** with TMS-acetylene in the presence of $Ti(OiPr)_4$ and Et_2Zn and catalytic amounts of (*R*)-BINOL gave the desired *anti*-configured propargylic alcohol **21a** (84%) together with minor amounts of the *syn*-isomer,[18] which could be readily removed by flash chromatography. The same procedure with aldehyde **19b** likewise resulted in an anti Felkin–Anh addition (dr = 9 : 1) in a similarly efficient manner, yielding the corresponding alkyne **21b** in 80% yield. To enable subsequent hydrozirconation, it was necessary to first protect the free hydroxyls of the addition products as silyl ethers with TBSOTf. The TMS group was then cleaved with potassium



Scheme 5 Synthesis of vinyl iodide fragments **19**.



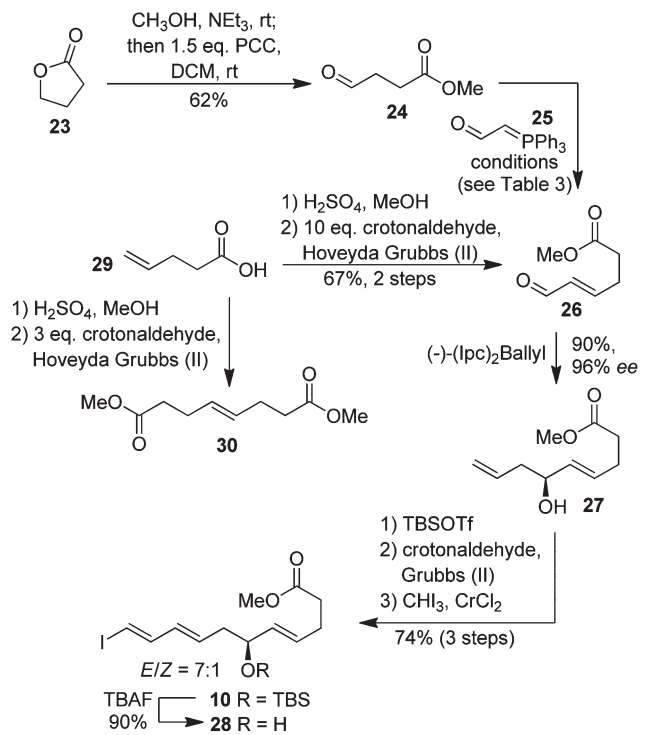
Scheme 6 Synthesis of the Western fragments **7** and **8**.

carbonate to obtain the corresponding terminal alkynes. Hydrozirconation[19] of the triple bond then proceeded smoothly after *in situ* generation of the Schwartz reagent.[20] Subsequent addition of elemental iodine[21] then afforded the desired (*E*)-configured vinyl iodides **8a** and **8b** in a regio- and stereoselective fashion.

The synthesis of the original side chain **3** was achieved in a sequence starting from Roche ester derived aldehyde **19b**, which was homologated by an asymmetric alkyne addition of propyne to afford the desired propargylic alcohol **22**. As expected, the addition reaction using (*R*)-BINOL as a chiral ligand resulted in the formation of **22** in useful selectivity (dr = 12 : 1). Due to subsequent difficulties in ensuing palladium-catalyzed cross coupling reactions by the presence of free hydroxy groups, the newly installed secondary alcohol function was protected by treatment of **22** with TBSOTf. The alkyne was then transformed selectively into a terminally stannylated olefin *via* palladium-catalyzed hydrostannylation[22] using $Bu_3SnH/Pd(PPh_3)_2Cl_2$.[23] Iodide **7** was then obtained after metal/halogen exchange[24] in a straightforward three-step sequence in 58% overall yield (35%, 4 steps, starting from **19b**). An alternative approach towards this Western fragment **7** *via* **21b** involved TBS protection, TMS cleavage, methylation and subsequent hydrostannylation followed by iodonolysis (Scheme 6, bottom part). This gave rise to **7** in two more steps but similarly high yields (56%, 5 steps). Furthermore, this second approach involved a more facile isolation protocol due to the low boiling point of propyne in comparison to TMS-acetylene.

Eastern fragments

For the synthesis of the Eastern dienyl iodide fragment **10**, we originally planned a route beginning from commercially available γ-butyrolactone **23**. Methanolysis under basic conditions afforded methyl γ-hydroxybutanoate, which had to be oxidized immediately to aldehyde **24**[25] to avoid relactonisation. Subsequent Wittig olefination would then provide (*E*)-methyl 6-oxohex-4-enoate **26** (Scheme 7). However, as shown in Table 3, standard Wittig conditions could not afford the desired α,β-unsaturated aldehyde **26** under various conditions (solvents, temperatures). Likewise, increasing the phosphonium ylide equivalents did not result in any conversion (entries 2–4). In addition, we also tried unsuccessfully to use substoichiometric equivalents of the Wittig reagent (entry 5).



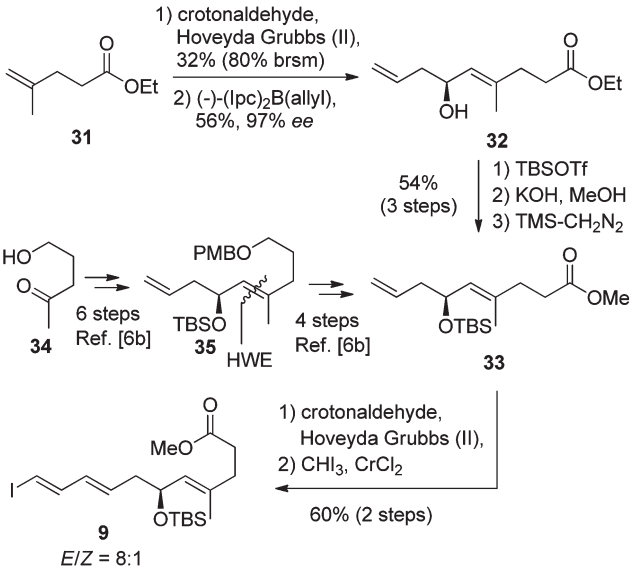
Scheme 7 Synthesis of vinyl iodide fragment **10**.

Table 3 Wittig reaction of aldehyde **24**

Entry	Conditions	Yield (%)
1	1.05 equiv. **25**, CH_3CN, 2 h, reflux	—
2	1.15 equiv. **25**, toluene, 1 h, 70 °C	—
3	1.24 equiv. **25**, toluene, 1.5 h reflux	—
4	1.50 equiv. **25**, DCM, 24 h, rt	—
5	0.33 equiv. **25**, DCM, 15 h, rt	—

Faced with these difficulties, we planned an alternative sequence. As shown in Scheme 7, it starts from commercially available pentenoic acid **29**. Acid-catalyzed esterification and subsequent cross metathesis of the methyl ester, best performed with a large excess of crotonaldehyde (10 equiv.) and Hoveyda Grubbs II catalyst (3 mol%), gave α,β-unsaturated aldehyde **26** in a straightforward fashion. Notably, using only 3 equiv. of crotonaldehyde resulted in the generation of dimeric ester **30**. Brown allylation[26] of aldehyde **26** under "salt-free" conditions[27] at −100 °C then gave the homoallylic alcohol **27** in 90% yield and high enantioselectivity (96% ee).[28] Finally, this alcohol was transformed to (*E*)-vinyl iodide fragment **10** over three steps. After initial attempts to directly homologate **27** by a cross metathesis leading mainly to cleavage to **26**, the more reactive, internal double bond was sterically shielded by a bulky TBS group. Cross metathesis then proceeded smoothly using crotonaldehyde (3.0 equiv.) and Grubbs II catalyst (5 mol%). Subsequently, Takai olefination[29] with iodoform and chromium(II) chloride in a mixed solvent system (dioxane–THF = 6 : 1)[30] gave dienyl iodide **10** in acceptable selectivity (*E*–*Z* = 7 : 1). Diene **10** proved to be highly labile to light resulting in *E*–*Z* isomerisations and had to be handled with extreme caution. For further investigations in the proposed palladium-catalyzed cross coupling reactions, the protecting group was removed with TBAF (1 M in THF) giving alcohol **28** in 90% yield.

In the course of our total synthesis of etnangien **4**, fragment **9** had been synthesized starting from commercially available ketone **34** in a 12 step procedure involving an HWE reaction, Brown allylation and Takai olefination as key-steps (6% overall yield). With regard to the length of this sequence and low *E*-selectivity of the involved HWE reaction (*E*–*Z* = 3 : 1), a more concise route seemed desirable. As shown in Scheme 8, this was realized within this study by starting from commercially available ethyl ester **31**, which was firstly converted to the corresponding α,β-unsaturated aldehyde with Hoveyda Grubbs II catalyst (5 mol%) and crotonaldehyde in an acceptable procedure considering that the starting material may be recovered (80% brsm). Larger amounts of metathesis catalyst did not result in higher degrees of conversion. Brown allylation, again under "salt-free" conditions at −100 °C, gave homoallylic alcohol **32** in high enantioselectivity (97% ee),[28] but only moderate yield (56%). After protection of the secondary alcohol **32** with TBSOTf, the ethyl ester was cleaved with potassium hydroxide in methanol. The resulting carboxylic acid was then transformed to methyl ester **33** with TMS-diazomethane. Cross metathesis with Hoveyda Grubbs II catalyst (5 mol%) in dry dichloromethane then resulted in the formation of the



Scheme 8 Synthesis of vinyl iodide fragment **9**.

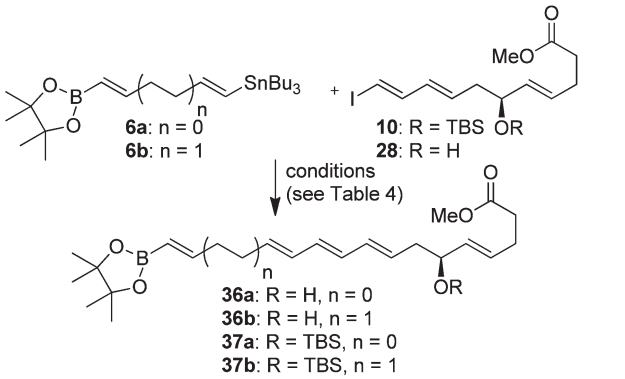
respective α,β-unsaturated aldehyde. Ultimately, Takai olefination with iodoform and chromium(II) chloride gave the desired, light sensitive dienyl iodide **9** in acceptable selectivity (8 : 1). Importantly, this route proceeds in only 7 steps and higher stereoselectivity as compared to our original sequence.

Fragment union and completion of the synthesis of the side chain analogues

For fragment union, our strategy relied on first coupling one of the vinyl iodide building blocks by a Stille coupling and subsequently attaching the other fragment by a Suzuki–Miyaura reaction. Accordingly, we first evaluated the Stille coupling of **6a** and **6b** with Eastern building block **28**. As shown in Table 4, this reaction was first studied under standard Stille conditions.[31] However, treatment of dienyl iodide **28** with $Pd_2(dba)_3$, $As(Ph)_3$ and diene **6a** in degassed DMF showed no conversion (entry 1). Similarly, no reaction was observed for stannane **6b** using the same proportions and conditions (entry 2). Also, with $PdCl_2(CH_3CN)_2$ (5 mol%) no conversion could be detected (entries 3 and 4). Larger amounts of the Pd(II)-catalyst (10 mol%) had no influence on the outcome (entries 5 and 6). Finally, we were successful using TBS protected vinyl iodide **10**. In detail, stannane **6a** (1.5 equiv.) and dienyl iodide **10** (1.0 equiv.) were treated with $PdCl_2(CH_3CN)_2$ (5 mol%) in degassed DMF, giving conjugated tetraene **37a** in 80% yield (entry 7). Using the same conditions and proportions also the Stille coupling of diene **6b** with **10** afforded pinacol borane **37b** with good results (68%, entry 8).

Efforts were then directed towards the implementation of a Suzuki–Miyaura reaction[32] of the derived pinacolboranes **37** with the Western fragment **8**. Due to the notorious instability of polyunsaturated subunits, we evaluated mild reaction conditions. In detail, $Ba(OH)_2$ proved to be a particularly suitable promoter allowing for the successful synthesis of the protected side chains **38** and **39** and treatment of pinacolborane **37a** and

Table 4 Stille coupling conditions hetero-bis-metallated dienes **6** with dienyl iodides **10** and **28**[a]



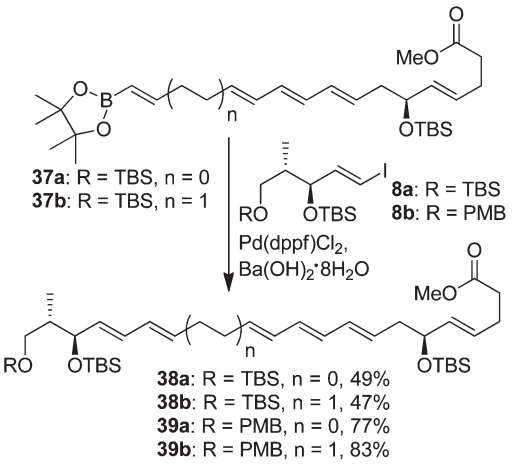
Entry	Conditions	Stannane	Iodide	Yield (%)
1	A	2.0 equiv. **6a**	1.0 equiv. **28**	—
2	A	2.0 equiv. **6b**	1.0 equiv. **28**	—
3	B	2.0 equiv. **6a**	1.0 equiv. **28**	—
4	B	2.0 equiv. **6b**	1.0 equiv. **28**	—
5	C	2.0 equiv. **6a**	1.0 equiv. **28**	—
6	C	2.0 equiv. **6b**	1.0 equiv. **28**	—
7	B	1.5 equiv. **6a**	1.0 equiv. **10**	80
8	B	1.5 equiv. **6b**	1.0 equiv. **10**	68

[a] Condition A: 5 mol% $Pd_2(dba)_3$, $As(Ph)_3$, DMF, rt, 12 h. Condition B: 5 mol% $PdCl_2(CH_3CN)_2$, DMF, rt, 12 h. Condition C: 10 mol% $PdCl_2(CH_3CN)_2$.

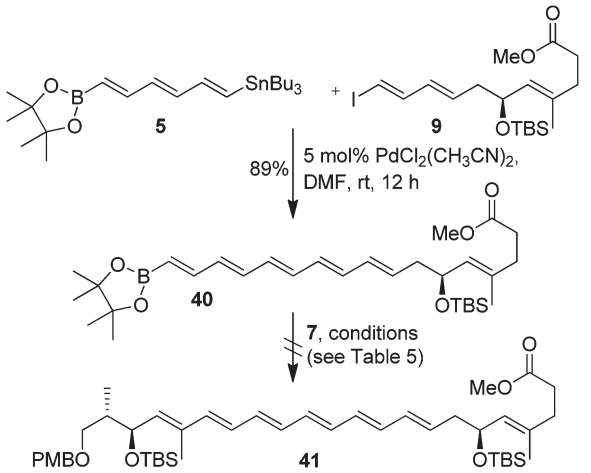
iodide **8a** with $Pd(dppf)Cl_2$ (15 mol%) as the catalyst and $Ba(OH)_2$[33] in DMF afforded pentaene **38a** in 49% yield. The Suzuki coupling of borane **38b** bearing an isolated diene moiety with vinyl iodide **8a** showed similar conversion to obtain tris-TBS ether **38b** in 47% yield and cross coupling of diene **37a** and PMB-protected vinyl iodide **8b** afforded the desired methyl ester **39a** in 77% yield. Finally, Suzuki coupling of pinacolborane **37b** with iodide **8b** gave polyene compound **39b** (47%). Altogether, four different types of protected side chains were obtained using this route (Scheme 9).

With this reliable method for the construction of simplified etnangien side chains established, efforts were then directed to access the original side chain **3** by applying the same methodologies. As depicted in Scheme 10, we started the cross coupling sequence with the union of stannane **5** with dienyl iodide **9**. Using the previously evaluated Stille conditions with $Pd(CH_3CN)_2Cl_2$, pentaene **40** was obtained in high yields (89%). However, on treatment of pinacolborane with iodide **7** in the presence of $Pd(dppf)Cl_2$ (15 mol%) and $Ba(OH)_2{\cdot}8H_2O$, according to conditions evaluated before, no conversion was observed. Therefore ester **40** and iodide **7** were subjected to various alternative Suzuki conditions to effectuate the coupling sequence. These included $Pd(dppf)Cl_2$, Ph_3As and K_3PO_4 in degassed DMF (entry 2) and $Pd_2(dba)_3$, Ph_3As and K_3PO_4 in DMF (entry 3), but no conversion could be obtained (Table 5).

We therefore resorted to an alternative route by changing the order of coupling the iodide fragments. Accordingly, pinacolborane **42** was initially prepared from vinyl iodide **7** and



Scheme 9 Suzuki–Miyaura coupling of pinacolboranes **37** with vinyl iodides **8**.



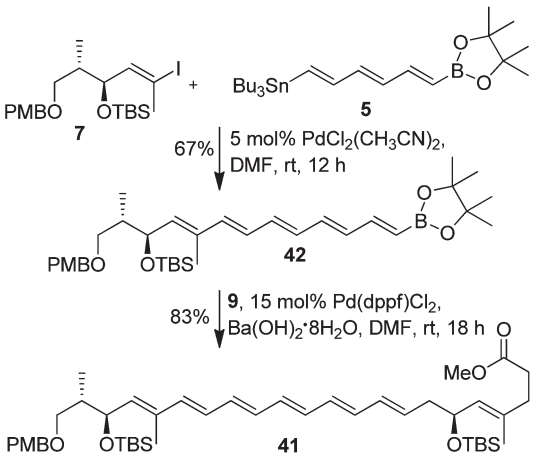
Scheme 10 Convergent Stille/Suzuki–Miyaura coupling sequence towards the protected etnangien side chain **41**.

Table 5 Suzuki coupling conditions

Entry	Catalyst	Conditions	Yield (%)
1	$Pd(dppf)Cl_2$ (15 mol%)	$Ba(OH)_2{\cdot}8H_2O$, DMF, rt, 18 h	—
2	$Pd(dppf)Cl_2$ (10 mol%)	Ph_3As, K_3PO_4, DMF, rt, 18 h	—
3	$Pd_2(dba)_3$ (5 mol%)	Ph_3As, K_3PO_4 3 M in H_2O, DMF, rt, 18 h	—

bis-metallated triene **5** under the Stille conditions as before in good yield (67%, Scheme 11). Satisfyingly, the resulting borane (**42**) then underwent a Suzuki–Miyaura coupling using $Pd(dppf)Cl_2$ and $Ba(OH)_2$ giving the desired protected side chain **41** in 83% yield.

With these polyenes in hand, we then focused on the removal of the TBS protection group. This proved to be an extremely challenging task, due to the extreme lability of some of these compounds. As shown in Table 6, we attempted a

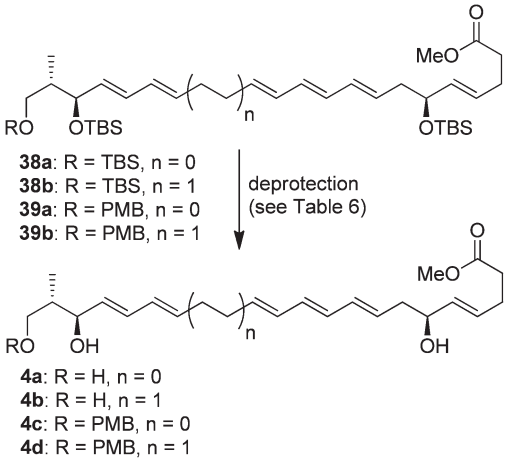


Scheme 11 Alternative Stille/Suzuki–Miyaura coupling sequence towards the etnangien side chain **3**.

wide variety of different deprotection conditions, giving however initially only unsatisfactory results. First attempts of global TBS deprotection of **38a** under mild, basic conditions with TASF in wet DMF gave no conversion, even after stirring the reaction over prolonged times (entry 1). Moreover, we tried to remove the TBS groups using HF-pyridine and TBS protected polyene **38a** and compound **39a** were treated with 70% HF-pyridine in THF at 0 °C, however no conversion was initially observed and on prolonged reaction times, only decomposition resulted (entries 2 and 3). Inspired by our previously established TBS deprotections in the course of our total synthesis of etnangien,[6] we also tried the same conditions and proportions involving treatment of silyl ethers **38** and **39** with TBAF, buffered with AcOH. However, again no traces of the desired compounds could be detected (entries 4–7). Another unsatisfactory result was achieved by applying 1.5 N hydrochloric acid in methanol. Finally, we tried to cleave the TBS ethers with aqueous hydrofluoric acid giving the first promising results. However, difficulties resulted in trying to isolate the products by using a conventional aqueous work-up with saturated ammonium chloride solution (entries 12–15), resulting in partial decompositions. Another disappointing and challenging problem was the poor solubility of silyl ethers **38a** and **39a** in acetonitrile. Finally, we turned our attention to Kishi's method[34] for global removal of silyl ethers by TBAF and a work-up procedure using $CaCO_3$, Dowex and methanol. In our case, we treated the protected polyenes **38** and **39** (entries 16–19) with 1 M TBAF in THF (2.5 equiv. for each TBS group) and stirred at room temperature overnight. Fortunately, we could clearly observe complete conversion. After anhydrous work-up using the reported protocol we isolated the desired deprotected side chain derivatives *via* preparative TLC in a high level of purity (entries 16–19).

In a similar fashion, completion of the synthesis of the original side chain was achieved by using the Kishi protocol. Removal of the secondary, allylic silyl ethers was cleanly effected by TBAF giving the desired, polyunsaturated diol **3** in preparative useful yields (58%), considering the lability of this compound (Scheme 12).

Table 6 Global TBS deprotection of polyenes **38** and **39**[a]



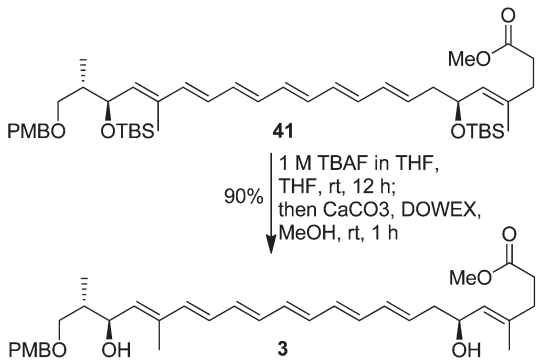
Entry	Conditions	Polyene	Product	Yield (%)
1	A	**38a**	**4a**	—
2	B	**38a**	**4a**	—
3	B	**39a**	**4c**	—
4	C	**38a**	**4a**	—
5	C	**38b**	**4b**	—
6	C	**39a**	**4c**	—
7	C	**39b**	**4d**	—
8	D	**38a**	**4a**	—
9	D	**38b**	**4b**	—
10	D	**39a**	**4c**	—
11	D	**39b**	**4d**	—
12	E	**38a**	**4a**	34[b]
13	E	**38b**	**4b**	78[b]
14	E	**39a**	**4c**	21[b]
15	E	**39b**	**4d**	93[b]
16	F	**38a**	**4a**	59
17	F	**38b**	**4b**	95
18	F	**39a**	**4c**	29
19	F	**39b**	**4d**	61

[a] Condition A: TASF, wet DMF, 0 °C to rt, 18 h. Condition B: 70% HF-pyridine, THF, 0 °C to rt, 5 h. Condition C: 2 M TBAF and 0.2 M AcOH in DMF, DMF, 0 °C to rt, 18 h. Condition D: 1.5 N HCl in MeOH, MeOH, 0 °C to rt, 18 h. Condition E: 35% aq. HF, CH_3CN, rt, 0.5–1 h. Condition F: 1 M TBAF in THF, THF, rt, 12 h; then $CaCO_3$, DOWEX, MeOH, rt, 1 h. [b] Impure compounds.

Bioactivity

The potent antibiotic activity of etnangien (**1**) based on RNA-polymerase inhibition prompted us to likewise analyse the side chain analogues for their antimicrobial potential. Table 7 summarizes their inhibitory activities against different microorganisms, in direct comparison to etnangien (**1**) and its methyl ester (**2**). As previously reported, bacteria belonging to the Corynebacterineae, such as *Nocardia corallina* and some *Mycobacteria*, were particularly sensitive to (**1**) and (**2**), while yeast and Gram-negative *Escherichia coli* proved to be rather resistant. In agreement with these results, the novel side chain analogues likewise showed no antimicrobial activity against

Gram-negative *E. coli* and the yeast *Saccharomyces cerevisiae*. However, in contrast to the authentic natural product, no activity against Gram-positive bacteria was observed for most side chain analogues, with the exception of compound **4b**. Triol **4b** possesses low inhibitor effects against *Bacillus subtilis*, which is in the same level as the methyl ester derivative (**2**) but slightly lower than the parental natural product etnangien. In addition, *Corynebacterium mediolanum* showed a small sensitivity to **4b**. Notably, the original etnangien side chain (**3**) showed no antimicrobial potential. In summary, the results indicate the importance of the macrocyclic core for biological potency. In combination with previous findings in our group,[11] these data suggest that both the macrocycle and the side chain are vital for full antibacterial activity. For the further biological evaluation, the side chains were also tested against different mammalian cell lines (Table 7). The parental natural product etnangien (**1**) is known for being tolerated by cell cultures of L-929 mouse fibroblasts. All side chains show slightly lower IC_{50} values in a micromolar scope. Compound **4b** exhibits the most pronounced antiproliferative profile up to ten times higher than its polyene congeners **4a**, **4c**, **4d** and **3** and around 40 times greater than etnangien (**1**).

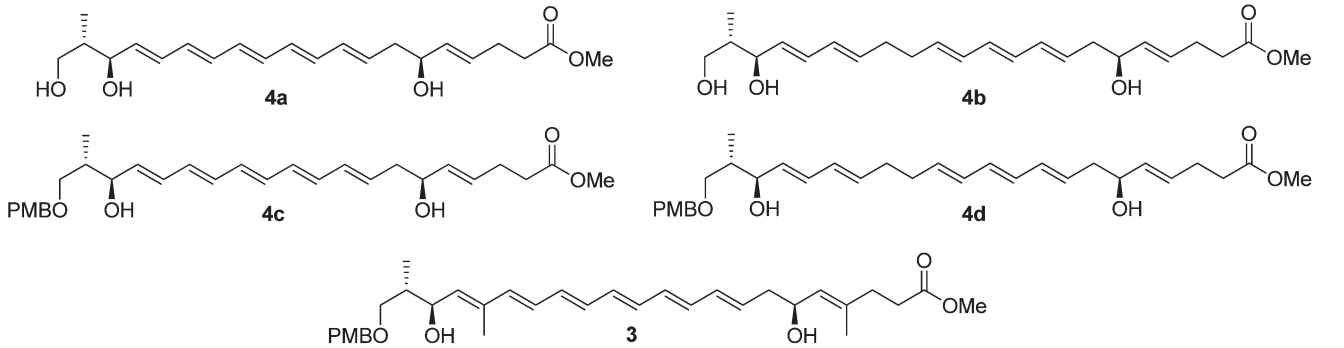


Scheme 12 Global TBS deprotection.

Conclusion

In conclusion, an efficient and highly stereoselective synthesis of simplified side chain analogues of the potent macrolide antibiotic etnangien was accomplished based on a convergent

Table 7 Antimicrobial and cytotoxic activity of simplified etnangien analogues **3** and **4** in comparison to etnangien (**1**) and its methyl ester (**2**)



	MIC[a] (μg mL^{-1})						
Test organism	**1**	**2**	**4a**	**4b**	**4c**	**4d**	**3**
Gram-positive bacteria							
Staphylococcus aureus	1	2.5	>80	80[b]	>80	>80	>40
Bacillus subtilis	10	20	>80	20	>80	>80	>40
Corynebacterium mediolanum	0.06	n.d.	>80	40	>80	>80	>40
Corynebacterium glutanicum	0.03	0.24	>80	80[b]	80[b]	>80	>40
Mycobacterium phlei	0.12	n.d.	>40	>40	>40	>40	>40
Micrococcus luteus	0.39	0.06	>80	>80	>80	>80	>40
Gram-negative bacterium							
Escherichia coli	>80	>20	>80	>80	>80	>80	>40
Yeast							
Saccharomyces cerevisiae	>80	>40	>80	>80	>80	>80	>40
Cell lines	IC_{50} (μg mL^{-1})						
L-929 (mouse, connective fibroblast)	74	n.d.	12	1.8	20	21	7.8
KB-3-1 (human, cervix carcinoma)	n.d.	n.d.	14	3.0	20	15	6
U-937 (human, histiocytic lymphoma)	n.d.	n.d.	3.6	1.4	6.5	10	n.d.
MCF7 (human, breast adenocarcinoma)	n.d.	n.d.	5.2	4.2	6.9	12	n.d.
HUVEC (human, umbilical vein endothelial cells)	n.d.	n.d.	7.0	2.6	14	13	n.d.
PtK2 (kangaroo rat, kidney epithelial cells)	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	15

[a] Experiments were run in duplicate. [b] Incomplete inhibition; n.d.: not determined.

late-stage coupling strategy. It proceeds in 9 steps (longest linear sequence) for polyenes **4a**, **4b**, **4c** and **4d** and 10–13% yield starting from the commercially available acid **29**. The modular synthesis of these compounds was effected in an efficient manner by a late stage diversification sequence based on hetero-bis-metallated alkenes. These reagents were obtained in a reliable and generally useful three-step sequence. In addition, we demonstrated the true applicability of these reagents in the efficient construction of the highly unsaturated, original etnangien side chain **3** requiring 10 steps (longest linear sequence, 12% yield) starting from the commercially available (*S*)-(+)Roche ester. Importantly, the partially saturated analogues proved to be much more stable as compared to the original fully conjugated side chains, which demonstrate the general usefulness of our approach. Along this synthesis, considerable time and effort had to be invested to a few critical steps. After several unsuccessful attempts to connect the stannane bearing terminus of the Stille/Suzuki–Miyaura systems **6a** and **6b** to unprotected dienyl iodide **28** the coupling was achieved using the TBS protected iodide **10** and $PdCl_2(CH_3CN)_2$ as the catalyst. Subsequent Suzuki–Miyaura coupling afforded the desired polyenes **38** and **39**. The most challenging part appeared late. Global deprotection of all TBS groups was extremely demanding, resulting in total decomposition. Ultimately, the removal of the silyl ethers using TBAF critically depends on an anhydrous work-up procedure. This finally enabled us to attain the goal in preparatively useful yields.

Truncation of the macrocycle leads to absolute loss of activity, which suggests that only the combination of macrocycle and side chain enables etnangien to undergo interaction with the target protein. The presented convergent synthesis of novel etnangien analogues and their biological data should be instructive and amenable to construct analogues combining simplified and stable side chains with the macrocycle. This may lead to novel potent but simplified and more stable RNA-polymerase inhibitors.

It is expected that polyunsaturated hetero-bis-metallated alkenes as well as partially saturated analogues thereof will be further explored and applied to the synthesis of functional polyene molecules and designed derivatives thereof.

Experimental

General synthetic procedures

All reactions were performed under an atmosphere of argon in flame-dried glassware which had been cooled under argon unless stated otherwise. All flasks were equipped with rubber septa and reactants were handled using standard Schlenk techniques. Temperatures above rt (23 °C) refer to oil bath temperatures which were controlled by a temperature modulator. For cooling, the following baths were used: ethanol/liquid nitrogen (−98 °C), acetone/dry ice (−78 °C), water/ice (0 °C). All reagents, anhydrous DMF and anhydrous 1,4-dioxane were purchased from commercial suppliers (Sigma-Aldrich, Alfa Aesar, Strem) in the highest grade available and used without further purification unless otherwise stated. Anhydrous solvents (THF, diethyl ether and dichloromethane) were freshly obtained from a solvent drying system MB SPS-800. Reactions were monitored *via* TLC on silica gel 60 F_{254} precoated plates (0.2 mm SiO_2, Machery-Nagel) and visualized using UV light and/or staining with a solution of CAM (1 g $Ce(SO_4)_2$, 2.5 g $(NH_4)_6Mo_7O_{24}$, 8 mL conc. H_2SO_4 in 100 mL H_2O) and subsequent heating. For column chromatography, silica gel (pore size 60 Å, 40–63 μm) obtained from Aldrich was used. Solvents were distilled prior to use. Optical rotations were measured with a Perkin Elmer 241 polarimeter in a 10 mm cuvette and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on Bruker AC-300, DRX-300, AVB-400, DRX-500 and Avance III 600 spectrometers with ^{13}C operating frequencies of 75, 100, 125 and 150 MHz, respectively. Data for ^1H NMR spectra are reported as follows: chemical shift (multiplicity, coupling constants in Hertz, number of hydrogens). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), br (broad). Mass spectra (MS) and high-resolution-mass spectra (HR-MS) were recorded at the Department of Organic Chemistry on the following mass spectrometers: Bruker ICR APEX-QE, Vacuum Generators ZAB-2F, Finnigan MAT TSQ 700 and JEOL JMS-700. Ionization processes and mol peaks were given.

General procedure for hydrostannylation of alkynes 15. Pd_2dba_3 (4.60 mg, 5.00 μmol, 0.5 mol%), tricyclohexylphosphonium tetrafluoroborate (7.40 mg, 20.0 μmol, 2.0 mol%) and diisopropylethylamine (5.20 mg, 40.0 μmol, 4 mol%) were added successively to dry dichloromethane (10 mL) and the resulting mixture was stirred at room temperature for 10 minutes. Alkyne (1.00 mmol, 1.0 equiv.) was added and the reaction mixture was cooled to 0 °C. *n*-Bu_3SnH (1.20 mmol, 1.2 equiv.) was diluted in dry dichloromethane (5 mL) and added dropwise *via* a syringe over 5 minutes. The reaction was then stirred at 0 °C for 2 hours. The reaction mixture was concentrated under reduced pressure and purified by silica gel chromatography (petroleum ether–ethyl acetate, 9 : 1) to afford the corresponding vinylstannane.

(*E*)-5-(Tributylstannyl)prop-2-en-1-ol 16a. The reaction was performed according to the general procedure as described above for Pd_2dba_3 (82.0 mg, 89.0 μmol, 0.5 mol%), tricyclohexylphosphonium tetrafluoroborate (131 mg, 365 μmol, 2.0 mol%), diisopropylethylamine (92.0 mg, 712 μmol, 4 mol%) in dichloromethane (100 mL), propargyl alcohol **15a** (1.00 g, 17.8 mmol, 1.0 equiv.), Bu_3SnH (6.23 g, 21.4 mmol, 1.2 equiv.) in dichloromethane (50 mL) to give stannane **16a** as a yellow oil (3.88 g, 11.2 mmol, 63%). R_f = 0.34 (*n*-hexane–ethyl acetate, 9 : 1); ^1H NMR (300.132 MHz, $CDCl_3$) δ = 0.90 (m, 15 H), 1.31 (dq, J = 14.5 Hz, J = 7.3 Hz, 6 H), 1.49 (m, 6 H), 4.18 (dd, J = 5.9 Hz, J = 3.2 Hz, 2 H), 6.18 (m, 2 H); ^{13}C NMR (75.48 MHz, $CDCl_3$) δ = 9.4, 13.7, 27.3, 29.1, 66.4, 128.3, 147.0; EI MS (70 eV, m/z (%)): 291 ($[M]^+ - C_4H_9$, 100).

(2*E*,4*E*)-5-(Tributylstannyl)penta-2,4-dien-1-ol 16b. The reaction was performed according to the general procedure as described above for Pd_2dba_3 (5.60 mg, 6.10 μmol, 0.5 mol%),

tricyclohexylphosphonium tetrafluoroborate (9.60 mg, 24.4 μmol, 2.0 mol%), diisopropylethylamine (6.36 mg, 48.8 μmol, 4.0 mol%) in dry dichloromethane (7 mL), pent-2,4-diyn-1-ol **15b** (100 mg, 1.22 mmol, 1.0 equiv.), Bu_3SnH (426 mg, 1.46 mmol, 1.2 equiv.) in dry dichloromethane (4 mL) to give stannane **16b** as a yellow oil (273 mg, 732 mmol, 60%). R_f = 0.24 (*n*-hexane–ethyl acetate, 9 : 1); ^{1}H NMR (300.132 MHz, $CDCl_3$) δ = 0.90 (m, 15 H), 1.32 (dq, J = 14.8 Hz, J = 7.2 Hz, 6 H), 1.50 (m, 6 H), 4.21 (t, J = 5.4 Hz, 2 H), 5.80 (dt, J = 15.5 Hz, J = 5.8 Hz, 1 H), 6.26 (m, 2 H), 6.55 (dd, J = 18.9 Hz, J = 8.8 Hz, 1 H); ^{13}C NMR (75.48 MHz, $CDCl_3$) δ = 9.5, 13.7, 27.3, 29.1, 63.3, 130.7, 134.6, 135.1, 145.9; HR-MS (EI): found m/z = 317.0930 ($C_{13}H_{25}OSn$ $[M - C_4H_9]^+$), calculated m/z = 317.0922.

(*E*)-4-(Tributylstannyl)but-3-en-1-ol 16c. The reaction was performed according to the general procedure as described above for Pd_2dba_3 (20.4 mg, 22.3 μmol, 0.5 mol%), tricyclohexylphosphonium tetrafluoroborate (33.0 mg, 89.0 μmol, 2 mol%), diisopropylethylamine (23.0 mg, 178 μmol, 4 mol%) in dichloromethane (20 mL), but-3-yn-1-ol **15c** (312 mg, 4.45 mmol, 1.0 equiv.), Bu_3SnH (1.55 g, 5.34 mmol, 1.2 equiv.) in dichloromethane (15 mL) to give stannane **16c** as a yellow oil (1.16 g, 6.25 mmol, 72%). R_f = 0.31 (petroleum ether–ethyl acetate, 9 : 1); ^{1}H NMR (300.132 MHz, $CDCl_3$) δ = 0.89 (m, 15 H), 1.31 (dq, J = 14.7 Hz, J = 7.2 Hz, 6 H), 1.50 (m, 6 H), 2.43 (q, J = 6.0 Hz, 2 H), 3.69 (q, J = 6.1 Hz, 2 H), 6.01 (m, 2 H); ^{13}C NMR (75.48 MHz, $CDCl_3$) δ = 9.4, 13.7, 27.2, 29.1, 41.2, 61.4, 132.2, 144.8; HR-MS (EI): found m/z = 305.0941 ($[M]^+ - C_4H_9$), calculated m/z = 305.0927.

(*E*)-5-(Tributylstannyl)pent-4-en-1-ol 16d. The reaction was performed according to the general procedure as described above for Pd_2dba_3 (9.20 mg, 0.01 mmol, 0.5 mol%), tricyclohexylphosphonium tetrafluoroborate (14.8 mg, 0.04 mmol, 2.0 mol%), diisopropylethylamine (10.4 mg, 0.08 mmol, 4.0 mol%) in dichloromethane (10 mL), pent-4-yn-1-ol **15d** (168 mg, 2.00 mmol, 1.0 equiv.), Bu_3SnH (698 mg, 2.40 mmol, 1.2 equiv.) in dry dichloromethane (6 mL) to give stannane **16d** as a colourless oil (675 mg, 1.80 mmol, 90%). R_f = 0.31 (*n*-hexane–ethyl acetate, 8 : 1); ^{1}H NMR (500.130 MHz, $CDCl_3$) δ = 0.88 (m, 15 H), 1.31 (dq, J = 14.8 Hz. J = 7.3 Hz, 6 H), 1.49 (m, 6 H) 1.69 (qiun, J = 7.0 Hz, 2 H), 2.23 (td, J = 7.3 Hz, J = 4.8 Hz, 2 H), 3.67 (m, 2 H), 5.96 (m, 2 H); ^{13}C NMR (125.78 MHz, $CDCl_3$) δ = 9.4, 13.7, 27.3, 29.1, 31.8, 34.1, 62.6, 128.2, 148.6; HR-MS (EI): found m/z = 319.1093 ($[M]^+ - C_4H_9$), calculated m/z = 319.0645.

(*E*)-7-(Tributylstannyl)hept-6-en-1-ol 16e. The reaction was performed according to the general procedure as described above for Pd_2dba_3 (82.0 mg, 89.0 μmol, 0.5 mol%), tricyclohexylphosphonium tetrafluoroborate (131 mg, 365 μmol, 0.02 equiv.), diisopropylethylamine (92.0 mg, 712 μmol, 0.04 equiv.) in dry dichloromethane (100 mL), hept-6-yn-1-ol **15e** (2.00 g, 17.8 mmol, 1.0 equiv.), Bu_3SnH (6.23 g, 21.4 mmol, 1.2 equiv.) in dry dichloromethane (50 mL) to give stannane **16e** as a colourless oil (5.24 g, 13.0 mmol, 73%). R_f = 0.26 (petroleum ether–ethyl acetate, 9 : 1); ^{1}H NMR (500.130 MHz, $CDCl_3$) δ = 0.89 (m, 15 H), 1.46 (m, 18 H), 2.17 (m, 2 H), 3.66 (m, 2 H), 5.94 (m, 2 H); ^{13}C NMR (125.78 MHz, $CDCl_3$) δ = 9.4, 13.7, 25.2, 27.2, 28.7, 29.1, 32.6, 37.8, 63.0, 127.3, 149.4; HR-MS (EI): found m/z = 347.1400 ($C_{15}H_{31}OSn$ $[M - C_4H_9]^+$), calculated m/z = 347.1391.

(*E*)-9-(Tributylstannyl)non-8-en-1-ol 16f. The reaction was performed according to the general procedure as described above for Pd_2dba_3 (82.0 mg, 89.0 μmol, 0.5 mol%), tricyclohexylphosphonium tetrafluoroborate (131 mg, 365 μmol, 0.02 equiv.), diisopropylethylamine (92.0 mg, 712 μmol, 0.04 equiv.) in dry dichloromethane (100 mL), non-8-yn-1-ol **15f** (2.50 g, 17.8 mmol, 1.0 equiv.), Bu_3SnH (6.23 g, 21.4 mmol, 1.2 equiv.) in dry dichloromethane (50 mL) to give stannane **16f** as a light yellow oil (5.81 g, 13.5 mmol, 76%). R_f = 0.28 (petroleum ether–ethyl acetate, 9 : 1); ^{1}H NMR (300.132 MHz, $CDCl_3$) δ = (m, 15 H), 1.43 (m, 22 H), 2.13 (m, 2 H), 3.64 (m, 2 H), 5.91 (m, 2 H); ^{13}C NMR (75.48 MHz, $CDCl_3$) δ = 9.4, 13.7, 25.7, 27.3, 28.8, 29.1, 29.1, 29.3, 32.8, 37.8, 63.1, 127.1, 149.7; HR-MS (EI): found m/z = 375.1713 ($C_{17}H_{35}OSn$ $[M - C_4H_9]^+$), calculated m/z = 375.1704.

(*E*)-3-(Tributylstannyl)acrylaldehyde 12a. Activated MnO_2 (8.52 g, 97.9 mmol, 17 equiv.) was suspended in dichloromethane (55 mL). (*E*)-5-(Tributylstannyl)prop-2-en-1-ol **16a** (2.00 g, 5.76 mmol, 1 equiv.) in dichloromethane (35 mL) was added at room temperature and the mixture was stirred for 2 h. The mixture was filtered through a short pad of celite with dichloromethane (30 mL) and ethyl acetate (50 mL). The solvent was evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (petroleum ether–ethyl acetate, 12 : 1) to afford the corresponding aldehyde **12a** (1.76 g, 5.07 mmol, 88%) as a yellow oil. R_f = 0.75 (*n*-hexane–ethyl acetate, 10 : 1); ^{1}H NMR (300.132 MHz, $CDCl_3$): δ = 0.90 (m, 10 H), 1.02 (m, 5 H), 1.32 (dq, J = 14.8 Hz, J = 7.2 Hz, 6 H), 1.53 (m, 6 H), 6.63 (dd, J = 19.2 Hz, J = 7.5 Hz, 1 H), 7.80 (d, J = 19.2 Hz, 1 H), 9.42 (d, J = 7.5 Hz, 1 H); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 10.2, 14.0, 27.6, 29.4, 148.0, 163.7, 194.1; HR-MS (EI^+): found m/z = 289.0623 ($C_{11}H_{21}OSn$ $[M - C_4H_9]^+$), calculated m/z = 289.0176.

(2*E*,4*E*)-5-(Tributylstannyl)penta-2,4-dienal 12b. Activated MnO_2 (198 mg, 2.28 mmol, 17 equiv.) was suspended in dichloromethane (1.5 mL). (2*E*,4*E*)-5-(Tributylstannyl)penta-2,4-dien-1-ol **16b** (50.0 mg, 134 μmol, 1.0 equiv.) in dichloromethane (0.5 mL) was added at room temperature and the mixture was stirred for 2 h. The mixture was filtered through a short pad of celite with dichloromethane (3 mL) and ethyl acetate (5 mL). The solvent was evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (petroleum ether–ethyl acetate, 12 : 1) to afford aldehyde **12b** (42.7 mg, 115 μmol, 86%) as a yellow oil. R_f = 0.43 (*n*-pentane–diethyl ether, 100 : 5); ^{1}H NMR (300.132 MHz, $CDCl_3$) δ = 0.94 (m, 15 H), 1.33 (dq, J = 14.6 Hz, J = 7.2 Hz, 6 H), 1.54 (m, 6 H), 6.07 (dd, J = 15.1 Hz, J = 8.0 Hz, 1 H), 6.80 (m, 1 H), 7.02 (m, 2 H), 9.58 (d, J = 8.0 Hz, 1 H); ^{13}C NMR (75.48 MHz, $CDCl_3$) δ = 9.7, 13.7, 27.2, 29.0, 130.1, 144.2, 151.4, 153.5, 194.4; HR-MS (EI): found m/z = 315.0773 ($C_{13}H_{23}OSn$ $[M - C_4H_9]^+$), calculated m/z = 317.0765.

(*E*)-5-(Tributylstannyl)pent-4-enal 12d. To a solution of (*E*)-5-(tributylstannyl)pent-4-enal **16d** (50.0 mg, 133 μmol, 1.0

equiv.) in dichloromethane (3 mL) was added a spatula load of dried 4 Å powdered molecular sieves, followed by NMO (40.8 mg, 400 μmol, 3.0 equiv.) and TPAP (4.60 mg, 13.3 μmol, 0.1 equiv.). The reaction mixture was stirred at 0 °C for 30 min then directly purified by flash chromatography (SiO_2, petroleum ether–ethyl acetate, 20 : 1), yielding the desired aldehyde **12d** (39.8 mg, 107 μmol, 80%) as a colourless oil. R_f = 0.73 (petroleum ether–ethyl acetate, 10 : 1); ^{1}H NMR (300.132 MHz, $CDCl_3$) δ = 0.88 (m, 15 H), 1.30 (m, 6 H), 1.49 (m, 6 H), 2.51 (m, 4 H), 5.97 (m, 2 H), 9.78 (t, J = 1.6 Hz, 1 H); ^{13}C NMR (75.48 MHz, $CDCl_3$) δ = 9.4, 13.7, 27.2, 29.1, 29.9, 42.7, 129.2, 146.3, 202.3; HR-MS (EI): found m/z = 317.0947 ($C_{13}H_{25}OSn$ $[M - C_4H_9]^+$), calculated m/z = 317.0489.

(*E*)-7-(Tributylstannyl)hept-6-enal 12e. To a solution of (*E*)-7-(tributylstannyl)hept-6-en-1-ol **16e** (50.0 mg, 124 μmol, 1.0 equiv.) in dichloromethane (3 mL) was added a spatula load of dried 4 Å powdered molecular sieves, followed by NMO (43.6 mg, 371 μmol, 3.0 equiv.) and TPAP (4.40 mg, 12.4 μmol, 0.1 equiv.). The reaction mixture was stirred at 0 °C for 30 min then directly purified by flash chromatography (SiO_2, petroleum ether–ethyl acetate, 20 : 1), yielding the desired aldehyde **12e** (40.3 mg, 100 μmol, 81%) as a colourless liquid; R_f = 0.60 (*n*-hexane–ethyl acetate, 9 : 1). ^{1}H NMR (300.132 MHz, $CDCl_3$) δ = 0.88 (m, 15 H), 1.31 (dq, J = 14.6 Hz, J = 7.2 Hz, 6 H), 1.57 (m, 10 H), 2.17 (td, J = 7.4 Hz, J = 4.4 Hz, 2 H), 2.44 (td, J = 7.3 Hz, J = 1.8 Hz, 2 H), 5.86 (m, 2 H), 9.77 (t, J = 1.9 Hz, 1 H); ^{13}C NMR (75.48 MHz, $CDCl_3$) δ = 9.4, 13.7, 21.6, 27.3, 28.3, 29.1, 37.4, 43.8, 128.0, 148.7, 202.7; HR-MS (ESI): found m/z = 425.1841 ($C_{19}H_{38}OSnNa$), calculated m/z = 425.1840.

(*E*)-9-(Tributylstannyl)non-8-enal 12f. To a solution of (*E*)-7-(tributylstannyl)non-8-en-1-ol **16f** (50.0 mg, 116 μmol, 1.0 equiv.) in dichloromethane (3 mL) was added a spatula load of dried 4 Å powdered molecular sieves, followed by NMO (40.8 mg, 348 μmol, 3.0 equiv.) and TPAP (4.10 mg, 11.6 μmol, 0.1 equiv.). The reaction mixture was stirred at 0 °C for 30 min then directly purified by flash chromatography (SiO_2, petroleum ether–ethyl acetate, 20 : 1), yielding the desired aldehyde **12f** (40.7 mg, 94.8 mmol, 82%) as a colourless liquid. R_f = 0.60 (*n*-hexane–ethyl acetate, 9 : 1). R_f = 0.29 (*n*-hexane–ethyl acetate, 9 : 1). ^{1}H NMR (300.132 MHz, $CDCl_3$) δ = 0.88 (m, 15 H), 1.47 (m, 20 H), 2.13 (m, 2 H), 2.42 (td, J = 7.3 Hz, J = 1.8 Hz, 2 H), 5.89 (m, 2 H), 9.77 (t, J = 1.8 Hz, 1 H); ^{13}C NMR (75.48 MHz, $CDCl_3$) δ = 9.4, 13.7, 22.0, 27.3, 28.6, 28.8, 29.0, 29.1, 37.7, 43.9, 127.3, 149.5, 202.8; HR-MS (ESI): found m/z = 453.2153 ($C_{21}H_{42}OSnNa$), calculated m/z = 453.2153.

General procedure for the boryl-Takai olefination of aldehydes 12. The following process was conducted in the dark. A solution of aldehyde (1.00 mmol, 1.0 equiv.) and dioxaborolane (422 mg, 2.00 mmol, 2.0 equiv.) in THF (8.5 mL) was added *via* a syringe to a mixture of anhydrous chromium(II) chloride (983 mg, 8.00 mmol, 8 equiv.) in THF (8.5 mL). A solution of lithium iodide (535 mg, 4.00 mmol, 4.0 equiv.) in THF (8.5 mL) was added *via* a syringe and the reaction mixture was stirred at 25 °C for 12 h. The reaction was quenched by the addition of water. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (2 × 20 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was passed through a pad of celite and the filter cake was washed thoroughly with Et_2O. After concentration of the residue the crude product was purified by chromatography (SiO_2, petroleum ether–diethyl ether, 100 : 1) to afford the corresponding pinacolborane.

Triene 5. The reaction was performed according to the general procedure as described above for (2*E*,4*E*)-5-(tributylstannyl)penta-2,4-dienal **12b** (531 mg, 1.43 mmol, 1.0 equiv.) and 2-(dichloromethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (603 mg, 2.86 mmol, 2.0 equiv.) in THF (11 mL), anhydrous chromium chloride (1.41 g, 11.4 mmol, 8.0 equiv.) in THF (11 mL), lithium iodide (766 mg, 5.72 mmol, 4.0 equiv.) in THF (11 mL) to afford triene **5** (526 mg, 1.06 mmol, 74%) as an orange oil. R_f = 0.57 (*n*-hexane–diethyl ether, 100 : 1); ^{1}H NMR (300.132 MHz, $CDCl_3$): δ = 0.92 (m, 15 H), 1.43 (m, 24 H), 5.58 (d, J = 17.6 Hz, 1 H), 6.31 (m, 3 H), 6.60 (m, 1 H), 7.04 (dd, J = 17.6 Hz, J = 9.9 Hz, 1 H); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 9.6, 13.7, 24.8, 26.6, 27.3, 29.1, 83.2, 133.1, 138.6, 138.9, 146.5, 149.8; HR-MS (EI): found m/z = 439.1838 $C_{20}H_{46}BO_2Sn$ ($[M - C_4H_9]^+$), calculated m/z = 439.1825.

Tributyl((1*E*,3*E*)-4-(4,4,5,5-tetramethyl-1,3,2 dioxaborolan-2-yl)-buta-1,3-dienyl)-stannane 6a. The reaction was performed according to the general procedure as described above for (*E*)-3-(tributylstannyl)acrylaldehyde **12a** (200 mg, 0.58 mmol, 1.0 equiv.) and 2-(dichloromethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (244 mg, 1.16 mmol, 2.0 equiv.) in THF (5 mL), anhydrous chromium(II) chloride (548 mg, 4.46 mmol, 8 equiv.) in THF (5 mL), lithium iodide (298 mg, 2.23 mmol, 4.0 equiv.) in THF (5 mL) to afford the conjugated diene **6a** (260 mg, 550 mmol, 75%) as a green-clear liquid. R_f = 0.48 (*n*-hexane–ethyl acetate, 100 : 5); ^{1}H NMR (300.132 MHz, $CDCl_3$): δ = 0.91 (m, 15 H), 1.30 (m, 18 H), 1.50 (m, 6 H), 5.48 (d, J = 17.5 Hz, 1 H), 6.52 (m, 2 H), 6.97 (dd, J = 17.6 Hz, J = 9.0 Hz, 1 H); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 9.1, 13.3, 24.3, 24.5, 26.8, 28.6, 82.7, 140.0, 148.1, 151.8; HR-MS (EI): found m/z = 413.1687 $C_{18}H_{44}BO_2Sn$ ($[M - C_4H_9]^+$), calculated m/z = 413.1235.

Tributyl((1*E*,5*E*)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-hexa-1,5-dienyl)stannane 6b. The reaction was performed according to the general procedure as described above for (*E*)-5-(tributylstannyl)pent-4-enal **12d** (715 mg, 1.92 mmol, 1.0 equiv.) and 2-(dichloromethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (810 mg, 3.84 mmol, 2.0 equiv.) in THF (12 mL), anhydrous chromium(II) chloride (1.89 g, 15.4 mmol, 8.0 equiv.) in THF (12 mL), lithium iodide (1.03 g, 7.68 mmol, 4.0 equiv.) in THF (12 mL) to afford diene **6b** (740 mg, 1.49 μmol, 76%) as a colourless oil. R_f = 0.38 (*n*-hexane–diethyl ether, 100 : 5); ^{1}H NMR (300.132 MHz, $CDCl_3$): δ = 0.87 (m, 15 H), 1.30 (m, 18 H), 1.50 (m, 6 H), 2.26 (m, 4 H), 5.45 (d, J = 17.9 Hz, 1 H), 5.94 (m, J = 5.5 Hz, J = 18.8 Hz, 2 H), 6.65 (d, J = 17.9 Hz, 1 H); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 9.0, 13.3, 24.3, 26.8, 28.7, 34.8, 35.8, 82.6, 127.3, 148.0, 153.5. HR-MS (ESI): found m/z = 521.2578 ($C_{24}H_{47}BO_2SnNa$), calculated m/z = 521.2589.

Tributyl((1*E*,7*E*)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-octa-1,7-dien-1-yl)stannane 6c. The reaction was performed

according to the general procedure as described above for (*E*)-7-(tributylstannyl)hept-6-enal **12e** (317 mg, 790 μmol, 1.0 equiv.) and 2-(dichloromethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (333 mg, 1.58 mmol, 2.0 equiv.) in THF (6 mL), anhydrous chromium chloride (777 mg, 6.43 mmol, 8.0 equiv.) in THF (6 mL), lithium iodide (432 mg, 3.16 mmol, 4.0 equiv.) in THF (6 mL) to afford diene **6c** (404 mg, 769 μmol, 97%) as a colourless liquid. R_f = 0.66 (petroleum ether–ethyl acetate, 100 : 5); ^{1}H NMR (300.132 MHz, $CDCl_3$): δ = 0.86 (m, 15 H), 1.43 (m, 28 H), 2.13 (m, 4 H), 4.96 (m, 1 H), 5.43 (dt, J = 17.8 Hz, J = 1.5 Hz, 1 H), 5.83 (m, 1 H), 6.63 (dt, J = 18.0 Hz, J = 6.5 Hz, 1 H); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 9.4, 13.7, 24.8, 27.2, 28.4, 29.0, 29.1, 33.6, 35.6, 37.7, 83.0, 114.3, 127.3, 138.9, 149.4, 154.5; HR-MS (ESI): found m/z = 565.2641 ($C_{26}H_{51}BO_2SnK$), calculated m/z = 565.2643.

Tributyl((1*E*,9*E*)-10-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-deca-1,9-dien-1-yl)stannane 6d. The reaction was performed according to the general procedure as described above for (*E*)-9-(tributylstannyl)non-8-enal **12f** (35.0 mg, 81.5 μmol, 1.0 equiv.) and 2-(dichloromethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (34.4 mg, 163 mmol, 2.0 equiv.) in THF (1 mL), anhydrous chromium(II) chloride (80.1 mg, 652 μmol, 8.0 equiv.) in THF (1 mL), lithium iodide (43.6 mg, 326 μmol, 4.0 equiv.) in THF (1 mL) to afford diene **6d** as a colourless oil (40.1 mg, 72.5 μmol, 89%). R_f = 0.64 (petroleum ether–ethyl acetate, 10 : 1); ^{1}H NMR (300.132 MHz, $CDCl_3$ δ = 0.85 (m, 15 H), 1.38 (m, 32 H), 2.14 (m, 4 H), 5.43 (d, J = 17.9 Hz, 1 H), 5.90 (m, 2 H), 6.64 (dt, J = 17.9, 6.4 Hz, 1 H); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 9.4, 13.7, 24.8, 27.3, 27.5, 28.2, 28.8, 28.9, 29.1, 29.1, 35.8, 37.9, 83.0, 114.1, 127.0, 149.8, 154.8; HR-MS (ESI): found m/z = 425.1841 ($C_{28}H_{55}BO_2SnK$), calculated m/z = 425.1840.

(*S*)-Methyl 3-(*tert*-butyldimethylsilyloxy)-2-methylpropanoate 43. A mixture of imidazole (5.75 g, 84.5 mmol, 5.0 equiv.), 4-(dimethylamino)-pyridine (206 mg, 1.69 mmol, 0.1 equiv.) and *tert*-butyldimethylsilyl chloride (6.38 g, 42.3 mmol, 2.5 equiv.) was dissolved in acetonitrile (40 mL). The (*S*)-(+)Roche ester (2.00 g, 16.9 mmol, 1.0 equiv.) dissolved in acetonitrile (2 mL). After stirring for 2 h at room temperature the reaction was quenched by addition of saturated aqueous sodium hydrogen carbonate (200 mL). The phases were separated and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried over magnesium sulfate, filtrated and concentrated under reduced pressure. Purification of the residue by chromatography (SiO_2, *n*-hexane–ethyl acetate 20 : 1) afforded TBS ether **43** as a colourless, oily liquid (3.89 g, 16.7 mmol, 99%). R_f = 0.63 (*n*-hexane–ethyl acetate, 10 : 1); $[\alpha]_D^{22}$ = +15.4 (c = 1.12, $CHCl_3$); ^{1}H NMR (300.132 MHz, $CDCl_3$): δ = 0.04 (s, 6 H), 0.87 (s, 9 H), 1.14 (d, J = 7.3 Hz, 3 H), 2.65 (sxt, J = 6.8 Hz, 1 H), 3.65 (m, 4 H), 3.78 (dd, J = 9.9 Hz, J = 7.0 Hz, 1 H); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = −5.3, 13.4, 18.2, 25.8, 42.5, 51.5, 65.2, 175.5; HR-MS (ESI): found m/z = 271.1123 ($C_{11}H_{24}O_3SiK$), calculated m/z = 271.1126.

(*R*)-3-(*tert*-Butyldimethylsilyloxy)-2-methylpropan-1-ol 44. A solution of ester **43** (5.84 g, 25.1 mmol, 1.0 equiv.) in dichloromethane (90 mL) under an argon atmosphere was cooled down to −78 °C and treated with DIBAL-H (75.3 mL, 1 M in dichloromethane, 75.3 mmol, 3.0 equiv.) over a period of 45 min. After stirring for 2 h at −78 °C, the reaction mixture was diluted by adding Et_2O (90 mL), warmed to room temperature and treated with H_2O (26 mL) carefully. The resulting mixture was stirred until a gel was formed. Then NaOH (3 N, 30 mL) was added and stirred until the gel dissolved. The organic layer was separated, the aqueous phase was extracted with Et_2O (3 × 100 mL) and the combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. After purification by chromatography (SiO_2, *n*-hexane–ethyl acetate 10 : 1), the desired, pure alcohol **44** was obtained as a colourless liquid (4.32 g, 21.1 mmol, 84%). R_f = 0.21 (*n*-hexane–ethyl acetate, 10 : 1); $[\alpha]_D^{22}$ = +2.14 (c = 1.06, $CHCl_3$); ^{1}H NMR (300.132 MHz, $CDCl_3$): δ = 0.08 (s, 6 H), 0.84 (d, J = 7.0 Hz, 3 H), 0.90 (s, 9 H), 1.86–2.03 (m, 1 H), 2.85 (t, J = 5.3 Hz, 1 H), 3.55 (dd, J = 9.9 Hz, J = 7.7 Hz, 1 H), 3.59–3.66 (m, 2 H), 3.74 (dd, J = 9.9 Hz, J = 4.4 Hz, 1 H); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = −5.8, 13.1, 18.2, 25.8, 37.0, 68.3, 68.7; HR-MS (ESI): found m/z = 227.1437 ($C_{10}H_{24}O_2SiNa$), calculated m/z = 227.1438.

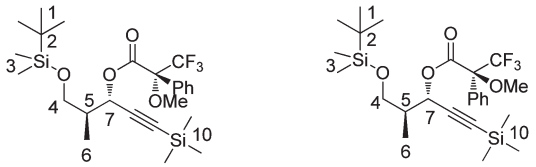
(*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-methylpropanal 19a. At 0 °C Dess-Martin periodinane (291 mg, 685 μmol, 1.4 equiv.) was added to a solution of alcohol **44** (100 mg, 489 μmol, 1.0 equiv.) in dichloromethane (5 mL). The solution was allowed to warm to room temperature within 2.5 h. After evaporation of the solvent under vacuum, purification by flash chromatography (SiO_2, *n*-hexane–ethyl acetate 12 : 1) provided the desired aldehyde **19a** as a colourless liquid (78.8 mg, 389 μmol, 80%). R_f = 0.53 (*n*-hexane–ethyl acetate, 10 : 1); $[\alpha]_D^{22}$ = +19.5 (c = 1.00, $CHCl_3$); ^{1}H NMR (300.132 MHz, $CDCl_3$): δ = 0.06 (s, 6 H), 0.88 (s, 9 H), 1.10 (d, J = 7.0 Hz, 3 H), 2.54 (m, 1 H), 3.84 (dd, J = 7.2 Hz, J = 5.8 Hz, 2 H), 9.74 (d, J = 1.6 Hz, 1 H); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = −5.6, 10.3, 25.8, 48.8, 63.4, 204.7; HR-MS (EI): found m/z = 202.1349 ($C_{10}H_{22}0_2Si$), calculated m/z = 202.1389.

Propargylic alcohol 21a. TMS-acetylene **20a** (4.33 mL, 30.6 mmol, 4.0 equiv.) was added to Et_2Zn (27.8 mL, 1.1 M in toluene, 30.6 mmol, 4.0 equiv.) carefully. The mixture was heated to reflux for 1 h, during which time a large amount of grey precipitate formed in the reaction flask. The mixture was cooled to room temperature, and (*R*)-BINOL (876 mg, 3.06 mmol, 0.4 equiv.), Et_2O (140 mL) and $Ti(OiPr)_4$ (2.18 g, 7.66 mmol, 1.0 equiv.) were added. After 1 h, aldehyde **19a** (1.55 g, 7.66 mmol, 1.0 equiv.) was added, and the mixture was stirred overnight. The reaction was quenched with 1 M tartaric acid (50 mL) and the mixture was stirred for 30 min. The mixture was partitioned in a separatory funnel, and the aqueous portion was extracted with Et_2O (3 × 60 mL). The combined organic extracts were washed with brine and dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, petroleum ether–ethyl acetate, 100 : 2.5 to 100 : 5) to afford **21a** as a light yellow, oily liquid (1.93 g, 6.42 mmol, 84%). R_f = 0.49 (petroleum ether–ethyl acetate, 100 : 5); $[\alpha]_D^{22}$ = +5.54 (c = 1.42, $CHCl_3$); ^{1}H NMR (300.132 MHz, $CDCl_3$): δ = 0.08 (s, 3 H), 0.08

(s, 3 H), 0.17 (s, 9 H), 0.90 (s, 9 H), 1.02 (d, J = 7.0 Hz, 3 H), 1.93 (dqd, J = 13.3 Hz, J = 6.8 Hz, J = 6.8 Hz, J = 6.8 Hz, J = 4.0 Hz, 1 H), 3.57 (dd, J = 9.9 Hz, J = 6.6 Hz, 1 H), 3.93 (dd, J = 9.9 Hz, J = 4.0 Hz, 1 H), 4.39 (d, J = 6.2 Hz, 1 H); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = −5.7, −0.1, 12.9, 18.2, 25.8, 40.4, 66.8, 67.21, 89.8, 105.7; HR-MS (ESI): found m/z = 323.1836 ($C_{15}H_{32}0_2Si_2Na$), calculated m/z = 323.1833.

Mosher's esters of 21a

*(R)-Mosher's ester **45** and (S)-Mosher's ester **46**.*



45 **46**

(*R*)-Mosher's acid (11.7 mg, 49.9 μmol, 3.0 equiv.) was diluted in toluene (200 μL) at 0 °C. To the reaction mixture DMAP (13.7 mg, 54.9 μmol, 3.3 equiv.), NEt_3 (11.4 mg, 54.9 μmol, 3.3 equiv.), Yamaguchi reagent (7.21 mg, 49.9 μmol, 3.0 equiv.) and a solution of propargylic alcohol **21a** (5.00 mg, 16.6 μmol, 1.0 equiv.) in toluene (200 μL) were added and stirred at room temperature. After 3 h the mixture was treated with pH 7 buffer (500 μL) and quenched with water (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 3 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, petroleum ether–ethyl acetate, 30 : 1) to afford the desired ester **45** for ^{1}H NMR analysis. R_f = 0.61 (petroleum ether–ethyl acetate, 20 : 1); ^{1}H NMR (300.132 MHz, $CDCl_3$): δ = 0.05 (s, 3 H), 0.07 (s, 3 H), 0.16 (s, 9 H), 0.91 (s, 9 H), 1.00 (d, J = 6.6 Hz, 3 H), 2.14 (m, 1 H), 3.56 (s, 3 H), 3.59 (m, 2 H), 5.68 (d, J = 6.2 Hz, 1 H), 7.41 (m, 3 H), 7.54 (m, 2 H). The same procedure and proportions have been performed using (*S*)-Mosher's acid to get diastereomer **46**. R_f = 0.65 (petroleum ether–ethyl acetate, 20 : 1); ^{1}H NMR (300.132 MHz, $CDCl_3$): δ = 0.04 (s, 3 H), 0.05 (s, 3 H), 0.19 (s, 9 H), 0.90 (s, 9 H), 0.96 (d, J = 6.6 Hz, 3 H), 2.09 (m, 1 H), 3.50 (m, 2 H), 3.60 (s, 3 H), 5.72 (d, J = 6.2 Hz, 1 H), 7.40 (m, 3 H), 7.58 (m, 2 H) (Table 8).

Bis-TBS ether 47. 2,6-Lutidine (649 mg, 5.59 mmol, 4.2 equiv.) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.13 g, 4.26 mmol, 3.2 equiv.) were added slowly to a solution of alcohol **21a** (400 mg, 1.33 mmol, 1.0 equiv.) in dichloromethane (5 mL) at −78 °C. After stirring for 1 h, the reaction was quenched by addition of aqueous saturated $NaHCO_3$ (10 mL) and extracted with dichloromethane (3 × 7 mL). The combined organic phases were dried with $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (SiO_2, *n*-hexane–ethyl acetate, 30 : 1) to afford the protected alcohol **47** as a colourless liquid (548 mg, 1.32 mmol, 99%). R_f = 0.22 (petroleum ether–ethyl acetate, 50 : 1); $[\alpha]_D^{22}$ = −17.1 (c = 1.00, $CHCl_3$); ^{1}H NMR (300.132 MHz, $CDCl_3$): δ = 0.05 (s, 3 H), 0.05 (s, 3 H), 0.11 (s, 3 H), 0.14 (s, 3 H), 0.16 (s, 9 H), 0.90 (s, 9 H), 0.91 (s, 9 H), 0.96 (d, J = 7.0 Hz, 3 H), 1.87 (m, 1 H), 3.58 (dd, J = 6.0 Hz, J = 3.5 Hz, 2 H), 4.45 (d, J = 6.2 Hz, 1 H); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = −5.5, −5.3, −5.1, −4.5, −0.1, 12.1, 12.3, 25.7, 25.9, 42.7, 64.5, 64.9, 89.6, 106.2; HR-MS (ESI): found m/z = 437.2701 ($C_{21}H_{46}O_2Si_3Na$), calculated m/z = 437.2698.

Terminal alkyne 48. Potassium carbonate (198 mg, 1.43 mmol, 1.1 equiv.) was added to a solution of the TMS-protected alkyne **47** (540 mg, 1.30 mmol, 1.0 equiv.) in MeOH (5 mL). The reaction mixture was stirred vigorously at room temperature for 1 h. The reaction was quenched by addition of saturated aqueous NH_4Cl and the volatiles were removed *in vacuo*. The residue was extracted with diethyl ether (3 × 2.5 mL), the combined organic phases were washed with water (2.5 mL), brine (2.5 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, petroleum ether–ethyl acetate 50 : 1) provided the desired terminal alkyne **48** as a colourless liquid (401 mg, 1.17 mmol, 90%). R_f = 0.41 (petroleum ether–ethyl acetate, 50 : 1); $[\alpha]_D^{22}$ = −12.6 (c = 1.00, $CHCl_3$); ^{1}H NMR (300.132 MHz, $CDCl_3$): δ = 0.05 (s, 3 H), 0.05 (s, 3 H), 0.11 (s, 3 H), 0.14 (s, 3 H), 0.90 (s, 9 H), 0.91 (s, 9 H), 0.97 (d, J = 6.6 Hz, 4 H), 1.91 (spt, J = 6.5 Hz, 1 H), 2.37 (d, J = 2.2 Hz, 1 H), 3.57 (d, J = 6.2 Hz, 3 H), 4.50 (dd, J = 5.9 Hz, J = 1.8 Hz, 1 H); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = −5.5, −5.4, −5.2, −4.6, 11.8, 18.2, 18.3, 25.8, 25.9, 42.8, 64.2, 64.4, 73.0, 83.9; HR-MS (ESI): found m/z = 365.2312 ($C_{18}H_{38}O_2Si_2Na$), calculated m/z = 365.2303.

Vinyl iodode 8a. To $ZrCp_2Cl_2$ (188 mg, 642 μmmol, 1.1 equiv.) in THF (1.5 mL) cooled to 0 °C was added slowly a solution of DIBAL-H (642 μL, 1 M in THF, 642 μmol, 1.1 equiv.) under argon. The resultant suspension was stirred for 30 min at 0 °C, followed by addition of alkyne **48** (200 mg, 584 μmol, 1.0 equiv.) in THF (500 μL). The mixture was warmed to room temperature and stirred until a homogeneous solution resulted and then cooled to −78 °C, followed by addition of I_2 (188 mg, 759 μmol, 1.3 equiv.) in THF (1 mL). After 30 min at −78 °C the reaction mixture was quenched with 1 N HCl, extracted with diethyl ether, washed successively with saturated aqueous $Na_2S_2O_3$, $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography (SiO_2, petroleum ether) afforded vinyl iodide **8a** as a colourless liquid (203 mg, 426 μmol, 73%). R_f = 0.57 (petroleum ether–ethyl acetate, 50 : 1); $[\alpha]_D^{22}$ = +4.76 (c = 1.00, $CHCl_3$); ^{1}H NMR (300.132 MHz, $CDCl_3$): δ = 0.03 (s, 3 H), 0.05 (s, 9 H), 0.82 (d, J = 6.9 Hz, 3 H), 0.90 (s, 9 H), 0.90 (s, 9 H), 1.78 (dquin, J = 12.8 Hz, J = 6.5 Hz, J = 6.5 Hz, J = 6.5 Hz, J = 6.5 Hz, 1 H), 3.51 (dd, J = 6.1 Hz, J = 2.5 Hz, 2 H), 4.18 (m, 1 H), 6.18 (dd, J = 14.3 Hz,

Table 8 Determination of the absolute configuration[35]

Proton's positions	(*S*)-Mosher's ester **46** [ppm]	(*R*)-Mosher's ester **45** [ppm]	$\Delta\delta = \delta_S - \delta_R$
1	0.90	0.91	−0.01
3a	0.04	0.05	−0.01
3b	0.05	0.07	−0.02
4	3.50	3.59	−0.09
5	2.09	2.14	−0.05
6	0.96	1.00	−0.04

J = 1.1 Hz, 1 H), 6.53 (dd, J = 14.4 Hz, J = 6.7 Hz, 1 H); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = −5.5, −5.4, −5.0, −4.5, 11.9, 18.2, 18.2, 25.8, 25.9, 42.2, 64.5, 76.1, 76.3, 147.2; HR-MS (ESI): found m/z = 493.1434 ($C_{18}H_{39}IO_2Si_2Na$), calculated m/z = 493.1426.

(*S*)-Methyl 3-(4-methoxybenzyloxy)-2-methylpropanoate 49. To the solution of (*S*)-(+)Roche ester (526 mg, 4.45 mmol, 1.0 equiv.) in dichloromethane (6 mL) PMB(HNC)CCl_3 (1.20 g, 4.45 mmol, 1.0 equiv.) and CSA (62.0 mg, 267 μmol, 0.06 equiv.) were added and the solution was stirred for 16 h. Then saturated $NaHCO_3$ solution (6 mL) was added and the aqueous layer extracted three times with dichloromethane (5 mL). The combined organic phases were washed with saturated $NaHCO_3$ solution (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and the organic solvent was removed under reduced pressure. After purification by chromatography (SiO_2, petroleum ether–ethyl acetate, 4 : 1) ester **49** was obtained as a colourless, oily liquid (1.05 g, 4.41 mmol, 99%). R_f = 0.78 (petroleum ether–ethyl acetate, 3 : 1); $[\alpha]_D^{22}$ = +9.26 (c = 1.00, $CHCl_3$); ^{1}H NMR (500.130 MHz, $CDCl_3$): δ = 1.18 (d, J = 7.1 Hz, 3 H), 2.78 (sxt, J = 6.9 Hz, 1 H), 3.47 (dd, J = 9.2 Hz, J = 5.9 Hz, 1 H), 3.64 (dd, J = 9.2 Hz, J = 7.3 Hz, 1 H), 3.70 (s, 3 H), 3.81 (s, 3 H), 4.46 (m, 2 H), 6.88 (d, J = 8.5 Hz, 2 H), 7.25 (d, J = 8.5 Hz, 2 H); ^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 13.7, 39.9, 51.4, 55.0, 71.4, 72.5, 113.4, 128.9, 129.9, 158.9, 175.1; HR-MS (ESI): found m/z = 261.1097 ($C_{13}H_{18}0_4Na$), calculated m/z = 261.1103.

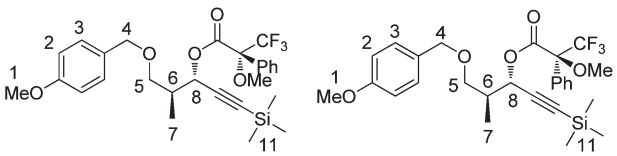
(*R*)-3-(4-Methoxybenzyloxy)-2-methylpropan-1-ol 50. A solution of ester **49** (1.00 g, 4.20 mmol, 1.0 equiv.) in dichloromethane (14 mL) under an argon atmosphere was cooled down to −78 °C and treated with DIBAL-H (12.6 mL, 1 M in hexane, 12.6 mmol, 3.0 equiv.) over a period of 45 min. After stirring for 2 h at −78 °C, the reaction mixture was diluted by adding Et_2O (15 mL), warmed to room temperature and treated with H_2O (6 mL) carefully. The resulting mixture was stirred until a gel was formed. Then NaOH (2 N, 8 mL) was added and stirred until the gel dissolved. The organic layer was separated, the aqueous phase was extracted with Et_2O (3 × 10 mL) and the combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. After purification by chromatography (SiO_2, *n*-hexane–ethyl acetate 3 : 1), the desired alcohol **50** was obtained as a colourless liquid (799 mg, 3.80 mmol, 90%). R_f = 0.22 (*n*-hexane–ethyl acetate, 3 : 1); $[\alpha]_D^{22}$ = +15.9 (c = 1.00, $CHCl_3$); ^{1}H NMR (300.130 MHz, $CDCl_3$): δ = 0.92 (d, J = 7.0 Hz, 3 H), 2.10 (m, 1 H), 2.46 (br. s, 1 H), 3.44 (m, 1 H), 3.57 (dd, J = 9.1 Hz, J = 4.6 Hz, 1 H), 3.65 (m, 2 H), 3.85 (s, 3 H), 4.49 (s, 2 H), 6.93 (d, J = 8.6 Hz, 2 H), 7.29 (d, J = 8.6 Hz, 2 H); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 13.0, 35.1, 54.8, 67.5, 72.6, 74.7, 113.4, 128.8, 129.7, 158.8; HR-MS (ESI): found m/z = 233.1147 ($C_{12}H_{18}0_3Na$), calculated m/z = 233.1148.

(*S*)-3-(4-Methoxybenzyloxy)-2-methylpropanal 19b. At 0 °C Dess-Martin periodinane (565 mg, 1.33 mmol, 1.4 equiv.) was added to a solution of alcohol **50** (200 mg, 951 μmol, 1.0 equiv.) in dichloromethane (10 mL). The solution was allowed to warm to room temperature within 3 h. After evaporation of the solvent *in vacuo* purification by flash chromatography (SiO_2, petroleum ether–ethyl acetate 10 : 1) provided the desired aldehyde **19b** as a colourless liquid (190 mg, 904 μmol, 95%). R_f = 0.23 (petroleum ether–ethyl acetate, 10 : 1); $[\alpha]_D^{22}$ = +30.5 (c = 1.00, $CHCl_3$); ^{1}H NMR (300.132 MHz, $CDCl_3$): δ = 1.17 (d, J = 7.3 Hz, 3 H), 2.70 (sxt, J = 7.0 Hz, 1 H), 3.67 (m, 2 H), 3.86 (s, 3 H), 4.51 (s, 2H), 6.93 (d, J = 8.8 Hz, 2 H), 7.29, (d, J = 8.4 Hz, 2 H), 9.76 (d, J = 1.5 Hz, 1 H); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 10.7, 46.8, 55.2, 69.8, 72.9, 113.8, 129.2, 129.9, 159.2, 204.0; HR-MS (EI^+): found m/z = 208.1091 ($C_{12}H_{16}O_3$), calculated m/z = 208.1099.

Propargylic alcohol 21b. TMS acetylene **20a** (421 μL, 3.04 mmol, 4.0 equiv.) was added to Et_2Zn (2.76 mL, 1.1 M in toluene, 2.76 mmol, 4.0 equiv.) carefully. The mixture was heated to reflux for 1 h, during which time a large amount of grey precipitate formed in the reaction flask. The mixture was cooled to room temperature, and (*R*)-BINOL (87.0 mg, 304 μmol, 0.4 equiv.), Et_2O (14 mL) and $Ti(OiPr)_4$ (226 μL, 759 μmol, 1.0 equiv.) were added. After 1 h, aldehyde **19b** (158 mg, 759 μmol, 1.0 equiv.) was added, and the mixture was stirred overnight. The reaction was quenched with 1 M tartaric acid (6 mL) and the mixture was stirred for 30 min. The mixture was partitioned in a separatory funnel, and the aqueous phase was extracted with Et_2O (3 × 7 mL). The combined organic extracts were washed with brine and dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, petroleum ether–ethyl acetate, 100 : 2.5 to 100 : 5) to afford **21b** as a light yellow oil (185 mg, 604 μmol, 80%). R_f = 0.47 (petroleum ether–ethyl acetate, 5 : 1); $[\alpha]_D^{22}$ = +7.13 (c = 1.00, $CHCl_3$); ^{1}H NMR (300.132 MHz, $CDCl_3$): δ = 0.17 (s, 9 H), 1.05 (d, J = 7.0 Hz, 3 H), 2.06 (sxtd, J = 6.8 Hz, J = 6.8 Hz, J = 6.8 Hz, J = 6.8 Hz, J = 6.8 Hz, J = 4.4 Hz, 1 H), 3.44 (dd, J = 9.3 Hz, J = 6.8 Hz, 1 H), 3.68 (dd, J = 9.3 Hz, J = 4.2 Hz, 1 H), 3.81 (s, 3 H), 4.40 (d, J = 6.2 Hz, 1 H), 4.46 (d, J = 2.9 Hz, 2 H), 6.88 (d, J = 8.8 Hz, 2 H), 7.26 (d, J = 8.8 Hz, 2 H); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = −0.1, 13.2, 39.2, 55.2, 66.8, 73.1, 73.3, 89.9, 105.5, 113.8, 129.2, 129.9, 159.2; HR-MS (ESI): found m/z = 329.1547 ($C_{17}H_{26}0_3SiNa$), calculated m/z = 329.1543.

Mosher's esters of 21b

*(R)-Mosher's ester **51** and (S)-Mosher's ester **52**.*



51 **52**

(*R*)-Mosher's acid (41.2 mg, 176 μmol, 3.0 equiv.) was diluted in toluene (800 μL) at 0 °C. To the reaction mixture DMAP (23.7 mg, 194 μmol, 3.3 equiv.), NEt_3 (19.6 mg, 194 μmol, 3.3 equiv.), Yamaguchi reagent (42.9 mg, 176 μmol, 3.0 equiv.) and a solution of propargylic alcohol **21b** (18.0 mg, 58.7 μmol, 1.0 equiv.) in toluene (800 μL) were added and stirred at room temperature. After 3 h the mixture was treated with pH 7 buffer (2 mL) and quenched with water (4 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were

Table 9 Determination of the absolute configuration[35]

Proton's positions	(*S*)-Mosher's ester **52** [ppm]	(*R*)-Mosher's ester **51** [ppm]	$\Delta\delta = \delta_S - \delta_R$
4	4.39	4.41	−0.02
6	2.21	2.26	−0.05
7	1.00	1.03	−0.03
11	0.17	0.16	+0.01

dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, petroleum ether–ethyl acetate, 30 : 1) to afford the desired ester **51** for ^{1}H NMR analysis. R_f = 0.43 (petroleum ether–ethyl acetate, 10 : 1); ^{1}H NMR (300.132 MHz, $CDCl_3$): δ = 0.16 (s, 9 H), 1.03 (d, J = 6.7 Hz, 3 H), 2.26 (m, 1 H), 3.40 (m, 2 H), 3.52 (s, 3 H), 3.81 (s, 3 H), 4.41 (m, 2 H), 5.70 (d, J = 5.8 Hz, 1 H), 6.89 (d, J = 8.6 Hz, 2 H), 7.26 (m, 2 H), 7.39 (m, 3 H), 7.52 (m, 2 H). The same procedure and proportions have been performed using (*S*)-Mosher's acid to get diastereomer **52**. R_f = 0.38 (petroleum ether–ethyl acetate, 10 : 1); ^{1}H NMR (300.132 MHz, $CDCl_3$): δ = 0.17 (s, 9 H), 1.00 (d, J = 6.9 Hz, 3 H), 2.21 (m, 1 H), 3.30 (m, 1 H), 3.40 (m, 1 H), 3.59 (s, 3 H), 3.81 (s, 3 H), 4.39 (d, J = 3.4 Hz, 2 H), 5.74 (d, J = 6.1 Hz, 1 H), 6.89 (d, J = 8.7 Hz, 2 H), 7.25 (d, J = 8.7 Hz, 3 H), 7.38 (m, 3 H), 7.56 (m, 2 H) (Table 9).

TBS ether 53. 2,6-Lutidine (587 mg, 5.48 mmol, 4.2 equiv.) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.10 g, 4.18 mmol, 3.2 equiv.) were added slowly to a solution of alcohol **21b** (400 mg, 1.31 mmol, 1.0 equiv.) in dichloromethane (5 mL) at −78 °C. After stirring for 1 h, the reaction was quenched by addition of aqueous saturated $NaHCO_3$ (10 mL) and extracted with dichloromethane (3 × 7 mL). The combined organic phases were dried with $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (SiO_2, *n*-hexane–ethyl acetate, 50 : 1) to afford the protected alcohol **53** as a colourless liquid (528 mg, 1.25 mmol, 96%). R_f = 0.33 (petroleum ether–ethyl acetate, 50 : 1); $[\alpha]_D^{22}$ = −13.3 (c = 1.00, $CHCl_3$); ^{1}H NMR (300.132 MHz, $CDCl_3$): δ = 0.10 (s, 3 H) 0.14 (s, 3 H) 0.16 (m, 9 H) 0.90 (s, 9 H) 1.01 (d, J = 7.0 Hz, 3 H) 2.02 (spt, J = 6.5 Hz, 1 H) 3.39 (dd, J = 9.3 Hz, J = 6.0 Hz, 1 H) 3.50 (dd, J = 9.3 Hz, J = 6.0 Hz, 1 H) 3.81 (s, 3 H) 4.44 (m, 3 H) 6.88 (d, J = 8.6 Hz, 2 H) 7.26 (d, J = 8.6 Hz, 2 H); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = −5.1, −4.5, −0.2, 12.7, 18.2, 25.8, 40.5, 55.2, 65.2, 71.1, 72.7, 89.7, 106.1, 113.7, 129.1, 130.8, 159.0; HR-MS (ESI): found m/z = 443.2410 ($C_{23}H_{40}O_3Si_2Na$), calculated m/z = 443.2408.

Terminal alkyne 54. Potassium carbonate (63.3 mg, 458 μmol, 1.1 equiv.) was added to a solution of the TMS protected alkyne **53** (175 mg, 416 μmol, 1.0 equiv.) in MeOH (1.5 mL). The reaction mixture was stirred vigorously at room temperature for 1 h. The reaction was quenched by addition of saturated aqueous NH_4Cl and the volatiles were removed *in vacuo*. The residue was extracted with diethyl ether (3 × 1 mL), the combined organic phases were washed with water (1 mL), brine (1 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, petroleum ether–ethyl acetate 50 : 1) provided the desired terminal alkyne **54** (141 mg, 404 μmol, 97%). R_f = 0.17 (petroleum ether–ethyl acetate, 50 : 1); $[\alpha]_D^{22}$ = −10.7 (c = 1.00, $CHCl_3$); ^{1}H NMR (300.132 MHz, $CDCl_3$): δ = 0.11 (s, 3 H), 0.15 (s, 3 H), 0.91 (s, 9 H), 1.03 (d, J = 7.0 Hz, 3 H), 2.06 (spt, J = 6.4 Hz, 1 H), 2.37 (d, J = 2.0 Hz, 1 H), 3.40 (dd, J = 9.3 Hz, J = 5.8 Hz, 1 H), 3.49 (dd, J = 9.3 Hz, J = 7.0 Hz, 1 H), 3.82 (s, 3 H), 4.44 (s, 2 H), 6.89 (d, J = 8.6 Hz, 2 H), 7.26 (d, J = 8.6 Hz, 2 H); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = −5.2, −4.6, 12.3, 18.2, 25.8, 40.5, 55.3, 64.5, 71.6, 72.7, 73.1, 83.8, 113.7, 129.1, 130.7, 159.1; HR-MS (ESI): found m/z = 371.2022 ($C_{20}H_{32}O_3SNa$), calculated m/z = 371.2013.

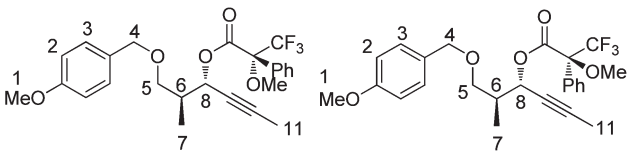
Vinyl iodode 8b. To $ZrCp_2Cl_2$ (45.0 mg, 157 μmmol, 1.1 equiv.) in THF (250 μL) cooled to 0 °C was added slowly a solution DIBAL-H (156 μL, 1 M in THF, 156 μmol, 1.0 equiv.) under argon. The resulting suspension was stirred for 30 min at 0 °C, followed by addition of alkyne **54** (50.0 mg, 143 μmol, 1.0 equiv.) in THF (150 μL). The mixture was warmed to room temperature and stirred until a homogeneous solution resulted and then cooled to −78 °C, followed by addition of I_2 (47.2 mg, 186 μmol, 1.30 equiv.) in THF (200 μL). After 1 h at −78 °C the reaction mixture was quenched with 1 N HCl, extracted with diethyl ether, washed successively with saturated aqueous $Na_2S_2O_3$, $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography (SiO_2, petroleum ether) afforded vinyl iodide **8b** as a colourless liquid (46.5 mg, 97.6 μmol, 62%). R_f = 0.19 (petroleum ether–ethyl acetate, 50 : 1); $[\alpha]_D^{22}$ = +1.39 (c = 1.00, $CHCl_3$); ^{1}H NMR (300.132 MHz, $CDCl_3$): δ = 0.02 (s, 3 H), 0.04 (s, 3 H), 0.89 (m, 12 H), 1.92 (dquin, J = 12.8 Hz, J = 6.5 Hz, J = 6.5 Hz, J = 6.5 Hz, J = 6.5 Hz, 1 H), 3.34 (m, 2 H), 3.82 (s, 3 H), 4.15 (m, 1 H), 4.41 (m, 2 H), 6.14 (dd, J = 14.4 Hz, J = 1.0 Hz, 1 H), 6.48 (dd, J = 14.4 Hz, J = 6.7 Hz, 1 H), 6.89 (d, J = 8.7 Hz, 2 H), 7.25 (d, J = 9.2 Hz, 2 H); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = −5.0, −4.5, 12.5, 18.2, 25.8, 39.9, 55.3, 71.5, 72.7, 76.4, 76.5, 113.8, 129.2, 130.6, 147.1, 159.1; HR-MS (ESI): found m/z = 499.1132 ($C_{20}H_{33}IO_3SiNa$), calculated m/z = 499.1136.

Propargylic alcohol 22. A two-necked flask equipped with a Dewar condenser was loaded with Et_2Zn (28.0 mL, 1.1 M in toluene, 30.7 mmol, 4.0 equiv.) carefully. While propyne (1.23 g, 30.7 mmol, 4.0 equiv.) was bubbled through the solution, the mixture was slowly heated to reflux for 1 h, meanwhile a large amount of grey precipitate was formed. The mixture was cooled to room temperature, and (*R*)-BINOL (879 mg, 3.07 mmol, 0.4 equiv.), Et_2O (145 mL) and $Ti(OiPr)_4$ (2.27 g, 7.68 mmol, 1.0 equiv.) were added. After 1 h, aldehyde **8b** (1.60 g, 7.68 mmol, 1.0 equiv.) was added, and the mixture was stirred overnight. The reaction was quenched with 1 M tartaric acid (50 mL) and the mixture was stirred for 30 min. The mixture was partitioned in a separatory funnel, and the aqueous portion was extracted with Et_2O (3 × 60 mL). The combined organic extracts were washed with brine and dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, petroleum ether–ethyl acetate, 3 : 1) to afford **22** as a colourless liquid (1.14 g, 4.59 mmol, 60%). R_f = 0.30 (petroleum ether–ethyl acetate, 4 : 1); $[\alpha]_D^{22}$ = +10.4 (c = 1.00, $CHCl_3$); ^{1}H NMR

(300.132 MHz, $CDCl_3$): δ = 1.02 (d, J = 6.9 Hz, 3 H), 1.85 (d, J = 2.2 Hz, 3 H), 2.02 (m, 1 H), 3.10 (br. s., 1 H), 3.44 (dd, J = 9.3 Hz, J = 6.9 Hz, 1 H), 3.64 (dd, J = 9.2 Hz, J = 4.5 Hz, 1 H), 3.81 (s, 3 H), 4.36 (dd, J = 6.3 Hz, J = 2.2 Hz, 1 H), 4.46 (d, J = 1.4 Hz, 2 H), 6.88 (d, J = 8.5 Hz, 2 H), 7.26 (d, J = 8.8 Hz, 2 H); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 3.5, 13.2, 39.5, 55.2, 66.6, 73.0, 73.4, 79.0, 81.4, 113.8, 129.2, 130.0, 159.2; HR-MS (ESI): found m/z = 271.1305 ($C_{15}H_{20}O_3Na$), calculated m/z = 271.1305.

Mosher's esters of 22

*(R)-Mosher's ester **55** and (S)-Mosher's ester **56**.*



55 **56**

(*R*)-Mosher's ester (14.1 mg, 60.4 μmol, 3.0 equiv.) was diluted in toluene (400 μL) at 0 °C. To the reaction mixture DMAP (9.59 mg, 78.5 μmol, 3.3 equiv.), NEt_3 (7.94 mg, 78.5 μmol, 3.3 equiv.), Yamaguchi reagent (14.7 mg, 60.4 μmol, 3.0 equiv.) and a solution of propargylic alcohol **22** (5.10 mg, 20.1 μmol, 1.0 equiv.) in toluene (400 μL) were added and stirred at room temperature. After 3 h the mixture was treated with pH 7 buffer (1 mL) and quenched with water (2 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, petroleum ether–ethyl acetate, 30 : 1) to afford the desired ester **55** for ^{1}H NMR analysis. R_f = 0.13 (petroleum ether–ethyl acetate, 10 : 1); ^{1}H NMR (300.132 MHz, $CDCl_3$): δ = 1.01 (d, J = 6.6 Hz, 3 H), 1.83 (d, J = 2.2 Hz, 3 H), 2.24 (m, 1 H), 3.40 (m, 2 H), 3.52 (s, 3 H), 3.81 (s, 3 H), 4.43 (s, 2 H), 5.69 (m, 1 H), 6.51 (d, J = 6.6 Hz, 3 H), 6.88 (d, J = 8.8 Hz, 2 H), 7.26 (m, 3 H), 7.39 (m, 3 H), 7.53 (m, 2 H). The same procedure and proportions have been performed using (*S*)-Mosher's ester to get diastereomer **56**. R_f = 0.14 (petroleum ether–ethyl acetate, 10 : 1); ^{1}H NMR (300.132 MHz, $CDCl_3$): δ = 0.97 (d, J = 6.6 Hz, 3 H), 1.86 (d, J = 2.2 Hz, 3 H), 2.20 (m, 1 H), 3.28 (dd, J = 9.3 Hz, J = 5.5 Hz, 1 H), 3.39 (dd, J = 9.3 Hz, J = 6.7 Hz, 1 H), 3.60 (s, 3 H), 3.82 (s, 3 H), 4.38 (d, J = 4.4 Hz, 1 H), 5.71 (dq, J = 5.8 Hz, J = 2.0 Hz, 2 H), 6.89 (d, J = 8.5 Hz, 2 H), 7.25 (d, J = 8.8 Hz, 3 H), 7.38 (m, 3 H), 7.56 (m, 2 H) (Table 10).

TBS ether 57 *via* TBS protection of 22. 2,6-Lutidine (587 mg, 5.48 mmol, 4.2 equiv.) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.10 g, 4.18 mmol, 3.2 equiv.) were added slowly to a solution of alcohol **22** (400 mg, 1.31 mmol, 1.0 equiv.) in dichloromethane (5 mL) at −78 °C. After stirring for 1 h, the reaction was quenched by addition of aqueous saturated $NaHCO_3$ (10 mL) and extracted with dichloromethane (3 × 7 mL). The combined organic phases were dried with $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (SiO_2, *n*-hexane–ethyl acetate, 50 : 1) to afford the protected alcohol **57** as a colourless liquid (528 mg, 1.25 mmol, 96%). *Via* methylation of **54**: Alkyne **54** (500 mg, 1.43 mmol, 1.0 equiv.) was dissolved in THF (3.0 mL) and cooled to −78 °C. After addition of *n*-butyllithium the mixture was stirred at 0 °C for 5 min. Again cooling to −78 °C MeI was added slowly and the reaction mixture was stirred at room temperature overnight, quenched with saturated aqueous NH_4Cl and extracted with MTBE (3×). The organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, petroleum ether–ethyl acetate, 50 : 1) to afford **57** as a colourless liquid (515 mg, 1.42 mmol, 99%). R_f = 0.22 (petroleum ether–ethyl acetate, 50 : 1); $[\alpha]_D^{22}$ = +7.40 (c = 1.07, $CHCl_3$); ^{1}H NMR (300.132 MHz, $CDCl_3$): δ = 0.10 (s, 3 H), 0.13 (s, 3 H), 0.90 (s, 9 H), 1.00 (d, J = 6.7 Hz, 3 H), 1.82 (d, J = 2.2 Hz, 3 H), 2.00 (spt, J = 6.5 Hz, 1 H), 3.36 (dd, J = 9.2 Hz, J = 6.2 Hz, 1 H), 3.50 (dd, J = 9.2 Hz, J = 6.3 Hz, 1 H), 3.81 (s, 3 H), 4.44 (m, 3 H), 6.88 (d, J = 8.7 Hz, 2 H), 7.26 (d, J = 8.7 Hz, 2 H); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = −5.1, −4.5, 3.5, 12.6, 18.2, 25.8, 40.8, 55.3, 65.0, 72.0, 72.7, 79.1, 80.9, 113.7, 129.1, 130.9, 159.0; HR-MS (ESI): found m/z = 363.2352 ($C_{21}H_{35}0_30_3Si$), calculated m/z = 363.2350.

Vinyl stannane 58. TBS ether **57** (100 mg, 276 μmol, 1.0 equiv.) and $Pd(PPh)_3$ (8.00 mg, 11.0 μmol, 4 mol%) were dissolved in dry THF (800 μL) and Bu_3SnH (88.0 μL, 334 μmol, 1.2 equiv.) was added dropwise over 30 min at room temperature. The mixture was stirred for an additional 30 min and concentrated *in vacuo*. After purification of the residue by column chromatography (SiO_2, petroleum ether–ethyl acetate, 100 : 1) stannane **58** was obtained as a colourless liquid (122 mg, 187 μmol, 68%). R_f = 0.47 (petroleum ether–ethyl acetate, 20 : 1); $[\alpha]_D^{22}$ = −4.10 (c = 1.13, $CHCl_3$); ^{1}H NMR (300.132 MHz, $CDCl_3$): δ = 0.06 (s, 3 H), 0.07 (s, 3 H), 0.95 (m, 27 H), 1.36 (m, 6 H), 1.55 (m, 6 H), 1.90 (d, J = 1.9 Hz, 3 H), 3.28 (dd, J = 9.1 Hz, J = 6.6 Hz, 1 H), 3.52 (dd, J = 9.1 Hz, J = 6.0 Hz, 1 H), 3.86 (s, 3 H), 4.44 (m, 2 H), 4.67 (dd, J = 8.2 Hz, J = 4.7 Hz, 1 H), 5.58 (dd, J = 8.1 Hz, J = 1.8 Hz, 1 H), 6.92 (d, J = 8.5 Hz, 2 H), 7.31 (d, J = 8.5 Hz, 2 H); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = −5.0, −4.3, 9.1, 12.0, 13.7, 18.2, 19.7, 25.9, 27.4, 29.2, 40.5, 55.2, 68.8, 72.6, 72.7, 113.7, 128.8, 131.0, 137.9, 143.9, 159.0; HR-MS (ESI): found m/z = 677.3387 ($C_{33}H_{62}0_30_3SiSnNa$), calculated m/z = 677.3382.

Vinyl iodide 7. A solution of I_2 (25.2 mg, 99.2 μmol, 1.1 equiv.) in dry dichloromethane (600 μL) was added to a stirred solution of stannane **58** (61.8 mg, 94.5 μmol, 1.0 equiv.) in dichloromethane (600 μmol) at 0 °C. The resulting brown mixture was stirred at 0 °C for an additional 15 min and quenched with saturated aqueous $Na_2S_2O_3$ (100 μL). This was diluted with saturated aqueous $NaHCO_3$ (2 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers

Table 10 Determination of the absolute configuration[35]

Proton's positions	(*S*)-Mosher's ester **56** [ppm]	(*R*)-Mosher's ester **55** [ppm]	$\Delta\delta = \delta_S - \delta_R$
4	4.38	4.43	−0.05
7	0.97	1.01	−0.04
6	2.20	2.24	−0.04
11	1.86	1.83	0.03

were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, petroleum ether–ethyl acetate, 100 : 1) to provide vinyl iodide **7** (41.4 mg, 84.4 μmol, 89%) as a light yellow, clear liquid. R_f = 0.40 (petroleum ether–ethyl acetate, 20 : 1); $[\alpha]_D^{22}$ = +4.50 (*c* = 1.10, $CHCl_3$); ^{1}H NMR (300.132 MHz, $CDCl_3$): δ = 0.03 (s, 6 H), 0.88 (s, 9 H), 0.94 (d, *J* = 6.9 Hz, 3 H), 1.79 (m, 1 H), 2.40 (d, *J* = 1.4 Hz, 3 H), 3.26 (dd, *J* = 9.0 Hz, *J* = 5.4 Hz, 1 H), 3.40 (dd, *J* = 9.0 Hz, *J* = 6.5 Hz, 1 H), 3.82 (s, 3 H), 4.43 (m, 3 H), 6.18 (dq, *J* = 8.9 Hz, *J* = 1.4 Hz, 1 H), 6.89 (d, *J* = 8.7 Hz, 2 H), 7.25 (d, *J* = 8.7 Hz, 2 H); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = −5.1, −4.5, 12.5, 13.6, 16.4, 18.1, 25.8, 26.6, 28.5, 29.1, 40.3, 55.3, 71.4, 71.6, 72.7, 95.4, 113.7, 129.1, 130.7, 143.2, 159.1; HR-MS (ESI): found *m*/*z* = 491.1478 ($C_{21}H_{36}I0_3$), calculated *m*/*z* = 491.1473.

Methyl-4-oxobutanoate 24. The lactone **23** (2.58 g, 30.0 mmol, 1.0 equiv.) was treated with methanol (30.0 mL, 741 mmol, 25 equiv.) and triethylamine (18.2 g, 180.0 mmol, 6.0 equiv.) and stirred at room temperature for 15 h. The resulting crude methyl 4-hydroxybutanoate was taken up in dichloromethane (90.0 mL) and sodium acetate (780 mg, 9.60 mmol, 3.2 equiv.) and pyridinium chlorochromate (9.81 g, 45.0 mmol, 15 equiv.) were added. After being stirred at room temperature for 1.5 h, diethyl ether (500 mL) was added, the reaction mixture was filtered through celite, and the filtrate was concentrated at reduced pressure. The residue was purified by chromatography (SiO_2, *n*-hexane–ethyl acetate, 2 : 1) to give ester **24** as a colourless liquid (2.15 g, 18.6 mmol, 62%). R_f = 0.39 (*n*-hexane–ethyl acetate, 2 : 1); ^{1}H NMR (300.132 MHz, $CDCl_3$): δ = 2.66 (q, *J* = 6.2 Hz, 2H), 2.83 (t, *J* = 6.3 Hz, 3H), 3.71 (s, 3H), 9.83 (s, 1H); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 26.3, 38.5, 51.9, 172.7, 199.9; EI-MS (70 eV, *m*/*z* (%)): 116 ($[M]^+$, 4), 101 (45), 84 (100).

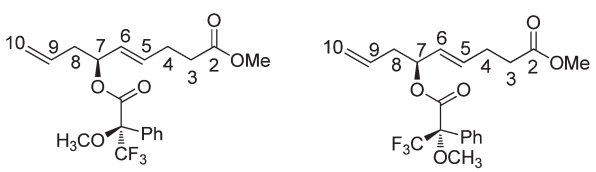
Methyl-pent-4-enoate 59. A solution of pent-4-enoic acid **29** (10.0 g, 100 mmol, 1.0 equiv.) in dried CH_3OH (170 mL, 420 mol, 42 equiv.) was treated with concentrated H_2SO_4 (1.00 mL). After refluxing for 3 h, the reaction mixture was washed with water (2 × 140 mL) and the resulting mixture was extracted with Et_2O (3 × 200 mL), dried with $MgSO_4$ and concentrated. The residue was purified by Vigreux distillation to afford the pure ester **59** as a colourless liquid (8.24 g, 72.2 mmol, 72%). R_f = 0.63 (*n*-hexane–ethyl acetate, 8 : 1); ^{1}H NMR (300.132 MHz, CDCl3) δ = 2.39 (m, 4 H), 3.68 (s, 3 H), 5.03 (m, 2 H), 5.82 (m, 1 H); ^{13}C NMR (75.48 MHz, $CDCl_3$) δ = 28.4, 33.9, 51.1, 115.1, 136.2, 173.1; EI MS (70 eV, *m*/*z* (%)): 114 ($[M]^+$, 27.5), 55 (100).

(*E*)-Methyl 6-oxohex-4-enoate 26. Crotonaldehyde (6.14 g, 87.6 mmol, 10 equiv.) dissolved in dried dichloromethane (30 mL) was added to a solution of olefin **59** (1.00 g, 8.76 mmol, 1.0 equiv.) in deuterated dichloromethane (10 mL). Hoveyda–Grubbs catalyst second generation (165 mg, 3.0 mol%) was added and the reaction mixture was heated to 40 °C under an argon atmosphere for 2 h. After stirring, the mixture was concentrated under reduced pressure and purified by flash chromatography (SiO_2, *n*-hexane–ethyl acetate, 4 : 1) to afford aldehyde **26** as a brown liquid (1.16 g, 8.16 mmol, 93%). R_f = 0.24 (*n*-hexane–ethyl acetate, 4 : 1); ^{1}H NMR (300.132 MHz, $CDCl_3$) δ = 2.53 (m, 2 H), 2.65 (m, 2 H), 3.68 (s, 3 H), 6.12 (dd, *J* = 15.3 Hz, *J* = 7.8 Hz, 1 H), 6.85 (dt, *J* = 15.7 Hz, *J* = 6.4 Hz, 1 H), 9.49 (d, *J* = 7.7 Hz, 1 H); ^{13}C NMR (75.48 MHz, $CDCl_3$) δ = 27.1, 31.4, 51.4, 132.9, 155.3, 172.0, 193.3; HR-MS (EI) found *m*/*z* = 142.0654 ($C_7H_{10}O_3$), calculated *m*/*z* = 142.0630.

(*S*,*E*)-Methyl 6-hydroxynona-4,8-dienoate 27. Allylmagnesium bromide (5.63 mL, 1.00 M in diethyl ether, 5.63 mmol, 4.0 equiv.) was added dropwise to a well-stirred solution of (−)-$(Ipc)_2BOMe$ (1.78 g, 5.63 mmol, 4.0 equiv.) in diethyl ether (6 mL) at 0 °C. Following addition, stirring was continued for 1 h at room temperature and ether was removed under vacuum. The residue was carefully extracted with pentane (2 × 25 mL) under argon while the reaction mixture was stirred. Next, stirring was discontinued to permit the Mg^{2+} salts to settle, and the clear supernatant pentane extract was transferred into another flask with a double-ended needle through a filter. The combined organic phases were concentrated under vacuum. The residue was dissolved in diethyl ether (5 mL) and cooled to −98 °C. To the resulting mixture a solution of aldehyde **26** (200 mg, 1.41 mmol, 1.0 equiv.) in diethyl ether (2.5 mL) was added slowly and stirred at −98 °C. After 3 h the reaction mixture was allowed to warm to room temperature, treated with NaOH (550 μL, 3 N) and H_2O_2 (1.5 mL, 30%) and then heated to reflux for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and the organic phase separated. The aqueous layer was extracted with diethyl ether (2 × 3.5 mL), MTBE (2 × 2.5 mL) and ethyl acetate (2 × 1.5 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under vacuum. The residue was purified by flash chromatography (SiO_2, *n*-hexane–ethyl acetate, 3 : 1) to afford **27** as an colourless liquid (233 mg, 1.26 mmol, 90%). R_f = 0.21 (*n*-hexane–ethyl acetate, 5 : 1); $[\alpha]_D^{22}$ = −7.40 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (500.130 MHz, $CDCl_3$) δ = 2.33 (m, 6 H), 3.67 (s, 3 H), 4.12 (q, *J* = 6.3 Hz, 1 H), 5.13 (m, 2 H), 5.54 (dd, *J* = 15.5 Hz, *J* = 6.5 Hz, 1 H), 5.68 (dt, *J* = 15.4 Hz, *J* = 6.1 Hz, 1 H), 5.79 (td, *J* = 17.3 Hz, *J* = 7.1 Hz, 1 H); ^{13}C NMR (125.758 MHz, $CDCl_3$) δ = 27.4, 33.6, 41.9, 51.5, 71.4, 118.2, 129.5, 133.3, 134.2, 173.4; HR-MS (ESI): found *m*/*z* = 207.0994 ($C_{10}H_{16}O_3Na$), calculated *m*/*z* = 207.0992.

Mosher's esters of 27

*(*R*)-Mosher's ester **60** and (*S*)-Mosher's ester **61**.*



60 **61**

(*R*)-Mosher's ester (76.3 mg, 326 mmol, 3.0 equiv.) was diluted in toluene (1 mL) at 0 °C. To the reaction mixture DMAP (43.8 mg, 358 mmol, 3.3 equiv.), NEt_3 (36.3 mg, 358 mmol, 3.3 equiv.), Yamaguchi reagent (79.5 mg, 326 mmol, 3.0 equiv.) and a solution of homoallylic alcohol **27** (20.0 mg, 108 μmol, 1.0 equiv.) in toluene (1 mL) were added and stirred at room temperature. After 3 h the mixture was treated with pH 7

Table 11 Determination of the absolute configuration[35]

Proton's positions	(*S*)-Mosher's ester **61** [ppm]	(*R*)-Mosher's ester **60** [ppm]	$\Delta\delta = \delta_S - \delta_R$
3	2.39	2.34	+0.05
5	5.83	5.77	+0.06
6	5.63	5.41	+0.22
9	5.54	5.70	−0.06
10	5.03	5.12	−0.09

buffer (2.5 mL) and quenched with water (5 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 7 mL). The combined organic layers were dried over MgSO4, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, *n*-hexane–ethyl acetate, 10 : 1) to afford the desired ester **60** for ^{1}H NMR analysis. R_f = 0.50 (*n*-hexane–ethyl acetate, 3 : 1); ^{1}H NMR (300.132 MHz, $CDCl_3$): δ = 2.34 (m, 4 H), 2.44 (m, 2 H), 3.56 (s, 3 H), 3.67 (s, 3 H), 5.12 (m, 2 H), 5.41 (m, 1 H), 5.49 (m, 1 H), 5.70 (m, 1 H), 5.77 (m, 1 H), 7.40 (m, 3 H), 7.51 (m, 2 H). The same procedure and proportions have been performed using (*S*)-Mosher's ester to get diastereomer **61**. ^{1}H NMR (300.132 MHz, $CDCl_3$): δ = 2.39 (m, 6 H), 3.54 (s, 3 H), 3.66 (s, 3 H), 5.03 (m, 2 H), 5.48 (m, 1 H), 5.54 (m, 1 H), 5.63 (m, 1 H), 5.83 (m, 1 H), 7.40 (m, 3 H), 7.51 (m, 2 H) (Table 11).

(*S*,*E*)-Methyl 6-(*tert*-butyldimethylsilyloxy)nona-4,8-dienoat 62. 2,6-Lutidine (609 mg, 5.69 mmol, 2.1 equiv.) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.15 g, 4.34 mmol, 1.6 equiv.) were added slowly to a solution of alcohol **27** (500 mg, 2.71 mmol, 1.0 equiv.) in dichloromethane (8 mL) at −78 °C. After stirring for 1 h, the reaction was quenched by addition of aqueous saturated $NaHCO_3$ and extracted with dichloromethane (3 × 10 mL). The combined organic phases were dried with $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (SiO_2, *n*-hexane–ethyl acetate, 30 : 1) to afford the protected alcohol **62** as a colourless liquid (803 mg, 2.69 mmol, 99%). R_f = 0.29 (*n*-hexane–ethyl acetate, 30 : 1); $[\alpha]_D^{22}$ = −2.30 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (300.132 MHz, $CDCl_3$) δ = 0.02 (d, *J* = 6.4 Hz, 6 H), 0.88 (s, 9 H), 2.22 (m, 2 H), 2.37 (m, 4 H), 3.67 (s, 3 H), 4.08 (q, *J* = 6.2 Hz, 1 H), 5.03 (m, 2 H), 5.52 (m, 2 H), 5.77 (m, 1 H); ^{13}C NMR (75.48 MHz, $CDCl_3$) δ = −4.8, −4.4, 18.2, 25.8, 27.4, 33.8, 43.1, 51.5, 73.0, 116.7, 128.0, 134.3, 135.1, 173.4; HR-MS (ESI): found *m*/*z* = 321.1860 ($C_{16}H_{30}O_3SiNa$), calculated *m*/*z* = 321.1856.

(*S*,4*E*,8*E*)-Methyl 6-(*tert*-butyldimethylsilyloxy)-10-oxodeca-4,8-dienoate 63. The protected alcohol **62** (1.00 g, 3.35 mmol, 1.0 equiv.) dissolved in dichloromethane (3 mL) was added to a well stirred solution of crotonaldehyde (0.70 g, 10.0 mmol, 3.0 equiv.) in dichloromethane (7 mL). After Grubbs catalyst second generation (142 mg, 5.0 mol%) was added, the reaction mixture was heated to 40 °C for 2 h, concentrated under reduced pressure and purified by flash chromatography (SiO_2, *n*-hexane–ethyl acetate, 10 : 1) to afford aldehyde **63** as a yellow-brown liquid (940 mg, 2.88 mmol, 86%). R_f = 0.28 (*n*-hexane–ethyl acetate, 10 : 1); $[\alpha]_D^{22}$ = +0.65 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (300.132 MHz, $CDCl_3$) δ = 0.02 (d, *J* = 4.7 Hz, 6 H), 0.87 (s, 9 H), 2.41 (m, 6 H), 3.66 (s, 3 H), 4.24 (q, *J* = 6.0 Hz, 1 H), 5.47 (m, 1 H), 5.62 (m, 1 H), 6.12 (dd, *J* = 15.6 Hz, *J* = 7.9 Hz, 1 H), 6.82 (dt, *J* = 15.6 Hz, *J* = 7.4 Hz, 1 H), 9.50 (d, *J* = 7.9 Hz, 1 H); ^{13}C NMR (75.48 MHz, $CDCl_3$) δ = −5.3, −4.7, 17.7, 25.3, 26.8, 33.2, 41.2, 51.1, 71.5, 128.8, 133.0, 134.4, 154.4, 172.8, 193.5; HR-MS (ESI): found *m*/*z* = 349.1807 ($C_{17}H_{30}O_4SiNa$), calculated *m*/*z* = 349.1811.

Dienyl iodide 10. To a cooled (0 °C) suspension of $CrCl_2$ (2.11 g, 17.2 mmol, 14 equiv.) in a mixed solvent (THF–dioxane, 1 : 6, 15 mL) was added dropwise a solution of aldehyde **63** (400 mg, 1.23 mmol, 1.00 equiv.) and iodoform (4.25 g, 10.8 mmol, 8.8 equiv.) in a mixed solvent (THF–dioxane, 1 : 6, 15 mL and 6 mL washing). The resulting brown mixture was stirred at room temperature for 4 h in the absence of light, quenched by sequential additions of aqueous saturated NH_4Cl (70 mL), saturated $Na_2S_2O_3$ (35 mL) and water (70 mL). The resulting mixture was extracted with diethyl ether (3 × 100 mL) and the combined organic phases were washed with saturated $Na_2S_2O_3$ (70 mL) and brine (70 mL), dried over $MgSO_4$ and concentrated under vacuum. Flash chromatography (SiO_2, *n*-hexane–ethyl acetate, 40 : 1 to 20 : 1) provided vinyl iodide **10** as a yellow oil (480 mg, 1.07 mmol, 87%, *E*–*Z* = 7 : 1 based on ^{1}H NMR integrations). R_f = 0.48 (*n*-hexane–ethyl acetate, 10 : 1); $[\alpha]_D^{22}$ = +3.50 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (300.132 MHz, $CDCl_3$) δ = 0.01 (d, *J* = 5.1 Hz, 6 H), 0.88 (s, 9 H), 2.21 (t, *J* = 6.7 Hz, 2 H), 2.37 (m, 4 H), 3.67 (s, 3 H), 4.11 (dd, *J* = 13.7 Hz, *J* = 6.5 Hz, 1 H), 5.45 (m, 1 H), 5.62 (m, 2 H), 5.98 (dd, *J* = 15.2 Hz, *J* = 10.6 Hz, 1 H), 6.19 (d, *J* = 14.3 Hz, 1 H), 6.99 (dd, *J* = 14.3 Hz, *J* = 10.6 Hz, 1 H); ^{13}C NMR (75.48 MHz, $CDCl_3$) δ = −4.4, −3.9, 18.6, 26.3, 27.8, 34.2, 42.1, 52.0, 73.2, 128.8, 132.5, 132.7, 134.6, 145.8, 173.8; HR-MS (ESI): found *m*/*z* = 473.0979 ($C_{18}H_{31}IO_3SiNa$), calculated *m*/*z* = 473.0985.

Alcohol 28. Protected alcohol **10** (147 mg, 326 μmol, 1.00 equiv.) was diluted in THF (3.50 mL) at 0 °C. The solution was treated dropwise with TBAF (4.08 mL, 4.08 mmol, 12.5 equiv.) and stirred for 4 h at 0 °C to 25 °C. Ethyl acetate (7.00 mL) and distilled water (7.00 mL) were added. The organic layer was separated and washed with brine (3 × 7.00 mL). The combined aqueous layers were extracted with ethyl acetate (17.5 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated. Flash chromatography (SiO_2, *n*-hexane–ethyl acetate, 2 : 1) could afford the deprotected alcohol **28** (99.0 mg, 294 μmol, 90%) as a yellow oil. R_f = 0.31 (*n*-hexane–ethyl acetate, 2 : 1); $[\alpha]_D^{22}$ = +7.10 (*c* = 2.66, $CHCl_3$); ^{1}H NMR (300.132 MHz, $CDCl_3$): δ = 2.29 (m, 2H), 2.39 (m, 4H), 3.68 (s, 3H), 4.13 (q, *J* = 6.2 Hz, 1H), 5.53 (m, 1H), 5.68 (m, 2H), 6.06 (dd, *J* = 15.3 Hz, *J* = 10.6 Hz, 1H), 6.25 (d, *J* = 14.5 Hz, 1H), 7.01 (dd, *J* = 14.3 Hz, *J* = 10.6 Hz, 1H); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 26.9, 33.1, 40.0, 51.2, 71.1, 77.4, 129.5, 130.4, 132.7, 132.8, 144.6, 172.9; HR-MS (ESI): found *m*/*z* = 359.0117 ($C_{12}H_{17}IO_3Na$), calculated *m*/*z* = 359.0120.

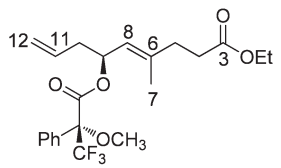
(*E*)-Ethyl 4-methyl-6-oxohex-4-enoate 64. The ester **31** (2.50 g, 17.6 mmol, 1 equiv.) and crotonaldehyde (14.5 mL, 176 mmol, 1 equiv.) were dissolved in dichloromethane (110 mL) and the Hoveyda–Grubbs catalyst second generation (551 mg,

880 μmol, 5 mol%) was added. After stirring under reflux for 4 h, the reaction mixture was concentrated under reduced pressure and purified by flash chromatography (SiO_2, petroleum ether–ethyl acetate, 4 : 1) to obtain ethyl ester **64** as a brown liquid (950 mg, 5.58 mmol, 32%, 80% brsm). R_f = 0.26 (petroleum ether–ethyl acetate, 4 : 1); ^{1}H NMR (600.130 MHz, $CDCl_3$): δ = 1.25 (t, J = 7.1 Hz, 3 H), 2.19 (d, J = 1.5 Hz, 3 H), 2.54 (m, 4 H), 4.14 (q, J = 7.3 Hz, 2 H), 5.86 (m, 1 H), 9.99 (d, J = 8.1 Hz, 1 H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 13.7, 17.2, 31.2, 34.6, 60.3, 126.8, 161.1, 171.7,190.6; HR-MS (EI): found m/z = 170.0937 ($C_9H_{14}O_3$), calculated m/z = 170.0943.

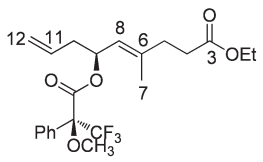
(*S*,*E*)-Ethyl 6-hydroxy-4-methylnona-4,8-dienoate 32. The ester **64** (935 mg, 5.49 mmol, 1 equiv.) was dissolved in diethyl ether (10 mL) and (−)-$(Ipc)_2$B(allyl) (1 M in diethyl ether, 10.5 mL, 10.5 mmol, 1.9 equiv.) was added. After stirring for 3.5 h at −100 °C, the reaction mixture was allowed to warm up to room temperature, sodium hydroxide (3.8 mL, 3 N) and hydrogen peroxide (7.5 mL, 30%) were added and the resulting mixture was heated under reflux for an additional 1 h. After quenching with a saturated aqueous solution of $NaHCO_3$ (14 mL), the organic layer was separated. The aqueous phase was washed with diethyl ether (2 × 20 mL), MTBE (2 × 16 mL) and ethyl acetate (2 × 8 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. After purification by column chromatography (SiO_2, petroleum ether–ethyl acetate, 5 : 1) homoallylic alcohol **32** was obtained as a slightly brown liquid (657 mg, 3.10 mmol, 56%); R_f = 0.17 (petroleum ether–ethyl acetate, 5 : 1); $[\alpha]_D^{22}$ = −17.40 (c = 0.77, $CHCl_3$); ^{1}H NMR (300.130 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.1 Hz, 3 H), 1.65 (br. s., 1 H), 1.70 (d, J = 1.5 Hz, 3 H), 2.35 (m, 4 H), 2.43 (m, 2 H), 4.13 (q, J = 7.3 Hz, 2 H), 4.41 (dt, J = 8.6 Hz, J = 6.3 Hz, 1 H), 5.10 (m, 1 H), 5.14 (m, 1 H), 5.22 (dq, J = 8.6 Hz, J = 1.3 Hz, 1 H), 5.79 (ddt, J = 17.3 Hz, J = 10.2 Hz, J = 7.1 Hz, J = 7.1 Hz, 1 H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 13.8, 16.2, 32.4, 33.9, 41.7, 59.9, 67.1, 117.6, 127.2, 133.8, 136.6, 172.7; HR-MS (ESI): found m/z = 235.1304 ($C_{12}H_{20}O_3Na$), calculated m/z = 235.1310.

Mosher's esters of 32

*(R)-Mosher's ester **65** and (S)-Mosher's ester **66**.*



65



66

(*R*)-Mosher's ester (23.9 mg, 102 μmol, 3.0 equiv.) was diluted in toluene (350 μL) at 0 °C. To the reaction mixture DMAP (13.7 mg, 112 μmol, 3.3 equiv.), NEt_3 (11.4 mg, 112 μmol, 3.3 equiv.), Yamaguchi reagent (24.9 mg, 102 μmol, 3.0 equiv.) and a solution of homoallylic alcohol **32** (7.25 mg, 34.0 μmol, 1.0 equiv.) in toluene (350 μL) were added and stirred at room temperature. After 3 h the mixture was treated with pH 7 buffer (800 μL) and quenched with water (1.6 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 2.2 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, petroleum ether–ethyl acetate, 10 : 1) to afford the desired ester **65** for ^{1}H NMR analysis. R_f = 0.54 (petroleum ether–ethyl acetate, 5 : 1); ^{1}H NMR (300.132 MHz, $CDCl_3$): δ = 1.25 (t, J = 7.1 Hz, 3 H), 1.79 (d, J = 1.5 Hz, 3 H), 2.42 (m, 6 H), 3.55 (s, 2 H), 4.12 (q, J = 7.0 Hz, 2 H), 5.12 (m, 3 H), 5.73 (m, 2 H), 7.39 (m, 3 H), 7.50 (m, 2 H). The same procedure and proportions have been performed using (*S*)-Mosher's ester to get diastereomer **66**. ^{1}H NMR (300.132 MHz, $CDCl_3$): δ = 1.25 (t, J = 7.1 Hz, 3 H), 1.80 (s, 3 H), 2.37 (m, 6 H), 3.54 (s, 3 H), 4.12 (q, J = 7.3 Hz, 2 H), 5.04 (m, 2 H), 5.24 (dd, J = 9.5 Hz, J = 1.1 Hz, 1 H), 5.62 (ddt, J = 17.0 Hz, J = 10.0 Hz, J = 7.1 Hz, J = 7.1 Hz, 1 H), 5.77 (dt, J = 9.1 Hz, J = 6.6 Hz, 1 H), 7.40 (m, 3 H), 7.52 (m, 2 H) (Table 12).

Table 12 Determination of the absolute configuration[35]

Proton's positions	(*S*)-Mosher's ester **66** [ppm]	(*R*)-Mosher's ester **65** [ppm]	$\Delta\delta = \delta_S - \delta_R$
7	1.80	1.79	+0.01
8	5.77	5.69	+0.08
11	5.62	5.76	−0.14
12	5.04	5.08	−0.04

(*S*,*E*)-Ethyl 6-((*tert*-butyldimethylsilyl)oxy)-4-methylnona-4,8-dienoate 67. The alcohol **33** (657 mg, 3.09 mmol, 1.0 equiv.) was dissolved in dichloromethane (10 mL) and TBSOTf (1.31 g, 4.94 mmol, 1.6 equiv.) and 2,6-lutidine (695 mg, 6.49 mmol, 2.1 equiv.) were added dropwise at −78 °C. After stirring for 1 h at this temperature, the reaction mixture was quenched with a concentrated aqueous solution of $NaHCO_3$ (19 mL), the organic layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 14.0 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. After purification by column chromatography (SiO_2, petroleum ether–ethyl acetate, 5 : 1), the product **67** was obtained as a clear, slightly brown liquid (996 mg, 3.05 mmol, 98%). R_f = 0.82 (petroleum ether–ethyl acetate, 4 : 1); $[\alpha]_D^{22}$ = +3.00 (c = 1.00, $CHCl_3$); ^{1}H NMR (300.130 MHz, $CDCl_3$): δ = 0.02 (d, J = 1.5 Hz, 6 H), 0.87 (s, 9 H), 1.26 (t, J = 7.1 Hz, 3 H), 1.64 (d, J = 1.1 Hz, 3 H), 2.25 (m, 6 H), 4.13 (q, J = 7.0 Hz, 2 H), 4.36 (dt, J = 8.6 Hz, J = 6.5 Hz, 1 H), 4.99 (m, 1 H), 5.04 (m, 1 H), 5.17 (dq, J = 8.6, J = 1.3 Hz, 1 H), 5.76 (ddt, J = 17.1 Hz, J = 10.2 Hz, J = 7.0 Hz, J = 7.0 Hz, 1 H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = −4.4, −3.9, −2.5, 14.6, 17.1, 18.6, 26.1, 26.3, 33.4, 34.7, 43.5, 60.7, 70.0, 116.9, 129.8, 133.6, 135.7, 173.6; HR-MS (ESI): found m/z = 349.2170 ($C_{18}H_{34}O_3SiNa$), calculated m/z = 349.2175.

Carboxylic acid 68. The ester **67** (950 mg, 2.91 mmol, 1.0 equiv.) was dissolved in methanol (2 mL), heated to 35 °C and potassium hydroxide (326 mg, 5.89 mmol, 2.0 equiv.) was added. After stirring for 1 h, the reaction mixture was quenched with distilled water (5 mL) and extracted with diethyl ether (3 × 5 mL). The aqueous phase was acidified with 2 N hydrochloric acid to pH 2, extracted with diethyl ether (3 × 5 mL), the combined organic layers were dried over Na_2SO_4,

filtered and concentrated under reduced pressure. After purification by column chromatography (SiO_2, petroleum ether–ethyl acetate, 5 : 1), the carboxylic acid **68** was obtained as a colourless liquid (596 mg, 2.00 mmol, 69%). R_f = 0.39 (petroleum ether–ethyl acetate, 5 : 1); $[\alpha]_D^{22}$ = +3.20 (c = 1.00, $CHCl_3$); ^{1}H NMR (300.130 MHz, $CDCl_3$): δ = 0.00 (s, 3 H), 0.03 (s, 3 H), 0.87 (s, 9 H), 1.64 (s, 3 H), 2.24 (m, 4 H), 2.52 (m, 2 H), 4.36 (m, 1 H), 5.03 (m, 2 H), 5.19 (dd, J = 8.6 Hz, J = 1.3 Hz, 1 H), 5.76 (m, 1 H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = −4.8, −4.3, −3.6, 16.6, 18.2, 25.6, 25.8, 32.5, 34.0, 43.1, 69.5, 116.6, 129.7,132.7,135.1, 179.1; HR-MS (ESI): found m/z = 321.1857 ($C_{16}H_{30}O_3SiNa$), calculated m/z = 321.1862.

Methyl ester 33. The carboxylic acid **68** (596 mg, 2.00 mmol, 1.0 equiv.) was dissolved in methanol and TMS-CH_2N_2 (14.1 mL 2 M in n-hexane, 28.0 mmol, 14.0 equiv.) was added dropwise at 0 °C. After stirring for 2.5 h at room temperature, the reaction mixture was concentrated and purified by column chromatography (SiO_2, petroleum ether–ethyl acetate, 30 : 1) to obtain the methyl ester **33** as a colourless oil (519 mg, 1.66 mmol, 83%). R_f = 0.42 (petroleum ether–ethyl acetate, 20 : 1); $[\alpha]_D^{22}$ = +2.50 (c = 1.00, $CHCl_3$); ^{1}H NMR (300.130 MHz, $CDCl_3$): δ = 0.00 (s, 3 H), 0.03 (s, 3 H), 0.87 (s, 9 H), 1.63 (s, 3 H), 2.21 (m, 4 H), 2.43 (m, 2 H), 3.67 (s, 3 H), 4.35 (dt, J = 8.4 Hz, J = 6.4 Hz, 1 H), 5.02 (m, 2 H), 5.16 (m, 1 H), 5.76 (ddt, J = 17.2 Hz, J = 10.2 Hz, J = 7.1 Hz, J = 7.1 Hz, 1 H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = −4.8, −4.3, 16.6, 18.2, 25.8, 32.7, 34.3, 43.1, 51.5, 69.5, 116.5, 129.5, 133.1, 135.2, 173.6; HR-MS (ESI): found m/z = 335.2013 ($C_{17}H_{32}O_3SiNa$), calculated m/z = 335.2018.

(*S*,4*E*,8*E*)-Methyl 6-((*tert*-butyldimethylsilyl)oxy)-4-methyl-10-oxodeca-4,8-dienoate 69. The methyl ester **33** (350 mg, 1.12 mmol, 1.0 equiv.) and crotonaldehyde (280 µL, 3.36 mmol, 3.0 equiv.) were dissolved in dichloromethane (7 mL) and Hoveyda–Grubbs II catalyst (35.0 mg, 56.0 µmol, 5 mol%) added. After stirring for 4 h under reflux, the reaction mixture was concentrated under reduced pressure and purified by column chromatography (SiO_2, petroleum ether–ethyl acetate, 10 : 1) to obtain the aldehyde **69** as a colourless oil (291 mg, 644 µmol, 58%). R_f = 0.21 (petroleum ether–ethyl acetate, 10 : 1); $[\alpha]_D^{22}$ = +0.80 (c = 1.00, $CHCl_3$); ^{1}H NMR (300.130 MHz, $CDCl_3$): δ = 0.00 (s, 3 H), 0.02 (s, 3 H), 0.86 (s, 9 H), 1.65 (d, J = 1.1 Hz, 3 H), 2.31 (m, 2 H), 2.47 (m, 4 H), 3.67 (s, 3 H), 4.50 (m, 1 H), 5.19 (dq, J = 8.6 Hz, J = 1.2 Hz, 1 H), 6.13 (ddt, J = 15.7 Hz, J = 7.9 Hz, J = 1.2 Hz, J = 1.2 Hz, 1 H), 6.83 (dt, J = 15.6 Hz, J = 7.4 Hz, 1 H), 9.50 (d, J = 8.1 Hz, 1 H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = −4.9, −4.3, 16.7, 18.1, 25.7, 32.5, 34.2, 41.8, 51.6, 68.5, 128.6, 134.3, 134.7, 155.1, 174.4, 193.9; HR-MS (ESI): found m/z = 363.1964 ($C_{18}H_{32}O_4SiNa$), calculated m/z = 363.1968.

(*S*,4*E*,8*E*,10*E*)-Methyl 6-((*tert*-butyldimethylsilyl)oxy)-11-iodo-4-methylundeca-4,8,10-trienoate 9. To a cooled (0 °C) suspension of $CrCl_2$ (182 mg, 1.48 mmol, 14 equiv.) in a mixed solvent (THF–dioxane, 1 : 6, 2.0 mL) was added dropwise a solution of aldehyde **69** (35.9 mg, 105 µmol, 1.0 equiv.) and iodoform (365 mg, 928 µmol, 8.8 equiv.) in a mixed solvent (THF–dioxane, 1 : 6, 1 mL and 0.5 mL washing). The resulting brown mixture was stirred at room temperature for 4 h in the absence of light, quenched by sequential additions of aqueous saturated NH_4Cl (6 mL), saturated $Na_2S_2O_3$ (3 mL) and water (6 mL). The resulting mixture was extracted with diethyl ether (3 × 5 mL) and the combined organic phases were washed with saturated $Na_2S_2O_3$ (6 mL) and brine (6 mL), dried over $MgSO_4$ and concentrated under vacuum. Flash chromatography (SiO_2, n-hexane–ethyl acetate, 40 : 1 to 20 : 1) provided vinyl iodide **9** as a colourless oil (39.8 mg, 77.1 µmol, 73%, E–Z = 7.7 : 1 based on ^{1}H NMR integrations). R_f = 0.62 (petroleum ether–ethyl acetate, 10 : 1); $[\alpha]_D^{22}$ = +1.80 (c = 1.00, $CHCl_3$); ^{1}H NMR (300.130 MHz, $CDCl_3$): δ = −0.01 (s, 3 H), 0.01 (s, 3 H), 0.86 (s, 9 H), 1.63 (m, 3 H), 2.18 (m, 4 H), 2.42 (m, 2 H), 3.67 (s, 3 H), 4.35 (dt, J = 8.4 Hz, J = 6.3 Hz, 1 H), 5.15 (d, J = 9.6 Hz, 1 H), 5.67 (dt, J = 15.1 Hz, J = 7.4 Hz, 1 H), 5.98 (dd, J = 15.2 Hz, J = 10.7 Hz, 1 H), 6.18 (d, J = 14.3 Hz, 1 H), 6.98 (dd, J = 14.3 Hz, J = 10.6 Hz, 1 H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = −4.8, −4.3, 16.6, 18.1, 25.8, 32.6, 34.2, 41.6, 51.6, 69.2, 129.3, 132.2, 133.4, 145.4, 173.5; HR-MS (ESI): found m/z = 487.1140 ($C_{19}H_{33}O_3SiNa$), calculated m/z = 487.1136.

Pinacolborane 37a. The following process was executed in the dark and conducted in an amber glass septum vial. $PdCl_2(CH_3CN)_2$ (6.25 mg, 24.1 µmol, 5.0 mol%) was added to a solution of the iodide **10** (217.0 mg, 482 µmol, 1.0 equiv.) and the stannane **6a** (325 mg, 963 µmol, 2.0 equiv.) in degassed, anhydrous DMF (1.7 mL). After stirring for 4 h the reaction mixture was diluted with diethyl ether (10 mL) and washed with a concentrated aqueous solution of NH_4Cl (20 mL). The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, petroleum ether–ethyl acetate, 40 : 1–20 : 1) afforded the product **37a** (194 mg, 385 µmol, 80%) as a yellow oil with little impurities of Bu_3SnI. R_f = 0.21 (petroleum ether–ethyl acetate, 20 : 1); $[\alpha]_D^{22}$ = +2.00 (c = 1.00, $CHCl_3$); ^{1}H NMR (600.130 MHz, $CDCl_3$): δ = 0.00 (s, 3 H), 0.02 (s, 3 H), 0.88 (m, 9 H), 1.28 (s, 12 H), 2.27 (m, 2 H), 2.36 (m, 4 H), 3.66 (s, 3 H), 4.10 (m, 1 H), 5.47 (dd, J = 15.3 Hz, J = 6.3 Hz, 1 H), 5.57 (m, 2 H), 5.72 (dt, J = 15.1, J = 7.6 Hz, 1 H), 6.10 (dd, J = 15.1 Hz, J = 10.6 Hz, 1 H), 6.17 (dd, J = 14.8 Hz, J = 10.8 Hz, 1 H), 6.28 (dd, J = 14.7 Hz, J = 10.6 Hz, 2 H), 6.38 (m, 1 H), 7.04 (dd, J = 17.7 Hz, J = 10.6 Hz, 1 H); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = −4.8, −4.4, 13.6, 17.5, 24.6, 24.8, 25.8, 26.8, 27.8, 33.8, 42.1, 51.5, 73.1, 83.2, 128.2, 130.7, 132.6, 132.6, 133.8, 134.3, 135.3, 136.7, 149.7, 173.4; HR-MS (ESI): found m/z = 525.3187 ($C_{28}H_{47}0_5SiNa$), calculated m/z = 525.3183.

Pinacolborane 37b. The following process was executed in the dark. $Pd(CH_3CN)_2Cl_2$ (1.44 mg, 5.55 µmol, 5.0 mol%) was added to a solution of the iodide **10** (50.0 mg, 111 µmol, 1.0 equiv.) and the stannane **6b** (55.2 mg, 111 µmol, 1.0 equiv.) in degassed, anhydrous DMF (400 µL) in an amber glass septum vial. After stirring for 4 h the reaction mixture was diluted with 6 mL of diethyl ether and washed with a saturated aqueous solution of NH_4Cl (6 mL). The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 5 mL).

The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, petroleum ether–ethyl acetate, 40 : 1–20 : 1) afforded the product **26b** (40.1 mg, 75.6 μmol, 68%) as a slightly yellow liquid. R_f = 0.21 (petroleum ether–ethyl acetate, 20 : 1); $[\alpha]_D^{22}$ = +7.60 (c = 1.00, $CHCl_3$); ^{1}H NMR (300.132 MHz, $CDCl_3$): δ = 0.00 (s, 3 H), 0.02 (s, 3 H), 0.88 (s, 9 H), 1.27 (s, 12 H), 2.24 (m, 6 H), 2.36 (m, 4 H), 3.67 (s, 3 H), 4.07 (q, J = 6.1 Hz, 1 H), 5.57 (m, 5 H), 6.09 (m, 4 H), 6.63 (dt, J = 18.0 Hz, J = 5.8 Hz, 1 H); ^{13}C NMR (75.57 MHz, $CDCl_3$): δ = −4.8, −4.4, 18.2, 24.8, 25.9, 27.4, 31.4, 33.8, 35.5, 42.1, 51.5, 73.3, 83.0, 128.0, 130.2, 130.8, 131.0, 131.2, 132.6, 133.4, 153.4, 173.4; HR-MS (ESI): found m/z = 553.3504 ($C_{30}H_{51}B0_5SiNa$), calculated m/z = 553.3497.

Tris-TBS ether 38a. The reaction was conducted in an amber glass septum vial in the absence of light. The iodide **8a** (46.6 mg, 99.0 μmol, 1.0 equiv.) and the pinacol borane **37a** (69.5 mg, 138 μmol, 1.4 equiv.) were diluted in anhydrous DMF (500 μL). Pd(dppf)Cl_2 (11.0 mg, 15.0 μmol, 15 mol%) and $Ba(OH)_2{\cdot}8H_2O$ (93.8 mg, 297 μmol, 3.0 equiv.) were added to the vigorous stirring solution sequentially. After stirring for 4 h the reaction mixture was quenched with diethyl ether (6 mL) and water (10 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. After purification by column chromatography (SiO_2, petroleum ether–ethyl acetate, 40 : 1) the product **38a** (34.7 mg, 48.2 μmol, 49%) was obtained as a clear, yellow liquid. R_f = 0.37 (petroleum ether–ethyl acetate, 40 : 1); $[\alpha]_D^{22}$ = +23.9 (c = 1.00, $CHCl_3$); ^{1}H NMR (600.130 MHz, $CDCl_3$): δ = 0.00 (s, 3 H), 0.01 (s, 3 H), 0.02 (s, 3 H), 0.04 (s, 9 H), 0.80 (d, J = 6.9 Hz, 3 H), 0.88 (s, 9 H), 0.89 (s, 9 H), 0.90 (s, 9 H), 1.78 (dt, J = 12.7 Hz, J = 6.4 Hz, 1 H), 2.27 (m, 2 H), 2.34 (m, 2 H), 2.39 (m, 2 H), 3.49 (dd, J = 9.8 Hz, J = 6.1 Hz, 1 H), 3.54 (dd, J = 9.9 Hz, J = 6.3 Hz, 1 H), 3.67 (s, 3 H), 4.10 (m, 1 H), 4.20 (m, 1 H), 5.48 (dd, J = 15.4 Hz, J = 6.2 Hz, 1 H), 5.57 (dt, J = 15.2 Hz, J = 6.3 Hz, 1 H), 5.66 (dq, J = 14.7 Hz, J = 7.3 Hz, 2 H), 6.09 (dd, J = 14.7 Hz, J = 9.6 Hz, 1 H), 6.22 (m, 7 H); ^{13}C NMR (150.90 MHz, $CDCl_3$): δ = −5.5, −5.4, −5.0, −4.8, −4.4, −4.2, 12.3, 18.2, 18.2, 18.3, 25.8, 25.9, 25.9, 27.4, 33.8, 42.2, 42.8, 51.5, 64.8, 73.2, 74.3, 128.1, 130.8, 131.3, 131.3, 132.3, 132.4, 132.4, 132.8, 133.0, 133.1, 134.3, 135.3, 173.4; HR-MS (ESI): found m/z = 741.4741 ($C_{40}H_{74}0_5Si_3Na$), calculated m/z = 741.4736.

Tris-TBS ether 38b. The following process was executed in the dark and conducted in an amber glass septum vial. The iodide **8a** (26.9 mg, 57.2 μmol, 1.0 equiv.) and the pinacol borane **37b** (42.5 mg, 80.1 μmol, 1.4 equiv.) were diluted in anhydrous DMF (500 μL). Pd(dppf)Cl_2 (6.30 mg, 8.60 μmol, 15 mol%) and $Ba(OH)_2{\cdot}8H_2O$ (54.0 mg, 171 μmol, 3.0 equiv.) were added to the vigorous stirring solution sequentially. After 3.5 h of stirring Pd(dppf)Cl_2 (6.30 mg, 8.60 μmol, 15 mol%) was added again and the reaction mixture was stirred for overall 4.5 h. For purification diethyl ether (20 mL) and water (20 mL) were added to the reaction mixture. After separation of the organic phase the aqueous phase was extracted with diethyl ether (3 × 25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. After purification by column chromatography (SiO_2, petroleum ether–ethyl acetate, 40 : 1) the product **38b** (20.1 mg, 26.9 μmol, 47%) was obtained as a clear, slightly yellow liquid. R_f = 0.51 (petroleum ether–ethyl acetate, 40 : 1); $[\alpha]_D^{22}$ = +7.60 (c = 1.00, $CHCl_3$); ^{1}H NMR (300.132 MHz, $CDCl_3$): δ = 0.00 (s, 3 H), 0.01 (s, 3 H), 0.02 (s, 3 H), 0.04 (s, 9 H), 0.80 (d, J = 7.0 Hz, 3 H), 0.88 (s, 9 H), 0.89 (s, 9 H), 0.90 (s, 9 H), 1.76 (dt, J = 12.8 Hz, J = 6.4 Hz, 1 H), 2.22 (m, 6 H), 2.37 (m, 4 H), 3.47 (dd, J = 9.9 Hz, J = 6.2 Hz, 1 H), 3.55 (dd, J = 9.9 Hz, J = 6.2 Hz, 1 H), 3.67 (s, 3 H), 4.10 (m, 2 H), 5.58 (m, 7 H), 6.07 (m, 5 H); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = −5.5, −5.4, −4.9, −4.8, −4.4, −4.2, 12.4, 18.2, 18.2, 18.3, 25.9, 25.90, 26.0, 27.4, 32.5, 32.6, 33.8, 42.1, 42.7, 51.5, 64.8, 73.3, 74.4, 128.0, 130.2, 130.3, 130.7, 130.9, 131.0, 131.2, 132.6, 132.7, 133.0, 133.6, 134.4, 173.4; HR-MS (ESI): found m/z = 769.5052 ($C_{42}H_{78}0_5Si_3Na$), calculated m/z = 769.5049.

Bis-TBS ether 39a. The following process was executed in the absence of light and conducted in an amber glass septum vial. The iodide **8b** (6.77 mg, 14.2 μmol, 1.0 equiv.) and the borane **37a** (10.0 mg, 19.9 μmol, 1.4 equiv.) were diluted in anhydrous DMF (100 μL). Pd(dppf)Cl_2 (3.12 mg, 4.26 μmol, 30 mol%) and $Ba(OH)_2{\cdot}8H_2O$ (13.4 mg, 42.6 μmol, 3.0 equiv.) were added to the vigorous stirring solution sequentially and the reaction mixture was stirred for 4 h. For purification diethyl ether (6 mL) and water (10 mL) were added. After separation of the organic phase the aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. After purification by column chromatography (SiO_2, petroleum ether–ethyl acetate, 40 : 1) the product **39a** (7.90 mg, 10.9 μmol, 77%) was obtained as a clear, yellow liquid. R_f = 0.17 (petroleum ether–ethyl acetate, 20 : 1); $[\alpha]_D^{22}$ = +12.03 (c = 1.00, $CHCl_3$); ^{1}H NMR (500.132 MHz, $CDCl_3$): δ = 0.00 (s, 3 H), 0.02 (s, 3 H), 0.03 (s, 3 H), 0.04 (s, 3 H), 0.89 (m, 21 H), 1.93 (dt, J = 12.3 Hz, J = 6.2 Hz, 1 H), 2.34 (m, 2 H), 2.26 (m, 2 H), 3.32 (dd, J = 8.8 Hz, J = 6.3 Hz, 1 H), 3.41 (dd, J = 8.8 Hz, J = 6.3 Hz, 1 H), 3.67 (s, 3 H), 3.81 (s, 3 H), 4.16 (m, 2 H), 4.37 (d, J = 11.5 Hz, 1 H), 4.45 (d, J = 11.5 Hz, 1 H), 5.48 (dd, J = 15.4 Hz, J = 6.0 Hz, 1 H), 5.57 (m, 1 H), 5.64 (m, 1 H), 5.71 (m, 2 H), 6.33 (m, 7 H), 6.88 (d, J = 8.5 Hz, 2 H), 7.26 (d, J = 9.3 Hz, 2 H); ^{13}C NMR (125.76 MHz, $CDCl_3$): δ = −4.9, −4.8, −4.4, −4.2, 12.9, 14.2, 18.2, 18.2, 25.8, 25.9, 27.4, 33.8, 40.5, 42.2, 51.5, 55.2, 60.4, 72.0, 72.6, 73.2, 74.6, 113.7, 128.1, 129.2, 130.8, 130.9, 131.3, 131.4, 132.3, 132.4, 132.5, 132.8, 133.1, 133.2, 134.3, 135.1, 159.0, 173.4; HR-MS (ESI): found m/z = 747.4452 ($C_{42}H_{68}0_6Si_2Na$), calculated m/z = 747.4447.

Bis-TBS ether 39b. The following process was executed in the dark and conducted in an amber glass septum vial. The iodide **8b** (6.43 mg, 13.5 μmol, 1.00 equiv.) and the pinacol borane **37b** (10.0 mg, 18.9 μmol, 1.4 equiv.) were diluted in anhydrous DMF (50 μL). Pd(dppf)Cl_2 (2.96 mg, 1.60 μmol, 30 mol%) and $Ba(OH)_2{\cdot}8H_2O$ (12.7 mg, 40.5 μmol, 3.0 equiv.) were added to the vigorous stirring solution sequentially. The reaction mixture was stirred for 4 h. For purification diethyl ether (6 mL) and water (10 mL) were added to the reaction mixture.

After separation of the organic phase the aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. After purification by column chromatography (SiO_2, petroleum ether–ethyl acetate, 40 : 1) the product **39b** (8.40 mg, 11.2 μmol, 83%) was obtained as a clear, slightly yellow liquid. R_f = 0.33 (petroleum ether–ethyl acetate, 40 : 1); $[\alpha]_D^{22}$ = +76.1 (c = 1.00, $CHCl_3$); ^{1}H NMR (600.130 MHz, $CDCl_3$): δ = 0.00 (s, 3 H), 0.01 (s, 3 H), 0.03 (s, 6 H), 0.88 (s, 21 H), 1.91 (dquin, J = 12.8 Hz, J = 6.5 Hz, 1 H), 2.22 (m, 6 H), 2.35 (t, J = 6.2 Hz, 2 H), 2.39 (m, 2 H), 3.30 (dd, J = 9.1 Hz, J = 6.7 Hz, 1 H), 3.43 (dd, J = 9.0 Hz, J = 5.9 Hz, 1 H), 3.67 (s, 3 H), 3.81 (s, 3 H), 4.08 (m, 1 H), 4.12 (t, J = 6.5 Hz, 1 H), 4.38 (d, J = 11.6 Hz, 1 H), 4.44 (d, J = 11.6 Hz, 1 H), 5.55 (m, 7 H), 6.06 (m, 5 H), 6.88 (d, J = 8.5 Hz, 2 H), 7.26 (d, J = 9.9 Hz, 2 H); ^{13}C NMR (150.90 MHz, $CDCl_3$): δ = −4.9, −4.8, −4.4, −4.1, 13.0, 18.2, 18.2, 25.9, 25.9, 27.4, 32.5, 32.5, 33.8, 40.4, 42.1, 51.5, 55.2, 72.1, 72.6, 73.3, 74.7, 113.7, 128.0, 129.1, 130.2, 130.2, 130.8, 130.9, 130.9, 131.0, 131.1, 132.6, 132.6, 133.1, 133.5, 134.3, 159.0, 173.5; HR-MS (ESI): found m/z = 775.4757 ($C_{44}H_{72}0_6Si_2Na$), calculated m/z = 775.4759.

Triol 4a. The following process was executed in the dark and conducted in an amber glass septum vial. To a stirred solution of TBS ether **38a** (19.8 mg, 27.5 μmol, 1.0 equiv.) in dry THF (1 mL) was added TBAF (193 μL, 1 M in THF, 193 μmol, 7.0 equiv.). After stirring the reaction overnight $CaCO_3$ (27.5 mg, 275 μmol, 10 equiv.), DOWEX 50WX8-200 (82.5 mg) and methanol (330 μL) were added and the resulting suspension was stirred at room temperature for 1 h. All insoluble materials were removed by filtration through a short pad of silica gel. The filter cake was washed with Et_2O thoroughly and the combined filtrates were concentrated *in vacuo*. Purification of the crude product by preparative TLC (SiO_2, petroleum ether–ethyl acetate, 1 : 3) afforded triol **4a** (6.10 mg, 16.2 μmol, 59%) as a shiny yellow, oily liquid. R_f = 0.26 (petroleum ether–ethyl acetate, 1 : 3); $[\alpha]_D^{22}$ = +0.30 (c = 0.54, $CHCl_3$); ^{1}H NMR (500.132 MHz, $CDCl_3$): δ = 0.86 (d, J = 7.1 Hz, 3 H), 1.82 (m, 1 H), 2.38 (m, 6 H), 3.53 (m, 2 H), 3.68 (s, 3 H), 4.11 (m, 2 H), 5.63 (m, 5 H), 6.12 (m, 7 H); ^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 13.6, 27.4, 33.6, 40.5, 41.0, 51.6, 67.5, 71.9, 78.5, 129.8, 130.2, 131.7, 131.8, 132.1, 132.2, 132.5, 133.1, 133.3, 133.8, 133.8, 134.6, 173.4; HR-MS (ESI): found m/z = 399.2143 ($C_{22}H_{32}0_5Na$), calculated m/z = 399.2142.

Triol 4b. The following process was executed in the dark and conducted in an amber glass septum vial. To a stirred solution of TBS ether **38b** (20.0 mg, 26.8 μmol, 1.0 equiv.) in dry THF (1 mL) was added TBAF (188 μL, 1 M in THF, 188 μmol, 7.0 equiv.). After stirring the reaction overnight $CaCO_3$ (26.8 mg, 268 μmol, 10 equiv.), DOWEX 50WX8-200 (80.4 mg) and methanol (320 μL) were added and the resulting suspension was stirred at room temperature for 1 h. All insoluble materials were removed by filtration through a short pad of silica gel. The filter cake was washed with Et_2O thoroughly and the combined filtrates were concentrated *in vacuo*. Purification of the crude product by preparative TLC (SiO_2, petroleum ether–ethyl acetate, 1 : 3) afforded triol **4b** (10.3 mg, 25.5 μmol, 95%) as a colourless, oily liquid. R_f = 0.31 (petroleum ether–ethyl acetate, 1 : 3); $[\alpha]_D^{22}$ = +1.20 (c = 1.00, $CHCl_3$); ^{1}H NMR (500.132 MHz, $CDCl_3$): δ = 0.85 (d, J = 6.9 Hz, 2 H), 1.82 (ddt, J = 14.5 Hz, J = 10.8 Hz, J = 7.3 Hz, J = 7.3 Hz, 1 H), 2.34 (m, 10 H), 3.65 (m, 2 H), 3.68 (s, 3 H), 4.05 (t, J = 7.7 Hz, 1 H), 4.13 (dt, J = 11.9 Hz, J = 5.8 Hz, 1 H), 5.63 (m, 6 H), 6.12 (m, 6 H); ^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 13.6, 27.4, 32.4, 32.4, 33.6, 40.5, 41.0, 51.6, 67.6, 71.8, 78.6, 128.8, 129.7, 129.8, 130.6, 130.9, 131.9, 132.2, 132.2, 133.4, 133.9, 133.9, 134.9, 173.4; HR-MS (ESI): found m/z = 427.2459 ($C_{24}H_{36}0_5Na$), calculated m/z = 427.2455.

Diol 4c. The following process was executed in the dark and conducted in an amber glass septum vial. To a stirred solution of TBS ether **39a** (10.0 mg, 13.8 μmol, 1.0 equiv.) in dry THF (1 mL) was added TBAF (69 μL, 1 M in THF, 69.0 μmol, 5.0 equiv.). After stirring the reaction overnight $CaCO_3$ (13.8 mg, 138 μmol, 10 equiv.), DOWEX 50WX8-200 (41.4 mg) and methanol (165 μL) were added and the resulting suspension was stirred at room temperature for 1 h. All insoluble materials were removed by filtration through a short pad of silica gel. The filter cake was washed with Et_2O thoroughly and the combined filtrates were concentrated *in vacuo*. Purification of the crude product by preparative TLC (SiO_2, petroleum ether–ethyl acetate, 1 : 1) afforded the diol **4c** (2.00 mg, 4.03 μmol, 29%) as a shiny yellow, oily liquid. R_f = 0.30 (petroleum ether–ethyl acetate, 1 : 1); $[\alpha]_D^{22}$ = +0.80 (c = 0.12, $CHCl_3$); ^{1}H NMR (399.982 MHz, $CDCl_3$): δ = 0.89 (d, J = 7.1 Hz, 3 H), 1.91 (ddd, J = 13.9 Hz, J = 6.9 Hz, J = 4.2 Hz, 1 H), 2.37 (m, 6 H), 3.43 (dd, J = 8.9 Hz, J = 7.7 Hz, 1 H), 3.58 (dd, J = 9.4 Hz, J = 4.1 Hz, 1 H), 3.68 (s, 3 H), 3.81 (s, 3 H), 4.08 (t, J = 6.7 Hz, 1 H), 4.13 (m, 1 H), 4.45 (s, 2 H), 5.55 (dd, J = 15.4 Hz, J = 6.4 Hz, 1 H), 5.69 (m, 4 H), 6.24 (m, 7 H), 6.89 (d, J = 8.5 Hz, 2 H), 7.25 (d, J = 8.5 Hz, 2 H); ^{13}C NMR (150.90 MHz, $CDCl_3$): δ = 13.8, 27.4, 29.7, 33.6, 38.9, 41.1, 51.6, 55.3, 71.9, 73.1, 74.3, 77.1, 113.7, 113.9, 129.3, 129.4, 129.8, 130.0, 131.5, 132.0, 132.4, 132.8, 132.9, 133.0, 133.1, 133.3, 134.0, 135.0, 159.0, 173.7; HR-MS (ESI): found m/z = 519.2713 ($C_{30}H_{40}0_6Na$), calculated m/z = 519.2717.

Diol 4d. The following process was executed in the dark and conducted in an amber glass septum vial. To a stirred solution of TBS ether **39b** (12.5 mg, 16.6 μmol, 1.0 equiv.) in dry THF (1 mL) was added TBAF (83 μL, 1 M in THF, 83.0 μmol, 5.0 equiv.). After stirring the reaction overnight $CaCO_3$ (16.6 mg, 166 μmol, 10 equiv.), DOWEX 50WX8-200 (49.8 mg) and methanol (200 μL) were added and the resulting suspension was stirred at room temperature for 1 h. All insoluble materials were removed by filtration through a short pad of silica gel. The filter cake was washed with Et_2O thoroughly and the combined filtrates were concentrated *in vacuo*. Purification of the crude product by preparative TLC (SiO_2, petroleum ether–ethyl acetate, 1 : 1) afforded the diol **4d** (5.30 mg, 10.1 μmol, 61%) as a light yellow, oily liquid. R_f = 0.37 (petroleum ether–ethyl acetate, 1 : 1); $[\alpha]_D^{22}$ = +4.20 (c = 0.52, $CHCl_3$); ^{1}H NMR (300.132 MHz, $CDCl_3$): δ = 0.88 (d, J = 7.0 Hz, 3 H), 1.90 (m, 1 H), 2.32 (m, 10 H), 3.44 (dd, J = 9.1 Hz, J = 7.4 Hz, 1 H), 3.57 (dd, J = 9.2 Hz, J = 4.4 Hz, 1 H), 3.68 (s, 3 H), 3.81 (s, 3 H), 4.03 (t, J = 6.9 Hz, 1 H), 4.13 (t, J = 6.3 Hz, 1 H), 4.45 (s, 2 H), 5.64

(m, 6 H), 6.12 (m, 6 H), 6.89 (d, J = 8.7 Hz, 3 H), 7.25 (d, J = 9.1 Hz, 3 H); ^{13}C NMR (150.90 MHz, $CDCl_3$): δ = 13.8, 27.4, 29.7, 32.4, 32.5, 33.6, 38.9, 41.0, 51.6, 55.3, 71.8, 73.1, 74.4, 113.8, 128.6, 129.3, 129.7, 129.9, 130.1, 130.5, 130.7, 131.6, 132.0, 132.4, 133.3, 133.9, 133.9, 134.1, 159.3, 173.4; HR-MS (ESI): found m/z = 547.3047 ($C_{32}H_{44}0_6Na$), calculated m/z = 547.3030.

Pinacolborane 40. The following process was executed in the dark. $Pd(CH_3CN)_2Cl_2$ (1.00 mg, 3.78 μmol, 5.0 mol%) was added to a solution of the iodide **9** (35.1 mg, 75.6 μmol, 1.0 equiv.) and the stannane **5** (56.1 mg, 113 μmol, 1.5 equiv.) in degassed, anhydrous DMF (300 μL) in an amber glass septum vial. After stirring for 4 h the reaction mixture was diluted with 3 mL of diethyl ether and washed with a saturated aqueous solution of NH_4Cl (5 mL). The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, petroleum ether–ethyl acetate, 40 : 1–20 : 1) afforded the product **40** (36.5 mg, 67.3 μmol, 89%) as a slightly yellow liquid. R_f = 0.24 (petroleum ether–ethyl acetate, 20 : 1); ^{1}H NMR (300.132 MHz, $CDCl_3$): δ = −0.01 (br. s, 3 H), 0.01 (br. s, 3 H), 0.86 (s, 9 H), 1.28 (s, 12 H), 1.62 (br. s, 3 H), 2.27 (m, 6 H), 3.67 (s, 3 H), 4.35 (m, 1 H), 5.16 (d, J = 7.4 Hz, 1 H), 5.57 (m, 1 H), 5.71 (td, J = 15.0 Hz, J = 7.5 Hz, 1 H), 6.30 (m, 8 H), 7.05 (dd, J = 17.4 Hz, J = 10.3 Hz, 1 H); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = −4.8, −4.3, 16.6, 18.2, 24.8, 25.8, 29.7, 32.7, 34.3, 42.1, 51.6, 69.7, 83.2, 129.5, 130.9, 131.9, 132.4, 132.6, 133.3, 134.0, 134.5, 135.5, 136.7, 149.7, 173.6; HR-MS (ESI): found m/z = 565.3498 ($C_{31}H_{51}B0_5SiNa$), calculated m/z = 565.3497.

Pinacolborane 42. The following process was executed in the dark. $Pd(CH_3CN)_2Cl_2$ (2.70 mg, 10.3 μmol, 5.0 mol%) was added to a solution of the iodide **7** (100 mg, 204 μmol, 1.0 equiv.) and the stannane **5** (151 mg, 306 μmol, 1.5 equiv.) in degassed, anhydrous DMF (2 mL) in an amber glass septum vial. After stirring for 12 h the reaction mixture was diluted with 10 mL of diethyl ether and washed with a saturated aqueous solution of NH_4Cl (20 mL). The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, petroleum ether–ethyl acetate, 30 : 1) afforded the product **42** (77.3 mg, 136 μmol, 67%) as an orange oil. R_f = 0.12 (petroleum ether–ethyl acetate, 30 : 1); $[\alpha]_D^{22}$ = +12.1 (c = 1.13, $CHCl_3$); ^{1}H NMR (300.132 MHz, $CDCl_3$): δ = −0.03 (s, 3 H), 0.01 (s, 3 H), 0.86 (s, 9 H), 0.88 (d, J = 4.1 Hz, 3 H), 1.29 (s, 12 H), 1.79 (s, 3 H), 1.93 (m, 1 H), 3.35 (dd, J = 8.9 Hz, J = 6.3 Hz, 1 H), 3.43 (dd, J = 9.1 Hz, J = 5.6 Hz, 1 H), 3.81 (s, 3 H), 4.40 (m, 2 H), 4.48 (dd, J = 9.2 Hz, J = 6.5 Hz, 1 H), 5.48 (d, J = 9.2 Hz, 1 H), 5.56 (d, J = 17.6 Hz, 1 H), 6.34 (m, 4 H), 6.88 (d, J = 8.5 Hz, 2 H), 7.07 (dd, J = 17.6 Hz, J = 10.0 Hz, 1 H), 7.25 (d, J = 9.6 Hz, 2 H); ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = −5.0, −4.2, 12.9, 13.0, 13.6, 17.5, 18.1, 24.8, 25.8, 26.8, 27.8, 40.9, 55.3, 70.7, 72.0, 72.6, 83.2, 113.7, 127.5, 129.1, 130.9, 133.7, 134.0, 136.1, 136.9, 139.7, 149.7, 159.0; HR-MS (ESI): found m/z = 591.3647 ($C_{33}H_{53}BO_5SiNa$), calculated m/z = 591.3654.

Bis-TBS ether 41. The following process was executed in the dark and conducted in an amber glass septum vial. The iodide **9** (6.43 mg, 13.5 μmol, 1.00 equiv.) and the pinacol borane **42** (10.0 mg, 18.9 μmol, 1.4 equiv.) were diluted in anhydrous DMF (50 μL). $Pd(dppf)Cl_2$ (2.96 mg, 1.60 μmol, 30 mol%) and $Ba(OH)_2{\cdot}8H_2O$ (12.7 mg, 40.5 μmol, 3.0 equiv.) were added to the vigorous stirring solution sequentially. The reaction mixture was stirred for 4 h. For purification diethyl ether (6 mL) and water (10 mL) were added to the reaction mixture. After separation of the organic phase the aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. After purification by column chromatography (SiO_2, petroleum ether–ethyl acetate, 40 : 1) the product **41** (8.40 mg, 11.2 μmol, 83%) was obtained as a clear, slightly yellow liquid. R_f = 0.40 (petroleum ether–ethyl acetate, 10 : 1); $[\alpha]_D^{22}$ = +32.7 (c = 1.17, $CHCl_3$); ^{1}H NMR (600.130 MHz, $CDCl_3$): δ = −0.04 (s, 3 H), 0.00 (s, 3 H), 0.01 (s, 3 H), 0.02 (s, 3 H), 0.86 (s, 9 H), 0.88 (m, 12 H), 1.62 (s, 3 H), 1.79 (s, 3 H), 1.91 (m, 1 H), 2.20 (m, 1 H), 2.32 (m, 3 H), 2.43 (m, 2 H), 3.35 (dd, J = 8.7 Hz, J = 6.3 Hz, 1 H), 3.43 (dd, J = 8.9 Hz, J = 5.6 Hz, 1 H), 3.67 (s, 3 H), 3.81 (s, 3 H), 4.34 (dd, J = 14.4 Hz, J = 6.6 Hz, 1 H), 4.40 (m, 2 H), 4.47 (dd, J = 9.0 Hz, J = 6.7 Hz, 1 H), 5.17 (m, 1 H), 5.44 (m, 1 H), 5.68 (m, 1 H), 6.11 (dd, J = 14.7 Hz, J = 9.5 Hz, 1 H), 6.20 (m, 1 H), 6.31 (m, 7 H), 6.88 (d, J = 8.5 Hz, 2 H), 7.26 (d, J = 8.5 Hz, 2 H); ^{13}C NMR (150.90 MHz, $CDCl_3$): δ = −5.0, −4.8, −4.3, −4.2, 13.0, 13.0, 16.7, 18.1, 18.2, 25.8, 32.6, 34.3, 40.9, 42.1, 51.6, 55.3, 69.7, 70.7, 72.0, 72.6, 113.7, 128.1, 129.1, 129.4, 130.9, 131.3, 131.6, 132.6, 132.7, 132.8, 133.0, 133.1, 133.2, 133.2, 133.9, 135.1, 137.5, 159.0, 173.6; HR-MS (ESI): found m/z = 801.4923 ($C_{46}H_{74}0_6Si_2Na$), calculated m/z = 801.4916.

Diol 3. The following process was executed in the dark and conducted in an amber glass septum vial. To a stirred solution of TBS ether **41** (19.4 mg, 24.9 μmol, 1.0 equiv.) in dry THF (1.5 mL) was added TBAF (124 μL, 1 M in THF, 124 μmol, 5.0 equiv.). After stirring the reaction overnight $CaCO_3$ (24.9 mg, 249 μmol, 10 equiv.), DOWEX 50WX8-200 (74.7 mg) and methanol (300 μL) were added and the resulting suspension was stirred at room temperature for 1 h. All insoluble materials were removed by filtration through a short pad of silica gel. The filter cake was washed with Et_2O thoroughly and the combined filtrates were concentrated *in vacuo*. Purification of the crude product by preparative TLC (SiO_2, petroleum ether–ethyl acetate, 1 : 1) afforded diol **3** (8.00 mg, 14.5 μmol, 58%) as a shiny orange, oily liquid. R_f = 0.22 (petroleum ether–ethyl acetate, 1 : 1); $[\alpha]_D^{22}$ = −1.00 (c = 0.61, $CHCl_3$); ^{1}H NMR (600.130 MHz, $CDCl_3$): δ = 0.83 (d, J = 7.0 Hz, 3 H), 1.70 (s, 3 H), 1.82 (s, 3 H), 1.94 (m, 1 H), 2.33 (m, 4 H), 2.45 (m, 2 H), 3.46 (t, J = 8.5 Hz, 1 H), 3.59 (dd, J = 9.2 Hz, J = 4.0 Hz, 1 H), 3.67 (s, 3 H), 3.81 (s, 3 H), 4.41 (m, 2 H), 4.47 (s, 2 H), 5.22 (d, J = 8.6 Hz, 1 H), 5.48 (d, J = 8.9 Hz, 1 H), 5.68 (m, 1 H), 6.25 (m, 8 H), 6.89 (d, J = 8.4 Hz, 2 H), 7.26 (d, J = 8.4 Hz, 2 H); ^{13}C NMR (150.90 MHz, $CDCl_3$): δ = 13.0, 13.4, 16.7, 32.5, 34.3,

39.2, 41.2, 51.6, 55.3, 68.0, 72.8, 73.1, 74.5, 113.8, 127.6, 128.7, 129.4, 129.8, 130.0, 132.6, 132.7, 132.9, 133.1, 133.4, 133.6, 133.6, 133.8, 136.1, 137.1, 137.4, 159.3, 173.6; HR-MS (ESI): found m/z = 573.3189 ($C_{34}H_{46}0_6Na$), calculated m/z = 573.3187.

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