

## Total Synthesis of Discodermolide: Optimization of the Effective Synthetic Route

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**Abstract:** An efficient and modulable total synthesis of discodermolide (DDM), a unique marine anticancer polyketide is described including related alternative synthetic approaches. Particularly notable is the repeated application of a crotyltitanation reaction to yield homoallylic (*Z*)-*O*-ene-carbamate alcohols with excellent selectivity. Advantage was taken of this reaction not only for the stereocontrolled 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 through 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:** allylation •  
cross-coupling • discodermolide •  
nickel • total synthesis

### Introduction

In 1990, Gunasekera and co-workers reported the isolation of discodermolide (DDM) (**1**),<sup>[1]</sup> 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.<sup>[2]</sup> The cytotoxicity values reported for discodermolide against 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 potent 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.<sup>[3]</sup> Extensive investigation of the site and mode of binding of DDM to  $\beta$ -tubulin as well as the determination of its bioactive conformation led to the proposal of a pharmacophore model.<sup>[2d]</sup> Due to the potential therapeutic applications and the extreme scarcity of this compound, considerable synthetic efforts directed towards DDM were provided, culminating in several total syntheses,<sup>[4]</sup> including the development of a preparative-scale approach.<sup>[5]</sup> Phase I clinical trials were initiated from Novartis Pharma AG; however, despite encouraging results, trials were suspended due to adverse toxicity at high doses.<sup>[6]</sup> Owing to the remarkable profile of DDM and its potential as a lead structure, conception and synthesis of analogues have to be developed.

In this full account, we report synthetic details of our total synthesis of DDM (**1**), including related alternative synthetic approaches that enabled us to develop the final effective synthetic route.<sup>[7]</sup> The modulable character of this ap-

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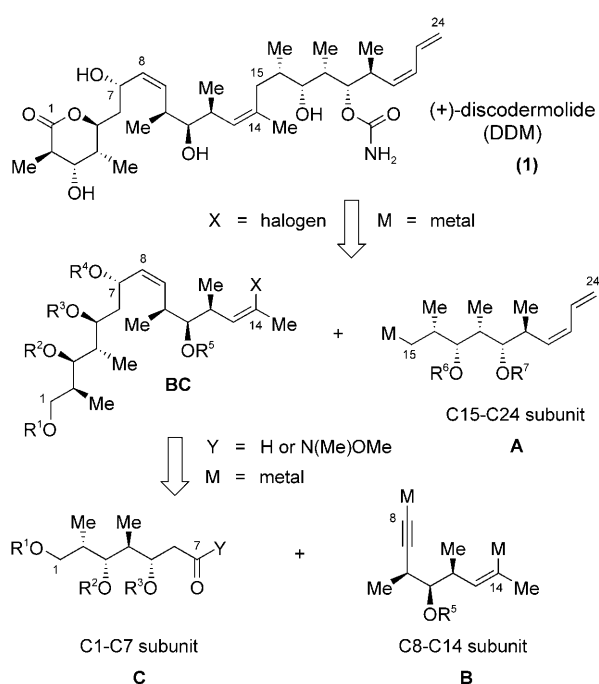
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proach might allow structural modifications of DDM and, therefore, the elaboration and investigation of novel discodermolide structural analogues.

## Results and Discussion

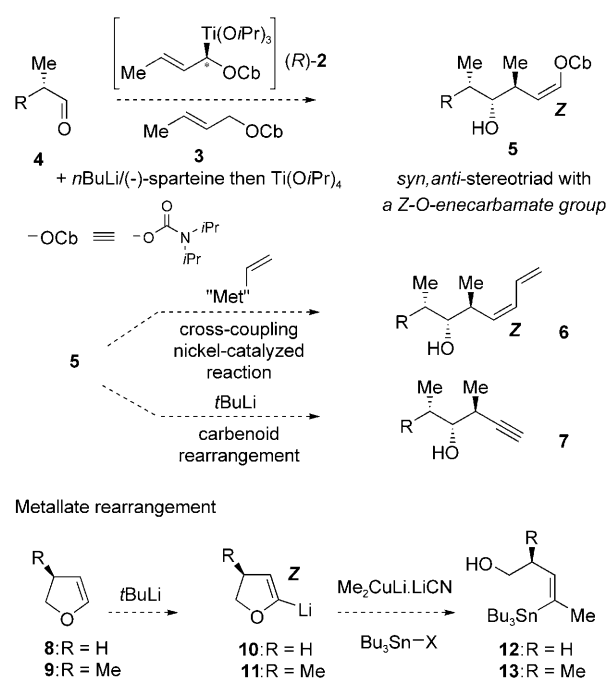
**Retrosynthetic and strategic considerations:** Our synthetic strategy relies upon the disassembly of DDM into three fragments of similar size and stereochemical complexity (**A** C15–C24, **B** C8–C14, **C** C1–C7; Scheme 1). The linkage of these subunits appears to us to be optimally convergent, the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



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  $\alpha$ -(*S*)-methyl aldehyde **4**. As exemplified in Scheme 2, this crotyltitanation reaction initially developed by Hoppe,<sup>[8]</sup> and widely used in total syntheses by our group,<sup>[9]</sup> yielded homoallylic adducts **5** encompassing a *syn*–*anti* methyl–hydroxy–methyl triad linked to a (*Z*)-*O*-enecarbamate group, with excellent diastereoselectivity. The enantioenriched (*R*)- $\alpha$ -(*N,N*-diisopropylcarbamoyloxy)crotyltitanium **2** could easily be prepared in situ from deprotonation of crotyl diisopropylcarbamate **3** with *n*BuLi/(–)-sparteine and tetra(isopropoxy)titanium.<sup>[10]</sup>

Our plan was precisely to take advantage of the reactivity of this terminal (*Z*)-*O*-enecarbamate function in two ways. First, a nickel-catalyzed cross-coupling reaction would con-



Scheme 2. Crotyltitanation of aldehyde **4**. Insaturation setup from (*Z*)-acyclic or cyclic enol ether.

figure the terminal C21–C24 (*Z*)-diene **6** of fragment **A**,<sup>[11]</sup> whereas a carbenoid rearrangement would install the terminal C8–C9 alkyne **7** of subunit **B** in one step.<sup>[12]</sup>

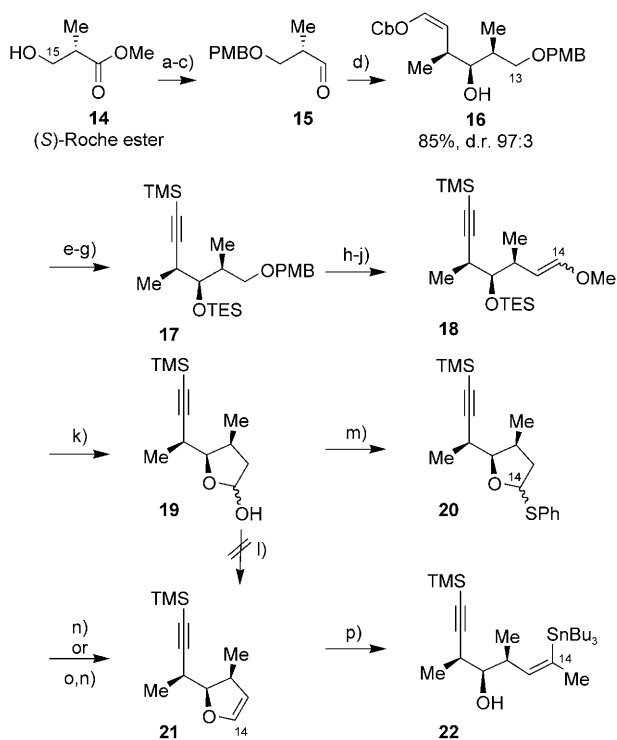
Another highlight of our strategy was the stereocontrolled building of the C13=C14 trisubstituted (*Z*)-double bond. With our C14–C15 disconnection, elected by several research groups, the elaboration of the pivotal segment **B**, which encompassed a (*Z*)-vinyl halide at the C14-position, was needed 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,<sup>[13]</sup> but the yields were modest and the *Z/E* stereoselectivity remained disappointing.<sup>[14]</sup> 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**. This attractive reaction, first examined by Fujisawa<sup>[15]</sup> and developed by Kocienski<sup>[16]</sup> and our group,<sup>[17]</sup> would allow the construction of various (*Z*) or (*E*)-trisubstituted double bonds, in expected good yields and with 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 strongly supports the crucial role of the middle part of the DDM molecule.<sup>[2b]</sup> The preparation of this C8–C14 fragment region **B** was a real challenge; the strategy involved two main stages, a crotyltitanation for the setup of the C10–C12 *anti*–*syn* stereotriad and a dyotropic rearrangement to build the C13=C14 trisubstituted (*Z*)-double bond. Two alterna-

tive routes were examined, which differed in the ordering of the two key steps.

The first sequence started with the commercially available (*S*)-(+)-Roche ester **14** (Scheme 3). Protection of **14** as a *p*-methoxybenzyl ether<sup>[18]</sup> was followed by reduction of the



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,  $\text{NaHCO}_3$ ,  $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ ; d) (*R*)-**2**, cyclohexane/pentane 1:7,  $-78^\circ\text{C}$ , 2 h, 85% (2 steps, c–d), d.r. 97:3; e) TESOTf, 2,6-lutidine,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}\rightarrow\text{RT}$ , 2 h, 97%; f) *t*BuLi,  $\text{Et}_2\text{O}$ ,  $-30^\circ\text{C}\rightarrow-20^\circ\text{C}$ , 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) DDO,  $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$  95:5,  $0^\circ\text{C}\rightarrow\text{RT}$ , 30 min, 86%; i) IBX, DMSO, RT, 3 h; j) (methoxymethyl)triphenylphosphonium chloride, LiHMDS,  $-10^\circ\text{C}$ , 1 h, 85%; k) acetone/ $\text{H}_2\text{O}$  9:1, HCl,  $65^\circ\text{C}$ , 1 h, 61% (3 steps, h–k); l) PTSA, PPTS,  $\text{CuSO}_4$ ,  $\text{NH}_4\text{NO}_3$  or Burgess reagent; m) PhSH,  $\text{BF}_3\cdot\text{OEt}_2$ , 4 Å MS,  $\text{Et}_2\text{O}$ , 1 h, 80%; n) DBU, neat,  $245^\circ\text{C}$ , 30%; o) *m*CPBA,  $\text{NaHCO}_3$ , PhH,  $0^\circ\text{C}$ , 1 h, then, reflux, 1 h, 19%; p) *t*BuLi,  $\text{Me}_2\text{CuLi}\cdot\text{LiCN}$ , THF/ $\text{Et}_2\text{O}$  1:2,  $0^\circ\text{C}\rightarrow\text{RT}$ , 3 h, then *n*Bu<sub>3</sub>SnCl,  $-30^\circ\text{C}\rightarrow\text{RT}$ , 5 h, 20%. *m*CPBA = 3-chloroperbenzoic acid; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DDO = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; d.r. = diastomeric ratio; HMDS = hexamethyldisilazane; IBX = 2-iodoxybenzoic acid; MS = molecular sieves; PMB = *p*-methoxybenzyl; PPTS = pyridinium *p*-toluenesulfonate; PTSA = *p*-toluenesulfonic acid; TEMPO = tetramethylpiperdinyloxy free radical; TES = triethylsilyl; TMS = trimethylsilyl.

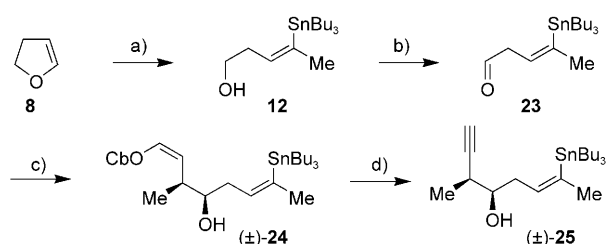
methyl ester to the primary alcohol and subsequent oxidation to aldehyde **15**.<sup>[19]</sup> The crotyltitanation reaction of chiral aldehyde **15**, with enantioenriched reagent (*R*)-**2** led to the desired diastereomer **16** in good yield and with an excellent diastereomeric ratio (97:3) (Scheme 3). Obtention of a *O*-enecarbamate moiety by the crotyltitanation process allowed for the generation of alkyne **17** by a Fritsch–Butten-

berg–Wiechell rearrangement.<sup>[12]</sup> Enol ether **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 ether **18**, accompanied by removal of the TES group afforded lactol **19**.

The next step should allow us to build the C13=C14 tri-substituted functionalized (*Z*)-double bond by means of 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 expected. Specifically, all attempts to effect a direct elimination (PTSA,<sup>[20]</sup> PPTS,<sup>[21]</sup>  $\text{CuSO}_4$ ,<sup>[22]</sup>  $\text{NH}_4\text{NO}_3$ ,<sup>[23]</sup> or Burgess reagent)<sup>[24]</sup> from compound **19** failed to give the expected DHF **21**. However, lactol **19** could be smoothly converted to hemithioketal **20**. Upon DBU pyrolysis of **20** with concomitant distillation of the elimination product,<sup>[25]</sup> the desired dihydrofuran **21** was obtained in 30% yield. Attempts to improve this outcome by conversion of phenyl sulfide **20** into the corresponding sulfoxide derivative<sup>[26]</sup> and subsequent elimination delivered DHF **21** in only 19% yield. Application to **21** of dyotropic rearrangement conditions (1,2-cuprate transfer from cyano-Gilman dimethylcuprate followed by tri-*n*-butyltin trapping) led to the expected C8–C14 segment **22** in 20% yield. Unfortunately, this 15 step sequence afforded the C8–C14 subunit **22** in a very poor yield and thus could not provide 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 the DHF ring. By using the same approach, we inverted the order of the crotyltitanation–dyotropic rearrangement sequence. This required the introduction of a C13=C14-functionalized double bond bearing a metallic or halide function at a very early stage of synthesis. According to the literature, vinyl iodide hydrogenolysis occurred in the subsequent Lindlar reduction step,<sup>[41]</sup> and, therefore, we choose to introduce a vinyl tin function as the precursor of the vinyl halide core at the C14 position.

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 prepare 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 commercially available 2,3-dihydrofuran **8** proceeded smoothly,<sup>[27]</sup> significant problems were encountered during conversion of homoallylic alcohol **12** into aldehyde **23**. Extensive screening was performed. Classical oxidation methods, such as Swern,<sup>[28]</sup> Doering–Parikh,<sup>[29]</sup> or the use of PCC<sup>[30]</sup> led to decomposition with loss of the tin function. On the other hand, milder reagents, such as tetrapropylammonium perruthenate (TPAP)/*N*-methylmorpholine *N*-oxide (NMO)<sup>[31]</sup> or IBX<sup>[32]</sup> resulted in recovery of the starting material. The Saigo–Mukaiyama protocol,<sup>[33]</sup> employing 1,1'-(azodicarbonyl)dipiperidine (ADD) as a hydride acceptor

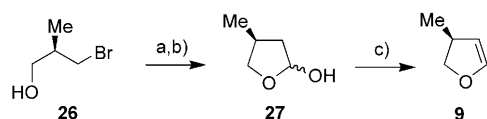


Scheme 4. a) *t*BuLi, Me<sub>2</sub>CuLi-LiCN, THF/Et<sub>2</sub>O/1:2, 0°C→RT, 3 h, then *n*Bu<sub>3</sub>SnCl, -30°C→RT, 5 h, 61%; b) TEMPO (10 mol%), BAIB, CH<sub>2</sub>Cl<sub>2</sub>, RT, 2 h; c) (±)-2 (from 3, *n*BuLi/TMEDA, Et<sub>2</sub>O), Et<sub>2</sub>O, -78°C, 2 h, 63% (2 steps b and c); d) *t*BuLi, Et<sub>2</sub>O, -30°C→-20°C, 30 min, 70%. BAIB = [bis(acetoxy)iodo]benzene.

failed, resulting only in the recovery of the starting material, despite encouraging Marshall precedent.<sup>[34]</sup>

Finally, we were pleased to find that the use of TEMPO-free radicals and a suitable co-oxidant led to a significant improvement. Recourse to BAIB as a co-oxidant delivered cleanly the oxidation product.<sup>[35]</sup> Unfortunately, fast protodesannylation of **23** upon purification or even shelf storage was observed. Therefore, the crude product was directly subjected to crotyltitanation conditions with racemic (±)-**2**. The *O*-enecarbamate (±)-**24** was then converted into terminal alkyne (±)-**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, the 12-desmethyl C8–C14 fragment (±)-**24** could be obtained in only four steps, from commercially available 2,3-dihydrofuran **8**, in 26.9% overall yield.

With secured information on the C14 tin function stability in hand, the stage was set for the synthesis of DHF **9** bearing a methyl group at the C12-position (Scheme 5). Prepara-

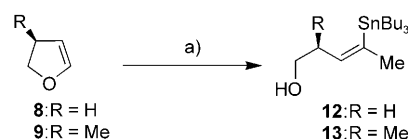


Scheme 5. a) NaCN, DMSO, 60°C, 24 h, 92%; b) DIBAL-H, CH<sub>2</sub>Cl<sub>2</sub>, -78°C, 2 h, 82%; c) PTSA, quinoline, 160°C→245°C, 45 min, 85%. DIBAL-H = diisobutylaluminum hydride.

tion of DHF **9** was achieved from 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 cyclization of the  $\gamma$ -hydroxy aldehyde.

After several attempts, a straightforward dehydration with PTSA in quinoline with simultaneous distillation of the volatile elimination product from the reaction mixture cleanly afforded the desired DHF **9** in 85% yield (Scheme 5).<sup>[36]</sup> This expeditious three-step sequence furnished the enantiopure DHF **9** in 64% overall yield.

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 disappointing 27% yield (Scheme 6; Table 1,



Scheme 6. Cuprate rearrangement with methyl transfer from DHF **8** or **9**. a) 1) *t*BuLi (1.2 equiv), THF, -60°C 10 min then 0°C 50 min; 2) MeLi (5 equiv), CuCN (2 equiv), Et<sub>2</sub>O, additive (see Table 1), 0°C→RT; 3) *n*Bu<sub>3</sub>SnCl, -30°C→RT, 5 h.

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

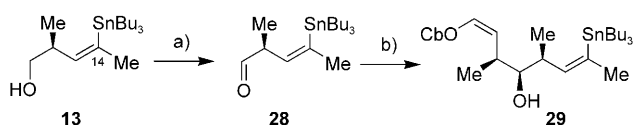
Entry	Starting material	Additive	Conditions	Yield of ( <i>Z</i> )- <b>12</b> or ( <i>Z</i> )- <b>13</b> [%]
1	<b>8</b>	none <sup>[a,b]</sup>	RT, 3 h	61
2	<b>9</b>	none <sup>[a,b]</sup>	RT, 3 h	27
3	<b>8</b>	BF <sub>3</sub> ·OEt <sub>2</sub> (2.5 equiv) <sup>[a,b]</sup>	RT, 3 h	13
4	<b>8</b>	TMSCl (4 equiv) <sup>[a,b]</sup>	RT, 3 h	46
5	<b>8</b>	HMPA (5 equiv) <sup>[a,b]</sup>	RT, 3 h	29
6	<b>8</b>	DMPU (5 equiv) <sup>[a,b]</sup>	RT, 3 h	0
7	<b>8</b>	DMF (20 equiv) <sup>[a,b]</sup>	RT, 3 h	0
8	<b>8</b>	TMEDA (10 equiv) <sup>[a,b]</sup>	RT, 3 h	45
9	<b>8</b>	pyridine (10 equiv) <sup>[a,b]</sup>	RT, 3 h	16
10	<b>8</b>	thiophene (20 equiv) <sup>[a,b]</sup>	RT, 12 h	55
11	<b>8</b>	tetrahydro-thiophene (20 equiv) <sup>[a,b]</sup>	RT, 12 h	67
12	<b>8</b>	DMS (Et <sub>2</sub> O/DMS 4:1) <sup>[b]</sup>	RT, 12 h	76
13	<b>8</b>	none <sup>[a,c]</sup>	RT, 3 h	22
14	<b>9</b>	DMS (Et <sub>2</sub> O/DMS 4:1) <sup>[b]</sup>	RT, 12 h	68

[a] THF/Et<sub>2</sub>O 1:2. [b] MeLi/CuCN. [c] MeMgBr (4 equiv), CuBr·Me<sub>2</sub>S (2 equiv). DMPU = *N,N'*-dimethylpropyleneurea; HMPA = hexamethylphosphoramide.

entry 2). To improve this result, 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/Et<sub>2</sub>O solvent mixture. The results, from commercial DHF **8** as a model, are summarized in Table 1. 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, the use of sulfur additives resulted in appreciable yields (Table 1, entries 10–12). Thereby, a 4:1 mixture of Et<sub>2</sub>O and 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·Me<sub>2</sub>S (Table 1, entry 13), versus cyanocuprates, gave disappointing results and yields remained below 22%.

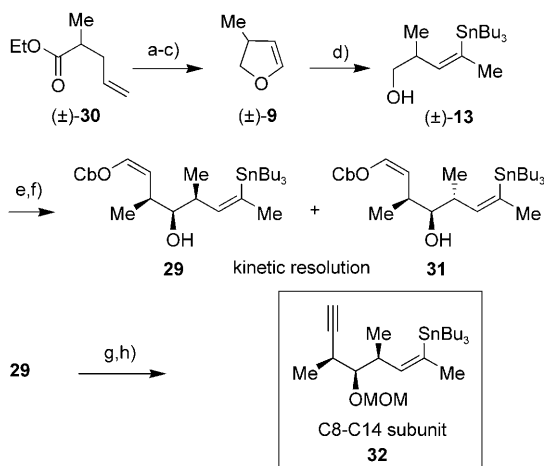
Application of optimized conditions to DHF **9** led to the (*Z*)-tin derivative **13** in a substantial 68% yield (Table 1, entry 14).

We developed a useful and efficient dimethylsulfide-promoted methyl transfer in the 1,2-cuprate rearrangement leading to (*Z*)-trisubstituted olefins. With an efficient supply of alkene **13** being assured, the synthesis of the C8–C14 subunit **B** was tackled. In agreement with the model C12-desmethyl series, compound **13** was converted to carbamate **29** as a single diastereomer in 87% yield after oxidation to aldehyde **28** with TEMPO/BAIB and crotyltitanation (Scheme 7). To confirm the (*S*)-C11 secondary hydroxy center configuration, **29** was derivatized to the (*R*)- and (*S*)- $\alpha$ -methoxy-phenylacetic acid (MPA) ester (see the Experimental Section for details).<sup>[37]</sup>



Scheme 7. a) TEMPO (10 mol %), BAIB, CH<sub>2</sub>Cl<sub>2</sub>, RT, 2 h; b) (*R*)-**2**, cyclohexane/pentane 1:7, –78°C, 3 h, 87% (2 steps, a and b).

DHF **9** was also prepared in racemic form. After some experimentation, it was found that the most effective approach started from commercially available ethyl 2-methyl-4-pentenoate ((±)-**30**) (Scheme 8). Reduction of ester function followed by ozonolysis of the terminal double bond and dehydration of the corresponding lactol led to the desired DHF (±)-**9**. Oxidation of the 1,2-cuprate transfer product (±)-**13**

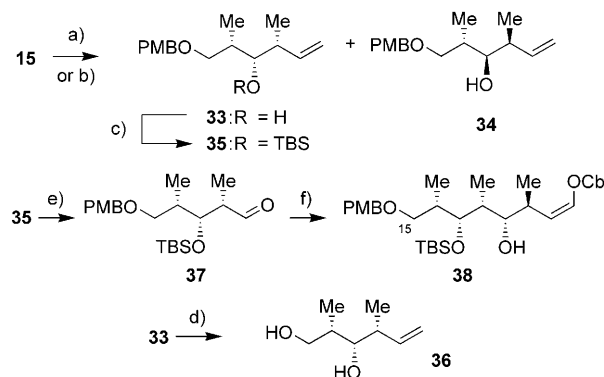


Scheme 8. a) LAH, Et<sub>2</sub>O, 0°C→RT, 3 h; b) O<sub>3</sub>, Sudan III, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 1:1, –78°C, 7 h then PPh<sub>3</sub>, –78°C→RT, overnight, 80% (2 steps, a and b), anomeric ratio 2:1; c) PTSA, quinoline, 160–245°C, 45 min, 85%; d) *t*BuLi, Me<sub>2</sub>CuLi–LiCN, Et<sub>2</sub>O/DMS 4:1, 0°C→RT, 18 h, then *n*Bu<sub>3</sub>SnCl, –30°C→RT, 5 h, 68%; e) TEMPO (10 mol %), BAIB, CH<sub>2</sub>Cl<sub>2</sub>, RT, 2 h; f) (*R*)-**2**, cyclohexane/pentane 1:7, –78°C, 3 h, compound **29** 42% (2 steps, e and f), compound **31** 14% (2 steps, e and f); g) *t*BuLi, THF, –40→–20°C, 20 min, 78%; h) MOMCl, TBAI, Hunig's base, CH<sub>2</sub>Cl<sub>2</sub>, RT, 18 h, 92%. DMS = dimethyl sulfide; Hunig's base = diisopropylethylamine; LAH = lithium aluminum hydride; MOM = methoxymethyl; TBAI = tetra-*n*-butylammonium iodide.

followed by 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.

From carbamate **29**,  $\alpha$ -elimination reaction upon a *t*BuLi treatment and subsequent C11 secondary alcohol protection as the methoxymethyl ether furnished alkyne **32** (Scheme 8). Subunit **32** was obtained in eight steps in 13.9 or 26.3% yields, respectively, from pentenoate (±)-**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 using the racemic DHF (±)-**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 **15** under Keck's conditions (BF<sub>3</sub>·OEt<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub>),<sup>[38]</sup> led to a 85:15 mixture of diastereomers **33** and **34**. Felkin–Anh selectivity was optimized to 95:5 when replacing CH<sub>2</sub>Cl<sub>2</sub> by Et<sub>2</sub>O and performing the reaction at a lower temperature (Scheme 9). Howev-



Scheme 9. a) Tri-*n*-butylcrotylstannane, BF<sub>3</sub>·OEt<sub>2</sub>, Et<sub>2</sub>O, –100°C, 2 h, 74%, d.r. 95:5; b) (*Z*)-2-butene, *n*BuLi, *t*BuOK, [(–)-Ipc]<sub>2</sub>BOMe, BF<sub>3</sub>·OEt<sub>2</sub>, 65%, d.r. 100:0; c) TBSOTf, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>, 0°C→RT, 2 h, 92%; d) DDQ, CH<sub>2</sub>Cl<sub>2</sub>/H<sub>2</sub>O 95:5, 0°C→RT, 2 h, 75%; e) O<sub>3</sub>, Sudan III, Py, CH<sub>2</sub>Cl<sub>2</sub>/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%, d.r. 100:0. Ipc = isopinocampheyl, Py = pyridine.

er, large-scale production of **33** was impeded by difficulties associated with diastereomer separation. This difficulty was readily overcome by using the chiral crotylborane procedure developed by Brown.<sup>[39]</sup> The desired homoallylic alcohol **33** was cleanly formed in a stereospecific manner from the (*Z*)-crotyldiisopinocampheylborane reagent derived from (–)-Ipc<sub>2</sub>B(OMe).

The absolute configuration of the stereogenic centers of **33** was confirmed by chemical correlation. Cleavage of the PMB moiety was accomplished to provide the known triol **36**. The NMR spectroscopic data and the specific optical rotation were in agreement with the literature.<sup>[40]</sup>

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 total stereocontrol.

On the basis of extensive precedent, we predicted that the unique isomer from this addition would be the C18–C20 *syn-anti* stereoisomer **38**. This assignment was confirmed by applying the Rychnovsky method<sup>[41]</sup> and analysis of the <sup>1</sup>H NMR vicinal coupling constants of the corresponding acetones (see the Experimental Section for details).

Application of this crotyltitanation reaction was also instrumental in the preparation of the required terminal (*Z*)-diene. As previously described by our group,<sup>[11]</sup> the direct vinylation of a (*Z*)-*O*-enecarbamate moiety was carried out in the presence of [Ni(acac)<sub>2</sub>] 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 vi-

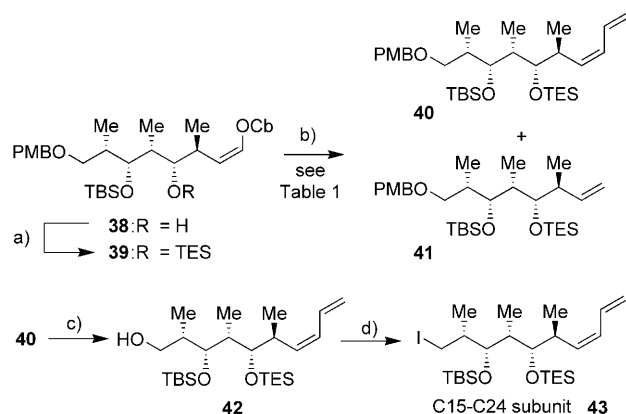
nylmagnesium bromide solution was unreliable for this cross-coupling. Furthermore, even with the same batch, the selectivity between the cross-coupled product and the reduced compound decreased during the time of storage. We decided to prepare ourselves the vinylmagnesium bromide. Three methods were explored. First, direct insertion of magnesium into vinyl bromide<sup>[42]</sup> led to reliable results but with a modest selectivity in favor of the desired compound **40**, that is, 80:20 (Table 2, entry 2). The vinylmagnesium reagent was also generated in situ, by transmetalation of the vinyl-lithium derivative with magnesium bromide.<sup>[43]</sup> When the vinyl-lithium was produced from vinyl bromide by metal-halogen exchange,<sup>[44]</sup> no reaction occurred (Table 2, entry 3). On the other hand, the preparation of the vinyl-lithium from tetra-*v*inyltin and MeLi,<sup>[45]</sup> cleanly afforded the cross-coupled product **40** in modest yield (Table 2, entry 4).

The reaction with solely vinyl-lithium species (without magnesium salts) produced from tetra-*v*inyltin and MeLi,<sup>[45]</sup> led to a significant improvement (Table 2, entry 5). This method allowed the selective formation of the cross-coupled product **42** in a reproducible 80% yield (no reduction product was recovered). Use of tetra-*v*inylstannane and MeLi allowed the scaling up the cross-coupling reaction to 2.5 g. To the best of our knowledge, it is the first example of a C(sp<sup>2</sup>)-C(sp<sup>2</sup>) cross-coupling between a vinyl-lithium and a vinylic electrophilic species.<sup>[46]</sup>

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.<sup>[47]</sup> The C15–C24 subunit **43**, bearing five contiguous stereogenic centers 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** started 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). It was envisaged to rely upon a substrate-directable epoxidation/oxirane regioselective ring-opening sequence for the installation of the missing C5 chiral center. The epoxidation of homoallylic alcohol **45** turned out to be more difficult than expected. The use of *m*CPBA, [Mo(CO)<sub>6</sub>]/TBHP<sup>[48]</sup> or [VO(O*i*Pr)<sub>3</sub>]/TBHP never gave more than 40% selectivity, whereas recourse to [VO(acac)<sub>2</sub>]/TBHP<sup>[49]</sup> 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 scaling up, this reaction was not reproducible. Pure **46** was then subjected to a regioselective ring opening by a cyanogilman divinyl cuprate, (CH<sub>2</sub>=CH)<sub>2</sub>CuLi·LiCN,<sup>[50]</sup> to ensure the formation of the alkene **48** in 86% yield. Finally, cleavage of the *OBn* 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 center by hetero-Michael addition on  $\alpha,\beta$ -unsaturated Weinreb amide **53**, which in turn could be derived from aldehyde **50** through a crotyltitanation reaction and homo-

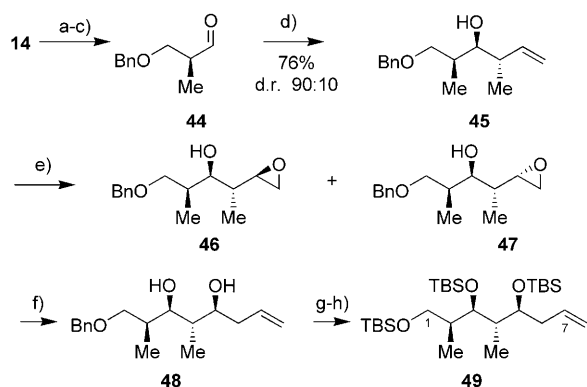


Scheme 10. a) TESOTf, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>, 0°C→RT, 1.5 h, 76%; b) [Ni(acac)<sub>2</sub>], Et<sub>2</sub>O, 0°C, overnight, vinylmagnesium bromide, see Table 1; c) DDQ, CH<sub>2</sub>Cl<sub>2</sub>/H<sub>2</sub>O 95:5, 0°C→RT, 40 min, 72%; d) I<sub>2</sub>, PPh<sub>3</sub>, imid, C<sub>6</sub>H<sub>6</sub>/Et<sub>2</sub>O, 0°C→RT, 2 h, 79%. acac = acetylacetonate; imid = imidazole.

Table 2. Results of direct vinylation of a (*Z*)-*O*-enecarbamate by a [Ni(acac)<sub>2</sub>]-catalyzed cross-coupling reaction from compound **39**.

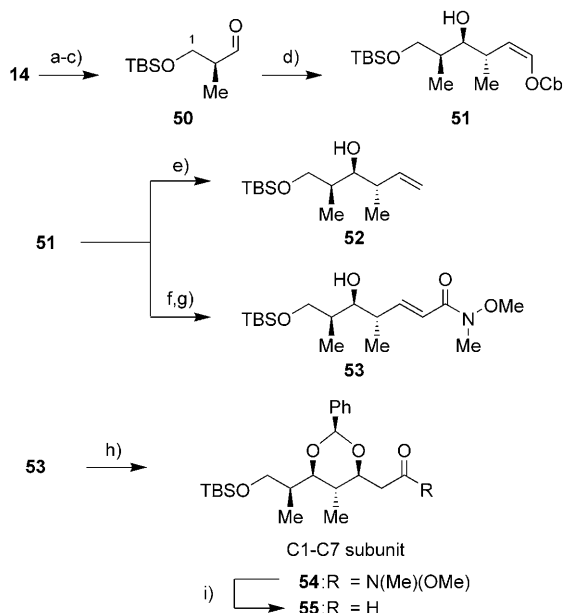
Entry	Conditions	<b>40</b>	<b>41</b>	Yield [%] <sup>[a]</sup>
1	CH <sub>2</sub> =CH–MgBr <sup>[b]</sup>	100→0	0→100	35→80
2	CH <sub>2</sub> =CH–Br, Mg	80	20	65
3	CH <sub>2</sub> =CH–Br, <i>t</i> BuLi, MgBr <sub>2</sub> ·OEt <sub>2</sub>	–	–	– <sup>[c]</sup>
4	(CH <sub>2</sub> =CH) <sub>4</sub> Sn, MeLi,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

[a] Isolated yield of the **40** and **41** mixture. [b] Commercial reagent. [c] Only the starting material was recovered. [d] 10% of starting material was recovered.



Scheme 11. a)  $\text{CCl}_3\text{C}(\text{N})\text{OBn}$ ,  $\text{TfOH}$  (5 mol %),  $\text{CH}_2\text{Cl}_2/\text{cyclohexane}$  1:2,  $0^\circ\text{C}\rightarrow\text{RT}$ , 40 h, 84%; b) LAH, THF,  $0^\circ\text{C}\rightarrow\text{RT}$ , 3 h, 94% c) IBX, DMSO, RT, 3 h, 92%; d) (*E*)-2-butene, *n*BuLi, *t*BuOK,  $[(-)\text{-Ipc}]_2\text{BOMe}$ ,  $\text{BF}_3\cdot\text{OEt}_2$ , 76%, d.r. 90:10; e)  $[\text{VO}(\text{acac})_2]$ , TBHP,  $\text{CH}_2\text{Cl}_2$ , 78%, d.r. 90:10; f)  $\text{CH}_2=\text{CH}-\text{Br}$ , *t*BuLi, CuCN, THF,  $-78\rightarrow 0^\circ\text{C}$ , overnight, 86%; g) Li,  $\text{NH}_3$ , THF,  $-78^\circ\text{C}$ , 1 h; h) TBSOTf, 2,6-lutidine,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}\rightarrow\text{RT}$ , 3 h, 99% (2 steps, g and h). TBHP = *tert*-butyl hydroperoxide.

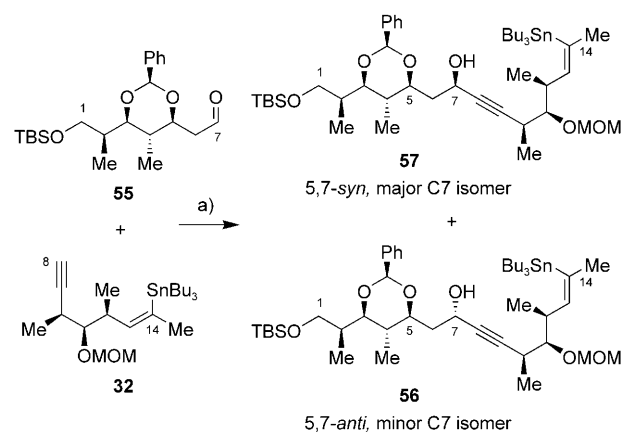
gation (Scheme 12). Thus, crotyltitanation of aldehyde **50** (which was prepared from (*S*)-Roche ester **14**) cleanly led to the *syn-anti* homoallylic alcohol **51**. A cross-metathesis (CM) reaction between alkene **51** and *N*-methoxy-*N*-methylacrylamide was tested.<sup>[51]</sup> None of the 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 electron-



Scheme 12. a) TBSCl, imid, DMF, RT, 3 h, 94%; b) DIBAL-H,  $\text{CH}_2\text{Cl}_2$ ,  $-20^\circ\text{C}$ , 30 min, 92%; c)  $(\text{COCl})_2$ , DMSO,  $\text{Et}_3\text{N}$ ,  $-55^\circ\text{C}\rightarrow\text{RT}$ , 1 h; d) (*R*)-**2**, cyclohexane/pentane 1:7,  $-78^\circ\text{C}$ , 3 h, 66% (2 steps, c and d); e)  $[\text{Ni}(\text{acac})_2]$  (10 mol %), *i*PrMgBr, THF, RT overnight, 50%; f)  $\text{O}_3$ , Sudan III,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , 1 h, then  $\text{PPh}_3$ ,  $-78^\circ\text{C}\rightarrow\text{RT}$ , 3 h, 87%; g)  $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{C}(\text{O})\text{NMe}(\text{OMe})$ , NaH, THF,  $0^\circ\text{C}\rightarrow\text{RT}$ , 45 min, 86%; h) PhCHO, KHMDS, THF,  $-20^\circ\text{C}$ , 45 min, 79%; i) DIBAL-H,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , 1 h, 93%.

ic reasons. Thus, the vinylic function of compound **51** was deoxygenated by hydride reduction with *iso*-propylmagnesium chloride in a nickel-catalyzed reaction to furnish **52**.<sup>[52]</sup> More surprisingly, the CM reactions between *N*-methoxy-*N*-methylacrylamide or methyl acrylate and terminal olefinic compound **52** failed when using Grubbs 2nd-generation or Hoveyda catalyst. Gratifyingly, a two-step sequence involving an oxidative cleavage of the double bond, followed by a Horner–Wadsworth–Emmons reaction (HWE) with commercially available diethyl (*N*-methoxy-*N*-methylcarbamoylmethyl)phosphonate, gave the  $\alpha,\beta$ -unsaturated Weinreb amide **53**. Reaction of **53** with benzaldehyde mediated by KHMDS afforded benzylidene **54** in 79% yield with an excellent diastereoselectivity (d.r. > 95:5).<sup>[53]</sup> After reduction of **54** into aldehyde **55** by treatment with DIBAL-H,<sup>[54]</sup> the last C1–C7 subunit, bearing four stereocenters, was obtained in 32.7% overall yield for eight steps.

**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 sta-



Scheme 13. a) **32**, *t*BuLi, THF,  $-78^\circ\text{C}$ , 30 min, then **55**,  $-78\rightarrow 0^\circ\text{C}$ , 3 h, 50%, d.r. 1:2.

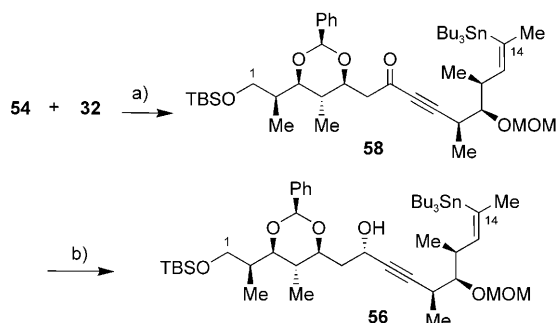
bility of the sterically hindered trisubstituted (*Z*)-vinyl stannane provided encouraging precedent with regard to the chemoselectivity issue. Although the lithiated acetylide of **32** was chemoselectively produced by action of *t*BuLi at low temperature, its reaction with aldehyde **55** afforded a 2:1 mixture of separable C7 diastereomers **56** and **57** in a modest 50% yield.

To assign the C7 stereochemistry of both these epimers, each C7 isomeric secondary alcohol was independently subjected to the formation of (*R*)- and (*S*)-MPA ester derivatives (see the Experimental Section for details). To our surprise, the desired and expected 5,7-*anti* diol **56** was the minor product (Scheme 13).<sup>[55]</sup>

A more appropriate solution was found with the addition of acetylenic derivative **32** to Weinreb amide **54** followed by



stereoselective reduction of ynone **58** (Scheme 14). Preliminary assays were conducted by using *t*BuLi as a metallating agent and afforded cleanly the desired adduct **58** in 80% yield. However, upon attempted optimization and scale up,

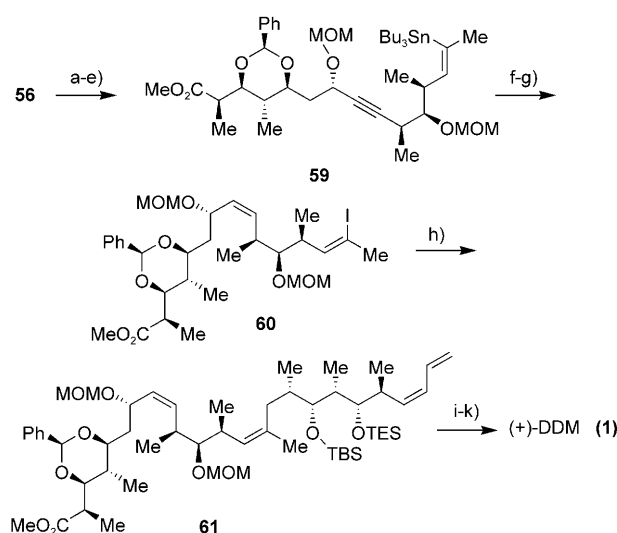


Scheme 14. a) **32**, *n*BuLi/Et<sub>2</sub>O, THF, -40°C, 50 min, then **54**, -40 → >0°C, 1 h, 81%; b) (*S*)-(-)-2-methyl-CBS-oxazaborolidine, BH<sub>3</sub>·Me<sub>2</sub>S, THF, -30°C, 2 h, 95%, d.r. 98:2. CBS = Corey–Bakshi–Shibata.

this reaction was not reproducible. During these initial attempts, however, it was noticed that Weinreb amide **54** was totally consumed with the production of a significant amount of benzaldehyde, which indicated a probable retro-hetero-Michael reaction, followed by a vinylogous retroaldol reaction. After careful optimization, it was found that this addition reaction proceeded best when using a solution of *n*BuLi generated by treatment of butyl bromide by lithium metal in Et<sub>2</sub>O,<sup>[56]</sup> 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<sup>[57]</sup> provided alcohol **56** in high yield (95%) and diastereoselectivity (d.r. > 98:2).

The 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 reaction and TBS-ether cleavage protocol followed by oxidation of the resulting alcohol and esterification (Scheme 15). Subsequent standard Lindlar hydrogenation of the alkyne **59** seemed optimal relative to the discodermolide C8=C9 semi-reduction cases previously reported in the literature.<sup>[4]</sup> However, this reduction only resulted in recovery of the starting material. After some experimentation, it was found that the reaction preceded best when using a PtO<sub>2</sub> 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 subunit **43**. An alkyl-Suzuki reaction was performed according to the Marshall et al. procedure,<sup>[58]</sup> by using trialkyl boronate species prepared from alkyl iodide **43** with *t*BuLi and *B*-methoxy-9-BBN under [PdCl<sub>2</sub>(dppf)] and AsPh<sub>3</sub> conditions to afford the discodermolide backbone **60** in 60% yield.



Scheme 15. a) MOMCl, TBAI, Hunig's base, CH<sub>2</sub>Cl<sub>2</sub>, RT, 18 h, 86%; b) HF/Py, Py/THF, RT, 4 h, 96%; c) TEMPO (10 mol%), BAIB, CH<sub>2</sub>Cl<sub>2</sub>, RT, 3 h; d) NaClO<sub>2</sub>, NaH<sub>2</sub>PO<sub>4</sub>, 2-methyl-but-2-ene, *t*BuOH/H<sub>2</sub>O, RT, 1 h; e) TMSCHN<sub>2</sub>, C<sub>6</sub>H<sub>6</sub>/MeOH, RT, 15 min, 66% (3 steps, c–e); f) H<sub>2</sub>, PtO<sub>2</sub> (30 mol%), AcOEt, RT, 12 h; g) I<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0°C, 10 min, 71% (2 steps, f and g); h) **43**, *t*BuLi, Et<sub>2</sub>O, -78°C, 5 min, *B*-methoxy-9-BBN, THF, -78°C → RT, then **60**, Cs<sub>2</sub>CO<sub>3</sub>, [PdCl<sub>2</sub>(dppf)], AsPh<sub>3</sub>, DMF, H<sub>2</sub>O, 18 h, 60%; i) PSA, MeOH, 0°C, 1 h, 77%; j) Cl<sub>3</sub>CC(O)NCO, CH<sub>2</sub>Cl<sub>2</sub>, RT, 15 min, then K<sub>2</sub>CO<sub>3</sub>, MeOH, RT, 1.5 h, 64%; k) HCl 4 N, THF, RT, 72 h, 70%. BBN = borabicyclo[3.3.1]nonane; dppf = (diphenylphosphino)ferrocene.

Selective cleavage of the C19 TES-ether followed by reaction with trichloroacetylisocyanate furnished the corresponding carbamate.<sup>[59]</sup> Final total deprotection with concomitant lactonization by following the procedure established in the previous total syntheses<sup>[4]</sup> afforded discodermolide **1** in 70% yield. The spectroscopic and analytical data of the synthetic samples of **1** and their *in vitro* cytotoxicity levels were in full accord with those of the natural product reported in the literature.

## Conclusions

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



For 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 and the construction of the middle C8–C14 fragment in two sequential stages (dyotropic rearrangement/crotyltitanation). 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 dis-codermolide structural analogues.

## Experimental Section

**General:** All reactions were carried out in oven or flame-dried glassware under an argon atmosphere by employing standard techniques in handling air-sensitive materials. All solvents employed were reagent grade. THF and diethyl ether (Et<sub>2</sub>O) were freshly distilled from sodium/benzophenone under nitrogen immediately prior to use. Dichloromethane, cyclohexane and pentane were freshly distilled over calcium hydride. All other reagents were used as supplied. Reactions were magnetically stirred and monitored by TLC 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 by 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. <sup>1</sup>H NMR spectra were recorded by using an internal deuterium lock at ambient temperature on a JEOL JNM-ECX 270 or 400 MHz spectrometer. Internal references of δ<sub>H</sub> = 7.26 and 1.96 ppm were used for CDCl<sub>3</sub> and CD<sub>3</sub>CN, respectively. Spectroscopic data are represented as follows: chemical shift (in ppm), multiplicity (s = single, d = doublet, t = triplet, q = quartet), integration, coupling constant (*J*/Hz<sup>-1</sup>). <sup>13</sup>C NMR spectra were recorded on a Jeol 67.5 or 100.5 MHz spectrometer. Internal references of δ<sub>C</sub> = 77.16 and 118.26 ppm were used for CDCl<sub>3</sub> and CD<sub>3</sub>CN, respectively. IR spectra were recorded on a Nicolet Impact-400 and wavelength ( $\bar{\nu}$ ) is given in cm<sup>-1</sup>. 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, CH<sub>4</sub>). Mass spectral data are reported as *m/z*. Optical rotations were recorded on a Jasco P-1010 digital polarimeter at 589 nm and are reported as follows: [ $\alpha$ ]<sub>D</sub><sup>20</sup>, concentration (*c* in g/100 mL), and solvent. Elemental analysis were performed on a CHN 240 Perkin–Elmer instrument by the Service de Microanalyses, Centre d'Etudes Pharmaceutiques, Chatenay-Malabry, F-92296. HRMS were obtained on a Thermo-Electron MAT-95 spectrometer in the ICMMO, Mass Spectrometry Laboratory, Orsay University, 91405 Orsay. IUPAC nomenclature was used for all compounds. RN refers CAS registration numbers. See Supporting Information for further experimental procedures.

**(3Z)-4-(Tributylstanny)pent-3-en-1-ol (23):** BAIB (10.4 g, 32.2 mmol, 1.1 equiv) was added 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 CH<sub>2</sub>Cl<sub>2</sub> (100 mL). The mixture was stirred until the starting material had disappeared (2 h). After this time, the mixture was diluted with cyclohexane, washed with an aqueous saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution and extracted with cyclohexane. The combined organic phases were washed with a saturated aqueous NaHCO<sub>3</sub> solution and brine, dried over MgSO<sub>4</sub>, and the solvent was removed under reduced pressure. The crude aldehyde **23** was directly used in the next step. <sup>1</sup>H NMR (400.0 MHz, CDCl<sub>3</sub>): δ = 9.67 (t, *J* = 2.1 Hz, 1H), 6.16 (tq, *J* = 7.3, 1.9, *J*<sub>H<sub>17</sub>Sn</sub> = *J*<sub>H<sub>19</sub>Sn</sub> = 122.1 Hz, 1H), 2.89 (dd, *J* = 7.3, 2.1 Hz, 2H), 1.98 (d, *J* = 1.9, *J*<sub>H<sub>17</sub>Sn</sub> = *J*<sub>H<sub>19</sub>Sn</sub> = 38.9 Hz, 3H;

CH<sub>3</sub>), 1.60–1.40 (m, 6H; 3 CH<sub>2</sub>), 1.39–1.20 (m, 6H; 3 CH<sub>2</sub>), 1.02–0.84 ppm (m, 15H; 3 CH<sub>2</sub>, 3 CH<sub>3</sub>).

**(1Z,6Z,3R/S,4R/S)-1-[(*N,N*-Diisopropyl)carbamoyloxy]-4-hydroxy-3-methyl-7-(tributylstanny)oct-1,6-diene ((±)-24):** A solution of *n*BuLi (1.6 M in hexane, 44 mL, 70.0 mmol, 2.04 equiv) was added 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 Et<sub>2</sub>O (70 mL) at –78°C. After 30 min at –78°C, Ti(O*i*Pr)<sub>4</sub> (52.0 mL, 176.0 mmol, 6.0 equiv) was quickly added by 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 Et<sub>2</sub>O (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 Et<sub>2</sub>O-saturated aqueous NH<sub>4</sub>Cl solution. After extraction with Et<sub>2</sub>O, the organic layer was washed with brine, dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/Et<sub>2</sub>O 95:5 to 60:40) to give the title compound ((±)-**24** (7.4 g, 44% for 2 steps). <sup>1</sup>H NMR (400.0 MHz, CDCl<sub>3</sub>): δ = 7.12 (d, *J* = 6.4 Hz, 1H), 6.10 (ddq, *J* = 5.9, 5.5, 1.4, *J*<sub>H<sub>17</sub>Sn</sub> = *J*<sub>H<sub>19</sub>Sn</sub> = 131.0 Hz, 1H), 4.67 (dd, *J* = 9.9, 6.4 Hz, 1H), 4.19–4.11 (brs, 1H), 3.80–3.75 (brs, 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, *J*<sub>H<sub>17</sub>Sn</sub> = *J*<sub>H<sub>19</sub>Sn</sub> = 41.7 Hz, 3H; CH<sub>3</sub>), 1.78 (brd, *J* = 3.0 Hz, 1H; OH), 1.58–1.38 (m, 6H; 3 CH<sub>2</sub>), 1.38–1.17 (m, 18H; 3 CH<sub>2</sub>, 4 CH<sub>3</sub>), 1.07 (d, *J* = 7.3 Hz, 3H; CH<sub>3</sub>), 0.96–0.85 ppm (m, 15H; 3 CH<sub>2</sub>, 3 CH<sub>3</sub>); <sup>13</sup>C NMR (100.5 MHz, CDCl<sub>3</sub>): δ = 152.3 (C), 141.9 (C), 136.4 (*J*<sub>13C,17Sn</sub> = *J*<sub>13C,19Sn</sub> = 28.1 Hz; CH), 135.3 (CH), 111.9 (CH), 74.1 (CH), 45.4 (CH), 45.2 (CH), 39.6 (*J*<sub>13C,17Sn</sub> = *J*<sub>13C,19Sn</sub> = 30.7 Hz; CH<sub>2</sub>), 35.4 (CH), 28.8 (*J*<sub>13C,17Sn</sub> = *J*<sub>13C,19Sn</sub> = 19.2 Hz; 3 CH<sub>2</sub>), 27.5 (*J*<sub>13C,17Sn</sub> = *J*<sub>13C,19Sn</sub> = 56.5 Hz; 3 CH<sub>2</sub>), 26.8 (*J*<sub>13C,17Sn</sub> = *J*<sub>13C,19Sn</sub> = 46.0 Hz; CH<sub>3</sub>), 21.1 (2 CH<sub>3</sub>), 20.3 (2 CH<sub>3</sub>), 17.0 (CH<sub>3</sub>), 13.2 (3 CH<sub>3</sub>), 9.6 ppm (*J*<sub>13C,17Sn</sub> = 313.4, *J*<sub>13C,19Sn</sub> = 326.8 Hz; 3 CH<sub>2</sub>); IR (film):  $\bar{\nu}$  = 3470, 2957, 2925, 2872, 2855, 1712, 1705, 1679, 1642, 1456, 1444, 1371, 1306, 1211, 1147, 1134, 1065, 1001, 961, 903, 885, 865, 762 cm<sup>-1</sup>.

**(3R/S,4R/S,6Z)-4-Hydroxy-3-methyl-7-(tributylstanny)oct-6-en-1-yne ((±)-25):** A solution of *t*BuLi (1.5 M in pentane, 27.2 mL, 40.8 mmol, 3.0 equiv) was slowly added to a solution of the preceding carbamate ((±)-**24** (8.4 g, 13.6 mmol, 1.0 equiv) in Et<sub>2</sub>O (100 mL) at –40°C. The solution was stirred for 20 min at –20°C and was then quenched by the addition of a saturated aqueous NH<sub>4</sub>Cl solution, and extracted with Et<sub>2</sub>O. The combined organic phases were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel (cyclohexane/Et<sub>2</sub>O 90:10 to 80:20) to give ((±)-**25** (4.7 g, 78%). <sup>1</sup>H NMR (270.0 MHz, CDCl<sub>3</sub>): δ = 6.00 (ddq, *J* = 7.7, 6.5, 1.7, *J*<sub>H<sub>17</sub>Sn</sub> = *J*<sub>H<sub>19</sub>Sn</sub> = 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, *J*<sub>H<sub>17</sub>Sn</sub> = *J*<sub>H<sub>19</sub>Sn</sub> = 41.6 Hz, 3H; CH<sub>3</sub>), 1.50–1.33 (m, 6H; 3 CH<sub>2</sub>), 1.32–1.11 (m, 10H; 1 OH, 1 CH<sub>3</sub>, 3 CH<sub>2</sub>), 0.98–0.74 ppm (m, 15H, 3 CH<sub>2</sub>, 3 CH<sub>3</sub>); <sup>13</sup>C NMR (67.5 MHz, CDCl<sub>3</sub>): δ = 142.8 (C), 136.1 (*J*<sub>13C,17Sn</sub> = *J*<sub>13C,19Sn</sub> = 26.8 Hz; CH), 85.1 (C), 74.0 (CH), 71.0 (CH), 40.1 (CH<sub>2</sub>), 32.2 (CH), 29.2 (*J*<sub>13C,17Sn</sub> = *J*<sub>13C,19Sn</sub> = 19.5 Hz; 3 CH<sub>2</sub>), 27.4 (*J*<sub>13C,17Sn</sub> = *J*<sub>13C,19Sn</sub> = 56.2 Hz; 3 CH<sub>2</sub>), 17.3 (CH<sub>3</sub>), 13.7 (3 CH<sub>3</sub>), 9.6 ppm (*J*<sub>13C,17Sn</sub> = 314.4, *J*<sub>13C,19Sn</sub> = 328.8 Hz; 3 CH<sub>2</sub>); IR (film):  $\bar{\nu}$  = 3311, 2956, 2926, 2871, 2854, 1712, 1463, 1376, 1260, 1192, 1072, 1039, 960 cm<sup>-1</sup>.

**(2R/S,4R/S)-4-Methyltetrahydrofuran-2-ol ((±)-27):** A solution of commercial ethyl 4-methylpentenoate ((±)-**30** (30 g, 211 mmol, 1.0 equiv) in Et<sub>2</sub>O (200 mL) was added to a solution of LiAlH<sub>4</sub> (6.4 g, 169 mmol, 0.8 equiv) in Et<sub>2</sub>O (100 mL) at 0°C over 30 min. After the reaction mixture had been stirred for 4 h at 20°C, the mixture was cooled at 0°C and H<sub>2</sub>O (6.5 mL), an aqueous NaOH 15% solution (6.5 mL), and further H<sub>2</sub>O (19.5 mL) were added successively. The mixture was stirred for 2 h, and filtered through a pad of Celite. The filtrate was dried over MgSO<sub>4</sub> and the solvent was removed under reduced pressure. The crude 2-methylpent-4-en-1-ol was directly used in the next step. <sup>1</sup>H NMR (400.0 MHz, CDCl<sub>3</sub>): δ = 5.75 (dddd, *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 ppm (d,  $J=6.9$  Hz, 3H; CH<sub>3</sub>); <sup>13</sup>C NMR (100.5 MHz, CDCl<sub>3</sub>):  $\delta=136.9$  (CH), 116.0 (CH<sub>2</sub>), 67.7 (CH<sub>2</sub>), 37.7 (CH<sub>2</sub>), 35.5 (CH), 16.3 ppm (CH<sub>3</sub>); MS (GC, EI):  $m/z$ : 82 [M-18]<sup>+</sup>, 67, 58.

A stream of ozone was bubbled into 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 CH<sub>2</sub>Cl<sub>2</sub>/MeOH (1:1, 200 mL) at -78 °C until the pink solution became colorless (ca. 7 h). Then PPh<sub>3</sub> (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. After this time, the solvents were removed under reduced pressure (20 mmHg) and the product was distilled out of the reaction mixture by using a microdistillation apparatus under reduced pressure (0.2 mmHg) at 70 °C to give lactol ( $\pm$ )-**27** (19.7 g, 80%) as a colorless oil and a 1:2 mixture of two diastereomers. RN: 34314-85-7; first anomer: <sup>1</sup>H NMR (400.0 MHz, CDCl<sub>3</sub>):  $\delta=5.46$  (d,  $J=5.0$  Hz, 1H), 4.09 (t,  $J=7.8$  Hz, 1H; H<sub>a</sub>-11), 3.32 (dd,  $J=7.8, 7.3$  Hz, 1H; H<sub>b</sub>-11), 2.80 (brs, 1H; OH), 2.24 (dddqd,  $J=9.2, 7.8, 7.3, 6.9, 6.9$  Hz, 1H), 1.97 (dd,  $J=12.8, 6.9$  Hz, 1H), 1.51 (ddd,  $J=12.8, 9.2, 5.0$  Hz, 1H), 1.03 ppm (d,  $J=6.9$  Hz, 3H; CH<sub>3</sub>); second anomer: <sup>1</sup>H NMR (400.0 MHz, CDCl<sub>3</sub>):  $\delta=5.46$  (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 (brs, 1H; OH), 2.58–2.48 (m, 1H), 1.76–1.70 (m, 1H), 1.47–1.40 (m, 1H), 1.09 ppm (d,  $J=6.4$  Hz, 3H; CH<sub>3</sub>); first anomer: <sup>13</sup>C NMR (100.5 MHz, CDCl<sub>3</sub>):  $\delta=98.9$  (CH), 74.4 (CH<sub>2</sub>), 41.8 (CH<sub>2</sub>), 31.4 (CH), 17.8 ppm (CH<sub>3</sub>); second anomer: <sup>13</sup>C NMR (100.5 MHz, CDCl<sub>3</sub>):  $\delta=99.4$  (CH), 73.5 (CH<sub>2</sub>), 41.8 (CH<sub>2</sub>), 33.3 (CH), 17.3 ppm (CH<sub>3</sub>); IR (film):  $\tilde{\nu}=3406, 2960, 2935, 2875, 1455, 1379, 1346, 1290, 1122, 1095, 1056, 1002, 927$  cm<sup>-1</sup>; MS (GC, EI):  $m/z$ : 101, 84, 72, 56.

#### (4S)-3-Methyl-2,3-dihydrofuran (**9**) and (4R/S)-3-methyl-2,3-dihydrofuran [( $\pm$ )-**9**]

**Preparation of optically pure 9:** Sodium cyanide (4.62 g, 94.4 mmol, 1.2 equiv) was added 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). The reaction was stirred for 24 h at 20 °C. After this time, the solution was poured out into water and extracted three times with EtOAc. To extract the remainder of the compound, the aqueous solution was carefully acidified to pH 5 by using 10% sulfuric acid. After extracting the aqueous layer three more times, the combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, and the solvent was removed under reduced pressure. (2S)-3-Cyano-2-methyl propan-1-ol (7.6 g, 89%) was collected and used directly in the next step. <sup>1</sup>H NMR (400.0 MHz, CDCl<sub>3</sub>):  $\delta=3.65$  (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 ppm (d,  $J=6.9$  Hz, 3H; CH<sub>3</sub>); <sup>13</sup>C NMR (100.5 MHz, CDCl<sub>3</sub>):  $\delta=118.7$  (C), 65.6 (CH<sub>2</sub>), 32.8 (CH), 20.8 (CH<sub>2</sub>), 15.8 ppm (CH<sub>3</sub>); IR (film):  $\tilde{\nu}=3416, 2967, 2933, 2880, 2251, 1644, 1464, 1424, 1387, 1350, 1044, 993$  cm<sup>-1</sup>; MS (GC, EI):  $m/z$ : 99, 69, 59, 54.

A solution of DIBAL-H (1 M in CH<sub>2</sub>Cl<sub>2</sub>, 86 mL, 86 mmol, 2.5 equiv) was added to a solution of the preceding nitrile derivative (3.4 g, 34 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (60 mL) at -78 °C. The mixture was stirred at -78 °C until the starting material had disappeared and it was then diluted with AcOEt and poured into a solution of Rochelle's salt (C<sub>4</sub>H<sub>4</sub>KNaO<sub>6</sub>·4H<sub>2</sub>O, 78 g, 8.0 equiv). After the reaction mixture had been stirred for 12 h, it was extracted with AcOEt, and the combined organic phases were washed with brine, dried over MgSO<sub>4</sub>, and the solvent was removed under reduced pressure. (2R/S,4S)-4-Methyl tetrahydrofuran-2-ol **27** was obtained as a 1:2 diastereomeric mixture (2.87 g, 82%). RN: 34314-85-7 (see above for analytical data for racemic 4-methyltetrahydrofuran-2-ol ( $\pm$ )-**27**).

A solution of the above optically active lactol **27** (5.0 g, 49 mmol, 1.0 equiv) and PTSA (25 mg, 0.11 mmol, 0.0022 equiv) in quinoline (2.5 mL) was heated from 160 to 245 °C. Distillation of a mixture of the title compound with water was achieved in 45 min (b.p. 80–90 °C). After separation of water, dihydrofuran **9** was obtained (3.5 g, 85%). RN: 1708-27-6; <sup>1</sup>H NMR (400.0 MHz, CDCl<sub>3</sub>):  $\delta=6.30$  (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 ppm (d,  $J=6.9$  Hz, 3H; CH<sub>3</sub>); <sup>13</sup>C NMR (100.5 MHz, CDCl<sub>3</sub>):  $\delta=145.3$  (CH), 106.6 (CH), 76.8 (CH<sub>2</sub>), 36.6 (CH), 20.8 ppm (CH<sub>3</sub>).

**Preparation of ( $\pm$ )-9:** ( $\pm$ )-**9** was obtained from racemic lactol ( $\pm$ )-**27** using the procedure described for the preparation of **9** from lactol **27**.

**(2S,3Z)-2-Methyl-4-tributylstannyl-pent-3-en-1-ol (13):** MeLi (1.6 M solution in Et<sub>2</sub>O, 94.4 mL, 151.0 mmol, 5.0 equiv) was added to a suspension of CuCN (5.41 g, 60.4 mmol, 2.0 equiv) in dry Et<sub>2</sub>O (10 mL) and DMS (40 mL) at -30 °C. The solution was stirred at -30 °C for 5 min and then allowed to warm up to 0 °C for 20 min (pale-yellow color). *t*BuLi (1.5 M solution in pentane, 24.2 mL, 36.2 mmol, 1.2 equiv) was added to a solution of dihydrofuran **9** (2.54 g, 30.2 mmol, 1.0 equiv) in dry Et<sub>2</sub>O (50 mL) at -60 °C. The mixture was stirred at 0 °C for 50 min. After this time, the solution of the lithio-dihydrofuran prepared above was added by cannula to the cyanocuprate (Et<sub>2</sub>O/DMS 4:1) and the reaction mixture was allowed to warm up to 20 °C (strong orange color) 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 NH<sub>4</sub>Cl solution and concentrated ammonia (4:1) at 0 °C and stirred for 1 h at 20 °C before extraction with Et<sub>2</sub>O. The organic layer was washed with water and brine, dried over MgSO<sub>4</sub>, and the solvent was removed under reduced pressure. The crude residue was purified by chromatography on silica gel (cyclohexane/Et<sub>2</sub>O 100:0 to 60:40) to give the title compound **13** (8.21 g, 68%). <sup>1</sup>H NMR (400.0 MHz, CDCl<sub>3</sub>):  $\delta=5.78$  (dq,  $J=9.6, 1.8, J_{\text{H},^{119}\text{Sn}}=J_{\text{H},^{117}\text{Sn}}=128.7$  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 (dddq,  $J=9.6, 8.7, 8.2, 6.9$  Hz, 1H), 1.92 (d,  $J=1.8, J_{\text{H},^{117}\text{Sn}}=J_{\text{H},^{119}\text{Sn}}=41.7$  Hz, 3H; CH<sub>3</sub>), 1.55–1.45 (m, 6H; 3CH<sub>2</sub>), 1.39–1.28 (m, 7H; OH, 3CH<sub>2</sub>), 0.95 (d,  $J=6.4$  Hz, 3H; CH<sub>3</sub>), 0.99–0.91 (m, 6H; 3CH<sub>2</sub>), 0.90 ppm (m, 9H; 3CH<sub>3</sub>); <sup>13</sup>C NMR (100.5 MHz, CDCl<sub>3</sub>):  $\delta=143.0$  ( $J_{^{13}\text{C},^{117}\text{Sn}}=J_{^{13}\text{C},^{119}\text{Sn}}=27.8$  Hz; CH), 140.9 (C), 67.3 (CH), 42.4 ( $J_{^{13}\text{C},^{117}\text{Sn}}=J_{^{13}\text{C},^{119}\text{Sn}}=33.6$  Hz; CH), 29.3 ( $J_{^{13}\text{C},^{117}\text{Sn}}=J_{^{13}\text{C},^{119}\text{Sn}}=20.4$  Hz; 3CH<sub>2</sub>), 27.5 ( $J_{^{13}\text{C},^{117}\text{Sn}}=J_{^{13}\text{C},^{119}\text{Sn}}=57.5$  Hz; 3CH<sub>2</sub>), 27.2 ( $J_{^{13}\text{C},^{117}\text{Sn}}=J_{^{13}\text{C},^{119}\text{Sn}}=46.0$  Hz; CH<sub>3</sub>), 17.4 (CH<sub>3</sub>), 13.7 (3CH<sub>2</sub>), 10.1 ppm ( $J_{^{13}\text{C},^{117}\text{Sn}}=314.4, J_{^{13}\text{C},^{119}\text{Sn}}=329.7$  Hz; 3CH<sub>2</sub>); IR (film):  $\tilde{\nu}=3327, 2956, 2928, 2920, 2871, 2853, 1678, 1623, 1483, 1456, 1377, 1340, 1292, 1072, 1037, 996, 864, 690, 668$  cm<sup>-1</sup>; MS (GC, CI, NH<sub>3</sub>):  $m/z$ : 373 [MH-H<sub>2</sub>O]<sup>+</sup>, 359 [MH-H<sub>2</sub>O-Bu]<sup>+</sup>, 291 [Bu<sub>3</sub>Sn]<sup>+</sup>, 261, 249, 235, 141, 113, 101, 85, 57; elemental analysis calcd (%) for C<sub>18</sub>H<sub>38</sub>OSn: 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):** BAIB (6.09 g, 18.9 mmol, 1.1 equiv) was added 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 CH<sub>2</sub>Cl<sub>2</sub> (40 mL). The mixture was stirred until the starting material had disappeared (2 h), and was then diluted with cyclohexane, washed with an aqueous saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution, and extracted with cyclohexane. The combined organic phases were washed with a saturated aqueous NaHCO<sub>3</sub> solution and brine, dried over MgSO<sub>4</sub>, and the solvent was removed under reduced pressure until the volume was approximately equal to 20 mL. This solution can be kept only for a few hours before use (the neat product **28** is more unstable). <sup>1</sup>H NMR (400.0 MHz, CDCl<sub>3</sub>):  $\delta=9.48$  (d,  $J=1.7$  Hz, 1H), 5.72 (dq,  $J=9.7, 1.6, J_{\text{H},^{117}\text{Sn}}=J_{\text{H},^{119}\text{Sn}}=122.1$  Hz, 1H), 2.89 (dq,  $J=9.7, 6.4, 1.7$  Hz, 1H), 1.89 (d,  $J=1.6, J_{\text{H},^{117}\text{Sn}}=J_{\text{H},^{119}\text{Sn}}=40.7$  Hz, 3H; CH<sub>3</sub>), 1.47–1.37 (m, 6H; 3CH<sub>2</sub>), 1.24 (sext,  $J=7.3$  Hz, 6H; 3CH<sub>2</sub>), 1.08 (d,  $J=6.4$  Hz, 3H; CH<sub>3</sub>), 0.91–0.86 (m, 6H; 3CH<sub>2</sub>), 0.83 ppm (t,  $J=7.3$  Hz, 9H; 3CH<sub>3</sub>); <sup>13</sup>C NMR (100.5 MHz, CDCl<sub>3</sub>):  $\delta=202.1$  (CH), 146.0 ( $J_{^{13}\text{C},^{117}\text{Sn}}=346.0, J_{^{13}\text{C},^{119}\text{Sn}}=362.3$  Hz, C), 136.2 ( $J_{^{13}\text{C},^{117}\text{Sn}}=J_{^{13}\text{C},^{119}\text{Sn}}=24.9$  Hz; CH), 53.1 ( $J_{^{13}\text{C},^{117}\text{Sn}}=J_{^{13}\text{C},^{119}\text{Sn}}=31.6$  Hz; CH), 29.1 ( $J_{^{13}\text{C},^{117}\text{Sn}}=J_{^{13}\text{C},^{119}\text{Sn}}=19.2$  Hz; 3CH<sub>2</sub>), 27.4 ( $J_{^{13}\text{C},^{117}\text{Sn}}=J_{^{13}\text{C},^{119}\text{Sn}}=40.3$  Hz; CH<sub>3</sub>, CH<sub>3</sub>), 27.3 ( $J_{^{13}\text{C},^{117}\text{Sn}}=J_{^{13}\text{C},^{119}\text{Sn}}=58.5$  Hz; 3CH<sub>2</sub>), 14.4 (CH<sub>3</sub>), 13.7 (3CH<sub>2</sub>), 10.1 ppm ( $J_{^{13}\text{C},^{117}\text{Sn}}=317.3, J_{^{13}\text{C},^{119}\text{Sn}}=332.6$  Hz; 3CH<sub>2</sub>); IR (film):  $\tilde{\nu}=2958, 2927, 2872, 2854, 2809, 1726, 1614, 1463, 1426, 1377, 1072, 999, 854, 689$  cm<sup>-1</sup>; MS (GC, CI, NH<sub>3</sub>):  $m/z$ : 331 [M-Bu]<sup>+</sup>, 291 [Bu<sub>3</sub>Sn]<sup>+</sup>, 275, 255, 235, 217, 189, 177, 159, 147, 135, 121, 97.

**(2R/S,3Z)-2-Methyl-4-tributylstannyl-pent-3-en-1-ol (( $\pm$ )-13):** The same protocol used before for the synthesis of **13** was employed to prepare ( $\pm$ )-**13** (16.5 g, 67%) from ( $\pm$ )-**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** (2.5 g). 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)** and **(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**: A solution of *n*BuLi (1.6 M in hexanes, 2.4 mL, 3.95 mmol, 3.0 equiv) was added 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. After 10 min, white crystals appeared. After 3 h of crystallization at –78 °C, a pre-cooled (–40 °C) solution of Ti(O*i*Pr)<sub>4</sub> (3.5 mL, 11.9 mmol, 9.0 equiv) in pentane (7 mL) was quickly added by cannula to the reaction mixture of lithio carbamate, which became limpid 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 Et<sub>2</sub>O-saturated aqueous NH<sub>4</sub>Cl solution. After extraction with Et<sub>2</sub>O, the organic layer was washed with brine, dried over MgSO<sub>4</sub>, 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 **29** (669 mg, 87% for 2 steps) as a single diastereomer. [ $\alpha$ ]<sub>D</sub><sup>20</sup> = +20.7 (*c* = 0.94 in CHCl<sub>3</sub>); <sup>1</sup>H NMR (400.0 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.15 (d, *J* = 6.4 Hz, 1H), 6.17 (dq, *J* = 9.9, 1.4, *J*<sub>H<sub>1</sub>,<sup>17</sup>Sn</sub> = *J*<sub>H<sub>1</sub>,<sup>19</sup>Sn</sub> = 134.0 Hz, 1H), 4.66 (dd, *J* = 9.8, 6.4 Hz, 1H), 4.19–4.02 (brs, 1H), 3.78–3.61 (brs, 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, *J*<sub>H<sub>1</sub>,<sup>17</sup>Sn</sub> = *J*<sub>H<sub>1</sub>,<sup>19</sup>Sn</sub> = 42.6 Hz, 3H; CH<sub>3</sub>), 1.72 (brd, *J* = 2.8 Hz, 1H; OH), 1.55–1.45 (m, 6H; 3 CH<sub>2</sub>), 1.38–1.16 (sext, *J* = 7.3 Hz, 6H; 3 CH<sub>2</sub>), 1.20–1.12 (m, 12H; 4 CH<sub>3</sub>), 1.00 (d, *J* = 6.9 Hz, 3H; CH<sub>3</sub>), 0.98 (d, *J* = 6.8 Hz, 3H; CH<sub>3</sub>), 0.99–0.92 (m, 6H; 3 CH<sub>2</sub>), 0.89 ppm (t, *J* = 7.3 Hz, 9H; 3 CH<sub>3</sub>); <sup>13</sup>C NMR (100.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 152.9 (C), 144.3 (*J*<sub>C<sup>13</sup>,<sup>17</sup>Sn</sub> = *J*<sub>C<sup>13</sup>,<sup>19</sup>Sn</sub> = 27.8 Hz; CH), 137.7 (*J*<sub>C<sup>13</sup>,<sup>17</sup>Sn</sub> = 375.7, *J*<sub>C<sup>13</sup>,<sup>19</sup>Sn</sub> = 392.0 Hz; C), 136.7 (CH), 113.2 (CH), 78.6 (CH), 47.1 (CH), 45.7 (CH), 41.3 (*J*<sub>C<sup>13</sup>,<sup>17</sup>Sn</sub> = *J*<sub>C<sup>13</sup>,<sup>19</sup>Sn</sub> = 32.6 Hz; CH), 34.5 (CH), 29.3 (*J*<sub>C<sup>13</sup>,<sup>17</sup>Sn</sub> = *J*<sub>C<sup>13</sup>,<sup>19</sup>Sn</sub> = 19.2 Hz; 3 CH<sub>2</sub>), 27.5 (*J*<sub>C<sup>13</sup>,<sup>17</sup>Sn</sub> = *J*<sub>C<sup>13</sup>,<sup>19</sup>Sn</sub> = 57.5 Hz; 3 CH<sub>2</sub>), 27.2 (*J*<sub>C<sup>13</sup>,<sup>17</sup>Sn</sub> = *J*<sub>C<sup>13</sup>,<sup>19</sup>Sn</sub> = 46.0 Hz; CH<sub>3</sub>), 21.7 (2 CH<sub>3</sub>), 20.4 (2 CH<sub>3</sub>), 17.6 (CH<sub>3</sub>), 14.2 (CH<sub>3</sub>), 13.8 (3 CH<sub>3</sub>), 10.0 ppm (*J*<sub>C<sup>13</sup>,<sup>17</sup>Sn</sub> = 313.4, *J*<sub>C<sup>13</sup>,<sup>19</sup>Sn</sub> = 326.8 Hz; 3 CH<sub>2</sub>); IR (film):  $\tilde{\nu}$  = 3490, 2957, 2929, 2872, 2851, 1705, 1463, 1455, 1441, 1370, 1301, 1289, 1210, 1135, 1065, 997, 862, 762 cm<sup>–1</sup>; MS (GC, CI, NH<sub>3</sub>): *m/z*: 530, 385, 327, 291 [Bu<sub>3</sub>Sn]<sup>+</sup>, 257, 235, 199, 177, 12, 86, 69; elemental analysis calcd (%) for C<sub>29</sub>H<sub>57</sub>NO<sub>5</sub>Sn: C 59.39, H 9.802, N 2.39; found: C 59.51, H 9.90, N 2.30.

**From racemic aldehyde (±)-28**: A solution of *n*BuLi (1.6 M in hexane, 23 mL, 36.8 mmol, 2.14 equiv) was added 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. After 10 min, white crystals appeared. After 3 h of crystallization at –78 °C, a pre-cooled (–40 °C) solution of Ti(O*i*Pr)<sub>4</sub> (30.5 mL, 103.2 mmol, 6.0 equiv) in pentane (30 mL) was quickly added by cannula to the reaction mixture of lithio carbamate, which became limpid 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 Et<sub>2</sub>O-saturated aqueous NH<sub>4</sub>Cl solution. After extraction with Et<sub>2</sub>O, the organic layer was washed with brine, dried over MgSO<sub>4</sub>, 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 **29** (8.50 g, 42% for 2 steps; see above for data) and its 12*R* minor isomer **31** (1.41 g, 14%). <sup>1</sup>H NMR (400.0 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.10 (d, *J* = 6.9 Hz, 1H), 5.88 (dq, *J* = 9.8, 1.7, *J*<sub>H<sub>1</sub>,<sup>17</sup>Sn</sub> = *J*<sub>H<sub>1</sub>,<sup>19</sup>Sn</sub> = 128.0 Hz, 1H), 4.86 (dd, *J* = 10.1, 6.9 Hz, 1H), 4.12–3.99 (brs, 1H), 3.91–3.78 (brs, 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, *J*<sub>H<sub>1</sub>,<sup>17</sup>Sn</sub> = *J*<sub>H<sub>1</sub>,<sup>19</sup>Sn</sub> = 40.3 Hz, 3H; CH<sub>3</sub>), 1.55–1.45 (m, 6H; 3 CH<sub>2</sub>), 1.38–1.16 (sext, *J* = 7.3 Hz, 19H; 3 CH<sub>2</sub> + OH + 4 CH<sub>3</sub>), 1.13 (d, *J* = 6.9 Hz, 3H; CH<sub>3</sub>), 0.96 (d, *J* = 6.4 Hz,

3H; CH<sub>3</sub>), 0.99–0.92 (m, 6H, 3 CH<sub>2</sub>), 0.89 ppm (t, *J* = 7.3 Hz, 9H; 3 CH<sub>3</sub>); <sup>13</sup>C NMR (100.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 152.6 (C), 144.3 (*J*<sub>C<sup>13</sup>,<sup>17</sup>Sn</sub> = *J*<sub>C<sup>13</sup>,<sup>19</sup>Sn</sub> = 28.8 Hz; CH), 142.2 (*J*<sub>C<sup>13</sup>,<sup>17</sup>Sn</sub> = 355.1, *J*<sub>C<sup>13</sup>,<sup>19</sup>Sn</sub> = 372.4 Hz; C), 135.3 (CH), 111.0 (CH), 77.7 (CH), 46.6 (CH), 46.0 (CH), 44.0 (*J*<sub>C<sup>13</sup>,<sup>17</sup>Sn</sub> = *J*<sub>C<sup>13</sup>,<sup>19</sup>Sn</sub> = 29.8 Hz; CH), 32.1 (CH), 29.1 (*J*<sub>C<sup>13</sup>,<sup>17</sup>Sn</sub> = *J*<sub>C<sup>13</sup>,<sup>19</sup>Sn</sub> = 20.2 Hz; 3 CH<sub>2</sub>), 27.4 (*J*<sub>C<sup>13</sup>,<sup>17</sup>Sn</sub> = *J*<sub>C<sup>13</sup>,<sup>19</sup>Sn</sub> = 57.6 Hz; 3 CH<sub>2</sub>), 27.2 (*J*<sub>C<sup>13</sup>,<sup>17</sup>Sn</sub> = *J*<sub>C<sup>13</sup>,<sup>19</sup>Sn</sub> = 42.2 Hz; CH<sub>3</sub>), 21.4 (2 CH<sub>3</sub>), 20.3 (2 CH<sub>3</sub>), 17.3 (CH<sub>3</sub>), 13.6 (3 CH<sub>3</sub>), 10.1 ppm (*J*<sub>C<sup>13</sup>,<sup>17</sup>Sn</sub> = 315.7, *J*<sub>C<sup>13</sup>,<sup>19</sup>Sn</sub> = 330.1 Hz; 3 CH<sub>2</sub>).

**(3S,4R,5S,6Z)-3,5-Dimethyl-4-[(methoxymethyl)oxy]-7-(tributylstannyl)-oct-6-en-1-yne (32)**: A solution of *t*BuLi (1.5 M in pentane, 27.2 mL, 40.8 mmol, 3.0 equiv) was slowly added to a solution of carbamate **29** (8.4 g, 13.6 mmol, 1.0 equiv) in Et<sub>2</sub>O (100 mL) at –40 °C. The solution was stirred for 20 min at –20 °C, and was then quenched by the addition of a saturated aqueous NH<sub>4</sub>Cl solution and extracted with Et<sub>2</sub>O. The combined organic phases were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel (cyclohexane/Et<sub>2</sub>O 90:10 to 80:20) to give (3*S*,4*R*,5*S*,6*Z*)-3,5-dimethyl-4-hydroxy-7-(tributylstannyl)-oct-6-en-1-yne (**32**). [ $\alpha$ ]<sub>D</sub><sup>20</sup> = –26.8 (*c* = 1.0 in CHCl<sub>3</sub>); <sup>1</sup>H NMR (400.0 MHz, CDCl<sub>3</sub>):  $\delta$  = 5.87 (dq, *J* = 9.6, 1.8, *J*<sub>H<sub>1</sub>,<sup>17</sup>Sn</sub> = *J*<sub>H<sub>1</sub>,<sup>19</sup>Sn</sub> = 133.3 Hz, 1H), 3.17 (ddd, *J* = 9.0, 7.5, 3.2 Hz, 1H), 2.73 (dq, *J* = 7.5, 6.9, 2.3 Hz, 1H), 2.16 (dq, *J* = 9.6, 6.9, 3.2 Hz, 1H), 2.14 (d, *J* = 2.3 Hz, 1H), 1.90 (d, *J* = 1.8, *J*<sub>H<sub>1</sub>,<sup>17</sup>Sn</sub> = *J*<sub>H<sub>1</sub>,<sup>19</sup>Sn</sub> = 40.8 Hz, 3H; CH<sub>3</sub>), 1.74 (d, *J* = 9.0 Hz, 1H; OH), 1.53–1.42 (m, 6H; 3 CH<sub>2</sub>), 1.34 (sext, *J* = 7.3 Hz, 6H; 3 CH<sub>2</sub>), 1.26 (d, *J* = 6.9 Hz, 3H; CH<sub>3</sub>), 1.08 (d, *J* = 6.9 Hz, 3H; CH<sub>3</sub>), 0.98–0.91 (m, 6H; 3 CH<sub>2</sub>), 0.89 ppm (t, *J* = 7.3 Hz, 9H; 3 CH<sub>3</sub>); <sup>13</sup>C NMR (100.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 142.8 (*J*<sub>C<sup>13</sup>,<sup>17</sup>Sn</sub> = *J*<sub>C<sup>13</sup>,<sup>19</sup>Sn</sub> = 28.8 Hz; CH), 138.8 (C), 84.8 (C), 78.0 (CH), 71.5 (CH), 43.2 (*J*<sub>C<sup>13</sup>,<sup>17</sup>Sn</sub> = *J*<sub>C<sup>13</sup>,<sup>19</sup>Sn</sub> = 33.6 Hz; CH), 30.4 (CH), 29.0 (*J*<sub>C<sup>13</sup>,<sup>17</sup>Sn</sub> = *J*<sub>C<sup>13</sup>,<sup>19</sup>Sn</sub> = 19.2 Hz; 3 CH<sub>2</sub>), 27.1 (*J*<sub>C<sup>13</sup>,<sup>17</sup>Sn</sub> = *J*<sub>C<sup>13</sup>,<sup>19</sup>Sn</sub> = 58.7 Hz; 3 CH<sub>2</sub>), 27.0 (*J*<sub>C<sup>13</sup>,<sup>17</sup>Sn</sub> = *J*<sub>C<sup>13</sup>,<sup>19</sup>Sn</sub> = 44.0 Hz; CH<sub>3</sub>), 18.4 (CH<sub>3</sub>), 17.0 (CH<sub>3</sub>), 13.4 (3 CH<sub>3</sub>), 9.7 ppm (*J*<sub>C<sup>13</sup>,<sup>17</sup>Sn</sub> = 314.4, *J*<sub>C<sup>13</sup>,<sup>19</sup>Sn</sub> = 328.8 Hz; 3 CH<sub>2</sub>); IR (film):  $\tilde{\nu}$  = 3560, 350, 3456, 3310, 2957, 2926, 2872, 2854, 1463, 1455, 1376, 1247, 1115, 1070, 1050, 997, 981, 960, 873, 862, 690, 663, 631 cm<sup>–1</sup>; elemental analysis calcd (%) for C<sub>22</sub>H<sub>42</sub>O<sub>2</sub>Sn: C 59.88, H 9.59; found: C 59.99, H 9.77.

Diisopropylethylamine (27.7 mL, 159 mmol, 20 equiv) and MOMCl (6.9 mL, 79.5 mmol, 10 equiv) were added 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 CH<sub>2</sub>Cl<sub>2</sub> (40 mL) at 0 °C. After the reaction mixture had been stirred for 12 h at 20 °C, it was quenched with a saturated aqueous NaHCO<sub>3</sub> solution and extracted with Et<sub>2</sub>O. The organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude residue was purified by chromatography on silica gel (cyclohexane/Et<sub>2</sub>O 98:2 to 90:10) to give the title compound **32** (3.53 g, 92%) as a yellow oil. [ $\alpha$ ]<sub>D</sub><sup>20</sup> = –20.6 (*c* = 0.98 in CHCl<sub>3</sub>); <sup>1</sup>H NMR (400.0 MHz, CDCl<sub>3</sub>):  $\delta$  = 5.87 (d, *J* = 9.6, *J*<sub>H<sub>1</sub>,<sup>17</sup>Sn</sub> = *J*<sub>H<sub>1</sub>,<sup>19</sup>Sn</sub> = 133.3 Hz, 1H), 4.80 (d, *J* = 7.3 Hz, 1H), 4.72 (d, *J* = 7.3 Hz, 1H), 3.45 (s, 3H; CH<sub>3</sub>), 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*<sub>H<sub>1</sub>,<sup>17</sup>Sn</sub> = *J*<sub>H<sub>1</sub>,<sup>19</sup>Sn</sub> = 40.8 Hz, 3H; CH<sub>3</sub>), 1.52–1.42 (m, 6H; 3 CH<sub>2</sub>), 1.32 (sext, *J* = 7.3 Hz, 6H; 3 CH<sub>2</sub>), 1.25 (d, *J* = 7.3 Hz, 3H; CH<sub>3</sub>), 1.02 (d, *J* = 6.9 Hz, 3H; CH<sub>3</sub>), 0.97–0.93 (m, 6H; 3 CH<sub>2</sub>), 0.89 ppm (t, *J* = 7.3 Hz, 9H; 3 CH<sub>3</sub>); <sup>13</sup>C NMR (100.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 143.6 (*J*<sub>C<sup>13</sup>,<sup>17</sup>Sn</sub> = *J*<sub>C<sup>13</sup>,<sup>19</sup>Sn</sub> = 28.7 Hz, CH), 138.5 (C), 98.4 (CH<sub>2</sub>), 86.1 (C), 85.9 (CH), 70.0 (CH), 56.3 (CH<sub>3</sub>), 42.8 (*J*<sub>C<sup>13</sup>,<sup>17</sup>Sn</sub> = *J*<sub>C<sup>13</sup>,<sup>19</sup>Sn</sub> = 30.1 Hz; CH), 30.0 (CH), 27.3 (*J*<sub>C<sup>13</sup>,<sup>17</sup>Sn</sub> = *J*<sub>C<sup>13</sup>,<sup>19</sup>Sn</sub> = 20.1 Hz; 3 CH<sub>2</sub>), 27.3 (*J*<sub>C<sup>13</sup>,<sup>17</sup>Sn</sub> = *J*<sub>C<sup>13</sup>,<sup>19</sup>Sn</sub> = 59.4 Hz; 3 CH<sub>2</sub>), 27.2 (*J*<sub>C<sup>13</sup>,<sup>17</sup>Sn</sub> = *J*<sub>C<sup>13</sup>,<sup>19</sup>Sn</sub> = 40.2 Hz; CH<sub>3</sub>), 18.8 (CH<sub>3</sub>), 17.7 (CH<sub>3</sub>), 13.7 (3 CH<sub>3</sub>), 9.9 ppm (*J*<sub>C<sup>13</sup>,<sup>17</sup>Sn</sub> = 314.4, *J*<sub>C<sup>13</sup>,<sup>19</sup>Sn</sub> = 328.7 Hz; 3 CH<sub>2</sub>); IR (film):  $\tilde{\nu}$  = 3312, 2956, 2926, 2872, 2823, 1458, 1376, 1146, 1096, 1035, 996, 668, 634 cm<sup>–1</sup>; elemental analysis calcd (%) for C<sub>24</sub>H<sub>46</sub>O<sub>2</sub>Sn: 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)** and **(3S,4R,5S)-3,5-dimethyl-6-(4-methoxybenzyloxy)hex-1-en-4-ol (34)**

**Brown reaction**: A solution of *cis*-2-butene (12.5 mL) in THF (10 mL) was slowly added 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. *n*BuLi (1.6 M in hexane, 44 mL, 70.3 mmol, 1.25 equiv) was then added dropwise

and the resulting yellow mixture was stirred at  $-78^{\circ}\text{C}$  for 5 min and at  $-45^{\circ}\text{C}$  for 20 min. The resulting orange solution was cooled to  $-78^{\circ}\text{C}$ , and a solution of (*-*)-*B*-methoxydiisopinocampheylborane (25 g, 78.7 mmol, 1.4 equiv) in  $\text{Et}_2\text{O}$  (46 mL) was added dropwise over ca. 15 min. The resulting white solution was stirred at  $-78^{\circ}\text{C}$  for 40 min.  $\text{BF}_3\cdot\text{OEt}_2$  (11.8 mL, 95.5 mmol, 1.7 equiv) was added dropwise followed after 5 min by the 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  $-78^{\circ}\text{C}$  for 5 h and the reaction was then quenched by the successive addition of an aqueous NaOH solution (2.5N, 66 mL) and an aqueous  $\text{H}_2\text{O}_2$  solution (30%, 20 mL). The acetone/dry ice bath was then removed, and the mixture was heated at  $45^{\circ}\text{C}$  for 45 min. The cloudy solution was cooled to  $20^{\circ}\text{C}$ , diluted with  $\text{Et}_2\text{O}$  (45 mL), washed with brine, dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The crude residue was distilled ( $85\text{--}90^{\circ}\text{C}$ , 3.3 mmHg) to remove most of the byproduct isopinocampheol. The remaining oil was then purified by chromatography on silica gel to give title compound **33**, which was used in the next step.

#### Crotylation reaction with crotylstannane—crotylstannane preparation

**Method 1:** *n*BuLi (1.4 M in hexane, 49 mL, 69 mmol, 1.0 equiv) was added to a solution of diisopropylamine (8.0 mL, 79 mmol, 1.15 equiv) in THF (130 mL) at  $0^{\circ}\text{C}$ . After 10 min,  $\text{HSnBu}_3$  (20.0 g, 69 mmol, 1.0 equiv) was added over 10 min to the LDA solution, and after stirring for 20 min at  $0^{\circ}\text{C}$ , the mixture was cooled to  $-40^{\circ}\text{C}$  and a solution of (*E*)-crotylchloride (6.2 g, 69 mmol, 1.0 equiv) in THF (70 mL) was added by cannula. The mixture was stirred for 15 min at  $-20^{\circ}\text{C}$  and then treated with a saturated aqueous  $\text{NH}_4\text{Cl}$  solution. After extraction with  $\text{Et}_2\text{O}$ , the organic layer was washed with water and brine, dried over  $\text{MgSO}_4$ , and the solvent was removed under reduced pressure. The residue was then distilled under reduced pressure ( $154\text{--}158^{\circ}\text{C}$ , 0.3 mbar) to give a mixture of (*E/Z*)-crotylstannane 50:50 (19.0 g, 81%).

**Method 2:** A solution of *trans*-butene (7 mL) in THF was added by cannula to freshly sublimed potassium *tert*-butoxide (4.0 g, 36 mmol, 1.2 equiv) in THF (70 mL) at  $-78^{\circ}\text{C}$ . *n*BuLi was then added dropwise (1.4 M in hexane, 26.6 mL, 37.2 mmol, 1.25 equiv). After the reaction mixture had been stirred for 1 h at  $-45^{\circ}\text{C}$ , tributyltin chloride (9.7 g, 30 mmol, 1.0 equivalent) was added slowly and the resulting mixture was allowed to warm to  $20^{\circ}\text{C}$  for 12 h. The reaction was then quenched by the addition of a saturated aqueous  $\text{NH}_4\text{Cl}$  solution. After extraction with  $\text{Et}_2\text{O}$ , the organic layer was washed with water and brine, dried over  $\text{MgSO}_4$ , and the solvent was removed under reduced pressure. The residue was then distilled under reduced pressure ( $154\text{--}158^{\circ}\text{C}$ , 0.3 mbar) to give a mixture of (*E/Z*)-crotylstannane 75:25 (3.25 g, 32%).

$\text{BF}_3\cdot\text{OEt}_2$  (9.0 g, 8.1 mL, 63.8 mmol, 2.2 equiv) was added to a solution of aldehyde **13** (6.0 g, 28.9 mmol, 1.0 equiv) in  $\text{Et}_2\text{O}$  (90 mL) at  $-100^{\circ}\text{C}$ . After the reaction mixture had been stirred for 10 min, crotyltributylstannane (13.3 g, 38.6 mmol, 1.1 equiv) was added and the resulting mixture was stirred for 3 h at  $-100\text{--}95^{\circ}\text{C}$ . After this time, a saturated aqueous  $\text{NaHCO}_3$  solution was added and the resulting mixture was extracted with  $\text{Et}_2\text{O}$ . The organic layer was washed with water and brine, dried over  $\text{MgSO}_4$ , and the solvent was 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%) and its diastereomer **34** (d.r. 91:9).

**Compound 33:**  $[\alpha]_{\text{D}}^{20} = -2.7$  ( $c = 9.6$  in  $\text{CHCl}_3$ );  $^1\text{H NMR}$  (400.0 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.26$  (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;  $\text{CH}_3$ ), 0.96 ppm (d,  $J = 6.6$  Hz, 3H;  $\text{CH}_3$ );  $^{13}\text{C NMR}$  (100.5 MHz,  $\text{CDCl}_3$ ):  $\delta = 159.2$  (C), 141.3 (CH), 130.3 (C), 129.2 (2CH), 114.5 ( $\text{CH}_2$ ), 113.8 (2CH), 75.4 (CH), 73.1 ( $\text{CH}_2$ ), 72.0 ( $\text{CH}_2$ ), 55.3 ( $\text{CH}_3$ ), 42.1 (CH), 35.4 (CH), 17.2 ( $\text{CH}_3$ ), 9.8 ppm ( $\text{CH}_3$ ); IR (film):  $\tilde{\nu} = 2960$ , 2907, 2870, 1612, 1513, 1462, 1365, 1302, 1210, 1173, 1093, 1037, 982, 914  $\text{cm}^{-1}$ ; MS (GC, CI,  $\text{CH}_4$ ):  $m/z$ : 293 [ $M+29$ ] $^+$ , 264, 246, 190, 161, 149, 137, 121, 109, 69, 57.

**Compound 34:**  $^1\text{H NMR}$  (400.0 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.26$  (d,  $J = 8.9$  Hz, 2H), 6.88 (d,  $J = 8.9$  Hz, 2H), 5.86 (ddd,  $J = 17.9$ , 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;  $\text{CH}_3$ ), 0.96 ppm (d,  $J = 6.6$  Hz, 3H;  $\text{CH}_3$ ).

**(3R,4S,5S)-4-(tert-Butyldimethylsilyloxy)-3,5-dimethyl-6-(4-methoxybenzyloxy)hex-1-ene (35):** 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) were added to a solution of alcohol **33** (5.64 g, 21.3 mmol, 1.0 equiv) in dried  $\text{CH}_2\text{Cl}_2$  (90 mL) at  $0^{\circ}\text{C}$ . After the reaction mixture had been stirred for 2 h at  $20^{\circ}\text{C}$ , it was partitioned between  $\text{Et}_2\text{O}$  and a saturated aqueous solution of  $\text{NH}_4\text{Cl}$  and extracted with  $\text{Et}_2\text{O}$ . The organic layer was washed with brine, dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate 98:2 to 95:5) to give the title compound **35** (6.30 g, 78%) as a yellow oil.  $[\alpha]_{\text{D}}^{20} = +1.3$  ( $c = 1.5$  in  $\text{CHCl}_3$ );  $^1\text{H NMR}$  (400.0 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.25$  (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;  $\text{CH}_3$ ), 0.89 (s, 9H; 3  $\text{CH}_3$ ), 0.85 (d,  $J = 6.6$  Hz, 3H;  $\text{CH}_3$ ), 0.04 (s, 3H;  $\text{CH}_3$ ), 0.02 ppm (s, 3H;  $\text{CH}_3$ );  $^{13}\text{C NMR}$  (100.5 MHz,  $\text{CDCl}_3$ ):  $\delta = 159.0$  (C), 142.0 (CH), 130.8 (C), 129.1 (2CH), 113.6 (2CH), 113.4 ( $\text{CH}_2$ ), 75.5 (CH), 73.4 ( $\text{CH}_2$ ), 72.4 ( $\text{CH}_2$ ), 55.2 ( $\text{CH}_3$ ), 42.6 (CH), 36.5 (CH), 26.1 (3  $\text{CH}_3$ ), 18.4 (C), 16.9 ( $\text{CH}_3$ ), 11.0 ( $\text{CH}_3$ ),  $-3.6$  ppm (2  $\text{CH}_3$ ); IR (film):  $\tilde{\nu} = 2959$ , 2855, 1653, 1615, 1513, 1462, 1360, 1301, 1246, 1172, 1103, 1039, 911, 836  $\text{cm}^{-1}$ ; MS (GC, CI,  $\text{CH}_4$ ):  $m/z$ : 407 [ $M+29$ ] $^+$ , 377, 363, 323, 271, 241, 199, 187, 161, 145, 121, 109, 89, 75; elemental analysis calcd (%) for  $\text{C}_{22}\text{H}_{38}\text{O}_5\text{Si}$ : 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  $0^{\circ}\text{C}$ , a solution of compound **33** (100 mg, 0.38 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (3 mL) was treated with water (0.15 mL) and DDO (72 mg, 0.317 mmol, 1.2 equiv). The mixture was stirred for 10 min at  $0^{\circ}\text{C}$ , warmed to  $20^{\circ}\text{C}$  and then stirred for an additional 30 min. The mixture was quenched with a saturated aqueous  $\text{NaHCO}_3$  solution, diluted with  $\text{CH}_2\text{Cl}_2$ , and washed with water and brine. The combined organic layers were dried over  $\text{MgSO}_4$ , filtered, and the solvent was 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%). RN: 108867-45-4;  $[\alpha]_{\text{D}}^{20} = +4.0$  ( $c = 1.5$  in  $\text{CHCl}_3$ );  $^1\text{H NMR}$  (270.0 MHz,  $\text{CDCl}_3$ ):  $\delta = 6.03\text{--}5.49$  (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 (brs, 1H; OH), 2.28–2.19 (m, 1H), 1.79–1.73 (m, 1H), 1.03 (d,  $J = 6.6$  Hz, 3H;  $\text{CH}_3$ ), 0.87 ppm (d,  $J = 6.9$  Hz, 3H;  $\text{CH}_3$ );  $^{13}\text{C NMR}$  (67.5 MHz,  $\text{CDCl}_3$ ):  $\delta = 140.8$  (CH), 114.7 ( $\text{CH}_2$ ), 76.5 (CH), 67.8 ( $\text{CH}_2$ ), 42.2 (CH), 36.5 (CH), 17.1 ( $\text{CH}_3$ ), 8.9 ppm ( $\text{CH}_3$ ); IR (film):  $\tilde{\nu} = 3464$ , 2957, 1655, 1264, 1105, 1094, 1023, 1016, 798  $\text{cm}^{-1}$ ; MS (GC, CI,  $\text{CH}_4$ ):  $m/z$ : 127 [ $MH-H_2O$ ] $^+$ , 125, 109, 97, 89, 83, 71, 57; elemental analysis calcd (%) for  $\text{C}_8\text{H}_{16}\text{O}_2$ : 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):** A stream of ozone was bubbled through a solution of compound **35** (6.3 g, 16.6 mmol, 1.0 equiv), pyridine (4 mL, 50 mmol, 3.0 equiv), and a small amount of Sudan III in  $\text{MeOH}/\text{CH}_2\text{Cl}_2$  (1:1, 200 mL) at  $-78^{\circ}\text{C}$  until the pink solution became colorless. The solution was treated with DMS (36.5 mL, 498 mmol, 30 equiv) and was then warmed to  $20^{\circ}\text{C}$  for 12 h. The solution was concentrated under reduced pressure, diluted with  $\text{Et}_2\text{O}$ , washed with water (3 $\times$ ), dried over  $\text{MgSO}_4$ , and the solvent was removed under reduced pressure. The crude **37** produced (6.0 g, 95%) was used in the next step without further purification.  $^1\text{H NMR}$  (400.0 MHz,  $\text{CDCl}_3$ ):  $\delta = 9.87$  (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,

3 H; CH<sub>3</sub>), 0.91 (s, 9H; 3 CH<sub>3</sub>), 0.86 (d, *J* = 6.9 Hz, 3H; CH<sub>3</sub>), 0.07 (s, 3H; CH<sub>3</sub>), 0.05 ppm (s, 3H; CH<sub>3</sub>); <sup>13</sup>C NMR (100.5 MHz, CDCl<sub>3</sub>): δ = 205.5 (C), 129.2 (2CH), 113.7 (2CH), 72.6 (CH<sub>2</sub>), 72.5 (CH<sub>2</sub>), 72.3 (CH), 55.2 (CH<sub>3</sub>), 51.3 (CH), 37.0 (CH), 25.9 (3CH<sub>3</sub>), 18.2 (C), 12.1 (CH<sub>3</sub>), 9.3 (CH<sub>3</sub>), -4.0 ppm (2CH<sub>3</sub>), one C atom was not detected; MS (GC, EI): *m/z*: 323 [M-tBu]<sup>+</sup>, 251, 199, 187, 137, 121, 107, 98, 89, 73, 59; elemental analysis calcd (%) for C<sub>21</sub>H<sub>30</sub>O<sub>4</sub>Si: 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)-Crotlyldiisopropylcarbamate preparation:* A solution of 2-buten-1-ol (*E/Z* mixture, 18.4 g, 255 mmol, 1.0 equiv) in THF (50 mL) was added to a suspension of NaH (60%, 12.2 g, 306 mmol, 1.2 equiv) in THF (50 mL) at 0°C over 20 min. After the reaction mixture had been stirred for 20 min at 20°C, it 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, and was then poured into an aqueous HCl 1 N solution (150 mL) and extracted with Et<sub>2</sub>O. The combined organic layers were washed with a saturated aqueous NaHCO<sub>3</sub> solution and brine, dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude residue was distilled (64°C, 0.1 mbar) to give (*E*)-crotlyldiisopropylcarbamate (50.0 g, 98%).

*Crotylation reaction with optically active crotlylitane:* A solution of *n*BuLi (1.4 M in hexanes, 25.5 mL, 35.5 mmol, 2.1 equiv) was added to a quick-stirred solution of the (*E*)-crotlyldiisopropylcarbamate (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, and after 10 min white crystals appeared. After 3 h of crystallization at -78°C, a pre-cooled (-40°C) solution of Ti(O*i*Pr)<sub>4</sub> (29.5 mL, 99.6 mmol, 6.0 equiv) in pentane (30 mL) was quickly added by 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 Et<sub>2</sub>O (250 mL) and aqueous HCl (0.5 N, 250 mL). After extraction with Et<sub>2</sub>O, the organic layer was washed with brine, dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate 90:10 to 80:20) to give the title compound **38** (7.1 g, 77%) as a single diastereomer.

**4,6-Acetonide derivative of 38:** A solution of tetrabutylammonium fluoride (1.0 M in THF, 345 μL, 345 μmol, 2.0 equiv) was added to a solution of compound **38** (100 mg, 172 μmol, 1.0 equiv) in THF (0.6 mL) at 20°C. The reaction mixture was stirred for 4 h, quenched by the addition of water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate 80:20 to 70:30) to give 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 (73 mg, 91%). [ $\alpha$ ]<sub>D</sub><sup>20</sup> = +0.8 (*c* = 0.75 in CHCl<sub>3</sub>); <sup>1</sup>H NMR (270.0 MHz, CDCl<sub>3</sub>): 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 (brs, 1H), 3.73 (s, 3H; CH<sub>3</sub>), 3.72–3.60 (brs, 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; 4CH<sub>3</sub>), 0.98 (d, *J* = 6.9 Hz, 3H; CH<sub>3</sub>), 0.88 (d, *J* = 6.9 Hz, 3H; CH<sub>3</sub>), 0.85 ppm (d, *J* = 6.9 Hz, 3H; CH<sub>3</sub>); <sup>13</sup>C NMR (67.5 MHz, CDCl<sub>3</sub>): 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 (CH<sub>2</sub>), 72.3 (CH<sub>2</sub>), 55.2 (CH<sub>3</sub>), 45.7 (2CH), 36.1 (CH), 35.6 (CH), 34.2 (CH), 21.0 (4CH<sub>3</sub>), 16.2 (CH<sub>3</sub>), 13.1 (CH<sub>3</sub>), 5.8 ppm (CH<sub>3</sub>); IR (film):  $\tilde{\nu}$  = 2969, 2934, 2873, 1708, 1692, 1513, 1441, 1370, 1305, 1247, 1210, 1135, 1063, 971 cm<sup>-1</sup>. 2,2-Dimethoxypropane (210 μL, 1.67 mmol, 12 equiv) and PPTS (10%) were added to a solution of the above diol (65 mg, 0.14 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> at 20°C. 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 the title product (59 mg, 84%). [ $\alpha$ ]<sub>D</sub><sup>20</sup> = +29.6 (*c* = 2.9 in CHCl<sub>3</sub>); <sup>1</sup>H NMR (270.0 MHz, CDCl<sub>3</sub>): 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 (brs, 1H), 3.75–3.58 (brs, 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; 4CH<sub>3</sub>), 1.27 (s, 3H; CH<sub>3</sub>), 1.25 (s, 3H; CH<sub>3</sub>), 0.96 (d, *J* = 6.6 Hz, 3H), 0.81 (d, *J* = 6.9 Hz, 3H), 0.75 ppm (d, *J* = 6.9 Hz, 3H); <sup>13</sup>C NMR (67.5 MHz, CDCl<sub>3</sub>): 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 (CH<sub>2</sub>), 71.1 (CH<sub>2</sub>), 55.1 (CH<sub>3</sub>), 46.1 (2CH), 34.9 (CH, C-16), 31.8 (CH), 30.9 (CH), 29.8 (CH<sub>2</sub>), 21.0 (4CH<sub>3</sub>), 19.4 (CH<sub>3</sub>), 15.8 (CH<sub>3</sub>), 14.8 (CH<sub>3</sub>), 4.9 ppm (CH<sub>3</sub>); IR (film):  $\tilde{\nu}$  = 2968, 2936, 1708, 1513, 1462, 1439, 1377, 1310, 1288, 1248, 1135, 1057, 1012 cm<sup>-1</sup>; MS (GC, CI, CH<sub>4</sub>): *m/z*: 534 [M+29]<sup>+</sup>, 506 [M+1]<sup>+</sup>; elemental analysis calcd (%) for C<sub>29</sub>H<sub>47</sub>NO<sub>6</sub>: C 68.88, H 9.37, N 2.77; found: C 68.75, H 9.32, N 2.85.

**2,4-Acetonide of 38:** A stream of ozone was bubbled into a cooled (-78°C) solution of the carbamate **38** (100 mg, 172 μmol, 1.0 equiv), pyridine (40 μL), and a small amount of Sudan III in MeOH/CH<sub>2</sub>Cl<sub>2</sub> (1:1, 10 mL) until the pink solution became colorless. Sodium borohydride (39 mg, 1.03 mmol, 6.0 equiv) was added at -78°C, the mixture was allowed to warm to 20°C and was then stirred for 6 h. After this time, the reaction mixture was cooled, treated with a saturated aqueous solution of NH<sub>4</sub>Cl and extracted with Et<sub>2</sub>O. The organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 70:30) to give (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 (60 mg, 79%). [ $\alpha$ ]<sub>D</sub><sup>20</sup> = -0.73 (*c* = 1.1 in CHCl<sub>3</sub>); <sup>1</sup>H NMR (270.0 MHz, CDCl<sub>3</sub>): 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; 3CH<sub>3</sub>), 0.87–0.70 (m, 9H; 3CH<sub>3</sub>), 0.03 ppm (s, 6H; 2CH<sub>3</sub>); <sup>13</sup>C NMR (67.5 MHz, CDCl<sub>3</sub>): δ = 159.0 (C), 130.7 (C), 129.1 (2CH), 113.6 (2CH), 77.6 (CH), 73.9 (CH<sub>2</sub>), 73.6 (CH), 72.4 (CH<sub>2</sub>), 68.4 (CH<sub>2</sub>), 55.2 (CH<sub>3</sub>), 38.5 (CH), 35.8 (CH), 32.8 (CH), 26.1 (3CH<sub>3</sub>), 18.4 (C), 12.1 (CH<sub>3</sub>), 10.5 (CH<sub>3</sub>), 9.6 (CH<sub>3</sub>), -3.6 ppm (2CH<sub>3</sub>); IR (film):  $\tilde{\nu}$  = 2958, 2933, 2856, 1653, 1618, 1559, 1514, 1423, 1344, 1270, 1103, 1037, 837 cm<sup>-1</sup>.

2,2-Dimethoxypropane (180 μL, 1.50 mmol, 12 equiv) and PPTS (10 mol%) were added to a solution of the preceding diol (55 mg, 125 μmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) at 20°C. The reaction mixture was stirred for 2 h and 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 the title product, the 2,4-acetonide of **38**, (46 mg, 78%) and the starting diol (22 mg). [ $\alpha$ ]<sub>D</sub><sup>20</sup> = +12.2 (*c* = 1.2 in CHCl<sub>3</sub>); <sup>1</sup>H NMR (270.0 MHz, CDCl<sub>3</sub>): 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; 2CH<sub>3</sub>), 0.87 (d, *J* = 5.3 Hz, 3H; CH<sub>3</sub>), 0.84 (s, 9H; 3CH<sub>3</sub>), 0.80 (d, *J* = 6.9 Hz, 3H; CH<sub>3</sub>), 0.63 (d, *J* = 6.6 Hz, 3H; CH<sub>3</sub>), 0.00 ppm (s, 6H; 2CH<sub>3</sub>); <sup>13</sup>C NMR (67.5 MHz, CDCl<sub>3</sub>): δ = 159.5 (C), 131.5 (C), 129.5 (2CH), 114.5 (2CH), 98.5 (C), 75.2 (CH), 74.2 (CH<sub>2</sub>), 73.6 (CH), 72.8 (CH<sub>2</sub>), 67.0 (CH<sub>2</sub>), 55.8 (CH<sub>3</sub>), 38.2 (CH), 36.8 (CH), 31.3 (CH), 29.3 (CH<sub>3</sub>), 26.7 (3CH<sub>3</sub>), 19.4 (CH<sub>3</sub>), 19.0 (C), 12.8 (CH<sub>3</sub>), 11.0 (CH<sub>3</sub>), 10.5 (CH<sub>3</sub>), -3.6 ppm (2CH<sub>3</sub>); IR (film):  $\tilde{\nu}$  = 3256, 1684, 1653, 1550, 1501, 1445, 1359, 1248, 1101, 1032, 846 cm<sup>-1</sup>; MS (GC, CI, CH<sub>4</sub>): *m/z*: 481 [M+H]<sup>+</sup>; elemental analysis calcd (%) for C<sub>27</sub>H<sub>48</sub>O<sub>5</sub>Si: C 67.45, H 10.06; found: C 67.32, H 10.24.

**(1Z,3S,4S,5R,6S,7S)-6-(tert-Butyldimethylsilyloxy)-1-[(N,N-diisopropyl)-carbamoyloxy]-8-(4-methoxybenzyloxy)-4-(triethylsilyloxy)-3,5,7-trimethyl oct-1-ene (39):** 2,6-Lutidine (0.9 mL, 7.50 mmol, 4.0 equiv) and TESOTf (0.9 mL, 3.76 mmol, 2.5 equiv) were added to a solution of **38** (1.09 g, 1.88 mmol, 1.0 equiv) in dried CH<sub>2</sub>Cl<sub>2</sub> (15 mL) at 0°C. After the reaction mixture had been stirred for 2 h at 20°C, it was partitioned between Et<sub>2</sub>O and a saturated aqueous solution of NH<sub>4</sub>Cl and was extract-

ed with Et<sub>2</sub>O. The organic layer was washed with brine, dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate 95:5 to 90:10) to give the title compound **39** (985 mg, 76%) of as a colorless oil.  $[\alpha]_D^{20} = +14.4$  ( $c = 0.8$  in CHCl<sub>3</sub>); <sup>1</sup>H NMR (400.0 MHz, CDCl<sub>3</sub>):  $\delta = 7.22$  (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 (brs, 1H), 3.82–3.69 (brs, 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; 4CH<sub>3</sub>), 1.01 (d,  $J = 7.2$  Hz, 3H; CH<sub>3</sub>), 0.97–0.87 (m, 12H; 4CH<sub>3</sub>), 0.85 (s, 9H; 3CH<sub>3</sub>), 0.80 (d,  $J = 7.2$  Hz, 3H; CH<sub>3</sub>), 0.60 (q,  $J = 7.6$  Hz, 6H; 3CH<sub>2</sub>), 0.02 (s, 3H; CH<sub>3</sub>), 0.01 ppm (s, 3H; CH<sub>3</sub>); <sup>13</sup>C NMR (100.5 MHz, CDCl<sub>3</sub>):  $\delta = 159.0$  (C), 153.0 (C), 133.7 (CH), 130.7 (C), 129.2 (2CH), 113.6 (2CH), 112.7 (CH), 77.0 (CH), 73.9 (CH), 73.6 (CH<sub>2</sub>), 72.6 (CH<sub>2</sub>), 55.2 (CH<sub>3</sub>), 45.4 (2CH), 42.9 (CH), 38.7 (CH), 32.4 (CH), 26.1 (3CH<sub>3</sub>), 21.5 (4CH<sub>3</sub>), 20.3 (CH<sub>3</sub>), 18.4 (C), 12.2 (CH<sub>3</sub>), 11.1 (CH<sub>3</sub>), 7.0 (3CH<sub>3</sub>), 5.5 (3CH<sub>2</sub>), 3.2 ppm (2CH<sub>3</sub>); IR (film):  $\tilde{\nu} = 2966$ , 2937, 2877, 1710, 1514, 1460, 1439, 1306, 1249, 1060, 1042, 1005, 837 cm<sup>-1</sup>; elemental analysis calcd (%) for C<sub>38</sub>H<sub>71</sub>NO<sub>6</sub>Si<sub>2</sub>: C 65.75, H 10.31, N 2.02; found: C 65.72, H 10.27, N 1.97.

**(3Z,5S,6S,7R,8S,9S)-8-(tert-Butyldimethylsilyloxy)-10-(4-methoxybenzyl-oxy)-6-(triethylsilyloxy)-5,7,9-trimethyl deca-1,3-diene (40) and (3Z,5S,6S,7R,8S,9S)-6-(tert-butylidimethylsilyloxy)-8-(4-methoxybenzyl-oxy)-6-(triethylsilyloxy)-3,5,7-trimethyl-1-decene (41)**

**Reaction with vinylmagnesium bromide:** A solution of the vinyl carbamate **39** (700 mg, 1.01 mmol, 1.0 equiv) in Et<sub>2</sub>O (10 mL, 3 mL rinse) and vinylmagnesium bromide (sol. 1 M in THF, 15.1 mL, 15.1 mmol, 15 equiv) were added to a stirred suspension of [Ni(acac)<sub>2</sub>] (26 mg, 0.10 mmol, 0.1 equiv) in Et<sub>2</sub>O (10 mL) at 0°C. The resulting mixture was stirred for 24 h at 0°C. After this time, a saturated aqueous NH<sub>4</sub>Cl solution was added and the solution was extracted with Et<sub>2</sub>O. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate 100:0 to 90:10) to give diene **40** (460 mg, 80%) and compound **41** (less than 5% yield).

**Reaction with vinylolithium:** MeLi (1.6 M in Et<sub>2</sub>O, 18 mL, 28.8 mmol, 10 equiv) was added to a solution of tetravinyltin (1.7 g, 7.48 mmol, 2.6 equiv) in Et<sub>2</sub>O (12 mL) at 0°C. After the reaction mixture had been stirred for 30 min, it was added by cannula to a stirred solution of the carbamate **39** (2.0 g, 2.88 mmol, 1.0 equiv) and [Ni(acac)<sub>2</sub>] (74 mg, 0.288 mmol, 0.1 equiv) in Et<sub>2</sub>O (4 mL) at -5/0°C. After the reaction mixture had been stirred for a further 6 h, the same amount of [Ni(acac)<sub>2</sub>] was added and the resulting mixture was stirred for another 12 h at 0°C. Then a saturated aqueous NH<sub>4</sub>Cl solution was added and the solution was extracted with Et<sub>2</sub>O. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate 98:2 to 80:20) to give **40** (1.33 g, 80%).

**Compound 40:**  $[\alpha]_D^{20} = +8.9$  ( $c = 2.1$  in CHCl<sub>3</sub>); <sup>1</sup>H NMR (400.0 MHz, CDCl<sub>3</sub>):  $\delta = 7.24$  (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; 9CH<sub>3</sub>), 0.59 (q,  $J = 7.8$  Hz, 6H; 3CH<sub>2</sub>), 0.04 ppm (s, 6H; 2CH<sub>3</sub>); <sup>13</sup>C NMR (100.5 MHz, CDCl<sub>3</sub>):  $\delta = 159.0$  (C), 135.0 (CH), 132.5 (CH), 130.8 (C), 129.2 (2CH), 129.0 (CH), 117.1 (CH<sub>2</sub>), 113.6 (2CH), 77.5 (CH), 73.2 (CH<sub>2</sub>), 73.1 (CH), 72.5 (CH<sub>2</sub>), 55.2 (CH<sub>3</sub>), 40.2 (CH), 38.0 (CH), 36.5 (CH), 26.2 (3CH<sub>3</sub>), 18.7 (C), 18.5 (CH<sub>3</sub>), 11.9 (CH<sub>3</sub>), 11.5 (CH<sub>3</sub>), 7.2 (3CH<sub>3</sub>), 5.6 (3CH<sub>2</sub>), -3.3 ppm (2CH<sub>3</sub>); IR (film):  $\tilde{\nu} = 2957$ , 2857, 1616, 1490 cm<sup>-1</sup>; elemental analysis calcd (%) for C<sub>33</sub>H<sub>60</sub>O<sub>4</sub>Si<sub>2</sub>: C 68.69, H 10.48; found: C 68.48, H 10.67.

**Compound 41:** <sup>1</sup>H NMR (400.0 MHz, CDCl<sub>3</sub>):  $\delta = 7.24$  (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 (qdd,  $J = 6.9$ , 5.9, 4.8 Hz, 1H), 0.99 (d,  $J = 6.9$  Hz, 3H; CH<sub>3</sub>), 0.93 (t,  $J = 7.8$  Hz, 9H; 3CH<sub>3</sub>), 0.88 (s, 9H; 3CH<sub>3</sub>), 0.86 (d,  $J = 6.9$  Hz, 3H; CH<sub>3</sub>), 0.85 (d,  $J = 6.9$  Hz, 3H; CH<sub>3</sub>), 0.59 (q,  $J = 7.8$  Hz, 6H; 3CH<sub>2</sub>), 0.03 ppm (s, 6H; 2CH<sub>3</sub>); <sup>13</sup>C NMR (100.5 MHz, CDCl<sub>3</sub>):  $\delta = 159.0$  (C), 141.2 (C), 131.2 (CH), 129.3 (2CH), 114.6 (CH<sub>2</sub>), 113.6 (2CH), 77.0 (CH), 73.3 (CH<sub>2</sub>), 73.2 (CH), 72.6 (CH<sub>2</sub>), 55.3 (CH<sub>3</sub>), 39.6 (CH), 37.9 (CH), 33.5 (CH), 26.2 (3CH<sub>3</sub>), 18.5 (C), 18.5 (CH<sub>3</sub>), 11.7 (CH<sub>3</sub>), 11.5 (CH<sub>3</sub>), 7.2 (3CH<sub>3</sub>), 5.6 (3CH<sub>2</sub>), -3.4 ppm (2CH<sub>3</sub>).

**(3Z,5S,6S,7R,8S,9S)-8-(tert-Butyldimethylsilyloxy)-10-hydroxy-6-(triethylsilyloxy)-5,7,9-trimethyl deca-1,3-diene (42):** DDO (117 mg, 0.52 mmol, 1.1 equiv) was added to a solution of compound **40** (249 mg, 0.43 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (6 mL)/H<sub>2</sub>O (300  $\mu$ L) at 0°C. The mixture was stirred for 10 min at 0°C, warmed to 20°C and was then stirred for an additional 30 min. The mixture was quenched with a saturated aqueous NaHCO<sub>3</sub> solution, diluted with Et<sub>2</sub>O, and washed with water and brine. The combined organic layers were dried over MgSO<sub>4</sub>, 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%).  $[\alpha]_D^{20} = +11.4$  ( $c = 1.2$  in CHCl<sub>3</sub>); <sup>1</sup>H NMR (400.0 MHz, CDCl<sub>3</sub>):  $\delta = 6.58$  (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; CH<sub>3</sub>), 0.98 (t,  $J = 7.8$  Hz, 9H; 3CH<sub>3</sub>), 0.94 (d,  $J = 6.9$  Hz, 3H; CH<sub>3</sub>), 0.85 (s, 9H; 3CH<sub>3</sub>), 0.83 (d,  $J = 6.9$  Hz, 3H; CH<sub>3</sub>), 0.65 (q,  $J = 7.8$  Hz, 6H; 3CH<sub>2</sub>), 0.11 ppm (s, 3H; CH<sub>3</sub>), 0.08 ppm (s, 3H; CH<sub>3</sub>); <sup>13</sup>C NMR (100.5 MHz, CDCl<sub>3</sub>):  $\delta = 134.6$  (CH), 132.5 (CH), 129.2 (CH), 117.7 (CH<sub>2</sub>), 78.0 (CH), 73.7 (CH), 66.2 (CH<sub>2</sub>), 40.8 (CH), 40.2 (CH), 35.9 (CH), 26.2 (3CH<sub>3</sub>), 19.2 (CH<sub>3</sub>), 18.5 (C), 12.5 (CH<sub>3</sub>), 11.9 (CH<sub>3</sub>), 7.4 (3CH<sub>3</sub>), 5.8 (3CH<sub>2</sub>), -3.5 (CH<sub>3</sub>), -3.7 ppm (CH<sub>3</sub>); IR (film):  $\tilde{\nu} = 3405$ , 2956, 2930, 2878, 2858, 1461, 1252, 1096, 1076, 1006, 837, 772, 737 cm<sup>-1</sup>; elemental analysis calcd (%) for C<sub>25</sub>H<sub>52</sub>O<sub>3</sub>Si<sub>2</sub>: 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):** A solution of iodine (167 mg, 0.66 mmol, 1.5 equiv) in Et<sub>2</sub>O (2 mL) was added slowly to a solution of compound **42** (200 mg, 0.44 mmol, 1.0 equiv), triphenylphosphine (PPh<sub>3</sub>, 218 mg, 0.83 mmol, 1.9 equiv), and imidazole (57 mg, 0.83 mmol, 1.9 equiv) in a benzene/Et<sub>2</sub>O mixture (1.5 mL:3 mL) at 0°C. After the reaction mixture had been stirred for 2 h at 20°C, a 1 M Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution was added and the reaction mixture was extracted with Et<sub>2</sub>O. The organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/Et<sub>2</sub>O 100:0 to 80:20) to give the title compound **43** (197 mg, 79%).  $[\alpha]_D^{20} = +11.3$  ( $c = 0.68$  in CHCl<sub>3</sub>); <sup>1</sup>H NMR (400.0 MHz, CDCl<sub>3</sub>):  $\delta = 6.58$  (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 (qdm,  $J = 6.9$ , 4.6 Hz, 1H), 1.01 (d,  $J = 6.9$  Hz, 3H; CH<sub>3</sub>), 0.98 (t,  $J = 7.8$  Hz, 9H; 3CH<sub>3</sub>), 0.98 (d,  $J = 6.9$  Hz, 3H; CH<sub>3</sub>), 0.91 (s, 9H; 3CH<sub>3</sub>), 0.90 (d,  $J = 6.9$  Hz, 3H; CH<sub>3</sub>), 0.64 (q,  $J = 7.8$  Hz, 6H; 3CH<sub>2</sub>), 0.10 (s, 3H; CH<sub>3</sub>), 0.09 ppm (s, 3H; CH<sub>3</sub>); <sup>13</sup>C NMR (100.5 MHz, CDCl<sub>3</sub>):  $\delta = 134.1$  (CH), 132.5 (CH), 129.0 (CH), 117.4 (CH<sub>2</sub>), 77.1 (CH), 75.0 (CH), 41.9 (CH), 40.4 (CH), 35.8 (CH), 25.9 (3CH<sub>3</sub>), 18.8 (CH<sub>3</sub>), 18.4 (C), 15.0 (CH<sub>3</sub>), 13.4 (CH<sub>2</sub>), 11.9 (CH<sub>3</sub>), 7.0 (3CH<sub>3</sub>), 5.5 (3CH<sub>2</sub>), -3.8 ppm (2CH<sub>3</sub>); IR (film):  $\tilde{\nu} = 2950$ , 2930, 2877, 2857, 1461, 1097, 1028, 1005, 836 cm<sup>-1</sup>; elemental analysis calcd (%) for C<sub>25</sub>H<sub>51</sub>IO<sub>2</sub>Si<sub>2</sub>: C 52.98, H 9.07; found: C 53.17, H 9.25.

**(1Z,3S,4S,5S)-6-(tert-Butyldimethylsilyloxy)-1-[(N,N-diisopropyl)carbamoyloxy]-3,5-dimethyl-hex-1-en-4-ol (51):** A solution of *n*BuLi (1.37 M in hexanes, 30.6 mL, 41.9 mmol, 2.1 equiv) was added to a quick-stirred so-

lution 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. After 10 min, white crystals appeared, and after 3 h of crystallization at –78 °C, a pre-cooled (–40 °C) solution of Ti(O*i*Pr)<sub>4</sub> (34.7 mL, 117.6 mmol, 6.0 equiv) in pentane (30 mL) was quickly added by cannula to the reaction mixture of lithio carbamate, which became limp 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 Et<sub>2</sub>O (250 mL)/aqueous HCl (0.5 N, 250 mL). After extraction with Et<sub>2</sub>O, the organic layer was washed with brine, dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate 95:5 to 70:30) to give the title compound **51** (4.30 g, 58%) and its 3,4-bis-*epi* diastereomer (*de* = 95:5; *de* = diastereomeric excess).

**Compound 51:** [ $\alpha$ ]<sub>D</sub><sup>20</sup> = +20.1 (*c* = 1.0 in CHCl<sub>3</sub>); <sup>1</sup>H NMR (400.0 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.13 (d, *J* = 6.4 Hz, 1H), 4.73 (dd, *J* = 9.6, 6.4 Hz, 1H), 4.22–4.11 (brs, 1H), 3.82–3.70 (brs, 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; 4CH<sub>3</sub>), 0.97 (d, *J* = 6.9 Hz, 3H; CH<sub>3</sub>), 0.94 (d, *J* = 6.9 Hz, 3H; CH<sub>3</sub>), 0.90 (s, 9H; 3CH<sub>3</sub>), 0.08 ppm (s, 6H; 2CH<sub>3</sub>); <sup>13</sup>C NMR (100.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 153.0 (C), 135.9 (CH), 113.9 (CH), 77.0 (CH), 68.0 (CH<sub>2</sub>), 47.0 (CH), 45.2 (CH), 36.6 (CH), 34.0 (CH), 26.0 (3CH<sub>3</sub>), 21.6 (2CH<sub>3</sub>), 20.5 (2CH<sub>3</sub>), 18.3 (C), 17.4 (CH<sub>3</sub>), 9.4 (CH<sub>3</sub>), –5.50 ppm (2CH<sub>3</sub>); IR (film):  $\tilde{\nu}$  = 3493, 2959, 2930, 2858, 1708, 1472, 1439, 1370, 1304, 1290, 1256, 1211, 1156, 1134, 1092, 1061, 837 cm<sup>–1</sup>; MS (GC, EI): *m/z*: 344 [M–*t*Bu]<sup>+</sup>, 326, 302, 228, 212, 199, 184, 145, 128, 115, 86, 73; elemental analysis calcd (%) for C<sub>21</sub>H<sub>43</sub>NO<sub>4</sub>Si: 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:** <sup>1</sup>H NMR (400.0 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.07 (d, *J* = 6.4 Hz, 1H), 4.97 (dd, *J* = 9.6, 6.4 Hz, 1H), 4.25–4.05 (brs, 1H), 4.20 (s, 1H; OH), 3.85–3.67 (brs, 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; 4CH<sub>3</sub>), 1.14 (d, *J* = 6.9 Hz, 3H; CH<sub>3</sub>), 0.90 (s, 9H; 3CH<sub>3</sub>), 0.76 (d, *J* = 6.9 Hz, 3H; CH<sub>3</sub>), 0.09 ppm (s, 6H; 2CH<sub>3</sub>); <sup>13</sup>C NMR (100.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 153.5 (C), 135.1 (CH), 111.5 (CH), 80.5 (CH), 69.5 (CH<sub>2</sub>), 46.9 (CH), 45.5 (CH), 38.1 (CH), 33.5 (CH), 25.9 (3CH<sub>3</sub>), 21.6 (2CH<sub>3</sub>), 20.5 (2CH<sub>3</sub>), 18.3 (C), 18.2 (CH<sub>3</sub>), 13.2 (CH<sub>3</sub>), –5.5 ppm (2CH<sub>3</sub>).

**(2S,3S,4S)-1-(*tert*-Butyldimethylsilyloxy)-2,4-dimethyl-hex-5-en-3-ol (52):** A solution of isopropylmagnesium chloride in THF (1.55 M, 8.0 mL, 12.4 mmol, 10 equiv) was slowly added to a solution of carbamate **51** (500 mg, 1.24 mmol, 1.0 equiv) and [Ni(acac)<sub>2</sub>] (32 mg, 0.12 mmol, 10 mol%) in THF (5 mL) at 20 °C. After the reaction mixture had been stirred for 12 h, a saturated aqueous NH<sub>4</sub>Cl solution was added, and the reaction mixture was extracted with Et<sub>2</sub>O. The combined organic layers were washed with water and brine, dried over MgSO<sub>4</sub>, filtered, and the solvent was 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%). RN: 106296-58-6; <sup>1</sup>H NMR (400.0 MHz, CDCl<sub>3</sub>):  $\delta$  = 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; 2CH<sub>3</sub>), 0.90 (s, 9H; 3CH<sub>3</sub>), 0.07 ppm (s, 6H; 2CH<sub>3</sub>); <sup>13</sup>C NMR (100.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 142.3 (CH), 115.3 (CH<sub>2</sub>), 77.2 (CH), 68.8 (CH<sub>2</sub>), 42.0 (CH), 36.1 (CH), 26.0 (3CH<sub>3</sub>), 18.4 (C), 16.9, 9.5 (2CH<sub>3</sub>), –5.4 (CH<sub>3</sub>), –5.5 ppm (CH<sub>3</sub>).

**(2E,4S,5S,6S)-*N*-Methyl-*N*-methoxy-7-(*tert*-butyldimethylsilyloxy)-4,6-dimethyl-5-hydroxy-hept-2-enamide (53):** A stream of ozone was bubbled into a cooled (–78 °C) solution of **51** (1.05 g, 2.61 mmol, 1.0 equiv) and a small amount of Sudan III in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) until the pink solution became colorless. 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 (2*R*,3*R*,4*S*)-5-(*tert*-butyldimethylsilyloxy)-2,4-dimethyl-3-hydroxy-pentanal (590 mg, 87%). RN: 209251-54-7; <sup>1</sup>H NMR (400.0 MHz, CDCl<sub>3</sub>):  $\delta$  = 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; CH<sub>3</sub>), 0.98 (d, *J* = 6.9 Hz, 3H; CH<sub>3</sub>), 0.90 (s, 9H; 3CH<sub>3</sub>), 0.08 ppm (s, 6H; 2CH<sub>3</sub>); <sup>13</sup>C NMR (100.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 205.9 (CH), 75.4 (CH), 67.8 (CH<sub>2</sub>), 49.7 (CH), 35.8 (CH), 26.0 (3CH<sub>3</sub>), 18.3 (C), 10.6 (CH<sub>3</sub>), 9.4 (CH<sub>3</sub>), –5.5 ppm (2CH<sub>3</sub>).

A solution of commercial diethyl *N*-methoxy-*N*-methylphosphonoacetamide (3.9 mL, 19.1 mmol, 2.0 equiv) was added 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. 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 (2*R*,3*R*,4*S*)-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. After 5 min, the mixture was allowed to warm to 20 °C for 1 h and was then quenched by the addition of a saturated aqueous NH<sub>4</sub>Cl solution. The aqueous layer was separated and extracted with Et<sub>2</sub>O (2 ×). The combined organic phases were washed with water and brine, dried over MgSO<sub>4</sub>, filtered, and the solvent was 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%) as a pale-yellow oil. [ $\alpha$ ]<sub>D</sub><sup>20</sup> = –3.3 (*c* = 1.0 in CHCl<sub>3</sub>); <sup>1</sup>H NMR (400.0 MHz, CDCl<sub>3</sub>):  $\delta$  = 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; CH<sub>3</sub>), 3.69 (dd, *J* = 6.4, 5.0 Hz, 1H), 3.68 (dd, *J* = 9.8, 5.0 Hz, 1H), 3.24 (s, 3H; CH<sub>3</sub>), 2.84 (brs, 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; CH<sub>3</sub>), 0.96 (d, *J* = 7.3 Hz, 3H; CH<sub>3</sub>), 0.90 (s, 9H; 3CH<sub>3</sub>), 0.09 ppm (s, 6H; 2CH<sub>3</sub>); <sup>13</sup>C NMR (100.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 167.0 (C), 150.9 (CH), 119.1 (CH), 77.3 (CH), 68.6 (CH<sub>2</sub>), 61.8 (CH<sub>3</sub>, CH<sub>3</sub>), 40.9 (CH), 36.2 (CH), 32.4 (CH<sub>3</sub>), 26.0 (3CH<sub>3</sub>), 18.3 (C), 16.6 (CH<sub>3</sub>), 9.5 (CH<sub>3</sub>), –5.5 ppm (2CH<sub>3</sub>); IR (film):  $\tilde{\nu}$  = 3444, 2958, 2930, 2857, 1650, 1627, 1471, 1417, 1385, 1255, 1093, 1004, 850 cm<sup>–1</sup>; MS (GC, EI): *m/z*: 288 [M–*t*Bu]<sup>+</sup>, 267, 246, 227, 203, 187, 172, 145, 115, 89, 75, 55; elemental analysis calcd (%) for C<sub>17</sub>H<sub>35</sub>NO<sub>4</sub>Si: 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):** KHMDS (0.5 M solution in toluene, 175  $\mu$ L, 87.5  $\mu$ mol, 0.1 equiv) was added to a solution of compound **53** (300 mg, 0.87 mmol, 1.0 equiv) and freshly distilled benzaldehyde (97  $\mu$ L, 0.96 mmol, 1.1 equiv) in dry THF (9 mL) at 0 °C. The yellow solution obtained was stirred for 15 min. This sequence (addition of KHMDS/stirring) was repeated twice, after which the solution was quenched by the addition of a saturated aqueous NH<sub>4</sub>Cl solution. The organic layer was washed with water and brine, dried over MgSO<sub>4</sub>, filtered, and the solvent was 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%) as a pale-yellow oil. [ $\alpha$ ]<sub>D</sub><sup>20</sup> = +21.9 (*c* = 0.6 in CHCl<sub>3</sub>); <sup>1</sup>H NMR (400.0 MHz, CDCl<sub>3</sub>):  $\delta$  = 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; CH<sub>3</sub>), 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 (dqdd, *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; CH<sub>3</sub>), 0.89 (s, 9H; 3CH<sub>3</sub>), 0.85 (d, *J* = 6.9 Hz, 3H; CH<sub>3</sub>), 0.03 ppm (s, 6H; 2CH<sub>3</sub>); <sup>13</sup>C NMR (100.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 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 (CH<sub>2</sub>), 61.6 (CH<sub>3</sub>), 36.7 (CH<sub>2</sub>), 36.0 (CH), 35.4 (CH), 32.2 (CH<sub>3</sub>), 26.0 (3CH<sub>3</sub>), 18.4 (C), 12.0 (CH<sub>3</sub>), 9.8 (CH<sub>3</sub>), –5.3 ppm (2CH<sub>3</sub>); IR (film):  $\tilde{\nu}$  = 2956, 2930, 2857, 1666, 1483, 1403, 1387, 1256, 1149, 1090, 1029, 837 cm<sup>–1</sup>; MS (GC, EI): *m/z*: 394 [M–*t*Bu]<sup>+</sup>, 330, 288, 258, 243, 221, 199, 185, 172, 145, 115, 89, 75, 55; elemental analysis calcd (%) for C<sub>24</sub>H<sub>41</sub>NO<sub>4</sub>Si: 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):** DIBAL-H (1 M so-



lution in  $\text{CH}_2\text{Cl}_2$ , 10.0 mL, 9.96 mmol, 3.0 equiv) was added to a solution of Weinreb amide **54** (1.50 g, 3.32 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (20 mL) at  $-78^\circ\text{C}$ . The yellow solution was stirred at  $-78^\circ\text{C}$  for 1 h. After this time, the mixture was quenched by the addition of ethyl acetate (15 mL). The mixture was allowed to warm to  $20^\circ\text{C}$  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  $20^\circ\text{C}$  for 2 h and then the organic layer was extracted with  $\text{Et}_2\text{O}$  ( $2 \times$ ). The combined organic extracts were washed with brine, dried over  $\text{MgSO}_4$ , 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 **55** (1.21 g, 93%) as a pale-yellow oil.  $[\alpha]_D^{20} = +12.3$  ( $c = 1.0$  in  $\text{CHCl}_3$ );  $^1\text{H NMR}$  (400.0 MHz,  $\text{CDCl}_3$ ):  $\delta = 9.83$  (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 (dqdd,  $J = 9.2, 7.3, 6.0, 1.8$  Hz, 1H), 1.78 (ddq,  $J = 10.6, 9.6, 6.9$  Hz, 1H), 0.90 (s, 9H; 3  $\text{CH}_3$ ), 0.90 (d,  $J = 7.3$  Hz, 3H;  $\text{CH}_3$ ), 0.88 (d,  $J = 6.9$  Hz, 3H;  $\text{CH}_3$ ), 0.04 ppm (s, 6H; 2  $\text{CH}_3$ );  $^{13}\text{C NMR}$  (100.5 MHz,  $\text{CDCl}_3$ ):  $\delta = 201.6$  (C), 138.6 (C), 128.7 (CH), 128.2 (2CH), 126.1 (2CH), 100.3 (CH), 80.1 (CH), 77.4 (CH), 64.9 ( $\text{CH}_2$ ), 47.0 ( $\text{CH}_2$ ), 36.6 (CH), 35.1 (CH), 26.0 (3  $\text{CH}_3$ ), 18.4 (C), 11.8 ( $\text{CH}_3$ ), 9.7 ( $\text{CH}_3$ ),  $-5.3$  ppm (2  $\text{CH}_3$ ); IR (film):  $\tilde{\nu} = 2955, 2929, 2882, 2856, 1728, 1471, 1462, 1402, 1256, 1101, 1073, 1029, 837$   $\text{cm}^{-1}$ ; MS (GC, EI):  $m/z$ : 335 [ $M - t\text{Bu}$ ] $^+$ , 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**) and **[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:** A solution of  $t\text{BuLi}$  (1.5 M in pentane, 295  $\mu\text{L}$ , 0.44 mmol, 1.98 equiv) was added to a solution of alkyne **32** (305 mg, 0.62 mmol, 2.5 equiv) in THF (3 mL) at  $-78^\circ\text{C}$ . The resulting mixture was stirred for 30 min at  $-78^\circ\text{C}$  and then a solution of aldehyde **55** (100 mg, 0.25 mmol, 1.0 equiv) in THF (1 mL) was slowly added. After the reaction mixture had been stirred for 3 h at  $0^\circ\text{C}$ , a saturated aqueous  $\text{NH}_4\text{Cl}$  solution was added and the reaction mixture was extracted with  $\text{Et}_2\text{O}$ . The organic layers were washed with water and brine, dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/ $\text{Et}_2\text{O}$  98:2 to 80:20) to furnish the title compound **56** (30 mg, 14%), its diastereomer **57** (74 mg, 34%), and the starting aldehyde **55** (14 mg, 14%).

**Compound 56:**  $[\alpha]_D^{20} = -1.33$  ( $c = 0.64$  in  $\text{CHCl}_3$ );  $^1\text{H NMR}$  (400.0 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.49$ –7.43 (m, 2H), 7.39–7.30 (m, 3H), 5.97 (dq,  $J = 9.6, 1.4$ ,  $J_{\text{H},^{17}\text{Sn}} = J_{\text{H},^{19}\text{Sn}} = 132.8$  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;  $\text{CH}_3$ ), 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 (ddd,  $J = 9.6, 6.9, 5.9$  Hz, 1H), 2.12 (ddd,  $J = 14.6, 7.8, 2.3$  Hz, 1H), 2.10 (dqdd,  $J = 9.2, 6.0, 1.4$  Hz, 1H), 1.95 (ddd,  $J = 14.6, 10.1, 2.7$  Hz, 1H), 1.89 (d,  $J = 1.4$ ,  $J_{\text{H},^{17}\text{Sn}} = J_{\text{H},^{19}\text{Sn}} = 44.8$  Hz, 3H;  $\text{CH}_3$ ), 1.76 (ddq,  $J = 10.1, 10.1, 6.4$  Hz, 1H), 1.54–1.43 (m, 6H; 3  $\text{CH}_2$ ), 1.33–1.29 (sext,  $J = 7.8$  Hz, 6H; 3  $\text{CH}_2$ ), 1.22 (d,  $J = 6.9$  Hz, 3H;  $\text{CH}_3$ ), 1.02 (d,  $J = 6.9$  Hz, 3H;  $\text{CH}_3$ ), 1.0–0.81 (m, 18H; 4  $\text{CH}_3$ , 3  $\text{CH}_2$ ), 0.89 (s; 3  $\text{CH}_3$ ), 0.81 (d,  $J = 6.4$  Hz, 3H;  $\text{CH}_3$ ), 0.04 ppm (s, 6H; 2  $\text{CH}_3$ );  $^{13}\text{C NMR}$  (100.5 MHz,  $\text{CDCl}_3$ ):  $\delta = 143.9$  ( $J_{\text{C},^{17}\text{Sn}} = J_{\text{C},^{19}\text{Sn}} = 26.8$  Hz; CH), 138.6 ( $J_{\text{C},^{17}\text{Sn}} = J_{\text{C},^{19}\text{Sn}} = 385.3$  Hz; C), 137.7 (C), 128.3 (CH), 127.9 (2CH), 125.7 (2CH), 99.8 (CH), 98.1 ( $\text{CH}_2$ ), 87.0 (CH), 85.5 (C), 82.5 (C), 80.1 (CH), 79.6 (CH), 64.7 ( $\text{CH}_2$ ), 60.0 (CH), 59.6 ( $\text{CH}_3$ ), 42.2 ( $J_{\text{C},^{17}\text{Sn}} = J_{\text{C},^{19}\text{Sn}} = 30.6$  Hz; CH), 42.1 ( $\text{CH}_2$ ), 36.4 (CH), 34.7 (CH), 30.0 (CH), 29.1 ( $J_{\text{C},^{17}\text{Sn}} = J_{\text{C},^{19}\text{Sn}} = 19.1$  Hz; 3  $\text{CH}_2$ ), 27.3 ( $J_{\text{C},^{17}\text{Sn}} = J_{\text{C},^{19}\text{Sn}} = 57.5$  Hz; 3  $\text{CH}_2$ ), 26.7 ( $J_{\text{C},^{17}\text{Sn}} = J_{\text{C},^{19}\text{Sn}} = 44.1$  Hz;  $\text{CH}_3$ ), 25.8 (3  $\text{CH}_3$ ), 18.6 ( $\text{CH}_3$ ), 18.1 (C), 16.6 ( $\text{CH}_3$ ), 13.6 (3  $\text{CH}_3$ ), 11.5 ( $\text{CH}_3$ ), 9.8 ( $J_{\text{C},^{17}\text{Sn}} = 313.4$ ,  $J_{\text{C},^{19}\text{Sn}} = 327.8$  Hz; 3  $\text{CH}_2$ ), 9.5 ( $\text{CH}_3$ ),  $-5.5$  ppm (2  $\text{CH}_3$ ); IR (film):  $\tilde{\nu} = 2956, 2928, 2855, 2360, 2341, 1594, 1455, 1404, 1375, 1255, 1149, 1095, 1050, 836, 775, 695,$

663, 661  $\text{cm}^{-1}$ ; elemental analysis calcd (%) for  $\text{C}_{46}\text{H}_{82}\text{O}_6\text{SiSn}$ : C 62.93, H 9.41; found: C 63.10, H 9.55.

**Compound 57:**  $^1\text{H NMR}$  (400.0 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.47$ –7.24 (m, 2H), 7.39–7.30 (m, 3H), 6.00 (dq,  $J = 9.6, 1.4$ ,  $J_{\text{H},^{17}\text{Sn}} = J_{\text{H},^{19}\text{Sn}} = 137.4$  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;  $\text{CH}_3$ ), 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,  $J = 1.4$ ,  $J_{\text{H},^{17}\text{Sn}} = J_{\text{H},^{19}\text{Sn}} = 42.6$  Hz, 3H;  $\text{CH}_3$ ), 1.80–1.71 (m, 1H), 1.53–1.45 (m, 6H; 3  $\text{CH}_2$ ), 1.32 (sext,  $J = 7.3$  Hz, 6H; 3  $\text{CH}_2$ ), 1.21 (d,  $J = 6.9$  Hz, 3H;  $\text{CH}_3$ ), 1.00 (d,  $J = 6.9$  Hz, 3H;  $\text{CH}_3$ ), 1.00–0.86 (m, 18H; 4  $\text{CH}_3$ , 3  $\text{CH}_2$ ), 0.90 (s, 9H; 3  $\text{CH}_3$ ), 0.82 (d,  $J = 6.9$  Hz, 3H), 0.04 ppm (s, 6H; 2  $\text{CH}_3$ );  $^{13}\text{C NMR}$  (100.5 MHz,  $\text{CDCl}_3$ ):  $\delta = 144.2$  (CH), 138.7 (C), 137.8 (C), 128.7 (CH), 128.2 (2CH), 126.0 (2CH), 100.5.1 (CH), 98.3 ( $\text{CH}_2$ ), 87.4 (CH), 85.7 (C), 82.5 (C), 81.7 (CH), 80.4 (CH), 65.0 ( $\text{CH}_2$ ), 61.8 (CH), 56.3 ( $\text{CH}_3$ ), 42.3 (CH), 41.2 ( $\text{CH}_2$ ), 36.7 (CH), 35.2 (CH), 30.3 (CH), 29.3 ( $J_{\text{C},^{17}\text{Sn}} = J_{\text{C},^{19}\text{Sn}} = 20.1$  Hz; 3  $\text{CH}_2$ ), 27.6 ( $J_{\text{C},^{17}\text{Sn}} = J_{\text{C},^{19}\text{Sn}} = 57.5$  Hz; 3  $\text{CH}_2$ ), 27.3 ( $J_{\text{C},^{17}\text{Sn}} = J_{\text{C},^{19}\text{Sn}} = 46.0$  Hz;  $\text{CH}_3$ ), 26.1 (3  $\text{CH}_3$ ), 18.8 ( $\text{CH}_3$ ), 18.5 (C), 16.5 ( $\text{CH}_3$ ), 13.9 (3  $\text{CH}_3$ ), 11.9 ( $\text{CH}_3$ ), 10.1 ( $J_{\text{C},^{17}\text{Sn}} = 312.5$ ,  $J_{\text{C},^{19}\text{Sn}} = 329.8$  Hz; 3  $\text{CH}_2$ ), 9.8 ( $\text{CH}_3$ ),  $-5.5$  ppm (2  $\text{CH}_3$ ).

**Reduction of ynone 58 (vide infra):** A solution of (*S*)-CBS-oxazaborolidine in toluene (1 M, 8.22 mL, 8.22 mmol, 2.0 equiv) and  $\text{BH}_3 \cdot \text{Me}_2\text{S}$  (2 M in THF, 10.3 mL, 20.5 mmol, 5.0 equiv) were added to a solution of compound **58** (3.6 g, 4.1 mmol, 1.0 equiv) in THF (20 mL) at  $-30^\circ\text{C}$ . The resulting mixture was stirred for 2 h at  $-30^\circ\text{C}$  and was then quenched with EtOH and extracted with  $\text{Et}_2\text{O}$ . The organic layers were washed with water and brine, dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/ $\text{AcOEt}$  95:5 to 70:30) to give the title compound **56** (6.88 g, 95%).

**Compound 57 was also obtained by enantioselective reduction of ynone 58:** A solution of (*R*)-CBS-oxazaborolidine in toluene (1 M, 171  $\mu\text{L}$ , 0.171 mmol, 2.0 equiv) and  $\text{BH}_3 \cdot \text{Me}_2\text{S}$  (2 M in THF, 214  $\mu\text{L}$ , 0.43 mmol, 5.0 equiv) were added to a solution of ynone **58** (75 mg, 0.085 mmol, 1.0 equiv) in THF (0.5 mL) at  $-30^\circ\text{C}$ . The resulting mixture was stirred for 2 h at  $-30^\circ\text{C}$  and was then quenched with EtOH and extracted with  $\text{Et}_2\text{O}$ . The organic layers were washed with water and brine, dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/ $\text{AcOEt}$  95:5 to 70:30) to give **57** (63 mg, 90%).

**[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-oxo-dec-8-en-3-yn-1-yl]-5-methyl-2-phenyl-1,3-dioxinan (**58**)**

**Coupling reaction with *t*BuLi:** A solution of  $t\text{BuLi}$  (1.5 M in pentane, 295  $\mu\text{L}$ , 0.44 mmol, 1.98 equiv) was added to a solution of alkyne **32** (215 mg, 0.44 mmol, 2.0 equiv) in THF (3 mL) at  $-78^\circ\text{C}$ . The resulting mixture was stirred for 30 min at  $-78^\circ\text{C}$  and then a solution of amide **54** (100 mg, 0.22 mmol, 1.0 equiv) in THF (1 mL) was slowly added. After the reaction mixture had been stirred for 3 h at  $0^\circ\text{C}$ , a saturated aqueous  $\text{NH}_4\text{Cl}$  solution was added and the reaction mixture was extracted with  $\text{Et}_2\text{O}$ . The organic layers were washed with water and brine, dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/ $\text{Et}_2\text{O}$  98:2 to 80:20) to furnish the title compound **58** (156 mg, 81%).

**Coupling reaction with *n*BuLi—preparation of *n*BuLi in  $\text{Et}_2\text{O}$ :** Small pieces of lithium (wire containing 0.5–1% Na, 4.3 g, 619 mmol, 2.48 equiv) were introduced to a four-necked flask (500 mL) containing dry  $\text{Et}_2\text{O}$  (100 mL) and equipped with a thermometer, a mechanical stirrer, and a dropping funnel under argon. After starting the stirrer, 30 drops of a *n*-butylbromide (27 mL, 250 mmol, 1.0 equiv) solution in  $\text{Et}_2\text{O}$  (50 mL) were added from the dropping funnel. After a few minutes, the solution became slightly cloudy and bright spots appeared on the lithium. The reaction mixture was then cooled to  $-10^\circ\text{C}$  by immersing in a  $-30^\circ\text{C}$  nitrogen/acetone bath. The remainder of the *n*-butylbromide solution was added over 20 min while keeping the internal temperature below  $-10^\circ\text{C}$ . After the addition was complete, the reaction mixture was allowed to warm up gradually to 0 and then  $10^\circ\text{C}$  with stirring over 1.5 h.

The pale-blue solution was then filtered whilst being transferred to a flask by cannula, titrated by a standard method (1.23 M, 74%), and kept under argon at 4°C.

A solution of *n*BuLi in Et<sub>2</sub>O (1.23 M, 2.8 mL, 3.44 mmol, 1.98 equiv) was added to a solution of alkyne **32** (1.7 g, 3.5 mmol, 2.0 equiv) in THF (25 mL) at -40°C. The resulting mixture was stirred for 50 min at -40°C and then a solution of amide **54** (789 mg, 1.75 mmol, 1.0 equiv) in THF (12 mL) was slowly added. After the reaction mixture had been stirred for 1 h at 0°C, a saturated aqueous NH<sub>4</sub>Cl solution was added and the reaction mixture was extracted with Et<sub>2</sub>O. The organic layers were washed with water and brine, dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/Et<sub>2</sub>O 98:2 to 80:20) to furnish the title compound **58** (1.22 g, 81%). [ $\alpha$ ]<sub>D</sub><sup>20</sup> = +13.4 (*c* = 0.94 in CHCl<sub>3</sub>); <sup>1</sup>H NMR (400.0 MHz, CDCl<sub>3</sub>):  $\delta$  = 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, 2 Hz, 1H), 3.51 (dd, *J* = 9.6, 5.9 Hz, 1H), 3.39 (s, 3H; CH<sub>3</sub>), 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 (dddm, *J* = 9.2, 5.9, 1.4 Hz, 1H), 1.88 (d, *J* = 1.4, *J*<sub>H<sup>117</sup>Sn</sub> = *J*<sub>H<sup>119</sup>Sn</sub> = 41.2 Hz, 3H; CH<sub>3</sub>), 1.72 (ddq, *J* = 9.6, 9.6, 6.9 Hz, 1H), 1.54–1.43 (m, 6H; 3 CH<sub>2</sub>), 1.32 (sext, *J* = 7.3 Hz, 6H; 3 CH<sub>2</sub>), 1.24 (d, *J* = 6.9 Hz, 3H; CH<sub>3</sub>), 1.00 (d, *J* = 6.9 Hz, 3H; CH<sub>3</sub>), 0.95–0.87 (m, 27H; 7 CH<sub>3</sub> + 3 CH<sub>2</sub>), 0.80 (d, *J* = 6.9 Hz, 3H; CH<sub>3</sub>), 0.04 ppm (s, 6H; 2 CH<sub>3</sub>); <sup>13</sup>C NMR (100.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 185.3 (C), 143.4 (CH), 138.8 (C), 138.7 (C), 128.4 (CH), 128.0 (2 CH), 126.0 (2 CH), 99.9 (CH), 98.3 (CH<sub>2</sub>), 96.5 (C), 85.2 (CH), 83.0 (C), 80.3 (CH), 78.2 (CH), 65.0 (CH<sub>2</sub>), 56.4 (CH<sub>3</sub>), 49.5 (CH<sub>2</sub>), 42.8 (*J*<sub>13C,117Sn</sub> = *J*<sub>13C,119Sn</sub> = 30.6 Hz; CH), 36.7 (CH), 35.0 (CH), 30.8 (CH), 29.4 (3 CH<sub>2</sub>), 27.5 (*J*<sub>13C,117Sn</sub> = *J*<sub>13C,119Sn</sub> = 58.4 Hz; CH<sub>3</sub>, 3 CH<sub>2</sub>), 26.0 (3 CH<sub>3</sub>), 18.4 (C), 17.8 (CH<sub>3</sub>), 17.1 (CH<sub>3</sub>), 13.8 (3 CH<sub>3</sub>), 11.9 (CH<sub>3</sub>), 10.1 (*J*<sub>13C,117Sn</sub> = 313.4, *J*<sub>13C,119Sn</sub> = 328.8 Hz; 3 CH<sub>2</sub>), 9.7 (CH<sub>3</sub>), -5.2 ppm (2 CH<sub>3</sub>); IR (film):  $\tilde{\nu}$  = 2956, 2855, 2212, 1678, 1465, 1403, 1376, 1345, 1255, 1215, 1147, 1092, 1032, 837, 758, 699 cm<sup>-1</sup>; elemental analysis calcd (%) for C<sub>46</sub>H<sub>80</sub>O<sub>6</sub>SiSn: C 63.08, H 9.21; found: C 63.18, H 9.32.

**[2S,4R(1R),5S,6S(2S,5S,6R,7S,8Z)]-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 (59):** Diisopropylethylamine (34.1 mL, 196 mmol, 20 equiv) and MOMCl (5.95 mL, 78.4 mmol, 10 equiv) were added 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 CH<sub>2</sub>Cl<sub>2</sub> (35 mL) at 0°C. After the reaction mixture had been stirred for 12 h at 20°C, it was quenched with a saturated aqueous NaHCO<sub>3</sub> solution and extracted with Et<sub>2</sub>O. The organic layers were washed with brine, dried over MgSO<sub>4</sub>, 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 **[2S,4R(1S),5S,6S(2S,5S,6R,7S,8Z)]-4-[2-(tert-butyl-dimethylsilyloxy)-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** (6.2 g, 86%) as a yellow oil. [ $\alpha$ ]<sub>D</sub><sup>20</sup> = -17.2 (*c* = 1.52 in CHCl<sub>3</sub>); <sup>1</sup>H NMR (400.0 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.49–7.47 (m, 2H), 7.37–7.30 (m, 3H), 6.00 (d, 1H, *J* = 9.6, *J*<sub>H<sup>117</sup>Sn</sub> = *J*<sub>H<sup>119</sup>Sn</sub> = 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; CH<sub>3</sub>), 3.36 (s, 3H; CH<sub>3</sub>), 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*<sub>H<sup>117</sup>Sn</sub> = *J*<sub>H<sup>119</sup>Sn</sub> = 41.7 Hz, 3H; CH<sub>3</sub>), 1.87–1.83 (m, 1H), 1.66–1.63 (m, 1H), 1.52–1.45 (m, 6H; 3 CH<sub>2</sub>), 1.33 (sext, *J* = 7.3 Hz, 6H; 3 CH<sub>2</sub>), 1.18 (d, *J* = 7.3 Hz, 3H; CH<sub>3</sub>), 0.98 (d, *J* = 6.9 Hz, 3H; CH<sub>3</sub>), 0.98–0.85 (m, 18H; 4 CH<sub>3</sub> + 3 CH<sub>2</sub>), 0.89 (s, 9H; 3 CH<sub>3</sub>), 0.81 (d, *J* = 6.4 Hz, 3H; CH<sub>3</sub>), 0.05 ppm (s, 6H; 2 CH<sub>3</sub>); <sup>13</sup>C NMR (100.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 144.2 (*J*<sub>13C,117Sn</sub> = *J*<sub>13C,119Sn</sub> = 29.7 Hz; CH), 139.1 (C), 137.5 (C), 128.3 (CH), 128.0 (2 CH), 125.8 (2 CH), 99.6 (CH), 98.1 (CH<sub>2</sub>), 93.6 (CH<sub>2</sub>), 87.7 (C), 85.3 (C), 80.1 (C), 80.0 (CH), 77.6 (CH), 65.0 (CH<sub>2</sub>), 61.0 (CH), 56.1 (CH<sub>3</sub>), 55.5 (CH<sub>3</sub>), 42.0 (CH), 39.9 (CH<sub>2</sub>), 36.6 (CH), 35.2 (CH), 30.2 (CH), 29.2 (*J*<sub>13C,117Sn</sub> = *J*<sub>13C,119Sn</sub> = 20.1 Hz; 3 CH<sub>2</sub>), 27.4 (*J*<sub>13C,117Sn</sub> = *J*<sub>13C,119Sn</sub> = 58.4 Hz; CH<sub>3</sub>), 26.9 (*J*<sub>13C,117Sn</sub> = *J*<sub>13C,119Sn</sub> = 53.6 Hz;

3 CH<sub>2</sub>), 25.9 (3 CH<sub>3</sub>), 18.5 (CH<sub>3</sub>), 18.3 (C), 16.3 (CH<sub>3</sub>), 13.7 (3 CH<sub>3</sub>), 11.6 (CH<sub>3</sub>), 9.9 (*J*<sub>13C,117Sn</sub> = 313.4, *J*<sub>13C,119Sn</sub> = 327.8 Hz; 3 CH<sub>2</sub>), 9.6 (CH<sub>3</sub>), -5.4 ppm (2 CH<sub>3</sub>); IR (film):  $\tilde{\nu}$  = 2956, 2928, 2380, 2341, 1456, 1402, 1375, 1350, 1250, 1158, 1098, 1015, 920, 837, 775, 690, 663 cm<sup>-1</sup>; elemental analysis calcd (%) for C<sub>48</sub>H<sub>86</sub>O<sub>7</sub>SiSn: C 62.53, H 9.40; found: C 62.33, H 9.59.

A HF-pyridine stock solution (500  $\mu$ L, prepared from commercial HF-pyridine 2 mL/pyridine 4 mL/THF 10 mL) was added to a solution of the preceding di-MOM ether (100 mg, 0.108 mmol, 1.0 equiv) in THF (1 mL) at 0°C. After the reaction mixture had been stirred for 4 h at 20°C, the resulting mixture was quenched with a saturated aqueous NaHCO<sub>3</sub> solution and extracted with Et<sub>2</sub>O. The organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/AcOEt 70:30 to 40:60) to give **[2S,4R(1S),5S,6S(2S,5S,6R,7S,8Z)]-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%). [ $\alpha$ ]<sub>D</sub><sup>20</sup> = -35.9 (*c* = 1.19 in CHCl<sub>3</sub>); <sup>1</sup>H NMR (400.0 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.46–7.43 (m, 2H), 7.38–7.33 (m, 3H), 6.01 (dq, 1H, *J* = 9.6, 1.4, *J*<sub>H<sup>117</sup>Sn</sub> = *J*<sub>H<sup>119</sup>Sn</sub> = 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; CH<sub>3</sub>), 3.34 (s, 3H; CH<sub>3</sub>), 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, *J*<sub>H<sup>117</sup>Sn</sub> = *J*<sub>H<sup>119</sup>Sn</sub> = 43.0 Hz, 3H; CH<sub>3</sub>), 1.89–1.85 (m, 1H), 1.83 (dq, *J* = 6.9, 6.4, 3.4 Hz, 1H), 1.49–1.38 (m, 6H; 3 CH<sub>2</sub>), 1.37–1.28 (sext, *J* = 7.3 Hz, 6H; 3 CH<sub>2</sub>), 1.18 (d, *J* = 6.9 Hz, 3H; CH<sub>3</sub>), 1.43 (d, *J* = 6.9 Hz, 3H; CH<sub>3</sub>), 1.03 (d, *J* = 6.9 Hz, 3H; CH<sub>3</sub>), 1.02–0.88 (m, 15H; 3 CH<sub>2</sub> + 3 CH<sub>3</sub>), 0.85 ppm (d, *J* = 6.9 Hz, 3H; CH<sub>3</sub>); <sup>13</sup>C NMR (100.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 144.1 (CH), 138.5 (C), 137.5 (C), 128.5 (CH), 128.1 (2 CH), 125.7 (2 CH), 99.9 (CH), 98.0 (CH<sub>2</sub>), 93.6 (CH<sub>2</sub>), 87.7 (C), 85.2 (CH), 83.5 (CH or CH<sub>2</sub>), 80.3 (C), 77.5 (CH or CH<sub>2</sub>), 66.7 (CH or CH<sub>2</sub>), 60.9 (CH), 56.1 (CH<sub>3</sub>), 55.4 (CH<sub>3</sub>), 41.9 (*J*<sub>13C,117Sn</sub> = *J*<sub>13C,119Sn</sub> = 34.4 Hz; CH), 39.8 (CH<sub>2</sub>), 35.5 (CH), 35.3 (CH), 30.1 (CH), 29.2 (*J*<sub>13C,117Sn</sub> = *J*<sub>13C,119Sn</sub> = 19.2 Hz; 3 CH<sub>2</sub>), 27.4 (*J*<sub>13C,117Sn</sub> = *J*<sub>13C,119Sn</sub> = 58.5 Hz; 3 CH<sub>2</sub>), 27.2 (*J*<sub>13C,117Sn</sub> = *J*<sub>13C,119Sn</sub> = 46.0 Hz; CH<sub>3</sub>), 18.5 (CH<sub>3</sub>), 16.3 (CH<sub>3</sub>), 13.6 (3 CH<sub>3</sub>), 11.5 (CH<sub>3</sub>), 9.8 (*J*<sub>13C,117Sn</sub> = 314.4, *J*<sub>13C,119Sn</sub> = 327.8 Hz; 3 CH<sub>2</sub>), 9.5 ppm (CH<sub>3</sub>); IR (film):  $\tilde{\nu}$  = 3380, 2956, 2927, 2872, 2852, 1590, 1454, 1436, 1376, 1351, 1154, 1098, 1029, 699 cm<sup>-1</sup>; elemental analysis calcd (%) for C<sub>42</sub>H<sub>72</sub>O<sub>7</sub>Sn: C 62.46, H 8.98; found: C 62.58, H 9.00.

BAIB (1.44 g, 4.46 mmol, 1.1 equiv) and TEMPO (160 mg, 0.81 mmol, 0.2 equiv) were added to a solution of the preceding alcohol (3.3 g, 4.05 mmol, 1.0 equiv) in dried CH<sub>2</sub>Cl<sub>2</sub> (20 mL). After the reaction mixture had been stirred for 3 h at 20°C, a 1 M Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution was added, and the reaction mixture was extracted with Et<sub>2</sub>O. The organic layers were washed with a saturated aqueous NaHCO<sub>3</sub> solution, brine, dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude **[2S,4R(1R),5S,6S(2S,5S,6R,7S,8Z)]-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. <sup>1</sup>H NMR (400.0 MHz, CDCl<sub>3</sub>):  $\delta$  = 9.80 (s, 1H), 7.42–7.32 (m, 5H), 6.00 (dq, *J* = 8.2, 1.4, *J*<sub>H<sup>117</sup>Sn</sub> = *J*<sub>H<sup>119</sup>Sn</sub> = 135.1 Hz, 1H), 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; CH<sub>3</sub>), 3.35 (s, 3H; CH<sub>3</sub>), 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, *J*<sub>H<sup>117</sup>Sn</sub> = *J*<sub>H<sup>119</sup>Sn</sub> = 41.2 Hz, 3H; CH<sub>3</sub>), 1.89–1.84 (m, 1H), 1.84 (ddq, *J* = 10.1, 9.6, 6.4 Hz, 1H), 1.51–1.44 (m, 6H; 3 CH<sub>2</sub>), 1.33 (sext, *J* = 7.3 Hz, 6H; 3 CH<sub>2</sub>), 1.23 (d, *J* = 6.9 Hz, 3H; CH<sub>3</sub>), 1.19 (d, *J* = 7.3 Hz, 3H; CH<sub>3</sub>), 0.99 (d, *J* = 6.9 Hz, 3H; CH<sub>3</sub>), 0.96–0.88 (m, 15H; 3 CH<sub>2</sub> + 3 CH<sub>3</sub>), 0.90 ppm (d, *J* = 6.4 Hz, 3H); <sup>13</sup>C NMR (100.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 204.0 (C), 144.0 (*J*<sub>13C,117Sn</sub> = *J*<sub>13C,119Sn</sub> = 32.6 Hz; CH), 137.9 (C), 137.2 (C), 128.0 (2 CH), 127.3 (CH), 125.6 (2 CH), 99.6 (CH), 98.0 (CH<sub>2</sub>), 94.2 (CH<sub>2</sub>), 87.7 (C), 86.2 (CH), 80.6 (CH), 80.2 (C), 77.0 (CH), 60.7 (CH), 56.1 (CH<sub>3</sub>), 55.4 (CH<sub>3</sub>), 47.2 (CH), 41.9 (*J*<sub>13C,117Sn</sub> = *J*<sub>13C,119Sn</sub> = 34.4 Hz; CH), 39.7 (CH<sub>2</sub>), 34.9 (CH), 30.1 (CH), 29.1 (*J*<sub>13C,117Sn</sub> = *J*<sub>13C,119Sn</sub> = 21.0 Hz; 3 CH<sub>2</sub>), 27.3 (*J*<sub>13C,117Sn</sub> = *J*<sub>13C,119Sn</sub> = 57.4 Hz; 3 CH<sub>2</sub>), 27.2 (*J*<sub>13C,117Sn</sub> = *J*<sub>13C,119Sn</sub> = 46.0 Hz; CH<sub>3</sub>), 18.4 (CH<sub>3</sub>), 16.3 (CH<sub>3</sub>), 13.6 (3 CH<sub>3</sub>), 13.5 (CH<sub>3</sub>), 9.8 (3 CH<sub>2</sub>), 6.8 (CH<sub>3</sub>).

A solution of  $\text{NaClO}_2$  (549 mg, 6.07 mmol, 1.5 equiv) and  $\text{NaH}_2\text{PO}_4$  (729 mg, 6.07 mmol, 1.5 equiv) in  $\text{H}_2\text{O}$  (21 mL) was added to a solution of the preceding aldehyde (3.26 g, 4.05 mmol, 1.0 equiv) in *tert*-butanol (245 mL) and 2-methyl-2-butene (55 mL). After the reaction mixture had been stirred for 1 h at 20°C, the same quantity of  $\text{NaClO}_2$  and  $\text{NaH}_2\text{PO}_4$  solution was added. The resulting mixture was stirred for 1 h and was then quenched by the addition of a 0.1 N HCl solution. The mixture was extracted with  $\text{CH}_2\text{Cl}_2$  and the organic layers were washed with brine, dried over  $\text{MgSO}_4$ , 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-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.  $^1\text{H NMR}$  (400.0 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.43–7.40 (m, 2H), 7.33–7.28 (m, 3H), 6.00 (d,  $J$  = 8.2 Hz, 1H,  $J_{\text{H},^{13}\text{C}} = J_{\text{H},^{19}\text{Sn}} = 133.3$  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;  $\text{CH}_3$ ), 3.35 (s, 3H;  $\text{CH}_3$ ), 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,  $J_{\text{H},^{13}\text{C}} = J_{\text{H},^{19}\text{Sn}} = 42.6$  Hz, 3H;  $\text{CH}_3$ ), 1.89–1.85 (m, 1H), 1.64 (ddq,  $J$  = 10.1, 9.6, 6.4 Hz, 1H), 1.53–1.42 (m, 6H; 3  $\text{CH}_2$ ), 1.31 (d,  $J$  = 6.9 Hz, 3H;  $\text{CH}_3$ ), 1.30 (sext,  $J$  = 7.3 Hz, 6H; 3  $\text{CH}_2$ ), 1.17 (d,  $J$  = 6.9 Hz, 3H;  $\text{CH}_3$ ), 0.98 (d,  $J$  = 6.4 Hz, 3H;  $\text{CH}_3$ ), 0.94–0.85 ppm (m, 18H; 3  $\text{CH}_2$ , 4  $\text{CH}_3$ );  $^{13}\text{C NMR}$  (100.5 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 178.0 (C), 144.2 ( $J_{^{13}\text{C},^{117}\text{Sn}} = J_{^{13}\text{C},^{19}\text{Sn}} = 29.0$  Hz; CH), 138.2 (C), 137.6 (C), 128.5 (CH), 128.1 (2CH), 125.7 (2CH), 99.7 (CH), 98.1 (CH<sub>2</sub>), 93.7 (CH<sub>2</sub>), 88.0 (C), 85.3 (CH), 81.8 (CH), 80.0 (C), 77.0 (CH), 61.0 (CH), 56.2 (CH<sub>3</sub>), 55.5 (CH<sub>3</sub>), 42.1 (CH), 40.7 (CH), 39.8 (CH<sub>2</sub>), 35.5 (CH), 30.2 (CH), 29.2 ( $J_{^{13}\text{C},^{117}\text{Sn}} = J_{^{13}\text{C},^{19}\text{Sn}} = 19.2$  Hz; 3  $\text{CH}_2$ ), 27.3 ( $J_{^{13}\text{C},^{117}\text{Sn}} = J_{^{13}\text{C},^{19}\text{Sn}} = 57.4$  Hz; 3  $\text{CH}_2$ ), 27.2 ( $J_{^{13}\text{C},^{117}\text{Sn}} = J_{^{13}\text{C},^{19}\text{Sn}} = 36.4$  Hz;  $\text{CH}_3$ ), 18.6 (CH<sub>3</sub>), 16.4 (CH<sub>3</sub>), 15.2 (CH<sub>3</sub>), 13.7 (3  $\text{CH}_3$ ), 11.5 (CH<sub>3</sub>), 9.9 ppm ( $J_{^{13}\text{C},^{117}\text{Sn}} = 310.6$ ,  $J_{^{13}\text{C},^{19}\text{Sn}} = 331.8$  Hz; 3  $\text{CH}_2$ ).

A (trimethylsilyl)diazomethane solution (2 M in hexane, 4.05 mmol, 1.0 equiv) was added to a solution of the preceding acid (3.3 g, 4.05 mmol, 1.0 equiv) in benzene (160 mL)/MeOH (45 mL) until a yellow tint persisted. The resulting mixture was stirred for 15 min and was then concentrated in vacuum. The residue was purified by chromatography on silica gel (cyclohexane/AcOEt 90:10 to 80:20) to give the expected product **59** (2.32 g, 69% over 3 steps).  $[\alpha]_{\text{D}}^{20} = -34.5$  ( $c = 0.96$  in  $\text{CHCl}_3$ );  $^1\text{H NMR}$  (400.0 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.45–7.42 (m, 2H), 7.37–7.31 (m, 3H), 6.00 (dq,  $J$  = 9.6, 1.8,  $J_{\text{H},^{13}\text{C}} = J_{\text{H},^{19}\text{Sn}} = 132.8$  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;  $\text{CH}_3$ ), 3.43 (s, 3H;  $\text{CH}_3$ ), 3.36 (s, 3H;  $\text{CH}_3$ ), 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,  $J_{\text{H},^{13}\text{C}} = J_{\text{H},^{19}\text{Sn}} = 42.1$  Hz, 3H;  $\text{CH}_3$ ), 1.87–1.83 (m, 1H), 1.75 (ddq,  $J$  = 10.5, 9.6, 6.9 Hz, 1H), 1.57–1.51 (m, 6H; 3  $\text{CH}_2$ ), 1.37 (sext,  $J$  = 7.3 Hz, 6H; 3  $\text{CH}_2$ ), 1.24 (d,  $J$  = 7.3 Hz, 3H;  $\text{CH}_3$ ), 1.19 (d,  $J$  = 6.9 Hz, 3H;  $\text{CH}_3$ ), 1.00–0.80 (m, 15H; 3  $\text{CH}_2$ , 3  $\text{CH}_3$ ), 0.85 (d,  $J$  = 6.9 Hz, 3H;  $\text{CH}_3$ );  $^{13}\text{C NMR}$  (100.5 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 174.8 (C), 144.4 ( $J_{^{13}\text{C},^{117}\text{Sn}} = J_{^{13}\text{C},^{19}\text{Sn}} = 27.8$  Hz; CH), 138.6 (C), 137.7 ( $J_{^{13}\text{C},^{117}\text{Sn}} = J_{^{13}\text{C},^{19}\text{Sn}} = 369.0$  Hz; C), 128.6 (CH), 128.5 (2CH), 125.8 (2CH), 99.7 (CH), 98.2 (CH<sub>2</sub>), 93.8 (CH), 87.9 (C), 85.4 (C), 82.2 (CH), 80.5 (C), 77.0 (CH), 61.1 (CH), 56.2 (CH<sub>3</sub>), 55.7 (CH<sub>3</sub>), 52.1 (CH<sub>3</sub>), 42.2 ( $J_{^{13}\text{C},^{117}\text{Sn}} = J_{^{13}\text{C},^{19}\text{Sn}} = 42.6$  Hz; CH), 41.1 (CH), 39.9 (CH<sub>2</sub>), 35.8 (CH), 30.3 (CH), 29.4 ( $J_{^{13}\text{C},^{117}\text{Sn}} = J_{^{13}\text{C},^{19}\text{Sn}} = 19.2$  Hz; 3  $\text{CH}_2$ ), 27.6 ( $J_{^{13}\text{C},^{117}\text{Sn}} = J_{^{13}\text{C},^{19}\text{Sn}} = 57.4$  Hz; 3  $\text{CH}_2$ ), 27.4 ( $J_{^{13}\text{C},^{117}\text{Sn}} = J_{^{13}\text{C},^{19}\text{Sn}} = 44.1$  Hz;  $\text{CH}_3$ ), 18.7 (CH<sub>3</sub>), 16.5 (CH<sub>3</sub>), 13.8 (3  $\text{CH}_3$ ), 11.6 (CH<sub>3</sub>), 10.0 ( $J_{^{13}\text{C},^{117}\text{Sn}} = 312.4$ ,  $J_{^{13}\text{C},^{19}\text{Sn}} = 327.8$  Hz; 3  $\text{CH}_2$ ), 9.3 ppm (CH<sub>3</sub>); IR (film):  $\tilde{\nu}$  = 2955, 2927, 2872, 2853, 1745, 1454, 1403, 1349, 1375, 1207, 1154, 1110, 1029, 700  $\text{cm}^{-1}$ ; elemental analysis calcd (%) for  $\text{C}_{43}\text{H}_{72}\text{O}_8\text{Sn}$ : C 61.80, H 8.68; found: C 61.92, H 8.83.

**[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]deca-3,8-dien-1-yl]-5-methyl-2-phenyl-1,3-dioxinan (60)**:  $\text{PtO}_2$  (20 mg, 0.088 mmol, 0.35 equiv) was added to a solution of the preceding ester (200 mg, 0.24 mmol, 1.0 equiv) in AcOEt (2.5 mL). The resulting suspension was stirred for 12 h at 20°C under a  $\text{H}_2$  atmosphere. After this time, the mixture was 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.  $^1\text{H NMR}$  (400.0 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.49–7.44 (m, 2H), 7.35–7.29 (m, 3H), 5.93 (dq,  $J$  = 8.2, 1.4,  $J_{\text{H},^{117}\text{Sn}} = J_{\text{H},^{19}\text{Sn}} = 136.0$  Hz, 1H), 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;  $\text{CH}_3$ ), 3.32 (s, 6H; 2  $\text{CH}_3$ ), 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,  $J_{\text{H},^{117}\text{Sn}} = J_{\text{H},^{19}\text{Sn}} = 42.1$  Hz, 3H;  $\text{CH}_3$ ), 1.70–1.60 (m, 2H), 1.51–1.44 (m, 6H; 3  $\text{CH}_2$ ), 1.32 (sext,  $J$  = 7.3 Hz, 6H; 3  $\text{CH}_2$ ), 1.23 (d,  $J$  = 6.9 Hz, 3H;  $\text{CH}_3$ ), 0.98 (d,  $J$  = 6.9 Hz, 3H;  $\text{CH}_3$ ), 0.94 (d,  $J$  = 6.4 Hz, 3H;  $\text{CH}_3$ ), 0.92–0.82 ppm (m, 18H; 3  $\text{CH}_2$  + 4  $\text{CH}_3$ );  $^{13}\text{C NMR}$  (100.5 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 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 (CH<sub>2</sub>), 93.1 (CH<sub>2</sub>), 86.3 (CH), 82.2 (CH), 77.3 (CH), 66.2 (CH), 56.1 (CH<sub>3</sub>), 55.2 (CH<sub>3</sub>), 51.9 (CH<sub>3</sub>), 41.0 (2CH), 39.1 (CH<sub>2</sub>), 35.9 (CH), 35.8 (CH), 29.2 ( $J_{^{13}\text{C},^{117}\text{Sn}} = J_{^{13}\text{C},^{19}\text{Sn}} = 19.2$  Hz; 3  $\text{CH}_2$ ), 27.4 ( $J_{^{13}\text{C},^{117}\text{Sn}} = J_{^{13}\text{C},^{19}\text{Sn}} = 57.5$  Hz; 3  $\text{CH}_2$ ), 27.2 ( $J_{^{13}\text{C},^{117}\text{Sn}} = J_{^{13}\text{C},^{19}\text{Sn}} = 42.2$  Hz;  $\text{CH}_3$ ), 17.7 (CH<sub>3</sub>), 15.6 (CH<sub>3</sub>), 14.2 (CH<sub>3</sub>), 13.7 (3  $\text{CH}_3$ ), 11.6 (CH<sub>3</sub>), 9.9 ppm ( $J_{^{13}\text{C},^{117}\text{Sn}} = 313.4$ ,  $J_{^{13}\text{C},^{19}\text{Sn}} = 326.8$  Hz; 3  $\text{CH}_2$ ).

An iodine solution (48 mg, 0.19 mmol, 0.98 equiv) in  $\text{CH}_2\text{Cl}_2$  (16 mL) was added to a solution of the preceding compound (168 mg, 0.2 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (4 mL) at 0°C over 30 min. The resulting solution was immediately added to a 1 M  $\text{Na}_2\text{S}_2\text{O}_3$  solution and the organic phase was then concentrated under reduced pressure. The residue was taken up with  $\text{Et}_2\text{O}$  (3 mL) and a 0.7 M KF solution (600  $\mu\text{L}$ ). After the reaction mixture had been stirred for 3 h at 20°C, the solution was filtered and extracted with  $\text{Et}_2\text{O}$ . The organic layers were washed with brine, dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/ $\text{Et}_2\text{O}$  80:20 to 50:50) to give the title compound **60** (96 mg, 71% for 2 steps).  $[\alpha]_{\text{D}}^{20} = +3.70$  ( $c = 0.78$  in  $\text{CHCl}_3$ );  $^1\text{H NMR}$  (400.0 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 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;  $\text{CH}_3$ ), 3.35 (s, 6H; 2  $\text{CH}_3$ ), 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;  $\text{CH}_3$ ), 1.99 (ddm,  $J$  = 11.0, 1.8 Hz, 1H), 1.70 (ddq,  $J$  = 10.1, 9.6, 6.9 Hz, 1H), 1.72–1.64 (m, 1H), 1.25 (d,  $J$  = 6.9 Hz, 3H;  $\text{CH}_3$ ), 1.08 (d,  $J$  = 6.9 Hz, 3H;  $\text{CH}_3$ ), 0.96 (d,  $J$  = 6.9 Hz, 3H;  $\text{CH}_3$ ), 0.89 ppm (d,  $J$  = 6.9 Hz, 3H;  $\text{CH}_3$ );  $^{13}\text{C NMR}$  (100.5 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 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 (CH<sub>2</sub>), 95.9 (C), 93.1 (CH<sub>2</sub>), 85.6 (CH), 82.1 (CH), 77.6 (CH), 66.1 (CH), 56.1 (CH<sub>3</sub>), 55.2 (CH<sub>3</sub>), 51.9 (CH<sub>3</sub>), 43.9 (CH), 41.0 (CH), 39.2 (CH or CH<sub>2</sub>), 35.7 (CH), 35.3 (CH<sub>3</sub>), 33.6 (CH or CH<sub>2</sub>), 18.4 (CH<sub>3</sub>), 14.7 (CH<sub>3</sub>), 11.7 (CH<sub>3</sub>), 9.2 ppm (CH<sub>3</sub>); IR (film):  $\tilde{\nu}$  = 3428, 2952, 2928, 2880, 2821, 1744, 1454, 1435, 1398, 1207, 1152, 1090, 1045  $\text{cm}^{-1}$ ; elemental analysis calcd (%) for  $\text{C}_{51}\text{H}_{74}\text{IO}_8$ : 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)**: *t*BuLi (1.5 M in pentane, 355  $\mu\text{L}$ , 0.53 mmol, 3.8 equiv) was rapidly added to a solution of the alkyl iodide **43** (145 mg, 0.26 mmol, 1.8 equiv) in  $\text{Et}_2\text{O}$  (3.7 mL) at  $-80^\circ\text{C}$ . After 2 min, 9-MeOBBN (1 M in hexane, 602  $\mu\text{L}$ , 0.60 mmol, 4.3 equiv) followed by THF (3.7 mL) was added. The resulting mixture was stirred 10 min at  $-78^\circ\text{C}$  and was then allowed to warm to 20°C over a period of 1 h 15 min. An aqueous 3.5 M  $\text{Cs}_2\text{CO}_3$  solution was then added (220  $\mu\text{L}$ , 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,  $[\text{PdCl}_2(\text{dppf})]$  (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  $\text{Et}_2\text{O}$ , the organic layers were washed with brine, dried over  $\text{MgSO}_4$ , filtered, and the sol-

vent was removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/Et<sub>2</sub>O 80:20 to 60:40) to give the title compound **61** (87 mg, 60%). [ $\alpha$ ]<sub>D</sub><sup>20</sup> = +13.8 (c = 0.90 in CHCl<sub>3</sub>); <sup>1</sup>H NMR (400.0 MHz, CDCl<sub>3</sub>):  $\delta$  = 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, CH<sub>3</sub>), 3.55 (dd, *J* = 6.9, 3.2 Hz, 1H), 3.44 (dd, *J* = 4.6, 4.1 Hz, 1H), 3.34 (s, 3H; CH<sub>3</sub>), 3.33 (s, 3H; CH<sub>3</sub>), 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; CH<sub>3</sub>), 1.22 (d, *J* = 6.9 Hz, 3H; CH<sub>3</sub>), 1.06–0.83 (m; 8CH<sub>3</sub>), 0.91 (s, 9H; 3CH<sub>3</sub>), 0.68 (q, *J* = 7.8 Hz, 6H; 3CH<sub>2</sub>), 0.63 (d, *J* = 6.4 Hz, 3H; CH<sub>3</sub>), 0.07 ppm (s, 6H; 2CH<sub>3</sub>); <sup>13</sup>C NMR (100.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 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 (CH<sub>2</sub>), 99.6 (CH), 97.8 (CH<sub>2</sub>), 92.5 (CH<sub>2</sub>), 86.9 (CH), 82.2 (CH), 78.0 (CH), 77.0 (2CH), 66.4 (CH), 56.0 (CH<sub>3</sub>), 55.2 (CH<sub>3</sub>), 51.9 (CH<sub>3</sub>), 41.9, 41.0, 40.3, 39.0, 36.2, 35.8, 35.3, 35.0, 34.4 (7CH, 2CH<sub>2</sub>), 26.9 (3CH<sub>3</sub>), 23.1 (CH<sub>3</sub>), 18.5 (C), 18.5, 17.4, 16.5, 14.2, 11.6, 11.3, 9.3 (7CH<sub>3</sub>, CH<sub>2</sub>-2), 7.2 (3CH<sub>3</sub>), 5.7 (3CH<sub>2</sub>), –3.1 (CH<sub>3</sub>), –3.2 ppm (CH<sub>3</sub>); IR (film):  $\tilde{\nu}$  = 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<sup>-1</sup>; HRMS (ESI): *m/z*: calcd for C<sub>56</sub>H<sub>98</sub>O<sub>10</sub>NaSi<sub>2</sub>: 1009.6591; found: 1009.6591.

**Discodermolide 1:** PTSA (3 mg, 0.015 mmol, 0.28 equiv) was added to a solution of compound **61** (53 mg, 0.054 mmol, 1.0 equiv) in MeOH (6.5 mL) at 0°C. After the reaction mixture had been stirred for 1 h at 0°C, triethylamine was added (0.3 equiv), and the solvent was 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%). [ $\alpha$ ]<sub>D</sub><sup>20</sup> = +11.0 (c = 0.90 in CHCl<sub>3</sub>); <sup>1</sup>H NMR (400.0 MHz, CDCl<sub>3</sub>):  $\delta$  = 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; CH<sub>3</sub>), 3.63 (dd, *J* = 5.5, 2.8 Hz, 1H), 3.33 (s, 6H; 2CH<sub>3</sub>), 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; CH<sub>3</sub>), 1.65–1.55 (ddq, *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; CH<sub>3</sub>), 1.01 (d, *J* = 6.9 Hz, 3H; CH<sub>3</sub>), 0.96 (d, *J* = 6.4 Hz, 3H; CH<sub>3</sub>), 0.95–0.91 (m, 6H; 2CH<sub>3</sub>), 0.91 (s, 9H; 3CH<sub>3</sub>), 0.87 (d, *J* = 6.4 Hz, 3H; CH<sub>3</sub>), 0.70 (d, *J* = 6.9 Hz, 3H; CH<sub>3</sub>), 0.10 ppm (s, 6H; 2CH<sub>3</sub>); <sup>13</sup>C NMR (100.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 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 (CH<sub>2</sub>), 99.6 (CH), 97.9 (CH<sub>2</sub>), 93.2 (CH<sub>2</sub>), 86.8 (CH), 82.0 (CH), 79.0 (CH), 77.8 (CH), 76.7 (CH), 66.4 (CH), 56.1 (CH<sub>3</sub>), 55.3 (CH<sub>3</sub>), 51.9 (CH<sub>3</sub>), 41.1, 39.1, 38.0, 36.7, 36.3, 35.9, 35.3, 34.7, 34.4 (7CH, 2CH<sub>2</sub>), 26.3 (3CH<sub>3</sub>), 23.3 (CH<sub>3</sub>), 18.5 (C), 17.6, 17.1, 16.4, 13.4, 11.7, 9.5, 9.3 (7CH<sub>3</sub>), –3.1 (CH<sub>3</sub>), –3.6 ppm (CH<sub>3</sub>); IR (film):  $\tilde{\nu}$  = 2377, 2957, 2929, 2883, 2857, 1591, 1462, 1434, 1395, 1257, 1153, 1093, 1036, 874 cm<sup>-1</sup>; HRMS (ESI): *m/z*: calcd for C<sub>30</sub>H<sub>84</sub>O<sub>10</sub>NaSi: 895.5726; found: 895.5721.

Trichloroacetylisocyanate (16  $\mu$ L, 0.14 mmol, 1.05 equiv) was added to a solution of the preceding alcohol (114 mg, 0.13 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL). After the reaction mixture had been stirred for 15 min at 20°C, the resulting mixture was concentrated in vacuo and the residue taken up in MeOH (13 mL). K<sub>2</sub>CO<sub>3</sub> (99 mg, 0.71 mmol, 5.5 equiv) was added and the resulting solution was stirred for 1 h 15 min and then concentrated in vacuo and extracted with AcOEt. The organic layers were

washed with water, brine, dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/AcOEt 90:10 to 50:50) to give [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%) as a pale colorless oil. [ $\alpha$ ]<sub>D</sub><sup>20</sup> = +17.4 (c = 0.80 in CHCl<sub>3</sub>); <sup>1</sup>H NMR (400.0 MHz, CDCl<sub>3</sub>):  $\delta$  = 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), 4.82 (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; CH<sub>3</sub>), 3.43 (dd, *J* = 4.6, 4.1 Hz, 1H), 3.32 (s, 6H; 2CH<sub>3</sub>), 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; CH<sub>3</sub>), 1.25 (d, *J* = 7.3 Hz, 3H; CH<sub>3</sub>), 1.01 (d, *J* = 6.9 Hz, 3H; CH<sub>3</sub>), 0.94–0.85 (m, 12H; 4CH<sub>3</sub>), 0.91 (s, 9H; 3CH<sub>3</sub>), 0.73 (d, *J* = 6.9 Hz, 3H; CH<sub>3</sub>), 0.07 (s, 3H; CH<sub>3</sub>), 0.05 ppm (s, 3H; CH<sub>3</sub>); <sup>13</sup>C NMR (100.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 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 (CH<sub>2</sub>), 99.7 (CH), 97.8 (CH<sub>2</sub>), 93.2 (CH<sub>2</sub>), 86.9 (CH), 82.1 (CH), 78.8 (CH), 77.0 (2CH), 66.4 (CH), 56.0 (CH<sub>3</sub>), 55.2 (CH<sub>3</sub>), 51.9 (CH<sub>3</sub>), 41.2 (CH), 39.2 (CH<sub>2</sub>), 37.8 (CH), 36.3 (CH), 35.9 (CH<sub>3</sub>), 35.3 (CH), 35.1 (CH), 34.4 (CH), 29.7 (CH), 26.2 (3CH<sub>3</sub>), 23.0 (CH<sub>3</sub>), 18.5 (C), 18.5 (CH<sub>3</sub>), 17.5, 16.5, 11.7, 10.1 (4CH<sub>3</sub>), 13.7 (CH<sub>3</sub>), 9.4 (CH<sub>3</sub>), –3.3 (CH<sub>3</sub>), –3.6 ppm (CH<sub>3</sub>); IR (film):  $\tilde{\nu}$  = 3359, 2981, 2930, 2884, 2857, 1728, 1598, 1455, 1435, 1395, 1363, 1326, 1258, 1214, 1146, 1094, 1035, 836, 773, 757 cm<sup>-1</sup>; HRMS (ESI): *m/z*: calcd for C<sub>51</sub>H<sub>88</sub>O<sub>11</sub>NaSi: 938.5784; found: 938.5793.

HCl (4N, 1.5 mL) was added to a solution of the preceding compound (14 mg, 0.015 mmol, 1.0 equiv) in THF (1.5 mL). The resulting mixture was stirred for 72 h at 20°C and then solid NaHCO<sub>3</sub> was added and the mixture extracted with AcOEt (3 $\times$ ). The organic layers were washed with water, brine, dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5 to 90:10) to give the title compound (+)-discodermolide (**1**) (6.2 mg, 70%) as a white solid. [ $\alpha$ ]<sub>D</sub><sup>20</sup> = +16.2 (c = 1.0 in MeOH); <sup>1</sup>H NMR (400.0 MHz, CDCl<sub>3</sub>):  $\delta$  = 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+2OH), 1.72–1.60 (m; 3H+OH), 1.64 (s, 3H; CH<sub>3</sub>), 1.32 (d, *J* = 7.3 Hz, 3H; CH<sub>3</sub>), 1.08 (d, *J* = 6.9 Hz, 3H; CH<sub>3</sub>), 1.01 (d, *J* = 7.3 Hz, 3H; CH<sub>3</sub>), 0.98 (d, *J* = 6.4 Hz, 3H; CH<sub>3</sub>), 0.98 (d, *J* = 6.4 Hz, 3H; CH<sub>3</sub>), 0.95 (d, *J* = 6.4 Hz, 3H; CH<sub>3</sub>), 0.83 ppm (d, *J* = 5.9 Hz, 3H; CH<sub>3</sub>); <sup>13</sup>C NMR (100.5 MHz, CDCl<sub>3</sub>):  $\delta$  = 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 (CH<sub>2</sub>), 79.1 (CH), 78.8 (CH), 77.7 (CH), 75.7 (CH), 73.4 (CH), 64.5 (CH), 43.4 (CH), 41.1 (CH<sub>2</sub>), 37.5 (CH), 36.4 (CH), 35.9 (CH<sub>2</sub>), 35.6 (CH), 35.0 (CH), 33.2 (CH), 30.0 (CH), 23.6 (CH<sub>3</sub>), 18.6 (CH<sub>3</sub>), 17.7 (CH<sub>3</sub>), 16.1 (CH<sub>3</sub>), 16.0 (CH<sub>3</sub>), 13.9 (CH<sub>3</sub>), 12.9 (CH<sub>3</sub>), 9.3 ppm (CH<sub>3</sub>); <sup>1</sup>H NMR (400.0 MHz, CD<sub>3</sub>CN):  $\delta$  = 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; CH<sub>3</sub>), 1.21 (d, *J* = 7.3 Hz, 3H; CH<sub>3</sub>), 1.03 (d, *J* = 6.4 Hz, 3H; CH<sub>3</sub>), 1.01 (d, *J* = 6.4 Hz, 3H; CH<sub>3</sub>), 0.97 (d, *J* = 6.9 Hz, 3H; CH<sub>3</sub>), 0.90 (d, *J* = 6.9 Hz, 3H; CH<sub>3</sub>), 0.82 (d, *J* = 6.9 Hz, 3H; CH<sub>3</sub>), 0.75 ppm (d, *J* =

5.9 Hz, 3H; CH<sub>3</sub>); <sup>13</sup>C NMR (100.5 MHz, CD<sub>3</sub>CN): δ = 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 (CH<sub>2</sub>), 79.7 (CH), 79.2 (CH), 77.4 (CH), 75.9 (CH), 73.1 (CH), 63.3 (CH), 44.0 (CH), 42.1 (CH<sub>2</sub>), 38.4 (CH), 37.1 (CH), 36.5 (CH<sub>2</sub>), 36.2 (CH), 36.1 (CH), 34.4 (CH), 34.2 (CH), 23.3 (CH<sub>3</sub>), 19.7 (CH<sub>3</sub>), 18.1 (CH<sub>3</sub>), 17.6 (CH<sub>3</sub>), 15.8 (CH<sub>3</sub>), 15.6 (CH<sub>3</sub>), 13.1 (CH<sub>3</sub>), 9.2 ppm (CH<sub>3</sub>); HRMS (ESI): *m/z*: calcd for C<sub>33</sub>H<sub>55</sub>O<sub>8</sub>NNa: 616.3820 [M+Na]<sup>+</sup>; found: 616.3816.

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