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Total Synthesis of Discodermolide: Optimization of the Effective Tactic

Elsa de Lemos,^[a] François-Hugues Porée,^[a] Arnaud Bourin,^[a] Julien Barbion,^[a] Evangelos Agouridas,^[a] Marie-Isabelle Lannou,^[a] Alain Commerçon,^[b] Jean-François Betzer,^{*[a]} Ange Pancrazi,^{*[a]} Janick Ardisson^{*[a]}

Abstract: An efficient and modulable total synthesis of discodermolide (DDM), a unique anticancer polyketide of marine sponge origin is described including related alternative synthetic approaches. Particularly notable is the repeated application of crotyltitanation reaction to yield homoallylic (*Z*)-*O*-ene-carbamate alcohols in excellent selectivity. Advantage was taken of this reaction not only for the sterecontrolled building of the *syn-anti* methyl-

hydroxy-methyl triads of DDM but also for the direct construction of the terminal (*Z*)-diene. Of particular interest is also the installation of the C13-C14 (*Z*) double bond utilizing a highly selective dyotropic rearrangement. The preparation of the middle C8-C14 fragment in two sequential stages and its coupling to the C1-C7 moiety was a real challenge and required careful optimization. Several synthetic routes were explored to allow

high and reliable yields. Due to the flexibility and robust character of this approach, it might enable a systematic structural variation of DDM and therefore the elaboration and exploration of novel discodermolide structural analogues.

Keywords: discodermolide - total synthesis - allylation - cuprate rearrangement - nickel cross-coupling reaction

Introduction

In 1990, Gunasekera and co-workers reported the isolation of discodermolide (DDM) **1**,^[1] a unique polyketide marine metabolite obtained in low yields from the Caribbean deep-water sponge *Discodermia dissoluta*. Biological studies revealed DDM to be a potent microtubule-stabilizing agent that, like Taxol (Paclitaxel), arrests cells at the G2/M boundary of the cell cycle.^[2] The IC50 values reported for discodermolide in breast, prostate, colon, lung, and ovarian cancer cell lines are generally in the low nM range. Comparative studies showed that DDM was 1000-fold more active than Taxol in promoting the same microtubule polymerization/bundling. This product is also more water-soluble than taxoid compounds, and acts synergistically in combination with paclitaxel.^[3] Extensive investigation of the site and mode of binding of DDM to β -tubulin as well as the determination of its bioactive conformation led to the proposal of a pharmacophore model.^[4] Due to the potential therapeutic applications and the extreme scarcity of this compound, there has been considerable synthetic efforts directed towards DDM, culminating in several total syntheses,^[5] including development of a preparative-scale approach.^[6] Phase I clinical trials were initiated from Novartis Pharma AG; however,

despite encouraging results, trials were suspended due to adverse toxicity at higher doses.^[7] Owing to the remarkable profile of DDM and its potential as lead structure, conception and synthesis of analogues have to be developed.

In this full account, we report full details of our total synthesis of DDM **1** including related alternative synthetic approaches.^[8] Due to the flexibility and robust character of this approach, it might allow a systematic structural variation of DDM and therefore the elaboration and exploration of novel discodermolide structural analogues.

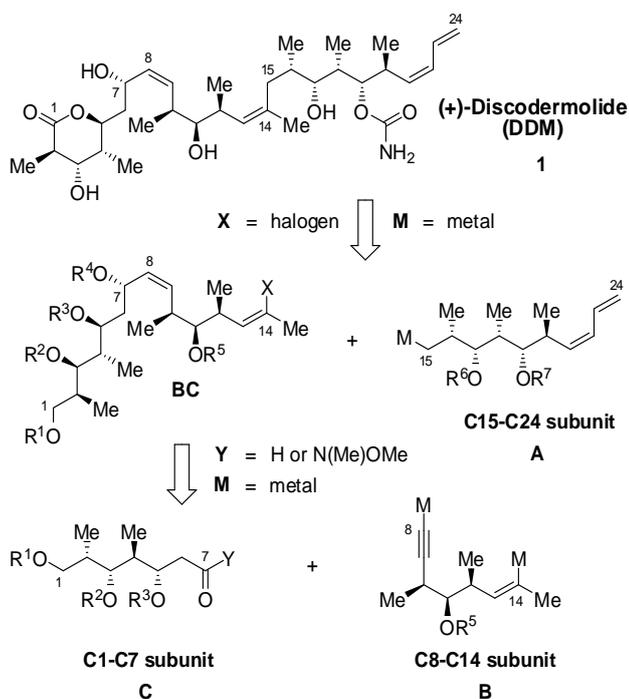
Results and Discussion

Retrosynthetic and strategic considerations: Our synthetic strategy coincides in the disassembly of DDM into three fragments of similar size and stereochemical complexity (**A** C15-C24, **B** C8-C14, **C** C1-C7) (Scheme 1). The joining of these subunits appears us to be optimally convergent, the two internal (*Z*)-alkenes C8-C9 and C13-C14 being pivotal in the choice of disconnection strategies either in acetylide addition to aldehyde/reduction sequence or Pd-catalyzed sp^2 - sp^3 coupling.

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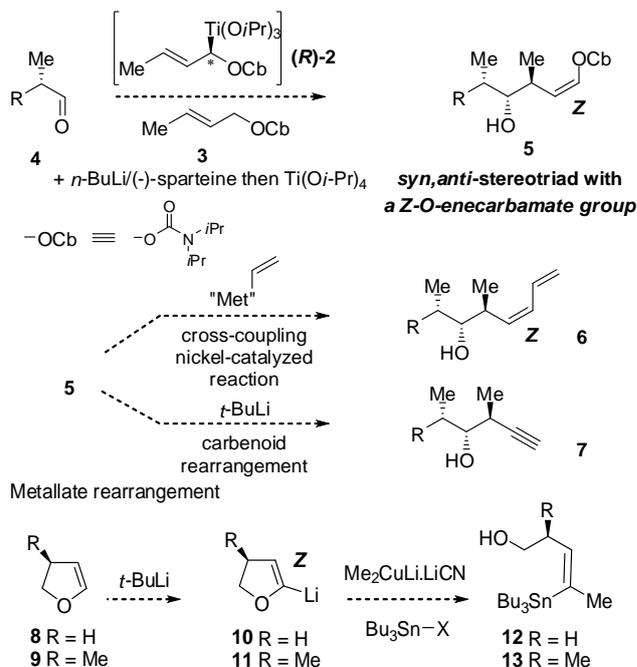
(If supporting information is submitted, please include the following line:
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Scheme 1. Retrosynthetic analysis of discodermolide.

A central feature of our approach was the repeated matched addition of the chiral secondary (*R*)-crotyltitanium reagent **2** to α -(*S*)-methyl aldehydes **4**. As exemplified in Scheme 2, this crotyltitanation reaction initially developed by Hoppe^[9] and widely used in total synthesis by our group,^[10] yielded homoallylic adducts **5** encompassing *syn-anti* methyl-hydroxy-methyl triad linked to a (*Z*)-*O*-enecarbamate group, in excellent diastereoselectivity. The enantioenriched (*R*)- α -(*N,N*-diisopropylcarbamoyloxy)-crotyltitanium **2** could easily be prepared *in situ* from the deprotonation of crotyl diisopropylcarbamate **3**, with *n*-BuLi/(*-*)-sparteine and tetra(isopropoxy)titanium.^[11]

Our plan was precisely to take advantage of the reactivity of this terminal (*Z*)-*O*-enecarbamate function in two ways. First, nickel-catalyzed cross-coupling reaction would configure the terminal C21-C24 (*Z*) diene **6** of fragment **A**,^[12] whereas a carbenoid rearrangement would install the terminal C8-C9 alkyne **7** of **B** subunit in one step.^[13]



Scheme 2. Crotyltitanation of aldehyde. Insaturations set-up from (*Z*) acyclic or cyclic enol ether.

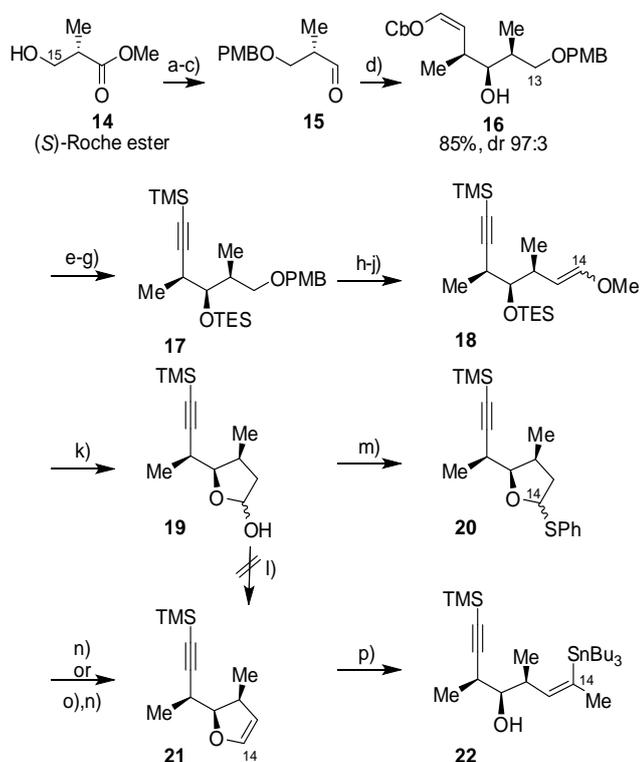
Another highlight of our strategy was the stereocontrolled building of the C13-C14 trisubstituted (*Z*) double bond. With our C14-C15 disconnection, elected by several research groups, the elaboration of the pivotal segment C8-C14 **B**, which encompassing (*Z*) vinyl halide in C-14 position, was needed for the sp^2 - sp^3 cross-coupling reaction between **A** and **B**. A (*Z*) vinyl iodide can be obtained in one step, by Zhao aldehyde olefination,^[14] but the yields were modest and the *Z/E* stereoselectivity remained disappointing.^[15] To circumvent this reaction, we considered focusing on a dyotropic rearrangement of the 5-lithiodihydrofurans **10** and **11**, obtained by metalation of cyclic enol ethers **8** and **9** leading to (*Z*)-alkenes **12** and **13**. These rearrangements of such lithiated species were first examined by Fujisawa^[16] and developed by Kocienski^[17] and our group.^[18] This attractive reaction would allow the construction of various (*Z*) or (*E*) trisubstituted double bonds, in expected good yields and a total control of their geometry.

This retrosynthetic plan should ultimately allow for modifications of every substructure embedded into the frame of the natural compounds.

Preparation of the building blocks: The recent determination of the DDM bioactive "U"-shaped conformation confirmed the crucial nature of the middle part of DDM molecule.^[4] The preparation of this C8-C14 fragment region **B** was a real challenge; the strategy involved two main stages, crotyltitanation set up of the C10-C12 *anti-syn* stereotriad and dyotropic rearrangement building of the C13-C14 trisubstituted (*Z*) double bond. Two alternative routes were examined, differing in the ordering of the two key steps.

The first sequence commenced with the commercially available (*S*)-(+)-Roche ester **14** (Scheme 3). Protection of **14** as a *p*-methoxybenzyl ether^[19] was followed by reduction of the methyl ester to the primary alcohol and subsequent oxidation to aldehyde **15**.^[20] The crotyltitanation reaction of chiral aldehyde **15**, with enantioenriched reagent (*R*)-**2** led to the desired diastereomer **16** in good yield and excellent diastereomeric ratio (97:3) (Scheme 3).

Obtention of a *O*-enecarbamate moiety during the crotyltitanation process allowed for the generation of the alkyne **17**, by a Fritsch-Buttenberg-Wiechell rearrangement.^[13] Enol **18** was readily available from **17**, after PMB ether cleavage with DDQ, IBX oxidation of the resulting alcohol and subsequent aldehyde homologation with the commercially available (methoxymethyl)triphenylphosphonium ylide. Aqueous acidic hydrolysis of the resulting enol **18** accompanied by removal of the TES group afforded lactol **19**.



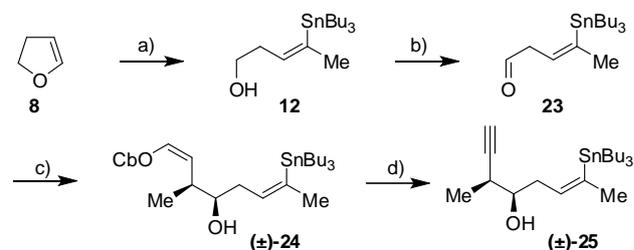
Scheme 3. a) $\text{CCl}_3\text{C}(\text{N})\text{OPMB}$, PPTS (5 mol%), $\text{CH}_2\text{Cl}_2/\text{cyclohexane}$ 1:2, RT, 40 h, 88%; b) LAH, THF, $0^\circ\text{C} \rightarrow \text{RT}$, 3 h, 95%; c) TEMPO (2 mol%), NaOCl, KBr, NaHCO_3 , $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$; d) (*R*)-**2**, cyclohexane/pentane 1:7, -78°C , 2 h, 85% (two steps, c-d), dr 97:3; e) TESOTf, 2,6-lutidine, CH_2Cl_2 , $0^\circ\text{C} \rightarrow \text{RT}$, 2 h, 97%; f) *t*-BuLi, Et_2O , $-30^\circ\text{C} \rightarrow -20^\circ\text{C}$, 45 min, 84%; g) *n*-BuLi, THF, $-78^\circ\text{C} \rightarrow 0^\circ\text{C}$, 1 h, then TMSCl, $-78^\circ\text{C} \rightarrow \text{RT}$, overnight, 92%; h) DDQ, $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ 95:5, $0^\circ\text{C} \rightarrow \text{RT}$, 30 min, 86%; i) IBX, DMSO, RT, 3 h; j) (methoxymethyl)triphenylphosphonium chloride, LiHMDS, -10°C , 1 h, 85%; k) Acetone/ H_2O 9:1, HCl, 65°C , 1 h, 61% (three steps, h-k); l) PTSA, PPTS, CuSO_4 , NH_4NO_3 or Burgess reagent; m) PhSH, $\text{BF}_3 \cdot \text{OEt}_2$, 4 Å MS, Et_2O , 1 h, 80%; n) DBU, neat, 245°C , 30%; o) *m*CPBA, NaHCO_3 , PhH, 0°C , 1 h, then, reflux, 1 h, 19%. p) *t*-BuLi, $\text{Me}_2\text{CuLi} \cdot \text{LiCN}$, THF/ Et_2O 1:2, $0^\circ\text{C} \rightarrow \text{RT}$, 3 h, then *n*-Bu₃SnCl, $-30^\circ\text{C} \rightarrow \text{RT}$, 5 h, 20%. TES=triethylsilyl, TMS=trimethylsilyl, DDQ=2,3-dichloro-5,6-dicyano-1,4-benzoquinone, IBX=2-iodoxybenzoic acid, HMDS=hexamethyldisilazane, PTSA=*p*-toluenesulfonic acid, PPTS=pyridinium *p*-toluenesulfonate, MS=molecular sieves, DBU=1,8-diazabicyclo[5.4.0]undec-7-ene, *m*CPBA=3-chloroperbenzoic acid.

We next turned to build the C13-C14 trisubstituted functionalized (*Z*) double bond via a dyotropic rearrangement. However, the envisaged transformation of lactol **19** into the 2,3-dihydrofuran (DHF) derivative **21**, turned out to be more difficult than anticipated. Specifically, all attempts to effect a direct elimination (PTSA,^[21] PPTS^[22], CuSO_4 ,^[23] NH_4NO_3 ,^[24] or Burgess reagent^[25]) from compound **19** failed to give the expected DHF **21**. Lactol **19** could be smoothly converted to hemithioketal **20**. Upon DBU pyrolysis of **20** with concomitant distillation of the elimination product,^[26] the desired dihydrofuran **21** was obtained in 30% yield. Attempts to improve this outcome by conversion of phenyl sulfide **20** into corresponding sulfoxide derivative^[27] and subsequent

elimination, delivered DHF **21** in only 19% yield. Application of dyotropic rearrangement conditions (1,2-cuprate transfer in presence of cyano-Gilman dimethylcuprate and tri-*n*-butyltin trapping) to **21** led to the expected C8-C14 segment **22** in 20% yield. This 15 steps sequence to obtain the C8-C14 subunit **22** and the very poor yield of the last two steps did not allow for providing sufficient quantities to carry on the synthesis.

The formation of the DHF ring with an alkyne part was a critical step in the synthesis. The strategy was reconsidered and an alternative tactic was suggested based on an earlier formation of DHF ring. With the same approach, we inverted the order of the crotyltitanation-dyotropic rearrangement sequence. This approach implied the introduction of C13-C14 functionalized double bond bearing a metallic or halide function in a very early stage of synthesis. According to literature,^[4] we choose to introduce in C14 position, a vinyl tin function, precursor of the vinyl halide core.

Stability of the vinyl stannane function during C8-C14 subunit elaboration was a challenging problem. With the aim to determine the chemical compatibility of this moiety, we decided to construct a C12-desmethyl model (\pm)-**25** (Scheme 4). While the formation of alkene **12** in one step by metallate rearrangement with a cyano-Gilman dimethylcuprate from the commercially available 2,3-dihydrofuran **8** proceeded smoothly,^[28] significant problems were encountered during conversion of homoallylic alcohol **12** into aldehyde **23**. Extensive screening was performed. Classical oxidations as, Swern,^[29] Doering-Parikh^[30] or PCC^[31] led to decomposition with the loss of the tin function. On the other hand, milder reagents as TPAP/NMO^[32] or IBX^[33] resulted in recovery of the starting material. The Saigo-Mukaiyama protocol,^[34] employing 1,1'-(azodicarbonyl)dipiperidine (ADD) as a hydride acceptor failed, resulting only in the recovery of the starting material, despite encouraging Marshall precedence.^[35]

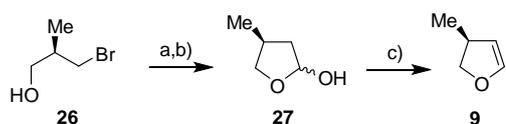


Scheme 4. a) *t*-BuLi, $\text{Me}_2\text{CuLi} \cdot \text{LiCN}$, THF/ Et_2O 1:2, $0^\circ\text{C} \rightarrow \text{RT}$, 3 h, then *n*-Bu₃SnCl, $-30^\circ\text{C} \rightarrow \text{RT}$, 5 h, 61%; b) TEMPO (10 mol%), BAIB, CH_2Cl_2 , RT, 2 h; c) (\pm)-**2** (from **3**, *n*-BuLi/TMEDA, Et_2O , Et_2O , -78°C , 2 h, 63% (two steps b and c); d) *t*-BuLi, Et_2O , $-30^\circ\text{C} \rightarrow -20^\circ\text{C}$, 30 min, 70%.

Therefore we were pleased to see that the application of TEMPO free radical and a suitable co-oxidant led to a significant improvement. Recourse to [bis(acetoxy)iodo]benzene (BAIB) as co-oxidant delivered cleanly the oxidation product.^[36] In return, fast protodesannylation upon purification or even shelf storage of **23** was observed. Therefore, the crude product was directly subjected to crotyltitanation conditions with the racemic (\pm)-**2**. The *O*-enecarbamate (\pm)-**24** was then converted into terminal alkyne (\pm)-**25** by *t*-BuLi treatment. After the difficulties encountered during the oxidation step, it was gratifying to find that the (*Z*)-vinyl stannane function was sufficiently stable toward crotyltitanation conditions and especially upon *t*-BuLi treatment. Thus 12-desmethyl C8-C14

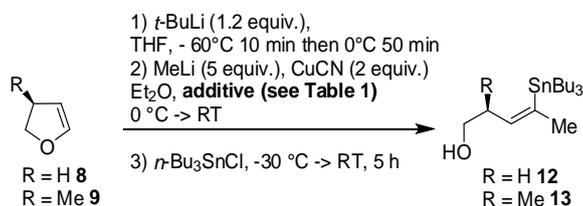
fragment (\pm)-**24** could be obtained in only 4 steps, from commercially available 2,3-dihydrofuran **8**, in 26.9% overall yield.

With secured information on tin stability in hand, the stage was set for the synthesis of DHF **9** bearing a methyl group in C12 position (DDM numbering (Scheme 5). Preparation of DHF **9** was realized from the commercially available (*R*)-3-bromo-2-methyl-1-propanol **26**. Cyanide displacement of the bromide and partial reduction of the nitrile function led to lactol **27** after spontaneous cyclisation of the γ -hydroxy aldehyde. After several protocols used, a straightforward dehydration with PTSA in quinoline with simultaneous distillation of the volatile elimination product from the reaction mixture afforded cleanly the desired DHF **9** in 85% yield and mostly in a neat form (Scheme 5).^[37] This expeditious three-step sequence furnished the enantiopure DHF **9** in 64% overall yield.



Scheme 5. a) NaCN, DMSO, 60 °C, 24 h, 92%; b) DIBAL-H, CH₂Cl₂, -78 °C, 2 h, 82%; c) PTSA, quinoline, 160 °C → 245 °C, 45 min, 85. DIBAL-H=diisobutylaluminium hydride, PTSA=*p*-toluenesulfonic acid.

DHF **9** was subjected to metallate rearrangement under the standard laboratory conditions with a cyano-Gilman dimethylcuprate to afford the expected trisubstituted (*Z*)-alkene **13** in a low 27% yield (Scheme 6, Table 1, entry 2). It was decided to investigate the influence of different reaction parameters. To this end, the solvent and/or cuprate ligands were modified with regard to the classical 1:2 THF/Et₂O solvent mixture. The results are summarized in Table 1, from commercial DHF **8** as a model. It was envisaged to activate the C-O bond of the dihydrofuran ring by addition of Lewis acids (table 1, entries 3 – 4), to promote organometallic dissociation (table 1, entries 5 – 7) or to modify the cuprate ligands in presence of TMEDA or pyridine (table 1, entries 8 – 9), but without significant effect. However, recourse to sulphur additives resulted in appreciable yields (table 1, entries 10 – 12). Thereby, a 4:1 mixture of Et₂O and dimethylsulfide (DMS) (table 1, entry 12) allowed the formation of the expected (*Z*)-alkene **12** in a satisfactory 76% yield. It was noted, however, that the magnesio-cuprates prepared from MeMgBr and CuBr.Me₂S (table 1, entry 13), versus cyanocuprates, gave disappointing results and yields remained below 22%.



Scheme 6 Cuprate rearrangement with methyl transfer from DHF **8** or **9**.

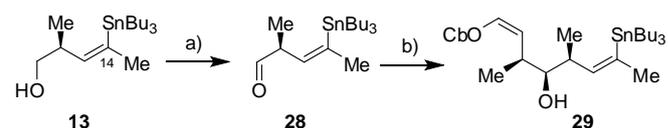
Table 1. Results of cuprate rearrangement with methyl transfer from DHF **8** or **9**.

Entry	Starting material	Additive	Conditions	(<i>Z</i>)- 12 or - 13 yield (%)
1	8	None ^{[a],[b]}	RT 3 h	61
2	9	None ^{[a],[b]}	RT 3 h	27
3	8	BF ₃ •OEt ₂ (2.5 equiv.) ^{[a],[b]}	RT 3 h	13
4	8	TMSCl (4 equiv.) ^{[a],[b]}	RT 3 h	46
5	8	HMPA (5 equiv.) ^{[a],[b]}	RT 3 h	29
6	8	DMPU (5 equiv.) ^{[a],[b]}	RT 3 h	0
7	8	DMF (20 equiv.) ^{[a],[b]}	RT 3 h	0
8	8	TMEDA (10 equiv.) ^{[a],[b]}	RT 3 h	45
9	8	Pyridine (10 equiv.) ^{[a],[b]}	RT 3 h	16
10	8	Thiophene (20 equiv.) ^{[a],[b]}	RT 12 h	55
11	8	Tetrahydrothiophene (20 equiv.) ^{[a],[b]}	RT 12 h	67
12	8	DMS (Et ₂ O/DMS 4:1) ^[b]	RT 12 h	76
13	8	None ^{[a],[c]}	RT 3 h	22
14	9	DMS (Et ₂ O/DMS 4:1) ^[b]	RT 12 h	68

[a] THF/Et₂O 1:2. [b] MeLi/CuCN. [c] MeMgBr (4 equiv.), CuBr•Me₂S (2 equiv.).

Application of optimized conditions to DHF **9** led to the (*Z*)-tin derivative **13** in a substantial 68% yield (Table 1, entry 14).

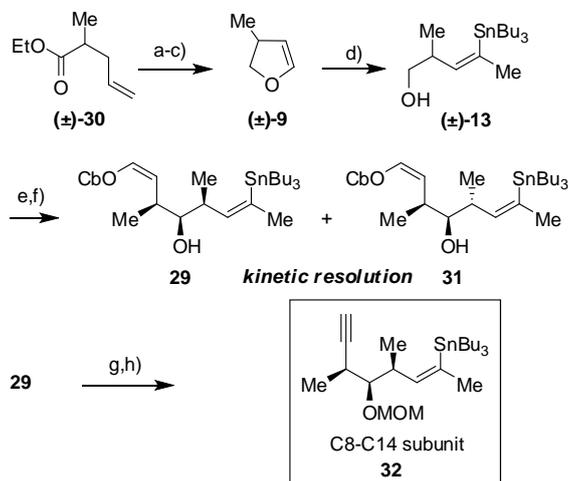
We developed a useful and efficient dimethylsulfide-promoted methyl transfer in the 1,2 cuprate rearrangement leading to (*Z*)-trisubstituted olefins. With a good supply of alkene **13** being assured, the synthesis of the C8-C14 subunit **B** was tackled. In agreement with model C12-*des*methyl series, compound **13** was converted to carbamate **29** as a single diastereomer in 84% yield after oxidation to aldehyde **28** with TEMPO/BAIB and crotyltitanation (Scheme 7). To confirm the (*S*)-C11 secondary hydroxy centre configuration, **29** was derivatized to the (*R*)- and (*S*)- α -methoxy-phenylacetic acid (MPA) ester (see experimental part).^[38]



Scheme 7. a) TEMPO (10 mol%), BAIB, CH₂Cl₂, RT, 2 h; b) (*R*)-2, cyclohexane/pentane 1:7, -78 °C, 3 h, 84% (two steps, a and b). DMS=dimethyl sulphide, TEMPO=2,2,6,6-tetramethyl-1-piperidinyloxy free radical, BAIB=[bis(acetoxy)iodo]benzene.

DHF **9** was also prepared in racemic form. After some experimentation, it was found that the most effective approach

started from the commercial available ethyl 2-methyl-4-pentenoate (\pm)-**30** (Scheme 8). Reduction of ester function followed by ozonolysis of terminal double bond and dehydration of the corresponding lactol led to the desired DHF (\pm)-**9**. Oxidation of the 1,2 cuprate transfer product (\pm)-**13** and crotyltitanation delivered the required Felkin-Anh homoallylic alcohols **29** in 42% yield and a minor diastereomer **31** in 14% yield. At this stage of the synthesis, it is important to point out that these C12-epimeric compounds **29/31** were easily separated by flash chromatography.

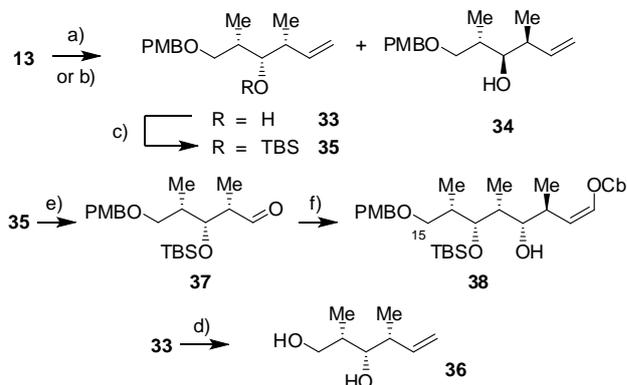


Scheme 8. a) LAH, Et₂O, 0 °C → RT, 3 h; b) O₃, sudan III, CH₂Cl₂/MeOH 1:1, -78 °C, 7 h then PPh₃, -78 °C → RT, overnight, 80% (two steps, a and b), anomeric ratio 2:1; c) PTSA, quinoline, 160 °C → 245 °C, 45 min, 85%; d) *t*-BuLi, Me₂CuLi.LiCN, Et₂O/DMS 4:1, 0 °C → RT, 18 h, then *n*-Bu₃SnCl, -30 °C → RT, 5 h, 68%; e) TEMPO (10 mol%), BAIB, CH₂Cl₂, RT, 2 h; f) (*R*)-**2**, cyclohexane/pentane 1:7, -78 °C, 3 h, compound **29** 42% (two steps, e and f) and compound **31** 14% (two steps, e and f); g) *t*-BuLi, THF, -40 °C → -20 °C, 20 min, 78%; h) MOMCl, TBAI, Hunig's base, CH₂Cl₂, RT, 18 h, 92%. LAH=lithium aluminium hydride, PTSA=*p*-toluenesulfonic acid, TEMPO=2,2,6,6-tetramethyl-1-piperidinyloxy free radical, BAIB=[bis(acetoxy)iodo]benzene, MOM=methoxymethyl, TBAI=tetra-*n*-butylammonium iodide, Hunig's base=diisopropylethylamine.

From carbamate **29**, α -elimination reaction upon a *t*BuLi treatment and subsequent C11 secondary alcohol protection as methoxymethyl ether furnished alkyne **32** (Scheme 8). Subunit **32** was obtained in eight steps in 13.9% or 26.3%, respectively from pentenoate (\pm)-**30** (with a kinetic resolution step) or enantiopure propanol **26**. However, taking into account the cost of the starting material **26** and the convenient separation of the C12-epimeric compounds, we preferred recourse to the racemic DHF (\pm)-**9** to produce C8-C14 subunit **32** on a multigram scale.

The synthesis of the C15-C24 subunit **A** started with the C16-C18 *syn-syn* motif preparation, planned by a substrate-based crotylation reaction. The addition of the achiral tri-*n*-butylcrotylstannane on chiral aldehyde **13** under Keck's conditions (BF₃·OEt₂ in CH₂Cl₂),^[39] led to a 85:15 mixture of diastereomers **33** and **34**. Felkin-Anh selectivity was optimized to 95:5 when replacing CH₂Cl₂ by Et₂O (Scheme 9). However, large scale production of **33** was impeded by difficulties associated with diastereomer separation. This difficulty was readily overcome using chiral crotylborane procedure developed by Brown.^[40] The desired homoallylic alcohol **33** was delivered cleanly in a stereospecific manner from the (*Z*)-crotyldiisopinocampheylborane reagent derived from (-)-Ipc₂B(OMe).

The absolute configuration of the stereogenic centres of **33** was confirmed by chemical correlation. Cleavage of the PMB moiety was accomplished to provide the known triol **36**. The NMR data and the specific optical rotation were in agreement with literature.^[41]



Scheme 9. a) Tri-*n*-butylcrotylstannane, BF₃·OEt₂, Et₂O, -100 °C, 2 h, 74%, dr 95:5; b) (*Z*)-2-butene, *n*-BuLi, *t*-BuOK, [(-)-Ipc]₂BOMe, BF₃·OEt₂, 65%, dr 100:0; c) TBSOTf, 2,6-lutidine, CH₂Cl₂, 0 °C → RT, 2 h, 92%; d) DDQ, CH₂Cl₂/H₂O 95:5, 0 °C → RT, 2 h, 75%; e) O₃, sudan III, Py, CH₂Cl₂/MeOH 1:1, -78 °C, 2 h then DMS, -78 °C → RT, overnight; f) (*R*)-**2**, cyclohexane/pentane 1:7, -78 °C, 3 h, 77%, dr 100:0. PMB=*p*-methoxybenzyl, PPTS=pyridium *p*-toluenesulfonate, LAH=lithium aluminium hydride, TEMPO=2,2,6,6-tetramethyl-1-piperidinyloxy free radical, Ipc=isopinocampheyl, TBS=*tert*-butyldimethylsilyl, DDQ=2,3-dichloro-5,6-dicyano-1,4-benzoquinone, TBAF=tetra-*n*-butylammonium fluoride, Py=pyridine, DMS=dimethyl sulfide.

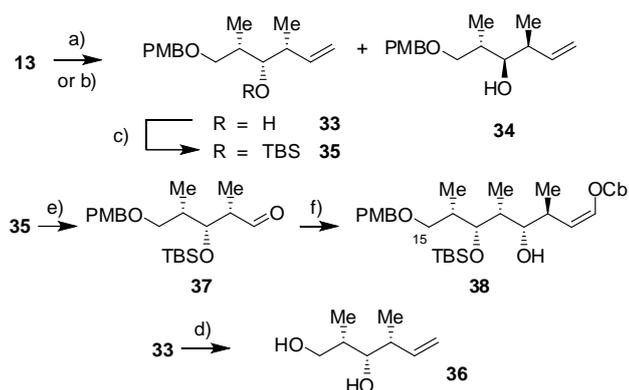
For the construction of the second C18-C20 *syn-anti* stereotriad, we selected a crotyltitanation reaction. After protection of the C17 hydroxy group of **33** as TBS ether, an oxidative cleavage of corresponding alkene **35** by ozonolysis delivered the aldehyde **37**. When the crotyltitanation reaction was realized with the chiral, non-racemic (*R*)-**2**, the desired isomer **38** was provided in 77% yield with a total stereocontrol.

On the basis of extensive precedent, we had predicted that the unique isomer from this addition would be the C18-C20 *syn-anti* stereoisomer **38**. This assignment was confirmed applying the Rychnovsky method^[42] and analysis of the ¹H NMR vicinal coupling constants of corresponding acetones (see experimental section).

Application of this crotyltitanation reaction was also instrumental in the preparation of the required terminal (*Z*)-diene. As previously described in our group,^[12] the direct vinylation of a *Z*-*O*-encarbamate moiety was performed in the presence of Ni(acac)₂ with commercially available vinylmagnesium bromide. In this way, from carbamate **39**, this reaction gave highly variable but mostly disappointing low yields (Scheme 10, see Table 2 entry 1). The cross-coupled product **40** was generated solely or as a mixture with the corresponding inseparable reduced compound **41** (selectivity varying from 100:0 to 0:100). The quality of commercial vinylmagnesium bromide solution was unreliable. Furthermore, even with the same batch, the selectivity in cross-coupled product decreased during the time of storage. We decided to prepare ourselves the vinylmagnesium bromide. Three methods were explored. First, direct insertion of magnesium into vinyl bromide^[43] led to reliable results but with a modest selectivity into the desired compound **40**, i.e. 80:20 (entry 2). The vinylmagnesium reagent was also generated in situ, by transmetalation of the vinylolithium derivative with magnesium bromide.^[44] When the vinylolithium was

produced from vinyl bromide by metal-halogen exchange,^[45] no reaction occurred (entry 3). On the other hand, the preparation of the vinylolithium from tetravinyltin and MeLi,^[46] afforded cleanly the cross-coupled product **40** in modest yield (entry 4).

The reaction with the solely vinylolithium species (without magnesium salts), produced from tetravinyltin and MeLi,^[46] led to a significant improvement (entry 5). This method allowed for the selective formation of the cross-coupled product **42** in reproducible 80% yield (no reduction product was recovered). Use of tetravinylstannane and MeLi authorized to scale up the cross-coupling reaction to 2.5 g. To the best of our knowledge, it is the first example of a C(sp²)-C(sp²) cross-coupling between a vinylolithium and a vinylic electrophilic species.^[47]



Scheme 10. a) TESOTf, 2,6-lutidine, CH₂Cl₂, 0 °C → RT, 1.5 h, 78%; b) Ni(acac)₂, Et₂O, 0 °C, overnight, vinylmagnesium bromide, see Table 1; c) DDQ, CH₂Cl₂/H₂O 95:5, 0 °C → RT, 40 min, 72%; d) I₂, PPh₃, imid, C₆H₆/Et₂O, 0 °C → RT, 2 h, 79%. TES=triethylsilyl, acac=acetylacetonate, DDQ=2,3-dichloro-5,6-dicyano-1,4-benzoquinone, imid=imidazole.

Table 2. Results of direct vinylation of a *Z*-*O*-enecarbamate under a Ni(acac)₂ catalyzed cross-coupling reaction from compound **39**.

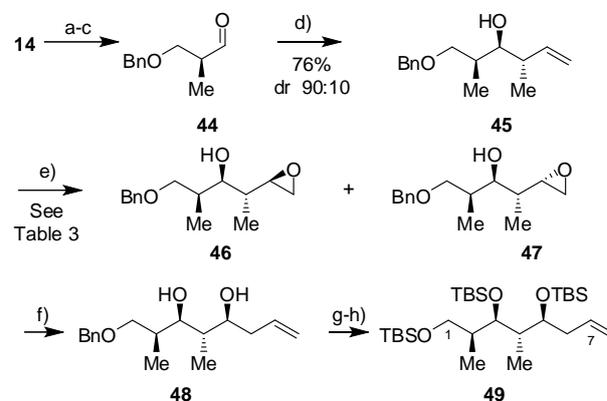
Entry	Conditions	40	41	Yield ^[a]
1	CH ₂ =CH-MgBr ^[b]	100 → 0	0 → 100	35 → 80%
2	CH ₂ =CH-Br, Mg	80	20	65%
3	CH ₂ =CH-Br, <i>t</i> -BuLi, MgBr ₂ •OEt ₂	-	-	- ^[c]
4	(CH ₂ =CH) ₄ Sn, MeLi, MgBr ₂ •OEt ₂	100	0	50% ^[d]
5	(CH ₂ =CH) ₄ Sn, MeLi	100	0	80%

[a] Isolated yield of **42** and **43** mixture. [b] Commercial reagent. [c] Only the starting material was recovered. [d] 10% of starting material was recovered.

To achieve the synthesis of subunit **43**, the PMB ether was removed by treatment with DDQ and the resulting alcohol **42** was transformed into alkyl iodide **43** under optimized Garegg conditions in a benzene/diethyl ether mixture under high dilution.^[48] The C15-C24 subunit **43**, bearing five contiguous stereogenic centres and a terminal diene, was obtained in 13.7% overall yield for 11 steps.

Our initial approach to the synthesis of the third building block C1-C7 C commenced with standard Brown crotylation of aldehyde

44 (derived from (*S*) Roche ester **14**), to afford the desired *syn-anti* homoallylic alcohol **45** in 76% yield (Scheme 11).^[49] It was envisaged to rely upon substrate-directable epoxidation/oxirane regioselective ring opening sequence for the installation of the missing C5 chiral centre.

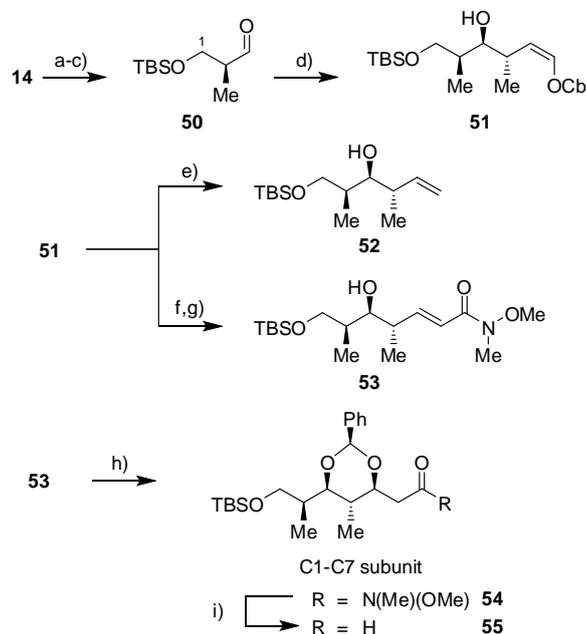


Scheme 11 a) CCl₃C(N)OBn, TfOH (5 mol%), CH₂Cl₂/cyclohexane 1:2, 0 °C → RT, 40 h, 84%; b) LAH, THF, 0 °C → RT, 3 h, 94% c) IBX, DMSO, RT, 3 h, 92%; d) (*E*)-2-butene, *n*-BuLi, *t*-BuOK, [(*-*)-Ipc]₂BOMe, BF₃•OEt₂, 76%, dr 90:10; e) VO(acac)₂, TBHP, CH₂Cl₂, 78%, dr 90:10; f) CH₂=CH-Br, *t*-BuLi, CuCN, THF, -78 °C → 0 °C, overnight, 86%; g) Li, NH₃, THF, -78 °C, 1 h; h) TBSOTf, 2,6-lutidine, CH₂Cl₂, 0 °C → RT, 3 h, 99% (two steps, g and h). Ipc=isopinocampheyl, Tf=trifluoromethanesulfonyl, LAH=lithium aluminium hydride, IBX=2-iodoxybenzoic acid, acac=acetylacetonate, TBHP=*tert*-butyl hydroperoxide, TBS=*tert*-butyldimethylsilyl.

The epoxydation of homoallylic alcohol **45** turned out to be more difficult than anticipated. The use of *m*CPBA, Mo(CO)₆/TBHP or VO(O*i*-Pr)₃/TBHP never gave more than 40% of selectivity, while recourse to VO(acac)₂/TBHP^[50] led to a significant improvement (78% yield of oxiranes **46** and **47** as a 90:10 mixture of separable diastereomers). However, upon attempted optimization and up-scaling, this reaction was not reproducible. Pure **46** was then subjected to a regioselective ring opening by a cyano-Gilman divinyl cuprate, (CH₂=CH)₂CuLi•LiCN,^[51] to ensure the formation of the alkene **48** in 86% yield. Finally, cleavage of the O-Bn group with lithium in liquid ammonia followed by silylation afforded the C1-C7 subunit **49**.

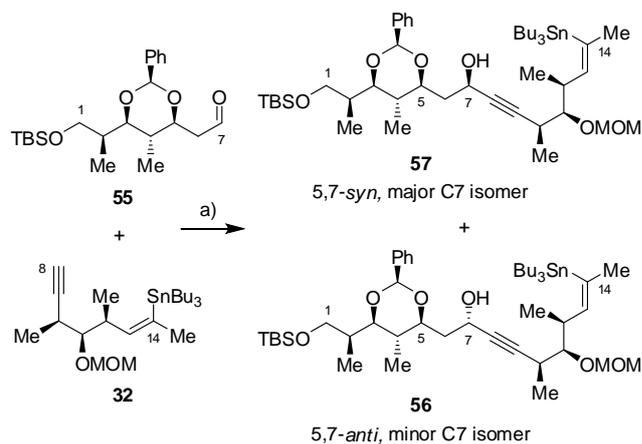
An alternative route allowed the generation of the C5 chiral centre by hetero-Michael addition on α,β -unsaturated Weinreb amide **53**, which in turn could be derived from aldehyde **50** through crotyltitanation reaction and homologation (Scheme 12). Thus, crotyltitanation of aldehyde **50** (which was prepared from (*S*) Roche ester **14**) delivered cleanly the *syn-anti* homoallylic alcohol **51**. A cross-metathesis (CM) reaction between alkene **51** and *N*-methoxy-*N*-methylacrylamide was experimented.^[52] None of the desired product was formed and most of the starting material was recovered. We suspected that the *N,N*-diisopropyl-*O*-enecarbamate function could have deleterious effects for steric or/and electronic reasons. Thus, the vinylic function of compound **51** was deoxygenated by hydride reduction with *i*-propylmagnesium bromide in a nickel catalyzed reaction to furnish **52**.^[53] More surprisingly, the CM reactions between *N*-methoxy-*N*-methylacrylamide or methyl acrylate and terminal olefinic compound **52** failed using Grubbs II or Hoveyda catalyst. Gratifyingly, a two-step sequence involving an oxidative cleavage of double bond, followed by a Horner-Wadsworth-Emmons reaction (HWE) with the commercially available diethyl (*N*-methoxy-*N*-

methylcarbamoylmethyl)phosphonate, delivered the α,β -unsaturated Weinreb amide **53**. Reaction of **53** with benzaldehyde mediated by KHMDS afforded benzylidene **54** in 79% yield with an excellent diastereoselectivity (dr > 95:5).^[54] After reduction of **54** into aldehyde **55** by treatment with DIBAL-H,^[55] the last C1-C7 subunit, bearing four stereocentres, was obtained in 32.7% overall yield for 8 steps.



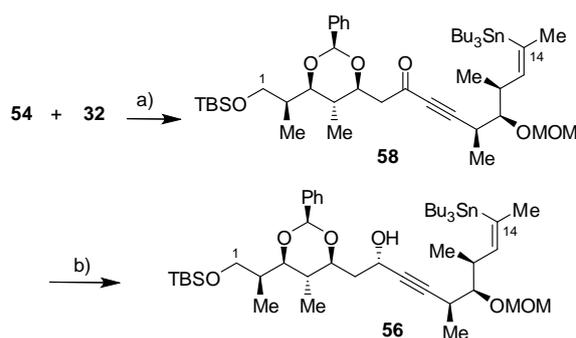
Scheme 12 a) TBSCl, imid, DMF, 0 °C \rightarrow RT, overnight, 98%; b) DIBAL-H, CH₂Cl₂, -20 °C, 30 min, 92%; c) (COCl)₂, DMSO, Et₃N, -55 °C \rightarrow RT, 1 h; d) (*R*)-**2**, cyclohexane/pentane 1:7, -78 °C, 3 h, 66% (two steps, c and d); e) Ni(acac)₂ (10 mol%), *i*-PrMgBr, THF, R.T, overnight, 50%; f) O₃, sudan III, CH₂Cl₂, -78 °C, 1 h, then PPh₃, -78 °C \rightarrow RT, 3 h, 87%; g) (EtO)₂P(O)CH₂C(O)NMe(OMe), NaH, THF, 0 °C \rightarrow RT, 45 min, 86%; h) PhCHO, KHMDS, THF, -20 °C, 45 min, 79%; i) DIBAL-H, CH₂Cl₂, -78 °C, 1 h, 93%. TBS=*tert*-butyldimethylsilyl, imid=imidazole, DIBAL-H=diisobutylaluminium, HMDS=hexamethyldisilazane.

Completion of the total synthesis of discodermolide: With access to the required fragments now reliable, the stage was set for the coupling. The first coupling reaction involved an addition of the C8-C14 acetylenic compound **32** to C1-C7 aldehyde **55** (Scheme 13). Previous observations on the stability of the sterically hindered trisubstituted *Z*-vinyl stannane provided encouraging precedence with regard to the chemoselectivity issue. Although lithiated acetylide of **32** was chemoselectively produced by action of *t*-BuLi at low temperature, its reaction with aldehyde **55** afforded a 2:1 mixture of separable C7 diastereomers **56** and **57** in modest 50% yield. To assign the C7 stereochemistry of these both epimers, each C7 isomeric secondary alcohol was independently subjected to the formation of (*R*)- and (*S*)-MPA ester derivatives (see experimental part). To our surprise, the desired and expected 5,7-*anti* diol **56** was the minor product (Scheme 13).^[56]



Scheme 13 a) **32**, *t*-BuLi, THF, -78 °C, 30 min, then **55**, -78 °C \rightarrow 0 °C, 3 h, 50%, dr 1:2.

A more appropriate solution was found with the addition of acetylenic derivative **32** on Weinreb amide **54** followed by stereoselective reduction of ynone **58** (Scheme 14). Preliminary assays were conducted using *t*-BuLi as metallating agent and afforded cleanly the desired adduct **58** in 80% yield. However, upon attempted optimization and up-scaling, this reaction was not reproducible. During these initial tries, however, it was noticed that Weinreb amide **54** was totally consumed with production of significant amount of benzaldehyde, indicating a probable retro hetero-Michael followed by a vinylogous retro-aldol reaction. After careful optimization, it was found that this addition reaction proceeded best using a solution of *n*-BuLi generated by treatment of butyl bromide by lithium metal in Et₂O,^[57] whereas protocols involving commercial *n*-BuLi, LDA or LiHMDS did not bring any significant improvement. This procedure led cleanly and faster to the desired ynone **58** in a reliable 81% yield. Subsequent reagent-controlled stereoselective reduction of **58** with (*S*)-CBS reagent^[58] provided alcohol **56** in high yield (95%) and diastereoselectivity (dr > 98:2).



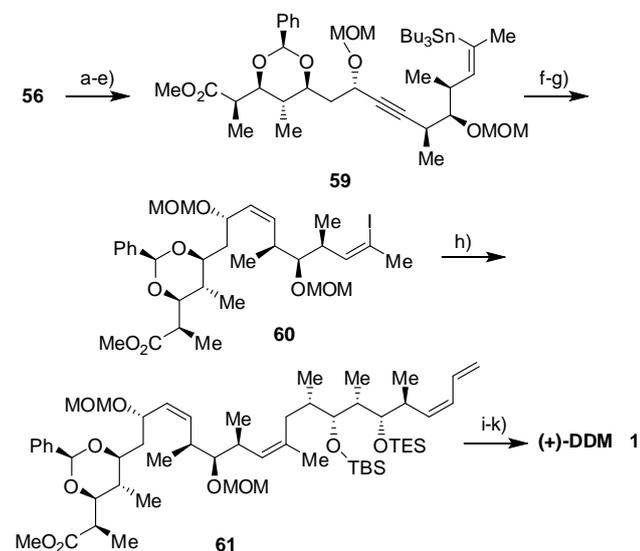
Scheme 14. a) **32**, *n*-BuLi/Et₂O, THF, -40 °C, 50 min, then **54**, -40 °C \rightarrow 0 °C, 1 h, 80%; b) (*S*)-(-)-2-Methyl-CBS-oxazaborolidine, BH₃·Me₂S, THF, -30 °C, 2 h, 95%, dr 98:2. CBS= Corey-Bakshi-Shibata.

Coupling of the two C1-C7 and C8-C14 fragments now in hand required the consecutive formation of vinyl iodide **60**, in view of an alkyl-Suzuki reaction with the C15-C24 subunit **43**. Alcohol **56** was smoothly converted to methyl ester **59** by a two-step MOM-protection and TBS-ether cleavage protocol following by oxidation of the resulting alcohol and esterification (Scheme 15). Subsequent standard Lindlar reduction of the alkyne **59** seemed optimal as

compared to discodermolide C8-C9 semi-reduction cases previously reported in the literature.^[4] However, this reduction resulted only in recovery of starting material. After some experimentation, it was found that the reaction proceeded best using PtO₂ protocol without overreduction. Consecutive iododestannylation furnished the desired (*Z*)-vinyl iodide **60** in 71% for two steps.

The stage was set for the coupling of the vinyl iodide **60** and C15-C24 sub-unit **43**. Alkyl-Suzuki reaction was performed according to Marshall et al. procedure,^[59] by using trialkyl boronate species made from alkyl iodide **43** with *t*-BuLi and *B*-methoxy-9-BBN under [Pd(dppf)Cl₂] and AsPh₃ conditions to afford the discodermolide backbone **60** in 60% yield.

Selective cleavage of the C19 TES-ether followed by reaction with trichloroacetylisocyanate furnished corresponding carbamate.^[60] Final total deprotection with concomitant lactonization following the procedure established in the previous total syntheses^[4] afforded discodermolide **1** in 70% yield. The spectroscopic and analytic data of the synthetic samples of **1** as well as their *in vitro* cytotoxicity levels were in full accord with those of the natural product reported in the literature.



Scheme 15. a) MOMCl, TBAI, Hunig's base, CH₂Cl₂, RT, 18 h, 86%; b) HF/Py, Py/THF, RT, 4 h, 96%; c) TEMPO (10 mol%), BAIB, CH₂Cl₂, RT, 3 h; d) NaClO₂, NaH₂PO₄, 2-methyl-but-2-ene, *t*-BuOH/H₂O, RT, 1 h; e) TMSCHN₂, C₆H₆/MeOH, RT, 15 min, 66% (three steps, c-e); f) H₂, PtO₂ (30 mol%), AcOEt, RT, 12 h; g) **2**, CH₂Cl₂, 0 °C, 10 min, 71% (two steps, f and g); h) **43**, *t*-BuLi, Et₂O, -78 °C, 5 min, *B*-methoxy-9-BBN, THF, -78 °C → RT, then **60**, CsCO₃, PdCl₂dppf, AsPh₃, DMF, H₂O, 18 h, 60%; i) PTSA, MeOH, 0 °C, 1 h, 77%; j) Cl₃CC(O)NCO, CH₂Cl₂, RT, 15 min, then K₂CO₃, MeOH, RT, 1.5 h, 64%; k) HCl 4N, THF, RT, 72 h, 70%. MOM=methoxymethyl, TBAI=tetra-*n*-butylammonium iodide, Py=pyridine, TEMPO=2,2,6,6-tetramethyl-1-piperidinyloxy free radical, TMS=trimethylsilyl, BBN=borabicyclo[3.3.1]nonane, dppf=(diphenylphosphino)ferrocene.

Conclusion

The investigation outlined above resulted in a total synthesis of the anticancer marine metabolite discodermolide **1** in 1.6% overall yield over 21 linear steps. The chosen approach bears witness to the maturity of crotyltitanation reaction with enantiomerically-defined secondary crotyltitanate reagent. The repeated application of this reaction yielded homoallylic (*Z*)-O-enecarbamate alcohols **16**, **29**, **38** and **51** in excellent diastereoselectivity. Moreover, advantage

was taken of these alkenyl carbamates to form the next carbon-carbon bond. Particularly notable is the direct construction of the terminal C21-C24 (*Z*) diene **40**, with high geometric control, utilizing an original cross-coupling nickel-catalyzed reaction. Another highlight of our strategy was the 1,2 cuprate rearrangement of the dihydrofuran **9** leading to the stereocontrolled building of the C13-C14 trisubstituted (*Z*) alkene **13** with total selectivity.

Of the key steps employed en route to **1**, the most significant problems were posed by the methyl transfer during the C13-C14 trisubstituted (*Z*) double bond installation, the construction of the middle C8-C14 fragment in two sequential stages (dyotropic rearrangement/crotyltitanation), and the coupling of the C8-C14 acetylenic sub-unit to the C1-C7 moiety. After careful optimization, these reactions allowed high and reliable yields. Hence, this study illustrates the notion that the total synthesis of complex target molecules remains the ultimate test for the performance, scope and limitations of any newly development methodology.

The strategy is flexible enough to accommodate systematic structural variations and therefore to provide novel discodermolide structural analogues.

Experimental Section

All reactions were carried out in oven or flame-dried glassware under an argon atmosphere employing standard techniques in handling air-sensitive materials. All solvents were employing reagent grade. Tetrahydrofuran (THF) and diethyl ether (Et₂O) were freshly distilled from sodium/benzophenone under nitrogen immediately prior to use. Dichloromethane (DCM), cyclohexane and pentane were freshly distilled over calcium hydride. All other reagents were used as supplied. Reactions were magnetically stirred and monitored by thin layer chromatography with 0.20 mm SDS 60F254 pre-coated silica gel plates. Visualization was accomplished with UV light then treatment with a 10 % ethanolic phosphomolybdic acid solution followed with heating. Flash chromatography was performed with silica gel 60 (particle size 0.040-0.063 mm) supplied by SDS. Yield refers to chromatography and spectroscopically pure compounds, unless otherwise noted. ¹H NMR spectra were recorded using an internal deuterium lock at ambient temperature on a JEOL JNM-ECX 270 or 400 MHz spectrometer. Internal references of δ_H 7.26 and 1.96 were used respectively for CDCl₃ and CD₃CN. Data are represented as follows: chemical shift (in ppm), multiplicity (s = single, d = doublet, t = triplet, q = quartet), integration, coupling constant (J/Hz). ¹³C-NMR spectra were recorded on a Jeol 67.5 or 100.5 MHz spectrometer. Internal references of δ_C 77.16 and 118.26 were used respectively for CDCl₃ and CD₃CN. Infrared spectra were recorded on a Nicolet Impact-400 and wavelength (ν) is given in cm⁻¹. Mass spectra were recorded on a GC/MS coupling unit with a MSD 5973 spectrometer and a Hewlett-Packard HP-GC 6890 chromatograph. Ionization was obtained either by electronic impact (EI) or chemical ionization with methane (CI, CH₄). Mass spectral data are reported as m/z. Optical rotations were recorded on a Jasco P-1010 digital polarimeter at 589 nm and reported as follows: [α]_D²⁰, concentration (c in g/100 mL) and solvent. Elemental analysis was performed on a CHN 240 Perkin-Elmer instrument by the Service de Microanalyses, Centre d'Etudes Pharmaceutiques, Chatenay-Malabry, F-92296. High-resolution mass-spectra were obtained on a Thermo-Electron MAT-95 spectrometer in the ICMMO, Mass Spectrometry Laboratory, Orsay University, F-91 405 Orsay. IUPAC nomenclature was used for all compounds.

(2*S*)-3-(4-Methoxybenzyloxy)-2-methyl propanal (**15**): *p*-Methoxybenzylalcohol (20.0 g, 144.7 mmol, 1.0 equiv) was added to a suspension of NaH (60 % in mineral oil, 0.58 g, 14.5 mmol, 0.1 equiv) in anhydrous diethyl ether (45 mL) over 30 min at 20 °C. The mixture was stirred for 1 h and cooled to 0 °C. Trichloroacetonitrile (23.0 g, 16 mL, 159.2 mmol, 1.1 equiv) was then introduced over 10 min. After 1.5 h the solution was concentrated *in vacuo*. The crude residue was treated with a mixture of pentane (150 mL) and methanol (0.6 mL), stirred at 20 °C for 30 min, and filtered through a pad of celite. Concentration gave the trichloroimidate (40.2 g, 98 % yield) as yellow oil which was used without further purification. A solution of commercial methyl (5*S*)-(+)-3-hydroxy-2-methylpropionate **14** (13.9 g, 118 mmol, 1.0 equiv) and pyridinium *p*-toluene sulfonate (PPTS, 1.48 g, 5.9 mmol, 0.05 equiv) in an anhydrous mixture of CH₂Cl₂ (50 mL)/cyclohexane (100 mL) was cooled to 0 °C and treated with crude trichloroimidate (40.2 g, 142 mmol, 1.2 equiv) over 10 min. After 3 h, the mixture was warmed to 20 °C and stirred for 24 h. The solution was filtered through a pad of celite and the solvents were removed under reduced pressure. The crude (2*R*)-3-(4-methoxybenzyloxy)-2-methyl propan-1-ol was directly used in the next step without

further purification. RN: 132969-71-2; $[\alpha]_D^{20} = +8.3$ ($c = 1.57$, CHCl_3); $^1\text{H NMR}$ (400.0 MHz, CDCl_3): $\delta = 7.26$ (d, $J = 8.7$ Hz, 2H), 6.88 (d, $J = 8.7$ Hz, 2H), 4.50 (s, 2H), 3.80 (s, 3H), 3.70 (s, 3H), 3.65 (dd, $J = 8.9$, 7.3 Hz, 1H), 3.48 (dd, $J = 8.9$, 5.9 Hz, 1H), 2.79 (dq, $J = 7.3$, 7.3, 5.9 Hz, 1H), 1.19 (d, $J = 7.3$ Hz, 3H, CH_3); $^{13}\text{C NMR}$ (100.5 MHz, CDCl_3): $\delta = 174.9$ (C), 158.9 (C), 129.9 (2CH), 128.9 (C), 113.4 (2CH), 72.4 (CH_2), 71.3 (CH_2), 54.8 (CH), 51.3 (CH₃), 39.8 (CH), 13.6 (CH₃); MS (GC, CI, CH_4): m/z : 267 ($\text{M}^+ + 29$), 237, 223, 207, 187, 161, 149, 137, 121, 101, 87; IR (Film) $\nu = 2939, 2858, 1741, 1729, 1612, 1513, 1462, 1364, 1302, 1248, 1200, 1175, 1089, 1034, 820 \text{ cm}^{-1}$.

A solution of the above ester compound (28.1 g, 118 mmol, 1.0 equiv) in anhydrous THF (50 mL) was added to a suspension of LiAlH_4 (5.0 g, 130 mmol, 1.1 equiv) in THF (110 mL) at 0 °C. The reaction mixture was stirred for 3 h at 20 °C then cooled to 0 °C and quenched by successive addition of water (5 mL), 15 % NaOH (5 mL), and then water (15 mL). The resulting mixture was filtered through a pad of celite then treated with MgSO_4 , filtered, and the solvent was removed under reduced pressure. The residue was then purified by chromatography on silica gel (cyclohexane/ethyl acetate 80:20 to 50:50) to give 20.0 g (81 % yield over 2 steps) of (2R)-3-(4-methoxybenzyloxy) 2-methyl propanol. RN: 136320-64-4; $[\alpha]_D^{20} = +14.6$ ($c = 0.87$, CHCl_3); $^1\text{H NMR}$ (400.0 MHz, CDCl_3): $\delta = 7.26$ (d, $J = 8.6$ Hz, 2H), 6.90 (d, $J = 8.6$ Hz, 2H), 4.47 (s, 2H), 3.82 (s, 3H), 3.62 (bd, $J = 5.9$ Hz, 2H), 3.54 (dd, $J = 9.2$, 5.0 Hz, 1H), 3.41 (dd, $J = 9.2$, 7.7 Hz, 1H), 2.64 (bs, 1H, OH), 2.07 (dq, $J = 7.7$, 6.9, 5.9, 5.0 Hz, 1H), 0.87 (d, $J = 6.9$ Hz, 3H, CH_3); $^{13}\text{C NMR}$ (100.5 MHz, CDCl_3): $\delta = 159.2$ (C), 130.0 (C), 129.2 (2CH), 113.8 (2CH), 75.3 (CH_2), 73.0 (CH_2), 68.0 (CH_2), 55.2 (CH_3), 35.5 (CH), 13.4 (CH_3); MS (GC, CI, CH_4): m/z : 239 ($\text{M}^+ + 29$), 210, 201, 161, 149, 137, 121, 103, 91, 73, 55; IR (Film) $\nu = 3301, 2952, 2859, 1612, 1513, 1462, 1363, 1302, 1246, 1173, 1090, 1034, 819 \text{ cm}^{-1}$.

To a vigorously stirred solution of (2R)-3-(4-methoxybenzyloxy) 2-methyl propanol (6.0 g, 28.5 mmol, 1.0 equiv), NaHCO_3 (7.2 g, 86 mmol, 3 equiv), KBr (3.4 g, 28.5 mmol, 1.0 equiv) and TEMPO (90 mg, 0.57 mmol, 0.2 equiv) in CH_2Cl_2 (60 mL) / H_2O (30 mL) at 0 °C was added dropwise a solution of NaOCl 9.6 % (33 mL, 57 mmol, 1.9 equiv). The mixture was stirred for 10 min and then quenched with a solution of $\text{Na}_2\text{S}_2\text{O}_5$ 1M and extracted with diethyl ether. The organic layer was washed with water and brine, dried over MgSO_4 and the solvent removed under reduced pressure to give the title compound **15** as orange oil (5.8 g, 98 % yield) which was used directly without further purification. (**15**): RN: 132969-60-9; $^1\text{H NMR}$ (400.0 MHz, CDCl_3): $\delta = 9.72$ (d, $J = 1.7$ Hz, 1H), 7.25 (d, $J = 8.6$ Hz, 2H), 6.89 (d, $J = 8.6$ Hz, 2H), 4.47 (s, 2H), 3.82 (s, 3H), 3.65 (dd, $J = 9.2$, 6.4 Hz, 1H), 3.62 (dd, $J = 9.2$, 5.3 Hz, 1H), 2.66 (q, $J = 7.3$, 6.4, 5.3, 1.7 Hz, 1H), 1.13 (d, $J = 7.3$ Hz, 3H, CH_3).

(1Z,3R,4R,5S)-1-((N,N-Diisopropyl)carbamoyloxy)-3,5-dimethyl-4-hydroxy-6-(4-methoxybenzyloxy) hex-1-ene (16): To a quick stirred solution of (*E*)-crotyldiisopropylcarbamate (749 mg, 3.74 mmol, 2.0 equiv) and (-)-sparteine (885 mg, 3.74 mmol, 2.0 equiv) in pentane (5.0 mL) and cyclohexane (830 μL) at -78 °C, was added a solution of *n*-BuLi (1.6 M in hexanes, 2.3 mL, 3.74 mmol, 2.0 equiv) and after 10 min white crystals appeared. After 3 h of crystallisation at -78 °C, a precooled (-40 °C) solution of titanate tetraisopropoxide ($\text{Ti}(\text{O}^i\text{Pr})_4$, 3.4 mL, 11.2 mmol, 6.0 equiv) in pentane (2.0 mL) was quickly added via cannula to the reaction mixture of lithiocarbamate which became limpid and turn orange. After 1 h at -78 °C aldehyde **15** (390 mg, 1.87 mmol, 1.0 equiv) in pentane (1.5 mL) was slowly added to the orange solution. The reaction mixture was stirred for 3 h at -78 °C and quenched by addition of methanol (7.0 mL). The solution was poured into a mixture of diethyl ether-aqueous hydrochloric acid solution (0.5 N). After extraction with diethyl ether, the organic layer was washed with brine, dried over MgSO_4 , filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/diethyl ether 90:10 to 50:60) to give the desired compound **16** (598 mg) and its **3,4-bis-epi diastereomer** (19 mg) (85 % yield, selectivity 97:3). (**16**): $^1\text{H NMR}$ (270.0 MHz, CDCl_3): $\delta = 7.18$ (d, $J = 8.9$ Hz, 2H), 7.05 (d, $J = 6.6$ Hz, 1H), 6.79 (d, $J = 8.9$ Hz, 2H), 4.63 (dd, $J = 9.9$, 6.6 Hz, 1H), 4.37 (s, 2H), 4.08 (bs, 1H), 3.73 (s, 3H, CH_3), 3.68 (bs, 1H), 3.54 (dd, $J = 8.9$, 6.2 Hz, 1H), 3.49 (dd, $J = 9.2$, 2.87 Hz, 1H), 3.45 (dd, $J = 8.9$, 5.7 Hz, 1H), 2.87 (dd, $J = 9.9$, 9.2, 6.9 Hz, 1H), 2.28 (bs, 1H, OH), 2.00 (q, $J = 6.9$, 6.2, 5.7, 2.7 Hz, 1H), 1.30-1.10 (m, 12H, 4 CH_3), 0.90 (d, $J = 6.9$ Hz, 3H, CH_3), 0.87 (d, $J = 6.9$ Hz, 3H, CH_3); $^{13}\text{C NMR}$ (67.5 MHz, CDCl_3): $\delta = 158.9$ (C), 152.8 (C), 135.9 (CH), 130.3 (C), 129.0 (2CH), 113.6 (3CH), 75.7 (CH), 74.0 (CH), 72.7 (CH_2), 55.0 (CH_3), 46.8 (CH), 45.4 (CH), 35.1 (CH), 33.8 (CH), 21.4 (2 CH_3), 20.2 (2 CH_3), 17.2 (CH_3), 9.8 (CH_3); MS (GC, CI, CH_4): m/z : 407, 348, 319, 262, 199, 174, 137, 121. (**3,4-bis-epi diastereomer of 16**): $^1\text{H NMR}$ (270.0 MHz, CDCl_3): $\delta = 7.20$ (d, $J = 8.9$ Hz, 2H), 7.08 (d, $J = 6.6$ Hz, 1H), 6.79 (d, $J = 8.9$ Hz, 2H), 4.89 (dd, $J = 9.5$, 6.2 Hz, 1H), 4.39 (s, 2H), 4.10 (bs, 1H), 3.75 (s, 3H, CH_3), 3.73 (bs, 1H), 3.54 (m, 1H), 3.49 (m, 1H), 3.43 (dd, $J = 8.9$, 5.7 Hz, 1H), 2.90 (m, 1H), 2.25 (m, 1H), 2.21 (bs, 1H, OH), 1.21 (m, 12H, 4 CH_3), 1.10 (d, $J = 6.9$ Hz, 3H, CH_3), 0.80 (d, $J = 6.9$ Hz, 3H, CH_3).

(3R,4R,5S)-3,5-Dimethyl-6-(4-methoxybenzyloxy)-4-(triethylsilyloxy)-1-(trimethylsilyl) hex-1-yne (17): To a solution of carbamate **16** (3.0 g, 7.43 mmol, 1.0 equiv) in dried CH_2Cl_2 (65 mL) at 0 °C were added 2,6-lutidine (2.6 mL, 22.3 mmol, 3.0 equiv) and TESOTf (2.4 mL, 11.1 mmol, 1.5 equiv). After stirring for 2 h at 20 °C, the reaction was partitioned between diethyl ether and a saturated aqueous NH_4Cl

solution and extracted with diethyl ether. The organic layer was washed with brine, dried over MgSO_4 , filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/diethyl ether 100:0 to 85:15) to give the (1Z,3R,4R,5S)-1-((*N,N*-diisopropyl)carbamoyloxy)-3,5-dimethyl-4-(triethylsilyloxy)-6-(4-methoxybenzyloxy) hex-1-yne (3.77 g, 97 % yield) as a yellow oil. $^1\text{H NMR}$ (270.0 MHz, CDCl_3): $\delta = 7.16$ (d, $J = 8.6$ Hz, 2H), 6.94 (d, $J = 6.6$ Hz, 1H), 6.79 (d, $J = 8.6$ Hz, 2H), 4.71 (dd, $J = 9.9$, 6.6 Hz, 1H), 4.32 (s, 2H), 4.01 (bs, 1H), 3.72 (s, 3H, CH_3), 3.68 (bs, 1H), 3.58 (dd, $J = 4.8$, 3.8 Hz, 1H), 3.33 (dd, $J = 8.9$, 6.3 Hz, 1H), 3.15 (dd, $J = 8.9$, 6.9 Hz, 1H), 2.78 (m, 1H), 1.86 (m, 1H), 1.25-1.10 (m, 12H, 4 CH_3), 0.91 (d, $J = 7.9$ Hz, 3H, CH_3), 0.86 (t, $J = 7.6$ Hz, 9H, 3 CH_3), 0.83 (d, $J = 6.9$ Hz, 3H, CH_3), 0.51 (q, $J = 7.6$ Hz, 6H, 3 CH_2); $^{13}\text{C NMR}$ (67.5 MHz, CDCl_3): $\delta = 158.9$ (C), 152.7 (C), 134.4 (CH), 130.5 (C), 128.9 (2CH), 113.5 (CH), 113.4 (2CH), 76.3 (CH), 72.8 (CH_2), 72.4 (CH_2), 54.9 (CH_3), 46.4 (CH), 45.4 (CH), 37.7 (CH), 34.2 (CH), 21.2 (2 CH_3), 20.1 (2 CH_3), 18.6 (CH_3), 11.8 (CH₃), 6.9 (3 CH_2), 5.3 (3 CH_2); MS (GC, CI, CH_4): m/z : 420, 313, 251, 193, 161, 128, 115; elemental analysis calcd (%) for $\text{C}_{29}\text{H}_{51}\text{NO}_5\text{Si}$: C 66.75, H 9.85, N 2.68; found: C 66.28, H 9.91, N 2.42.

To a solution of the preceding carbamate (3.77 g, 7.23 mmol, 1.0 equiv) in diethyl ether (80 mL) at -30 °C was added dropwise *t*-BuLi (1.5 M in pentane, 9.5 mL, 14.3 mmol, 1.98 equiv). The resulting solution was stirred for 45 min between -25/-20 °C and then quenched by addition of a saturated aqueous NH_4Cl solution and extracted with diethyl ether. The organic layer was washed with brine, dried over MgSO_4 , filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/diethyl ether 90:10) to give the (3R,4R,5S)-3,5-dimethyl-6-(4-methoxybenzyloxy)-4-(triethylsilyloxy) hex-1-yne (2.3 g, 84 % yield) as a yellow oil. $^1\text{H NMR}$ (270.0 MHz, CDCl_3): $\delta = 7.17$ (d, $J = 8.2$ Hz, 2H), 6.77 (d, $J = 8.2$ Hz, 2H), 4.33 (s, 2H), 3.70 (s, 3H, CH_3), 3.70-3.67 (m, 1H), 3.33 (dd, $J = 8.9$, 6.3 Hz, 1H), 3.20 (dd, $J = 8.9$, 6.3 Hz, 1H), 2.54-2.50 (m, 1H), 1.97-1.91 (m, 2H), 1.08 (d, $J = 6.9$ Hz, 3H, CH_3), 0.88 (t, $J = 7.5$ Hz, 9H, 3 CH_3), 0.81 (d, $J = 6.9$ Hz, 3H, CH_3), 0.57 (q, $J = 7.5$ Hz, 6H, 3 CH_2); $^{13}\text{C NMR}$ (67.5 MHz, CDCl_3): $\delta = 159.0$ (C), 130.6 (C), 129.2 (2CH), 113.6 (2CH), 87.5 (C), 75.0 (CH), 73.0 (CH), 72.5 (CH), 69.6 (CH), 55.1 (CH₃), 36.5 (CH), 31.4 (CH), 17.4 (CH₃), 11.3 (CH₃), 7.0 (3 CH_3), 5.4 (3 CH_2); MS (GC, CI, CH_4): m/z : 347 ($\text{M}^+ + 29$), 323, 227, 187, 173, 137, 121.

To a solution of the preceding alkyne (2.3 g, 6.11 mmol, 1.0 equiv) in THF at -78 °C was added *n*-BuLi (1.6 M in hexane, 4.0 mL, 6.42 mmol, 1.05 equiv). After 10 min the bath was removed and the reaction mixture was stirred for 1 h at 0 °C. The solution was cooled to -78 °C and freshly distilled TMSCl was added (2.1 mL, 24.4 mmol, 4.0 equiv). The solution was warmed to 20 °C overnight. After addition of Et_3N (6.0 equiv) the mixture was partitioned between diethyl ether and a saturated aqueous NH_4Cl solution and extracted with diethyl ether. The organic layer was washed with brine, dried over MgSO_4 , filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/diethyl ether 100:0 to 90:10) to give protected alkyne **17** (2.54 g, 92 % yield). (**17**): $^1\text{H NMR}$ (270.0 MHz, CDCl_3): $\delta = 7.12$ (d, $J = 8.6$ Hz, 2H), 6.74 (d, $J = 8.6$ Hz, 2H), 4.29 (2d, $J = 11.5$ Hz, 2H), 3.67 (s, 3H, CH_3), 3.63 (dd, $J = 6.6$, 3.0 Hz, 1H), 3.30 (dd, $J = 9.2$, 7.3 Hz, 1H), 3.12 (dd, $J = 9.2$, 6.6 Hz, 1H), 2.45 (quint, $J = 6.6$ Hz, 1H), 1.87 (ddd, $J = 7.3$, 7.2, 6.6 Hz, 1H), 0.99 (d, $J = 7.2$ Hz, 3H, CH_3), 0.83 (t, $J = 7.2$ Hz, 9H, 3 CH_3), 0.73 (d, $J = 6.6$ Hz, 3H, CH_3), 0.52 (q, $J = 7.2$ Hz, 6H, 3 CH_2), 0.00 (s, 9H, 3 CH_3); $^{13}\text{C NMR}$ (67.5 MHz, CDCl_3): $\delta = 159.0$ (C), 130.6 (C), 129.2 (2CH), 113.6 (2CH), 110.8 (C), 85.2 (C), 75.0 (CH), 73.0 (CH₂), 72.4 (CH_2), 55.1 (CH₃), 36.4 (CH), 32.5 (CH), 17.6 (CH₃), 10.9 (CH₃), 7.0 (3 CH_2), 5.4 (3 CH_2), 0.00 (3 CH_3); MS (GC, EI): m/z : 449, 433, 341, 323, 269, 227, 187, 173, 137, 121.

(1E/Z,3S,4R,5S)-3,5-Dimethyl-1-methoxy-4-(triethylsilyloxy)-7-(trimethylsilyl) hept-6-yn-1-ene (18): At 0 °C, a solution of protected alcohol **17** (2.08 g, 4.64 mmol, 1.0 equiv) in CH_2Cl_2 (48 mL) was treated with water (2.4 mL) and DDQ (1.27 g, 5.57 mmol, 1.2 equiv). The mixture was stirred for 10 min at 0 °C, warmed to 20 °C and stirred an additional 30 min. The mixture was quenched with a saturated aqueous NaHCO_3 solution, diluted with CH_2Cl_2 , washed with water and brine. The combined organic layers were dried over MgSO_4 , filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate 80:20) to give the (2S,3R,4R)-2,4-dimethyl-3-(triethylsilyloxy)-1-(trimethylsilyl) hex-5-yn-1-ol (1.31 g, 86 % yield). $^1\text{H NMR}$ (270.0 MHz, CDCl_3): $\delta = 3.58$ -3.49 (m, 3H), 2.53-2.48 (m, 1H), 1.90 (bs, 1H, OH), 1.79-1.70 (m, 1H), 1.03 (d, $J = 7.3$ Hz, 3H, CH_3), 0.83 (t, $J = 7.6$ Hz, 9H, 3 CH_3), 0.74 (d, $J = 6.9$ Hz, 3H, CH_3), 0.50 (q, $J = 7.6$ Hz, 6H, 3 CH_2), 0.00 (s, 9H, 3 CH_3); $^{13}\text{C NMR}$ (67.5 MHz, CDCl_3): $\delta = 110.0$ (C), 86.0 (C), 76.5 (CH), 65.3 (CH_2), 39.4 (CH), 31.5 (CH), 17.6 (CH₃), 12.4 (CH₃), 7.0 (3 CH_3), 5.3 (3 CH_2), 0.0 (3 CH_3); MS (GC, EI): m/z : 327, 299, 269, 225, 203.

To a solution of IBX (2.72 g, 9.72 mmol, 2.2 equiv) in DMSO (35 mL) at 20 °C was added the preceding alcohol (1.45 g, 4.42 mmol, 1.0 equiv) in DMSO (10 mL). The mixture was stirred for 3 h, and then cooled to 0 °C. H_2O was added and the solution was filtered through a pad of celite and then extracted with diethyl ether (3X). The organic layer was washed with water, brine, dried over MgSO_4 and the solvent removed under reduced pressure. The crude (2S,3S,4S)-2,4-dimethyl-3-(triethylsilyloxy)-6-(trimethylsilyl) hex-5-yn-1-ol was used without further purification (1.31 g, 90 % yield). $^1\text{H NMR}$ (270.0 MHz, CDCl_3): $\delta = 9.71$ (s, 1H), 3.96 (t, $J = 5.0$ Hz, 1H), 2.54 (qd, $J = 6.9$, 5.0 Hz, 1H), 2.43 (qd, $J = 7.3$, 5.0 Hz, 1H), 1.05 (d, $J = 7.3$ Hz, 3H, CH_3), 0.98 (d, $J =$

= 6.9 Hz, 3H, CH₃), 0.83 (t, *J* = 7.6 Hz, 9H, 3CH₃), 0.50 (q, *J* = 7.6 Hz, 6H, 3CH₂), 0.00 (s, 9H, 3CH₃).

To a cooled (-10 °C) stirred suspension of (methoxymethyl)triphenylphosphonium chloride (3.14 g, 9.15 mmol, 2.3 equiv) in 30 mL of anhydrous THF was added 7.96 mL of lithium bis(trimethylsilyl)amide (1.0 *M* in THF, 7.96 mmol, 2.0 equiv) which became deep red. After 5 min aldehyde prepared before (1.31 g, 3.98 mmol, 1.0 equiv) in THF (5 mL, 5 mL rinse) was added via cannula. The resulting solution was kept at -10 °C for 1 h and then diluted with a saturated aqueous NaHCO₃ solution. After extraction with Et₂O and concentration of the organic layer, the residue was rapidly filtered through a pad of silica (cyclohexane/ethyl acetate 90:10) to remove most of the phosphine by-product and concentrated again. Olefin **18** was used without further purification in the lactolisation step (selectivity *Z/E* 4:6). (**18**): *Trans isomer*: ¹H NMR (270.0 MHz, CDCl₃): δ = 6.18 (d, *J* = 12.9 Hz, 1H), 4.53 (dd, *J* = 12.9, 9.2 Hz, 1H), 3.43 (s, 3H, CH₃), 3.24 (dd, *J* = 5.9, 5.0 Hz, 1H), 2.50 (m, 1H), 2.20 (m, 1H), 1.02 (d, *J* = 6.9 Hz, 3H, CH₃), 0.85 (t, *J* = 7.9 Hz, 9H, 3CH₃), 0.80 (d, *J* = 6.9 Hz, 3H, CH₃), 0.51 (q, *J* = 7.9 Hz, 6H, 3CH₂), 0.00 (s, 9H, 3CH₃). *Cis isomer*: ¹H NMR (270.0 MHz, CDCl₃): δ = 5.67 (d, *J* = 6.3 Hz, 1H), 4.20 (dd, *J* = 9.6, 6.3 Hz, 1H), 3.37 (s, 3H, CH₃), 3.36 (dd, *J* = 5.9, 5.3 Hz, 1H), 2.50 (m, 1H), 2.20 (m, 1H), 1.01 (d, *J* = 6.9 Hz, 3H, CH₃), 0.84 (t, *J* = 7.9 Hz, 9H, 3CH₃), 0.80 (d, *J* = 6.9 Hz, 3H, CH₃), 0.51 (q, *J* = 7.9 Hz, 6H, 3CH₂), 0.00 (s, 9H, 3CH₃); MS (GC, EI): *m/z*: 354, 337, 309, 269, 229, 199, 175, 155, 139.

(2*R*,4*S*,5*R*(1*S*))-4-Methyl-5-(1-methyl-3-(trimethylsilyl)-prop-2-yn-1-yl)

tetrahydrofuran-2-ol (19): Compound **18** was dissolved in acetone/water (9:1, 40 mL) and concentrated HCl (140 μL) was added. Then the solution was heated at 65 °C for 1 h, and the reaction was quenched by addition of a saturated aqueous NaHCO₃ solution and extracted with Et₂O. The organic layer was washed with water, brine, dried over MgSO₄ and concentrated. The residue was purified by chromatography on silica gel (cyclohexane/Et₂O 80:20) to give 553 mg of lactol **19** (61 % yield from alcohol **17**). (**19**): ¹H NMR (270.0 MHz, CDCl₃): δ = 5.50 (d, *J* = 5.0 Hz, 1H), 3.89 (dd, *J* = 6.9, 4.6 Hz, 1H), 3.23 (bs, 1H, OH), 2.41 (m, 1H), 2.22 (m, 1H), 1.97 (m, 1H), 1.75 (m, 1H), 1.08 (d, *J* = 6.9 Hz, 3H, CH), 0.95 (d, *J* = 6.9 Hz, 3H, CH₃), 0.00 (s, 9H, 3CH₃); ¹³C NMR (67.5 MHz, CDCl₃): δ = 109.4 (C), 98.3 (CH), 85.2 (C), 84.4 (CH), 41.2 (CH₂), 33.9 (CH), 28.6 (CH), 18.7 (CH₃), 13.5 (CH₃), 0.00 (3CH₃); MS (GC, EI): *m/z*: 208, 193, 173, 126, 117, 109, 87.

(2*R*,4*S*,5*R*(1*S*))-4-Methyl-5-(1-methyl-3-(trimethylsilyl)-prop-2-ynyl)-2-

phenylsulfanyl tetrahydrofuran (20): To an ice-cold solution of lactol **19** (553 mg, 2.44 mmol, 1.0 equiv) and thiophenol (290 μL, 2.78 mmol, 1.14 equiv) in anhydrous Et₂O (25 mL) containing activated 4A molecular sieves, was added dropwise via syringe BF₃·OEt₂ (460 μL, 3.78 mmol, 1.55 equiv). After 1 h the reaction was quenched by the addition of a 4*N* NaOH solution and extracted with Et₂O. The organic layer was washed with water, brine, dried over MgSO₄ and concentrated. The residue was purified by chromatography on silica gel (cyclohexane/Et₂O 95:5) to give 622 mg of thio-product **20** (80 % yield). (**20**): ¹H NMR (270.0 MHz, CDCl₃): δ = 7.45 (dd, *J* = 7.9, 1.7 Hz, 2H), 7.13 (d, *J* = 1.7 Hz, 2H), 7.09 (d, *J* = 7.9 Hz, 1H), 5.51 (dd, *J* = 6.9, 5.0 Hz, 1H), 3.84 (dd, *J* = 7.6, 5.2 Hz, 1H), 2.46 (m, 1H), 2.18 (m, 2H), 2.02 (m, 1H), 1.05 (d, *J* = 7.3 Hz, 3H, CH₃), 0.81 (d, *J* = 6.9 Hz, 3H, CH₃), 0.00 (s, 9H, 3CH₃); ¹³C NMR (67.5 MHz, CDCl₃): δ = 135.4 (C), 132.0 (2CH), 128.5 (2CH), 127.0 (CH), 109.0 (C), 86.2 (CH), 85.2 (C), 83.3 (CH), 40.8 (CH₂), 34.1 (CH), 27.7 (CH), 17.8 (CH₃), 13.6 (CH₃), 0.00 (3CH₃); MS (GC, EI): *m/z*: 318, 209, 193, 167, 151, 137, 121.

(4*R*,5*S*(1*S*))-4-Methyl-5-(1-methyl-3-(trimethylsilyl)-prop-2-ynyl)-2,3-dihydrofuran

(21): a) To a solution of the thio-ether **20** (300 mg, 0.9 mmol) and DBU (160 μL, 1.05 mmol, 1.1 equiv) was rapidly heated (40 min) at 200 °C in a short distillation apparatus (Kugelrohr), then the mixture was distilled under vacuum (15 mmHg) at 200-240 °C to furnish the title compound **21** (60 mg, 30% yield). b) To a solution of the thio-ether **20** (335 mg, 1.05 mmol, 1.0 equiv) in dry benzene (30 mL) containing NaHCO₃ (88 mg, 3.16 mmol, 3.0 equiv) was added at 0 °C *m*-CPBA (70-75 % purity, 310 mg, 1.26 mmol, 1.2 equiv) in benzene. After 1 h Et₃N (440 μL, 3.16 mmol, 3.0 equiv) the resulting sulfoxide was added and the mixture was heated at reflux for 1 h then cooled to 20 °C. The solution was partitioned between a saturated aqueous NaHCO₃ solution and Et₂O. After extraction the organic layer was washed with water in order to remove most of the benzene, dried over MgSO₄ and concentrated carefully. The residue was distilled in a Kugelrohr apparatus (80-90 °C, 7.10⁻² Torr) to give dihydrofuran **21** (42 mg, 19 % yield). (**21**): ¹H NMR (270.0 MHz, CDCl₃): δ = 6.26 (dd, *J* = 2.6, 1.6 Hz, 1H), 4.91 (t, *J* = 2.6 Hz, 1H), 4.09 (t, *J* = 8.3 Hz, 1H), 2.78 (m, 2H), 1.19 (d, *J* = 7.3 Hz, 3H, CH₃), 0.92 (d, *J* = 6.6 Hz, 3H, CH₃), 0.00 (s, 9H, 3CH₃); ¹³C NMR (67.5 MHz, CDCl₃): δ = 144.8 (CH), 108.5 (C), 107.5 (CH), 86.4 (CH), 83.3 (C), 37.6 (CH), 27.5 (CH), 18.7 (CH₃), 14.0 (CH₃), 0.00 (3CH₃); MS (GC, EI): *m/z*: 208, 193, 126, 119, 109, 97, 83.

(3*S*,4*R*,5*S*,6*Z*)-3,5-Dimethyl-4-hydroxy-7-(tributylstannyl)-1-trimethylsilyl-oct-6-

en-1-yne (22): To a suspension of CuCN (12 mg, 0.12 mmol, 2.0 equiv) of in dry Et₂O (3 mL) at -30 °C was added MeLi (1.6 *M* solution in diethyl ether, 1.9 mL, 3.0 mmol, 5.0 equiv). The solution was stirred at -30 °C for 5 min and allowed to warm up to 0 °C for 20 min (pale yellow colour). To a solution of 2,3-dihydrofuran **21** (125 mg, 0.6 mmol, 1.0 equiv) in dry THF (3 mL) at -60 °C was added *t*-BuLi (1.5 *M* solution in

pentane, 0.45 mL, 0.7 mmol, 1.2 equiv). The mixture was stirred at 0 °C for 50 min. Then the solution of the lithio-dihydrofuran, prepared above, was diluted with 4 mL of THF and added via cannula to the cyanocuprate and the reaction mixture was heated to 35 °C for 3 h. The mixture was cooled at -30 °C and tri-*n*-butyltin chloride (0.85 mL, 3.0 mmol, 5.0 equiv) was added. The reaction mixture was allowed to warm up to 20 °C over 12 h. Finally the reaction mixture was poured into a mixture of a saturated aqueous NH₄Cl solution and concentrated ammonia (4:1) at 0 °C and stirred for 1 h at 20 °C before extraction with diethyl ether. The organic layer was washed with water, brine, dried over MgSO₄ and the solvent was removed under reduced pressure. The crude residue was purified by chromatography on silica gel (cyclohexane/diethyl ether 100:0 to 50:50) to give the title compound **22** (48 mg, 20 % yield). (**22**): ¹H NMR (400.0 MHz, CDCl₃): δ = 5.87 (dq, *J* = 9.6, 1.8 Hz, *J*_{H-117Sn} = *J*_{H-119Sn} = 135.0 Hz, 1H), 3.17 (ddd, *J* = 9.0, 7.5, 3.2 Hz, 1H), 2.73 (m, 1H), 2.32 (m, 1H), 1.90 (d, *J* = 2.0 Hz, *J*_{H-117Sn} = *J*_{H-119Sn} = 41.0 Hz, 3H, CH₃), 1.74 (d, *J* = 9.0 Hz, 1H, OH), 1.53-1.42 (m, 6H, 3CH₂), 1.34 (sext, *J* = 7.5 Hz, 6H, 3CH₂), 1.26 (d, *J* = 7.0 Hz, 3H, CH₃), 1.08 (d, *J* = 7.0 Hz, 3H, CH₃), 1.0-0.90 (m, 6H, 3CH₂), 0.87 (t, *J* = 7.5 Hz, 9H, 3CH₃), 0.00 (s, 9H, 3CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 142.9 (CH, *J*_{13C-117Sn} = *J*_{13C-119Sn} = 28.8 Hz), 138.1 (C), 109.0 (C), 85.0 (C), 78.0 (CH), 43.5 (CH, *J*_{13C-117Sn} = *J*_{13C-119Sn} = 33.6 Hz), 30.2 (CH), 29.0 (3CH₂, *J*_{13C-117Sn} = *J*_{13C-119Sn} = 19.2 Hz), 27.1 (3CH₂, *J*_{13C-117Sn} = *J*_{13C-119Sn} = 58.7 Hz), 27.0 (CH₃, *J*_{13C-117Sn} = *J*_{13C-119Sn} = 44.0 Hz), 18.4 (CH₃), 17.0 (CH₃), 13.4 (3CH₃), 9.7 (3CH₂, *J*_{13C-117Sn} = 314.4 Hz, *J*_{13C-119Sn} = 328.8 Hz), 0.00 (3CH₃).

(3*Z*)-4-(Tributylstannyl) pent-3-en-1-ol (12): To a suspension of CuCN (10.5 g, 120 mmol, 2.0 equiv) of in dry Et₂O (60 mL) at -30 °C was added MeLi (1.6 *M* solution in diethyl ether, 188 mL, 300 mmol, 5.0 equiv). The solution was stirred at -30 °C for 5 min and allowed to warm up to 0 °C for 20 min (pale yellow colour). To a solution of commercial 2,3-dihydrofuran **8** (4.6 g, 60 mmol, 1.0 equiv) in dry THF (60 mL) at -60 °C was added *t*-BuLi (1.5 *M* solution in pentane, 48 mL, 72 mmol, 1.2 equiv). The mixture was stirred at 0 °C for 50 min. Then the solution of the lithio-dihydrofuran, prepared above, was diluted with 80 mL of THF and added via cannula to the cyanocuprate and the reaction mixture was heated to 35 °C for 3 h. The mixture was cooled at -30 °C and tri-*n*-butyltin chloride (49.1 mL, 181.2 mmol, 5.0 equiv) was added. The reaction mixture was allowed to warm up to 20 °C over 12 h. Finally the reaction mixture was poured into a mixture of a saturated aqueous NH₄Cl solution and concentrated ammonia (4:1) at 0 °C and stirred for 1 h at 20 °C before extraction with diethyl ether. The organic layer was washed with water, brine, dried over MgSO₄ and the solvent was removed under reduced pressure. The crude residue was purified by chromatography on silica gel (cyclohexane/diethyl ether 100:0 to 50:50) to give the title compound **12** (11.0 g, 49 % yield). (**12**): ¹H NMR (400.0 MHz, CDCl₃): δ = 6.05 (tq, *J* = 6.4, 1.4 Hz, *J*_{H-117Sn} = *J*_{H-119Sn} = 128.7 Hz, 1H), 3.63 (q, *J* = 7.3 Hz, 2H), 2.25 (td, *J* = 7.3, 6.4 Hz, 2H), 1.92 (d, *J* = 1.4 Hz, *J*_{H-117Sn} = *J*_{H-119Sn} = 41.7 Hz, 3H, CH₃), 1.50-1.42 (m, 7H, OH, 3CH₂), 1.31 (sext, *J* = 7.3 Hz, 6H, 3CH₂), 0.95-0.91 (m, 6H, 3CH₂), 0.90 (t, *J* = 7.3 Hz, 9H, 3CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 142.0 (C, *J*_{13C-117Sn} = *J*_{13C-119Sn} = 377.6 Hz), 136.1 (CH, *J*_{13C-117Sn} = *J*_{13C-119Sn} = 26.7 Hz), 62.3 (CH₂), 38.0 (CH₂, *J*_{13C-117Sn} = *J*_{13C-119Sn} = 33.4 Hz), 29.3 (3CH₂, *J*_{13C-117Sn} = *J*_{13C-119Sn} = 19.3 Hz), 27.5 (3CH₂, *J*_{13C-117Sn} = *J*_{13C-119Sn} = 57.1 Hz), 27.0 (CH₃, *J*_{13C-117Sn} = *J*_{13C-119Sn} = 46.0 Hz), 13.5 (3CH₃), 10.0 (3CH₂, *J*_{13C-117Sn} = 314.4 Hz, *J*_{13C-119Sn} = 328.8 Hz); MS (GC, CI, CH₄): *m/z*: 319 (M⁺-57), 289, 261, 245, 233, 207, 177, 137, 121.

(3*Z*)-4-(Tributylstannyl)-pent-3-en-1-al (23): To a solution of alcohol **12** (11.0 g, 29.3 mmol, 1.0 equiv) and TEMPO (457 mg, 2.93 mmol, 0.1 equiv) in CH₂Cl₂ (100 mL) was added BAIB (10.4 g, 32.2 mmol, 1.1 equiv). The mixture was stirred until disappearance of starting material (2 h), diluted with cyclohexane, washed with an aqueous saturated Na₂S₂O₃ solution, and extracted with cyclohexane. The combined organic phases were washed with a saturated aqueous NaHCO₃ solution, brine, dried over MgSO₄ and the solvent was removed under reduced pressure. The crude aldehyde **23** was directly used in the next step. (**23**): ¹H NMR (400.0 MHz, CDCl₃): δ = 9.67 (t, *J* = 2.1 Hz, 1H), 6.16 (tq, *J* = 7.3, 1.9 Hz, *J*_{H-117Sn} = *J*_{H-119Sn} = 122.1 Hz, 1H), 2.89 (dd, *J* = 7.3, 2.1 Hz, 2H), 1.98 (d, *J* = 1.9 Hz, *J*_{H-117Sn} = *J*_{H-119Sn} = 38.9 Hz, 3H, CH₃), 1.60-1.40 (m, 6H, 3CH₂), 1.39-1.20 (m, 6H, 3CH₂), 1.02-0.84 (m, 15H, 3CH₂ + 3CH₃).

(1*Z*,6*Z*,3*R*,5*R*(4*R*))-1-(*N,N*-Diisopropyl)carbamoyloxy-4-hydroxy-3-methyl-7-

(tributylstannyl) oct-1,6-diene [(+/-)-24]: To a quick stirred solution of the (*E*)-crotyl (diisopropyl)carbamate (11.7 g, 59.0 mmol, 2.0 equiv) and TMEDA (6.8 g, 59.0 mmol, 2.0 equiv) in diethyl ether (70 mL) at -78 °C was added a solution of *n*-BuLi (1.6 *M* in hexane, 44 mL, 70.0 mmol, 2.04 equiv). After 30 min at -78 °C, titanium tetrakispropoxide (Ti(O^{*i*}Pr)₄, 52.0 mL, 176.0 mmol, 6.0 equiv) was quickly added via cannula to the reaction mixture of lithio carbamate which turned orange. After 30 min at -78 °C, aldehyde **23** (10.9 g, 29.3 mmol, 1.0 equiv) in diethyl ether (15 mL) was slowly added to the orange solution, and the mixture was stirred for 3 h at -78 °C. The solution was then poured into a mixture of Et₂O-saturated aqueous NH₄Cl solution. After extraction with Et₂O, the organic layer was washed with brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/Et₂O 95:5 to 60:40) to give the title compound (+/-)-**24** (7.4 g, 44 % yield for 2 steps). [(+/-)-**24**]: ¹H NMR (400.0 MHz, CDCl₃): δ = 7.12 (d, *J* = 6.4 Hz, 1H), 6.10 (ddq, *J* = 5.9, 5.5, 1.4 Hz, *J*_{H-117Sn} = *J*_{H-119Sn} = 131.0 Hz, 1H), 4.67 (dd, *J* = 9.9, 6.4 Hz, 1H), 4.19-4.11 (bs, 1H), 3.80-3.75 (bs, 1H), 3.51 (dddd, *J* = 8.6, 5.0, 3.4, 3.0 Hz, 1H), 2.81 (ddq, *J* = 9.9, 8.6, 7.3 Hz, 1H), 2.30-2.15 (m, 1H), 2.10-2.06 (m, 1H), 1.92 (d, *J* = 1.4 Hz, *J*_{H-117Sn} = *J*_{H-119Sn} = 41.7 Hz, 3H,

CH₃), 1.78 (bd, *J* = 3.0 Hz, 1H, OH), 1.58-1.38 (m, 6H, 3CH₂), 1.38-1.17 (m, 18H, 3CH₂ + 4CH₃), 1.07 (d, *J* = 7.3 Hz, 3H, CH₃), 0.96-0.85 (m, 15H, 3CH₂ + 3CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 152.3 (C), 141.9 (C), 136.4 (CH, *J* _{13C-117Sn} = *J* _{13C-119Sn} = 28.1 Hz), 135.3 (CH), 111.9 (CH), 74.1 (CH), 45.4 (CH), 45.2 (CH), 39.6 (CH₂, *J* _{13C-117Sn} = *J* _{13C-119Sn} = 30.7 Hz), 35.4 (CH), 28.8 (3CH₂, *J* _{13C-117Sn} = *J* _{13C-119Sn} = 19.2 Hz), 27.5 (3CH₂, *J* _{13C-117Sn} = *J* _{13C-119Sn} = 56.5 Hz), 26.8 (CH₃, *J* _{13C-117Sn} = *J* _{13C-119Sn} = 46.0 Hz), 21.1 (2CH₃), 20.3 (2CH₃), 17.0 (CH₃), 13.2 (3CH₃), 9.6 (3CH₂, *J* _{13C-117Sn} = 313.4 Hz, *J* _{13C-119Sn} = 326.8 Hz); IR (Film) ν = 3470, 2957, 2925, 2872, 2855, 1712, 1705, 1679, 1642, 1456, 1444, 1371, 1306, 1211, 1147, 1134, 1065, 1001, 961, 903, 885, 865, 762 cm⁻¹.

(3*R*,4*R*,5*S*,6*Z*)-4-Hydroxy-3-methyl-7-(tributylstannyl)-oct-6-en-1-yne [(+)-25]:

To a solution of the preceding carbamate (+)-24 (8.4 g, 13.6 mmol, 1.0 equiv) in diethyl ether (100 mL) at -40 °C was slowly added a solution of *t*-BuLi (1.5 M in pentane, 27.2 mL, 40.8 mmol, 3.0 equiv). The solution was stirred for 20 min at -20 °C then quenched by addition of a saturated aqueous NH₄Cl solution, and extracted with diethyl ether. The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel (cyclohexane/Et₂O 90:10 to 80:20) to give (+)-25 (4.7 g, 78 % yield). [(+)-25]: ¹H NMR (270.0 MHz, CDCl₃): δ = 6.00 (ddq, *J* = 7.7, 6.5, 1.7 Hz, *J* _{1H-117Sn} = *J* _{1H-119Sn} = 129.0 Hz, 1H), 3.47-3.42 (m, 1H), 2.54 (qdd, *J* = 6.9, 4.0, 2.6 Hz, 1H), 2.26 (m, 1H), 2.16 (m, 1H), 2.14 (d, *J* = 2.3 Hz, 1H), 1.86 (d, *J* = 1.7 Hz, *J* _{1H-117Sn} = *J* _{1H-119Sn} = 41.6 Hz, 3H, CH₃), 1.50-1.33 (m, 6H, 3CH₂), 1.32-1.11 (m, 10H, 1OH + 1CH₃ + 3CH₂), 0.98-0.74 (m, 15H, 3CH₂ + 3CH₃); ¹³C NMR (67.5 MHz, CDCl₃): δ = 142.8 (C), 136.1 (CH, *J* _{13C-117Sn} = *J* _{13C-119Sn} = 26.8 Hz), 85.1 (C), 74.0 (CH), 71.0 (CH), 40.1 (CH₂), 32.2 (CH), 29.2 (3CH₂, *J* _{13C-117Sn} = *J* _{13C-119Sn} = 19.5 Hz), 27.4 (3CH₂, *J* _{13C-117Sn} = *J* _{13C-119Sn} = 56.2 Hz), 17.3 (CH₃), 13.7 (3CH₃), 9.6 (3CH₂, *J* _{13C-117Sn} = 314.4 Hz, *J* _{13C-119Sn} = 328.8 Hz); IR (Film) ν = 3311, 2956, 2926, 2871, 2854, 1712, 1463, 1376, 1260, 1192, 1072, 1039, 960 cm⁻¹.

(2*R*,5*R*,4*R*,3*S*)-4-Methyltetrahydrofuran-2-ol [(±)-27]: To a solution of LiAlH₄ (6.4 g, 169 mmol, 0.8 equiv) in Et₂O (100 mL) at 0 °C was added over 30 min a solution of commercial ethyl 4-methylpentanoate (±)-30 (30 g, 211 mmol, 1.0 equiv) in Et₂O (200 mL). After stirring for 4 h at 20 °C, the mixture was cooled at 0 °C and successively were added H₂O (6.5 mL), an aqueous NaOH 15 % solution (6.5 mL) and H₂O (19.5 mL). The mixture was stirred for 2 h, and filtered through a pad of celite. The filtrate was dried over MgSO₄ and the solvent was removed under reduced pressure. The crude 2-methylpent-4-en-1-ol was directly used in the next step. ¹H NMR (400.0 MHz, CDCl₃): δ = 5.75 (ddd, *J* = 17.0, 10.1, 7.3, 6.9 Hz, 1H), 4.97 (dd, *J* = 17.0, 1.4 Hz, 1H), 4.94 (dd, *J* = 10.1, 1.4 Hz, 1H), 3.55 (ddd, *J* = 6.9, 6.0, 4.6 Hz, 1H), 3.45 (ddd, *J* = 6.4, 6.0, 4.6 Hz, 1H), 2.10 (ddd, *J* = 8.2, 6.9, 6.0 Hz, 1H), 1.88 (ddd, *J* = 8.2, 7.3, 6.4 Hz, 1H), 1.66 (quinttd, *J* = 6.9, 6.4, 6.0 Hz, 1H), 1.40 (t, *J* = 4.6 Hz, 1H, OH), 0.85 (d, *J* = 6.9 Hz, 3H, CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 136.9 (CH), 116.0 (CH₂), 67.7 (CH₂), 37.7 (CH₂), 35.5 (CH), 16.3 (CH₃); MS (GC, EI): *m/z*: 82 (M-18), 67, 58.

To a solution of the preceding 2-methyl-pent-4-en-1-ol (24.2 g, 241.5 mmol, 1.0 equiv) and Sudan III (small amount) in CH₂Cl₂/MeOH (100 mL:100 mL) at -78 °C was bubbled a stream of ozone until the pink solution became colourless (ca 7 h). Then PPh₃ (63.3 g, 241.5 mmol, 1.0 equiv) was cautiously added (over 30 min), the cold bath was removed and the mixture was stirred at 20 °C for one night. The solvents were removed under reduced pressure (20 mm Hg) and the product was distilled out of the reaction mixture using a microdistillation apparatus under reduced pressure (0.2 mmHg) at 70 °C to give lactol (±)-27 (19.7 g, 80 %) as a mixture 1:2 of two diastereomers as a colourless oil. [(±)-27]: RN: 34314-85-7; *first anomer*: ¹H NMR (400.0 MHz, CDCl₃): δ = 5.46 (d, *J* = 5.0 Hz, 1H), 4.09 (t, *J* = 7.8 Hz, 1H), 3.32 (dd, *J* = 7.8, 7.3 Hz, 1H), 2.80 (bs, 1H, OH), 2.24 (dddq, *J* = 9.2, 7.8, 7.3, 6.9, 6.9 Hz, 1H), 1.97 (dd, *J* = 12.8, 6.9 Hz, 1H), 1.51 (dd, *J* = 12.8, 9.2, 5.0 Hz, 1H), Ha-11, 1.03 (d, *J* = 6.9 Hz, 3H, CH₃); *second anomer*: ¹H NMR (400.0 MHz, CDCl₃): δ = 5.46 (d, *J* = 4.6 Hz, 1H), 3.95 (dd, *J* = 8.2, 6.6 Hz, 1H), 3.55 (dd, *J* = 8.7, 8.2 Hz, 1H), 2.92 (bs, 1H, OH), 2.58-2.48 (m, 1H), 1.76-1.70 (m, 1H), 1.47-1.40 (m, 1H), 1.09 (d, *J* = 6.4 Hz, 3H, CH₃); *first anomer*: ¹³C NMR (100.5 MHz, CDCl₃): δ = 98.9 (CH), 74.4 (CH₂), 41.8 (CH₂), 31.4 (CH), 17.8 (CH₃); *second anomer*: ¹³C NMR (100.5 MHz, CDCl₃): δ = 99.4 (CH), 73.5 (CH₂), 41.8 (CH₂), 33.3 (CH), 17.3 (CH₃); MS (GC, EI): *m/z*: 101, 84, 72, 56; IR (Film) ν = 3406, 2960, 2935, 2875, 1455, 1379, 1346, 1290, 1122, 1095, 1056, 1002, 927 cm⁻¹.

(4*R*,5*S*)-3-Methyl-2,3-dihydro-furan [(±)-9]: To a solution of lactol (±)-27 (19.7 g, 192.9 mmol, 1.0 equiv), thiophenol (21.3 g, 192.9 mmol, 1.0 equiv) and 4 Å molecular sieves in dry diethyl ether (400 mL) at 0 °C was added dropwise boron trifluoride ethyl etherate (BF₃·OEt₂, 24.4 mL, 192.9 mmol, 1.0 equiv). The cold bath was removed and the mixture was stirred 2 h at 20 °C. The reaction mixture was removed by filtration through a pad of celite and the solid was washed with diethyl ether. The combined filtrate and washings were neutralized by addition of 4*N* aqueous NaOH solution (58 mL, 232 mmol, 1.2 equiv). The organic layer was dried over MgSO₄, filtered and the solvent removed under reduced pressure. Purification by flash chromatography on silica gel (cyclohexane/diethyl ether 100:0 to 75:25) gave 4-methyl-2-phenylsulfanyl-tetrahydro-furan (31.5 g, 84 % yield) as a 1:1 mixture of diastereomers as yellow oil. *First anomer*: ¹H NMR (400.0 MHz, CDCl₃): δ = 7.54-7.48 (m, 2H), 7.34-7.20 (m, 3H), 5.70 (dd, *J* = 7.3, 4.1 Hz, 1H), 4.18 (dd, *J* = 8.2, 6.9 Hz, 1H), 3.53 (dd, *J* = 8.2, 5.1 Hz, 1H), 2.50 (ddq, *J* = 7.6, 7.3, 6.9, 6.9, 5.1 Hz, 1H), 2.17 (ddd, *J* = 12.0, 7.6, 4.1 Hz,

1H), 2.02 (dt, *J* = 12.0, 7.3 Hz, 1H), 1.08 (d, *J* = 6.9 Hz, 3H, CH₃); *second anomer*: ¹H NMR (400.0 MHz, CDCl₃): δ = 7.54-7.48 (m, 2H), 7.34-7.20 (m, 3H), 5.63 (dd, *J* = 6.9, 6.9 Hz, 1H), 4.02 (dd, *J* = 8.6, 7.3 Hz, 1H), 3.56 (dd, *J* = 9.6, 8.6 Hz, 1H), 2.63 (ddd, *J* = 13.3, 8.2, 6.9 Hz, 1H), 2.30 (dddq, *J* = 9.6, 9.0, 8.2, 7.3, 6.4 Hz, 1H), 1.53 (ddd, *J* = 13.3, 9.0, 6.9 Hz, 1H), 1.11 (d, *J* = 6.4 Hz, 3H, CH₃); *first anomer*: ¹³C NMR (100.5 MHz, CDCl₃): δ = 135.8 (C), 130.6 (CH), 128.8 (2CH), 126.6 (2CH), 87.2 (CH), 74.2 (CH₂), 41.0 (CH₂), 32.7 (CH), 18.7 (CH₃); *second anomer*: ¹³C NMR (100.5 MHz, CDCl₃): δ = 136.1 (C), 130.9 (CH), 128.8 (2CH), 126.7 (2CH), 87.2 (CH), 73.5 (CH₂), 41.0 (CH₂), 33.6 (CH), 16.3 (CH₃); MS (GC, EI): *m/z*: 194 (M⁺), 164, 149, 135, 123, 110, 85, 77, 69, 57, 50; IR (Film) ν = 3058, 2961, 2930, 2871, 2360, 2341, 1584, 1481, 1439, 1067, 1037, 1007, 901, 741 cm⁻¹.

Hemithioacetal elimination: A mixture of the above hemithioacetal (15.2 g, 78.2 mmol, 1.0 equiv) and DBU (14.3 g, 93.9 mmol, 1.2 equiv) in a microdistillation apparatus were heated from 160 °C to 240 °C (over 30 min). The elimination product was simultaneously distilled out of the reaction mixture and the temperature was kept at 240 °C until the distillation ceased to give the neat DHF (±)-9 (3.72 g, 57 %).

Lactol elimination: A solution of lactol (±)-27 (4.0 g, 39 mmol, 1.0 equiv) and *p*-toluene sulfonic acid (16 mg, 0.09 mmol, 0.0022 equiv) in quinoline (2.1 mL) was heated from 160 °C to 245 °C. Distillation of a mixture of the title compound with water was achieved in 45 min (bp: 80-90 °C). After separation of water, 2.8 g of dihydrofuran (±)-9 were obtained with 85 % yield. [(±)-9]: see above for data

(4*S*)-3-Methyl-2,3-dihydro-furan (9): To a solution of commercially available (*R*)-3-bromo-2-methyl-propanol 26 (13.1 g, 85.8 mmol, 1.0 equiv) in DMSO (140 mL) was added sodium cyanide (4.62 g, 94.4 mmol, 1.2 equiv). The reaction was stirred for 24 h, at 20 °C. The solution was then poured into water, and extracted three times with EtOAc. To extract the remainder of the compound, the aqueous solution was carefully acidified to pH = 5 using 10 % sulfuric acid. After extracting the aqueous layer three more times, the combined organic layers were washed with brine, dried over MgSO₄ and the solvent removed under reduced pressure. The (2*S*)-3-cyano-2-methyl propan-1-ol (7.6 g, 89 % yield) was collected and used directly in the next step. ((2*S*)-3-cyano-2-methyl propan-1-ol): ¹H NMR (400.0 MHz, CDCl₃): δ = 3.65 (ddd, *J* = 10.5, 5.0, 4.6 Hz, 1H), 3.50 (ddd, *J* = 10.5, 7.3, 5.0 Hz, 1H), 2.62 (t, *J* = 5.0 Hz, 1H, OH), 2.50 (dd, *J* = 16.7, 5.5 Hz, 1H), 2.37 (dd, *J* = 16.7, 6.9 Hz, 1H), 2.06 (dq, *J* = 7.3, 6.9, 5.5, 4.6 Hz, 1H), 1.08 (d, *J* = 6.9 Hz, 3H, CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 118.7 (C), 65.6 (CH₂), 32.8 (CH), 20.8 (CH₂), 15.8 (CH₃); IR (Film) ν = 3416, 2967, 2933, 2880, 2251, 1644, 1464, 1424, 1387, 1350, 1044, 993; MS (GC, EI): *m/z*: 99, 69, 59, 54.

To a solution of the preceding nitrile derivative (3.4 g, 34 mmol, 1.0 equiv) in CH₂Cl₂ (60 mL) at -78 °C was slowly added a solution of DIBAL-H (1 M in CH₂Cl₂, 86 mL, 86 mmol, 2.5 equiv). The mixture was stirred at -78 °C until disappearance of the starting material, then diluted with AcOEt and poured into a solution of Rochelle salt (C₄H₄KNaO₆·4H₂O, 78 g, 8.0 equiv). After stirring for 12 h the mixture was extracted with AcOEt, the combined organic phases were washed with brine, dried over MgSO₄ and the solvent removed under reduced pressure. The (2*R*,5*S*)-4-methyl tetrahydrofuran-2-ol 27 was obtained as a 1:2 diastereomeric mixture (2.87 g, 82 % yield). (27): RN: 34314-85-7. (See above analysis description of racemic 4-methyltetrahydrofuran-2-ol (±)-27).

A solution of the above optically active lactol 27 (5.0 g, 49 mmol, 1.0 equiv) and *p*-toluene sulfonic acid (25 mg, 0.11 mmol, 0.0022 equiv) in quinoline (2.5 mL) was heated from 160 °C to 245 °C. Distillation of a mixture of the title compound with water was achieved in 45 min (bp: 80-90 °C). After separation of water, 3.5 g of dihydrofuran 9 were obtained with 85 % yield (9): RN: 1708-27-6; ¹H NMR (400.0 MHz, CDCl₃): δ = 6.30 (dd, *J* = 2.8, 2.3 Hz, 1H), 4.94 (dd, *J* = 2.8, 2.3 Hz, 1H), 4.38 (dd, *J* = 9.6, 8.7 Hz, 1H), 3.85 (dd, *J* = 8.7, 6.4 Hz, 1H), 3.03 (dq, *J* = 9.6, 6.9, 6.4, 2.3 Hz, 1H), 1.07 (d, *J* = 6.9 Hz, 3H, CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 145.3 (CH), 106.6 (CH), 76.8 (CH₂), 36.6 (CH), 20.8 (CH₃).

(2*S*,3*Z*)-2-Methyl-4-tributylstannyl-pent-3-en-1-ol (13): To a suspension of CuCN (5.41 g, 60.4 mmol, 2.0 equiv) of in dry Et₂O (10 mL) and dimethyl sulfide (40 mL) at -30 °C was added MeLi (1.6 M solution in diethyl ether, 94.4 mL, 151.0 mmol, 5.0 equiv). The solution was stirred at -30 °C for 5 min and allowed to warm up to 0 °C for 20 min (pale yellow colour). To a solution of dihydrofuran 9 (2.54 g, 30.2 mmol, 1.0 equiv) in dry diethyl ether (50 mL) at -60 °C was added *t*-BuLi (1.5M solution in pentane, 24.2 mL, 36.2 mmol, 1.2 equiv). The mixture was stirred at 0 °C for 50 min. Then the solution of the lithio-dihydrofuran, prepared above, was added via cannula to the cyanocuprate (Et₂O/DMS 4:1) and the reaction mixture was allowed to warm up to 20 °C (strong orange colour) over 12 h. The mixture was cooled at -30 °C and tri-*n*-butyltin chloride (49.1 mL, 181.2 mmol, 5.0 equiv) was added. The reaction mixture was allowed to warm up to 20 °C over 5 h. Finally the reaction mixture was poured into a mixture of a saturated aqueous NH₄Cl solution and concentrated ammonia (4:1) at 0 °C and stirred for 1h at 20 °C before extraction with diethyl ether. The organic layer was washed with water, brine, dried over MgSO₄ and the solvent was removed under reduced pressure. The crude residue was purified by chromatography on silica gel (cyclohexane/diethyl ether 100:0 to 60:40) to give the title compound 13 (8.21 g, 68 %

yield). **(13)**: ¹H NMR (400.0 MHz, CDCl₃): δ = 5.78 (dq, *J* = 9.6, 1.8 Hz, *J*_{H₁₁₇Sn} = *J*_{H₁₁₉Sn} = 128.7 Hz, 1H), 3.47 (ddd, *J* = 10.5, 8.7, 6.0 Hz, 1H), 3.36 (ddd, *J* = 10.5, 8.2, 3.7 Hz, 1H), 2.16 (dddd, *J* = 9.6, 8.7, 8.2, 6.9 Hz, 1H), 1.92 (d, *J* = 1.8 Hz, *J*_{H₁₁₇Sn} = *J*_{H₁₁₉Sn} = 41.7 Hz, 3H, CH₃), 1.55-1.45 (m, 6H, 3CH₂), 1.39-1.28 (m, 7H, OH + 3CH₂), 0.95 (d, *J* = 6.4 Hz, 3H, CH₃), 0.99-0.91 (m, 6H, 3CH₂), 0.90 (m, 9H, 3CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 143.0 (CH, *J*_{13C,117Sn} = *J*_{13C,119Sn} = 27.8 Hz), 140.9 (C), 67.3 (CH), 42.4 (CH, *J*_{13C,117Sn} = *J*_{13C,119Sn} = 33.6 Hz), 29.3 (3CH₂, *J*_{13C,117Sn} = *J*_{13C,119Sn} = 20.4 Hz), 27.5 (3CH₂, *J*_{13C,117Sn} = *J*_{13C,119Sn} = 57.5 Hz), 27.2 (CH₃, *J*_{13C,117Sn} = *J*_{13C,119Sn} = 46.0 Hz), 17.4 (CH₃), 13.7 (3CH₃), 10.1 (3CH₂, *J*_{13C,117Sn} = 314.4 Hz, *J*_{13C,119Sn} = 329.7 Hz); MS (GC, CI, NH₃): *m/z*: 373 (MH⁺ - H₂O), 359 (MH⁺ - H₂O - Bu), 291 (Bu₃Sn⁺), 261, 249, 235, 141, 113, 101, 85, 57; IR (Film) ν = 3327, 2956, 2928, 2920, 2871, 2853, 1678, 1623, 1483, 1456, 1377, 1340, 1292, 1072, 1037, 996, 864, 690, 668 cm⁻¹; elemental analysis calcd (%) for C₁₈H₃₈O₃Sn: C 55.55, H 9.84; found: C 55.73, H 10.02.

(2S,3Z)-2-Methyl-4-tributylstannyl-pent-3-en-1-ol (28): To a solution of alcohol **13** (6.7 g, 17.2 mmol, 1.0 equiv) and TEMPO (538 mg, 3.45 mmol, 0.2 equiv) in CH₂Cl₂ (40 mL) was added BAIB (6.09 g, 18.9 mmol, 1.1 equiv). The mixture was stirred until disappearance of starting material (2 h), diluted with cyclohexane, washed with an aqueous saturated Na₂S₂O₃ solution, and extracted with cyclohexane. The combined organic phases were washed with a saturated aqueous NaHCO₃ solution, brine, dried over MgSO₄ and the solvent was removed under reduced pressure until the volume is approximately equal to 20 mL. This solution can be kept only few hour before use (the neat product **28** is more instable). **(28)**: ¹H NMR (400.0 MHz, CDCl₃): δ = 9.48 (d, *J* = 1.7 Hz, 1H), 5.72 (dq, *J* = 9.7, 1.6 Hz, *J*_{H₁₁₇Sn} = *J*_{H₁₁₉Sn} = 122.1 Hz, 1H), 2.89 (dq, *J* = 9.7, 6.4, 1.7 Hz, 1H), 1.89 (d, *J* = 1.6 Hz, *J*_{H₁₁₇Sn} = *J*_{H₁₁₉Sn} = 40.7 Hz, 3H, CH₃), 1.47-1.37 (m, 6H, 3CH₂), 1.24 (sext, *J* = 7.3 Hz, 6H, 3CH₂), 1.08 (d, *J* = 6.4 Hz, 3H, CH₃), 0.91-0.86 (m, 6H, 3CH₂), 0.83 (t, *J* = 7.3 Hz, 9H, 3CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 202.1 (CH), 146.0 (C, *J*_{13C,117Sn} = 346.0 Hz, *J*_{13C,119Sn} = 362.3 Hz), 136.2 (CH, *J*_{13C,117Sn} = *J*_{13C,119Sn} = 24.9 Hz), 53.1 (CH, *J*_{13C,117Sn} = *J*_{13C,119Sn} = 31.6 Hz), 29.1 (3CH₂, *J*_{13C,117Sn} = *J*_{13C,119Sn} = 19.2 Hz), 27.4 (CH₃, *J*_{13C,117Sn} = *J*_{13C,119Sn} = 40.3 Hz, CH₃), 27.3 (3CH₂, *J*_{13C,117Sn} = *J*_{13C,119Sn} = 58.5 Hz), 14.4 (CH₃), 13.7 (3CH₃), 10.1 (3CH₂, *J*_{13C,117Sn} = 317.3 Hz, *J*_{13C,119Sn} = 332.6 Hz); MS (GC, CI, NH₃): *m/z*: 331 (M⁺ - Bu), 291 (Bu₃Sn⁺), 275, 255, 235, 217, 189, 177, 159, 147, 135, 121, 97; IR (Film) ν = 2958, 2927, 2872, 2854, 2809, 1726, 1614, 1463, 1426, 1377, 1072, 999, 854, 689 cm⁻¹.

(2R/S,3Z)-2-Methyl-4-tributylstannyl-pent-3-en-1-ol [(±)-13]: The same protocol used before for the synthesis of **13** was employed to prepare (±)-**13** (16.5 g, 67 % yield) from (±)-**9** (5 g). See above for data

(2R/S,3Z)-2-Methyl-4-tributylstannyl-pent-3-en-1-ol [(±)-28]: The same protocol used before for the synthesis of **28** was employed to prepare (±)-**28** from (±)-**13** (2.5g). See above for data

(1Z,3S,4S,5S,6Z)-1-((*N,N*-Diisopropyl)carbamoyloxy)-3,5-dimethyl-7-tributylstannyl-octa-1,6-dien-4-ol (29):

(1Z,3S,4S,5R,6Z)-1-((*N,N*-Diisopropyl)carbamoyloxy)-3,5-dimethyl-7-tributylstannyl-octa-1,6-dien-4-ol (**31**): From optically pure aldehyde **28**: To a quick stirred solution of the (*E*)-crotyldiisopropylcarbamate (787 mg, 3.95 mmol, 3.0 equiv) and (-)-sparteine (925 mg, 3.95 mmol, 3.0 equiv) in pentane (6 mL) and cyclohexane (1 mL) at -78 °C, was added a solution of *n*-BuLi (1.6 M in hexanes, 2.4 mL, 3.95 mmol, 3.0 equiv), and after 10 min white crystals appeared. After 3 h of crystallization at -78 °C, a pre-cooled (-40 °C) solution of titanium tetraisopropoxide (Ti(O*i*Pr)₄, 3.5 mL, 11.9 mmol, 9.0 equiv) in pentane (7 mL) was quickly added via cannula to the reaction mixture of lithio carbamate which became limp and turned orange. After 1 h at -78 °C aldehyde **28** (513 mg, 1.30 mmol, 1.0 equiv) in cyclohexane (5 mL) was slowly added to the orange solution, and the mixture was stirred for 3 h at -78 °C. The solution was then poured into a mixture of Et₂O-saturated aqueous NH₄Cl solution. After extraction with Et₂O, the organic layer was washed with brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/AcOEt 95:5 to 80:20) to give the title compound **29** (669 mg, 87 % yield for two steps) as a single diastereomer. **(29)**: [α]_D²⁰ = + 20.7 (*c* = 0.94, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃): δ = 7.15 (d, *J* = 6.4 Hz, 1H), 6.17 (dq, *J* = 9.9, 1.4 Hz, *J*_{H₁₁₇Sn} = *J*_{H₁₁₉Sn} = 134.0 Hz, 1H), 4.66 (dd, *J* = 9.8, 6.4 Hz, 1H), 4.19-4.02 (bs, 1H), 3.78-3.61 (bs, 1H), 3.25 (dt, *J* = 8.0, 2.8 Hz, 1H), 2.86 (ddq, *J* = 9.8, 8.0, 6.9 Hz, 1H), 2.18 (dq, *J* = 9.9, 6.8, 2.8 Hz, 1H), 1.90 (d, *J* = 1.4 Hz, *J*_{H₁₁₇Sn} = *J*_{H₁₁₉Sn} = 42.6 Hz, 3H, CH₃), 1.72 (bd, *J* = 2.8 Hz, 1H, OH), 1.55-1.45 (m, 6H, 3CH₂), 1.38-1.16 (sext, *J* = 7.3 Hz, 6H, 3CH₂), 1.20-1.12 (m, 12H, 4CH₃), 1.00 (d, *J* = 6.9 Hz, 3H, CH₃), 0.98 (d, *J* = 6.8 Hz, 3H, CH₃), 0.99-0.92 (m, 6H, 3CH₂), 0.89 (t, *J* = 7.3 Hz, 9H, 3CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 152.9 (C), 144.3 (CH, *J*_{13C,117Sn} = *J*_{13C,119Sn} = 27.8 Hz), 137.7 (C, *J*_{13C,117Sn} = 375.7 Hz, *J*_{13C,119Sn} = 392.0 Hz), 136.7 (CH), 113.2 (CH), 78.6 (CH), 47.1 (CH), 45.7 (CH), 41.3 (CH, *J*_{13C,117Sn} = *J*_{13C,119Sn} = 32.6 Hz), 34.5 (CH), 29.3 (3CH₂, *J*_{13C,117Sn} = *J*_{13C,119Sn} = 19.2 Hz), 27.5 (3CH₂, *J*_{13C,117Sn} = *J*_{13C,119Sn} = 57.5 Hz), 27.2 (CH₃, *J*_{13C,117Sn} = *J*_{13C,119Sn} = 46.0 Hz), 21.7 (2CH₃), 20.4 (2CH₃), 17.6 (CH₃), 14.2 (CH₃), 13.8 (3CH₃), 10.0 (3CH₂, *J*_{13C,117Sn} = 313.4 Hz, *J*_{13C,119Sn} = 326.8 Hz); IR (Film) ν = 3490, 2957, 2929, 2872, 2851, 1705, 1463, 1455, 1441, 1370, 1301, 1289, 1210, 1135, 1065, 997, 862, 762 cm⁻¹; MS (GC, CI, NH₃): *m/z*: 530, 385, 327, 291 (Bu₃Sn⁺),

257, 235, 199, 177, 12, 86, 69; elemental analysis calcd (%) for C₂₉H₅₇NO₅Sn: C 59.39, H 9.802, N 2.39; found: C 59.51, H 9.90, N 2.30.

From racemic aldehyde (±)-**28**: To a quick stirred solution of the (*E*)-crotyldiisopropylcarbamate (6.84 g, 34.4 mmol, 2.0 equiv) and (-)-sparteine (8.30 g, 35.4 mmol, 2.06 equiv) in pentane (36 mL) and cyclohexane (6 mL) at -78 °C, was added a solution of *n*-BuLi (1.6 M in hexane, 23 mL, 36.8 mmol, 2.14 equiv), and after 10 min white crystals appeared. After 3 h of crystallization at -78 °C, a pre-cooled (-40 °C) solution of titanium tetraisopropoxide (Ti(O*i*Pr)₄, 30.5 mL, 103.2 mmol, 6.0 equiv) in pentane (30 mL) was quickly added via cannula to the reaction mixture of lithio carbamate which became limp and turned orange. After 1 h at -78 °C aldehyde (±)-**28** (6.66 g, 17.2 mmol, 1.0 equiv) in cyclohexane (5 mL) was slowly added to the orange solution, and the mixture was stirred for 3 h at -78 °C. The solution was then poured into a mixture of Et₂O-saturated aqueous NH₄Cl solution. After extraction with Et₂O, the organic layer was washed with brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/AcOEt 95:5 to 80:20) to give the title compound **29** (8.50 g, 42 % yield for two steps) and its 12R minor isomer **31** (1.41 g, 14 % yield). **(29)**: see above for data. **(31)**: ¹H NMR (400.0 MHz, CDCl₃): δ = 7.10 (d, *J* = 6.9 Hz, 1H), 5.88 (dq, *J* = 9.8, 1.7 Hz, *J*_{H₁₁₇Sn} = *J*_{H₁₁₉Sn} = 128.0 Hz, 1H), 4.86 (dd, *J* = 10.1, 6.9 Hz, 1H), 4.12-3.99 (bs, 1H), 3.91-3.78 (bs, 1H), 3.19 (dd, *J* = 8.4, 2.6 Hz, 1H), 2.92 (dq, *J* = 10.1, 6.9, 2.6 Hz, 1H), 2.00 (dq, *J* = 9.8, 8.4, 6.4 Hz, 1H), 1.92 (d, *J* = 1.7 Hz, *J*_{H₁₁₇Sn} = *J*_{H₁₁₉Sn} = 40.3 Hz, 3H, CH₃), 1.55-1.45 (m, 6H, 3CH₂), 1.38-1.16 (sext, *J* = 7.3 Hz, 19H, 3CH₂+ OH + 4CH₃), 1.13 (d, *J* = 6.9 Hz, 3H, CH₃), 0.96 (d, *J* = 6.4 Hz, 3H, CH₃), 0.99-0.92 (m, 6H, 3CH₂), 0.89 (t, *J* = 7.3 Hz, 9H, 3CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 152.6 (C), 144.3 (CH, *J*_{13C,117Sn} = *J*_{13C,119Sn} = 28.8 Hz), 142.2 (C, *J*_{13C,117Sn} = 355.1 Hz, *J*_{13C,119Sn} = 372.4 Hz), 135.3 (CH), 111.0 (CH), 77.7 (CH), 46.6 (CH), 46.0 (CH), 44.0 (CH, *J*_{13C,117Sn} = *J*_{13C,119Sn} = 29.8 Hz), 32.1 (CH), 29.1 (3CH₂, *J*_{13C,117Sn} = *J*_{13C,119Sn} = 20.2 Hz), 27.4 (3CH₂, *J*_{13C,117Sn} = *J*_{13C,119Sn} = 57.6 Hz), 27.2 (CH₃, *J*_{13C,117Sn} = *J*_{13C,119Sn} = 42.2 Hz), 21.4 (2CH₃), 20.3 (2CH₃), 18.7 (CH₃), 17.3 (CH₃), 13.6 (3CH₃), 10.1 (3CH₂, *J*_{13C,117Sn} = 315.7 Hz, *J*_{13C,119Sn} = 330.1 Hz).

(*R*)-mandelic ester of **29**:

(*R*)-mandelic ester of **31**: a) from pure carbamate **29**: To a solution of compounds **29** (150 mg, 0.24 mmol, 1.0 equiv), obtained from optically pure aldehyde **28**, in CH₂Cl₂ (5 mL) at 20 °C were successively added (*R*)-(-)-methoxyphenylacetic acid (80 mg, 0.48 mmol, 2.0 equiv), DCC (100 mg, 0.48 mmol, 2.0 equiv) and DMAP (10 mg, 0.09 mmol, 0.4 equiv). The resulting mixture was stirred for 4 h at 20 °C then quenched with a saturated aqueous NaHCO₃ solution and extracted with Et₂O. The organic layers were washed with water and brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/Et₂O 85:15) to give 154 mg (84 % yield) of the title (*R*)-mandelic ester of **29** compound. b) from a mixture of carbamates **29** and **31**: To a solution of compounds **29** and **31** (125 mg, 0.21 mmol, 1.0 equiv), obtained from racemic aldehyde (±)-**28**, in CH₂Cl₂ (5 mL) at 20 °C were successively added (*R*)-(-)-methoxyphenylacetic acid (71 mg, 0.43 mmol, 2.0 equiv), DCC (88 mg, 0.43 mmol, 2.0 equiv) and DMAP (5 mg, 0.08 mmol, 0.4 equiv). The resulting mixture was stirred for 4 h at 20 °C then quenched with a saturated aqueous NaHCO₃ solution and extracted with Et₂O. The organic layers were washed with water and brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/Et₂O 85:15) to give 85 mg (54 % yield) of the (*R*)-mandelic ester of **29** and 14 mg of its 3,4-*bis* *epi* diastereomer (*R*)-mandelic ester of **31**, 9 % yield). (*R*)-mandelic ester of **29**: [α]_D²⁰ = + 42.1 (*c* = 1.4, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃): δ = 7.46-7.42 (m, 2H), 7.38-7.22 (m, 3H), 6.82 (d, *J* = 6.4 Hz, 1H), 5.68 (dq, *J* = 9.6, 1.8 Hz, *J*_{H₁₁₇Sn} = *J*_{H₁₁₉Sn} = 131.2 Hz, 1H), 4.83 (t, *J* = 6.0 Hz, 1H), 4.77 (s, 1H), 4.46 (dd, *J* = 9.6, 6.4 Hz, 1H), 4.17-4.03 (bs, 1H), 3.67-3.53 (bs, 1H), 3.43 (s, 3H, CH₃), 2.90 (dq, *J* = 9.6, 6.9, 6.0 Hz, 1H), 2.23 (dq, *J* = 9.6, 6.9, 6.0 Hz, 1H), 1.77 (d, *J* = 1.8 Hz, *J*_{H₁₁₇Sn} = *J*_{H₁₁₉Sn} = 41.7 Hz, 3H, CH₃), 1.52-1.42 (m, 6H, 3CH₂), 1.31 (sext, *J* = 7.3 Hz, 6H, 3CH₂), 1.25-1.18 (m, 12H, 4CH₃), 0.93-0.87 (m, 18H, 4CH₃ + 3CH₂), 0.71 (d, *J* = 6.9 Hz, 3H, CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 170.6 (C), 152.7 (C), 142.0 (CH, *J*_{13C,117Sn} = *J*_{13C,119Sn} = 29.7 Hz), 139.1 (C, *J*_{13C,117Sn} = *J*_{13C,119Sn} = 384.4 Hz), 136.7 (C), 135.6 (CH), 128.8 (2CH), 128.6 (2CH), 127.4 (CH), 110.8 (CH), 83.0 (CH), 80.6 (CH), 57.5 (CH₃), 47.1 (CH), 45.5 (CH), 40.8 (CH, *J*_{13C,117Sn} = *J*_{13C,119Sn} = 30.7 Hz), 32.9 (CH), 29.3 (3CH₂, *J*_{13C,117Sn} = *J*_{13C,119Sn} = 19.2 Hz), 27.6 (3CH₂, *J*_{13C,117Sn} = *J*_{13C,119Sn} = 57.5 Hz), 27.2 (CH₃, *J*_{13C,117Sn} = *J*_{13C,119Sn} = 42.2 Hz), 21.7 (2CH₃), 20.4 (2CH₃), 17.9 (CH₃), 17.0 (CH₃), 13.8 (3CH₃), 10.0 (3CH₂, *J*_{13C,117Sn} = 314.4 Hz, *J*_{13C,119Sn} = 328.8 Hz); IR (Film) ν = 2960, 2928, 2872, 2851, 1751, 1710, 1453, 1439, 1374, 1308, 1288, 1210, 1174, 1152, 1135, 1120, 1056, 1000 cm⁻¹; elemental analysis calcd (%) for C₃₈H₆₅NO₅Sn: C 62.13, H 8.92, N 1.91; found: C 62.20, H 9.05, N 1.85. (*R*)-mandelic ester of **31**: [α]_D²⁰ = - 36.7 (*c* = 0.9, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃): δ = 7.47-7.41 (m, 2H), 7.40-7.30 (m, 3H), 7.05 (d, *J* = 6.4 Hz, 1H), 5.12 (dq, *J* = 9.6, 1.8 Hz, *J*_{H₁₁₇Sn} = *J*_{H₁₁₉Sn} = 131.7 Hz, 1H), 4.77 (dd, *J* = 7.8, 4.6 Hz, 1H), 4.69 (s, 1H), 4.67 (dd, *J* = 9.6, 6.4 Hz, 1H), 4.29-4.12 (bs, 1H), 3.85-3.71 (bs, 1H), 3.43 (s, 3H, CH₃), 3.00 (dq, *J* = 9.6, 6.9, 7.8 Hz, 1H), 2.13 (dq, *J* = 9.6, 6.4, 6.6 Hz, 1H), 1.58 (d, *J* = 1.8 Hz, *J*_{H₁₁₇Sn} = *J*_{H₁₁₉Sn} = 42.1 Hz, 3H, CH₃), 1.50-1.39 (m, 6H, 3CH₂), 1.38-1.19 (m, 18H, 3CH₂ + 4CH₃), 0.98 (d, *J* = 6.9 Hz, 3H, CH₃), 0.93-0.87 (m, 15H, 3CH₂ + 3CH₃), 0.69 (d, *J* = 6.4 Hz, 3H, CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 170.2 (C), 153.0 (C), 142.1 (CH, *J*_{13C,117Sn} = *J*_{13C,119Sn} = 27.8 Hz),

138.6 (C), 136.9 (C), 135.8 (CH), 128.8 (2CH), 128.7 (2CH), 127.5 (CH), 112.4 (CH), 82.6 (CH), 80.4 (CH), 57.6 (CH₃), 47.2 (CH), 45.6 (CH), 40.2 (CH, $J_{13C,117Sn} = J_{13C,119Sn} = 32.6$ Hz), 32.9 (CH), 29.3 (3CH₂, $J_{13C,117Sn} = J_{13C,119Sn} = 20.1$ Hz), 27.5 (3CH₂, $J_{13C,117Sn} = J_{13C,119Sn} = 58.5$ Hz), 27.0 (CH₃, $J_{13C,117Sn} = J_{13C,119Sn} = 45.1$ Hz), 21.8 (2CH₃), 20.5 (2CH₃), 17.6 (CH₃), 15.0 (CH₃), 13.8 (3CH₃), 9.7 (3CH₂, $J_{13C,117Sn} = J_{13C,119Sn} = 32.8$ Hz); IR (Film) $\nu = 2959, 2928, 2873, 2851, 1752, 1710, 1455, 1439, 1373, 1310, 1285, 1210, 1172, 1154, 1118, 1063, 1005$ cm⁻¹.

(S)- mandelic ester of **29**:

(S)- mandelic ester of 31: a from pure carbamate **29**: To a solution of compound **29** (150 mg, 0.24 mmol, 1.0 equiv), obtained from optically pure aldehyde **28**, in CH₂Cl₂ (5 mL) at 20 °C were successively added (S)-(-)-methoxyphenylacetic acid (80 mg, 0.48 mmol, 2.0 equiv), DCC (100 mg, 0.48 mmol, 2.0 equiv) and DMAP (10 mg, 0.09 mmol, 0.4 equiv). The resulting mixture was stirred for 4 h at 20 °C then quenched with a saturated aqueous NaHCO₃ solution and extracted with Et₂O. The organic layers were washed with water and brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/Et₂O 85:15) to give 160 mg (87 % yield) of the **(S)-mandelic ester of 29** compound. **b**) from a mixture of carbamates **29** and **31**: To a solution of compounds **29** and **31** (97 mg, 0.165 mmol, 1.0 equiv), obtained from racemic aldehyde (+/-)-**28**, in CH₂Cl₂ (5 mL) at 20 °C were successively added (S)-(-)-methoxyphenylacetic acid (55 mg, 0.33 mmol, 2.0 equiv), DCC (68 mg, 0.33 mmol, 2.0 equiv) and DMAP (4 mg, 0.07 mmol, 0.4 equiv). The resulting mixture was stirred for 4 h at 20 °C then quenched with a saturated aqueous NaHCO₃ solution and extracted with Et₂O. The organic layers were washed with water and brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/Et₂O 85:15) to give 82 mg (68 % yield) of **(S)-mandelic ester of 29** and 24 mg of **(S)-mandelic ester of 31** (20 % yield). **((S)- mandelic ester of 29)**: $[\alpha]_D^{20} = +58.6$ ($c = 1.1$, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃): $\delta = 7.49-7.41$ (m, 2H), 7.40-7.30 (m, 3H), 7.04 (d, $J = 6.4$ Hz, 1H), 5.13 (dq, $J = 9.4, 1.6$ Hz, $J_{1H,117Sn} = J_{1H,119Sn} = 131.9$ Hz, 1H), 4.77 (dd, $J = 7.8, 4.6$ Hz, 1H), 4.69 (s, 1H), 4.67 (dd, $J = 9.9, 6.4$ Hz, 1H), 4.28-4.11 (bs, 1H), 3.88-3.71 (bs, 1H), 3.43 (s, 3H, CH₃), 3.0 (ddq, $J = 9.9, 7.8, 6.9$ Hz, 1H), 2.13 (ddq, $J = 9.4, 6.9, 4.6$ Hz, 1H), 1.58 (d, $J = 1.6$ Hz, $J_{1H,117Sn} = J_{1H,119Sn} = 41.7$ Hz, 3H, CH₃), 1.49-1.38 (m, 6H, 3CH₂), 1.37-1.19 (m, 18H, 3CH₂ + 4CH₃), 0.98 (d, $J = 6.9$ Hz, 3H, CH₃), 0.93-0.83 (m, 15H, 3CH₂ + 3CH₃), 0.69 (d, $J = 6.9$ Hz, 3H, CH₃); ¹³C NMR (100.5 MHz, CDCl₃): $\delta = 170.2$ (C), 153.0 (C), 142.1 (CH, $J_{13C,117Sn} = J_{13C,119Sn} = 30.7$ Hz), 138.6 (C, $J_{13C,117Sn} = 368.1$ Hz, $J_{13C,119Sn} = 396.8$ Hz), 136.9 (C), 135.8 (CH), 128.8 (2CH), 128.7 (2CH), 127.5 (CH), 112.4 (CH), 82.6 (CH), 80.4 (CH), 57.6 (CH₃), 47.2 (CH), 45.6 (CH), 40.3 (CH, $J_{13C,117Sn} = J_{13C,119Sn} = 33.6$ Hz), 32.9 (CH), 29.3 (3CH₂, $J_{13C,117Sn} = J_{13C,119Sn} = 19.2$ Hz), 27.5 (3CH₂, $J_{13C,117Sn} = J_{13C,119Sn} = 57.5$ Hz), 27.0 (CH₃, $J_{13C,117Sn} = J_{13C,119Sn} = 45.1$ Hz), 21.8 (2CH₃), 20.5 (2CH₃), 17.6 (CH₃), 15.4 (CH₃), 13.8 (3CH₃), 9.7 (3CH₂, $J_{13C,117Sn} = J_{13C,119Sn} = 327.8$ Hz); IR (Film) $\nu = 2960, 2928, 2873, 2852, 1753, 1710, 1454, 1440, 1373, 1309, 1288, 1210, 1175, 1152, 1133, 1118, 1060, 1005$ cm⁻¹; elemental analysis calcd (%) for C₃₈H₆₅NO₅Sn: C 62.13, H 8.92, N 1.91; found: C 62.220, H 9.04, N 1.96. **((S)- mandelic ester of 31)**: $[\alpha]_D^{20} = -37.2$ ($c = 1.2$, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃): $\delta = 7.47-7.41$ (m, 2H), 7.40-7.29 (m, 3H), 6.82 (d, $J = 6.4$ Hz, 1H), 5.68 (dq, $J = 9.6, 1.4$ Hz, $J_{1H,117Sn} = J_{1H,119Sn} = 130.7$ Hz, 1H), 4.83 (t, $J = 6.0$ Hz, 1H), 4.77 (s, 1H), 4.45 (dd, $J = 9.6, 6.4$ Hz, 1H), 4.29-4.08 (bs, 1H), 3.73-3.61 (bs, 1H), 3.43 (s, 3H, CH₃), 2.90 (ddq, $J = 9.6, 6.9, 6.0$ Hz, 1H), 2.23 (dmd, $J = 9.6, 6.0$ Hz, 1H), 1.77 (d, $J = 1.4$ Hz, $J_{1H,117Sn} = J_{1H,119Sn} = 41.2$ Hz, 3H, CH₃), 1.50-1.39 (m, 6H, 3CH₂), 1.36-1.18 (m, 18H, 3CH₂ + 4CH₃), 0.95-0.81 (m, 18H, 4CH₃ + 3CH₂), 0.70 (d, $J = 6.9$ Hz, 3H, CH₃); ¹³C NMR (100.5 MHz, CDCl₃): $\delta = 170.6$ (C), 152.7 (C), 142.0 (CH, $J_{13C,117Sn} = J_{13C,119Sn} = 26.8$ Hz), 139.1 (C), 136.9 (C), 135.5 (CH), 128.8 (2CH), 128.7 (2CH), 127.5 (CH), 110.7 (CH), 83.0 (CH), 80.6 (CH), 57.5 (CH₃), 47.0 (CH), 45.4 (CH), 40.8 (CH, $J_{13C,117Sn} = J_{13C,119Sn} = 33.6$ Hz), 32.9 (CH), 29.3 (3CH₂, $J_{13C,117Sn} = J_{13C,119Sn} = 21.1$ Hz), 27.6 (3CH₂, $J_{13C,117Sn} = J_{13C,119Sn} = 57.5$ Hz), 27.2 (CH₃, $J_{13C,117Sn} = J_{13C,119Sn} = 44.1$ Hz), 21.7 (2CH₃), 20.5 (2CH₃), 17.9 (CH₃), 17.0 (CH₃), 13.8 (3CH₃), 10.0 (3CH₂, $J_{13C,117Sn} = 317.3$ Hz, $J_{13C,119Sn} = 329.7$ Hz); IR (Film) $\nu = 2960, 2927, 2870, 2849, 1752, 1710, 1454, 1439, 1375, 1309, 1288, 1210, 1174, 1152, 112, 1056, 1007$ cm⁻¹.

(3S,4R,5S,6Z)-3,5-Dimethyl-4-((methoxymethyl)oxy)-7-(tributylstannyl)-oct-6-en-1-yne (32): To a solution of carbamate **29** (8.4 g, 13.6 mmol, 1.0 equiv) in diethyl ether (10 mL) at -40 °C was slowly added a solution of *tert*-BuLi (1.5 M in pentane, 27.2 mL, 40.8 mmol, 3.0 equiv). The solution was stirred for 20 min at -20 °C then quenched by addition of a saturated aqueous NH₄Cl solution, and extracted with diethyl ether. The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel (cyclohexane/Et₂O 90:10 to 80:20) to give (3S,4R,5S,6Z)-3,5-dimethyl-4-hydroxy-7-(tributylstannyl)-oct-6-en-1-yne (4.7 g, 78 % yield). $[\alpha]_D^{20} = -26.8$ ($c = 1.0$, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃): $\delta = 5.87$ (dq, $J = 9.6, 1.8$ Hz, $J_{1H,117Sn} = J_{1H,119Sn} = 133.3$ Hz, 1H), 3.17 (ddd, $J = 9.0, 7.5, 3.2$ Hz, 1H), 2.73 (ddq, $J = 7.5, 6.9, 2.3$ Hz, 1H), 2.16 (ddq, $J = 9.6, 6.9, 3.2$ Hz, 1H), 2.14 (d, $J = 2.3$ Hz, 1H), 1.90 (d, $J = 1.8$ Hz, $J_{1H,117Sn} = J_{1H,119Sn} = 40.8$ Hz, 3H, CH₃), 1.74 (d, $J = 9.0$ Hz, 1H, OH), 1.53-1.42 (m, 6H, 3CH₂), 1.34 (sext, $J = 7.3$ Hz, 6H, 3CH₂), 1.26 (d, $J = 6.9$ Hz, 3H, CH₃), 1.08 (d, $J = 6.9$ Hz, 3H, CH₃), 0.98-0.91 (m, 6H, 3CH₂), 0.89 (t, $J = 7.3$ Hz, 9H, 3CH₃); ¹³C NMR (100.5 MHz, CDCl₃): $\delta = 142.8$ (CH, $J_{13C,117Sn} = J_{13C,119Sn} = 28.8$ Hz), 138.8 (C), 84.8 (C), 78.0 (CH), 71.5 (CH), 43.2 (CH, $J_{13C,117Sn} = J_{13C,119Sn} = 33.6$

Hz), 30.4 (CH), 29.0 (3CH₂, $J_{13C,117Sn} = J_{13C,119Sn} = 19.2$ Hz), 27.1 (3CH₂, $J_{13C,117Sn} = J_{13C,119Sn} = 58.7$ Hz), 27.0 (CH₃, $J_{13C,117Sn} = J_{13C,119Sn} = 44.0$ Hz), 18.4 (CH₃), 17.0 (CH₃), 13.4 (3CH₃), 9.7 (3CH₂, $J_{13C,117Sn} = J_{13C,119Sn} = 314.4$ Hz, $J_{13C,119Sn} = 328.8$ Hz); IR (Film) $\nu = 3560, 350, 3456, 3310, 2957, 2926, 2872, 2854, 1463, 1455, 1376, 1247, 1115, 1070, 1050, 997, 981, 960, 873, 862, 690, 663, 631$ cm⁻¹; elemental analysis calcd (%) for C₂₂H₄₂O₅Sn: C 59.88, H 9.59; found: C 59.99, H 9.77.

A mixture of hexanoyl chloride (62.2 g, 500 mmol, 1.0 equiv) and dimethoxymethane (38.0 g, 500 mmol, 1.0 equiv) with a few drops of HCl 3 N was heated at 55-60 °C for 12 h. Methoxymethyl chloride (MOMCl) was then distilled out (bp: 53-55 °C; 32.0 g, 80 % yield).

To a solution of the above alcohol (3.51 g, 7.95 mmol, 1.0 equiv), dimethylaminopyridine (194 mg, 1.59 mmol, 0.2 equiv) and TBAI (294 mg, 0.795 mmol, 0.1 equiv) in dried CH₂Cl₂ (40 mL) at 0 °C were added diisopropylethylamine (27.7 mL, 159 mmol, 20 equiv) and MOMCl (100.5 mmol, 20 equiv). After stirring for 12 h at 20 °C, the reaction was quenched with a saturated aqueous NaHCO₃ solution and extracted with Et₂O. The organic layers were washed with brine, dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The crude residue was purified by chromatography on silica gel (cyclohexane/Et₂O 98:2 to 90:10) to give the title compound **32** (3.53 g, 92 % yield) as a yellow oil. **(32)**: $[\alpha]_D^{20} = -20.6$ ($c = 0.98$, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃): $\delta = 5.87$ (d, $J = 9.6$ Hz, $J_{1H,117Sn} = J_{1H,119Sn} = 133.3$ Hz, 1H), 4.80 (d, $J = 7.3$ Hz, 1H), 4.72 (d, $J = 7.3$ Hz, 1H), 3.45 (s, 3H, CH₃), 3.19 (dd, $J = 7.8, 3.6$ Hz, 1H), 2.74 (qdd, $J = 7.3, 3.6, 2.7$ Hz, 1H), 2.33 (ddq, $J = 9.6, 7.8, 6.9$ Hz, 1H), 2.09 (d, $J = 2.7$ Hz, 1H), 1.88 (s, $J_{1H,117Sn} = J_{1H,119Sn} = 40.8$ Hz, 3H, CH₃), 1.52-1.42 (m, 6H, 3CH₂), 1.32 (sext, $J = 7.3$ Hz, 6H, 3CH₂), 1.25 (d, $J = 7.3$ Hz, 3H, CH₃), 1.02 (d, $J = 6.9$ Hz, 3H, CH₃), 0.97-0.93 (m, 6H, 3CH₂), 0.89 (t, $J = 7.3$ Hz, 9H, 3CH₃); ¹³C NMR (100.5 MHz, CDCl₃): $\delta = 143.6$ (CH, $J_{13C,117Sn} = J_{13C,119Sn} = 28.7$ Hz), 138.5 (C), 98.4 (CH₂), 86.1 (C), 85.9 (CH), 70.0 (CH), 56.3 (CH₃), 42.8 (CH, $J_{13C,117Sn} = J_{13C,119Sn} = 30.1$ Hz), 30.0 (CH), 27.3 (3CH₂, $J_{13C,117Sn} = J_{13C,119Sn} = 20.1$ Hz), 27.3 (3CH₂, $J_{13C,117Sn} = J_{13C,119Sn} = 59.4$ Hz), 27.2 (CH₃, $J_{13C,117Sn} = J_{13C,119Sn} = 40.2$ Hz), 18.8 (CH₃), 17.7 (CH₃), 13.7 (3CH₃), 9.9 (3CH₂, $J_{13C,117Sn} = 314.4$ Hz, $J_{13C,119Sn} = 328.7$ Hz); IR (Film) $\nu = 3312, 2956, 2926, 2872, 2823, 1458, 1376, 1146, 1096, 1035, 996, 668, 634$ cm⁻¹; elemental analysis calcd (%) for C₂₄H₄₆O₂Sn: C 59.39, H 9.55; found: C 59.55, H 9.73.

(3R,4S,5S)-3,5-Dimethyl-6-(4-methoxybenzyloxy) hex-1-en-4-ol (33)

(3S,4R,5S)-3,5-Dimethyl-6-(4-methoxybenzyloxy) hex-1-en-4-ol (34): *Brown reaction* - To a solution of freshly sublimed potassium *tert*-butoxide (7.56 g, 67.4 mmol, 1.2 equiv) in THF (100 mL) at -78 °C was slowly added a solution of *cis*-2-butene (12.5 mL) in THF (10 mL); *n*-BuLi (1.6 M in hexane, 44 mL, 70.3 mmol, 1.25 equiv) was then added dropwise and the yellow mixture was stirred at -78 °C for 5 min and at -45 °C for 20 min. The resulting orange solution was cooled to -78 °C, and a solution of (-)-*B*-diisopinocampheylmethoxyborane (25 g, 78.7 mmol, 1.4 equiv) in 46 mL of diethyl ether was added dropwise over ca. 15 min. The resulting white solution was stirred at -78 °C for 40 min. Boron trifluoride ethyl etherate (BF₃•OEt₂, 11.8 mL, 95.5 mmol, 1.7 equiv) was added dropwise followed after 5 min by addition of a solution of the aldehyde **13** (11.7 g, 56.2 mmol, 1.0 equiv) in THF (25 mL). The resulting solution was stirred at -78 °C for 5 h and the reaction was then quenched by successive addition of an aqueous NaOH solution (2.5 N, 66 mL) and an aqueous H₂O₂ solution (30 %, 20 mL). The acetone-dry ice bath was then removed, and the mixture was heated at 45 °C for 45 min. The cloudy solution was cooled to 20 °C, diluted with diethyl ether (45 mL), washed with brine, dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The crude residue was distilled (85-90 °C, 3.3 mm Hg) to remove most of the by-product isopinocampheol. The remaining oil was then purified by chromatography on silica gel to give the title compound **33** and used in the next step.

Crotylation reaction with crotylstannane - Crotylstannane preparation: method 1: To a solution of diisopropylamine (8.0 mL, 79 mmol, 1.15 equiv) in THF (130 mL) at 0 °C was added *n*-BuLi (1.4 M in hexane, 49 mL, 69 mmol, 1.0 equiv). 10 min later, HSnBus (20.0 g, 69 mmol, 1.0 equiv) was added over 10 min to the LDA solution. After stirring for 20 min at 0 °C, the mixture was cooled to -40 °C and a solution of (*E*)-crotylchloride (6.2 g, 69 mmol, 1.0 equiv) in THF (70 mL) was added via cannula. The mixture was stirred for 15 min at -20 °C and then treated by a saturated aqueous NH₄Cl solution. After extraction with diethyl ether, the organic layer was washed with water and brine, dried over MgSO₄ and the solvent removed under reduced pressure. The residue was then distilled under reduced pressure (154-158 °C, 0.3 mbar) to give a mixture of (*E*)/(*Z*)-crotylstannane 50:50 (19.0 g, 81 % yield). *Crotylstannane preparation: method 2* - To a freshly sublimed potassium *t*-butoxide (4.0 g, 36 mmol, 1.2 equiv) in THF (70 mL) at -78 °C was cannulated a solution of *trans*-butene (7 mL) in THF. *n*-BuLi was then added dropwise (1.4 M in hexane, 26.6 mL, 37.2 mmol, 1.25 equiv). After stirring for 1 h at -45 °C, tributyltin chloride (9.7 g, 30 mmol, 1.0 equivalent) was added slowly and the resulting mixture was allowed to warm to 20 °C for 12 h. The reaction was then quenched by addition of a saturated aqueous NH₄Cl solution. After extraction with diethyl ether, the organic layer was washed with water and brine, dried over MgSO₄ and the solvent removed under reduced pressure. The

residue was then distilled under reduced pressure (154–158 °C, 0.3 mbar) to give a mixture of (*E*)/(*Z*)-crotylstannane 75:25 (3.25 g, 32 % yield).

To a solution of aldehyde **13** (6.0 g, 28.9 mmol, 1.0 equiv) in diethyl ether (90 mL) at –100 °C was added BF₃·OEt₂ (9.0 g, 8.1 mL, 63.8 mmol, 2.2 equiv). After stirring for 10 min, crotyltributylstannane (13.3 g, 38.6 mmol, 1.1 equiv) was added; the resulting mixture was stirred for 3 h at –100 °C/–95 °C and then a saturated aqueous NaHCO₃ solution was added. After extraction with diethyl ether, the organic layer was washed with water and brine, dried over MgSO₄ and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate 90:10 to 70:30) to give the title compound **33** as a yellow oil (5.64 g, 74 % yield) and its diastereomer **34** (*dr* 91:9). (**33**): [α]_D²⁰ = –2.7 (*c* = 9.6, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃): δ = 7.26 (d, *J* = 8.9 Hz, 2H), 6.88 (d, *J* = 8.9 Hz, 2H), 5.63 (ddd, *J* = 17.2, 10.2, 8.6 Hz, 1H), 5.07 (dd, *J* = 17.2, 2.0 Hz, 1H), 4.99 (dd, *J* = 10.2, 2.0 Hz, 1H), 4.46 (d, *J* = 11.6 Hz, 1H), 4.42 (d, *J* = 11.6 Hz, 1H), 3.82 (s, 3H), 3.55–3.45 (m, 2H), 3.43 (dd, *J* = 9.1, 5.0 Hz, 1H), 2.70 (d, *J* = 3.0 Hz, 1H, OH), 2.23 (dq, *J* = 8.6, 7.3, 6.6 Hz, 1H), 1.92–1.79 (m, 1H), 1.10 (d, *J* = 6.6 Hz, 3H, CH₃), 0.96 (d, *J* = 6.6 Hz, 3H, CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 159.2 (C), 141.3 (CH), 130.3 (C), 129.2 (2CH), 114.5 (CH₂), 113.8 (2CH), 75.4 (CH), 73.1 (CH₂), 72.0 (CH₂), 55.3 (CH₃), 42.1 (CH), 35.4 (CH), 17.2 (CH₃), 9.8 (CH₃); MS (GC, CI, CH₄): *m/z*: 293 (M⁺ + 29), 264, 246, 190, 161, 149, 137, 121, 109, 69, 57; IR (Film) ν = 2960, 2907, 2870, 1612, 1513, 1462, 1365, 1302, 1210, 1173, 1093, 1037, 982, 914 cm^{–1}. (**34**): ¹H NMR (400.0 MHz, CDCl₃): δ = 7.26 (d, *J* = 8.9 Hz, 2H), 6.88 (d, *J* = 8.9 Hz, 2H), 5.86 (dd, *J* = 17.9, 10.1, 7.3 Hz, 1H), 5.07 (dd, *J* = 17.9, 1.4 Hz, 1H), 4.99 (dd, *J* = 10.1, 1.4 Hz, 1H), 4.46 (d, *J* = 11.6 Hz, 1H), 4.42 (d, *J* = 11.6 Hz, 1H), 3.82 (s, 3H), 3.67–3.60 (m, 1H), 3.55–3.45 (m, 2H), 2.70 (d, *J* = 3.0 Hz, 1H, OH), 2.25–2.22 (m, 1H), 1.92–1.79 (m, 1H), 1.04 (d, *J* = 6.9 Hz, 3H, CH₃), 0.96 (d, *J* = 6.6 Hz, 3H, CH₃).

(**3R,4S,5S**)-4-(*tert*-Butyldimethylsilyloxy)-3,5-dimethyl-6-(4-methoxybenzyloxy)

hex-1-ene (35): To a solution of alcohol **33** (5.64 g, 21.3 mmol, 1.0 equiv) in dried CH₂Cl₂ (90 mL) at 0 °C were added 2,6-lutidine (6.9 g, 7.5 mL, 64 mmol, 3.0 equiv) and TBSOTf (8.5 g, 7.35 mL, 32 mmol, 1.5 equiv). After stirring for 2 h at 20 °C, the reaction was partitioned between diethyl ether and a saturated aqueous solution of ammonium chloride and extracted with diethyl ether. The organic layer was washed with brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate 98:2 to 95:5) to give 6.30 g (78 % yield) of the title compound **35** as a yellow oil. (**35**): [α]_D²⁰ = +1.3 (*c* = 1.5, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃): δ = 7.25 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.79 (ddd, *J* = 17.6, 10.2, 7.8 Hz, 1H), 4.96 (dd, *J* = 17.6, 1.7 Hz, 1H), 4.92 (dd, *J* = 10.2, 1.7 Hz, 1H), 4.42 (d, *J* = 11.6 Hz, 1H), 4.38 (d, *J* = 11.6 Hz, 1H), 3.81 (s, 3H), 3.63 (dd, *J* = 6.9, 2.3 Hz, 1H), 3.35 (dd, *J* = 8.9, 7.9 Hz, 1H), 3.19 (dd, *J* = 8.9, 6.3 Hz, 1H), 2.34 (dq, *J* = 7.8, 6.9, 6.9 Hz, 1H), 1.97 (dq, *J* = 7.9, 6.6, 6.3, 2.3 Hz, 1H), 0.99 (d, *J* = 6.9 Hz, 3H, CH₃), 0.89 (s, 9H, 3CH₃), 0.85 (d, *J* = 6.6 Hz, 3H, CH₃), 0.04 (s, 3H, CH₃), 0.02 (s, 3H, CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 159.0 (C), 142.0 (CH), 130.8 (C), 129.1 (2CH), 113.6 (2CH), 113.4 (CH₂), 75.5 (CH), 73.4 (CH₂), 72.4 (CH₂), 55.2 (CH₃), 42.6 (CH), 36.5 (CH), 26.1 (3CH₃), 18.4 (C), 16.9 (CH₃), 11.0 (CH₃), –3.6 (2CH₃); MS (GC, CI, CH₄): *m/z*: 407 (M⁺ + 29), 377, 363, 323, 271, 241, 199, 187, 161, 145, 121, 109, 89, 75; IR (Film) ν = 2959, 2855, 1653, 1615, 1513, 1462, 1360, 1301, 1246, 1172, 1103, 1039, 911, 836 cm^{–1}; elemental analysis calcd (%) for C₂₂H₃₈O₃Si: C 69.79, H 10.12; found: C 70.16, H 10.35.

(**2S,3S,4R**)-2,4-Dimethyl-hex-5-ene-1,3-diol (**36**): At 0 °C a solution of compound **33** (100 mg, 0.38 mmol, 1.0 equiv) in CH₂Cl₂ (3 mL) was treated with water (0.15 mL) and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ, 72 mg, 0.317 mmol, 1.2 equiv). The mixture was stirred for 10 min at 0 °C, warmed to 20 °C, and stirred an additional 30 min. The mixture was quenched with a saturated aqueous NaHCO₃ solution, diluted with CH₂Cl₂, washed with water and brine. The combined organic layers were dried over MgSO₄, filtered and the solvent removed under reduced pressure. The crude residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate 60:40 then 50:50) to give the title compound **36** as white crystals (41 mg, 75 % yield). (**36**): RN: 108867-45-4; [α]_D²⁰ = +40 (*c* = 1.5, CHCl₃); ¹H NMR (270.0 MHz, CDCl₃): δ = 6.03–5.49 (m, 1H), 5.03–4.89 (m, 2H), 3.69–3.57 (m, 2H), 3.51 (dd, *J* = 9.2, 2.3 Hz, 1H), 2.49 (bs, 1H, OH), 2.28–2.19 (m, 1H), 1.79–1.73 (m, 1H), 1.03 (d, *J* = 6.6 Hz, 3H, CH₃), 0.87 (d, *J* = 6.9 Hz, 3H, CH₃); ¹³C NMR (67.5 MHz, CDCl₃): δ = 140.8 (CH), 114.7 (CH₂), 76.5 (CH), 67.8 (CH₃), 42.2 (CH), 36.5 (CH), 17.1 (CH₃), 8.9 (CH₃); IR (film) ν = 3464, 2957, 1655, 1264, 1105, 1094, 1023, 1016, 798 cm^{–1}; MS (GC, CI, CH₄): *m/z*: 127 (MH⁺ – H₂O), 125, 109, 97, 89, 83, 71, 57; elemental analysis calcd (%) for C₈H₁₆O₂: C 66.63, H 11.18; found: C 66.46, H 11.07.

(**2S,3R,4S**)-3-(*tert*-Butyldimethylsilyloxy)-2,4-dimethyl-5-(4-methoxybenzyloxy)

pentanal (37): To a –78 °C solution of compound **35** (6.3 g, 16.6 mmol, 1.0 equiv) in 200 mL of MeOH/CH₂Cl₂ (1:1), containing pyridine (4 mL, 50 mmol, 3.0 equiv) and a few amount of Sudan III was bubbled a stream of ozone until the pink solution became colourless. The solution was treated with dimethylsulfide (36.5 mL, 498 mmol, 30 equiv) and then warmed to 20 °C for 12 h. The solution was concentrated under reduced pressure, diluted with diethyl ether, washed with water (3x), dried over MgSO₄ and the solvent was removed under reduced pressure. The crude (**2S,3R,4S**)-3-(*tert*-butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)-2,4-dimethylpentanal **37** (6.0 g, 95 % yield) was used in the next step without further purification. (**37**): ¹H NMR (400.0

MHz, CDCl₃): δ = 9.87 (d, *J* = 0.8 Hz, 1H), 7.25 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 4.41 (d, *J* = 11.6 Hz, 1H), 4.36 (d, *J* = 11.6 Hz, 1H), 4.24 (dd, *J* = 5.1, 3.4 Hz, 1H), 3.82 (s, 3H), 3.37 (dd, *J* = 9.0, 7.3 Hz, 1H), 3.24 (dd, *J* = 9.0, 5.9 Hz, 1H), 2.54 (qdd, *J* = 6.9, 5.1, 0.8 Hz, 1H), 1.94 (dq, *J* = 7.3, 6.9, 5.9, 3.4 Hz, 1H), 1.05 (d, *J* = 6.9 Hz, 3H, CH₃), 0.91 (s, 9H, 3CH₃), 0.86 (d, *J* = 6.9 Hz, 3H, CH₃), 0.07 (s, 3H, CH₃), 0.05 (s, 3H, CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 205.5 (C), 129.2 (2CH), 113.7 (2CH), 72.6 (CH₂), 72.5 (CH₂), 72.3 (CH), 55.2 (CH₃), 51.3 (CH), 37.0 (CH), 25.9 (3CH₃), 18.2 (C), 12.1 (CH₃), 9.3 (CH₃), –4.0 (2CH₃), one C-arom not detected; MS (GC, EI): *m/z*: 323 (M⁺ – *t*-Bu), 251, 199, 187, 137, 121, 107, 98, 89, 73, 59; elemental analysis calcd (%) for C₂₁H₃₆O₄Si: C 66.67, H 9.53; found: C 66.60, H 9.67.

(**1Z,3S,4S,5R,6R,7S**)-6-(*tert*-Butyldimethylsilyloxy)-1-((*N,N*-diisopropyl)carbamoyloxy)-8-(4-methoxybenzyloxy)-3,5,7-trimethyl oct-1-en-4-ol (**38**): (*E*)-crotyldiisopropylcarbamate preparation - To a suspension of NaH (60 %), 12.2 g, 306 mmol, 1.2 equiv) in THF (50 mL) at 0 °C was added a solution of 2-buten-1-ol (*E/Z* mixture, 18.4 g, 255 mmol, 1.0 equiv) in THF (50 mL) over 20 min. After stirring 20 min at 20 °C, the reaction mixture was cooled to 0 °C and a solution of *N,N*-diisopropylcarbamoyl chloride (50 g, 306 mmol, 1.2 equiv) in THF (70 mL) was slowly added. The reaction mixture was stirred for 3 h at 20 °C, then poured into an aqueous HCl 1 *N* solution (150 mL) and extracted with diethyl ether. The combined organic layers were washed with a saturated aqueous NaHCO₃ solution and brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The crude residue was distilled (64 °C, 0.1 mbar) to give (*E*)-crotyldiisopropylcarbamate (50.0 g, 98 % yield).

Crotylation reaction with optically active crotyltitane - To a quick stirred solution of the (*E*)-crotyl diisopropylcarbamate (6.6 g, 33.2 mmol, 2.0 equiv) and (-)-sparteine (8.01 g, 34.2 mmol, 2.1 equiv), in pentane (30 mL) and cyclohexane (5 mL) at –78 °C, was added a solution of *n*-BuLi (1.4 *M* in hexanes, 25.5 mL, 35.5 mmol, 2.1 equiv), and after 10 min white crystals appeared. After 3 h of crystallization at –78 °C, a pre-cooled (–40 °C) solution of titanium tetraisopropoxide (Ti(O^{*i*}Pr)₄, 29.5 mL, 99.6 mmol, 6.0 equiv) in pentane (30 mL) was quickly added via cannula to the reaction mixture of lithio carbamate which became limpid and turned orange. After 1 h at –78 °C a solution of aldehyde **37** (6.32 g, 16.6 mmol, 1.0 equiv) in pentane (10 mL) was slowly added to the orange solution, and the mixture was stirred for 3 h at –78 °C. The solution was then poured into a mixture of diethyl ether (250 mL)-aqueous hydrochloric acid solution (0.5 *N*, 250 mL). After extraction with diethyl ether, the organic layer was washed with brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The crude residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate 90:10 to 80:20) to give 7.1 g (77 % yield) of the title compound **38** as a single diastereomer.

Crotylation reaction with racemic crotyltitane - To a solution of the (*E*)-crotyl diisopropylcarbamate (875 mg, 4.4 mmol, 2.0 equiv) and TMEDA (730 μL, 4.84 mmol, 2.2 equiv), in diethyl ether (6 mL) at –78 °C, was added a solution of *n*-BuLi (1.6 *M* in hexanes, 2.85 mL, 4.84 mmol, 2.2 equiv). After 30 min stirring at –78 °C, titanium tetraisopropoxide (Ti(O^{*i*}Pr)₄, 4.0 mL, 13.2 mmol, 6.0 equiv) was quickly added via cannula to the reaction mixture of lithio carbamate which became limpid and turned orange. After 30 min at –78 °C a solution of aldehyde **39** (840 mg, 2.2 mmol, 1.0 equiv) in diethyl ether (2 mL) was slowly added to the orange solution, and the mixture was stirred for 3 h at –78 °C. The solution was then poured into a mixture of diethyl ether - aqueous hydrochloric acid solution (0.5 *N*). After extraction with diethyl ether, the organic layer was washed with brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The crude residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate 90:10 to 80:20) to 632 mg of the title compound **38** and 299 mg of its **3,4-*epi*** diastereomer (73 % yield; selectivity 68:32). (**38**): [α]_D²⁰ = +16.6 (*c* = 1.2, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃): δ = 7.25 (d, *J* = 8.8 Hz, 2H), 7.15 (d, *J* = 6.6 Hz, 1H), 6.87 (d, *J* = 8.8 Hz, 2H), 4.62 (dd, *J* = 9.9, 6.6 Hz, 1H), 4.43 (s, 2H), 4.15 (m, 2H), 3.81 (s, 3H), 3.80 (dd, *J* = 5.9, 3.6 Hz, 1H), 3.42 (dd, *J* = 8.9, 6.5 Hz, 1H), 3.34 (ddd, *J* = 8.6, 2.7, 2.3 Hz, 1H), 3.23 (dd, *J* = 8.9, 7.6 Hz, 1H), 2.89–2.85 (m, 1H), 2.10–2.07 (m, 1H), 1.82 (d, *J* = 2.7 Hz, 1H, OH), 1.79–1.73 (m, 1H), 1.23 (m, 12H, 4CH₃), 0.96–0.88 (m, 9H, 3CH₃), 0.89 (s, 9H, 3CH₃), 0.06 (s, 3H, CH₃), 0.03 (s, 3H, CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 158.9 (C), 152.7 (C), 136.5 (CH), 130.6 (C), 129.1 (2CH), 113.6 (2CH), 113.4 (CH), 75.1 (CH), 74.7 (CH), 73.5 (CH₂), 72.3 (CH₂), 55.1 (CH₃), 45.3 (2CH), 37.9 (CH), 36.5 (CH), 34.4 (CH), 26.0 (3CH₃), 21.4 (4CH₃), 18.3 (C), 17.0 (CH₃), 11.2 (CH₃), 9.1 (CH₃), –3.8 (2CH₃); MS (GC, CI, CH₄): *m/z*: 379 (MH⁺ – *t*-Bu – OC(O)*N*^{*i*}Pr₂), 351, 323, 299, 273, 259, 243, 227, 215, 203, 187, 173, 161, 149, 137, 121, 99, 75; IR (Film) ν = 3511, 2969, 2932, 2856, 2361, 1709, 1513, 1441, 1302, 1211, 1134, 1043, 837 cm^{–1}; elemental analysis calcd (%) for C₃₂H₅₇NO₆Si: C 66.28, H 9.91, N 2.42; found: C 65.69, H 10.14, N 2.50. (**3,4-*epi*** diastereomer of **38**): [α]_D²⁰ = –7.8 (*c* = 1.0, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃): δ = 7.27 (d, *J* = 8.6 Hz, 2H), 7.11 (d, *J* = 6.3 Hz, 1H), 6.90 (d, *J* = 8.6 Hz, 2H), 4.95 (dd, *J* = 9.9, 6.3 Hz, 1H), 4.43 (s, 2H), 4.01 (dd, *J* = 3.3, 1.9 Hz, 1H), 3.92 (m, 2H), 3.83 (s, 3H), 3.69–3.65 (m, 1H), 3.42 (dd, *J* = 8.9, 6.5 Hz, 1H), 3.30–3.265 (m, 2H), 2.88–2.77 (m, 1H), 2.15–2.04 (m, 1H), 1.87 (m, 2H, H-18, OH), 1.27 (d, *J* = 6.6 Hz, 12H, 4CH₃), 1.16 (d, *J* = 6.9 Hz, 3H, CH₃), 1.05 (d, *J* = 6.9 Hz, 3H, CH₃), 0.93 (s, 9H, 3CH₃), 0.77 (d, *J* = 6.9 Hz, 3H, CH₃), 0.14 (s, 3H, CH₃), 0.06 (s, 3H, CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 159.0 (C), 152.9 (C), 130.5 (2CH), 130.6 (C), 129.0 (2CH), 113.7 (2CH), 110.8 (CH), 77.5 (2CH), 73.7 (CH₂), 72.4 (CH₂), 55.2 (CH₃), 46.0 (2CH), 41.4 (CH), 33.8 (CH), 33.2

(CH), 25.8 (3CH₃), 21.4 (4CH₃), 18.3 (CH₃), 18.0 (C), 13.6 (CH₃), 12.6 (CH₃), -4.1 (2CH₃). IR (Film) ν = 2959, 2762, 2362, 1709 cm⁻¹.

4,6-acetonide derivative of 38: To a solution of compound **38** (100 mg, 172 μ mol, 1.0 equiv) in THF (0.6 mL) at 20 °C was added a solution of tetrabutylammonium fluoride (TBAF) (1.0 M in THF, 345 μ L, 345 μ mol, 2.0 equiv). The reaction mixture was stirred for 4 h, quenched by addition of water and extracted with ethyl acetate. The organic layer was washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate 80:20 to 70:30) to give 73 mg (91 % yield) of the corresponding (2*S*,3*R*,4*R*,5*S*,6*S*)-3,5-dihydroxy-8-((*N,N*-diisopropyl)carbamoyloxy)-1-(4-methoxy-benzyloxy)-2,4,6-trimethyl oct-7-ene. [α]_D²⁰ = + 0.8 (*c* = 0.75, CHCl₃); ¹H NMR (270.0 MHz, CDCl₃): δ = 7.18 (d, *J* = 8.6 Hz, 2H), 7.08 (d, *J* = 6.3 Hz, 1H), 6.80 (d, *J* = 8.6 Hz, 2H), 4.53 (dd, *J* = 9.9, 6.3 Hz, 1H), 4.35 (s, 2H), 4.13-3.97 (bs, 1H), 3.73 (s, 3H, CH₃), 3.72-3.60 (bs, 1H), 3.66-3.63 (m, 1H), 3.35-3.33 (m, 2H), 3.32-3.28 (m, 1H), 2.88-2.73 (m, 1H), 2.00-1.85 (m, 1H, OH), 1.94-1.85 (m, 2H), 1.57-1.48 (m, 1H, OH), 1.21-1.16 (m, 12H, 4CH₃), 0.98 (d, *J* = 6.9 Hz, 3H, CH₃), 0.88 (d, *J* = 6.9 Hz, 3H, CH₃), 0.85 (d, *J* = 6.9 Hz, 3H, CH₃); ¹³C NMR (67.5 MHz, CDCl₃): δ = 158.9 (C), 152.5 (C), 137.2 (CH), 130.2 (C), 129.1 (2CH), 113.7 (2CH), 112.9 (CH), 78.5 (CH), 77.9 (CH), 73.9 (CH₂), 72.3 (CH₂), 55.2 (CH₃), 45.7 (2CH), 36.1 (CH), 35.6 (CH), 34.2 (CH), 21.0 (4CH₃), 16.2 (CH₃), 13.1 (CH₃), 5.8 (CH₃); IR (Film) ν = 2969, 2934, 2873, 1708, 1692, 1513, 1441, 1370, 1305, 1247, 1210, 1135, 1063, 971 cm⁻¹.

To a solution of the above diol (65 mg, 0.14 mmol, 1.0 equiv) in CH₂Cl₂ at 20 °C were added 2,2-dimethoxypropane (210 μ L, 1.67 mmol, 12 equiv) and pyridinium *p*-toluene sulfonate (PPTS, 10 %). The reaction mixture was stirred for 2 h. Then the solution was cooled to 0 °C and triethylamine (1 mL) was added. The reaction mixture was concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate 70:30) to give 59 mg (84 % yield) of the title product. (**4,6 acetonide of 38**): [α]_D²⁰ = + 29.6 (*c* = 2.9, CHCl₃); ¹H NMR (270.0 MHz, CDCl₃): δ = 7.18 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 6.3 Hz, 1H), 6.79 (d, *J* = 8.6 Hz, 2H), 4.49 (dd, *J* = 8.9, 6.3 Hz, 1H), 4.33 (s, 2H), 4.16-4.02 (bs, 1H), 3.75-3.58 (bs, 1H), 3.72 (s, 3H), 3.51 (dd, *J* = 9.6, 2.0 Hz, 1H), 3.36 (dd, *J* = 9.6, 2.0 Hz, 1H), 3.24 (d, *J* = 4.6 Hz, 2H), 2.78-2.63 (m, 1H), 1.83-1.73 (m, 1H), 1.50-1.42 (m, 1H), 1.27-1.16 (m, 12H, 4CH₃), 1.27 (s, 3H, CH₃), 1.25 (s, 3H, CH₃), 0.96 (d, *J* = 6.6 Hz, 3H), 0.81 (d, *J* = 6.9 Hz, 3H), 0.75 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (67.5 MHz, CDCl₃): δ = 159.0 (C), 153.2 (C), 134.9 (CH), 130.5 (C), 129.0 (2CH), 114.6 (CH), 113.6 (2CH), 98.8 (C), 77.5 (CH), 75.7 (CH), 72.7 (CH₂), 71.1 (CH₂), 55.1 (CH₃), 46.1 (2CH), 34.9 (CH, C-16), 31.8 (CH), 30.9 (CH), 29.8 (CH₃), 21.0 (4CH₃), 19.4 (CH₃), 15.8 (CH₃), 14.8 (CH₃), 4.9 (CH₃); IR (Film) ν = 2968, 2936, 1708, 1513, 1462, 1439, 1377, 1310, 1288, 1248, 1135, 1057, 1012 cm⁻¹; MS (GC, CI, CH₄): *m/z*: 534 (M + 29), 506 (M + 1); elemental analysis calcd (%) for C₂₉H₄₇NO₆: C 68.88, H 9.37, N 2.77; found C 68.75, H 9.32, N, 2.85.

2,4-acetonide of 38: To a cooled (-78 °C) solution of the carbamate **38** (100 mg, 172 μ mol, 1.0 equiv) in 10 mL of MeOH/CH₂Cl₂ (1:1) containing 40 μ L of pyridine and a few amount of Sudan III, was bubbled a stream of ozone until the pink solution became colourless. Sodium borohydride (39 mg, 1.03 mmol, 6.0 equiv) was added at -78 °C, and the mixture was allowed to warm to 20 °C and stirred for 6 h. The reaction mixture was then cooled, treated with a saturated aqueous solution of NH₄Cl and extracted with diethyl ether. The organic layers were washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 70:30) to give 60 mg (79 % yield) of (2*S*,3*R*,4*R*,5*S*,6*S*)-3-(*tert*-butyldimethylsilyloxy)-5,7-dihydroxy-1-(4-methoxy-benzyloxy)-2,4,6-trimethyl heptane. [α]_D²⁰ = - 0.73 (*c* = 1.1, CHCl₃); ¹H NMR (270.0 MHz, CDCl₃): δ = 7.22-7.18 (m, 2H), 6.85-6.79 (m, 2H), 4.36 (s, 2H), 3.75 (s, 3H), 3.86-3.67 (m, 3H), 3.80-3.70 (m, 1H, OH), 3.60-3.50 (m, 1H, OH), 3.50 (t, *J* = 10.6 Hz, 1H), 3.40-3.31 (m, 1H), 3.22-3.16 (m, 1H), 2.06-2.01 (m, 1H), 1.90-1.65 (m, 2H), 0.83 (s, 9H, 3CH₃), 0.87-0.70 (m, 9H, 3CH₃), 0.03 (s, 6H, 2CH₃); ¹³C NMR (67.5 MHz, CDCl₃): δ = 159.0 (C), 130.7 (C), 129.1 (2CH), 113.6 (2CH), 77.6 (CH), 73.9 (CH₂), 73.6 (CH), 72.4 (CH₂), 68.4 (CH), 55.2 (CH₃), 38.5 (CH), 35.8 (CH), 32.8 (CH), 26.1 (3CH₃), 18.4 (C), 12.1 (CH₃), 10.5 (CH₃), 9.6 (CH₃), -3.6 (2CH₃); IR (Film) ν = 2958, 2933, 2856, 1653, 1618, 1559, 1514, 1423, 1344, 1270, 1103, 1037, 837 cm⁻¹.

To a solution of the preceding diol (55 mg, 125 μ mol, 1.0 equiv) in CH₂Cl₂ (3 mL), at 20 °C were added 2,2-dimethoxypropane (180 μ L, 1.50 mmol, 12 equiv) and PPTS (10 mol %). The reaction mixture was stirred for 2 h. Then the solution was cooled to 0 °C and triethylamine (1 mL) was added. The reaction mixture was concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate 90:10 to 60:40) to give 46 mg (78 % yield) of the title product and 22 mg of starting diol. (**2,4-acetonide of 38**): [α]_D²⁰ = + 12.2 (*c* = 1.2, CHCl₃); ¹H NMR (270.0 MHz, CDCl₃): δ = 7.21 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 4.36 (s, 2H), 3.76 (s, 3H), 3.72 (dd, *J* = 7.6, 1.3 Hz, 1H), 3.63-3.49 (m, 2H), 3.43 (t, *J* = 11.3 Hz, 1H), 3.36-3.30 (m, 1H), 3.22-3.16 (m, 1H), 1.86-1.70 (m, 3H), 1.38-1.19 (m, 6H, 2CH₃), 0.87 (d, *J* = 5.3 Hz, 3H, CH₃), 0.84 (s, 9H, 3CH₃), 0.80 (d, *J* = 6.9 Hz, 3H, CH₃), 0.63 (d, *J* = 6.6 Hz, 3H, CH₃), 0.00 (s, 6H, 2CH₃); ¹³C NMR (67.5 MHz, CDCl₃): δ = 159.5 (C), 131.5 (C), 129.5 (2CH), 114.5 (2CH), 98.5 (C), 75.2 (CH), 74.2 (CH₂), 73.6 (CH), 72.8 (CH₂), 67.0 (CH₂), 55.8 (CH₃), 38.2 (CH), 36.8 (CH), 31.3 (CH), 29.3 (CH₃), 26.7 (3CH₃), 19.4 (CH₃), 19.0 (C), 12.8 (CH₃), 11.0 (CH₃), 10.5

(CH₃), -3.6 (2CH₃); IR (Film) ν = 3256, 1684, 1653, 1550, 1501, 1445, 1359, 1248, 1101, 1032, 846 cm⁻¹; MS (GC, CI, CH₄): *m/z*: 481 (MH⁺); elemental analysis calcd (%) for C₂₇H₄₈O₅Si: C 67.45, H 10.06; found: C 67.32, H 10.24.

(1*Z*,3*S*,4*S*,5*R*,6*S*,7*S*)-6-(*tert*-Butyldimethylsilyloxy)-1-((*N,N*-diisopropyl)carbamoyloxy)-8-(4-methoxybenzyloxy)-4-(triethylsilyloxy)-3,5,7-trimethyl oct-1-ene (**39**): To a solution of **38** (1.09 g, 1.88 mmol, 1.0 equiv) in dried CH₂Cl₂ (15 mL) at 0 °C were added 2,6-lutidine (0.9 mL, 7.50 mmol, 4.0 equiv) and TESOTf (0.9 mL, 3.76 mmol, 2.5 equiv). After stirring for 2 h at 20 °C, the mixture was partitioned between diethyl ether and saturated aqueous solution of ammonium chloride and extracted with diethyl ether. The organic layer was washed with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate 95:5 to 90:10) to give 985 mg (76 % yield) of the title compound **39** as an oil. (**39**): [α]_D²⁰ = + 14.4 (*c* = 0.8, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃): δ = 7.22 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 6.6 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 2H), 5.01 (dd, *J* = 9.2, 6.6 Hz, 1H), 4.38 (d, *J* = 11.1 Hz, 1H), 4.35 (d, *J* = 11.1 Hz, 1H), 4.11-3.95 (bs, 1H,), 3.82-3.69 (bs, 1H), 3.78 (s, 3H), 3.67 (dd, *J* = 6.3, 2.3 Hz, 1H), 3.53 (dd, *J* = 6.3, 5.3 Hz, 1H), 3.37 (dd, *J* = 8.6, 5.6 Hz, 1H), 3.16 (t, *J* = 8.6 Hz, 1H), 2.78-2.72 (m, 1H), 1.87-1.80 (m, 1H), 1.74-1.67 (m, 1H), 1.28-1.14 (m, 12H, 4CH₃), 1.01 (d, *J* = 7.2 Hz, 3H, CH₃), 0.97-0.87 (m, 12H, 4CH₃), 0.85 (s, 9H, 3CH₃), 0.80 (d, *J* = 7.2 Hz, 3H, CH₃), 0.60 (q, *J* = 7.6 Hz, 6H, 3CH₂), 0.02 (s, 3H, CH₃), 0.01 (s, 3H, CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 159.0 (C), 153.0 (C), 133.7 (CH), 130.7 (C), 129.2 (2CH), 113.6 (2CH), 113.7 (CH), 77.0 (CH), 73.9 (CH), 73.6 (CH₂), 72.6 (CH₂), 55.2 (CH₃), 45.4 (2CH), 42.9 (CH), 38.7 (CH), 32.4 (CH), 26.1 (3CH₃), 21.5 (4CH₃), 20.3 (CH₃), 18.4 (C), 12.2 (CH₃), 11.1 (CH₃), 7.0 (3CH₃), 5.5 (3CH₂), 3.2 (2CH₃); IR (Film) ν = 2966, 2937, 2877, 1710, 1514, 1460, 1439, 1306, 1249, 1060, 1042, 1005, 837 cm⁻¹; elemental analysis calcd (%) for C₃₈H₇₁NO₆Si₂: C, 65.75, H 10.31, N 2.02; found: C 65.72, H, 10.27, N 1.97.

(3*Z*,5*S*,6*S*,7*R*,8*S*,9*S*)-8-(*tert*-Butyldimethylsilyloxy)-10-(4-methoxybenzyloxy)-6-(triethylsilyloxy)-5,7,9-trimethyl deca-1,3-diene (**40**)

(**3*Z*,5*S*,6*S*,7*R*,8*S*,9*S*)-6-(*tert*-Butyldimethylsilyloxy)-8-(4-methoxybenzyloxy)-6-(triethylsilyloxy)-3,5,7-trimethyl-1-decene (**41**): Reaction with vinylmagnesium bromide - To a stirred suspension of Ni(acac)₂ (26 mg, 0.10 mmol, 0.1 equiv) in diethyl ether (10 mL) at 0 °C were added a solution of the vinyl carbamate **39** (700 mg, 1.01 mmol, 1.0 equiv) in diethyl ether (10 mL, 3 mL rinse) and vinylmagnesium bromide (sol. 1M in THF, 15.1 mL, 15.1 mmol, 15 equiv). The resulting mixture was stirred for 24 h at 0 °C. Then a saturated aqueous NH₄Cl solution was added and the solution was extracted with diethyl ether. The organic layer was washed with brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate 100:0 to 90:10) to give 460 mg (80 % yield) of diene **40** and compound **41**. Reaction with vinylolithium - To a solution of tetralyltin (1.7 g, 7.48 mmol, 2.6 equiv) in diethyl ether (12 mL) at 0 °C was added MeLi (1.6 M in diethyl ether, 18 mL, 28.8 mmol, 10 equiv). After 30 min stirring, the mixture was added via cannula to a stirred solution of the carbamate **39** (2.0 g, 2.88 mmol, 1.0 equiv) and Ni(acac)₂ (74 mg, 0.288 mmol, 0.1 equiv) in diethyl ether (4 mL) at -5 °C/0 °C. After 6 h stirring the same amount of Ni(acac)₂ was added and the resulting mixture was stirred for another 12 h at 0 °C. Then a saturated aqueous NH₄Cl solution was added and the solution was extracted with Et₂O. The organic layer was washed with brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate 98:2 to 80:20) to give 1.33 g (80 % yield) of **40**. (**40**): [α]_D²⁰ = + 8.9 (*c* = 2.1, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃): δ = 7.24 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.3 Hz, 2H), 6.57 (dt, *J* = 16.9, 10.0 Hz, 1H), 5.97 (t, *J* = 10.0 Hz, 1H), 5.48 (t, *J* = 10.0 Hz, 1H), 5.14 (d, *J* = 10.0 Hz, 1H), 5.07 (d, *J* = 16.9 Hz, 1H), 4.40 (d, *J* = 11.4 Hz, 1H), 4.35 (d, *J* = 11.4 Hz, 1H), 3.80 (s, 3H), 3.63 (dd, *J* = 5.5, 3.0 Hz, 1H), 3.51 (t, *J* = 4.0 Hz, 1H), 3.38 (dd, *J* = 16.5, 9.0 Hz, 1H), 3.16 (dd, *J* = 16.5, 9.0 Hz, 1H), 2.82 (m, 1H), 1.99-1.88 (m, 1H), 1.73-1.58 (m, 1H), 1.03-0.85 (m, 27H, 9CH₃), 0.59 (q, *J* = 7.8 Hz, 6H, 3CH₂), 0.04 (s, 6H, 2CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 159.0 (C), 135.0 (CH), 132.5 (CH), 130.8 (C), 129.2 (2CH), 129.0 (CH), 117.1 (CH₂), 113.6 (2CH), 77.5 (CH), 73.2 (CH₂), 73.1 (CH), 72.5 (CH₂), 55.2 (CH₃), 40.2 (CH), 38.0 (CH), 36.5 (CH), 26.2 (3CH₃), 18.7 (C), 18.5 (CH₃), 11.9 (CH₃), 11.5 (CH₃), 7.2 (3CH₃), 5.6 (3CH₂), -3.3 (2CH₃); IR (Film) ν = 2957, 2857, 1616, 1490 cm⁻¹; elemental analysis calcd (%) for C₃₃H₆₀O₄Si₂: C 68.69, H 10.48; found: C 68.48, H 10.67. (**41**): ¹H NMR (400.0 MHz, CDCl₃): δ = 7.24 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.80 (ddd, *J* = 15.1, 11.9, 8.2 Hz, 1H), 4.97 (d, *J* = 11.9 Hz, 1H), 4.96 (d, *J* = 15.1 Hz, 1H), 4.41 (d, *J* = 11.9 Hz, 1H), 4.35 (d, *J* = 11.9 Hz, 1H), 3.80 (s, 3H), 3.68 (dd, 1H, *J* = 5.9, 3.2 Hz), 3.48 (dd, *J* = 5.0, 4.8 Hz, 1H), 3.38 (dd, *J* = 8.7, 6.4 Hz, 1H), 3.18 (dd, *J* = 8.7, 7.3 Hz, 1H), 2.34 (dq, *J* = 8.2, 6.9, 5.0 Hz, 1H), 1.93 (dq, *J* = 7.3, 6.9, 6.4, 3.2 Hz, 1H), 1.69 (q, *J* = 6.9, 5.9, 4.8 Hz, 1H), 0.99 (d, *J* = 6.9 Hz, 3H, CH₃), 0.93 (t, *J* = 7.8 Hz, 9H, 3CH₃), 0.88 (s, 9H, 3CH₃), 0.86 (d, *J* = 6.9 Hz, 3H, CH₃), 0.85 (d, *J* = 6.9 Hz, 3H, CH₃), 0.59 (q, *J* = 7.8 Hz, 6H, 3CH₂), 0.03 (s, 6H, 2CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 159.0 (C), 141.2 (C), 131.2 (CH), 129.3 (2CH), 114.6 (CH₂), 113.6 (2CH), 77.0 (CH), 73.3 (CH₂), 73.2 (CH), 72.6 (CH₂), 55.3 (CH₃), 39.6 (CH), 37.9 (CH), 33.5 (CH), 26.2 (3CH₃), 18.5 (C), 18.5 (CH₃), 11.7 (CH₃), 11.5 (CH₃), 7.2 (3CH₃), 5.6 (3CH₂), -3.4 (2CH₃).**

(**3*Z*,5*S*,6*S*,7*R*,8*S*,9*S*)-8-(*tert*-Butyldimethylsilyloxy)-10-hydroxy-6-(triethylsilyloxy)-5,7,9-trimethyl deca-1,3-diene (**42**): To a solution of compound **40** (249 mg, 0.43**

mmol, 1.0 equiv) in CH₂Cl₂ (6 mL)/H₂O (300 μL) at 0 °C was added 2, 3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 117 mg, 0.52 mmol, 1.1 equiv). The mixture was stirred for 10 min at 0 °C, warmed to 20 °C and stirred for an additional 30 min. The mixture was quenched with a saturated aqueous NaHCO₃ solution, diluted with Et₂O, washed with water and brine. The combined organic layers were dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The crude residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate 95:5 to 80:20) to give the title compound **42** (142 mg, 72 % yield). (**42**): [α]_D²⁰ = +11.4 (c = 1.2, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃): δ = 6.58 (ddd, *J* = 16.9, 11.0, 10.5 Hz, 1H), 6.02 (t, *J* = 11.0 Hz, 1H), 5.60 (dd, *J* = 11.0, 10.1 Hz, 1H), 5.22 (d, *J* = 16.9 Hz, 1H), 5.13 (d, *J* = 10.5 Hz, 1H), 3.68 (t, *J* = 3.9 Hz, 1H), 3.60-3.56 (m, 1H), 3.51 (dd, *J* = 7.3, 3.9 Hz, 1H), 3.45-3.40 (m, 1H), 2.88 (dq, *J* = 10.1, 7.3, 3.9 Hz, 1H), 2.86 (m, 1H), 1.75 (dd, *J* = 5.5, 5.0 Hz, 1H, OH), 1.64 (dq, *J* = 7.3, 6.9, 3.9 Hz, 1H), 1.04 (d, *J* = 7.3 Hz, 3H, CH₃), 0.98 (t, *J* = 7.8 Hz, 9H, 3CH₃), 0.94 (d, *J* = 6.9 Hz, 3H, CH₃), 0.85 (s, 9H, 3CH₃), 0.83 (d, *J* = 6.9 Hz, 3H, CH₃), 0.65 (q, *J* = 7.8 Hz, 6H, 3CH₂), 0.11 (s, 3H, CH₃), 0.08 (s, 3H, CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 134.6 (CH), 132.5 (CH), 129.2 (CH), 117.7 (CH₂), 78.0 (CH), 73.7 (CH), 66.2 (CH₂), 40.8 (CH), 40.2 (CH), 35.9 (CH), 26.2 (3CH₃), 19.2 (CH₃), 18.5 (C), 12.5 (CH₃), 11.9 (CH₃), 7.4 (3CH₃), 5.8 (3CH₂), -3.5 (CH₃), -3.7 (CH₃); IR (Film) ν = 3405, 2956, 2930, 2878, 2858, 1461, 1252, 1096, 1076, 1006, 837, 772, 737 cm⁻¹; elemental analysis calcd (%) for C₂₅H₃₂O₃Si₂: C 65.73, H 11.47; found: C 65.56, H 11.62.

(3Z,5S,6S,7R,8S,9S)-8-(tert-Butyldimethylsilyloxy)-10-iodo-6-(triethylsilyloxy)-5,7,9-trimethyl deca-1,3-diene (43): To a solution of compound **42** (200 mg, 0.44 mmol, 1.0 equiv), triphenylphosphine (PPh₃, 218 mg, 0.83 mmol, 1.9 equiv) and imidazole (57 mg, 0.83 mmol, 1.9 equiv) in a benzene/Et₂O mixture (1.5 mL:3 mL) at 0 °C was slowly added a solution of iodine (167 mg, 0.66 mmol, 1.5 equiv) in Et₂O (2 mL). After stirring for 2 h at 20 °C, a 1 M Na₂S₂O₃ solution was added and the reaction mixture was extracted with Et₂O. The organic layers were washed with brine, dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/ Et₂O 100:0 to 80:20) to give the title compound **43** (197 mg, 79 % yield). (**43**): [α]_D²⁰ = +11.3 (c = 0.68, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃): δ = 6.58 (ddd, *J* = 16.9, 11.0, 10.1 Hz, 1H), 6.02 (t, *J* = 11.0 Hz, 1H), 5.55 (dd, *J* = 11.0, 10.1 Hz, 1H), 5.21 (d, *J* = 16.9 Hz, 1H), 5.12 (d, *J* = 10.1 Hz, 1H), 3.58 (t, *J* = 4.6 Hz, 1H), 3.50 (dd, *J* = 6.4, 3.7 Hz, 1H), 3.32 (dd, *J* = 9.6, 4.6 Hz, 1H), 2.98 (dd, *J* = 9.6, 9.2 Hz, 1H), 2.84 (dq, *J* = 10.1, 6.9, 4.6 Hz, 1H), 1.97 (dq, *J* = 9.2, 6.9, 4.6 Hz, 1H), 1.65 (q, *J* = 6.9, 4.6 Hz, 1H), 1.01 (d, *J* = 6.9 Hz, 3H, CH₃), 0.98 (t, *J* = 7.8 Hz, 9H, 3CH₃), 0.98 (d, *J* = 6.9 Hz, 3H, CH₃), 0.91 (s, 9H, 3CH₃), 0.90 (d, *J* = 6.9 Hz, 3H, CH₃), 0.64 (q, *J* = 7.8 Hz, 6H, 3CH₂), 0.10 (s, 3H, CH₃), 0.09 (s, 3H, CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 134.1 (CH), 132.5 (CH), 129.0 (CH), 117.4 (CH₂), 77.1 (CH), 75.0 (CH), 41.9 (CH), 40.4 (CH), 35.8 (CH), 25.9 (3CH₃), 18.8 (CH₃), 18.4 (C), 15.0 (CH₃), 13.4 (CH₂), 11.9 (CH₃), 7.0 (3CH₃), 5.5 (3CH₂), -3.8 (2CH₃); IR (Film) ν = 2950, 2930, 2877, 2857, 1461, 1097, 1028, 1005, 836 cm⁻¹; elemental analysis calcd (%) for C₂₅H₅₁IO₂Si₂: C 52.98, H 9.07; found: C 53.17, H 9.25.

(S)-3-Benzyloxy-2-methyl-propanal (44): Benzyl alcohol (20.0 g, 184.9 mmol, 1.0 equiv) was added to a suspension of NaH (60 % in mineral oil, 0.740 g, 18.5 mmol, 0.1 equiv) in anhydrous ether (45 mL) over 30 min at 20 °C. The mixture was stirred for 1 h and cooled to 0 °C. Trichloroacetonitrile (distilled) (20.5 mL, 204.5 mmol, 1.09 equiv.) was then introduced over 10 min. After 1.5 h the solution was concentrated with the water-bath temperature maintained below 40 °C. The residue was treated with a mixture of pentane (150 mL) and methanol (0.6 mL), stirred at 20 °C for 30 min, and filtered through a pad of celite. Concentration gave the trichloroimidate (44.0 g) as yellow oil, which was used without further purification.

A solution of methyl (S)-(+)-3-hydroxy-2-methylpropionate **14** (10 mL, 90.2 mmol, 1.0 equiv) in an anhydrous mixture of CH₂Cl₂/cyclohexane (1:2, 120 mL) was cooled to 0 °C and treated with crude trichloroimidate (27.3 g, 108.1 mmol, 1.2 equiv) and triflic acid (800 μL, 9.0 mmol, 0.1 equiv) over 10 min. After 3 h, the mixture was warmed to 20 °C and stirred for 40 h. The solution was filtered through a pad of celite and concentrated. The residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate 90:10) to give 15.8 g (84 % yield) of (S)-3-benzyloxy-2-methyl-propionic acid methyl ester as a yellow oil. RN: 74924-27-9; ¹H NMR (400.0 MHz, CDCl₃): δ = 7.37-7.27 (m, 5H), 4.52 (s, 2H), 3.69 (s, 3H), 3.65 (dd, *J* = 9.3, 1.7 Hz, 1H), 3.49 (dd, *J* = 9.3, 4.9 Hz, 1H), 2.79 (qdd, *J* = 7.1, 4.9, 1.7 Hz, 1H), 1.18 (d, *J* = 7.1 Hz, 3H); ¹³C NMR (100.5 MHz, CDCl₃): δ = 175.3 (C), 138.1 (C), 128.3 (2CH), 127.6 (2CH), 127.5 (CH), 73.0 (CH₂), 71.9 (CH₂), 51.7 (CH₃), 40.1 (CH), 13.9 (CH₃); MS (GC, EI, CH₄): *m/z*: 208, 176, 148, 121, 107, 102, 91, 85, 79, 65, 51.

A solution of the above compound (15.8 g, 75.8 mmol, 1.0 equiv) in anhydrous THF (50 mL) was cooled to 0 °C and slowly added to a solution of LiAlH₄ (1 M in THF, 68 mL, 68.2 mmol, 0.9 equiv) over 10 min, warmed gradually to 20 °C, and stirred for 3 h. The reaction mixture was cooled to 0 °C and quenched by addition of water (11 mL), 15 % NaOH (9 mL), and water (11 mL). The resultant mixture was treated with MgSO₄, filtered, and the solvent removed under reduced pressure. The residue was then purified by chromatography on silica gel (cyclohexane/ethyl acetate 90:10 to 80:20) to give 12.9 g (94 % yield) of (S)-3-benzyloxy-2-methylpropan-1-ol as an orange oil. RN: 63930-49-4; ¹H NMR (400.0 MHz, CDCl₃): δ = 7.38-7.27 (m, 5H), 4.52 (s, 2H), 3.64-3.53 (m,

3H), 3.42 (dd, *J* = 9.1, 8.2 Hz, 1H), 2.57 (dd, *J* = 6.7, 4.7 Hz, 1H, OH), 2.13-2.00 (m, 1H), 0.88 (d, *J* = 7.0 Hz, 3H, CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 137.9 (C), 128.4 (CH), 127.7 (2CH), 127.6 (2CH), 75.4 (CH₂), 73.3 (CH₂), 67.8 (CH₂), 35.5 (CH), 13.4 (CH₃); MS (GC, EI, CH₄): *m/z*: 180, 161, 120, 107, 91, 79, 65, 51.

To a solution of IBX (36.2 g, 129.4 mmol, 2.2 equiv) in DMSO (400 mL) at 20 °C was added the preceding alcohol (10.6 g, 58.8 mmol, 1.0 equiv) in DMSO (50 mL). The mixture was stirred for 3 h, and then cooled to 0 °C. H₂O was added and the solution was filtered through a pad of celite and then diluted with diethyl ether. The organic layer was washed with water (5X), brine (2X), dried over MgSO₄ and the solvent removed under reduced pressure. The crude (S)-3-benzyloxy-2-methyl-propanal **44** was used without further purification (10.1 g, 96 % yield). (**44**): RN: 79027-28-4; ¹H NMR (400.0 MHz, CDCl₃): δ = 9.65 (d, *J* = 1.7 Hz, 1H), 7.31-7.19 (m, 5H), 4.45 (s, 2H), 3.62-3.55 (m, 2H), 2.63-2.55 (m, 1H), 1.05 (d, *J* = 6.9 Hz, 3H, CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 203.9 (C), 137.9 (C), 128.4 (2CH), 127.8 (2CH), 127.7 (CH), 73.5 (CH₂), 70.0 (CH₂), 46.7 (CH), 10.6 (CH₃); MS (GC, EI, CH₄): *m/z*: 209, 108, 91, 79, 63, 51.

(2S,3S,4S)-1-Benzyloxy-2,4-dimethyl-hex-5-en-3-ol (45): To a solution of freshly sublimed potassium *tert*-butoxide (9.77 g, 87.1 mmol, 1.55 equiv) in THF (130 mL) at -78 °C was slowly added to a solution of *trans*-2-butene (26 mL) in THF (25 mL); *n*-BuLi (1.6 M in hexane, 55 mL, 87.8 mmol, 1.55 equiv) was then added and the yellow mixture was stirred at -78 °C for 5 min and at -45 °C for 20 min. The resulting orange solution was cooled to -78 °C, and a solution of (-)-*B*-diisopinocampheylmethoxyborane (25.1 g, 79.3 mmol, 1.4 equiv) in 46 mL of diethyl ether was added over ca. 15 min. The resulting white solution was stirred at -78 °C for 40 min. Boron trifluoride etherate (12.6 mL, 102.0 mmol, 1.8 equiv) was added followed after 5 min by addition of a solution of aldehyde **44** (10.1 g, 56.7 mmol, 1.0 equiv) in THF (25 mL). The resulting solution was stirred at -78 °C for 5 h. The reaction was then quenched by addition of aqueous NaOH (2.5 N, 66 mL) followed by aqueous H₂O₂ (30 %, 20 mL). The acetone-dry ice bath was then removed, and the mixture was heated at 45 °C for 45 min. The cloudy solution was cooled to 20 °C, diluted with diethyl ether (45 mL), washed with brine, dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The crude residue was purified by chromatography (cyclohexane/ethyl acetate 100:0 to 90:10) to give 11.0 g (83 % yield) of **45** and 1.27 g (9 % yield) of its **3,4-bis epi** diastereomer (92 % overall yield, *ee* 100 %, *de* 90:10). (**45**): [α]_D²⁰ = +12.1 (c = 5.5, CHCl₃); RN: 106357-28-2; ¹H NMR (400.0 MHz, CDCl₃): δ = 7.27-7.22 (m, 5H), 5.72 (ddd, *J* = 18.8, 10.6, 8.6 Hz, 1H), 5.07-5.01 (m, 2H), 4.44 (s, 2H), 3.50 (dd, *J* = 8.9, 5.9 Hz, 2H), 3.55-3.42 (m, 2H), 2.48-2.40 (m, 1H + OH), 1.92-1.87 (m, 1H), 0.90 (d, *J* = 7.3 Hz, 3H, CH₃), 0.88 (d, *J* = 7.3 Hz, 3H, CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 141.8 (CH), 138.2 (C), 128.3 (2CH), 127.5 (3CH), 115.6 (CH₂), 75.5 (CH), 74.7 (CH₂), 73.4 (CH₂), 41.9 (CH), 34.9 (CH), 15.1 (CH₃), 9.8 (CH₃); MS (GC, EI): *m/z*: 234, 215, 187, 107, 91, 79; IR (Film) ν = 2868, 1074, 1110, 997 cm⁻¹. (**3,4-bis epi isomer of 45**): RN: 106357-29-3; ¹H NMR (400.0 MHz, CDCl₃): δ = 7.31-7.18 (m, 5H), 5.83 (ddd, *J* = 18.1, 9.6, 8.6 Hz, 1H), 4.97 (m, 2H), 4.44 (s, 2H), 3.54-3.44 (m, 2H), 3.32-3.30 (m, 1H), 2.40-2.21 (m, 1H), 1.91-1.81 (m, 1H), 1.54 (bs, 1H, OH), 1.03 (d, *J* = 6.9 Hz, 3H, CH₃), 0.82 (d, *J* = 6.9 Hz, 3H, CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 139.7 (CH), 137.7 (C), 128.4 (2CH), 127.7 (2CH), 127.6 (C), 115.2 (CH₂), 79.7 (CH), 75.4 (CH₂), 73.4 (CH₂), 41.0 (CH), 36.2 (CH), 17.7 (CH₃), 13.8 (CH₃).

(2S,3R,4R,5S)-1-Benzyloxy-2,4-dimethyl-5,6-epoxy-hexan-3-ol (46)

(2S,3R,4R,5R)-1-Benzyloxy-2,4-dimethyl-5,6-epoxy-hexan-3-ol (47): To a solution of VO(acac)₂ (12 mg, 0.042 mmol, 2 mol %) in CH₂Cl₂ (6 mL) at 0 °C were added olefin **45** (500 mg, 2.13 mmol, 1.0 equiv) in CH₂Cl₂ (15 mL) and *t*-BHP (solution 5 M in decane, 640 μL, 3.20 mmol, 1.5 equiv). The temperature was maintained for 20 min and the reaction mixture was stirred overnight at 20 °C. The reaction mixture was partitioned between diethyl ether and a saturated aqueous solution of ammonium chloride and extracted with diethyl ether. The organic layer was washed with brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate 90:10) to give 374 mg (70 % yield) of **46**, 42 mg (8 % yield) of its C5 isomer **47** (78 % overall yield, selectivity 9:1) and 110 mg of starting material **45** (22 % recovered yield). (**46**): [α]_D²⁰ = +0.82 (c = 0.7, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃): δ = 7.25-7.16 (m, 5H), 4.48 (s, 2H), 3.72-3.69 (m, 1H), 3.50 (dd, *J* = 8.9, 6.3 Hz, 1H), 3.41 (dd, *J* = 8.9, 5.3 Hz, 1H), 2.92-2.87 (m, 1H), 2.84 (bs, 1H, OH), 2.64 (t, *J* = 4.6 Hz, 1H), 2.39 (dd, *J* = 4.6, 3.0 Hz, 1H), 1.94-1.83 (m, 1H), 1.43-1.29 (m, 1H), 0.84 (d, *J* = 6.9 Hz, 3H, CH₃), 0.80 (d, *J* = 6.9 Hz, 3H, CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 138.2 (C), 128.2 (2CH), 127.4 (3CH), 76.1 (CH), 74.2 (CH₂), 73.2 (CH₂), 55.5 (CH), 44.8 (CH₂), 39.0 (CH), 35.2 (CH), 12.4 (CH₃), 9.4 (CH₃); IR (Film) ν = 3471, 2968, 2862, 1653, 1559, 1541, 1496, 1461, 1453, 1410, 1365, 1310, 1258, 1205, 1103, 987, 886 cm⁻¹; MS (GC, EI): *m/z*: 250 (M⁺), 248, 232, 217, 201, 187, 177, 160, 148, 141, 123, 115, 107, 91, 79, 65, 55; elemental analysis calcd (%) for C₁₅H₂₂O₃: C 71.97, H 8.86; found: C 71.78, H 9.06. (**47**): ¹H NMR (400.0 MHz, CDCl₃): δ = 7.37-7.19 (m, 5H), 4.44 (s, 2H), 3.67-3.63 (m, 1H), 3.50 (d, *J* = 5.3 Hz, 2H), 2.89 (ddd, *J* = 6.9, 3.9, 2.9 Hz, 1H), 2.77 (dd, *J* = 4.3, 3.9 Hz, 1H), 2.64 (dd, *J* = 4.3, 2.9 Hz, 1H), 1.86-1.84 (m, 1H), 1.51-1.43 (m, 1H), 0.87 (d, *J* = 6.9 Hz, 3H, CH₃), 0.86 (d, *J* = 6.9 Hz, 3H, CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 137.9 (C), 128.4 (2CH), 127.7 (2CH), 127.5 (CH), 75.3 (CH₂), 73.4 (CH₂), 55.9 (CH),

47.6 (CH₂), 38.9 (CH), 34.7 (CH), 13.1 (CH₃), 9.3 (CH₃); MS (GC, EI): *m/z*: 250 (M⁺), 209, 189, 177, 160, 142, 123, 108, 91, 79, 65, 55.

(2S,3R,4S,5S)-1-Benzyloxy-2,4-dimethyl-oct-7-en-3,5-diol (48): To a solution of vinyl bromide (1 mL, 13.8 mmol, 4.8 equiv) in diethyl ether (20 mL) at -78 °C was slowly added *t*-BuLi (1.7 M, 16.3 mL, 27.7 mmol, 9.6 equiv). The temperature was maintained for 10 min then the mixture was stirred for 2 h at 20 °C. In a second flask CuCN (620 mg, 6.9 mmol, 2.4 equiv) was introduced and purged (3 times). THF (10 mL) was added and the resulting suspension was cooled to -78 °C. The freshly prepared solution of vinyl lithium was then slowly added, and the resulting yellow solution was stirred at -20 °C for 25 min. The solution was cooled to -78 °C and the epoxide **46** (722 mg, 2.88 mmol, 1.0 equiv) in THF (10 mL) was added. The resulting mixture was stirred at 0 °C overnight. A 25 % aqueous ammonia solution was added and the resulting biphasic solution was stirred vigorously until the aqueous layer turned night blue. The organic layer was washed with brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate 70:30) to give **48** (692 mg, 86 % yield). **(48):** ¹H NMR (400.0 MHz, CDCl₃): δ = 7.28-7.16 (m, 5H), 5.82 (tdd, *J* = 14.4, 10.5, 7.9 Hz, 1H), 5.24-5.18 (m, 2H), 4.60 (s, 2H), 4.15 (bs, 1H, OH), 4.05 (bs, 1H, OH), 3.70-3.66 (m, 1H), 3.61 (dt, *J* = 7.6, 3.0 Hz, 1H), 3.50-3.44 (m, 2H), 2.3-2.26 (m, 1H), 2.06 (dt, *J* = 15.0, 7.5 Hz, 1H), 1.93-1.81 (m, 1H), 1.66-1.52 (m, 1H), 1.05 (d, *J* = 6.9 Hz, 3H, CH₃), 0.85 (d, *J* = 6.9 Hz, 3H, CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 137.8 (C), 134.9 (CH), 128.2 (2CH), 127.5 (2CH), 127.4 (CH), 117.1 (CH₂), 78.1 (CH), 75.1 (CH₂), 75.0 (CH), 73.2 (CH₂), 40.0 (CH), 38.8 (CH₂), 34.9 (CH), 12.4 (CH₃), 9.1 (CH₃); IR (Film) ν = 3371, 2957, 2886, 1653, 1636, 1559, 1454, 1206, 1097, 1028, 983, 911 cm⁻¹; MS (GC, EI): *m/z*: 253, 219, 190, 179, 160, 145, 129, 118, 107, 91, 80, 69, 57, 55; elemental analysis calcd (%) for C₁₇H₂₆O₃: C 73.34, H 9.41; found: C 72.69, H 9.15.

(4S,5S,6R,7S)-4,6,8-Tris-(*tert*-butyldimethylsilyloxy)-5,7-dimethyl-oct-1-ene (49): To a night blue solution of lithium metal (124 mg, 17.9 mmol, 1.0 equiv) in liquid ammonia and anhydrous THF (10 mL) at -78 °C was added the benzylic product **48** (500 mg, 1.79 mmol, 1.0 equiv) in dry THF (10 mL). The reaction mixture was stirred at -78 °C for 1 h. Then the solution was quenched by addition of solid NH₄Cl (10 g) and the ammonia was allowed to evaporate by permitting the reaction to warm to 20 °C. A saturated aqueous solution of NH₄Cl was then added and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The crude (2S,3R,4S,5S)-2,4-dimethyl-oct-7-ene-1,3,5-triol compound was used without further purification in the next step (300 mg). ¹H NMR (400.0 MHz, CDCl₃): δ = 5.69 (ddt, *J* = 14.2, 8.2, 5.9 Hz, 1H), 5.10-5.06 (m, 2H), 4.75 (bs, 1H, OH), 4.08 (bs, 1H, OH), 3.79-3.75 (m, 1H), 3.68-3.55 (m, 3H), 2.29-2.23 (m, 1H), 2.08 (quint, *J* = 7.6 Hz, 1H), 1.81-1.76 (m, 1H), 1.65-1.54 (m, 1H), 0.86 (d, *J* = 7.3 Hz, 3H, CH₃), 0.70 (d, *J* = 7.3 Hz, 3H, CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 134.5 (CH), 118.1 (CH₂), 78.5 (CH), 75.8 (CH), 67.3 (CH₂), 40.2 (CH), 39.4 (CH₂), 36.0 (CH), 12.5 (CH₃), 8.6 (CH₃); MS (GC, EI): *m/z*: 188, 171, 161, 142.

To a solution of the preceding triol (200 mg, 1.06 mmol, 1.0 equiv) in dry CH₂Cl₂ (10 mL) at 0 °C were added 2,6-lutidine (1.1 mL, 9.56 mmol, 9.0 equiv) and TBSOTf (1.1 mL, 4.78 mmol, 4.5 equiv). The reaction mixture was stirred at 20 °C for 3 h, then quenched by addition of a saturated aqueous solution of NH₄Cl and extracted with CH₂Cl₂. The organic layer was washed with brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate 98:2) to give the title compound **49** (560 mg, 99 % yield). **(49):** [α]_D²⁰ = -2.70 (*c* = 1.2, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃): δ = 5.79 (dd, *J* = 17.5, 10.1, 7.1 Hz, 1H), 5.04-4.97 (m, 2H), 3.89 (dt, *J* = 8.2, 4.0 Hz, 1H), 3.77 (d, *J* = 7.9 Hz, 1H), 3.44 (t, *J* = 9.2 Hz, 1H), 3.32 (dd, *J* = 9.2, 7.3 Hz, 1H), 2.23-2.02 (m, 2H), 1.90-1.74 (m, 2H), 0.86 (s, 9H, 3CH₃), 0.85 (s, 9H, 3CH₃), 0.84 (d, *J* = 7.9 Hz, 3H, CH₃), 0.83 (s, 9H, 3CH₃), 0.80 (d, *J* = 7.9 Hz, 3H, CH₃), 0.00 (s, 6H, 2CH₃), -0.02 (s, 6H, 2CH₃), -0.05 (s, 6H, 2CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 136.2 (CH), 116.4 (CH₂), 72.1 (CH), 72.0 (CH), 66.1 (CH₂), 43.7 (CH), 38.7 (CH), 36.6 (CH₂), 26.3 (3CH₃), 25.9 (3CH₃), 25.3 (3CH₃), 18.3 (C), 18.2 (C), 18.1 (C), 10.6 (CH₃), 10.0 (CH₃), -2.9 (2CH₃), -3.4 (CH₃), -4.1 (CH₃), -4.2 (CH₃), -4.3 (CH₃); IR (Film) ν = 2955, 2930, 2886, 2858, 1645, 1472, 1388, 1361, 1254, 1069, 1044, 1005, 912, 833 cm⁻¹; MS (GC, EI): *m/z*: 474 (M⁺ - *t*-Bu), 433, 391, 357, 341, 317, 259, 243, 225, 185, 169, 147, 131, 115, 89, 73, 55; elemental analysis calcd (%) for C₂₈H₄₂O₃Si₃: C 63.33, H 11.77; found: C 63.12, H 11.98.

(2S)-3-(*tert*-Butyldimethylsilyloxy)-2-methyl-propanal (50): To a solution of commercial methyl-(S)-(+)-3-hydroxy-2-methylpropionate **14** (3.70 g, 31.3 mmol, 1.0 equiv) in dry DMF (30 mL) were added imidazole (6.70 g, 98.4 mmol, 3.0 equiv) and *tert*-butyldimethylsilyl chloride (7.06 g, 47 mmol, 1.5 equiv). After 3 h at 20 °C the mixture was quenched with a saturated aqueous NH₄Cl solution and diluted with diethyl ether. The organic layer was washed with water and brine, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. The crude residue was purified by chromatography on silica gel (cyclohexane/diethyl ether 100:0 to 90:10) to give 6.80 g (94 % yield) of (2S)-methyl-3-(*tert*-butyldimethylsilyloxy)-2-methyl propanoate as a colourless oil. RN: 93454-85-4; ¹H NMR (400.0 MHz, CDCl₃): δ = 3.78 (dd, *J* = 9.6, 6.9 Hz, 1H), 3.68 (s, 3H, CH₃), 3.66 (dd, *J* = 9.6, 6.0 Hz, 1H), 2.66 (qdd, *J* = 6.9, 6.9, 6.0 Hz, 1H), 1.14 (d, *J* = 6.9 Hz, 3H, CH₃), 0.88 (s, 9H, 3CH₃), 0.04 (s, 6H, 2CH₃); ¹³C

NMR (100.5 MHz, CDCl₃): δ = 175.4 (C), 65.3 (CH₂), 51.3 (CH₃), 42.6 (CH), 25.8 (3CH₃), 18.3 (C), 13.5 (CH₃), -5.5 (2CH₃); IR (Film) ν = 2930, 2885, 2858, 1744, 1472, 1436, 1389, 1362, 1257, 1199, 1176, 1098, 837, 777, 668 cm⁻¹; MS (GC, CI, NH₃): *m/z*: 250 (MH⁺ + NH₃), 233 (MH⁺), 201, 175, 132, 106, 91.

To a solution of (S)-3-(*tert*-butyldimethylsilyloxy)-2-methyl-propionic acid methyl ester (5.50 g, 23.7 mmol, 1.0 equiv) in CH₂Cl₂ (25 mL) at -35 °C was added diisobutylaluminum hydride (1 M solution in CH₂Cl₂, 50.0 mL, 50.0 mmol, 2.1 equiv). The solution was stirred 30 min at -20 °C. Then the mixture was quenched by addition of 10 % aqueous NaOH solution (55 mL of water, 5.50 g of NaOH, 137.5 mmol, 5.8 equiv). The mixture was allowed to warm to 20 °C and then diluted with diethyl ether. The organic layer was washed with water and brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The crude residue was purified by chromatography on silica gel (cyclohexane/diethyl ether 80:20 to 50:50) to give 4.46 g (92 % yield) of (2S)-3-(*tert*-butyldimethylsilyloxy)-2-methyl-propan-1-ol as a colourless oil. RN: 112057-64-4; ¹H NMR (400.0 MHz, CDCl₃): δ = 3.76 (dd, *J* = 9.6, 4.3 Hz, 1H), 3.66 (ddd, *J* = 11.2, 7.0, 4.6 Hz, 1H), 3.60 (ddd, *J* = 11.2, 7.8, 3.9 Hz, 1H), 3.55 (dd, *J* = 9.6, 8.2 Hz, 1H), 2.93 (dd, *J* = 7.0, 3.9 Hz, 1H, OH), 1.95 (dqdd, *J* = 8.2, 7.8, 6.9, 4.6, 4.3 Hz, 1H), 0.91 (s, 9H, 3CH₃), 0.83 (d, *J* = 6.9 Hz, 3H, CH₃), 0.08 (s, 6H, 2CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 68.9 (CH₂), 68.5 (CH₂), 36.9 (CH, C-2), 25.8 (3CH₃), 18.1 (C), 13.0 (CH₃), -5.6 (2CH₃); IR (Film) ν = 3354, 2955, 2857, 1472, 1389, 1361, 1258, 1090, 1040, 939, 836, 775, 667 cm⁻¹; MS (GC, CI, NH₃): *m/z*: 222 (MH⁺ + NH₃), 205 (MH⁺), 132, 92, 76, 74.

To a solution of oxalyl chloride (1.8 mL, 21.4 mmol, 1.2 equiv) in CH₂Cl₂ (60 mL) at -55 °C was added DMSO (3.1 mL, 42.9 mmol, 2.4 equiv). This was followed 5 min later with the addition via cannula of a solution of the preceding alcohol (3.65 g, 17.9 mmol, 1.0 equiv) in CH₂Cl₂ (20 mL). The resulting slurry was stirred for 1 h at -55 °C. Then triethylamine (12.5 mL, 89.3 mmol, 5.0 equiv) was added. The solution was warmed to 20 °C 5 min later and stirred for an additional hour at 20 °C. The solution was diluted with CH₂Cl₂ (80 mL) and washed with 90 mL of ice-cold 1M HCl and 90 mL of water. These phases were extracted with CH₂Cl₂ (180 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The crude (S)-3-(*tert*-butyldimethylsilyloxy)-2-methyl-propanal **50** was used without further purification (3.40 g, 94 % yield). **(50):** RN: 104701-87-3; ¹H NMR (400.0 MHz, CDCl₃): δ = 8.86 (d, *J* = 1.5 Hz, 1H), 3.78 (dd, *J* = 9.6, 6.9 Hz, 1H), 3.66 (dd, *J* = 9.6, 6.0 Hz, 1H), 2.66 (qddd, *J* = 6.9, 6.9, 6.0, 1.5 Hz, 1H), 1.14 (d, *J* = 6.9 Hz, 3H, CH₃), 0.88 (s, 9H, 3CH₃), 0.04 (s, 6H, 2CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 204.7 (C), 63.4 (CH₂), 48.8 (CH), 25.8 (3CH₃), 18.2 (C), 10.3 (CH₃), -5.5 (2CH₃); IR (Film) ν = 2956, 2930, 2885, 2858, 1737, 1472, 1389, 1362, 1256, 1100, 1033, 838, 771, 668 cm⁻¹; MS (GC, CI, NH₃): *m/z*: 220 (MH⁺ + NH₃), 203 (MH⁺), 145, 132, 115, 106, 91, 76, 74.

(1Z,3S,4S,5S)-6-(*tert*-Butyldimethylsilyloxy)-1-(*N,N*-diisopropyl)carbamoyloxy)-3,5-dimethyl-hex-1-en-4-ol (51): To a quick stirred solution of the (*E*)-crotyl diisopropylcarbamate (7.80 g, 39.2 mmol, 2.0 equiv) and (-)-sparteine (9.50 g, 40.4 mmol, 2.1 equiv) in pentane (36 mL) and cyclohexane (6 mL) at -78 °C, was added a solution of *n*-BuLi (1.37 M in hexanes, 30.6 mL, 41.9 mmol, 2.1 equiv), and after 10 min white crystals appeared. After 3 h of crystallization at -78 °C, a pre-cooled (-40 °C) solution of titanium tetraisopropoxide (Ti(O^{*i*}Pr)₄, 34.7 mL, 117.6 mmol, 6.0 equiv) in pentane (30 mL) was quickly added via cannula to the reaction mixture of lithio carbamate which became limpid and turned orange. After 1 h at -78 °C aldehyde **50** (3.96 g, 19.6 mmol, 1.0 equiv) in pentane (10 mL) was slowly added to the orange solution, and the mixture was stirred for 3 h at -78 °C. The solution was then poured into a mixture of diethyl ether (250 mL)-aqueous hydrochloric acid solution (0.5 N, 250 mL). After extraction with diethyl ether, the organic layer was washed with brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate 95:5 to 70:30) to give 4.30 g (58 % yield) of the title compound **51** and its **3,4-bis-epi** diastereomer (*de* 95:5). **(51):** [α]_D²⁰ = +20.1 (*c* = 1.0, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃): δ = 7.13 (d, *J* = 6.4 Hz, 1H), 4.73 (dd, *J* = 9.6, 6.4 Hz, 1H), 4.22-4.11 (bs, 1H), 3.82-3.70 (bs, 1H), 3.71 (d, *J* = 4.6 Hz, 2H), 3.54 (dt, *J* = 8.2, 2.3 Hz, 1H), 2.86 (ddq, *J* = 9.6, 8.2, 6.9 Hz, 1H), 2.69 (d, *J* = 2.3 Hz, 1H, OH), 1.84 (qtd, *J* = 6.9, 4.6, 2.3 Hz, 1H), 1.28-1.10 (m, 12H, 4CH₃), 0.97 (d, *J* = 6.9 Hz, 3H, CH₃), 0.94 (d, *J* = 6.9 Hz, 3H, CH₃), 0.90 (s, 9H, 3CH₃), 0.08 (s, 6H, 2CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 153.0 (C), 135.9 (CH), 113.9 (CH), 77.0 (CH), 68.0 (CH₂), 47.0 (CH), 45.2 (CH), 36.6 (CH), 34.0 (CH), 26.0 (3CH₃), 21.6 (2CH₃), 20.5 (2CH₃), 18.3 (C), 17.4 (CH₃), 9.4 (CH₃), -5.50 (2CH₃); IR (Film) ν = 3493, 2959, 2930, 2858, 1708, 1472, 1439, 1370, 1304, 1290, 1256, 1211, 1156, 1134, 1092, 1061, 837 cm⁻¹; MS (GC, EI): *m/z*: 344 (M⁺ - *t*-Bu), 326, 302, 228, 212, 199, 184, 145, 128, 115, 86, 73; elemental analysis calcd (%) for C₂₁H₄₃NO₄Si: C 62.80, H 10.79, N 3.49; found: C 62.61, H 10.87, N 3.35. **(3,4-bis-epi isomer of 51):** ¹H NMR (400.0 MHz, CDCl₃): δ = 7.07 (d, *J* = 6.4 Hz, 1H), 4.97 (dd, *J* = 9.6, 6.4 Hz, 1H), 4.25-4.05 (bs, 1H), 4.20 (s, 1H, OH), 3.85-3.67 (bs, 1H), 3.75 (dd, *J* = 10.1, 4.1 Hz, 1H), 3.60 (dd, *J* = 10.1, 9.4 Hz, 1H), 3.47 (dd, *J* = 8.7, 2.3 Hz, 1H), 2.85 (ddq, *J* = 9.6, 8.7, 6.9 Hz, 1H), 1.77 (dqdd, *J* = 9.4, 6.9, 4.1, 2.3 Hz, 1H), 1.33-1.19 (m, 12H, 4CH₃), 1.14 (d, *J* = 6.9 Hz, 3H, CH₃), 0.90 (s, 9H, 3CH₃), 0.76 (d, *J* = 6.9 Hz, 3H, CH₃), 0.09 (s, 6H, 2CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 153.5 (C), 135.1 (CH), 111.5 (CH), 80.5 (CH), 69.5 (CH₂), 46.9 (CH), 45.5 (CH), 38.1 (CH), 33.5 (CH), 25.9 (3CH₃), 21.6 (2CH₃), 20.5 (2CH₃), 18.3 (C), 18.2 (CH₃), 13.2 (CH₃), -5.5 (2CH₃).

(2S,3S,4S)-1-(tert-Butyldimethylsilyloxy)-2,4-dimethyl-hex-5-en-3-ol (52): To a solution of carbamate **51** (500 mg, 1.24 mmol, 1.0 equiv) and Ni(acac)₂ (32 mg, 0.12 mmol, 10 mol %) in THF (5 mL) at 20 °C was slowly added a solution of isopropylmagnesium chloride in THF (1.55 M, 8.0 mL, 12.4 mmol, 10 equiv). After stirring for 12 h, a saturated aqueous NH₄Cl solution was added, and the reaction mixture was extracted with diethyl ether. The combined organic layers were washed with water and brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The crude residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate 98:2 to 85:15) to give the title compound **52** (162 mg, 50 % yield). (**52**): RN: 106296-58-6; ¹H NMR (400.0 MHz, CDCl₃): δ = 5.84 (ddd, *J* = 16.5, 10.5, 8.2 Hz, 1H), 5.12 (dd, *J* = 16.5, 1.8 Hz, 1H), 5.09 (dd, *J* = 10.5, 1.8 Hz, 1H), 3.74 (dd, *J* = 9.8, 4.1 Hz, 1H), 3.71 (dd, *J* = 9.8, 5.0 Hz, 1H), 3.55 (ddd, *J* = 8.7, 2.3, 1.8 Hz, 1H), 2.89 (d, *J* = 2.3 Hz, 1H, OH), 2.27 (ddq, *J* = 8.7, 8.2, 6.9 Hz, 1H), 1.80 (qddd, *J* = 6.9, 5.0, 4.1, 1.8 Hz, 1H), 0.95 (d, *J* = 6.9 Hz, 6H, 2CH₃), 0.90 (s, 9H, 3CH₃), 0.07 (s, 6H, 2CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 142.3 (CH), 115.3 (CH₂), 77.2 (CH), 68.8 (CH₂), 42.0 (CH), 36.1 (CH), 26.0 (3CH₃), 18.4 (C), 16.9, 9.5 (2CH₃), -5.4 (CH₃), -5.5 (CH₃).

(2E,4S,5S,6S)-N-Methyl-N-methoxy-7-(tert-butyldimethylsilyloxy)-4,6-dimethyl-5-hydroxy-hept-2-enamide (53): To a cooled (-78 °C) solution of **51** (1.05 g, 2.61 mmol, 1.0 equiv) and a few amount of Sudan III in 50 mL of CH₂Cl₂ was bubbled a stream of ozone until the pink solution became colourless. The solution was treated with triphenylphosphine (686 mg, 2.61 mmol, 1.0 equiv) and the mixture was allowed to warm to 20 °C for 2 h. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate 90:10 to 60:40) to give 590 mg (87 % yield) of (2R,3R,4S)-5-(tert-butyldimethylsilyloxy)-2,4-dimethyl-3-hydroxy-pentanal. RN: 209251-54-7; ¹H NMR (400.0 MHz, CDCl₃): δ = 9.83 (d, *J* = 2.3 Hz, 1H), 4.06 (dt, *J* = 9.6, 1.8 Hz, 1H), 3.84 (dd, *J* = 9.8, 3.4 Hz, 1H), 3.73 (dd, *J* = 9.8, 4.3 Hz, 1H), 3.49 (d, *J* = 1.8 Hz, 1H, OH), 2.52 (dq, *J* = 9.6, 7.3, 2.3 Hz, 1H), 1.77 (qddd, *J* = 6.9, 4.3, 3.4, 1.8 Hz, 1H), 1.01 (d, *J* = 7.3 Hz, 3H, CH₃), 0.98 (d, *J* = 6.9 Hz, 3H, CH₃), 0.90 (s, 9H, 3CH₃), 0.08 (s, 6H, 2CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 205.9 (CH), 75.4 (CH), 67.8 (CH₂), 49.7 (CH), 35.8 (CH), 26.0 (3CH₃), 18.3 (C), 10.6 (CH₃), 9.4 (CH₃), -5.5 (2CH₃).

To a suspension of sodium hydride (powder, 60 % in oil, 763 mg, 19.1 mmol, 2.0 equiv) in dry THF (80 mL) at 0 °C was added dropwise a solution of commercial diethyl *N*-methoxy-*N*-methylphosphonoacetamide (3.9 mL, 19.1 mmol, 2.0 equiv). The solution was stirred at 20 °C for 1 h (until hydrogen evolution was not observed). The solution was cooled to 0 °C, and the preceding aldehyde (2R,3R,4S)-5-(tert-butyldimethylsilyloxy)-2,4-dimethyl-3-hydroxy-pentanal (2.48 g, 9.52 mmol, 1.0 equiv) in dry THF (20 mL) was added dropwise. 5 min later, the mixture was allowed to warm to 20 °C for 1 h and quenched by addition of a saturated aqueous NH₄Cl solution. The aqueous layer was separated and extracted with diethyl ether (2 x). The combined organic phases were washed with water and brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The crude residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate 70:30 to 40:60) to give **53** (2.83 g, 86 % yield) as a pale yellow oil. (**53**): [α]_D²⁰ = -3.3 (*c* = 1.0, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃): δ = 6.99 (dd, *J* = 15.6, 8.7 Hz, 1H), 6.49 (d, *J* = 15.6 Hz, 1H), 3.76 (dd, *J* = 9.8, 3.9 Hz, 1H), 3.71 (s, 3H, CH₃), 3.69 (dd, *J* = 6.4, 5.0 Hz, 1H), 3.68 (dd, *J* = 9.8, 5.0 Hz, 1H), 3.24 (s, 3H, CH₃), 2.84 (bs, 1H, OH), 2.50 (dq, *J* = 8.7, 6.9, 6.4 Hz, 1H), 1.82 (qddd, *J* = 7.3, 5.0, 5.0, 3.9 Hz, 1H), 1.01 (d, *J* = 6.9 Hz, 3H, CH₃), 0.96 (d, *J* = 7.3 Hz, 3H, CH₃), 0.90 (s, 9H, 3CH₃), 0.09 (s, 6H, 2CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 167.0 (C), 150.9 (CH), 119.1 (CH), 77.3 (CH), 68.6 (CH₂), 61.8 (CH₃, CH₃), 40.9 (CH), 36.2 (CH), 32.4 (CH₃), 26.0 (3CH₃), 18.3 (C), 16.6 (CH₃), 9.5 (CH₃), -5.5 (2CH₃); IR (Film) ν = 3444, 2958, 2930, 2857, 1650, 1627, 1471, 1417, 1385, 1255, 1093, 1004, 850 cm⁻¹; MS (GC, EI): *m/z*: 288 (M⁺ - *t*-Bu), 267, 246, 227, 203, 187, 172, 145, 115, 89, 75, 55; elemental analysis calcd (%) for C₁₇H₃₅NO₄Si: C 59.09, H 10.21, N 4.05; Found: C 58.95, H 10.28, N 3.94.

(2S,4S,5S,6R)-2-{6-(2-(tert-Butyldimethylsilyloxy)-1-methyl ethyl)-5-methyl-2-phenyl-1,3-dioxinan-4-yl}-N-methoxy-N-methyl-acetamide (54): To a solution of compound **53** (300 mg, 0.87 mmol, 1.0 equiv) and freshly distilled benzaldehyde (97 μL, 0.96 mmol, 1.1 equiv) in dry THF (9 mL) at 0 °C was added KHMDS (0.5 M solution in toluene, 175 μL, 87.5 μmol, 0.1 equiv) and the obtained yellow solution was stirred for 15 min. This sequence (addition of KHMDS/stirring) was repeated twice and the solution was quenched by addition of a saturated aqueous NH₄Cl solution. The organic layer was washed with water and brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 95:5 to 50:50) to give **54** (311 mg, 79 % yield) as a pale yellow oil. (**54**): [α]_D²⁰ = +21.9 (*c* = 0.6, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃): δ = 7.46-7.43 (m, 2H), 7.36-7.29 (m, 3H), 5.58 (s, 1H), 4.12 (ddd, *J* = 10.0, 9.6, 3.0 Hz, 1H), 3.74 (dd, *J* = 9.8, 1.7 Hz, 1H), 3.69 (dd, *J* = 9.6, 9.2 Hz, 1H), 3.65 (s, 3H, CH₃), 3.50 (dd, *J* = 9.6, 5.5 Hz, 1H), 3.22 (s, 3H), 2.92 (dd, *J* = 15.6, 9.6 Hz, 1H), 2.64 (dd, *J* = 15.6, 3.0 Hz, 1H), 2.01 (dq, *J* = 9.2, 6.9, 5.5, 1.7 Hz, 1H), 1.77 (ddq, *J* = 10.0, 9.8, 6.9 Hz, 1H), 0.90 (d, *J* = 6.9 Hz, 3H, CH₃), 0.89 (s, 9H, 3CH₃), 0.85 (d, *J* = 6.9 Hz, 3H, CH₃), 0.03 (s, 6H, 2CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 172.2 (C), 139.1 (C), 128.4 (CH), 128.0 (2CH), 126.1 (2CH), 100.0 (CH), 80.3 (CH), 79.2 (CH), 65.0 (CH₂), 61.6 (CH₃), 36.7 (CH₂), 36.0 (CH), 35.4 (CH), 32.2 (CH₃), 26.0 (3CH₃), 18.4 (C), 12.0 (CH₃), 9.8 (CH₃), -5.3 (2CH₃); IR (Film) ν = 2956, 2930, 2857, 1666, 1483, 1403, 1387,

1256, 1149, 1090, 1029, 837 cm⁻¹; MS (GC, EI): *m/z*: 394 (M⁺ - *t*-Bu), 330, 288, 258, 243, 221, 199, 185, 172, 145, 115, 89, 75, 55; elemental analysis calcd (%) for C₂₄H₄₁NO₅Si: C 63.82, H 9.15, N 3.10; Found: C 63.79, H 9.21, N 3.01.

(2S,4S,5S,6R)-2-{6-(2-(tert-Butyldimethylsilyloxy)-1-methyl ethyl)-5-methyl-2-phenyl-1,3-dioxinan-4-yl}-acetaldehyde (55): To a solution of Weinreb amide **54** (1.50 g, 3.32 mmol, 1.0 equiv) in CH₂Cl₂ (20 mL) at -78 °C was added diisobutylaluminum hydride (1 M solution in CH₂Cl₂, 10.0 mL, 9.96 mmol, 3.0 equiv). The yellow solution was stirred at -78 °C for 1 h. Then the mixture was quenched by addition of ethyl acetate (15 mL). The mixture was allowed to warm to 20 °C and a solution of Rochelle's salt (17.0 g, 60.2 mmol, 18.1 equiv, in 20 mL water) was added. The mixture was stirred at 20 °C for 2 h and the organic layer was extracted with diethyl ether (2 x). The combined organic extracts were washed with brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The crude residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate 95:5 to 80:20) to give **55** (1.21 g, 93 % yield) as a pale yellow oil. (**55**): [α]_D²⁰ = +12.3 (*c* = 1.0, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃): δ = 9.83 (dd, *J* = 2.3, 1.8 Hz, 1H), 7.48-7.43 (m, 2H), 7.40-7.31 (m, 3H), 5.58 (s, 1H), 4.07 (ddd, *J* = 9.6, 7.8, 3.7 Hz, 1H), 3.75 (dd, *J* = 10.6, 1.8 Hz, 1H), 3.66 (t, *J* = 9.2 Hz, 1H), 3.47 (dd, *J* = 9.2, 6.0 Hz, 1H), 2.74 (ddd, *J* = 10.5, 3.7, 1.8 Hz, 1H), 2.71 (ddd, *J* = 10.5, 7.8, 2.3 Hz, 1H), 2.02 (dq, *J* = 9.2, 7.3, 6.0, 1.8 Hz, 1H), 1.78 (ddq, *J* = 10.6, 9.6, 6.9 Hz, 1H), 0.90 (s, 9H, 3CH₃), 0.90 (d, *J* = 7.3 Hz, 3H, CH₃), 0.88 (d, *J* = 6.9 Hz, 3H, CH₃), 0.04 (s, 6H, 2CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 201.6 (C), 138.6 (C), 128.7 (CH), 128.2 (2CH), 126.1 (2CH), 100.3 (CH), 80.1 (CH), 77.4 (CH), 64.9 (CH₂), 47.0 (CH₂), 36.6 (CH), 35.1 (CH), 26.0 (3CH₃), 18.4 (C), 11.8 (CH₃), 9.7 (CH₃), -5.3 (2CH₃); IR (Film) ν = 2955, 2929, 2882, 2856, 1728, 1471, 1462, 1402, 1256, 1101, 1073, 1029, 837 cm⁻¹; MS (GC, EI): *m/z*: 335 (M⁺ - *t*-Bu), 281, 263, 243, 229, 211, 199, 185, 171, 157, 145, 131, 115, 101, 89, 75.

(2S,4R(1S),5S,6S(2S,5S,6R,7S,8Z))-4-(2-(tert-Butyldimethylsilyloxy)-1-methyl ethyl-1-yl)-6-[5,7-dimethyl-2-hydroxy-6-(methoxymethyl)oxy]-9-tributylstannyl-dec-8-en-3-yn-1-yl]-5-methyl-2-phenyl-1,3-dioxinan (56)

(2S,4R(1S),5S,6S(2R,5S,6R,7S,8Z))-4-(2-(tert-Butyldimethylsilyloxy)-1-methyl ethyl-1-yl)-6-[5,7-dimethyl-2-hydroxy-6-(methoxymethyl)oxy]-9-tributylstannyl-dec-8-en-3-yn-1-yl]-5-methyl-2-phenyl-1,3-dioxinan (57): *Coupling Reaction between B fragment (32) and C aldehyde (55):* To a solution of alkyne **32** (305 mg, 0.62 mmol, 2.5 equiv) in THF (3 mL) at -78 °C was added a solution of *t*-BuLi (1.5 M in pentane, 295 μL, 0.44 mmol, 1.98 equiv). The resulting mixture was stirred for 30 min at -78 °C then a solution of aldehyde **55** (100 mg, 0.25 mmol, 1.0 equiv) in THF (1 mL) was slowly added. After stirring for 3 h at 0 °C, a saturated aqueous NH₄Cl solution was added and the reaction mixture was extracted with Et₂O. The organic layers were washed with water and brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/Et₂O 98:2 to 80:20) to furnish 30 mg (14 % yield) of the title compound **56**, its diastereomer **57** (74 mg, 34 % yield) and the starting aldehyde **55** (14 mg, 14 % yield). (**56**): [α]_D²⁰ = -1.33 (*c* = 0.6, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃): δ = 7.49-7.43 (m, 2H), 7.39-7.30 (m, 3H), 5.97 (dq, *J* = 9.6, 1.4 Hz, *J*_{H₁₁,H₁₉Sn} = *J*_{H₁₁,H₁₉Sn} = 132.8 Hz, 1H), 5.59 (s, 1H), 4.80 (d, *J* = 6.9 Hz, 1H), 4.70 (d, *J* = 6.9 Hz, 1H), 4.70-4.67 (ddd, *J* = 7.8, 7.3, 2.7 Hz, 1H), 4.03 (ddd, *J* = 10.1, 10.1, 2.3 Hz, 1H), 3.73 (dd, *J* = 10.1, 1.4 Hz, 1H), 3.69 (dd, *J* = 9.6, 9.2 Hz, 1H), 3.50 (dd, *J* = 9.6, 6.0 Hz, 1H), 3.43 (s, 3H, CH₃), 3.23 (dd, *J* = 5.9, 5.0 Hz, 1H), 2.98 (d, *J* = 7.3 Hz, 1H, OH), 2.77 (qdd, *J* = 6.9, 5.0, 1.8 Hz, 1H), 2.24 (dq, *J* = 9.6, 6.9, 5.9 Hz, 1H), 2.12 (ddd, *J* = 14.6, 7.8, 2.3 Hz, 1H), 2.10 (ddm, *J* = 9.2, 6.0, 1.4 Hz, 1H), 1.95 (ddd, *J* = 14.6, 10.1, 2.7 Hz, 1H), 1.89 (d, *J* = 1.4 Hz, *J*_{H₁₁,H₁₉Sn} = *J*_{H₁₁,H₁₉Sn} = 44.8 Hz, 3H, CH₃), 1.76 (ddq, *J* = 10.1, 10.1, 6.4 Hz, 1H), 1.54-1.43 (m, 6H, 3CH₂), 1.33-1.29 (sext, *J* = 7.8 Hz, 6H, 3CH₂), 1.22 (d, *J* = 6.9 Hz, 3H, CH₃), 1.02 (d, *J* = 6.9 Hz, 3H, CH₃), 1.0-0.81 (m, 18H, 4CH₃+3CH₂), 0.89 (s, 3CH₃), 0.81 (d, *J* = 6.4 Hz, 3H, CH₃), 0.04 (s, 6H, 2CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 143.9 (CH), *J*_{13C,117Sn} = *J*_{13C,119Sn} = 26.8 Hz), 138.6 (C, *J*_{13C,117Sn} = *J*_{13C,119Sn} = 385.3 Hz), 137.7 (C), 128.3 (CH), 127.9 (2CH), 125.7 (2CH), 99.8 (CH), 98.1 (CH₂), 87.0 (CH), 85.5 (C), 82.5 (C), 80.1 (CH), 79.6 (CH), 64.7 (CH₂), 60.0 (CH), 59.6 (CH₃), 42.2 (CH), *J*_{13C,117Sn} = *J*_{13C,119Sn} = 30.6 Hz), 42.1 (CH₂), 36.4 (CH), 34.7 (CH), 30.0 (CH), 29.1 (3CH₂, *J*_{13C,117Sn} = *J*_{13C,119Sn} = 19.1 Hz), 27.3 (3CH₂, *J*_{13C,117Sn} = *J*_{13C,119Sn} = 57.5 Hz), 26.7 (CH₃, *J*_{13C,117Sn} = *J*_{13C,119Sn} = 44.1 Hz), 25.8 (3CH₃), 18.6 (CH₃), 18.1 (C), 16.6 (CH₃), 13.6 (3CH₃), 11.5 (CH₃), 9.8 (3CH₂, *J*_{13C,117Sn} = 313.4 Hz, *J*_{13C,119Sn} = 327.8 Hz), 9.5 (CH₃), -5.5 (2CH₃); IR (Film) ν = 2956, 2928, 2855, 2360, 2341, 1594, 1455, 1404, 1375, 1255, 1149, 1095, 1050, 836, 775, 695, 663, 661 cm⁻¹; elemental analysis calcd (%) for C₄₆H₈₂O₆SiSn: C 62.93, H 9.41; found: C 63.10, H 9.55. (**57**): ¹H NMR (400.0 MHz, CDCl₃): δ = 7.47-7.24 (m, 2H), 7.39-7.30 (m, 3H), 6.00 (dq, *J* = 9.6, 1.4 Hz, *J*_{H₁₁,H₁₉Sn} = *J*_{H₁₁,H₁₉Sn} = 137.4 Hz, 1H), 5.53 (s, 1H), 4.81 (d, *J* = 6.9 Hz, 1H), 4.77-4.70 (m, 1H), 4.71 (d, *J* = 6.9 Hz, 1H), 3.78-3.65 (m, 3H), 3.49 (dd, *J* = 9.6, 6.0 Hz, 1H), 3.43 (s, 3H, CH₃), 3.26 (t, *J* = 5.5 Hz, 1H), 2.89 (d, *J* = 3.2 Hz, 1H, OH), 2.74 (qdd, *J* = 6.9, 5.5, 2.7 Hz, 1H), 2.23 (dq, *J* = 9.6, 6.9, 5.5 Hz, 1H), 2.12 (ddd, *J* = 13.7, 6.0, 1.8 Hz, 1H), 2.06-1.96 (m, 2H, H-2), 1.90 (d, *J* = 1.4 Hz, 1H), *J*_{H₁₁,H₁₉Sn} = 42.6 Hz, 3H, CH₃), 1.80-1.71 (m, 1H), 1.53-1.45 (m, 6H, 3CH₂), 1.32 (sext, *J* = 7.3 Hz, 6H, 3CH₂), 1.21 (d, *J* = 6.9 Hz, 3H, CH₃), 1.00 (d, *J* = 6.9 Hz, 3H, CH₃), 1.00-0.86 (m, 18H, 4CH₃+3CH₂), 0.90 (s, 9H, 3CH₃), 0.82 (d, *J* = 6.9 Hz, 3H), 0.04 (s, 6H, 2CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 144.2 (CH), 138.7 (C), 137.8 (C), 128.7 (CH), 128.2 (2CH), 126.0 (2CH), 100.5.1 (CH), 98.3 (CH₂), 87.4 (CH), 85.7 (C), 82.5 (C), 81.7 (CH), 80.4 (CH), 65.0 (CH₂), 61.8 (CH), 56.3 (CH₃), 42.3 (CH), 41.2 (CH₂), 36.7 (CH),

35.2 (CH), 30.3 (CH), 29.3 (3CH₂, $J_{13C,117Sn} = J_{13C,119Sn} = 20.1$ Hz), 27.6 (3CH₂, $J_{13C,117Sn} = J_{13C,119Sn} = 57.5$ Hz), 27.3 (CH₃, $J_{13C,117Sn} = J_{13C,119Sn} = 46.0$ Hz), 26.1 (3CH₃), 18.8 (CH₃), 18.5 (C), 16.5 (CH₃), 13.9 (3CH₃), 11.9 (CH₃), 10.1 (3CH₂, $J_{13C,117Sn} = 312.5$ Hz, $J_{13C,119Sn} = 329.8$ Hz), 9.8 (CH₃), -5.5 (2CH₃).

Reduction of ynone 58 (vide infra): To a solution of compound **58** (3.6 g, 4.1 mmol, 1.0 equiv) in THF (20 mL) at -30 °C were added a solution of (S)-CBS-oxazaborolidine in toluene (1 M, 8.22 mL, 8.22 mmol, 2.0 equiv) and BH₃.Me₂S (2M in THF, 10.3 mL, 20.5 mmol, 5.0 equiv). The resulting mixture was stirred for 2 h at -30 °C then quenched with EtOH and extracted with Et₂O. The organic layers were washed with water and brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/AcOEt 95:5 to 70:30) to give the title compound **56** (6.88 g, 95 % yield).

Compound **57** was also obtained by énantioselective reduction of ynone **58**: To a solution of ynone **58** (75 mg, 0.085 mmol, 1.0 equiv) in THF (0.5 mL) at -30 °C were added a solution of (R)-CBS-oxazaborolidine in toluene (1M, 171 µL, 0.171 mmol, 2.0 equiv) and BH₃.Me₂S (2M in THF, 214 µL, 0.43 mmol, 5.0 equiv). The resulting mixture was stirred for 2 h at -30 °C then quenched with EtOH and extracted with Et₂O. The organic layers were washed with water and brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/AcOEt 95:5 to 70:30) to give 63 mg (90 % yield) of **57**.

(R)-Mandelate ester of 56: To a solution of compound **56** (40 mg, 0.045 mmol, 1.0 equiv) in CH₂Cl₂ (1 mL) at 20 °C were successively added (R)-(-)-methoxyphenylacetic acid (15 mg, 0.091 mmol, 2.0 equiv), DCC (9.5 mg, 0.091 mmol, 2.0 equiv) and DMAP (2 mg, 0.022 mmol, 0.4 equiv). The resulting mixture was stirred for 12 h at 20 °C then quenched with a saturated aqueous NaHCO₃ solution and extracted with Et₂O. The organic layers were washed with water and brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/AcOEt 95:5 to 70:30) to give 29 mg (63 % yield) of the title compound. **((R)-Mandelate ester of 56):** $[\alpha]_D^{20} = -29.5$ ($c = 0.52$, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃): δ = 7.50-7.47 (m, 4H), 7.36-7.30 (m, 6H), 6.01 (dq, $J = 9.6, 1.4$ Hz, $J_{1H,117Sn} = J_{1H,119Sn} = 131.2$ Hz, 1H), 5.83 (dt, $J = 11.5, 1.8$ Hz, 1H), 4.79 (d, $J = 6.9$ Hz, 1H), 4.78 (s, 1H), 4.74 (s, 1H), 4.68 (d, $J = 6.9$ Hz, 1H), 3.65 (t, $J = 9.2$ Hz, 1H), 3.46 (dd, $J = 9.2, 5.5$ Hz, 1H), 3.45 (s, 3H, CH₃), 3.44 (s, 3H, CH₃), 3.25 (t, $J = 5.5$ Hz, 1H), 3.24 (d, $J = 10.9$ Hz, 1H), 2.75 (qdd, $J = 6.9, 5.5, 1.8$ Hz, 1H), 2.48 (td, $J = 9.6, 1.8$ Hz, 1H), 2.18 (dq, $J = 9.6, 6.9, 5.5$ Hz, 1H), 2.11 (ddd, $J = 11.9, 11.5, 1.8$ Hz, 1H), 1.90 (d, $J = 1.4$ Hz, $J_{1H,117Sn} = J_{1H,119Sn} = 42.1$ Hz, 3H, CH₃), 1.87 (dq, $J = 9.2, 6.9, 5.5$ Hz, 1H), 1.73 (ddd, $J = 11.9, 9.6, 1.8$ Hz, 1H), 1.53-1.44 (m, 6H, 3CH₂), 1.45-1.42 (m, 1H), 1.32 (sext, $J = 7.8$ Hz, 6H, 3CH₂), 1.16 (d, $J = 6.9$ Hz, 3H, CH₃), 0.98 (d, $J = 6.9$ Hz, 3H, CH₃), 0.94 (s, 9H, 3CH₃), 0.95-0.90 (m, 6H, 3CH₂), 0.90 (m, 9H, 3CH₃), 0.81 (d, $J = 6.9$ Hz, 3H, CH₃), 0.52 (d, $J = 6.4$ Hz, 3H, CH₃), 0.07 (s, 3H, CH₃), 0.06 (s, 3H, CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 169.4 (C), 144.2 (CH), 138.8 (C), 137.7 (C), $J_{13C,117Sn} = J_{13C,119Sn} = 384.0$ Hz), 137.0 (C), 129.0 (CH), 128.9 (2CH), 128.3 (CH), 128.0 (2CH), 127.6 (2CH), 125.9 (2CH), 99.0 (CH), 98.3 (CH₂), 88.3 (C), 85.2 (CH), 82.3 (CH), (C), 79.6 (CH), 76.7 (CH), 65.1 (CH₃), 60.1 (CH), 57.3 (CH₃), 56.3 (CH₃), 42.0 (CH), 39.5 (CH₂), 36.7 (CH), 34.8 (CH), 30.3 (CH₂), 29.4 (3CH₂, $J_{13C,117Sn} = J_{13C,119Sn} = 19.2$ Hz), 27.5 (3CH₂, $J_{13C,117Sn} = J_{13C,119Sn} = 57.5$ Hz), 27.4 (CH₃, $J_{13C,117Sn} = J_{13C,119Sn} = 42.6$ Hz), 26.1 (3CH₃), 18.5 (C), 18.2 (CH₃), 16.3 (CH₃), 13.9 (3CH₃), 11.5 (CH₃), 10.1 (3CH₂), 9.8 (CH₃), -5.3 (CH₃), -5.2 (CH₃); IR (Film) $\nu = 2956, 2871, 2855, 1759, 1454, 1462, 1166, 1152, 1114, 1102, 1031$ cm⁻¹; elemental analysis calcd (%) for C₅₅H₉₀O₈SiSn: C 64.38, H 8.84; found: C 64.15, H 9.02.

(S)-Mandelate ester of 56: To a solution of compound **56** (40 mg, 0.045 mmol, 1.0 equiv) in CH₂Cl₂ (1 mL) at 20 °C were successively added (S)-(+)-methoxyphenylacetic acid (15 mg, 0.091 mmol, 2.0 equiv), DCC (9.5 mg, 0.091 mmol, 2.0 equiv) and DMAP (2 mg, 0.022 mmol, 0.4 equiv). The resulting mixture was stirred for 12 h at 20 °C then quenched with a saturated aqueous NaHCO₃ solution and extracted with Et₂O. The organic layers were washed with water and brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/AcOEt 95:5 to 70:30) to give 25 mg (62 % yield) of the title compound. **((S)-Mandelate ester of 56):** $[\alpha]_D^{20} = -1.40$ ($c = 0.60$, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃): δ = 7.51-7.47 (m, 4H), 7.37-7.27 (m, 6H), 6.00 (dq, $J = 9.6, 1.8$ Hz, $J_{1H,117Sn} = J_{1H,119Sn} = 134.6$ Hz, 1H), 5.82 (ddd, $J = 11.0, 2.3, 1.8$ Hz, 1H), 5.00 (s, 1H), 4.84 (s, 1H), 4.72 (d, $J = 6.9$ Hz, 1H), 4.60 (d, $J = 6.9$ Hz, 1H), 3.67 (dd, $J = 9.6, 9.2$ Hz, 1H), 3.49 (dd, $J = 9.6, 6.0$ Hz, 1H), 3.49-3.46 (m, 1H), 3.46 (s, 3H, CH₃), 3.40 (s, 3H, CH₃), 3.19 (t, $J = 5.5$ Hz, 1H), 3.10 (ddd, $J = 11.9, 10.5, 1.8$ Hz, 1H), 2.66 (qdd, $J = 7.3, 5.5, 1.8$ Hz, 1H), 2.31 (ddd, $J = 11.9, 11.5, 2.3$ Hz, 1H), 2.13 (dq, $J = 9.6, 6.9, 5.5$ Hz, 1H), 1.96 (mq, $J = 9.2, 6.9, 6.0$ Hz, 1H), 1.88 (d, $J = 1.4$ Hz, $J_{1H,117Sn} = J_{1H,119Sn} = 42.1$ Hz, 3H, CH₃), 1.84 (ddd, $J = 11.5, 11.0, 1.8$ Hz, 1H), 1.61-1.60 (m, 1H), 1.56-1.43 (m, 6H, 3CH₂), 1.31 (sext, $J = 7.8$ Hz, 6H, 3CH₂), 1.10 (d, $J = 7.3$ Hz, 3H, CH₃), 0.93 (d, $J = 6.9$ Hz, 3H, CH₃), 0.94 (s, 9H, 3CH₃), 0.93-0.89 (m, 6H, 3CH₂), 0.89 (t, 9H, $J = 7.3$ Hz, 3CH₃), 0.84 (d, $J = 6.9$ Hz, 3H, CH₃), 0.72 (d, $J = 6.9$ Hz, 3H, CH₃), 0.05 (s, 6H, 2CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 169.8 (C), 144.2 (CH), $J_{13C,117Sn} = J_{13C,119Sn} = 28.8$ Hz), 138.8 (C), 137.7 (C), 136.4 (C), 128.8 (CH), 128.7 (2CH), 128.3 (CH), 128.0 (2CH), 126.9 (2CH), 125.9 (2CH), 99.4 (CH), 98.2 (CH₂), 88.4 (C), 85.2 (CH), 83.1 (CH), 83.0 (C), 80.0 (CH), 79.0 (CH), 65.1 (CH₂), 61.3 (CH), 57.5

(CH₃), 56.2 (CH₃), 42.0 (CH), 39.1 (CH₂), 36.7 (CH), 35.1 (CH), 30.3 (CH), 29.3 (3CH₂, $J_{13C,117Sn} = J_{13C,119Sn} = 18.2$ Hz), 27.6 (3CH₂, $J_{13C,117Sn} = J_{13C,119Sn} = 57.5$ Hz), 27.6 (CH₃), 26.1 (3CH₃), 18.5 (C), 18.3 (CH₃), 16.2 (CH₃), 13.9 (3CH₃), 11.7 (CH₃), 10.0 (3CH₂, $J_{13C,117Sn} = 325.9$, $J_{13C,119Sn} = 312.5$ Hz), 9.8 (CH₃), -5.3 (CH₃), -5.2 (CH₃); IR (Film) $\nu = 2955, 2855, 1755, 1456, 1464, 1155, 1098, 1074, 1031$ cm⁻¹; elemental analysis calcd (%) for C₅₅H₉₀O₈SiSn: C 64.38, H 8.84; found: C 64.70, H 9.26.

(R)-Mandelate ester of 57: To a solution of compound **57** (100 mg, 0.11 mmol, 1.0 equiv) in CH₂Cl₂ (2 mL) at 20 °C were successively added (R)-(-)-methoxyphenylacetic acid (38 mg, 0.23 mmol, 2.0 equiv), DCC (47 mg, 0.23 mmol, 2.0 equiv) and DMAP (3 mg, 0.022 mmol, 0.2 equiv). The resulting mixture was stirred for 12 h at 20 °C then quenched with a saturated aqueous NaHCO₃ solution and extracted with Et₂O. The organic layers were washed with water and brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/AcOEt 95:5 to 70:30) to give 89 mg (79 % yield) of the title compound. **((R)-Mandelate ester of 57):** $[\alpha]_D^{20} = +1.76$ ($c = 1.44$, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃): δ = 7.50-7.47 (m, 4H), 7.39-7.30 (m, 6H), 6.00 (dq, $J = 9.6, 1.4$ Hz, $J_{1H,117Sn} = J_{1H,119Sn} = 132.8$ Hz, 1H), 5.71 (ddd, $J = 9.6, 5.0, 1.4$ Hz, 1H), 5.48 (s, 1H), 4.72 (s, 1H), 4.70 (d, $J = 6.9$ Hz, 1H), 4.57 (d, $J = 6.9$ Hz, 1H), 3.74-3.65 (m, 2H), 3.50 (dd, $J = 9.6, 6.0$ Hz, 1H), 3.45-3.39 (m, 1H, H-5), 3.35 (s, 3H, CH₃), 3.29 (s, 3H, CH₃), 3.19 (t, $J = 5.5$ Hz, 1H), 2.64 (qdd, $J = 6.9, 5.0, 1.4$ Hz, 1H), 2.22-2.08 (m, 3H), 2.05-1.97 (m, 1H), 1.89 (d, $J = 1.4$ Hz, $J_{1H,117Sn} = J_{1H,119Sn} = 41.9$ Hz, 3H, CH₃), 1.73-1.67 (m, 1H), 1.52-1.46 (m, 6H, 3CH₂), 1.32 (sext, $J = 7.3$ Hz, 6H, 3CH₂), 1.10 (d, $J = 7.3$ Hz, 3H, CH₃), 0.97-0.87 (m, 15H, 3CH₂ + 3CH₃), 0.94 (d, $J =$ not calculated, 3H, CH₃), 0.90 (s, 9H, 3CH₃), 0.86 (d, $J =$ not calculated, 3H, CH₃), 0.81 (d, $J = 6.9$ Hz, 3H, CH₃), 0.05 (s, 6H, 2CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 169.3 (C), 144.2 (CH, $J_{13C,117Sn} = J_{13C,119Sn} = 30.6$ Hz), 138.8 (C), 137.5 (C), $J_{13C,117Sn} = J_{13C,119Sn} = 371.8$ Hz), 135.9 (C), 128.6 (CH), 128.5 (2CH), 128.4 (CH), 128.0 (2CH), 127.4 (2CH), 125.9 (2CH), 99.8 (CH), 98.0 (CH₂), 89.3 (C), 84.9 (CH), 82.5 (CH), 80.2 (C), 79.2 (CH), 78.3 (CH), 64.9 (CH₂), 63.4 (CH), 57.3 (CH₃), 56.1 (CH₃), 42.3 (CH, $J_{13C,117Sn} = J_{13C,119Sn} = 32.6$ Hz), 38.4 (CH₂), 36.6 (CH), 34.8 (CH), 30.3 (CH), 29.2 (3CH₂, $J_{13C,117Sn} = J_{13C,119Sn} = 19.2$ Hz), 27.4 (3CH₂, $J_{13C,117Sn} = J_{13C,119Sn} = 57.4$ Hz), 27.3 (CH₃, $J_{13C,117Sn} = J_{13C,119Sn} = 46.0$ Hz), 25.9 (3CH₃), 18.4 (C), 18.3 (CH₃), 15.8 (CH₃), 13.7 (3CH₃), 11.5 (CH₃), 9.9 (3CH₂, $J_{13C,117Sn} = 313.4$ Hz, $J_{13C,119Sn} = 327.8$ Hz), 9.7 (CH₃), -5.5 (CH₃), -5.4 (CH₃); IR (Film) $\nu = 2955, 2871, 2855, 1758, 1462, 1455, 1250, 1149, 1102, 1031, 1002, 837, 698$ cm⁻¹; elemental analysis calcd (%) for C₅₅H₉₀O₈SiSn: C 64.38, H 8.84; found: C 64.22, H 9.12.

(S)-Mandelate ester of 57: To a solution of compound **57** (100 mg, 0.11 mmol, 1.0 equiv) in CH₂Cl₂ (2 mL) at 20 °C were successively added (S)-(+)-methoxyphenylacetic acid (38 mg, 0.23 mmol, 2.0 equiv), DCC (47 mg, 0.23 mmol, 2.0 equiv) and DMAP (3 mg, 0.022 mmol, 0.2 equiv). The resulting mixture was stirred for 12 h at 20 °C then quenched with a saturated aqueous NaHCO₃ solution and extracted with Et₂O. The organic layers were washed with water and brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/AcOEt 95:5 to 70:30) to give 81 mg (72 % yield) of the title compound. **((S)-Mandelate ester of 57):** $[\alpha]_D^{20} = +22.0$ ($c = 1.38$, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃): δ = 7.46-7.40 (m, 4H), 7.36-7.29 (m, 6H), 6.00 (dq, $J = 9.6, 1.8$ Hz, $J_{1H,117Sn} = J_{1H,119Sn} = 133.2$ Hz, 1H), 5.71 (ddd, $J = 10.0, 4.6, 1.4$ Hz, 1H), 5.43 (s, 1H), 4.76 (d, $J = 6.9$ Hz, 1H), 4.73 (s, 1H), 4.66 (d, $J = 6.9$ Hz, 1H), 3.72-3.61 (m, 3H), 3.49 (dd, $J = 9.6, 5.0$ Hz, 1H), 3.40 (s, 3H, CH₃), 3.38 (s, 3H, CH₃), 3.24 (dd, $J = 5.5, 5.0$ Hz, 1H), 2.73 (qdd, $J = 6.9, 5.0, 1.4$ Hz, 1H), 2.19 (qdd, $J = 9.6, 6.9, 5.5$ Hz, 1H), 2.06 (td, $J = 10.0, 2.3$ Hz, 1H), 2.00-1.93 (m, 1H), 1.90 (d, $J = 1.8$ Hz, $J_{1H,117Sn} = J_{1H,119Sn} = 42.6$ Hz, 3H, CH₃), 1.81 (ddd, $J = 13.7, 10.0, 4.6$ Hz, 1H), 1.65-1.64 (m, 1H), 1.53-1.46 (m, 6H, 3CH₂), 1.33 (sext, $J = 7.3$ Hz, 6H, 3CH₂), 1.19 (d, $J = 6.9$ Hz, 3H, CH₃), 1.00 (d, $J = 6.9$ Hz, 3H, CH₃), 0.97-0.86 (m, 15H, 3CH₂ + 3CH₃), 0.90 (s, 3CH₃), 0.84 (d, $J = 6.9$ Hz, 3H, CH₃), 0.74 (d, $J = 6.4$ Hz, 3H, CH₃), 0.04 (s, 6H, 2CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 169.2 (C), 144.1 (CH, $J_{13C,117Sn} = J_{13C,119Sn} = 27.8$ Hz), 138.7 (C), 137.7 (C), 135.9 (C), 128.6 (CH), 128.5 (2CH), 128.3 (CH), 127.9 (2CH), 127.2 (2CH), 125.9 (2CH), 99.7 (CH), 98.0 (CH₂), 89.2 (C), 85.1 (CH), 82.3 (CH), 80.1 (C), 78.9 (CH), 78.5 (CH), 65.8 (CH₂), 65.1 (CH), 57.3 (CH₃), 56.1 (CH₃), 42.3 (CH, $J_{13C,117Sn} = J_{13C,119Sn} = 31.6$ Hz), 38.2 (CH₂), 36.5 (CH), 34.6 (CH), 30.3 (CH), 29.2 (3CH₂, $J_{13C,117Sn} = J_{13C,119Sn} = 19.2$ Hz), 27.7 (3CH₂, $J_{13C,117Sn} = J_{13C,119Sn} = 57.4$ Hz), 27.4 (CH₃, $J_{13C,117Sn} = J_{13C,119Sn} = 40.2$ Hz), 25.9 (3CH₃), 18.6 (CH₃), 18.2 (C), 16.1 (CH₃), 13.7 (3CH₃), 11.6 (CH₃, CH₃-4), 9.9 (3CH₂, $J_{13C,117Sn} = 314.4$ Hz, $J_{13C,119Sn} = 331.6$ Hz), 9.6 (CH₃), -5.5 (2CH₃); IR (Film) $\nu = 2955, 2928, 2871, 2855, 1757, 1454, 1250, 1165, 1148, 1102, 1073, 1031, 1003, 837, 698$ cm⁻¹; elemental analysis calcd (%) for C₅₅H₉₀O₈SiSn: C 64.38, H 8.84; found: C 64.61, H 8.99.

(2S,4R(1S),5S,6S(5S,6R,7S,8Z))-4-(2-(*tert*-Butyldimethylsilyloxy)-1-methyl ethyl-1-yl)-6-{5,7-dimethyl-6-((methoxymethyl)oxy)-9-tributylstannyl-2-one-dec-8-en-3-yn-1-yl}-5-methyl-2-phenyl-1,3-dioxinan (58): **Coupling reaction using *t*-BuLi** - To a solution of alkyne **32** (215 mg, 0.44 mmol, 2.0 equiv) in THF (3 mL) at -78 °C was added a solution of *t*-BuLi (1.5 M in pentane, 295 µL, 0.44 mmol, 1.98 equiv). The resulting mixture was stirred for 30 min at -78 °C then a solution of amide **54** (100 mg, 0.22 mmol, 1.0 equiv) in THF (1 mL) was slowly added. After stirring for 3 h at 0 °C, a saturated aqueous NH₄Cl solution was added and the reaction mixture was extracted with Et₂O. The organic layers were washed with water and brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The residue was purified by

chromatography on silica gel (cyclohexane/Et₂O 98:2 to 80:20) to furnish 156 mg (81 % yield) of the title compound 58.

Coupling reaction using *n*-BuLi - Preparation of *n*-BuLi in diethyl ether - In a 500 mL four-necked flask equipped with a thermometer, a mechanical stirrer and a dropping funnel under argon containing 100 mL of dry diethyl ether were introduced small pieces of lithium (wire containing 0.5-1 % Na, 4.3 g, 619 mmol, 2.48 equiv). With the stirrer started, 30 drops of a *n*-butylbromide (27 mL, 250 mmol, 1.0 equiv) solution in diethyl ether (50 mL) were added from the dropping funnel. After a few min the solution became slightly cloudy and bright spots appeared on the lithium. The reaction mixture was then cooled to -10 °C by immersing in a -30 °C nitrogen-acetone bath. The remainder of the *n*-butylbromide solution was added over 20 min while keeping the internal temperature below -10 °C. After the addition was complete, the reaction mixture was allowed to warm up gradually to 0 °C then 10 °C with stirring during 1.5 h. The pale blue solution was then filtered while transferred to a flask via cannula, titrated with standard method (1.23 M, 74 % yield) and kept under argon at 4 °C.

To a solution of alkyne **32** (1.7 g, 3.5 mmol, 2.0 equiv) in THF (25 mL) at -40 °C was added a solution of *n*-BuLi in Et₂O (1.23 M, 2.8 mL, 3.44 mmol, 1.98 equiv). The resulting mixture was stirred for 50 min at -40 °C then a solution of amide **54** (789 mg, 1.75 mmol, 1.0 equiv) in THF (12 mL) was slowly added. After stirring for 1 h at 0 °C, a saturated aqueous NH₄Cl solution was added and the reaction mixture was extracted with Et₂O. The organic layers were washed with water and brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/Et₂O 98:2 to 80:20) to furnish the title compound **58** (1.22 g, 81 % yield). (**58**): [α]_D²⁰ = +13.4 (c = 0.94, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃): δ = 7.43-7.40 (m, 2H), 7.38-7.34 (m, 3H), 5.92 (dq, *J* = 6.9, 1.4 Hz, 1H), 5.54 (s, 1H), 4.71 (d, *J* = 6.9 Hz, 1H), 4.66 (d, *J* = 6.9 Hz, 1H), 4.20 (ddt, *J* = 9.6, 6.4, 5.9 Hz, 1H), 3.73 (dd, *J* = 9.6, 1.4 Hz, 1H), 3.69 (dd, *J* = 9.6, 9.2 Hz, 1H), 3.51 (dd, *J* = 9.6, 5.9 Hz, 1H), 3.39 (s, 3H, CH₃), 3.27 (dd, *J* = 6.4, 4.1 Hz, 1H), 2.87 (qd, *J* = 6.9, 4.1 Hz, 1H), 2.85 (d, *J* = 5.9 Hz, 2H), 2.22 (dq, *J* = 9.6, 6.9, 6.4 Hz, 1H), 1.98 (ddd, *J* = 9.2, 5.9, 1.4 Hz, 1H), 1.88 (d, *J* = 1.4 Hz, *J*_{H₁₁₇Sn} = *J*_{H₁₁₉Sn} = 41.2 Hz, 3H, CH₃), 1.72 (ddq, *J* = 9.6, 9.6, 6.9 Hz, 1H), 1.54-1.43 (m, 6H, 3CH₂), 1.32 (sext, *J* = 7.3 Hz, 6H, 3CH₂), 1.24 (d, *J* = 6.9 Hz, 3H, CH₃), 1.00 (d, *J* = 6.9 Hz, 3H, CH₃), 0.95-0.87 (m, 27H, 7CH₃ + 3CH₂), 0.80 (d, *J* = 6.9 Hz, 3H, CH₃), 0.04 (s, 6H, 2CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 185.3 (C), 143.4 (CH), 138.8 (C), 138.7 (C), 128.4 (CH), 128.0 (2CH), 126.0 (2CH), 99.9 (CH), 98.3 (CH₂), 96.5 (C), 85.2 (CH), 83.0 (C), 80.3 (CH), 78.2 (CH), 65.0 (CH₂), 56.4 (CH₃), 49.5 (CH₂), 42.8 (CH, *J*_{13C-117Sn} = *J*_{13C-119Sn} = 30.6 Hz), 36.7 (CH), 35.0 (CH), 30.8 (CH), 29.4 (3CH₂), 27.5 (CH₃ + 3CH₂, *J*_{13C-117Sn} = *J*_{13C-119Sn} = 58.4 Hz), 26.0 (3CH₂), 18.4 (C), 17.8 (CH₃), 17.1 (CH₃), 13.8 (3CH₃), 11.9 (CH₃), 10.1 (3CH₂, *J*_{13C-117Sn} = 313.4 Hz, *J*_{13C-119Sn} = 328.8 Hz), 9.7 (CH₃), -5.2 (2CH₃); IR (Film) ν = 2956, 2855, 2212, 1678, 1465, 1403, 1376, 1345, 1255, 1215, 1147, 1092, 1032, 837, 758, 699 cm⁻¹; elemental analysis calcd (%) for C₄₆H₈₀O₆SiSn: C 63.08, H 9.21; found: C 63.18, H 9.32.

(2*S*,4*R*(1*S*),5*S*,6*S*(2*S*,5*S*,6*R*,7*S*,8*Z*))-4-(2-*tert*-Butyldimethylsilyloxy)-1-methyl ethyl-1-yl)-6-[5,7-dimethyl-2,6-bis((methoxymethyl)oxy)-9-tributylstannyl-dec-8-en-3-yn-1-yl]-5-methyl-2-phenyl-1,3-dioxinan (59): To a solution of compound **56** (6.88 g, 7.84 mmol, 1.0 equiv), dimethylaminopyridine (192 mg, 1.57 mmol, 0.2 equiv) and TBAI (290 mg, 0.784 mmol, 0.1 equiv) in dried CH₂Cl₂ (35 mL) at 0 °C were added diisopropylethylamine (34.1 mL, 196 mmol, 20 equiv) and MOMCl (5.95 mL, 78.4 mmol, 10 equiv). After stirring for 12 h at 20 °C, the reaction was quenched with a saturated aqueous NaHCO₃ solution and extracted with Et₂O. The organic layers were washed with brine, dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/AcOEt 95:5 to 80:20) to give the title compound **59** (6.2 g, 86 % yield) as a yellow oil. (**59**): [α]_D²⁰ = -17.2 (c = 1.52, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃): δ = 7.49-7.47 (m, 2H), 7.37-7.30 (m, 3H), 6.00 (d, *J* = 9.6 Hz, 1H, *J*_{H₁₁₇Sn} = *J*_{H₁₁₉Sn} = 133.7 Hz), 5.51 (s, 1H), 5.04 (d, *J* = 6.4 Hz, 1H), 4.82-4.78 (m, 1H), 4.78 (d, *J* = 6.9 Hz, 1H), 4.70 (d, *J* = 6.9 Hz, 1H), 4.70 (d, *J* = 6.4 Hz, 1H), 3.75-3.67 (m, 3H), 3.51 (dd, *J* = 9.6, 5.9 Hz, 1H), 3.43 (s, 3H, CH₃), 3.36 (s, 3H, CH₃), 3.24 (t, *J* = 5.5 Hz, 1H), 2.72 (qd, *J* = 6.9, 5.5 Hz, 1H), 2.28-2.18 (dq, *J* = 9.6, 6.9, 5.5 Hz, 1H), 2.28-2.18 (m, 1H), 2.04-1.98 (m, 1H), 1.89 (s, *J*_{H₁₁₇Sn} = *J*_{H₁₁₉Sn} = 41.7 Hz, 3H, CH₃), 1.87-1.83 (m, 1H), 1.66-1.63 (m, 1H), 1.52-1.45 (m, 6H, 3CH₂), 1.33 (sext, *J* = 7.3 Hz, 6H, 3CH₂), 1.18 (d, *J* = 7.3 Hz, 3H, CH₃), 0.98 (d, *J* = 6.9 Hz, 3H, CH₃), 0.98-0.85 (m, 18H, 4CH₃ + 3CH₂), 0.89 (s, 9H, 3CH₃), 0.81 (d, *J* = 6.4 Hz, 3H, CH₃), 0.05 (s, 6H, 2CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 144.2 (CH, *J*_{13C-117Sn} = *J*_{13C-119Sn} = 29.7 Hz), 139.1 (C), 137.5 (C), 128.3 (CH), 128.0 (2CH), 125.8 (2CH), 99.6 (CH), 98.1 (CH₂), 93.6 (CH₂), 87.7 (C), 85.3 (C), 80.1 (C), 80.0 (CH), 77.6 (CH), 65.0 (CH₂), 61.0 (CH), 56.1 (CH₃), 55.5 (CH₃), 42.0 (CH), 39.9 (CH₂), 36.6 (CH), 35.2 (CH), 30.2 (CH), 29.2 (3CH₂, *J*_{13C-117Sn} = *J*_{13C-119Sn} = 20.1 Hz), 27.4 (CH₃, *J*_{13C-117Sn} = *J*_{13C-119Sn} = 58.4 Hz), 26.9 (3CH₂, *J*_{13C-117Sn} = *J*_{13C-119Sn} = 53.6 Hz), 25.9 (3CH₃), 18.5 (CH₃), 18.3 (C), 16.3 (CH₃), 13.7 (3CH₃), 11.6 (CH₃), 9.9 (3CH₂, *J*_{13C-117Sn} = 313.4 Hz, *J*_{13C-119Sn} = 327.8 Hz), 9.6 (CH₃), -5.4 (2CH₃); IR (Film) ν = 2956, 2928, 2380, 2341, 1456, 1402, 1375, 1350, 1250, 1158, 1098, 1015, 920, 837, 775, 690, 663 cm⁻¹; elemental analysis calcd (%) for C₄₈H₈₆O₇SiSn: C 62.53, H 9.40; found: C 62.33, H 9.59.

(2*S*,4*R*(1*R*),5*S*,6*S*(2*S*,3*S*,5*S*,6*R*,7*S*,8*Z*))-4-(2-Methoxycarbonyl-1-methyl ethyl-1-yl)-6-[5,7-dimethyl-9-iodo-2,6-bis((methoxymethyl)oxy)-deca-3,8-dien-1-yl]-5-methyl-2-

phenyl-1,3-dioxinan (60): To a solution of compound **59** (100 mg, 0.108 mmol, 1.0 equiv) in THF (1 mL) at 0 °C were added 500 μL of a HF, pyridine stock solution (prepared from commercial HF, pyridine 2 mL/ pyridine 4 mL/ THF 10 mL). After stirring for 4 h at 20 °C, the resulting mixture was quenched with a saturated aqueous NaHCO₃ solution and extracted with Et₂O. The organic layers were washed with brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/AcOEt 70:30 to 40:60) to give the (2*S*,4*R*(1*S*),5*S*,6*S*(2*S*,5*S*,6*R*,7*S*,8*Z*))-4-(2-hydroxy-1-methyl ethyl-1-yl)-6-[5,7-dimethyl-2,6-bis((methoxymethyl)oxy)-9-tributylstannyl-dec-8-en-3-yn-1-yl]-5-methyl-2-phenyl-1,3-dioxinan (84 mg, 96 % yield). [α]_D²⁰ = -35.9 (c = 1.19, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃): δ = 7.46-7.43 (m, 2H), 7.38-7.33 (m, 3H), 6.01 (dq, *J* = 9.6, 1.4 Hz, 1H, *J*_{H₁₁₇Sn} = *J*_{H₁₁₉Sn} = 132.8 Hz), 5.58 (s, 1H), 5.02 (d, *J* = 6.9 Hz, 1H), 4.79 (d, *J* = 6.4 Hz, 1H), 4.76 (d, *J* = 11.0 Hz, 1H), 4.70 (d, *J* = 6.4 Hz, 1H), 4.59 (d, *J* = 6.9 Hz, 1H), 3.83-3.73 (m, 4H), 3.44 (s, 3H, CH₃), 3.34 (s, 3H, CH₃), 3.24 (t, *J* = 5.5 Hz, 1H), 2.72 (qd, *J* = 6.9, 5.5 Hz, 1H), 2.28-2.23 (dq, *J* = 9.6, 6.9, 5.5 Hz, 1H), 2.28-2.23 (m, 1H), 2.06-2.02 (m, 1H), 1.89 (d, *J* = 1.4 Hz, *J*_{H₁₁₇Sn} = *J*_{H₁₁₉Sn} = 43.0 Hz, 3H, CH₃), 1.89-1.85 (m, 1H), 1.83 (dq, *J* = 6.9, 6.4, 3.4 Hz, 1H), 1.49-1.38 (m, 6H, 3CH₂), 1.37-1.28 (sext, *J* = 7.3 Hz, 6H, 3CH₂), 1.18 (d, *J* = 6.9 Hz, 3H, CH₃), 1.43 (d, *J* = 6.9 Hz, 3H, CH₃), 1.03 (d, *J* = 6.9 Hz, 3H, CH₃), 1.02-0.88 (m, 15H, 3CH₂ + 3CH₃), 0.85 (d, *J* = 6.9 Hz, 3H, CH₃); ¹³C NMR (100.5 MHz, CDCl₃): δ = 144.1 (CH), 138.5 (C), 137.5 (C), 128.5 (CH), 128.1 (2CH), 125.7 (2CH), 99.9 (CH), 98.0 (CH₂), 93.6 (CH₂), 87.7 (C), 85.2 (CH), 83.5 (CH or CH₂), 80.3 (C), 77.5 (CH or CH₂), 66.7 (CH or CH₂), 60.9 (CH), 56.1 (CH₃), 55.4 (CH₃), 41.9 (CH, *J*_{13C-117Sn} = *J*_{13C-119Sn} = 34.4 Hz), 39.8 (CH₂), 35.5 (CH), 35.3 (CH), 30.1 (CH), 29.2 (3CH₂, *J*_{13C-117Sn} = *J*_{13C-119Sn} = 19.2 Hz), 27.4 (3CH₂, *J*_{13C-117Sn} = *J*_{13C-119Sn} = 58.5 Hz), 27.2 (CH₃, *J*_{13C-117Sn} = *J*_{13C-119Sn} = 46.0 Hz), 18.5 (CH₃), 16.3 (CH₃), 11.5 (CH₃), 9.8 (3CH₂, *J*_{13C-117Sn} = 314.4 Hz, *J*_{13C-119Sn} = 327.8 Hz), 9.5 (CH₃); IR (Film) ν = 3380, 2956, 2927, 2872, 2852, 1590, 1454, 1436, 1376, 1351, 1154, 1098, 1029, 699 cm⁻¹; elemental analysis calcd (%) for C₄₂H₇₂O₇Sn: C 62.46, H 8.98; found: C 62.58, H 9.00.

To a solution of the preceding alcohol (3.3 g, 4.05 mmol, 1.0 equiv) in dried CH₂Cl₂ (20 mL) were added BAIB (1.44 g, 4.46 mmol, 1.1 equiv) and TEMPO (160 mg, 0.81 mmol, 0.2 equiv). After stirring for 3 h at 20 °C, a 1 M Na₂S₂O₃ solution was added, and the reaction mixture was extracted with Et₂O. The organic layers were washed with a saturated aqueous NaHCO₃ solution, brine, dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The crude (2*S*,4*R*(1*R*),5*S*,6*S*(2*S*,5*S*,6*R*,7*S*,8*Z*))-4-(2-formyl-1-methyl ethyl-1-yl)-6-[5,7-dimethyl-2,6-bis((methoxymethyl)oxy)-9-tributylstannyl-dec-8-en-3-yn-1-yl]-5-methyl-2-phenyl-1,3-dioxinan was used without further purification for the next step. ¹H NMR (400.0 MHz, CDCl₃): δ = 9.80 (s, 1H), 7.42-7.32 (m, 5H), 6.00 (dq, *J* = 8.2, 1.4 Hz, 1H, *J*_{H₁₁₇Sn} = *J*_{H₁₁₉Sn} = 135.1 Hz), 5.59 (s, 1H), 5.03 (d, *J* = 6.9 Hz, 1H), 4.80-4.76 (m, 1H), 4.78 (d, *J* = 6.9 Hz, 1H), 4.69 (d, *J* = 6.9 Hz, 1H), 4.58 (d, *J* = 6.9 Hz, 1H), 4.15 (dd, *J* = 10.1, 2.3 Hz, 1H), 3.84 (ddd, *J* = 9.6, 9.2, 1.4 Hz, 1H), 3.43 (s, 3H, CH₃), 3.35 (s, 3H, CH₃), 3.23 (t, *J* = 5.5 Hz, 1H), 2.72 (qd, *J* = 7.3, 5.5 Hz, 1H), 2.64 (qd, *J* = 6.9, 2.3 Hz, 1H), 2.28-2.18 (dq, *J* = 8.2, 6.9, 5.5 Hz, 1H), 2.28-2.18 (m, 1H), 1.89 (d, *J* = 1.4 Hz, *J*_{H₁₁₇Sn} = *J*_{H₁₁₉Sn} = 41.2 Hz, 3H, CH₃), 1.89-1.84 (m, 1H), 1.84 (ddq, *J* = 10.1, 9.6, 6.4 Hz, 1H), 1.51-1.44 (m, 6H, 3CH₂), 1.33 (sext, *J* = 7.3 Hz, 6H, 3CH₂), 1.23 (d, *J* = 6.9 Hz, 3H, CH₃), 1.19 (d, *J* = 7.3 Hz, 3H, CH₃), 0.99 (d, *J* = 6.9 Hz, 3H, CH₃), 0.96-0.88 (m, 15H, 3CH₂ + 3CH₃), 0.90 (d, *J* = 6.4 Hz, 3H); ¹³C NMR (100.5 MHz, CDCl₃): δ = 204.0 (C), 144.0 (CH, *J*_{13C-117Sn} = *J*_{13C-119Sn} = 32.6 Hz), 137.9 (C), 137.2 (C), 128.0 (2CH), 127.3 (CH), 125.6 (2CH), 99.6 (CH), 98.0 (CH₂), 94.2 (CH₂), 87.7 (C), 86.2 (CH), 80.6 (CH), 80.2 (C), 77.0 (CH), 60.7 (CH), 56.1 (CH₃), 55.4 (CH₃), 47.2 (CH), 41.9 (CH, *J*_{13C-117Sn} = *J*_{13C-119Sn} = 34.4 Hz), 39.7 (CH₂), 34.9 (CH), 30.1 (CH), 29.1 (3CH₂, *J*_{13C-117Sn} = *J*_{13C-119Sn} = 21.0 Hz), 27.3 (3CH₂, *J*_{13C-117Sn} = *J*_{13C-119Sn} = 57.4 Hz), 27.2 (CH₃, *J*_{13C-117Sn} = *J*_{13C-119Sn} = 46.0 Hz), 18.4 (CH₃), 16.3 (CH₃), 13.6 (3CH₃), 13.5 (CH₃), 9.8 (3CH₂), 6.8 (CH₃).

Chlorite oxidation - To a solution of the preceding aldehyde (3.26 g, 4.05 mmol, 1.0 equiv) in *t*-butanol (245 mL) and 2-methyl-2-butene (55 mL) was added a solution of NaClO₂ (549 mg, 6.07 mmol, 1.5 equiv) and NaH₂PO₄ (729 mg, 6.07 mmol, 1.5 equiv) in H₂O (21 mL). After stirring for 1 h at 20 °C, the same quantity of NaClO₂ and NaH₂PO₄ solution was added. The resulting mixture was stirred for 1 h then quenched by addition of a 0.1 N HCl solution and extracted with CH₂Cl₂. The organic layers were washed with brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The crude (2*S*,4*R*(1*R*),5*S*,6*S*(2*S*,5*S*,6*R*,7*S*,8*Z*))-4-(2-carboxy-1-methyl ethyl-1-yl)-6-[5,7-dimethyl-2,6-bis((methoxymethyl)oxy)-9-tributylstannyl-dec-8-en-3-yn-1-yl]-5-methyl-2-phenyl-1,3-dioxinan was used in the next step without further purification.

Jones oxidation - To a solution of the preceding alcohol (2*S*,4*R*(1*S*),5*S*,6*S*(2*S*,5*S*,6*R*,7*S*,8*Z*))-4-(2-hydroxy-1-methyl ethyl-1-yl)-6-[5,7-dimethyl-2,6-bis((methoxymethyl)oxy)-9-tributylstannyl-dec-8-en-3-yn-1-yl]-5-methyl-2-phenyl-1,3-dioxinan (84 mg, 0.10 mmol, 1.0 equiv) in acetone (1 mL) at 0 °C was slowly added (drop to drop) a solution of CrO₃ in sulfuric acid (2.66 M, 790 μL, 0.20 mmol, 2.0 equiv). After stirring for 15 min at 0 °C the mixture was extracted with CH₂Cl₂. The organic layers were washed with H₂O, brine, dried over MgSO₄ and the solvent was removed under reduced pressure. The crude acid derivative (74 mg) was directly used in the next step without further purification. ¹H NMR (400.0 MHz, CDCl₃): δ = 7.43-7.40 (m, 2H), 7.33-7.28 (m, 3H), 6.00 (d, *J* = 8.2 Hz, 1H, *J*_{H₁₁₇Sn} = *J*_{H₁₁₉Sn} = 133.3 Hz), 5.54 (s, 1H), 5.02 (d, *J* = 6.9 Hz, 1H), 4.79 (d, *J* = 6.4 Hz, 1H),

4.80-4.78 (m, 1H), 4.69 (d, $J = 6.4$ Hz, 1H), 4.09 (dd, $J = 10.1, 2.3$ Hz, 1H), 4.00 (d, $J = 6.9$ Hz, 1H), 3.79 (td, $J = 9.6, 1.4$ Hz, 1H), 3.43 (s, 3H, CH₃), 3.35 (s, 3H, CH₃), 3.23 (t, $J = 5.5$ Hz, 1H), 2.86 (qd, $J = 6.9, 2.3$ Hz, 1H), 2.72 (qd, $J = 6.9, 5.5$ Hz, 1H), 2.20 (dq, $J = 8.2, 6.4, 5.5$ Hz, 1H), 2.22-2.18 (m, 1H), 1.89 (s, $J_{\text{H},117\text{Sn}} = J_{\text{H},119\text{Sn}} = 42.6$ Hz, 3H, CH₃), 1.89-1.85 (m, 1H), 1.64 (ddd, $J = 10.1, 9.6, 6.4$ Hz, 1H), 1.53-1.42 (m, 6H, 3CH₂), 1.31 (d, $J = 6.9$ Hz, 3H, CH₃), 1.30 (sext, $J = 7.3$ Hz, 6H, 3CH₂), 1.17 (d, $J = 6.9$ Hz, 3H, CH₃), 0.98 (d, $J = 6.4$ Hz, 3H, CH₃), 0.94-0.85 (m, 18H, 3CH₂ + 4CH₃); ¹³C NMR (100.5 MHz, CDCl₃): $\delta = 178.0$ (C), 144.2 (CH, $J_{13\text{C},117\text{Sn}} = J_{13\text{C},119\text{Sn}} = 29.0$ Hz), 138.2 (C), 137.6 (C), 128.5 (CH), 128.1 (2CH), 125.7 (2CH), 99.7 (CH), 98.1 (CH₂), 93.7 (CH₂), 88.0 (C), 85.3 (CH), 81.8 (CH), 80.0 (C), 77.0 (CH), 61.0 (CH), 56.2 (CH₃), 55.5 (CH₃), 42.1 (CH), 40.7 (CH), 39.8 (CH₂), 35.5 (CH), 30.2 (CH), 29.2 (3CH₂, $J_{13\text{C},117\text{Sn}} = J_{13\text{C},119\text{Sn}} = 19.2$ Hz), 27.3 (3CH₂, $J_{13\text{C},117\text{Sn}} = J_{13\text{C},119\text{Sn}} = 57.4$ Hz), 27.2 (CH₃, $J_{13\text{C},117\text{Sn}} = J_{13\text{C},119\text{Sn}} = 36.4$ Hz), 18.6 (CH₃), 16.4 (CH₃), 15.2 (CH₃), 13.7 (3CH₃), 11.5 (CH₃), 9.9 (3CH₂, $J_{13\text{C},117\text{Sn}} = 310.6$ Hz, $J_{13\text{C},119\text{Sn}} = 331.8$ Hz).

To a solution of the preceding acid (3.3 g, 4.05 mmol, 1.0 equiv) in benzene (160 mL)/MeOH (45 mL) was added a (trimethylsilyl)diazomethane solution (2 M in hexane, 4.05 mmol, 1.0 equiv) until a yellow tint persisted. The resulting mixture was stirred 15 min then concentrated *in vacuo*. The residue was purified by chromatography on silica gel (cyclohexane/AcOEt 90:10 to 80:20) to give the (2*S*,4*R*(1*R*),5*S*,6*S*(2*S*,5*S*,6*R*,7*S*,8*Z*))-4-(2-methoxycarbonyl-1-methyl ethyl-1-yl)-6-{5,7-dimethyl-2-hydroxy-2,6-bis((methoxymethyl)oxy)-9-tributylstannyl-dec-8-en-3-yn-1-yl}-5-methyl-2-phenyl-1,3-dioxinan (61): $[\alpha]_{\text{D}}^{20} = -34.5$ (c = 0.96, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃): $\delta = 7.45$ -7.42 (m, 2H), 7.37-7.31 (m, 3H), 6.00 (dq, $J = 9.6, 1.8$ Hz, $J_{\text{H},117\text{Sn}} = J_{\text{H},119\text{Sn}} = 132.8$ Hz, 1H), 5.55 (s, 1H), 5.03 (d, $J = 6.4$ Hz, 1H), 4.81-4.77 (m, 1H), 4.79 (d, $J = 6.9$ Hz, 1H), 4.70 (d, $J = 6.9$ Hz, 1H), 4.56 (d, $J = 6.4$ Hz, 1H), 4.05 (dd, $J = 10.5, 3.2$ Hz, 1H), 3.78 (ddd, $J = 9.6, 9.1, 1.8$ Hz, 1H), 3.72 (s, 3H, CH₃), 3.43 (s, 3H, CH₃), 3.36 (s, 3H, CH₃), 3.23 (t, $J = 5.5$ Hz, 1H), 2.82 (qd, $J = 7.3, 3.2$ Hz, 1H), 2.72 (qd, $J = 6.9, 5.5$ Hz, 1H), 2.30-2.17 (dq, $J = 9.6, 6.9, 5.5$ Hz, 1H), 2.30-2.17 (m, 1H), 1.89 (d, $J = 1.8$ Hz, $J_{\text{H},117\text{Sn}} = J_{\text{H},119\text{Sn}} = 42.1$ Hz, 3H, CH₃), 1.87-1.83 (m, 1H), 1.75 (ddd, $J = 10.5, 9.6, 6.9$ Hz, 1H), 1.57-1.51 (m, 6H, 3CH₂), 1.37 (sext, $J = 7.3$ Hz, 6H, 3CH₂), 1.24 (d, $J = 7.3$ Hz, 3H, CH₃), 1.19 (d, $J = 6.9$ Hz, 3H, CH₃), 1.00-0.80 (m, 15H, 3CH₂ + 3CH₃), 0.85 (d, $J = 6.9$ Hz, 3H, CH₃); ¹³C NMR (100.5 MHz, CDCl₃): $\delta = 174.8$ (C), 144.4 (CH, $J_{13\text{C},117\text{Sn}} = J_{13\text{C},119\text{Sn}} = 27.8$ Hz), 138.6 (C), 137.7 (C, $J_{13\text{C},117\text{Sn}} = J_{13\text{C},119\text{Sn}} = 369.0$ Hz), 128.6 (CH), 128.5 (2CH), 125.8 (2CH), 99.7 (CH), 98.2 (CH₂), 93.8 (CH), 87.9 (C), 85.4 (C), 82.2 (CH), 80.5 (C), 77.0 (CH), 61.1 (CH), 56.2 (CH₃), 55.7 (CH₃), 52.1 (CH₃), 42.2 (CH, $J_{13\text{C},117\text{Sn}} = J_{13\text{C},119\text{Sn}} = 42.6$ Hz), 41.1 (CH), 39.9 (CH₂), 35.8 (CH), 30.3 (CH), 29.4 (3CH₂, $J_{13\text{C},117\text{Sn}} = J_{13\text{C},119\text{Sn}} = 19.2$ Hz), 27.6 (3CH₂, $J_{13\text{C},117\text{Sn}} = J_{13\text{C},119\text{Sn}} = 57.4$ Hz), 27.4 (CH₃, $J_{13\text{C},117\text{Sn}} = J_{13\text{C},119\text{Sn}} = 44.1$ Hz), 18.7 (CH₃), 16.5 (CH₃), 13.8 (3CH₃), 11.6 (CH₃), 10.0 (3CH₂, $J_{13\text{C},117\text{Sn}} = 312.4$ Hz, $J_{13\text{C},119\text{Sn}} = 327.8$ Hz), 9.3 (CH₃); IR (Film) $\nu = 2955, 2927, 2872, 2853, 1745, 1454, 1403, 1349, 1375, 1207, 1154, 1110, 1029, 700$ cm⁻¹; elemental analysis calcd (%) for C₄₃H₇₂O₈Sn: C 61.80, H 8.88; found: C 61.92, H 8.83.

To a solution of the preceding ester (200 mg, 0.24 mmol, 1.0 equiv) in AcOEt (2.5 mL) was added PtO₂ (20 mg, 0.088 mmol, 0.35 equiv). The resulting suspension was stirred for 12 h at 20 °C under H₂ atmosphere then filtered and the solvent was removed under reduced pressure. The crude (2*S*,4*R*(1*R*),5*S*,6*S*(2*S*,3*Z*,5*S*,6*R*,7*S*,8*Z*))-4-(2-methoxycarbonyl-1-methyl ethyl-1-yl)-6-{5,7-dimethyl-2,6-bis((methoxymethyl)oxy)-9-tributylstannyl-deca-3,8-dien-1-yl}-5-methyl-2-phenyl-1,3-dioxinan was used without further purification in the next step. ¹H NMR (400.0 MHz, CDCl₃): $\delta = 7.49$ -7.44 (m, 2H), 7.35-7.29 (m, 3H), 5.93 (dq, $J = 8.2, 1.4$ Hz, 1H, $J_{\text{H},117\text{Sn}} = J_{\text{H},119\text{Sn}} = 136.0$ Hz), 5.60 (s, 1H), 5.55 (t, $J = 10.5$ Hz, 1H), 5.25 (dd, $J = 10.5, 10.1$ Hz, 1H), 4.87 (dd, $J = 10.1, 9.2$ Hz, 1H), 4.72 (d, $J = 6.9$ Hz, 1H), 4.54 (s, 2H), 4.49 (d, $J = 6.9$ Hz, 1H), 4.05 (dd, $J = 10.1, 3.2$ Hz, 1H), 3.82 (dd, $J = 10.1, 9.2$ Hz, 1H), 3.74 (s, 3H, CH₃), 3.32 (s, 6H, 2CH₃), 3.14 (dd, $J = 6.9, 4.1$ Hz, 1H), 2.85-2.79 (qd, $J = 6.4, 3.2$ Hz, 1H), 2.85-2.79 (dq, $J = 10.9, 6.9, 6.9$ Hz, 1H), 2.17 (dq, $J = 8.2, 6.9, 4.1$ Hz, 1H), 2.00-1.91 (m, 1H), 1.85 (d, $J = 1.4$ Hz, $J_{\text{H},117\text{Sn}} = J_{\text{H},119\text{Sn}} = 42.1$ Hz, 3H, CH₃), 1.70-1.60 (m, 2H), 1.51-1.44 (m, 6H, 3CH₂), 1.32 (sext, $J = 7.3$ Hz, 6H, 3CH₂), 1.23 (d, $J = 6.9$ Hz, 3H, CH₃), 0.98 (d, $J = 6.9$ Hz, 3H, CH₃), 0.94 (d, $J = 6.4$ Hz, 3H, CH₃), 0.92-0.82 (m, 18H, 3CH₂ + 4CH₃); ¹³C NMR (100.5 MHz, CDCl₃): $\delta = 174.8$ (C), 144.7 (CH), 138.7 (CH), 137.3 (C), 136.5 (C), 129.0 (CH), 128.2 (CH), 127.9 (2CH), 125.7 (2CH), 99.5 (CH), 97.9 (CH₂), 93.1 (CH₂), 86.3 (CH), 82.2 (CH), 77.3 (CH), 66.2 (CH), 56.1 (CH₃), 55.2 (CH₃), 51.9 (CH₃), 41.0 (2CH), 39.1 (CH₂), 35.9 (CH), 35.8 (CH), 29.2 (3CH₂, $J_{13\text{C},117\text{Sn}} = J_{13\text{C},119\text{Sn}} = 19.2$ Hz), 27.4 (3CH₂, $J_{13\text{C},117\text{Sn}} = J_{13\text{C},119\text{Sn}} = 57.5$ Hz), 27.2 (CH₃, $J_{13\text{C},117\text{Sn}} = J_{13\text{C},119\text{Sn}} = 42.2$ Hz), 17.7 (CH₃), 15.6 (CH₃), 14.2 (CH₃), 13.7 (3CH₃), 11.6 (CH₃), 9.9 (3CH₂, $J_{13\text{C},117\text{Sn}} = 313.4$ Hz, $J_{13\text{C},119\text{Sn}} = 326.8$ Hz).

To a solution of the preceding compound (168 mg, 0.2 mmol, 1.0 equiv) in CH₂Cl₂ (4 mL) at 0 °C was added over 30 min an iodine solution (48 mg, 0.19 mmol, 0.98 equiv) in CH₂Cl₂ (16 mL). The resulting solution was immediately added with a 1 M Na₂S₂O₃ solution and the organic phase was then concentrated under reduced pressure. The residue was taken up with Et₂O (3 mL) and a 0.7 M KF solution (600 μ L). After stirring for 3h at 20 °C, the solution was filtered and extracted with Et₂O. The organic layers were washed with brine, dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/Et₂O 80:20 to 50:50) to give the title compound **60** (96 mg, 71 % yield for 2 steps). (**60**): $[\alpha]_{\text{D}}^{20} = +3.70$ (c = 0.78, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃): $\delta = 7.49$ -7.44 (m, 2H), 7.35-7.30 (m, 3H), 5.60 (t, $J = 10.5$ Hz, 1H), 5.59 (s, 1H), 5.28 (t,

$J = 10.5$ Hz, 1H), 5.24 (dq, $J = 8.2, 1.4$ Hz, 1H), 4.83 (ddd, $J = 10.5, 9.2, 1.8$ Hz, 1H), 4.72 (d, $J = 6.9$ Hz, 1H), 4.57 (s, 2H), 4.51 (d, $J = 6.9$ Hz, 1H), 4.08 (dd, $J = 10.1, 3.2$ Hz, 1H), 3.84 (dd, $J = 9.6, 9.2, 1.8$ Hz, 1H), 3.74 (s, 3H, CH₃), 3.35 (s, 6H, 2CH₃), 3.26 (t, $J = 5.5$ Hz, 1H), 2.86-2.78 (dq, $J = 10.5, 6.9, 5.5$ Hz, 1H), 2.86-2.78 (qd, $J = 6.9, 3.2$ Hz, 1H), 2.47 (dq, $J = 8.2, 6.9, 5.5$ Hz, 1H), 2.36 (d, $J = 1.4$ Hz, 3H, CH₃), 1.99 (ddm, $J = 11.0, 1.8$ Hz, 1H), 1.70 (ddd, $J = 10.1, 9.6, 6.9$ Hz, 1H), 1.72-1.64 (m, 1H), 1.25 (d, $J = 6.9$ Hz, 3H, CH₃), 1.08 (d, $J = 6.9$ Hz, 3H, CH₃), 0.96 (d, $J = 6.9$ Hz, 3H, CH₃), 0.89 (d, $J = 6.9$ Hz, 3H, CH₃); ¹³C NMR (100.5 MHz, CDCl₃): $\delta = 174.8$ (C), 138.8 (C), 137.9 (C), 135.8 (CH), 129.4 (CH), 128.2 (2CH), 127.9 (2CH), 125.7 (CH), 100.4 (CH), 99.4 (CH₂), 97.9 (C), 93.1 (CH₂), 85.6 (CH), 82.1 (CH), 77.6 (CH), 66.1 (CH), 56.1 (CH₃), 55.2 (CH₃), 51.9 (CH₃), 43.9 (CH), 41.0 (CH), 39.2 (CH or CH₂), 35.7 (CH), 35.3 (CH₃), 33.6 (CH or CH₂), 18.4 (CH₃), 14.7 (CH₃), 11.7 (CH₃), 9.2 (CH₃); IR (Film) $\nu = 3428, 2952, 2928, 2880, 2821, 1744, 1454, 1435, 1398, 1207, 1152, 1090, 1045$ cm⁻¹; elemental analysis calcd (%) for C₃₁H₄₇O₇: C 55.19, H 7.02; found: C 55.31, H 7.15.

(2*S*,4*R*(1*R*),5*S*,6*S*(2*S*,3*Z*,5*S*,6*R*,7*S*,8*Z*,11*S*,12*R*,13*S*,14*S*,15*S*,16*Z*))-4-(2-Methoxycarbonyl-1-methyl ethyl-1-yl)-6-{12-(*tert*-butyldimethylsilyloxy)-5,7,9,11,13,15-hexamethyl-2,6-bis((methoxymethyl)oxy)-14-(triethylsilyloxy)-nonadeca-3,8,16,18-tetraen-1-yl}-5-methyl-2-phenyl-1,3-dioxinan (61): In a 100 mL two-necked round-bottomed flask under argon at 20 °C was introduced 9-BBN dimer (5.0 g, 20.5 mmol, 1.0 equiv), and then THF (25 mL). Freshly distilled MeOH (1.8 mL, 45.1 mmol, 2.2 equiv) was slowly added. A strong H₂ degassing was observed. The reaction mixture was stirred for 30 min after the end of addition and then THF was distilled out. The crude 9-MeOBBN was finally distilled under reduced pressure (2-5 mbar; bp: 63-65 °C/ ltt: 12 mmHg; bp: 80-82 °C) to give 9-MeOBBN as a colourless oil (5.6 g, 92 % yield).

To a solution of the alkyl iodide **43** (145 mg, 0.26 mmol, 1.8 equiv) in Et₂O (3.7 mL) at -80 °C was rapidly added *t*-BuLi (1.5 M in pentane, 355 μ L, 0.53 mmol, 3.8 equiv); 2 min later were added 9-MeOBBN (1 M in hexane, 602 μ L, 0.60 mmol, 4.3 equiv) then THF (3.7 mL). The resulting mixture was stirred 10 min at -78 °C and allowed to warm to 20 °C during 1 h 15 min; an aqueous 3.5 M Cs₂CO₃ solution was then added (220 μ L, 0.77 mmol, 5.5 equiv), followed by the addition of the vinyl iodide **60** (96 mg, 0.14 mmol, 1.0 equiv) in DMF (3.7 mL). Finally PdCl₂dppf (12 mg, 0.014 mmol, 0.10 equiv) and triphenylarsine (7 mg, 0.021 mmol, 0.12 equiv) were added, and the resulting dark solution was stirred at 20 °C for 16 h. After extraction with Et₂O, the organic layers were washed with brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/Et₂O 80:20 to 60:40) to give the title compound **61** (87 mg, 60 % yield). (**61**): $[\alpha]_{\text{D}}^{20} = +13.8$ (c = 0.90, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃): $\delta = 7.47$ -7.44 (m, 2H), 7.35-7.30 (m, 3H), 6.57 (ddd, $J = 16.9, 11.0, 10.5$ Hz, 1H), 6.03 (dd, $J = 11.0, 10.5$ Hz, 1H), 5.58 (s, 1H), 5.54 (dd, $J = 11.9, 10.5$ Hz, 1H), 5.54 (t, $J = 10.5$ Hz, 1H), 5.20 (d, $J = 16.9$ Hz, 1H), 5.22 (dd, $J = 10.5, 10.1$ Hz, 1H), 5.11 (d, $J = 10.5$ Hz, 1H), 4.97 (d, $J = 10.1$ Hz, 1H), 4.84 (dd, $J = 11.0, 10.1$ Hz, 1H), 4.71 (d, $J = 6.9$ Hz, 1H), 4.54 (s, 2H), 4.50 (d, $J = 6.9$ Hz, 1H), 4.06 (dd, $J = 10.1, 3.2$ Hz, 1H), 3.82 (dd, $J = 10.1, 8.7$ Hz, 1H), 3.74 (s, 3H, CH₃), 3.55 (dd, $J = 6.9, 3.2$ Hz, 1H), 3.44 (dd, $J = 4.6, 4.1$ Hz, 1H), 3.34 (s, 3H, CH₃), 3.33 (s, 3H, CH₃), 3.07 (t, $J = 5.5$ Hz, 1H), 2.91-2.76 (m, 3H), 2.54 (dq, $J = 10.1, 6.4, 5.5$ Hz, 1H), 2.08-1.55 (tq, $J = 10.1, 6.4$ Hz, 1H), 2.08-1.55 (m, 6H), 1.55 (s, 3H, CH₃), 1.22 (d, $J = 6.9$ Hz, 3H, CH₃), 1.06-0.83 (m, 8CH₃), 0.91 (s, 9H, 3CH₃), 0.68 (q, $J = 7.8$ Hz, 6H, 3CH₂), 0.63 (d, $J = 6.4$ Hz, 3H, CH₃), 0.07 (s, 6H, 2CH₃); ¹³C NMR (100.5 MHz, CDCl₃): $\delta = 174.8$ (C), 138.8 (C), 136.8 (CH), 134.4 (CH), 132.3 (C), 132.1 (CH), 130.4 (CH), 128.9 (3CH), 128.2 (CH), 127.9 (2CH), 125.8 (CH), 117.4 (CH₂), 99.6 (CH), 97.8 (CH₂), 92.5 (CH₂), 86.9 (CH), 82.2 (CH), 78.0 (CH), 77.0 (2CH), 66.4 (CH), 56.0 (CH₃), 55.2 (CH₃), 51.9 (CH₃), 41.9, 41.0, 40.3, 39.0, 36.2, 35.8, 35.3, 35.0, 34.4 (7CH, 2CH₃), 26.9 (3CH₃), 23.1 (CH₃), 18.5 (C), 18.5, 17.4, 16.5, 14.2, 11.6, 11.3, 9.3 (7CH₃, CH₃-2), 7.2 (3CH₃), 5.7 (3CH₂), -3.1 (CH₃), -3.2 (CH₃); IR (Film) $\nu = 3383, 2957, 2931, 2878, 2857, 2821, 2359, 2340, 1747, 1733, 1657, 1455, 1462, 1435, 1396, 1374, 1328, 1252, 1143, 1094, 1045, 919, 835, 772, 739, 701$ cm⁻¹; HRMS (ESI) m/z : C₅₆H₉₈O₁₀NaSi₂: calculated 1009.6591; found 1009.6591.

Discodermolide 1: To a solution of compound **61** (53 mg, 0.054 mmol, 1.0 equiv) in MeOH (6.5 mL) at 0 °C was added *p*-toluene sulfonic acid (3 mg, 0.015 mmol, 0.28 equiv). After stirring for 1 h at 0 °C, triethylamine was added to the reaction mixture (0.3 equiv) and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/AcOEt, 95:5 to 70:30) to give the (2*S*,4*R*(1*R*),5*S*,6*S*(2*S*,3*Z*,5*S*,6*R*,7*S*,8*Z*,11*S*,12*R*,13*S*,14*S*,15*S*,16*Z*))-4-(2-methoxycarbonyl-1-methyl ethyl-1-yl)-6-{12-(*tert*-butyldimethylsilyloxy)-5,7,9,11,13,15-hexamethyl-14-hydroxy-2,6-bis((methoxymethyl)oxy)-nonadeca-3,8,16,18-tetraen-1-yl}-5-methyl-2-phenyl-1,3-dioxinan (36 mg, 77 % yield). $[\alpha]_{\text{D}}^{20} = +11.0$ (c = 0.90, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃): $\delta = 7.47$ -7.43 (m, 2H), 7.33-7.30 (m, 3H), 6.64 (ddd, $J = 16.9, 11.0, 10.1$ Hz, 1H), 6.16 (dd, $J = 11.0, 10.5$ Hz, 1H), 5.59 (s, 1H), 5.54 (dd, $J = 11.0, 10.1$ Hz, 1H), 5.33 (dd, $J = 10.5, 10.1$ Hz, 1H), 5.23 (dd, $J = 10.1, 9.6$ Hz, 1H), 5.20 (d, $J = 16.9$ Hz, 1H), 5.16 (d, $J = 10.1$ Hz, 1H), 4.99 (d, $J = 10.1$ Hz, 1H), 4.84 (dd, $J = 10.1, 9.6$ Hz, 1H), 4.71 (d, $J = 6.9$ Hz, 1H), 4.54 (s, 2H), 4.50 (d, $J = 6.9$ Hz, 1H), 4.06 (dd, $J = 10.5, 3.2$ Hz, 1H), 3.82 (t, $J = 9.6$ Hz, 1H), 3.74 (s, 3H, CH₃), 3.63 (dd, $J = 5.5, 2.8$ Hz, 1H), 3.33 (s, 6H, 2CH₃), 3.35-3.33 (m, 1H), 3.09 (t, $J = 5.5$ Hz, 1H), 2.86-2.75 (dq, $J = 11.0, 7.3, 5.5$ Hz, 1H), 2.86-2.75 (m, 2H),

2.54 (dq, $J = 10.1, 6.4, 5.5$ Hz, 1H), 2.19 (t, $J = 12.4$ Hz, 1H), 2.05-1.71 (m, 4H), 1.58 (s, 3H, CH₃), 1.65-1.55 (ddd, $J = 10.5, 9.6, 6.4$ Hz, 1H), 1.65-1.55 (m, 1H), 1.44 (s, 1H, OH), 1.22 (d, $J = 7.3$ Hz, 3H, CH₃), 1.01 (d, $J = 6.9$ Hz, 3H, CH₃), 0.96 (d, $J = 6.4$ Hz, 3H, CH₃), 0.95-0.91 (m, 6H, 2CH₃), 0.91 (s, 9H, 3CH₃), 0.87 (d, $J = 6.4$ Hz, 3H, CH₃), 0.70 (d, $J = 6.9$ Hz, 3H, CH₃), 0.10 (s, 6H, 2CH₃); ¹³C NMR (100.5 MHz, CDCl₃): $\delta = 174.8$ (C), 138.8 (C), 137.0 (CH), 134.7 (CH), 132.7 (C), 132.1 (CH), 131.1 (CH), 130.0 (CH), 129.1 (CH), 128.2 (2CH), 127.9 (2CH), 125.8 (CH), 118.5 (CH₂), 99.6 (CH), 97.9 (CH₂), 93.2 (CH₂), 86.8 (CH), 82.0 (CH), 79.0 (CH), 77.8 (CH), 76.7 (CH), 66.4 (CH), 56.1 (CH₃), 55.3 (CH₃), 51.9 (CH₃), 41.1, 39.1, 38.0, 36.7, 36.3, 35.9, 35.3, 34.7, 34.4 (7CH, 2CH₂), 26.3 (3CH₃), 23.3 (CH₃), 18.5 (C), 17.6, 17.1, 16.4, 13.4, 11.7, 9.5, 9.3 (7CH₃), -3.1 (CH₃), -3.6 (CH₃); IR (Film) $\nu = 2377, 2957, 2929, 2883, 2857, 1591, 1462, 1434, 1395, 1257, 1153, 1093, 1036, 874$ cm⁻¹; HRMS (ESI) m/z : C₅₀H₈₄O₁₀NaSi: calculated 895.5726; found: 895.5721.

To a solution of the preceding alcohol (114 mg, 0.13 mmol, 1.0 equiv) in CH₂Cl₂ (10 mL) was added trichloroacetylisocyanate (16 μ l, 0.14 mmol, 1.05 equiv). After stirring for 15 min at 20 °C, the resulting mixture was concentrated *in vacuo* and the residue taken up in MeOH (13 mL). K₂CO₃ (99 mg, 0.71 mmol, 5.5 equiv) was added and the resulting solution was stirred 1 h 15 min then concentrated *in vacuo* and extracted with AcOEt. The organic layers were washed with water, brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/AcOEt 90:10 to 50:50) to give the (2*S*,4*R*(1*R*),5*S*,6*S*(2*S*,3*Z*,5*S*,6*R*,7*S*,8*Z*,11*S*,12*R*,13*S*,14*S*,15*S*,16*Z*))-4-(2-methoxycarbonyl-1-methyl ethyl-1-yl)-6-{12-(*tert*-butyldimethylsilyloxy)-14-(carbamoyloxy)-5,7,9,11,13,15-hexamethyl-2,6-bis(methoxymethyl)oxy}-nonadeca-3,8,16,18-tetraen-1-yl}-5-methyl-2-phenyl-1,3-dioxinan (76 mg, 64 % yield) as a pale oil. [α]_D²⁰ = +17.4 ($c = 0.80$, CHCl₃); ¹H NMR (400.0 MHz, CDCl₃): $\delta = 7.50$ -7.44 (m, 2H), 7.34-7.30 (m, 3H), 6.60 (dt, $J = 16.9, 10.5$ Hz, 1H), 6.02 (dd, $J = 11.0, 10.5$ Hz, 1H), 5.58 (s, 1H), 5.58-5.52 (m, 1H), 5.53 (dd, $J = 12.8, 10.5$ Hz, 1H), 5.38 (dd, $J = 11.0, 10.5$ Hz, 1H), 5.28-5.18 (m, 3H), 5.14 (d, $J = 10.5$ Hz, 1H), 4.99 (d, $J = 10.1$ Hz, 1H), 4.84 (dd, $J = 10.1, 9.2$ Hz, 1H), 4.74-4.70 (m, 1H), 4.72 (d, $J = 6.9$ Hz, 1H), 4.54 (s, 2H), 4.50 (d, $J = 6.9$ Hz, 1H), 4.06 (dd, $J = 10.1, 3.2$ Hz, 1H), 3.81 (dd, $J = 9.6, 9.2$ Hz, 1H), 3.73 (s, 3H, CH₃), 3.43 (dd, $J = 4.6, 4.1$ Hz, 1H), 3.32 (s, 6H, 2 CH₃), 3.06 (t, $J = 5.5$ Hz, 1H), 2.99 (dq, $J = 10.5, 6.9, 3.7$ Hz, 1H), 2.83-2.79 (qdm, $J = 7.3, 5.5$ Hz, 1H), 2.81 (dq, $J = 10.1, 6.9, 5.5$ Hz, 1H), 2.52 (dq, $J = 10.1, 6.4, 5.5$ Hz, 1H), 2.15-1.79 (m, 5H), 1.74-1.52 (m, 2H), 1.57 (s, 3H, CH₃), 1.25 (d, $J = 7.3$ Hz, 3H, CH₃), 1.01 (d, $J = 6.9$ Hz, 3H, CH₃), 0.94-0.85 (m, 12H, 4CH₃), 0.91 (s, 9H, 3CH₃), 0.73 (d, $J = 6.9$ Hz, 3H, CH₃), 0.07 (s, 3H, CH₃), 0.05 (s, 3H, CH₃); ¹³C NMR (100.5 MHz, CDCl₃): $\delta = 174.9$ (C), 156.9 (C), 138.8 (CH), 137.0 (C), 133.6 (CH), 132.5 (CH), 132.1 (C), 130.1 (CH), 129.8 (CH), 129.0 (CH), 128.2 (CH), 127.9 (2CH), 125.8 (2CH), 117.9 (CH₂), 99.7 (CH), 97.8 (CH₂), 93.2 (CH₂), 86.9 (CH), 82.1 (CH), 78.8 (CH), 77.0 (2CH), 66.4 (CH), 56.0 (CH₃), 55.2 (CH₃), 51.9 (CH₃), 41.2 (CH), 39.2 (CH₂), 37.8 (CH), 36.3 (CH), 35.9 (CH₃), 35.3 (CH), 35.1 (CH), 34.4 (CH), 29.7 (CH), 26.2 (3CH₃), 23.0 (CH₃), 18.5 (C), 18.5 (CH₃), 17.5, 16.5, 11.7, 10.1 (4CH₃), 13.7 (CH₃), 9.4 (CH₃), -3.3 (CH₃), -3.6 (CH₃); IR (Film) $\nu = 3359, 2981, 2930, 2884, 2857, 1728, 1598, 1455, 1435, 1395, 1363, 1326, 1258, 1214, 1146, 1094, 1035, 836, 773, 757$ cm⁻¹; HRMS (ESI) m/z : C₅₁H₈₅O₁₁NaSi: calculated 938.5784; found 938.5793.

To a solution of the preceding compound (14 mg, 0.015 mmol, 1.0 equiv) in THF (1.5 mL) was added HCl (4 N, 1.5 mL). The resulting mixture was stirred 72 h at 20 °C then added with solid NaHCO₃ and extracted 3 times with AcOEt. The organic layers were washed with water, brine, dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (CH₂Cl₂/MeOH 95:5 to 90:10) to give the title compound (+)-**discoedermolide 1** (6.2 mg, 70 % yield) as a white solid. (1): [α]_D²⁰ = +16.2 ($c = 1.0$, MeOH); ¹H NMR (400.0 MHz, CDCl₃): $\delta = 6.61$ (ddd, $J = 16.9, 11.0, 10.5$ Hz, 1H), 6.03 (t, $J = 11.0$ Hz, 1H), 5.53 (dd, $J = 11.0, 7.8$ Hz, 1H), 5.42 (dd, $J = 11.0, 10.5$ Hz, 1H), 5.36 (dd, $J = 11.0, 10.5$ Hz, 1H), 5.23 (d, $J = 16.9$ Hz, 1H), 5.14 (d, $J = 10.5$ Hz, 1H), 5.12 (d, $J = 11.0$ Hz, 1H), 4.79-4.70 (m, 4H), 4.63 (ddd, $J = 10.1, 8.2, 1.8$ Hz, 1H), 3.73 (t, $J = 3.7$ Hz, 1H), 3.28 (dd, $J = 5.0, 4.6$ Hz, 1H), 3.21 (dd, $J = 8.9, 5.0$ Hz, 1H), 3.00 (dq, $J = 10.5, 6.9, 3.2$ Hz, 1H), 2.79 (m, 1H), 2.70 (qd, $J = 7.3, 3.7$ Hz, 1H), 2.61-2.54 (m, 1H, OH), 2.58 (m, 1H), 2.00-1.81 (m, 4H + 2 OH), 1.72-1.60 (m, 3H + OH), 1.64 (s, 3H, CH₃), 1.32 (d, $J = 7.3$ Hz, 3H, CH₃), 1.08 (d, $J = 6.9$ Hz, 3H, CH₃), 1.01 (d, $J = 7.3$ Hz, 3H, CH₃), 0.98 (d, $J = 6.4$ Hz, 3H, CH₃), 0.98 (d, $J = 6.4$ Hz, 3H, CH₃), 0.95 (d, $J = 6.4$ Hz, 3H, CH₃), 0.83 (d, $J = 5.9$ Hz, 3H, CH₃); ¹³C NMR (100.5 MHz, CDCl₃): $\delta = 174.3$ (C), 157.4 (C), 134.5 (CH), 133.8 (CH), 133.6 (C), 133.0 (CH), 132.2 (CH), 130.1 (CH), 129.8 (CH), 118.1 (CH₂), 79.1 (CH), 78.8 (CH), 77.7 (CH), 75.7 (CH), 73.4 (CH), 64.5 (CH), 43.4 (CH), 41.1 (CH₂), 37.5 (CH), 36.4 (CH), 35.9 (CH₂), 35.6 (CH), 35.0 (CH), 33.2 (CH), 30.0 (CH), 23.6 (CH₃), 18.6 (CH₃), 17.7 (CH₃), 16.1 (CH₃), 16.0 (CH₃), 13.9 (CH₃), 12.9 (CH₃), 9.3 (CH₃); ¹H NMR (400.0 MHz, CD₃CN): $\delta = 6.69$ (ddd, $J = 16.9, 11.0, 10.1$ Hz, 1H), 6.10 (t, $J = 11.0$ Hz, 1H), 5.56 (dd, $J = 10.5, 9.6$ Hz, 1H), 5.45 (dd, $J = 10.5, 9.2$ Hz, 1H), 5.41 (dd, $J = 11.0, 10.5$ Hz, 1H), 5.27 (d, $J = 16.9$ Hz, 1H), 5.17 (d, $J = 10.1$ Hz, 1H), 5.15-5.04 (m, 2H), 4.98 (d, $J = 10.1$ Hz, 1H), 4.74 (dd, $J = 8.2, 4.1$ Hz, 1H), 4.56-4.41 (m, 2H), 3.64 (t, $J = 4.1$ Hz, 1H), 3.16 (dd, $J = 7.3, 3.2$ Hz, 1H), 3.16-3.14 (m, 1H, OH), 3.09 (dd, $J = 6.9, 3.7$ Hz, 1H), 2.67-2.56 (m, 3H + OH), 2.35-2.10 (m, 4H + OH), 1.90-1.45 (m, 3H), 1.59 (s, 3H, CH₃), 1.21 (d, $J = 7.3$ Hz, 3H, CH₃), 1.03 (d, $J = 6.4$ Hz, 3H, CH₃), 1.01 (d, $J = 6.4$ Hz, 3H, CH₃), 0.97 (d, $J = 6.9$ Hz, 3H, CH₃), 0.90 (d, $J = 6.9$ Hz, 3H, CH₃), 0.82 (d, $J = 6.9$ Hz, 3H, CH₃), 0.75 (d, $J = 5.9$ Hz, 3H, CH₃); ¹³C NMR (100.5 MHz, CD₃CN): $\delta = 174.7$ (C), 158.3 (C), 134.0 (CH),

133.8 (CH), 133.7 (CH), 133.2 (CH), 131.1 (CH), 130.5 (CH), 118.1 (CH₂), 79.7 (CH), 79.2 (CH), 77.4 (CH), 75.9 (CH), 73.1 (CH), 63.3 (CH), 44.0 (CH), 42.1 (CH₂), 38.4 (CH), 37.1 (CH), 36.5 (CH₂), 36.2 (CH), 36.1 (CH), 34.4 (CH), 34.2 (CH), 23.3 (CH₃), 19.7 (CH₃), 18.1 (CH₃), 17.6 (CH₃), 15.8 (CH₃), 15.6 (CH₃), 13.1 (CH₃), 9.2 (CH₃); HRMS (ESI) m/z : calcd for C₃₃H₃₅O₈NNa: 616.3820 [$M^+ + Na$]; found 616.3816.

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