Total Synthesis of Discodermolide: Optimization of the Effective Synthetic Route

ARTICLE *in* CHEMISTRY - A EUROPEAN JOURNAL · NOVEMBER 2008

Impact Factor: 5.73 · DOI: 10.1002/chem.200801478 · Source: PubMed

10 AUTHORS, INCLUDING:

Julien Barbion

6 PUBLICATIONS **41** CITATIONS

SEE PROFILE

Marie-Isabelle Lannou

Université René Descartes - Paris 5

24 PUBLICATIONS **417** CITATIONS

SEE PROFILE

Jean-François Betzer

Natural Product Chemistry Institute

39 PUBLICATIONS **471** CITATIONS

SEE PROFILE

Ange Pancrazi

Université René Descartes - Paris 5

105 PUBLICATIONS **1,049** CITATIONS

SEE PROFILE

CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200801478

Total Synthesis of Discodermolide: Optimization of the Effective Synthetic Route

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

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**),[1] a unique polyketide marine metabolite obtained in low yields from the Caribbean deep-water sponge *Discodermia dissoluta*. Biological studies revealed DDM to be a potent microtubule-stabilizing agent that, like Taxol (Paclitaxel), arrests cells at the G2/M boundary of the cell cycle.[2] The 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.[3] Extensive investigation of the site and mode of binding of DDM to β-tubulin as well as the determination of its bioactive conformation led to the proposal of a pharmacophore model.[2d] 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,[4] including the development of a preparative-scale approach.[5] Phase I clinical trials were initiated from Novartis Pharma AG; however, despite encouraging results, trials were suspended due to adverse toxicity at high doses.[6] 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.[7] The modulable character of this ap-

[a] Dr. E. de Lemos, Dr. F.-H. Porée, Dr. A. Bourin, Dr. J. Barbion, Dr. E. Agouridas, Dr. M.-I. Lannou, Dr. J.-F. Betzer, Dr. A. Pancrazi, Prof. J. Ardisson
Université Paris Descartes
Faculté de Pharmacie, CNRS UMR 8638
4 avenue de l'Observatoire
75270 Paris Cedex (France)
Fax: (+33) 143291403
E-mail: jean.francois.betzer@icsn.cnrs-gif.fr
ange.pancrazi@parisdescartes.fr
janick.ardisson@parisdescartes.fr

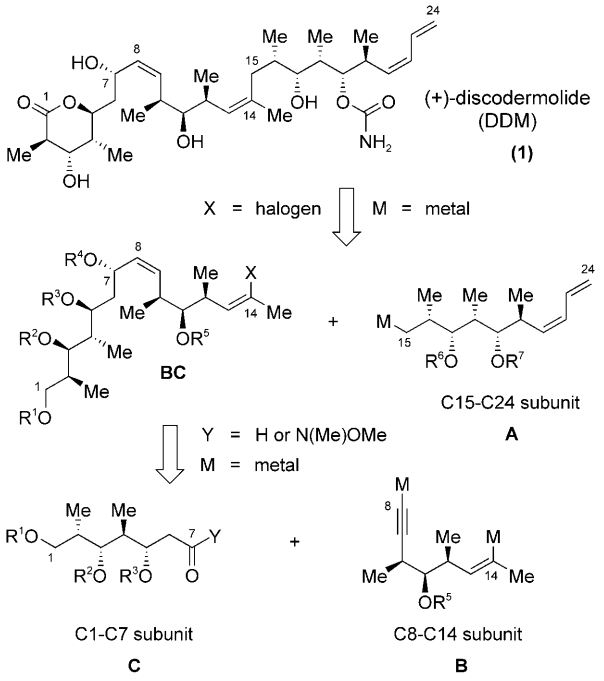
[b] Dr. A. Commerçon
Chemical&Analytical Sciences
Natural Product Chemistry, Sanofi-Aventis
Centre de Recherche de Vitry-Alfortville
13 Quai Jules Guesde
94403 Vitry-sur-Seine Cedex (France)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200801478.

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

Results and Discussion

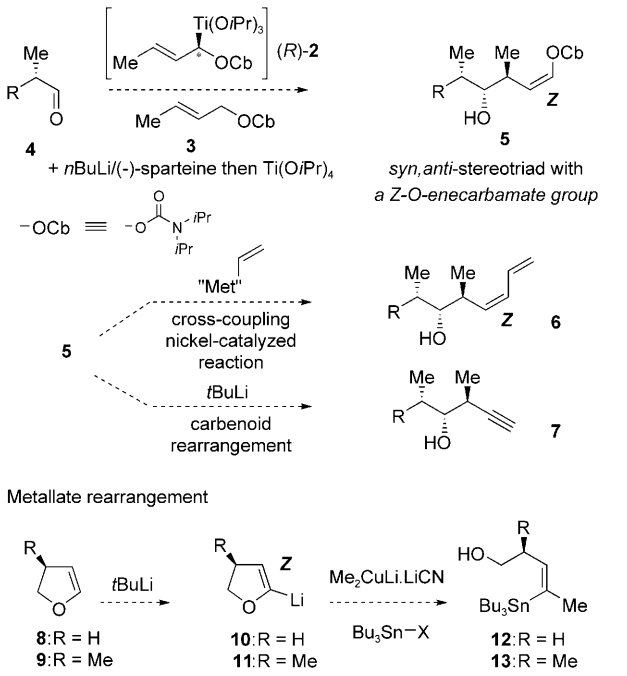
Retrosynthetic and strategic considerations: Our synthetic strategy relies upon the disassembly of DDM into three fragments of similar size and stereochemical complexity (**A** C15–C24, **B** C8–C14, **C** C1–C7; Scheme 1). The linkage of these subunits appears to us to be optimally convergent, the two 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 α-(*S*)-methyl aldehyde **4**. As exemplified in Scheme 2, this crotyltitanation reaction initially developed by Hoppe,[8] and widely used in total syntheses by our group,[9] 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*)-α-(*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.[10]

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**,[11] whereas a carbenoid rearrangement would install the terminal C8−C9 alkyne **7** of subunit **B** in one step.[12]

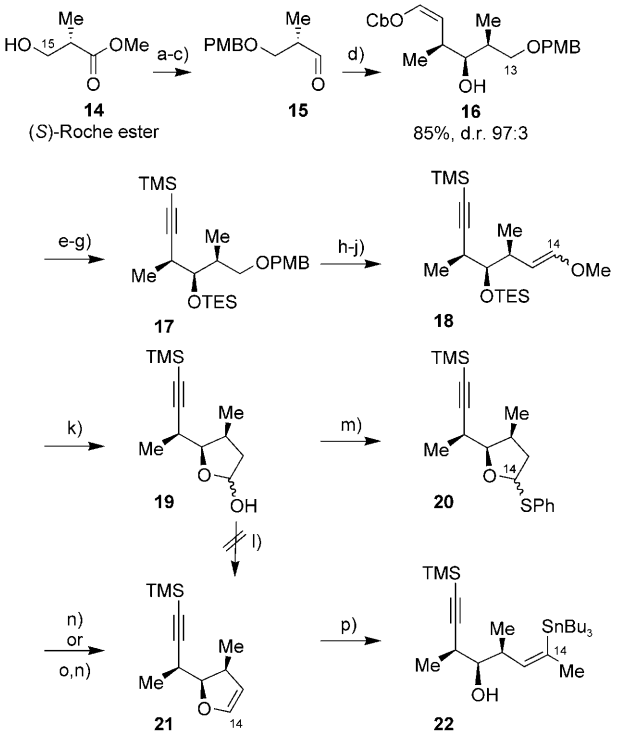
Another highlight of our strategy was the stereocontrolled building of the C13=C14 trisubstituted (*Z*)-double bond. With our C14−C15 disconnection, elected by several research groups, the elaboration of the pivotal segment **B**, which encompassed a (*Z*)-vinyl halide at the C14-position, was needed 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,[13] but the yields were modest and the *Z*/*E* stereoselectivity remained disappointing.[14] 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[15] and developed by Kocienski[16] and our group,[17] 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.[2b] 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[18] was followed by reduction of the



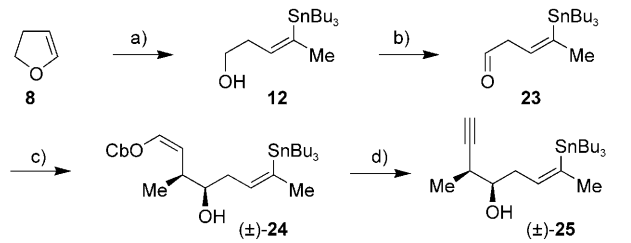
Scheme 3. a) $CCl_3C(N)OPMB$, PPTS (5 mol%), CH_2Cl_2/cyclohexane 1:2, RT, 40 h, 88%; b) LAH, THF, 0°C→RT, 3 h, 95%; c) TEMPO (2 mol%), NaOCl, KBr, $NaHCO_3$, CH_2Cl_2/H_2O; d) (*R*)-**2**, cyclohexane/pentane 1:7, −78°C, 2 h, 85% (2 steps, c–d), d.r. 97:3; e) TESOTf, 2,6-lutidine, CH_2Cl_2, 0°C→RT, 2 h, 97%; f) *t*BuLi, Et_2O, −30°C→−20°C, 45 min, 84%; g) *n*BuLi, THF, −78°C→0°C, 1 h, then TMSCl, −78°C→RT, overnight, 92%; h) DDQ, CH_2Cl_2/H_2O 95:5, 0°C→RT, 30 min, 86%; i) IBX, DMSO, RT, 3 h; j) (methoxymethyl)triphenylphosphonium chloride, LiHMDS, −10°C, 1 h, 85%; k) acetone/H_2O 9:1, HCl, 65°C, 1 h, 61% (3 steps, h–k); l) PTSA, PPTS, $CuSO_4$, NH_4NO_3 or Burgess reagent; m) PhSH, $BF_3{\cdot}OEt_2$, 4 Å MS, Et_2O, 1 h, 80%; n) DBU, neat, 245°C, 30%; o) *m*CPBA, $NaHCO_3$, PhH, 0°C, 1 h, then, reflux, 1 h, 19%; p) *t*BuLi, $Me_2CuLi{\cdot}LiCN$, THF/Et_2O/1:2, 0°C→RT, 3 h, then nBu_3SnCl, −30°C→RT, 5 h, 20%. *m*CPBA = 3-chloroperbenzoic acid; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; d.r. = diasteromeric 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**.[19] 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–Buttenberg–Wiechell rearrangement.[12] 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 trisubstituted 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,[20] PPTS,[21] $CuSO_4$,[22] NH_4NO_3,[23] or Burgess reagent)[24] 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,[25] 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[26] 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,[41] 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 (±)-**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,[27] significant problems were encountered during conversion of homoallylic alcohol **12** into aldehyde **23**. Extensive screening was performed. Classical oxidation methods, such as Swern,[28] Doering–Parikh,[29] or the use of PCC[30] 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)[31] or IBX[32] resulted in recovery of the starting material. The Saigo–Mukaiyama protocol,[33] employing 1,1′-(azodicarbonyl)dipiperidine (ADD) as a hydride acceptor

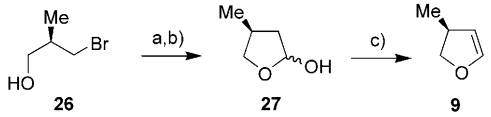


Scheme 4. a) *t*BuLi, $Me_2CuLi{\cdot}LiCN$, THF/Et_2O/1:2, 0°C→RT, 3 h, then nBu_3SnCl, −30°C→RT, 5 h, 61%; b) TEMPO (10 mol%), BAIB, CH_2Cl_2, RT, 2 h; c) (±)-**2** (from **3**, *n*BuLi/TMEDA, Et_2O), Et_2O, −78°C, 2 h, 63% (2 steps b and c); d) *t*BuLi, Et_2O, −30°C→−20°C, 30 min, 70%. BAIB = [bis(acetoxy)iodo]benzene.

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

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.[35] Unfortunately, fast proto-destannylation 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-de*s*methyl C8–C14 fragment (±)-**24** could be obtained in only four steps, from commercially available 2,3-dihydrofuran **8**, in 26.9% overall yield.

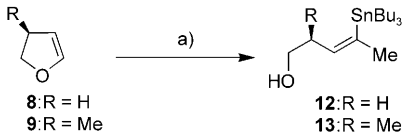
With secured information on the C14 tin function stability in hand, the stage was set for the synthesis of DHF **9** bearing a methyl group at the C12-position (Scheme 5). Preparation of DHF **9** was achieved from commercially available (*R*)-3-bromo-2-methyl-1-propanol (**26**). Cyanide displacement of the bromide and partial reduction of the nitrile function led to lactol **27** after spontaneous cyclization of the γ-hydroxy aldehyde.



Scheme 5. a) NaCN, DMSO, 60°C, 24 h, 92%; b) DIBAL-H, CH_2Cl_2, −78°C, 2 h, 82%; c) PTSA, quinoline, 160°C→245°C, 45 min, 85%. DIBAL-H = diisobutylaluminium hydride.

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).[36] 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, 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_2O 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_2O 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 $CuBr{\cdot}Me_2S$ (Table 1, entry 13), versus cyanocuprates, gave disappointing results and yields remained below 22%.



Scheme 6. Cuprate rearrangement with methyl transfer from DHF **8** or **9**. 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_2O, additive (see Table 1), 0°C→RT; 3) nBu_3SnCl, −30 C→RT, 5 h.

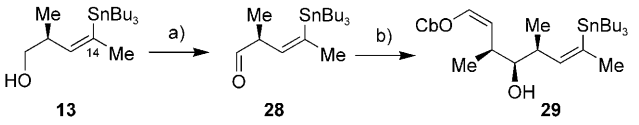
Table 1. Results of cuprate rearrangement with methyl transfer from DHF **8** or **9**.

Entry	Starting material	Additive	Conditions	Yield of (*Z*)-**12** or (*Z*)-**13** [%]
1	**8**	none[a,b]	RT, 3 h	61
2	**9**	none[a,b]	RT, 3 h	27
3	**8**	$BF_3{\cdot}OEt_2$ (2.5 equiv)[a,b]	RT, 3 h	13
4	**8**	TMSCl (4 equiv)[a,b]	RT, 3 h	46
5	**8**	HMPA (5 equiv)[a,b]	RT, 3 h	29
6	**8**	DMPU (5 equiv)[a,b]	RT, 3 h	0
7	**8**	DMF (20 equiv)[a,b]	RT, 3 h	0
8	**8**	TMEDA (10 equiv)[a,b]	RT, 3 h	45
9	**8**	pyridine (10 equiv)[a,b]	RT, 3 h	16
10	**8**	thiophene (20 equiv)[a,b]	RT, 12 h	55
11	**8**	tetrahydro-thiophene (20 equiv)[a,b]	RT, 12 h	67
12	**8**	DMS (Et_2O/DMS 4:1)[b]	RT, 12 h	76
13	**8**	none[a,c]	RT, 3 h	22
14	**9**	DMS (Et_2O/DMS 4:1)[b]	RT, 12 h	68

[a] THF/Et_2O 1:2. [b] MeLi/CuCN. [c] MeMgBr (4 equiv), $CuBr{\cdot}Me_2S$ (2 equiv). DMPU = *N*,*N*′-dimethylpropyleneurea; HMPA = hexamethylphosphoramide.

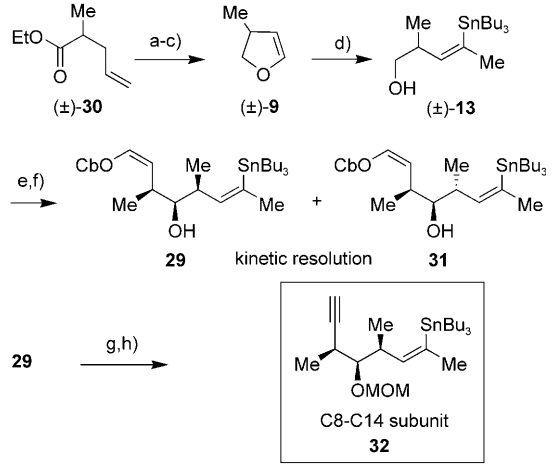
Application of optimized conditions to DHF **9** led to the (*Z*)-tin derivative **13** in a substantial 68% yield (Table 1, entry 14).

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*)-α-methoxy-phenylacetic acid (MPA) ester (see the Experimental Section for details).[37]



Scheme 7. a) TEMPO (10 mol%), BAIB, CH_2Cl_2, 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**

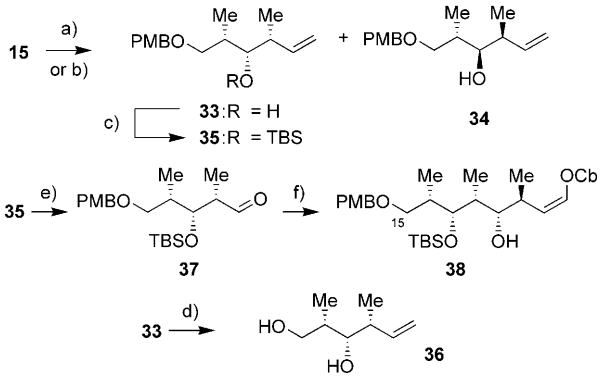


Scheme 8. a) LAH, Et_2O, 0 °C→RT, 3 h; b) O_3, Sudan III, CH_2Cl_2/MeOH 1:1, −78 °C, 7 h then PPh_3, −78 °C→RT, overnight, 80% (2 steps, a and b), anomeric ratio 2:1; c) PTSA, quinoline, 160→245 °C, 45 min, 85%; d) *t*BuLi, Me_2CuLi·LiCN, Et_2O/DMS 4:1, 0 °C→RT, 18 h, then nBu_3SnCl, −30 °C→RT, 5 h, 68%; e) TEMPO (10 mol%), BAIB, CH_2Cl_2, 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_2Cl_2, 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**, α-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_3·OEt_2 in CH_2Cl_2),[38] led to a 85:15 mixture of diastereomers **33** and **34**. Felkin–Anh selectivity was optimized to 95:5 when replacing CH_2Cl_2 by Et_2O and performing the reaction at a lower temperature (Scheme 9). Howev-



Scheme 9. a) Tri-*n*-butylcrotylstannane, BF_3·OEt_2, Et_2O, −100 °C, 2 h, 74%, d.r. 95:5; b) (*Z*)-2-butene, *n*BuLi, *t*BuOK, $[(-)\text{-Ipc}]_2$BOMe, BF_3·OEt_2, 65%, d.r. 100:0; c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C→RT, 2 h, 92%; d) DDQ, CH_2Cl_2/H_2O 95:5, 0 °C→RT, 2 h, 75%; e) O_3, Sudan III, Py, CH_2Cl_2/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.

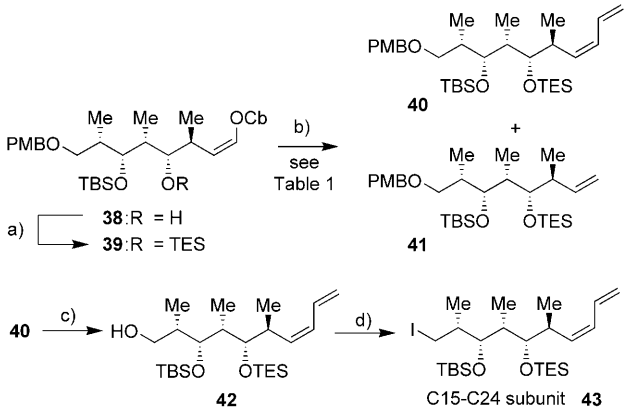
er, large-scale production of **33** was impeded by difficulties associated with diastereomer separation. This difficulty was readily overcome by using the chiral crotylborane procedure developed by Brown.[39] The desired homoallylic alcohol **33** was cleanly formed in a stereospecific manner from the (*Z*)-crotyldiisopinocampheylborane reagent derived from (−)-$Ipc_2B(OMe)$.

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.[40]

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[41] and analysis of the ^{1}H NMR vicinal coupling constants of the corresponding acetonides (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,[11] the direct vinylation of a (*Z*)-*O*-enecarbamate moiety was carried out in the presence of [Ni(acac)$_2$] with commercially available vinylmagnesium bromide. In this way, from carbamate **39**, this reaction gave highly variable but mostly disappointing low yields (Scheme 10, see Table 2 entry 1). The cross-coupled product **40** was generated solely or as a mixture with the corresponding inseparable reduced compound **41** (selectivity varying from 100:0 to 0:100). The quality of commercial vinylmagnesium bromide solution was unreliable 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[42] 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 transmetallation of the vinyllithium derivative with magnesium bromide.[43] When the vinyllithium was produced from vinyl bromide by metal–halogen exchange,[44] no reaction occurred (Table 2, entry 3). On the other hand, the preparation of the vinyllithium from tetravinyltin and MeLi,[45] cleanly afforded the cross-coupled product **40** in modest yield (Table 2, entry 4).



Scheme 10. a) TESOTf, 2,6-lutidine, CH_2Cl_2, 0°C→RT, 1.5 h, 76%; b) [Ni(acac)$_2$], Et_2O, 0°C, overnight, vinylmagnesium bromide, see Table 1; c) DDQ, CH_2Cl_2/H_2O 95:5, 0°C→RT, 40 min, 72%; d) I_2, PPh_3, imid, C_6H_6/Et_2O, 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)$_2$]-catalyzed cross-coupling reaction from compound **39**.

Entry	Conditions	**40**	**41**	Yield [%][a]
1	CH_2=CH–MgBr[b]	100→0	0→100	35→80
2	CH_2=CH–Br, Mg	80	20	65
3	CH_2=CH–Br, *t*BuLi, $MgBr_2$·OEt_2	–	–	–[c]
4	$(CH_2$=$CH)_4$Sn, MeLi, $MgBr_2$·OEt_2	100	0	50[d]
5	$(CH_2$=$CH)_4$Sn, MeLi	100	0	80

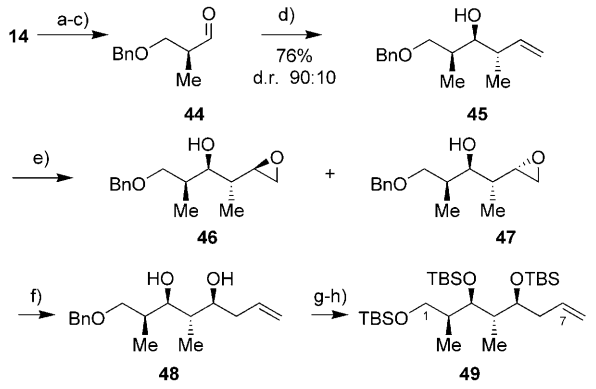
[a] Isolated yield of the **40** and **41** mixture. [b] Commercial reagent. [c] Only the starting material was recovered. [d] 10% of starting material was recovered.

The reaction with solely vinyllithium species (without magnesium salts) produced from tetravinyltin and MeLi,[45] 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 tetravinylstannane 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^2)–C(sp^2) cross-coupling between a vinyllithium and a vinylic electrophilic species.[46]

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.[47] The C15–C24 subunit **43**, bearing five contiguous stereogenic centers and a terminal diene, was obtained in 13.7% overall yield for 11 steps.

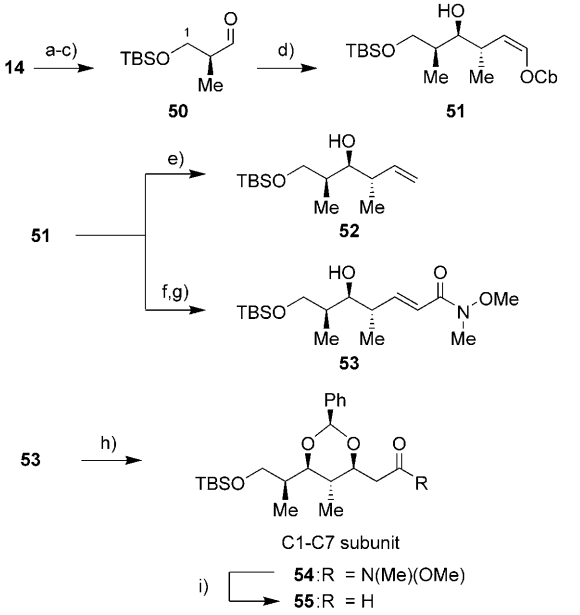
Our initial approach to the synthesis of the third building block C1–C7 **C** started with standard Brown crotylation of aldehyde **44** (derived from (*S*)-Roche ester **14**), to afford the desired *syn–anti* homoallylic alcohol **45** in 76% yield (Scheme 11). It was envisaged to rely upon a substrate-directable 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)$_6$]/TBHP[48] or [VO(O*i*Pr)$_3$]/TBHP never gave more than 40% selectivity, whereas recourse to [VO(acac)$_2$]/TBHP[49] 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 cyano-Gilman divinyl cuprate, $(CH_2$=$CH)_2$CuLi·LiCN,[50] to ensure the formation of the alkene **48** in 86% yield. Finally, cleavage of the *O*Bn group with lithium in liquid ammonia followed by silylation afforded the C1–C7 subunit **49**.

An alternative route allowed the generation of the C5 chiral center by hetero-Michael addition on α,β-unsaturated Weinreb amide **53**, which in turn could be derived from aldehyde **50** through a crotyltitanation reaction and homolo-



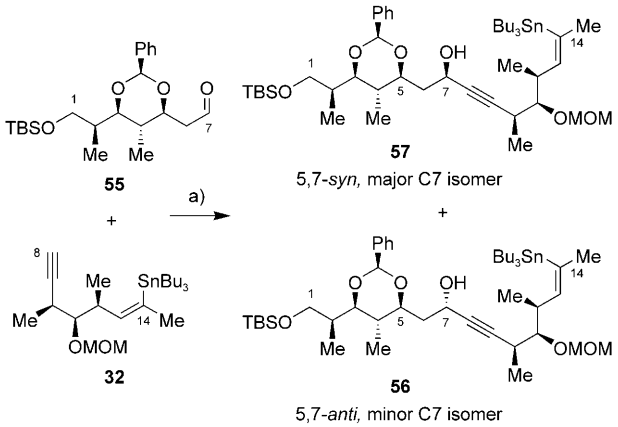
Scheme 11. a) $CCl_3C(N)OBn$, TfOH (5 mol%), CH_2Cl_2/cyclohexane 1:2, 0°C→RT, 40 h, 84%; b) LAH, THF, 0°C→RT, 3 h, 94% c) IBX, DMSO, RT, 3 h, 92%; d) (*E*)-2-butene, *n*BuLi, *t*BuOK, $[(-)\text{-Ipc}]_2BOMe$, $BF_3{\cdot}OEt_2$, 76%, d.r. 90:10; e) $[VO(acac)_2]$, TBHP, CH_2Cl_2, 78%, d.r. 90:10; f) $CH_2{=}CH{-}Br$, *t*BuLi, CuCN, THF, −78→0°C, overnight, 86%; g) Li, NH_3, THF, −78°C, 1 h; h) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C→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.[51] None of the desired product was formed and most of the starting material was recovered. We suspected that the *N*,*N*-diisopropyl-*O*-enecarbamate function could have deleterious effects for steric or/and electronic reasons. Thus, the vinylic function of compound **51** was deoxygenated by hydride reduction with *iso*-propylmagnesium chloride in a nickel-catalyzed reaction to furnish **52**.[52] 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 α,β-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).[53] After reduction of **54** into aldehyde **55** by treatment with DIBAL-H,[54] the last C1–C7 subunit, bearing four stereocenters, was obtained in 32.7% overall yield for eight steps.



Scheme 12. a) TBSCl, imid, DMF, RT, 3 h, 94%; b) DIBAL-H, CH_2Cl_2, −20°C, 30 min, 92%; c) $(COCl)_2$, DMSO, Et_3N, −55°C→RT, 1 h; d) (*R*)-**2**, cyclohexane/pentane 1:7, −78°C, 3 h, 66% (2 steps, c and d); e) $[Ni(acac)_2]$ (10 mol%), *i*PrMgBr, THF, RT overnight, 50%; f) O_3, Sudan III, CH_2Cl_2, −78°C, 1 h, then PPh_3, −78°C→RT, 3 h, 87%; g) $(EtO)_2P(O)CH_2C(O)NMe(OMe)$, NaH, THF, 0°C→RT, 45 min, 86%; h) PhCHO, KHMDS, THF, −20°C, 45 min, 79%; i) DIBAL-H, CH_2Cl_2, −78°C, 1 h, 93%.

Completion of the total synthesis of discodermolide: With access to the required fragments now reliable, the stage was set for the coupling. The first coupling reaction involved an addition of the C8–C14 acetylenic compound **32** to C1–C7 aldehyde **55** (Scheme 13). Previous observations on the stability of the sterically hindered trisubstituted (*Z*)-vinyl stannane provided encouraging 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.

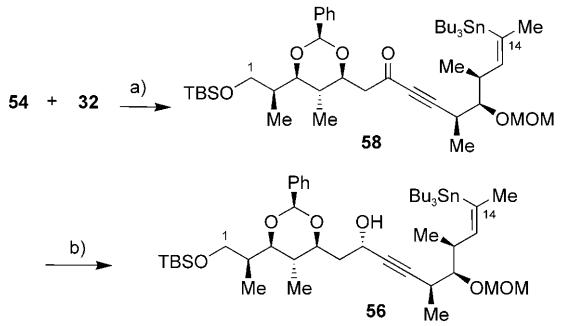


Scheme 13. a) **32**, *t*BuLi, THF, −78°C, 30 min, then **55**, −78→0°C, 3 h, 50%, d.r. 1:2.

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).[55]

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,

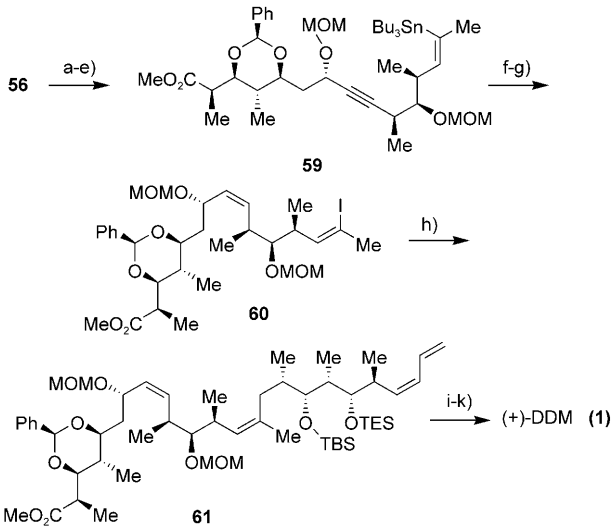


Scheme 14. a) **32**, *n*BuLi/Et_2O, THF, −40 °C, 50 min, then **54**, −40→>0 °C, 1 h, 81%; b) (*S*)-(−)-2-methyl-CBS-oxazaborolidine, BH_3·Me_2S, THF, −30 °C, 2 h, 95%, d.r. 98:2. CBS = Corey–Bakshi–Shibata.

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 retro-aldol 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_2O,[56] 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[57] 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.[4] 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_2 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,[58] by using trialkyl boronate species prepared from alkyl iodide **43** with *t*BuLi and *B*-methoxy-9-BBN under [$PdCl_2$(dppf)] and $AsPh_3$ conditions to afford the discodermolide backbone **60** in 60% yield.



Scheme 15. a) MOMCl, TBAI, Hunig's base, CH_2Cl_2, RT, 18 h, 86%; b) HF/Py, Py/THF, RT, 4 h, 96%; c) TEMPO (10 mol%), BAIB, CH_2Cl_2, RT, 3 h; d) $NaClO_2$, NaH_2PO_4, 2-methyl-but-2-ene, *t*BuOH/H_2O, RT, 1 h; e) $TMSCHN_2$, C_6H_6/MeOH, RT, 15 min, 66% (3 steps, c–e); f) H_2, PtO_2 (30 mol%), AcOEt, RT, 12 h; g) I_2, CH_2Cl_2, 0 °C, 10 min, 71% (2 steps, f and g); h) **43**, *t*BuLi, Et_2O, −78 °C, 5 min, *B*-methoxy-9-BBN, THF, −78 °C→RT, then **60**, Cs_2CO_3, [$PdCl_2$(dppf)], $AsPh_3$, DMF, H_2O, 18 h, 60%; i) PSA, MeOH, 0 °C, 1 h, 77%; j) $Cl_3CC(O)NCO$, CH_2Cl_2, RT, 15 min, then K_2CO_3, 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.[59] Final total deprotection with concomitant lactonization by following the procedure established in the previous total syntheses[4] 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 crotyltitane 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 discodermolide 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_2O) 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 phopshomolybdic 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. ^{1}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 $\delta_H = 7.26$ and 1.96 ppm were used for $CDCl_3$ and CD_3CN, 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^{-1}). ^{13}C NMR spectra were recorded on a Jeol 67.5 or 100.5 MHz spectrometer. Internals references of $\delta_C = 77.16$ and 118.26 ppm were used for $CDCl_3$ and CD_3CN, respectively. IR spectra were recorded on a Nicolet Impact-400 and wavelength ($\tilde{\nu}$) is given in cm^{-1}. Mass spectra were recorded on a GC/MS coupling unit with a MSD 5973 spectrometer and a Hewlett–Packard HP-GC 6890 chromatograph. Ionization was obtained either by electronic impact (EI) or chemical ionization with methane (CI, CH_4). 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: $[\alpha]_D^{20}$, 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, 91 405 Orsay. IUPAC nomenclature was used for all compounds. RN refers CAS registration numbers. See Supporting Information for further experimental procedures.

(3*Z*)-4-(Tributylstannyl)pent-3-en-1-al (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_2Cl_2 (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 $Na_2S_2O_3$ solution and extracted with cyclohexane. The combined organic phases were washed with a saturated aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude aldehyde **23** was directly used in the next step. ^{1}H NMR (400.0 MHz, $CDCl_3$): $\delta = 9.67$ (t, J = 2.1 Hz, 1H), 6.16 (tq, J = 7.3, 1.9, $J_{^1H,^{117}Sn} = J_{^1H,^{119}Sn}$ = 122.1 Hz, 1H), 2.89 (dd, J = 7.3, 2.1 Hz, 2H), 1.98 (d, J = 1.9, $J_{^1H,^{117}Sn} = J_{^1H,^{119}Sn}$ = 38.9 Hz, 3H; CH_3), 1.60–1.40 (m, 6H; 3 CH_2), 1.39–1.20 (m, 6H; 3 CH_2), 1.02–0.84 ppm (m, 15H; 3 CH_2, 3 CH_3).

(1*Z*,6*Z*,3*R*/*S*,4*R*/*S*)-1-[(*N*,*N*-Diisopropyl)carbamoyloxy]-4-hydroxy-3-methyl-7-(tributylstannyl)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_2O (70 mL) at −78 °C. After 30 min at −78 °C, $Ti(OiPr)_4$ (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_2O (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_2O-saturated aqueous NH_4Cl solution. After extraction with Et_2O, the organic layer was washed with brine, dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/Et_2O 95:5 to 60:40) to give the title compound (±)-**24** (7.4 g, 44% for 2 steps). ^{1}H NMR (400.0 MHz, $CDCl_3$): $\delta = 7.12$ (d, J = 6.4 Hz, 1H), 6.10 (ddq, J = 5.9, 5.5, 1.4, $J_{^1H,^{117}Sn} = J_{^1H,^{119}Sn}$ = 131.0 Hz, 1H), 4.67 (dd, J = 9.9, 6.4 Hz, 1H), 4.19–4.11 (br s, 1H), 3.80–3.75 (br s, 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, $J_{^1H,^{117}Sn} = J_{^1H,^{119}Sn}$ = 41.7 Hz, 3H; CH_3), 1.78 (br d, J = 3.0 Hz, 1H; OH), 1.58–1.38 (m, 6H; 3 CH_2), 1.38–1.17 (m, 18H; 3 CH_2, 4 CH_3), 1.07 (d, J = 7.3 Hz, 3H; CH_3), 0.96–0.85 ppm (m, 15H; 3 CH_2, 3 CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 152.3$ (C), 141.9 (C), 136.4 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn}$ = 28.1 Hz; CH), 135.3 (CH), 111.9 (CH), 74.1 (CH), 45.4 (CH), 45.2 (CH), 39.6 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn}$ = 30.7 Hz; CH_2), 35.4 (CH), 28.8 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn}$ = 19.2 Hz; 3 CH_2), 27.5 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn}$ = 56.5 Hz; 3 CH_2), 26.8 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn}$ = 46.0 Hz; CH_3), 21.1 (2 CH_3), 20.3 (2 CH_3), 17.0 (CH_3), 13.2 (3 CH_3), 9.6 ppm ($J_{^{13}C,^{117}Sn}$ = 313.4, $J_{^{13}C,^{119}Sn}$ = 326.8 Hz; 3 CH_2); IR (film): $\tilde{\nu}$ = 3470, 2957, 2925, 2872, 2855, 1712, 1705, 1679, 1642, 1456, 1444, 1371, 1306, 1211, 1147, 1134, 1065, 1001, 961, 903, 885, 865, 762 cm^{-1}.

(3*R*/*S*,4*R*/*S*,6*Z*)-4-Hydroxy-3-methyl-7-(tributylstannyl)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_2O (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_4Cl solution, and extracted with Et_2O. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel (cyclohexane/Et_2O 90:10 to 80:20) to give (±)-**25** (4.7 g, 78%). ^{1}H NMR (270.0 MHz, $CDCl_3$): $\delta = 6.00$ (ddq, J = 7.7, 6.5, 1.7, $J_{^1H,^{117}Sn} = J_{^1H,^{119}Sn}$ = 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, $J_{^1H,^{117}Sn} = J_{^1H,^{119}Sn}$ = 41.6 Hz, 3H; CH_3), 1.50–1.33 (m, 6H; 3 CH_2), 1.32–1.11 (m, 10H; 1 OH, 1 CH_3, 3 CH_2), 0.98–0.74 ppm (m, 15H, 3 CH_2, 3 CH_3); ^{13}C NMR (67.5 MHz, $CDCl_3$): $\delta = 142.8$ (C), 136.1 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn}$ = 26.8 Hz; CH), 85.1 (C), 74.0 (CH), 71.0 (CH), 40.1 (CH_2), 32.2 (CH), 29.2 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn}$ = 19.5 Hz; 3 CH_2), 27.4 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn}$ = 56.2 Hz; 3 CH_2), 17.3 (CH_3), 13.7 (3 CH_3), 9.6 ppm ($J_{^{13}C,^{117}Sn}$ = 314.4, $J_{^{13}C,^{119}Sn}$ = 328.8 Hz; 3 CH_2); IR (film): $\tilde{\nu}$ = 3311, 2956, 2926, 2871, 2854, 1712, 1463, 1376, 1260, 1192, 1072, 1039, 960 cm^{-1}.

(2*R*/*S*,4*R*/*S*)-4-Methyltetrahydrofuran-2-ol ((±)-27): A solution of commercial ethyl 4-methylpentenoate (±)-**30** (30 g, 211 mmol, 1.0 equiv) in Et_2O (200 mL) was added to a solution of $LiAlH_4$ (6.4 g, 169 mmol, 0.8 equiv) in Et_2O (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_2O (6.5 mL), an aqueous NaOH 15% solution (6.5 mL), and further H_2O (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 $MgSO_4$ and the solvent was removed under reduced pressure. The crude 2-methylpent-4-en-1-ol was directly used in the next step. ^{1}H NMR (400.0 MHz, $CDCl_3$): $\delta = 5.75$ (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_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ=136.9 (CH), 116.0 (CH_2), 67.7 (CH_2), 37.7 (CH_2), 35.5 (CH), 16.3 ppm (CH_3); MS (GC, EI): m/z: 82 $[M-18]^+$, 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_2Cl_2/MeOH (1:1, 200 mL) at −78 °C until the pink solution became colorless (ca. 7 h). Then PPh_3 (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 (±)-**27** (19.7 g, 80%) as a colorless oil and a 1:2 mixture of two diastereomers. RN: 34314-85-7; first anomer: ^{1}H NMR (400.0 MHz, $CDCl_3$): δ=5.46 (d, J=5.0 Hz, 1H), 4.09 (t, J=7.8 Hz, 1H; H_a-11), 3.32 (dd, J=7.8, 7.3 Hz, 1H; H_b-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_3); second anomer: ^{1}H NMR (400.0 MHz, $CDCl_3$): δ=5.46 (d, J=4.6 Hz, 1H), 3.95 (dd, J=8.2, 6.6 Hz, 1H), 3.55 (dd, J=8.7, 8.2 Hz, 1H), 2.92 (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_3); first anomer: ^{13}C NMR (100.5 MHz, $CDCl_3$): δ=98.9 (CH), 74.4 (CH_2), 41.8 (CH_2), 31.4 (CH), 17.8 ppm (CH_3); second anomer: ^{13}C NMR (100.5 MHz, $CDCl_3$): δ=99.4 (CH), 73.5 (CH_2), 41.8 (CH_2), 33.3 (CH), 17.3 ppm (CH_3); IR (film): $\tilde{\nu}$=3406, 2960, 2935, 2875, 1455, 1379, 1346, 1290, 1122, 1095, 1056, 1002, 927 cm^{-1}; MS (GC, EI): m/z: 101, 84, 72, 56.

(4*S*)-3-Methyl-2,3-dihydrofuran (9) and (4*R*/*S*)-3-methyl-2,3-dihydrofuran [(±)-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 $MgSO_4$, and the solvent was removed under reduced pressure. (2*S*)-3-Cyano-2-methyl propan-1-ol (7.6 g, 89%) was collected and used directly in the next step. ^{1}H NMR (400.0 MHz, $CDCl_3$): δ=3.65 (ddd, J=10.5, 5.0, 4.6 Hz, 1H), 3.50 (ddd, J=10.5, 7.3, 5.0 Hz, 1H), 2.62 (t, J=5.0 Hz, 1H; OH), 2.50 (dd, J=16.7, 5.5 Hz, 1H), 2.37 (dd, J=16.7, 6.9 Hz, 1H), 2.06 (dquintdd, J=7.3, 6.9, 5.5, 4.6 Hz, 1H), 1.08 ppm (d, J=6.9 Hz, 3H; CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ=118.7 (C), 65.6 (CH_2), 32.8 (CH), 20.8 (CH_2), 15.8 ppm (CH_3); IR (film): $\tilde{\nu}$=3416, 2967, 2933, 2880, 2251, 1644, 1464, 1424, 1387, 1350, 1044, 993 cm^{-1}; MS (GC, EI): m/z: 99, 69, 59, 54.

A solution of DIBAL-H (1 M in CH_2Cl_2, 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_2Cl_2 (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 ($C_4H_4KNaO_6$·4H_2O, 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 $MgSO_4$, and the solvent was removed under reduced pressure. (2*R*/*S*,4*S*)-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 (±)-**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; ^{1}H NMR (400.0 MHz, $CDCl_3$): δ=6.30 (dd, J=2.8, 2.3 Hz, 1H), 4.94 (dd, J=2.8, 2.3 Hz, 1H), 4.38 (dd, J=9.6, 8.7 Hz, 1H), 3.85 (dd, J=8.7, 6.4 Hz, 1H), 3.03 (dqdt, J=9.6, 6.9, 6.4, 2.3 Hz, 1H), 1.07 ppm (d, J=6.9 Hz, 3H; CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ=145.3 (CH), 106.6 (CH), 76.8 (CH_2), 36.6 (CH), 20.8 ppm (CH_3).

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

(2*S*,3*Z*)-2-Methyl-4-tributylstannyl-pent-3-en-1-ol (13): MeLi (1.6 M solution in Et_2O, 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_2O (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_2O (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_2O/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_4Cl solution and concentrated ammonia (4:1) at 0 °C and stirred for 1 h at 20 °C before extraction with Et_2O. The organic layer was washed with water and brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude residue was purified by chromatography on silica gel (cyclohexane/Et_2O 100:0 to 60:40) to give the title compound **13** (8.21 g, 68%). ^{1}H NMR (400.0 MHz, $CDCl_3$): δ=5.78 (dq, J=9.6, 1.8, $J_{^1H,^{117}Sn}$=$J_{^1H,^{119}Sn}$=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, $J_{^1H,^{117}Sn}$=$J_{^1H,^{119}Sn}$=41.7 Hz, 3H; CH_3), 1.55–1.45 (m, 6H; 3CH_2), 1.39–1.28 (m, 7H; OH, 3CH_2), 0.95 (d, J=6.4 Hz, 3H; CH_3), 0.99–0.91 (m, 6H; 3CH_2), 0.90 ppm (m, 9H; 3CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ=143.0 ($J_{^{13}C,^{117}Sn}$=$J_{^{13}C,^{119}Sn}$=27.8 Hz; CH), 140.9 (C), 67.3 (CH), 42.4 ($J_{^{13}C,^{117}Sn}$=$J_{^{13}C,^{119}Sn}$=33.6 Hz; CH), 29.3 ($J_{^{13}C,^{117}Sn}$=$J_{^{13}C,^{119}Sn}$=20.4 Hz; 3CH_2), 27.5 ($J_{^{13}C,^{117}Sn}$=$J_{^{13}C,^{119}Sn}$=57.5 Hz; 3CH_2), 27.2 ($J_{^{13}C,^{117}Sn}$=$J_{^{13}C,^{119}Sn}$=46.0 Hz; CH_3), 17.4 (CH_3), 13.7 (3CH_3), 10.1 ppm ($J_{^{13}C,^{117}Sn}$=314.4, $J_{^{13}C,^{119}Sn}$=329.7 Hz; 3CH_2); IR (film): $\tilde{\nu}$=3327, 2956, 2928, 2920, 2871, 2853, 1678, 1623, 1483, 1456, 1377, 1340, 1292, 1072, 1037, 996, 864, 690, 668 cm^{-1}; MS (GC, CI, NH_3): m/z: 373 $[M-H_2O]^+$, 359 $[M-H_2O-Bu]^+$, 291 $[Bu_3Sn]^+$, 261, 249, 235, 141, 113, 101, 85, 57; elemental analysis calcd (%) for $C_{18}H_{38}OSn$: C 55.55, H 9.84; found: C 55.73, H 10.02.

(2*S*,3*Z*)-2-Methyl-4-tributylstannyl-pent-3-en-1-al (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_2Cl_2 (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 $Na_2S_2O_3$ solution, and extracted with cyclohexane. The combined organic phases were washed with a saturated aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$, 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). ^{1}H NMR (400.0 MHz, $CDCl_3$): δ=9.48 (d, J=1.7 Hz, 1H), 5.72 (dq, J=9.7, 1.6, $J_{^1H,^{117}Sn}$=$J_{^1H,^{119}Sn}$=122.1 Hz, 1H), 2.89 (dqd, J=9.7, 6.4, 1.7 Hz, 1H), 1.89 (d, J=1.6, $J_{^1H,^{117}Sn}$=$J_{^1H,^{119}Sn}$=40.7 Hz, 3H; CH_3), 1.47–1.37 (m, 6H; 3CH_2), 1.24 (sext, J=7.3 Hz, 6H; 3CH_2), 1.08 (d, J=6.4 Hz, 3H; CH_3), 0.91–0.86 (m, 6H; 3CH_2), 0.83 ppm (t, J=7.3 Hz, 9H; 3CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ=202.1 (CH), 146.0 ($J_{^{13}C,^{117}Sn}$=346.0, $J_{^{13}C,^{119}Sn}$=362.3 Hz, C), 136.2 ($J_{^{13}C,^{117}Sn}$=$J_{^{13}C,^{119}Sn}$=24.9 Hz; CH), 53.1 ($J_{^{13}C,^{117}Sn}$=$J_{^{13}C,^{119}Sn}$=31.6 Hz; CH), 29.1 ($J_{^{13}C,^{117}Sn}$=$J_{^{13}C,^{119}Sn}$=19.2 Hz; 3CH_2), 27.4 ($J_{^{13}C,^{117}Sn}$=$J_{^{13}C,^{119}Sn}$=40.3 Hz; CH_3, CH_3), 27.3 ($J_{^{13}C,^{117}Sn}$=$J_{^{13}C,^{119}Sn}$=58.5 Hz; 3CH_2), 14.4 (CH_3), 13.7 (3CH_3), 10.1 ppm ($J_{^{13}C,^{117}Sn}$=317.3, $J_{^{13}C,^{119}Sn}$=332.6 Hz; 3CH_2); IR (film): $\tilde{\nu}$=2958, 2927, 2872, 2854, 2809, 1726, 1614, 1463, 1426, 1377, 1072, 999, 854, 689 cm^{-1}; MS (GC, CI, NH_3): m/z: 331 $[M-Bu]^+$, 291 $[Bu_3Sn]^+$, 275, 255, 235, 217, 189, 177, 159, 147, 135, 121, 97.

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

(2*R*/*S*,3*Z*)-2-Methyl-4-tributylstannyl-pent-3-en-1-al ((±)-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.

(1*Z*,3*S*,4*S*,5*S*,6*Z*)-1-[(*N*,*N*-Diisopropyl)carbamoyloxy]-3,5-dimethyl-7-tributylstannyl-octa-1,6-dien-4-ol (29) and (1*Z*,3*S*,4*S*,5*R*,6*Z*)-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 $Ti(OiPr)_4$ (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_2O-saturated aqueous NH_4Cl solution. After extraction with Et_2O, the organic layer was washed with brine, dried over $MgSO_4$, 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. $[\alpha]_D^{20} = +20.7$ ($c = 0.94$ in $CHCl_3$); ^{1}H NMR (400.0 MHz, $CDCl_3$): $\delta = 7.15$ (d, $J = 6.4$ Hz, 1H), 6.17 (dq, $J = 9.9$, 1.4, $J_{^1H,^{117}Sn} = J_{^1H,^{119}Sn} = 134.0$ 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 (dqd, $J = 9.9$, 6.8, 2.8 Hz, 1H), 1.90 (d, $J = 1.4$, $J_{^1H,^{117}Sn} = J_{^1H,^{119}Sn} = 42.6$ Hz, 3H; CH_3), 1.72 (brd, $J = 2.8$ Hz, 1H; OH), 1.55–1.45 (m, 6H; $3CH_2$), 1.38–1.16 (sext, $J = 7.3$ Hz, 6H; $3CH_2$), 1.20–1.12 (m, 12H; $4CH_3$), 1.00 (d, $J = 6.9$ Hz, 3H; CH_3), 0.98 (d, $J = 6.8$ Hz, 3H; CH_3), 0.99–0.92 (m, 6H; $3CH_2$), 0.89 ppm (t, $J = 7.3$ Hz, 9H; $3CH_3$); ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 152.9$ (C), 144.3 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 27.8$ Hz; CH), 137.7 ($J_{^{13}C,^{117}Sn} = 375.7$, $J_{^{13}C,^{119}Sn} = 392.0$ Hz; C), 136.7 (CH), 113.2 (CH), 78.6 (CH), 47.1 (CH), 45.7 (CH), 41.3 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 32.6$ Hz; CH), 34.5 (CH), 29.3 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 19.2$ Hz; $3CH_2$), 27.5 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 57.5$ Hz; $3CH_2$), 27.2 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 46.0$ Hz; CH_3), 21.7 ($2CH_3$), 20.4 ($2CH_3$), 17.6 (CH_3), 14.2 (CH_3), 13.8 ($3CH_3$), 10.0 ppm ($J_{^{13}C,^{117}Sn} = 313.4$, $J_{^{13}C,^{119}Sn} = 326.8$ Hz; $3CH_2$); IR (film): $\tilde{\nu} = 3490$, 2957, 2929, 2872, 2851, 1705, 1463, 1455, 1441, 1370, 1301, 1289, 1210, 1135, 1065, 997, 862, 762 cm^{-1}; MS (GC, CI, NH_3): *m*/*z*: 530, 385, 327, 291 $[Bu_3Sn]^+$, 257, 235, 199, 177, 12, 86, 69; elemental analysis calcd (%) for $C_{29}H_{57}NO_5Sn$: 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 $Ti(OiPr)_4$ (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_2O-saturated aqueous NH_4Cl solution. After extraction with Et_2O, the organic layer was washed with brine, dried over $MgSO_4$, 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 %). ^{1}H NMR (400.0 MHz, $CDCl_3$): $\delta = 7.10$ (d, $J = 6.9$ Hz, 1H), 5.88 (dq, $J = 9.8$, 1.7, $J_{^1H,^{117}Sn} = J_{^1H,^{119}Sn} = 128.0$ 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 (dqd, $J = 10.1$, 6.9, 2.6 Hz, 1H), 2.00 (dqd, $J = 9.8$, 8.4, 6.4 Hz, 1H), 1.92 (d, $J = 1.7$, $J_{^1H,^{117}Sn} = J_{^1H,^{119}Sn} = 40.3$ Hz, 3H; CH_3), 1.55–1.45 (m, 6H; $3CH_2$), 1.38–1.16 (sext, $J = 7.3$ Hz, 19H; $3CH_2 + OH + 4CH_3$), 1.13 (d, $J = 6.9$ Hz, 3H; CH_3), 0.96 (d, $J = 6.4$ Hz, 3H; CH_3), 0.99–0.92 (m, 6H, $3CH_2$), 0.89 ppm (t, $J = 7.3$ Hz, 9H; $3CH_3$); ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 152.6$ (C), 144.3 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 28.8$ Hz, CH), 142.2 ($J_{^{13}C,^{117}Sn} = 355.1$, $J_{^{13}C,^{119}Sn} = 372.4$ Hz, C), 135.3 (CH), 111.0 (CH), 77.7 (CH), 46.6 (CH), 46.0 (CH), 44.0 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 29.8$ Hz; CH), 32.1 (CH), 29.1 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 20.2$ Hz; $3CH_2$), 27.4 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 57.6$ Hz; $3CH_2$), 27.2 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 42.2$ Hz; CH_3), 21.4 ($2CH_3$), 20.3 ($2CH_3$), 18.7 (CH_3), 17.3 (CH_3), 13.6 ($3CH_3$), 10.1 ppm ($J_{^{13}C,^{117}Sn} = 315.7$, $J_{^{13}C,^{119}Sn} = 330.1$ Hz; $3CH_2$).

(3*S*,4*R*,5*S*,6*Z*)-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_2O (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_4Cl solution and extracted with Et_2O. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel (cyclohexane/Et_2O 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 (4.7 g, 78 %). $[\alpha]_D^{20} = -26.8$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (400.0 MHz, $CDCl_3$): $\delta = 5.87$ (dq, $J = 9.6$, 1.8, $J_{^1H,^{117}Sn} = J_{^1H,^{119}Sn} = 133.3$ Hz, 1H), 3.17 (ddd, $J = 9.0$, 7.5, 3.2 Hz, 1H), 2.73 (dqd, $J = 7.5$, 6.9, 2.3 Hz, 1H), 2.16 (dqd, $J = 9.6$, 6.9, 3.2 Hz, 1H), 2.14 (d, $J = 2.3$ Hz, 1H), 1.90 (d, $J = 1.8$, $J_{^1H,^{117}Sn} = J_{^1H,^{119}Sn} = 40.8$ Hz, 3H; CH_3), 1.74 (d, $J = 9.0$ Hz, 1H; OH), 1.53–1.42 (m, 6H; $3CH_2$), 1.34 (sext, $J = 7.3$ Hz, 6H; $3CH_2$), 1.26 (d, $J = 6.9$ Hz, 3H; CH_3), 1.08 (d, $J = 6.9$ Hz, 3H; CH_3), 0.98–0.91 (m, 6H; $3CH_2$), 0.89 ppm (t, $J = 7.3$ Hz, 9H; $3CH_3$); ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 142.8$ ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 28.8$ Hz; CH), 138.8 (C), 84.8 (C), 78.0 (CH), 71.5 (CH), 43.2 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 33.6$ Hz; CH), 30.4 (CH), 29.0 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 19.2$ Hz; $3CH_2$), 27.1 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 58.7$ Hz; 3CH), 27.0 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 44.0$ Hz; CH_3), 18.4 (CH_3), 17.0 (CH_3), 13.4 ($3CH_3$), 9.7 ppm ($J_{^{13}C,^{117}Sn} = 314.4$, $J_{^{13}C,^{119}Sn} = 328.8$ Hz; $3CH_2$); 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^{-1}; elemental analysis calcd (%) for $C_{22}H_{42}OSn$: 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_2Cl_2 (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 $NaHCO_3$ solution and extracted with Et_2O. The organic layers were washed with brine, dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude residue was purified by chromatography on silica gel (cyclohexane/Et_2O 98:2 to 90:10) to give the title compound **32** (3.53 g, 92 %) as a yellow oil. $[\alpha]_D^{20} = -20.6$ ($c = 0.98$ in $CHCl_3$); ^{1}H NMR (400.0 MHz, $CDCl_3$): $\delta = 5.87$ (d, $J = 9.6$, $J_{^1H,^{117}Sn} = J_{^1H,^{119}Sn} = 133.3$ Hz, 1H), 4.80 (d, $J = 7.3$ Hz, 1H), 4.72 (d, $J = 7.3$ Hz, 1H), 3.45 (s, 3H; CH_3), 3.19 (dd, $J = 7.8$, 3.6 Hz, 1H), 2.74 (qdd, $J = 7.3$, 3.6, 2.7 Hz, 1H), 2.33 (ddq, $J = 9.6$, 7.8, 6.9 Hz, 1H), 2.09 (d, $J = 2.7$ Hz, 1H), 1.88 (s, $J_{^1H,^{117}Sn} = J_{^1H,^{119}Sn} = 40.8$ Hz, 3H; CH_3), 1.52–1.42 (m, 6H; $3CH_2$), 1.32 (sext, $J = 7.3$ Hz, 6H; $3CH_2$), 1.25 (d, $J = 7.3$ Hz, 3H; CH_3), 1.02 (d, $J = 6.9$ Hz, 3H; CH_3), 0.97–0.93 (m, 6H; $3CH_2$), 0.89 ppm (t, $J = 7.3$ Hz, 9H; $3CH_3$); ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 143.6$ ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 28.7$ Hz, CH), 138.5 (C), 98.4 (CH_2), 86.1 (C), 85.9 (CH), 70.0 (CH), 56.3 (CH_3), 42.8 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 30.1$ Hz; CH), 30.0 (CH), 27.3 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 20.1$ Hz; $3CH_2$), 27.3 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 59.4$ Hz; $3CH_2$), 27.2 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 40.2$ Hz; CH_3), 18.8 (CH_3), 17.7 (CH_3), 13.7 ($3CH_3$), 9.9 ppm ($J_{^{13}C,^{117}Sn} = 314.4$, $J_{^{13}C,^{119}Sn} = 328.7$ Hz; $3CH_2$); IR (film): $\tilde{\nu} = 3312$, 2956, 2926, 2872, 2823, 1458, 1376, 1146, 1096, 1035, 996, 668, 634 cm^{-1}; elemental analysis calcd (%) for $C_{24}H_{46}O_2Sn$: C 59.39, H 9.55; found: C 59.55, H 9.73.

(3*S*,4*R*,5*S*)-3,5-Dimethyl-6-(4-methoxybenzyloxy)hex-1-en-4-ol (33) and (3*S*,4*R*,5*S*)-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 °C for 5 min and at −45 °C for 20 min. The resulting orange solution was cooled to −78 °C, and a solution of (−)-*B*-methoxydiisopinocamphenylborane (25 g, 78.7 mmol, 1.4 equiv) in Et_2O (46 mL) was added dropwise over ca. 15 min. The resulting white solution was stirred at −78 °C for 40 min. $BF_3{\cdot}OEt_2$ (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 °C for 5 h and the reaction was then quenched by the successive addition of an aqueous NaOH solution (2.5 N, 66 mL) and an aqueous H_2O_2 solution (30 %, 20 mL). The acetone/dry ice bath was then removed, and the mixture was heated at 45 °C for 45 min. The cloudy solution was cooled to 20 °C, diluted with Et_2O (45 mL), washed with brine, dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude residue was distilled (85–90 °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 °C. After 10 min, HS*n*Bu_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 °C, the mixture was cooled to −40 °C and a solution of (*E*)-crotylchloride (6.2 g, 69 mmol, 1.0 equiv) in THF (70 mL) was added by cannula. The mixture was stirred for 15 min at −20 °C and then treated with a saturated aqueous NH_4Cl solution. After extraction with Et_2O, the organic layer was washed with water and brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was then distilled under reduced pressure (154–158 °C, 0.3 mbar) to give a mixture of (*E*/*Z*)-crotylstannane 50:50 (19.0 g, 81 %).

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 °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 °C, tributyltin chloride (9.7 g, 30 mmol, 1.0 equivalent) was added slowly and the resulting mixture was allowed to warm to 20 °C for 12 h. The reaction was then quenched by the addition of a saturated aqueous NH_4Cl solution. After extraction with Et_2O, the organic layer was washed with water and brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was then distilled under reduced pressure (154–158 °C, 0.3 mbar) to give a mixture of (*E*/*Z*)-crotylstannane 75:25 (3.25 g, 32 %).

$BF_3{\cdot}OEt_2$ (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 Et_2O (90 mL) at −100 °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/−95 °C. After this time, a saturated aqueous $NaHCO_3$ solution was added and the resulting mixture was extracted with Et_2O. The organic layer was washed with water and brine, dried over $MgSO_4$, 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***: $[\alpha]_D^{20} = -2.7$ ($c = 9.6$ in $CHCl_3$); ^{1}H NMR (400.0 MHz, $CDCl_3$): $\delta = 7.26$ (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 (dqd, $J = 8.6$, 7.3, 6.6 Hz, 1H), 1.92–1.79 (m, 1H), 1.10 (d, $J = 6.6$ Hz, 3H; CH_3), 0.96 ppm (d, $J = 6.6$ Hz, 3H; CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 159.2$ (C), 141.3 (CH), 130.3 (C), 129.2 (2CH), 114.5 (CH_2), 113.8 (2CH), 75.4 (CH), 73.1 (CH_2), 72.0 (CH_2), 55.3 (CH_3), 42.1 (CH), 35.4 (CH), 17.2 (CH_3), 9.8 ppm (CH_3); IR (film): $\tilde{\nu} = 2960$, 2907, 2870, 1612, 1513, 1462, 1365, 1302, 1210, 1173, 1093, 1037, 982, 914 cm^{-1}; MS (GC, CI, CH_4): *m*/*z*: 293 $[M+29]^+$, 264, 246, 190, 161, 149, 137, 121, 109, 69, 57.

Compound ***34***: ^{1}H NMR (400.0 MHz, $CDCl_3$): $\delta = 7.26$ (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; CH_3), 0.96 ppm (d, $J = 6.6$ Hz, 3H; CH_3).

(3*R*,4*S*,5*S*)-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 CH_2Cl_2 (90 mL) at 0 °C. After the reaction mixture had been stirred for 2 h at 20 °C, it was partitioned between Et_2O and a saturated aqueous solution of NH_4Cl and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, 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. $[\alpha]_D^{20} = +1.3$ ($c = 1.5$ in $CHCl_3$); ^{1}H NMR (400.0 MHz, $CDCl_3$): $\delta = 7.25$ (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 (dqd, $J = 7.8$, 6.9, 6.9 Hz, 1H), 1.97 (dqdd, $J = 7.9$, 6.6, 6.3, 2.3 Hz, 1H), 0.99 (d, $J = 6.9$ Hz, 3H; CH_3), 0.89 (s, 9H; $3CH_3$), 0.85 (d, $J = 6.6$ Hz, 3H; CH_3), 0.04 (s, 3H; CH_3), 0.02 ppm (s, 3H; CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 159.0$ (C), 142.0 (CH), 130.8 (C), 129.1 (2CH), 113.6 (2CH), 113.4 (CH_2), 75.5 (CH), 73.4 (CH_2), 72.4 (CH_2), 55.2 (CH_3), 42.6 (CH), 36.5 (CH), 26.1 ($3CH_3$), 18.4 (C), 16.9 (CH_3), 11.0 (CH_3), −3.6 ppm ($2CH_3$); IR (film): $\tilde{\nu} = 2959$, 2855, 1653, 1615, 1513, 1462, 1360, 1301, 1246, 1172, 1103, 1039, 911, 836 cm^{-1}; MS (GC, CI, CH_4): *m*/*z*: 407 $[M+29]^+$, 377, 363, 323, 271, 241, 199, 187, 161, 145, 121, 109, 89, 75; elemental analysis calcd (%) for $C_{22}H_{38}O_3Si$: C 69.79, H 10.12; found: C 70.16, H 10.35.

(2*S*,3*S*,4*R*)-2,4-Dimethyl-hex-5-ene-1,3-diol (36): At 0 °C, a solution of compound **33** (100 mg, 0.38 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) was treated with water (0.15 mL) and DDQ (72 mg, 0.317 mmol, 1.2 equiv). The mixture was stirred for 10 min at 0 °C, warmed to 20 °C and then stirred for an additional 30 min. The mixture was quenched with a saturated aqueous $NaHCO_3$ solution, diluted with CH_2Cl_2, and washed with water and brine. The combined organic layers were dried over $MgSO_4$, 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; $[\alpha]_D^{20} = +40$ ($c = 1.5$ in $CHCl_3$); ^{1}H NMR (270.0 MHz, $CDCl_3$): $\delta = 6.03$–5.49 (m, 1H), 5.03–4.89 (m, 2H), 3.69–3.57 (m, 2H), 3.51 (dd, $J = 9.2$, 2.3 Hz, 1H), 2.49 (brs, 1H; OH), 2.28–2.19 (m, 1H), 1.79–1.73 (m, 1H), 1.03 (d, $J = 6.6$ Hz, 3H; CH_3), 0.87 ppm (d, $J = 6.9$ Hz, 3H; CH_3); ^{13}C NMR (67.5 MHz, $CDCl_3$): $\delta = 140.8$ (CH), 114.7 (CH_2), 76.5 (CH), 67.8 (CH_2), 42.2 (CH), 36.5 (CH), 17.1 (CH_3), 8.9 ppm (CH_3); IR (film): $\tilde{\nu} = 3464$, 2957, 1655, 1264, 1105, 1094, 1023, 1016, 798 cm^{-1}; MS (GC, CI, CH_4): *m*/*z*: 127 $[MH-H_2O]^+$, 125, 109, 97, 89, 83, 71, 57; elemental analysis calcd (%) for $C_8H_{16}O_2$: C 66.63, H 11.18; found C 66.46, H 11.07.

(2*S*,3*R*,4*S*)-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 MeOH/CH_2Cl_2 (1:1, 200 mL) at −78 °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 °C for 12 h. The solution was concentrated under reduced pressure, diluted with Et_2O, washed with water (3×), dried over $MgSO_4$, 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}H NMR (400.0 MHz, $CDCl_3$): $\delta = 9.87$ (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 (dqdd, $J = 7.3$, 6.9, 5.9, 3.4 Hz, 1H), 1.05 (d, $J = 6.9$ Hz,

3H; CH_3), 0.91 (s, 9H; $3CH_3$), 0.86 (d, $J=6.9$ Hz, 3H; CH_3), 0.07 (s, 3H; CH_3), 0.05 ppm (s, 3H; CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta=205.5$ (C), 129.2 (2CH), 113.7 (2CH), 72.6 (CH_2), 72.5 (CH_2), 72.3 (CH), 55.2 (CH_3), 51.3 (CH), 37.0 (CH), 25.9 ($3CH_3$), 18.2 (C), 12.1 (CH_3), 9.3 (CH_3), −4.0 ppm ($2CH_3$), one C atom was not detected; MS (GC, EI): m/z: 323 $[M-t\mathrm{Bu}]^+$, 251, 199, 187, 137, 121, 107, 98, 89, 73, 59; elemental analysis calcd (%) for $C_{21}H_{36}O_4Si$: C 66.67, H 9.53; found: C 66.60, H 9.67.

(1*Z*,3*S*,4*S*,5*R*,6*R*,7*S*)-6-(*tert*-Butyldimethylsilyloxy)-1-[(*N*,*N*-diisopropyl)-carbamoyloxy]-8-(4-methoxybenzyloxy)-3,5,7-trimethyl oct-1-en-4-ol (38)

(E)-Crotyldiisopropylcarbamate 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_2O. The combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude residue was distilled (64°C, 0.1 mbar) to give (*E*)-crotyldiisopropylcarbamate (50.0 g, 98%).

Crotylation reaction with optically active crotyltitane: 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*)-crotyl diisopropylcarbamate (6.6 g, 33.2 mmol, 2.0 equiv) and (−)-sparteine (8.01 g, 34.2 mmol, 2.1 equiv), in pentane (30 mL) and cyclohexane (5 mL) at −78°C, and after 10 min white crystals appeared. After 3 h of crystallization at −78°C, a pre-cooled (−40°C) solution of $Ti(OiPr)_4$ (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_2O (250 mL) and aqueous HCl (0.5 N, 250 mL). After extraction with Et_2O, the organic layer was washed with brine, dried over $MgSO_4$, 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 $MgSO_4$, 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%). $[\alpha]_D^{20}=+0.8$ ($c=0.75$ in $CHCl_3$); ^1H NMR (270.0 MHz, $CDCl_3$): $\delta=7.18$ (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 (br s, 1H), 3.73 (s, 3H; CH_3), 3.72–3.60 (br s, 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; $4CH_3$), 0.98 (d, $J=6.9$ Hz, 3H; CH_3), 0.88 (d, $J=6.9$ Hz, 3H; CH_3), 0.85 ppm (d, $J=6.9$ Hz, 3H; CH_3); ^{13}C NMR (67.5 MHz, $CDCl_3$): $\delta=158.9$ (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_2), 72.3 (CH_2), 55.2 (CH_3), 45.7 (2CH), 36.1 (CH), 35.6 (CH), 34.2 (CH), 21.0 ($4CH_3$), 16.2 (CH_3), 13.1 (CH_3), 5.8 ppm (CH_3); IR (film): $\tilde{\nu}=2969$, 2934, 2873, 1708, 1692, 1513, 1441, 1370, 1305, 1247, 1210, 1135, 1063, 971 cm^{-1}.

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_2Cl_2 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%). $[\alpha]_D^{20}=+29.6$ ($c=2.9$ in $CHCl_3$); ^1H NMR (270.0 MHz, $CDCl_3$): $\delta=7.18$ (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 (br s, 1H), 3.75–3.58 (br s, 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; $4CH_3$), 1.27 (s, 3H; CH_3), 1.25 (s, 3H; CH_3), 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); ^{13}C NMR (67.5 MHz, $CDCl_3$): $\delta=159.0$ (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_2), 71.1 (CH_2), 55.1 (CH_3), 46.1 (2CH), 34.9 (CH, C-16), 31.8 (CH), 30.9 (CH), 29.8 (CH_3), 21.0 ($4CH_3$), 19.4 (CH_3), 15.8 (CH_3), 14.8 (CH_3), 4.9 ppm (CH_3); IR (film): $\tilde{\nu}=2968$, 2936, 1708, 1513, 1462, 1439, 1377, 1310, 1288, 1248, 1135, 1057, 1012 cm^{-1}; MS (GC, CI, CH_4): m/z: 534 $[M+29]^+$, 506 $[M+1]^+$; elemental analysis calcd (%) for $C_{29}H_{47}NO_6$: 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 $MeOH/CH_2Cl_2$ (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_4Cl and extracted with Et_2O. The organic layers were washed with brine, dried over $MgSO_4$, 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%). $[\alpha]_D^{20}=-0.73$ ($c=1.1$ in $CHCl_3$); ^1H NMR (270.0 MHz, $CDCl_3$): $\delta=7.22$–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; $3CH_3$), 0.87–0.70 (m, 9H; $3CH_3$), 0.03 ppm (s, 6H; $2CH_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$): $\delta=159.0$ (C), 130.7 (C), 129.1 (2CH), 113.6 (2CH), 77.6 (CH), 73.9 (CH_2), 73.6 (CH), 72.4 (CH_2), 68.4 (CH_2), 55.2 (CH_3), 38.5 (CH), 35.8 (CH), 32.8 (CH), 26.1 ($3CH_3$), 18.4 (C), 12.1 (CH_3), 10.5 (CH_3), 9.6 (CH_3), −3.6 ppm ($2CH_3$); IR (film): $\tilde{\nu}=2958$, 2933, 2856, 1653, 1618, 1559, 1514, 1423, 1344, 1270, 1103, 1037, 837 cm^{-1}.

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_2Cl_2 (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). $[\alpha]_D^{20}=+12.2$ ($c=1.2$ in $CHCl_3$); ^1H NMR (270.0 MHz, $CDCl_3$): $\delta=7.21$ (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; $2CH_3$), 0.87 (d, $J=5.3$ Hz, 3H; CH_3), 0.84 (s, 9H; $3CH_3$), 0.80 (d, $J=6.9$ Hz, 3H; CH_3), 0.63 (d, $J=6.6$ Hz, 3H; CH_3), 0.00 ppm (s, 6H; $2CH_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$): $\delta=159.5$ (C), 131.5 (C), 129.5 (2CH), 114.5 (2CH), 98.5 (C), 75.2 (CH), 74.2 (CH_2), 73.6 (CH), 72.8 (CH_2), 67.0 (CH_2), 55.8 (CH_3), 38.2 (CH), 36.8 (CH), 31.3 (CH), 29.3 (CH_3), 26.7 ($3CH_3$), 19.4 (CH_3), 19.0 (C), 12.8 (CH_3), 11.0 (CH_3), 10.5 (CH_3), −3.6 ppm ($2CH_3$); IR (film): $\tilde{\nu}=3256$, 1684, 1653, 1550, 1501, 1445, 1359, 1248, 1101, 1032, 846 cm^{-1}; MS (GC, CI, CH_4): m/z: 481 $[M+H]^+$; elemental analysis calcd (%) for $C_{27}H_{48}O_5Si$: C 67.45, H 10.06; found: C 67.32, H 10.24.

(1*Z*,3*S*,4*S*,5*R*,6*S*,7*S*)-6-(*tert*-Butyldimethylsilyloxy)-1-[(*N*,*N*-diisopropyl)-carbamoyloxy]-8-(4-methoxybenzyloxy)-4-(triethylsilyloxy)-3,5,7-trimethyl oct-1-ene (39): 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_2Cl_2 (15 mL) at 0°C. After the reaction mixture had been stirred for 2 h at 20°C, it was partitioned between Et_2O and a saturated aqueous solution of NH_4Cl and was extract-

ed with Et_2O. 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 $CHCl_3$); ^{1}H NMR (400.0 MHz, $CDCl_3$): $\delta = 7.22$ (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 (br s, 1H), 3.82–3.69 (br s, 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; $4CH_3$), 1.01 (d, $J = 7.2$ Hz, 3H; CH_3), 0.97–0.87 (m, 12H; $4CH_3$), 0.85 (s, 9H; $3CH_3$), 0.80 (d, $J = 7.2$ Hz, 3H; CH_3), 0.60 (q, $J = 7.6$ Hz, 6H; $3CH_2$), 0.02 (s, 3H; CH_3), 0.01 ppm (s, 3H; CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 159.0$ (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_2), 72.6 (CH_2), 55.2 (CH_3), 45.4 (2CH), 42.9 (CH), 38.7 (CH), 32.4 (CH), 26.1 ($3CH_3$), 21.5 ($4CH_3$), 20.3 (CH_3), 18.4 (C), 12.2 (CH_3), 11.1 (CH_3), 7.0 ($3CH_3$), 5.5 ($3CH_2$), 3.2 ppm ($2CH_3$); IR (film): $\tilde{\nu} = 2966$, 2937, 2877, 1710, 1514, 1460, 1439, 1306, 1249, 1060, 1042, 1005, 837 cm^{-1}; elemental analysis calcd (%) for $C_{38}H_{71}NO_6Si_2$: C 65.75, H 10.31, N 2.02; found: C 65.72, H 10.27, N 1.97.

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

Reaction with vinylmagnesium bromide: A solution of the vinyl carbamate **39** (700 mg, 1.01 mmol, 1.0 equiv) in Et_2O (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 $[Ni(acac)_2]$ (26 mg, 0.10 mmol, 0.1 equiv) in Et_2O (10 mL) at 0°C. The resulting mixture was stirred for 24 h at 0°C. After this time, a saturated aqueous NH_4Cl solution was added and the solution was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, 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 vinyllithium: MeLi (1.6 M in Et_2O, 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_2O (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 $[Ni(acac)_2]$ (74 mg, 0.288 mmol, 0.1 equiv) in Et_2O (4 mL) at −5/0°C. After the reaction mixture had been stirred for a further 6 h, the same amount of $[Ni(acac)_2]$ was added and the resulting mixture was stirred for another 12 h at 0°C. Then a saturated aqueous NH_4Cl solution was added and the solution was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate 98:2 to 80:20) to give **40** (1.33 g, 80%).

*Compound **40***: $[\alpha]_D^{20} = +8.9$ ($c = 2.1$ in $CHCl_3$); ^{1}H NMR (400.0 MHz, $CDCl_3$): $\delta = 7.24$ (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; $9CH_3$), 0.59 (q, $J = 7.8$ Hz, 6H; $3CH_2$), 0.04 ppm (s, 6H; $2CH_3$); ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 159.0$ (C), 135.0 (CH), 132.5 (CH), 130.8 (C), 129.2 (2CH), 129.0 (CH), 117.1 (CH_2), 113.6 (2CH), 77.5 (CH), 73.2 (CH_2), 73.1 (CH), 72.5 (CH_2), 55.2 (CH_3), 40.2 (CH), 38.0 (CH), 36.5 (CH), 26.2 ($3CH_3$), 18.7 (C), 18.5 (CH_3), 11.9 (CH_3), 11.5 (CH_3), 7.2 ($3CH_3$), 5.6 ($3CH_2$), −3.3 ppm ($2CH_3$); IR (film): $\tilde{\nu} = 2957$, 2857, 1616, 1490 cm^{-1}; elemental analysis calcd (%) for $C_{33}H_{60}O_4Si_2$: C 68.69, H 10.48; found: C 68.48, H 10.67.

*Compound **41***: ^{1}H NMR (400.0 MHz, $CDCl_3$): $\delta = 7.24$ (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), 348 (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 (dqd, $J = 8.2$, 6.9, 5.0 Hz, 1H), 1.93 (dqdd, $J = 7.3$, 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_3), 0.93 (t, $J = 7.8$ Hz, 9H; $3CH_3$), 0.88 (s, 9H; $3CH_3$), 0.86 (d, $J = 6.9$ Hz, 3H; CH_3), 0.85 (d, $J = 6.9$ Hz, 3H; CH_3), 0.59 (q, $J = 7.8$ Hz, 6H; $3CH_2$), 0.03 ppm (s, 6H; $2CH_3$); ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 159.0$ (C), 141.2 (C), 131.2 (CH), 129.3 (2CH), 114.6 (CH_2), 113.6 (2CH), 77.0 (CH), 73.3 (CH_2), 73.2 (CH), 72.6 (CH_2), 55.3 (CH_3), 39.6 (CH), 37.9 (CH), 33.5 (CH), 26.2 ($3CH_3$), 18.5 (C), 18.5 (CH_3), 11.7 (CH_3), 11.5 (CH_3), 7.2 ($3CH_3$), 5.6 ($3CH_2$), −3.4 ppm ($2CH_3$).

(3*Z*,5*S*,6*S*,7*R*,8*S*,9*S*)-8-(*tert*-Butyldimethylsilyloxy)-10-hydroxy-6-(triethylsilyloxy)-5,7,9-trimethyl deca-1,3-diene (42): DDQ (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_2Cl_2 (6 mL)/H_2O (300 μL) 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 $NaHCO_3$ solution, diluted with Et_2O, and washed with water and brine. The combined organic layers were dried over $MgSO_4$, 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 the title compound **42** (142 mg, 72%). $[\alpha]_D^{20} = +11.4$ ($c = 1.2$ in $CHCl_3$); ^{1}H NMR (400.0 MHz, $CDCl_3$): $\delta = 6.58$ (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 (dqd, $J = 10.1$, 7.3, 3.9 Hz, 1H), 2.86 (m, 1H), 1.75 (dd, $J = 5.5$, 5.0 Hz, 1H; OH), 1.64 (dqd, $J = 7.3$, 6.9, 3.9 Hz, 1H), 1.04 (d, $J = 7.3$ Hz, 3H; CH_3), 0.98 (t, $J = 7.8$ Hz, 9H; $3CH_3$), 0.94 (d, $J = 6.9$ Hz, 3H; CH_3), 0.85 (s, 9H; $3CH_3$), 0.83 (d, $J = 6.9$ Hz, 3H; CH_3), 0.65 (q, $J = 7.8$ Hz, 6H; $3CH_2$), 0.11 ppm (s, 3H; CH_3), 0.08 ppm (s, 3H; CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 134.6$ (CH), 132.5 (CH), 129.2 (CH), 117.7 (CH_2), 78.0 (CH), 73.7 (CH), 66.2 (CH_2), 40.8 (CH), 40.2 (CH), 35.9 (CH), 26.2 ($3CH_3$), 19.2 (CH_3), 18.5 (C), 12.5 (CH_3), 11.9 (CH_3), 7.4 ($3CH_3$), 5.8 ($3CH_2$), −3.5 (CH_3), −3.7 ppm (CH_3); IR (film): $\tilde{\nu} = 3405$, 2956, 2930, 2878, 2858, 1461, 1252, 1096, 1076, 1006, 837, 772, 737 cm^{-1}; elemental analysis calcd (%) for $C_{25}H_{52}O_3Si_2$: C 65.73, H 11.47; found: C 65.56, H 11.62.

(3*Z*,5*S*,6*S*,7*R*,8*S*,9*S*)-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_2O (2 mL) was added slowly to a solution of compound **42** (200 mg, 0.44 mmol, 1.0 equiv), triphenylphosphine (PPh_3, 218 mg, 0.83 mmol, 1.9 equiv), and imidazole (57 mg, 0.83 mmol, 1.9 equiv) in a benzene/Et_2O 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 $Na_2S_2O_3$ solution was added and the reaction mixture was extracted with Et_2O. The organic layers were washed with, brine, dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/Et_2O 100:0 to 80:20) to give the title compound **43** (197 mg, 79%). $[\alpha]_D^{20} = +11.3$ ($c = 0.68$ in $CHCl_3$); ^{1}H NMR (400.0 MHz, $CDCl_3$): $\delta = 6.58$ (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 (dqd, $J = 10.1$, 6.9, 4.6 Hz, 1H), 1.97 (dqdm, $J = 9.2$, 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_3), 0.98 (t, $J = 7.8$ Hz, 9H; $3CH_3$), 0.98 (d, $J = 6.9$ Hz, 3H; CH_3), 0.91 (s, 9H; $3CH_3$), 0.90 (d, $J = 6.9$ Hz, 3H; CH_3), 0.64 (q, $J = 7.8$ Hz, 6H; $3CH_2$), 0.10 (s, 3H; CH_3), 0.09 ppm (s, 3H; CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 134.1$ (CH), 132.5 (CH), 129.0 (CH), 117.4 (CH_2), 77.1 (CH), 75.0 (CH), 41.9 (CH), 40.4 (CH), 35.8 (CH), 25.9 ($3CH_3$), 18.8 (CH_3), 18.4 (C), 15.0 (CH_3), 13.4 (CH_2), 11.9 (CH_3), 7.0 ($3CH_3$), 5.5 ($3CH_2$), −3.8 ppm ($2CH_3$); IR (film): $\tilde{\nu} = 2950$, 2930, 2877, 2857, 1461, 1097, 1028, 1005, 836 cm^{-1}; elemental analysis calcd (%) for $C_{25}H_{51}IO_2Si_2$: C 52.98, H 9.07; found: C 53.17, H 9.25.

(1*Z*,3*S*,4*S*,5*S*)-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 $Ti(OiPr)_4$ (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 limpid and turned orange. After 1 h at −78 °C, aldehyde **50** (3.96 g, 19.6 mmol, 1.0 equiv) in pentane (10 mL) was slowly added to the orange solution, and the mixture was stirred for 3 h at −78 °C. The solution was then poured into a mixture of Et_2O (250 mL)/ aqueous HCl (0.5 N, 250 mL). After extraction with Et_2O, the organic layer was washed with brine, dried over $MgSO_4$, 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***: $[\alpha]_D^{20} = +20.1$ ($c = 1.0$ in $CHCl_3$); H RMN (400.0 MHz, $CDCl_3$): $\delta = 7.13$ (d, $J = 6.4$ Hz, 1H), 4.73 (dd, $J = 9.6$, 6.4 Hz, 1H), 4.22–4.11 (br s, 1H), 3.82–3.70 (br s, 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; $4CH_3$), 0.97 (d, $J = 6.9$ Hz, 3H; CH_3), 0.94 (d, $J = 6.9$ Hz, 3H; CH_3), 0.90 (s, 9H; $3CH_3$), 0.08 ppm (s, 6H; $2CH_3$); ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 153.0$ (C), 135.9 (CH), 113.9 (CH), 77.0 (CH), 68.0 (CH_2), 47.0 (CH), 45.2 (CH), 36.6 (CH), 34.0 (CH), 26.0 ($3CH_3$), 21.6 ($2CH_3$), 20.5 ($2CH_3$), 18.3 (C), 17.4 (CH_3), 9.4 (CH_3), −5.50 ppm ($2CH_3$); IR (film): $\tilde{\nu} = 3493$, 2959, 2930, 2858, 1708, 1472, 1439, 1370, 1304, 1290, 1256, 1211, 1156, 1134, 1092, 1061, 837 cm^{-1}; MS (GC, EI): *m/z*: 344 $[M-t\mathrm{Bu}]^+$, 326, 302, 228, 212, 199, 184, 145, 128, 115, 86, 73; elemental analysis calcd (%) for $C_{21}H_{43}NO_4Si$: C 62.80, H 10.79, N 3.49; found: C 62.61, H 10.87, N 3.35.

3,4-bis-epi *isomer of* ***51***: ^1H NMR (400.0 MHz, $CDCl_3$): $\delta = 7.07$ (d, $J =$ 6.4 Hz, 1H), 4.97 (dd, $J = 9.6$, 6.4 Hz, 1H), 4.25–4.05 (br s, 1H), 4.20 (s, 1H; OH), 3.85–3.67 (br s, 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; $4CH_3$), 1.14 (d, $J = 6.9$ Hz, 3H; CH_3), 0.90 (s, 9H; $3CH_3$), 0.76 (d, $J =$ 6.9 Hz, 3H; CH_3), 0.09 ppm (s, 6H; $2CH_3$); ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 153.5$ (C), 135.1 (CH), 111.5 (CH), 80.5 (CH), 69.5 (CH_2), 46.9 (CH), 45.5 (CH), 38.1 (CH), 33.5 (CH), 25.9 ($3CH_3$), 21.6 ($2CH_3$), 20.5 ($2CH_3$), 18.3 (C), 18.2 (CH_3), 13.2 (CH_3), −5.5 ppm ($2CH_3$).

(2*S*,3*S*,4*S*)-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 $[Ni(acac)_2]$ (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_4Cl solution was added, and the reaction mixture was extracted with Et_2O. The combined organic layers were washed with water and brine, dried over $MgSO_4$, 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; ^1H NMR (400.0 MHz, $CDCl_3$): $\delta = 5.84$ (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; $2CH_3$), 0.90 (s, 9H; $3CH_3$), 0.07 ppm (s, 6H; $2CH_3$); ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 142.3$ (CH), 115.3 (CH_2), 77.2 (CH), 68.8 (CH_2), 42.0 (CH), 36.1 (CH), 26.0 ($3CH_3$), 18.4 (C), 16.9, 9.5 ($2CH_3$), −5.4 (CH_3), −5.5 ppm (CH_3).

(2*E*,4*S*,5*S*,6*S*)-*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_2Cl_2 (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; ^1H NMR (400.0 MHz, $CDCl_3$): $\delta = 9.83$ (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 (dqd, $J = 9.6$, 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_3), 0.98 (d, $J = 6.9$ Hz, 3H; CH_3), 0.90 (s, 9H; $3CH_3$), 0.08 ppm (s, 6H; $2CH_3$); ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 205.9$ (CH), 75.4 (CH), 67.8 (CH_2), 49.7 (CH), 35.8 (CH), 26.0 ($3CH_3$), 18.3 (C), 10.6 (CH_3), 9.4 (CH_3), −5.5 ppm ($2CH_3$).

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_4Cl solution. The aqueous layer was separated and extracted with Et_2O (2×). The combined organic phases were washed with water and brine, dried over $MgSO_4$, 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. $[\alpha]_D^{20} = -3.3$ ($c = 1.0$ in $CHCl_3$); ^1H NMR (400.0 MHz, $CDCl_3$): $\delta = 6.99$ (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_3), 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_3), 2.84 (br s, 1H; OH), 2.50 (dqd, $J = 8.7$, 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_3), 0.96 (d, $J = 7.3$ Hz, 3H; CH_3), 0.90 (s, 9H; $3CH_3$), 0.09 ppm (s, 6H, $2CH_3$); ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 167.0$ (C), 150.9 (CH), 119.1 (CH), 77.3 (CH), 68.6 (CH_2), 61.8 (CH_3, CH_3), 40.9 (CH), 36.2 (CH), 32.4 (CH_3), 26.0 ($3CH_3$), 18.3 (C), 16.6 (CH_3), 9.5 (CH_3), −5.5 ppm ($2CH_3$); IR (film): $\tilde{\nu} =$ 3444, 2958, 2930, 2857, 1650, 1627, 1471, 1417, 1385, 1255, 1093, 1004, 850 cm^{-1}; MS (GC, EI): *m/z*: 288 $[M-t\mathrm{Bu}]^+$, 267, 246, 227, 203, 187, 172, 145, 115, 89, 75, 55; elemental analysis calcd (%) for $C_{17}H_{35}NO_4Si$: C 59.09, H 10.21, N 4.05; found: C 58.95, H 10.28, N 3.94.

(2*S*,4*S*,5*S*,6*R*)-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 μL, 87.5 μmol, 0.1 equiv) was added to a solution of compound **53** (300 mg, 0.87 mmol, 1.0 equiv) and freshly distilled benzaldehyde (97 μL, 0.96 mmol, 1.1 equiv) in dry THF (9 mL) at 0 °C. 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_4Cl solution. The organic layer was washed with water and brine, dried over $MgSO_4$, 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. $[\alpha]_D^{20} = +21.9$ ($c = 0.6$ in $CHCl_3$); ^1H NMR (400.0 MHz, $CDCl_3$): $\delta = 7.46$–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_3), 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_3), 0.89 (s, 9H; $3CH_3$), 0.85 (d, $J =$ 6.9 Hz, 3H; CH_3), 0.03 ppm (s, 6H; $2CH_3$); ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 172.2$ (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_2), 61.6 (CH_3), 36.7 (CH_2), 36.0 (CH), 35.4 (CH), 32.2 (CH_3), 26.0 ($3CH_3$), 18.4 (C), 12.0 (CH_3), 9.8 (CH_3), −5.3 ppm ($2CH_3$); IR (film): $\tilde{\nu} = 2956$, 2930, 2857, 1666, 1483, 1403, 1387, 1256, 1149, 1090, 1029, 837 cm^{-1}; MS (GC, EI): *m/z*: 394 $[M-t\mathrm{Bu}]^+$, 330, 288, 258, 243, 221, 199, 185, 172, 145, 115, 89, 75, 55; elemental analysis calcd (%) for $C_{24}H_{41}NO_5Si$: C 63.82, H 9.15, N 3.10; found: C 63.79, H 9.21, N 3.01.

(2*S*,4*S*,5*S*,6*R*)-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 CH_2Cl_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 CH_2Cl_2 (20 mL) at −78 °C. The yellow solution was stirred at −78 °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 °C and a solution of Rochelle's salt (17.0 g, 60.2 mmol, 18.1 equiv, in 20 mL water) was added. The mixture was stirred at 20 °C for 2 h and then the organic layer was extracted with Et_2O (2×). The combined organic extracts were washed with brine, dried over $MgSO_4$, 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 $CHCl_3$); ^{1}H NMR (400.0 MHz, $CDCl_3$): $\delta = 9.83$ (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; $3CH_3$), 0.90 (d, $J = 7.3$ Hz, 3H; CH_3), 0.88 (d, $J = 6.9$ Hz, 3H; CH_3), 0.04 ppm (s, 6H; $2CH_3$); ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 201.6$ (C), 138.6 (C), 128.7 (CH), 128.2 (2CH), 126.1 (2CH), 100.3 (CH), 80.1 (CH), 77.4 (CH), 64.9 (CH_2), 47.0 (CH_2), 36.6 (CH), 35.1 (CH), 26.0 ($3CH_3$), 18.4 (C), 11.8 (CH_3), 9.7 (CH_3), −5.3 ppm ($2CH_3$); IR (film): $\tilde{\nu} = 2955$, 2929, 2882, 2856, 1728, 1471, 1462, 1402, 1256, 1101, 1073, 1029, 837 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.

[2*S*,4*R*(1*S*),5*S*,6*S*(2*S*,5*S*,6*R*,7*S*,8*Z*)]-4-[2-(*tert*-Butyldimethylsilyloxy)-1-methyl ethyl-1-yl]-6-{5,7-dimethyl-2-hydroxy-6-[(methoxymethyl)oxy]-9-tributylstannyl-dec-8-en-3-yn-1-yl}-5-methyl-2-phenyl-1,3-dioxinan (56) and [2*S*,4*R*(1*S*),5*S*,6*S*(2*R*,5*S*,6*R*,7*S*,8*Z*)]-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*BuLi (1.5 M in pentane, 295 μL, 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 °C. The resulting mixture was stirred for 30 min at −78 °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 °C, a saturated aqueous NH_4Cl solution was added and the reaction mixture was extracted with Et_2O. The organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/Et_2O 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 $CHCl_3$); ^{1}H NMR (400.0 MHz, $CDCl_3$): $\delta = 7.49$–7.43 (m, 2H), 7.39–7.30 (m, 3H), 5.97 (dq, $J = 9.6$, 1.4, $J_{^1H,^{117}Sn} = J_{^1H,^{119}Sn} = 132.8$ 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; 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 (dqd, $J = 9.6$, 6.9, 5.9 Hz, 1H), 2.12 (ddd, $J = 14.6$, 7.8, 2.3 Hz, 1H), 2.10 (dddm, $J = 9.2$, 6.0, 1.4 Hz, 1H), 1.95 (ddd, $J = 14.6$, 10.1, 2.7 Hz, 1H), 1.89 (d, $J = 1.4$, $J_{^1H,^{117}Sn} = J_{^1H,^{119}Sn} = 44.8$ Hz, 3H; CH_3), 1.76 (ddq, $J = 10.1$, 10.1, 6.4 Hz, 1H), 1.54–1.43 (m, 6H; $3CH_2$), 1.33–1.29 (sext, $J = 7.8$ Hz, 6H; $3CH_2$), 1.22 (d, $J = 6.9$ Hz, 3H; CH_3), 1.02 (d, $J = 6.9$ Hz, 3H; CH_3), 1.0–0.81 (m, 18H; $4CH_3$, $3CH_2$), 0.89 (s; $3CH_3$), 0.81 (d, $J = 6.4$ Hz, 3H; CH_3), 0.04 ppm (s, 6H; $2CH_3$); ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 143.9$ ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 26.8$ Hz; CH), 138.6 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 385.3$ Hz; C), 137.7 (C), 128.3 (CH), 127.9 (2CH), 125.7 (2CH), 99.8 (CH), 98.1 (CH_2), 87.0 (CH), 85.5 (C), 82.5 (C), 80.1 (CH), 79.6 (CH), 64.7 (CH_2), 60.0 (CH), 59.6 (CH_3), 42.2 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 30.6$ Hz; CH), 42.1 (CH_2), 36.4 (CH), 34.7 (CH), 30.0 (CH), 29.1 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 19.1$ Hz; $3CH_2$), 27.3 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 57.5$ Hz; $3CH_2$), 26.7 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 44.1$ Hz; CH_3), 25.8 ($3CH_3$), 18.6 (CH_3), 18.1 (C), 16.6 (CH_3), 13.6 ($3CH_3$), 11.5 (CH_3), 9.8 ($J_{^{13}C,^{117}Sn} = 313.4$, $J_{^{13}C,^{119}Sn} = 327.8$ Hz; $3CH_2$), 9.5 (CH_3), −5.5 ppm ($2CH_3$); IR (film): $\tilde{\nu} = 2956$, 2928, 2855, 2360, 2341, 1594, 1455, 1404, 1375, 1255, 1149, 1095, 1050, 836, 775, 695, 663, 661 cm^{-1}; elemental analysis calcd (%) for $C_{46}H_{82}O_6SiSn$: C 62.93, H 9.41; found: C 63.10, H 9.55.

*Compound **57***: ^{1}H NMR (400.0 MHz, $CDCl_3$): $\delta = 7.47$–7.24 (m, 2H), 7.39–7.30 (m, 3H), 6.00 (dq, $J = 9.6$, 1.4, $J_{^1H,^{117}Sn} = J_{^1H,^{119}Sn} = 137.4$ 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; 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 (dqd, $J = 9.6$, 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, $J = 1.4$, $J_{^1H,^{117}Sn} = J_{^1H,^{119}Sn} = 42.6$ Hz, 3H; CH_3), 1.80–1.71 (m, 1H), 1.53–1.45 (m, 6H; $3CH_2$), 1.32 (sext, $J = 7.3$ Hz, 6H; $3CH_2$), 1.21 (d, $J = 6.9$ Hz, 3H; CH_3), 1.00 (d, $J = 6.9$ Hz, 3H; CH_3), 1.00–0.86 (m, 18H; $4CH_3$, $3CH_2$), 0.90 (s, 9H; $3CH_3$), 0.82 (d, $J = 6.9$ Hz, 3H), 0.04 ppm (s, 6H; $2CH_3$); ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 144.2$ (CH), 138.7 (C), 137.8 (C), 128.7 (CH), 128.2 (2CH), 126.0 (2CH), 100.5.1 (CH), 98.3 (CH_2), 87.4 (CH), 85.7 (C), 82.5 (C), 81.7 (CH), 80.4 (CH), 65.0 (CH_2), 61.8 (CH), 56.3 (CH_3), 42.3 (CH), 41.2 (CH_2), 36.7 (CH), 35.2 (CH), 30.3 (CH), 29.3 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 20.1$ Hz; $3CH_2$), 27.6 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 57.5$ Hz; $3CH_2$), 27.3 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 46.0$ Hz; CH_3), 26.1 ($3CH_3$), 18.8 (CH_3), 18.5 (C), 16.5 (CH_3), 13.9 ($3CH_3$), 11.9 (CH_3), 10.1 ($J_{^{13}C,^{117}Sn} = 312.5$, $J_{^{13}C,^{119}Sn} = 329.8$ Hz; $3CH_2$), 9.8 (CH_3), −5.5 ppm ($2CH_3$).

*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 BH_3·Me_2S (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 °C. The resulting mixture was stirred for 2 h at −30 °C and was then quenched with EtOH and extracted with Et_2O. The organic layers were washed with water and brine, dried over $MgSO_4$, filtered, 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 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 μL, 0.171 mmol, 2.0 equiv) and BH_3·Me_2S (2 M in THF, 214 μL, 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 °C. The resulting mixture was stirred for 2 h at −30 °C and was then quenched with EtOH and extracted with Et_2O. The organic layers were washed with water and brine, dried over $MgSO_4$, filtered, 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 **57** (63 mg, 90%).

[2*S*,4*R*(1*S*),5*S*,6*S*(5*S*,6*R*,7*S*,8*Z*)]-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*BuLi (1.5 M in pentane, 295 μL, 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 °C. The resulting mixture was stirred for 30 min at −78 °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 °C, a saturated aqueous NH_4Cl solution was added and the reaction mixture was extracted with Et_2O. The organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/Et_2O 98:2 to 80:20) to furnish the title compound **58** (156 mg, 81%).

Coupling reaction with n*BuLi—preparation of* n*BuLi in Et_2O*: 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 Et_2O (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 Et_2O (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 °C by immersing in a −30 °C nitrogen/acetone bath. The remainder of the *n*-butylbromide solution was added over 20 min while keeping the internal temperature below −10 °C. After the addition was complete, the reaction mixture was allowed to warm up gradually to 0 and then 10 °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_2O (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_4Cl solution was added and the reaction mixture was extracted with Et_2O. The organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/Et_2O 98:2 to 80:20) to furnish the title compound **58** (1.22 g, 81%). $[\alpha]_D^{20} = +13.4$ ($c = 0.94$ in $CHCl_3$); ^{1}H NMR (400.0 MHz, $CDCl_3$): $\delta = 7.43$–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, $J = 9.6$, 9.2 Hz, 1H), 3.51 (dd, $J = 9.6$, 5.9 Hz, 1H), 3.39 (s, 3H; CH_3), 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 (dqd, $J = 9.6$, 6.9, 6.4 Hz, 1H), 1.98 (dddm, $J = 9.2$, 5.9, 1.4 Hz, 1H), 1.88 (d, $J = 1.4$, $J_{^1H,^{117}Sn} = J_{^1H,^{119}Sn} = 41.2$ Hz, 3H; CH_3), 1.72 (ddq, $J = 9.6$, 9.6, 6.9 Hz, 1H), 1.54–1.43 (m, 6H; $3CH_2$), 1.32 (sext, $J = 7.3$ Hz, 6H; $3CH_2$), 1.24 (d, $J = 6.9$ Hz, 3H; CH_3), 1.00 (d, $J = 6.9$ Hz, 3H; CH_3), 0.95–0.87 (m, 27H; $7CH_3 + 3CH_2$), 0.80 (d, $J = 6.9$ Hz, 3H; CH_3), 0.04 ppm (s, 6H; $2CH_3$); ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta =$ 185.3 (C), 143.4 (CH), 138.8 (C), 138.7 (C), 128.4 (CH), 128.0 (2CH), 126.0 (2CH), 99.9 (CH), 98.3 (CH_2), 96.5 (C), 85.2 (CH), 83.0 (C), 80.3 (CH), 78.2 (CH), 65.0 (CH_2), 56.4 (CH_3), 49.5 (CH_2), 42.8 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 30.6$ Hz; CH), 36.7 (CH), 35.0 (CH), 30.8 (CH), 29.4 ($3CH_2$), 27.5 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 58.4$ Hz; CH_3, $3CH_2$), 26.0 ($3CH_3$), 18.4 (C), 17.8 (CH_3), 17.1 (CH_3), 13.8 ($3CH_3$), 11.9 (CH_3), 10.1 ($J_{^{13}C,^{117}Sn} = 313.4$, $J_{^{13}C,^{119}Sn} = 328.8$ Hz; $3CH_2$), 9.7 (CH_3), −5.2 ppm ($2CH_3$); IR (film): $\tilde{\nu} =$ 2956, 2855, 2212, 1678, 1465, 1403, 1376, 1345, 1255, 1215, 1147, 1092, 1032, 837, 758, 699 cm^{-1}; elemental analysis calcd (%) for $C_{46}H_{80}O_6SiSn$: C 63.08, H 9.21; found: C 63.18, H 9.32.

[2*S*,4*R*(1*R*),5*S*,6*S*(2*S*,5*S*,6*R*,7*S*,8*Z*)]-4-(2-Methoxycarbonyl-1-methyl ethyl-1-yl)-6-{5,7-dimethyl-2-hydroxy-2,6-bis[(methoxymethyl)oxy]-9-tributylstannyl-dec-8-en-3-yn-1-yl}-5-methyl-2-phenyl-1,3-dioxinan (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_2Cl_2 (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 $NaHCO_3$ solution and extracted with Et_2O. The organic layers were washed with brine, dried over $MgSO_4$, 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 [2*S*,4*R*(1*S*),5*S*,6*S*(2*S*,5*S*,6*R*,7*S*,8*Z*)]-4-[2-(*tert*-butyldimethylsilyloxy)-1-methyl ethyl-1-yl]-6-{5,7-dimethyl-2,6-bis[(methoxymethyl)oxy]-9-tributylstannyl-dec-8-en-3-yn-1-yl}-5-methyl-2-phenyl-1,3-dioxinan (6.2 g, 86%) as a yellow oil. $[\alpha]_D^{20} = -17.2$ ($c = 1.52$ in $CHCl_3$); ^{1}H NMR (400.0 MHz, $CDCl_3$): $\delta = 7.49$–7.47 (m, 2H), 7.37–7.30 (m, 3H), 6.00 (d, 1H, $J = 9.6$, $J_{^1H,^{117}Sn} = J_{^1H,^{119}Sn} = 133.7$ 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_3), 3.36 (s, 3H; CH_3), 3.24 (t, $J = 5.5$ Hz, 1H), 2.72 (qd, $J = 6.9$, 5.5 Hz, 1H), 2.28–2.18 (dqd, $J = 9.6$, 6.9, 5.5 Hz, 1H), 2.28–2.18 (m, 1H), 2.04–1.98 (m, 1H), 1.89 (s, $J_{^1H,^{117}Sn} = J_{^1H,^{119}Sn} = 41.7$ Hz, 3H; CH_3), 1.87–1.83 (m, 1H), 1.66–1.63 (m, 1H), 1.52–1.45 (m, 6H; $3CH_2$), 1.33 (sext, $J = 7.3$ Hz, 6H; $3CH_2$), 1.18 (d, $J = 7.3$ Hz, 3H; CH_3), 0.98 (d, $J = 6.9$ Hz, 3H; CH_3), 0.98–0.85 (m, 18H; $4CH_3 + 3CH_2$), 0.89 (s, 9H; $3CH_3$), 0.81 (d, $J = 6.4$ Hz, 3H; CH_3), 0.05 ppm (s, 6H; $2CH_3$); ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 144.2$ ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 29.7$ Hz; CH), 139.1 (C), 137.5 (C), 128.3 (CH), 128.0 (2CH), 125.8 (2CH), 99.6 (CH), 98.1 (CH_2), 93.6 (CH_2), 87.7 (C), 85.3 (C), 80.1 (C), 80.0 (CH), 77.6 (CH), 65.0 (CH_2), 61.0 (CH), 56.1 (CH_3), 55.5 (CH_3), 42.0 (CH), 39.9 (CH_2), 36.6 (CH), 35.2 (CH), 30.2 (CH), 29.2 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 20.1$ Hz; $3CH_2$), 27.4 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 58.4$ Hz; CH_3), 26.9 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 53.6$ Hz; $3CH_2$), 25.9 ($3CH_3$), 18.5 (CH_3), 18.3 (C), 16.3 (CH_3), 13.7 ($3CH_3$), 11.6 (CH_3), 9.9 ($J_{^{13}C,^{117}Sn} = 313.4$, $J_{^{13}C,^{119}Sn} = 327.8$ Hz; $3CH_2$), 9.6 (CH_3), −5.4 ppm ($2CH_3$); IR (film): $\tilde{\nu} = 2956$, 2928, 2380, 2341, 1456, 1402, 1375, 1350, 1250, 1158, 1098, 1015, 920, 837, 775, 690, 663 cm^{-1}; elemental analysis calcd (%) for $C_{48}H_{86}O_7SiSn$: C 62.53, H 9.40; found: C 62.33, H 9.59.

A HF·pyridine stock solution (500 μL, 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 $NaHCO_3$ solution and extracted with Et_2O. The organic layers were washed with brine, dried over $MgSO_4$, 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 [2*S*,4*R*(1*S*),5*S*,6*S*(2*S*,5*S*,6*R*,7*S*,8*Z*)]-4-(2-hydroxy-1-methyl ethyl-1-yl)-6-{5,7-dimethyl-2,6-bis[(methoxymethyl)oxy]-9-tributylstannyl-dec-8-en-3-yn-1-yl}-5-methyl-2-phenyl-1,3-dioxinan (84 mg, 96%). $[\alpha]_D^{20} = -35.9$ ($c = 1.19$ in $CHCl_3$); ^{1}H NMR (400.0 MHz, $CDCl_3$): $\delta = 7.46$–7.43 (m, 2H), 7.38–7.33 (m, 3H), 6.01 (dq, 1H, $J = 9.6$, 1.4, $J_{^1H,^{117}Sn} = J_{^1H,^{119}Sn} = 132.8$ 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_3), 3.34 (s, 3H; CH_3), 3.24 (t, $J = 5.5$ Hz, 1H), 2.72 (qd, $J = 6.9$, 5.5 Hz, 1H), 2.28–2.23 (dqd, $J = 9.6$, 6.9, 5.5 Hz, 1H), 2.28–2.23 (m, 1H), 2.06–2.02 (m, 1H), 1.89 (d, $J = 1.4$, $J_{^1H,^{117}Sn} = J_{^1H,^{119}Sn} = 43.0$ Hz, 3H; CH_3), 1.89–1.85 (m, 1H), 1.83 (dqd, $J = 6.9$, 6.4, 3.4 Hz, 1H), 1.49–1.38 (m, 6H; $3CH_2$), 1.37–1.28 (sext, $J = 7.3$ Hz, 6H; $3CH_2$), 1.18 (d, $J = 6.9$ Hz, 3H; CH_3), 1.43 (d, $J = 6.9$ Hz, 3H; CH_3), 1.03 (d, $J = 6.9$ Hz, 3H; CH_3), 1.02–0.88 (m, 15H; $3CH_2 + 3CH_3$), 0.85 ppm (d, $J = 6.9$ Hz, 3H; CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 144.1$ (CH), 138.5 (C), 137.5 (C), 128.5 (CH), 128.1 (2CH), 125.7 (2CH), 99.9 (CH), 98.0 (CH_2), 93.6 (CH_2), 87.7 (C), 85.2 (CH), 83.5 (CH or CH_2), 80.3 (C), 77.5 (CH or CH_2), 66.7 (CH or CH_2), 60.9 (CH), 56.1 (CH_3), 55.4 (CH_3), 41.9 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 34.4$ Hz; CH), 39.8 (CH_2), 35.5 (CH), 35.3 (CH), 30.1 (CH), 29.2 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 19.2$ Hz; $3CH_2$), 27.4 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 58.5$ Hz; $3CH_2$), 27.2 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 46.0$ Hz; CH_3), 18.5 (CH_3), 16.3 (CH_3), 13.6 ($3CH_3$), 11.5 (CH_3), 9.8 ($J_{^{13}C,^{117}Sn} = 314.4$, $J_{^{13}C,^{119}Sn} = 327.8$ Hz; $3CH_2$), 9.5 ppm (CH_3); IR (film): $\tilde{\nu} = 3380$, 2956, 2927, 2872, 2852, 1590, 1454, 1436, 1376, 1351, 1154, 1098, 1029, 699 cm^{-1}; elemental analysis calcd (%) for $C_{42}H_{72}O_7Sn$: 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_2Cl_2 (20 mL). After the reaction mixture had been stirred for 3 h at 20°C, a 1 M $Na_2S_2O_3$ solution was added, and the reaction mixture was extracted with Et_2O. The organic layers were washed with a saturated aqueous $NaHCO_3$ solution, brine, dried over $MgSO_4$, 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-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. ^{1}H NMR (400.0 MHz, $CDCl_3$): $\delta = 9.80$ (s, 1H), 7.42–7.32 (m, 5H), 6.00 (dq, $J = 8.2$, 1.4, $J_{^1H,^{117}Sn} = J_{^1H,^{119}Sn} = 135.1$ 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_3), 3.35 (s, 3H; CH_3), 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 (dqd, $J = 8.2$, 6.9, 5.5 Hz, 1H), 2.28–2.18 (m, 1H), 1.89 (d, $J = 1.4$, $J_{^1H,^{117}Sn} = J_{^1H,^{119}Sn} = 41.2$ Hz, 3H; CH_3), 1.89–1.84 (m, 1H), 1.84 (ddq, $J = 10.1$, 9.6, 6.4 Hz, 1H), 1.51–1.44 (m, 6H; $3CH_2$), 1.33 (sext, $J = 7.3$ Hz, 6H; $3CH_2$), 1.23 (d, $J = 6.9$ Hz, 3H; CH_3), 1.19 (d, $J = 7.3$ Hz, 3H; CH_3), 0.99 (d, $J = 6.9$ Hz, 3H; CH_3), 0.96–0.88 (m, 15H; $3CH_2 + 3CH_3$), 0.90 ppm (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta = 204.0$ (C), 144.0 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 32.6$ Hz; CH), 137.9 (C), 137.2 (C), 128.0 (2CH), 127.3 (CH), 125.6 (2CH), 99.6 (CH), 98.0 (CH_2), 94.2 (CH_2), 87.7 (C), 86.2 (CH), 80.6 (CH), 80.2 (C), 77.0 (CH), 60.7 (CH), 56.1 (CH_3), 55.4 (CH_3), 47.2 (CH), 41.9 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 34.4$ Hz; CH), 39.7 (CH_2), 34.9 (CH), 30.1 (CH), 29.1 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 21.0$ Hz; $3CH_2$), 27.3 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 57.4$ Hz; $3CH_2$), 27.2 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn} = 46.0$ Hz; CH_3), 18.4 (CH_3), 16.3 (CH_3), 13.6 ($3CH_3$), 13.5 (CH_3), 9.8 ($3CH_2$), 6.8 (CH_3).

A solution of $NaClO_2$ (549 mg, 6.07 mmol, 1.5 equiv) and NaH_2PO_4 (729 mg, 6.07 mmol, 1.5 equiv) in H_2O (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 $NaClO_2$ and NaH_2PO_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 CH_2Cl_2 and the organic layers were washed with brine, dried over $MgSO_4$, 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}H NMR (400.0 MHz, $CDCl_3$): δ = 7.43–7.40 (m, 2H), 7.33–7.28 (m, 3H), 6.00 (d, J = 8.2 Hz, 1H, $J_{^1H,^{117}Sn} = J_{^1H,^{119}Sn}$ = 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; CH_3), 3.35 (s, 3H; 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 (dqd, J = 8.2, 6.4, 5.5 Hz, 1H), 2.22–2.18 (m, 1H), 1.89 (s, $J_{^1H,^{117}Sn} = J_{^1H,^{119}Sn}$ = 42.6 Hz, 3H; 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; 3CH_2), 1.31 (d, J = 6.9 Hz, 3H; CH_3), 1.30 (sext, J = 7.3 Hz, 6H; 3CH_2), 1.17 (d, J = 6.9 Hz, 3H; CH_3), 0.98 (d, J = 6.4 Hz, 3H; CH_3), 0.94–0.85 ppm (m, 18H; 3CH_2, 4CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 178.0 (C), 144.2 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn}$ = 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_2), 93.7 (CH_2), 88.0 (C), 85.3 (CH), 81.8 (CH), 80.0 (C), 77.0 (CH), 61.0 (CH), 56.2 (CH_3), 55.5 (CH_3), 42.1 (CH), 40.7 (CH), 39.8 (CH_2), 35.5 (CH), 30.2 (CH), 29.2 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn}$ = 19.2 Hz; 3CH_2), 27.3 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn}$ = 57.4 Hz; 3CH_2), 27.2 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn}$ = 36.4 Hz; CH_3), 18.6 (CH_3), 16.4 (CH_3), 15.2 (CH_3), 13.7 (3CH_3), 11.5 (CH_3), 9.9 ppm ($J_{^{13}C,^{117}Sn}$ = 310.6, $J_{^{13}C,^{119}Sn}$ = 331.8 Hz; 3CH_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). $[\alpha]_D^{20} = -34.5$ (c = 0.96 in $CHCl_3$); ^{1}H NMR (400.0 MHz, $CDCl_3$): δ = 7.45–7.42 (m, 2H), 7.37–7.31 (m, 3H), 6.00 (dq, J = 9.6, 1.8, $J_{^1H,^{117}Sn} = J_{^1H,^{119}Sn}$ = 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; CH_3), 3.43 (s, 3H; CH_3), 3.36 (s, 3H; 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 (dqd, J = 9.6, 6.9, 5.5 Hz, 1H), 2.30–2.17 (m, 1H), 1.89 (d, J = 1.8, $J_{^1H,^{117}Sn} = J_{^1H,^{119}Sn}$ = 42.1 Hz, 3H; 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; 3CH_2), 1.37 (sext, J = 7.3 Hz, 6H; 3CH_2), 1.24 (d, J = 7.3 Hz, 3H; CH_3), 1.19 (d, J = 6.9 Hz, 3H; CH_3), 1.00–0.80 (m, 15H; 3CH_2, 3CH_3), 0.85 (d, J = 6.9 Hz, 3H; CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 174.8 (C), 144.4 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn}$ = 27.8 Hz; CH), 138.6 (C), 137.7 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn}$ = 369.0 Hz; C), 128.6 (CH), 128.5 (2CH), 125.8 (2CH), 99.7 (CH), 98.2 (CH_2), 93.8 (CH), 87.9 (C), 85.4 (C), 82.2 (CH), 80.5 (C), 77.0 (CH), 61.1 (CH), 56.2 (CH_3), 55.7 (CH_3), 52.1 (CH_3), 42.2 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn}$ = 42.6 Hz; CH), 41.1 (CH), 39.9 (CH_2), 35.8 (CH), 30.3 (CH), 29.4 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn}$ = 19.2 Hz; 3CH_2), 27.6 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn}$ = 57.4 Hz; 3CH_2), 27.4 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn}$ = 44.1 Hz; CH_3), 18.7 (CH_3), 16.5 (CH_3), 13.8 (3CH_3), 11.6 (CH_3), 10.0 ($J_{^{13}C,^{117}Sn}$ = 312.4, $J_{^{13}C,^{119}Sn}$ = 327.8 Hz; 3CH_2), 9.3 ppm (CH_3); IR (film): $\tilde{\nu}$ = 2955, 2927, 2872, 2853, 1745, 1454, 1403, 1349, 1375, 1207, 1154, 1110, 1029, 700 cm^{-1}; elemental analysis calcd (%) for $C_{43}H_{72}O_8Sn$: 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-9-iodo-2,6-bis[(methoxymethyl)oxy]deca-3,8-dien-1-yl}-5-methyl-2-phenyl-1,3-dioxinan (60): 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 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}H NMR (400.0 MHz, $CDCl_3$): δ = 7.49–7.44 (m, 2H), 7.35–7.29 (m, 3H), 5.93 (dq, J = 8.2, 1.4, $J_{^1H,^{117}Sn} = J_{^1H,^{119}Sn}$ = 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; CH_3), 3.32 (s, 6H; 2CH_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 (dqd, J = 10.9, 6.9, 6.9 Hz, 1H), 2.17 (dqd, J = 8.2, 6.9, 4.1 Hz, 1H), 2.00–1.91 (m, 1H), 1.85 (d, J = 1.4, $J_{^1H,^{117}Sn} = J_{^1H,^{119}Sn}$ = 42.1 Hz, 3H; CH_3), 1.70–1.60 (m, 2H), 1.51–1.44 (m, 6H; 3CH_2), 1.32 (sext, J = 7.3 Hz, 6H; 3CH_2), 1.23 (d, J = 6.9 Hz, 3H; CH_3), 0.98 (d, J = 6.9 Hz, 3H; CH_3), 0.94 (d, J = 6.4 Hz, 3H; CH_3), 0.92–0.82 ppm (m, 18H; 3CH_2 + 4CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 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_2), 93.1 (CH_2), 86.3 (CH), 82.2 (CH), 77.3 (CH), 66.2 (CH), 56.1 (CH_3), 55.2 (CH_3), 51.9 (CH_3), 41.0 (2CH), 39.1 (CH_2), 35.9 (CH), 35.8 (CH), 29.2 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn}$ = 19.2 Hz; 3CH_2), 27.4 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn}$ = 57.5 Hz; 3CH_2), 27.2 ($J_{^{13}C,^{117}Sn} = J_{^{13}C,^{119}Sn}$ = 42.2 Hz; CH_3), 17.7 (CH_3), 15.6 (CH_3), 14.2 (CH_3), 13.7 (3CH_3), 11.6 (CH_3), 9.9 ppm ($J_{^{13}C,^{117}Sn}$ = 313.4, $J_{^{13}C,^{119}Sn}$ = 326.8 Hz; 3CH_2).

An iodine solution (48 mg, 0.19 mmol, 0.98 equiv) in CH_2Cl_2 (16 mL) was added to a solution of the preceding compound (168 mg, 0.2 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL) at 0 °C over 30 min. The resulting solution was immediately added to a 1 M $Na_2S_2O_3$ solution and the organic phase was then concentrated under reduced pressure. The residue was taken up with Et_2O (3 mL) and a 0.7 M KF solution (600 μL). After the reaction mixture had been stirred for 3 h at 20 °C, the solution was filtered and extracted with Et_2O. The organic layers were washed with brine, dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/Et_2O 80:20 to 50:50) to give the title compound **60** (96 mg, 71% for 2 steps). $[\alpha]_D^{20} = +3.70$ (c = 0.78 in $CHCl_3$); ^{1}H NMR (400.0 MHz, $CDCl_3$): δ = 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; CH_3), 3.35 (s, 6H; 2CH_3), 3.26 (t, J = 5.5 Hz, 1H), 2.86–2.78 (dqd, J = 10.5, 6.9, 5.5 Hz, 1H), 2.86–2.78 (qd, J = 6.9, 3.2 Hz, 1H), 2.47 (dqd, J = 8.2, 6.9, 5.5 Hz, 1H), 2.36 (d, J = 1.4 Hz, 3H; 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; CH_3), 1.08 (d, J = 6.9 Hz, 3H; CH_3), 0.96 (d, J = 6.9 Hz, 3H; CH_3), 0.89 ppm (d, J = 6.9 Hz, 3H; CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 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_2), 97.9 (C), 93.1 (CH_2), 85.6 (CH), 82.1 (CH), 77.6 (CH), 66.1 (CH), 56.1 (CH_3), 55.2 (CH_3), 51.9 (CH_3), 43.9 (CH), 41.0 (CH), 39.2 (CH or CH_2), 35.7 (CH), 35.3 (CH_3), 33.6 (CH or CH_2), 18.4 (CH_3), 14.7 (CH_3), 11.7 (CH_3), 9.2 ppm (CH_3); IR (film): $\tilde{\nu}$ = 3428, 2952, 2928, 2880, 2821, 1744, 1454, 1435, 1398, 1207, 1152, 1090, 1045 cm^{-1}; elemental analysis calcd (%) for $C_{31}H_{47}IO_8$: 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 μL, 0.53 mmol, 3.8 equiv) was rapidly added to a solution of the alkyliodide **43** (145 mg, 0.26 mmol, 1.8 equiv) in Et_2O (3.7 mL) at −80 °C. After 2 min, 9-MeOBBN (1 M in hexane, 602 μL, 0.60 mmol, 4.3 equiv) followed by THF (3.7 mL) was added. The resulting mixture was stirred 10 min at −78 °C and was then allowed to warm to 20 °C over a period of 1 h 15 min. An aqueous 3.5 M Cs_2CO_3 solution was then added (220 μL, 0.77 mmol, 5.5 equiv), followed by the addition of the vinyliodide **60** (96 mg, 0.14 mmol, 1.0 equiv) in DMF (3.7 mL). Finally, [$PdCl_2$(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 Et_2O, the organic layers were washed with brine, dried over $MgSO_4$, filtered, and the sol-

vent was removed under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/Et_2O 80:20 to 60:40) to give the title compound **61** (87 mg, 60%). $[\alpha]_D^{20}=+13.8$ ($c=0.90$ in $CHCl_3$); ^{1}H NMR (400.0 MHz, $CDCl_3$): $\delta=7.47$–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_3), 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_3), 3.33 (s, 3H; CH_3), 3.07 (t, $J=5.5$ Hz, 1H), 2.91–2.76 (m, 3H), 2.54 (dqd, $J=10.1$, 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_3), 1.22 (d, $J=6.9$ Hz, 3H; CH_3), 1.06–0.83 (m; 8CH_3), 0.91 (s, 9H; 3CH_3), 0.68 (q, $J=7.8$ Hz, 6H; 3CH_2), 0.63 (d, $J=6.4$ Hz, 3H; CH_3), 0.07 ppm (s, 6H; 2CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta=174.8$ (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_2), 99.6 (CH), 97.8 (CH_2), 92.5 (CH_2), 86.9 (CH), 82.2 (CH), 78.0 (CH), 77.0 (2CH), 66.4 (CH), 56.0 (CH_3), 55.2 (CH_3), 51.9 (CH_3), 41.9, 41.0, 40.3, 39.0, 36.2, 35.8, 35.3, 35.0, 34.4 (7CH, 2CH_2), 26.9 (3CH_3), 23.1 (CH_3), 18.5 (C), 18.5, 17.4, 16.5, 14.2, 11.6, 11.3, 9.3 (7CH_3, CH_3-2), 7.2 (3CH_3), 5.7 (3CH_2), −3.1 (CH_3), −3.2 ppm (CH_3); 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^{-1}; HRMS (ESI): m/z: calcd for $C_{56}H_{98}O_{10}NaSi_2$: 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%). $[\alpha]_D^{20}=+11.0$ ($c=0.90$ in $CHCl_3$); ^{1}H NMR (400.0 MHz, $CDCl_3$): $\delta=7.47$–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_3), 3.63 (dd, $J=5.5$, 2.8 Hz, 1H), 3.33 (s, 6H; 2CH_3), 3.35–3.33 (m, 1H), 3.09 (t, $J=5.5$ Hz, 1H), 2.86–2.75 (dqd, $J=11.0$, 7.3, 5.5 Hz, 1H), 2.86–2.75 (m, 2H), 2.54 (dqd, $J=10.1$, 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_3), 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_3), 1.01 (d, $J=6.9$ Hz, 3H; CH_3), 0.96 (d, $J=6.4$ Hz, 3H; CH_3), 0.95–0.91 (m, 6H; 2CH_3), 0.91 (s, 9H; 3CH_3), 0.87 (d, $J=6.4$ Hz, 3H; CH_3), 0.70 (d, $J=6.9$ Hz, 3H; CH_3), 0.10 ppm (s, 6H; 2CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta=174.8$ (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_2), 99.6 (CH), 97.9 (CH_2), 93.2 (CH_2), 86.8 (CH), 82.0 (CH), 79.0 (CH), 77.8 (CH), 76.7 (CH), 66.4 (CH), 56.1 (CH_3), 55.3 (CH_3), 51.9 (CH_3), 41.1, 39.1, 38.0, 36.7, 36.3, 35.9, 35.3, 34.7, 34.4 (7CH, 2CH_2), 26.3 (3CH_3), 23.3 (CH_3), 18.5 (C), 17.6, 17.1, 16.4, 13.4, 11.7, 9.5, 9.3 (7CH_3), −3.1 (CH_3), −3.6 ppm (CH_3); IR (film): $\tilde{\nu}=2377$, 2957, 2929, 2883, 2857, 1591, 1462, 1434, 1395, 1257, 1153, 1093, 1036, 874 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{50}H_{84}O_{10}NaSi$: 895.5726; found: 895.5721.

Trichloroacetylisocyanate (16 μL, 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_2Cl_2 (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_2CO_3 (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 $MgSO_4$, 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. $[\alpha]_D^{20}=+17.4$ ($c=0.80$ in $CHCl_3$); ^{1}H NMR (400.0 MHz, $CDCl_3$): $\delta=7.50$–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_3), 3.43 (dd, $J=4.6$, 4.1 Hz, 1H), 3.32 (s, 6H; 2CH_3), 3.06 (t, $J=5.5$ Hz, 1H), 2.99 (dqd, $J=10.5$, 6.9, 3.7 Hz, 1H), 2.83–2.79 (qdm, $J=7.3$, 5.5 Hz, 1H), 2.81 (dqd, $J=10.1$, 6.9, 5.5 Hz, 1H), 2.52 (dqd, $J=10.1$, 6.4, 5.5 Hz, 1H), 2.15–1.79 (m, 5H), 1.74–1.52 (m, 2H), 1.57 (s, 3H; CH_3), 1.25 (d, $J=7.3$ Hz, 3H; CH_3), 1.01 (d, $J=6.9$ Hz, 3H; CH_3), 0.94–0.85 (m, 12H; 4CH_3), 0.91 (s, 9H; 3CH_3), 0.73 (d, $J=6.9$ Hz, 3H; CH_3), 0.07 (s, 3H; CH_3), 0.05 ppm (s, 3H; CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta=174.9$ (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_2), 99.7 (CH), 97.8 (CH_2), 93.2 (CH_2), 86.9 (CH), 82.1 (CH), 78.8 (CH), 77.0 (2CH), 66.4 (CH), 56.0 (CH_3), 55.2 (CH_3), 51.9 (CH_3), 41.2 (CH), 39.2 (CH_2), 37.8 (CH), 36.3 (CH), 35.9 (CH_2), 35.3 (CH), 35.1 (CH), 34.4 (CH), 29.7 (CH), 26.2 (3CH_3), 23.0 (CH_3), 18.5 (C), 18.5 (CH_3), 17.5, 16.5, 11.7, 10.1 (4CH_3), 13.7 (CH_3), 9.4 (CH_3), −3.3 (CH_3), −3.6 ppm (CH_3);. 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^{-1}; HRMS (ESI): m/z: calcd for $C_{51}H_{85}O_{11}NaSi$: 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 $NaHCO_3$ was added and the mixture extracted with AcOEt (3×). The organic layers were washed with water, brine, dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH 95:5 to 90:10) to give the title compound (+)-discodermolide (**1**) (6.2 mg, 70%) as a white solid. $[\alpha]_D^{20}=+16.2$ ($c=1.0$ in MeOH); ^{1}H NMR (400.0 MHz, $CDCl_3$): $\delta=6.61$ (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 (dqd, $J=10.5$, 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_3), 1.32 (d, $J=7.3$ Hz, 3H; CH_3), 1.08 (d, $J=6.9$ Hz, 3H; CH_3), 1.01 (d, $J=7.3$ Hz, 3H; CH_3), 0.98 (d, $J=6.4$ Hz, 3H; CH_3), 0.98 (d, $J=6.4$ Hz, 3H; CH_3), 0.95 (d, $J=6.4$ Hz, 3H; CH_3), 0.83 ppm (d, $J=5.9$ Hz, 3H; CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$): $\delta=174.3$ (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_2), 79.1 (CH), 78.8 (CH), 77.7 (CH), 75.7 (CH), 73.4 (CH), 64.5 (CH), 43.4 (CH), 41.1 (CH_2), 37.5 (CH), 36.4 (CH), 35.9 (CH_2), 35.6 (CH), 35.0 (CH), 33.2 (CH), 30.0 (CH), 23.6 (CH_3), 18.6 (CH_3), 17.7 (CH_3), 16.1 (CH_3), 16.0 (CH_3), 13.9 (CH_3), 12.9 (CH_3), 9.3 ppm (CH_3); ^{1}H NMR (400.0 MHz, CD_3CN): $\delta=6.69$ (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_3), 1.21 (d, $J=7.3$ Hz, 3H; CH_3), 1.03 (d, $J=6.4$ Hz, 3H; CH_3), 1.01 (d, $J=6.4$ Hz, 3H; CH_3), 0.97 (d, $J=6.9$ Hz, 3H; CH_3), 0.90 (d, $J=6.9$ Hz, 3H; CH_3), 0.82 (d, $J=6.9$ Hz, 3H; CH_3), 0.75 ppm (d, $J=$

5.9 Hz, 3H; CH_3); ^{13}C NMR (100.5 MHz, CD_3CN): $\delta = 174.7$ (C), 158.3 (C), 134.0 (CH), 133.8 (CH), 133.7 (CH), 133.2 (CH), 131.1 (CH), 130.5 (CH), 118.1 (CH_2), 79.7 (CH), 79.2 (CH), 77.4 (CH), 75.9 (CH), 73.1 (CH), 63.3 (CH), 44.0 (CH), 42.1 (CH_2), 38.4 (CH), 37.1 (CH), 36.5 (CH_2), 36.2 (CH), 36.1 (CH), 34.4 (CH), 34.2 (CH), 23.3 (CH_3), 19.7 (CH_3), 18.1 (CH_3), 17.6 (CH_3), 15.8 (CH_3), 15.6 (CH_3), 13.1 (CH_3), 9.2 ppm (CH_3); HRMS (ESI): *m/z*: calcd for $C_{33}H_{55}O_8NNa$: 616.3820 $[M+Na]^+$; found: 616.3816.

Acknowledgements

We thank Sanofi-Aventis for a fellowship for E.d.L. Technical support from Paris XI University (Châtenay-Malabry and Orsay centers) is gratefully acknowledged (elemental analysis and HRMS).

[1] a) S. P. Gunasekera, R. E. Longley, R. A. Isbrucker, *J. Nat. Prod.* **2002**, *65*, 1830–1837; b) S. P. Gunasekera, M. Gunasekera, R. E. Longley, G. K. Schulte, *J. Org. Chem.* **1990**, *55*, 4912–4915; Correction: *J. Org. Chem.* **1991**, *56*, 1346; c) S. P. Gunasekera, G. K. Paul, R. E. Longley, R. A. Isbruker, S. A. Pomponi, *J. Nat. Prod.* **2002**, *65*, 1643–1648.

[2] a) A. Canales, R. Matesanz, N. M. Gardner, J. M. Andreu, I. Paterson, J. F. Diaz, J. Jimenez-Barbero, *Chem. Eur. J.* **2008**, *14*, 7557–7569; b) V. M. Sánchez-Pedregal, K. Kubicek, J. Meiler, I. Lyothier, I. Paterson, T. Carlomagno, *Angew. Chem.* **2006**, *118*, 7548–7554; *Angew. Chem. Int. Ed.* **2006**, *45*, 7388–7394; c) S. Xia, C. S. Kenesky, P. V. Rucker, A. B. Smith, III, G. A. Orr, S. B. Horwitz, *Biochemistry* **2006**, *45*, 11762–11775; d) S. Honore, K. Kamath, D. Braguer, L. Wilson, C. Briand, M. A. Jordan, *Mol. Cancer Ther.* **2003**, *2*, 1303–1311; e) L. He, G. A. Orr, S. B. Horwitz, *Drug Discovery Today* **2001**, *6*, 1153–1164; f) L. He, H. Y. Chia-Ping, S. B. Horwitz, *Mol. Cancer Ther.* **2001**, *1*, 3–10; g) L. A. Martello, M. J. LaMarche, L. He, T. J. Beauchamp, A. B. Smith, III, S. B. Horwitz, *Chem. Biol.* **2001**, *8*, 843–855; h) M. Kalesse, *ChemBioChem* **2000**, *1*, 171–175; i) E. ter Haar, R. J. Kowalski, E. Hamel, C. M. Lin, R. E. Longley, S. P. Gunasekera, H. S. Rosenkranz, B. W. Day, *Biochemistry* **1996**, *35*, 243–250; j) R. Balachandran, E. ter Haar, M. J. Welsh, S. G. Grant, B. W. Day, *Anti-Cancer Drugs* **1998**, *9*, 67–76.

[3] a) G. S. Huang, L. Lopez-Barcons, B. S. Freeze, A. B. Smith III, G. L. Goldberg, S. B. Horwitz, H. M. McDaid, *Clin. Cancer Res.* **2006**, *12*, 298–304; b) L. A. Martello, H. M. McDaid, D. L. Regl, C.-P. H. Yang, D. Meng, T. R. R. Pettus, M. D. Kaufman, H. Arimoto, S. J. Danishefsky, A. B. Smith, III, S. B. Horwitz, *Clin. Cancer Res.* **2000**, *6*, 1978–1987.

[4] Total synthesis: a) J. B. Nerenberg, D. T. Hung, P. K. Somers, S. L. Schreiber, *J. Am. Chem. Soc.* **1993**, *115*, 12621–12622; b) D. T. Hung, J. B. Nerenberg, S. L. Schreiber, *J. Am. Chem. Soc.* **1996**, *118*, 11054–11080; c) A. B. Smith, III, Y. Qiu, D. R. Jones, K. Kobayashi, *J. Am. Chem. Soc.* **1995**, *117*, 12011–12012; d) A. B. Smith, III, T. J. Beauchamp, M. J. LaMarche, M. D. Kaufman, Y. Qiu, H. Arimoto, D. R. Jones, K. Kobayashi, *J. Am. Chem. Soc.* **2000**, *122*, 8654–8664, and references therein; e) S. S. Harried, G. Yang, M. A. Strawn, D. C. Myles, *J. Org. Chem.* **1997**, *62*, 6098–6099; f) S. S. Harried, C. P. Lee, G. Yang, T. I. H. Lee, D. C Myles, *J. Org. Chem.* **2003**, *68*, 6646–6660; g) J. A. Marshall, Z.-H. Lu, B. A. Johns, *J. Org. Chem.* **1998**, *63*, 817–823; h) J. A. Marshall, B. A. Johns, *J. Org. Chem.* **1998**, *63*, 7885–7892; i) I. Paterson, G. J. Florence, K. Gerlach, J. P. Scott, *Angew. Chem.* **2000**, *112*, 385–388; *Angew. Chem. Int. Ed. 2000, 39*, 377–380; j) I. Paterson, G. J. Florence, *Eur. J. Org. Chem.* **2003**, 2193–2208; k) I. Paterson, I. Lyothier, *J. Org. Chem.* **2005**, *70*, 5494–5507, and references therein; l) A. Arefolov, J. S. Panek, *J. Am. Chem. Soc.* **2005**, *127*, 5596–5603, and references therein. For recent reviews on syntheses and analogue design and activity see: m) S. J. Shaw, *Mini-Rev. Med. Chem.* **2008**, *8*, 276–284; n) A. B. Smith, III, B. S. Freeze, *Tetrahedron* **2008**, *64*, 261–298; o) G. J. Florence, N. M. Gardner, I. Paterson, *Nat. Prod. Rep.* **2008**, *25*, 342–375.

[5] a) S. J. Mickel, D. Niederer, R. Daeffler, A. Osmani, E. Kuesters, E. Schmid, K. Schaer, R. Gamboni, W. Chen, E. Loeser, F. R. Kinder, Jr., K. Konigsberger, K. Prasad, T. M. Ramsey, O. Repič, R.-M. Wang, G. Florence, I. Lyothier, I. Paterson, *Org. Process Res. Dev.* **2004**, *8*, 122–130, and the four precedent papers; b) S. J. Mickel, R. Daeffler, W. Prikoszovich, *Org. Process Res. Dev.* **2005**, *9*, 113–120; c) O. Loiseleur, G. Koch, J. Cercus, F. Schürch, *Org. Process Res. Dev.* **2005**, *9*, 259–271.

[6] a) A. Mita, C. Lockhart, T. L. Chen, K. Bocinski, J. Curtright, W. Cooper, L. Hammond, M. Rothenberg, E. Rowinsky, S. Sharma, *J. Clin. Oncol.* **2004**, *22* (14S–ASCO Annual Meeting Proceedings, Post-Meeting Edition), abstract 2025.

[7] Preliminary communication: E. de Lemos, F. H. Porée, A. Commerçon, J.-F. Betzer, A. Pancrazi, J. Ardisson, *Angew. Chem.* **2007**, *119*, 1949–1953; *Angew. Chem. Int. Ed.* **2007**, *46*, 1917–1921.

[8] a) D. Hoppe, *Angew. Chem.* **1984**, *96*, 930–946; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 932–948; b) D. Hoppe, O. Zschage, *Angew. Chem.* **1989**, *101*, 67–69; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 69–71; c) D. Hoppe, O. Zschage, *Tetrahedron* **1992**, *4R*, 8389–8392.

[9] a) V. Fargeas, P. Le Ménez, I. Berque, J. Ardisson, A. Pancrazi, *Tetrahedron* **1996**, *52*, 6613–6634; b) I. Berque, P. Le Ménez, P. Razon, C. Anies, A. Pancrazi, J. Ardisson, A. Neuman, T. Prangé, J.-D. Brion, *Synlett* **1998**, 1132–1134; c) I. Berque, P. Le Ménez, P. Razon, A. Pancrazi, J. Ardisson, J.-D. Brion, *Synlett* **1998**, 1135–1137; d) I. Berque, P. Le Ménez, P. Razon, J. Mahuteau, J.-P. Férézou, A. Pancrazi, J. Ardisson, J.-D. Brion, *J. Org. Chem.* **1999**, *64*, 373–381.

[10] D. Hoppe, T. Hense, D. Hoppe, T. Hense, *Angew. Chem.* **1997**, *109*, 2376–2410; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2282–2316.

[11] F.-H. Porée, A. Clavel, J.-F. Betzer, A. Pancrazi, J. Ardisson, *Tetrahedron Lett.* **2003**, *44*, 7553–7556.

[12] a) P. Fritsch, *Liebigs Ann. Chem.* **1894**, *279*, 319–323; b) W. P. Buttenberg, *Liebigs Ann. Chem.* **1894**, *279*, 324–337; c) H. Wiechell, *Liebigs Ann. Chem.* **1894**, *279*, 337–344; for reviews see: d) M. Braun, *Angew. Chem.* **1998**, *110*, 444–465; *Angew. Chem. Int. Ed.* **1998**, *37*, 430–451; e) R. Knorr, *Chem. Rev.* **2004**, *104*, 3795–3849.

[13] a) G. Stork, K. Zhao, *Tetrahedron Lett.* **1989**, *30*, 2173–2174; b) J. Chen, T. Wang, K. Zhao, *Tetrahedron Lett.* **1994**, *35*, 2827–2828.

[14] a) 41% yield with 85:15 *Z*/*E* ratio. A. B. Smith, III, Y. Qiu, D. R. Jones, K. Kobayashi, *J. Am. Chem. Soc.* **1995**, *117*, 12011–12012; H. Arimoto, M. D. Kaufman, K. Kobayashi, Y. Qiu, A. B. Smith, III, *Synlett* **1998**, 765–767; b) 46% yield with 90:10 (*Z*)/(*E*) ratio. A. B. Smith, III, T. J. Beauchamp, M. J. LaMarche, M. D. Kaufman, Y. Qiu, H. Arimoto, D. R. Jones, K. Kobayashi, *J. Am. Chem. Soc.* **2000**, *122*, 8654–8664; c) 40% yield with 70:30 to 90:10 *Z*/*E* ratio was obtained with small amounts of reduced product arising from the non-iodinated ylide. J. A. Marshall, B. A. Johns, *J. Org. Chem.* **1998**, *63*, 7885–7892.

[15] T. Fujisawa, Y. Kurita, M. Kawashima, T. Sato, *Chem. Lett.* **1982**, 1641–1642.

[16] a) P. Kocienski, S. Wadman, K. Cooper, *J. Am. Chem. Soc.* **1989**, *111*, 2363–2365; b) P. Kocienski, C. Barber, *Pure Appl. Chem.* **1990**, *62*, 1933–1940; c) P. Kocienski in *Organic Synthesis via Organometallics (OSM 4, Aachen)* (Eds.: E. Enders, H.-J. Gais, W. Keim), Vieweg, Wiesbaden (Germany), **1993**, pp. 203–223.

[17] P. Le Ménez, J.-D. Brion, J.-F. Betzer, A. Pancrazi, J. Ardisson, *Synlett* **2003**, 955–958.

[18] a) T. Iversen, D. R. Bundle, *J. Chem. Soc. Chem. Commun.* **1981**, 1240–1241; b) N. Nakajima, K. Horita, R. Abe, O. Yonemitsu, *Tetrahedron Lett.* **1988**, *29*, 4139–4142; c) L. C. Diaz, G. Z. Melgar, L. S. A. Jardim, *Tetrahedron Lett.* **2005**, *46*, 4427–4431.

[19] P. L. Anelli, C. Biffi, F. Montanari, S. Quici, *J. Org. Chem.* **1987**, *52*, 2559–2562.

[20] D. J. Clarke, R. S. Robinson, *Tetrahedron* **2002**, *58*, 2831–2837.

[21] D. Enders, M. Kroll, G. Raabe, J. Runsink, *Angew. Chem.* **1998**, *110*, 1770–1773; *Angew. Chem. Int. Ed.* **1998**, *37*, 1673–1675.

[22] J. Wiemann, L. T. Thuan, *Bull. Soc. Chim. Fr.* **1958**, 199–203.

[23] C. Botteghi, G. Consiglio, G. Ceccarelli, A. Stefani, *J. Org. Chem.* **1972**, *37*, 1835–1837.
[24] L. Keller, F. Dumas, J. d'Angelo, *Eur. J. Org. Chem.* **2003**, 2488–2497.
[25] J.-P. Ducoux, P. Le Menez, N. Kunesch, E. Wenkert, *J. Org. Chem.* **1993**, *58*, 1290–1292.
[26] E. J. Corey, M. A. Letavic, *J. Am. Chem. Soc.* **1995**, *117*, 9616–9617.
[27] P. Le Ménez, J.-D. Brion, N. Lensen, E. Chelain, A. Pancrazi, J. Ardisson, *Synthesis* **2003**, 2530–2534.
[28] A. J. Mancuso, S.-L. Huang, D. Swern, *J. Org. Chem.* **1978**, *43*, 2480–2482.
[29] J. R. Parikh, W. v. E. Doering, *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.
[30] E. J. Corey, J. W. Suggs, *Tetrahedron Lett.* **1975**, *16*, 2647–2650.
[31] S. V. Ley, J. Norman, W. P. Griffith, S. P. Marsden, *Synthesis* **1994**, 639–666.
[32] a) M. Frigerio, M. Santagostino, *Tetrahedron Lett.* **1994**, *35*, 8019–8022; b) M. Frigerio, M. Santagostino, S. Sputore, G. Palmisano, *J. Org. Chem.* **1995**, *60*, 7272–7276.
[33] K. Narasaka, A. Morikawa, K. Saigo, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2773–2776.
[34] J. A. Marshall, W. Y. Gung, *Tetrahedron* **1989**, *45*, 1043–1052.
[35] A. DeMico, R. Margarita, L. Parlanti, A. Vescovi, G. Piancatelli, *J. Org. Chem.* **1997**, *62*, 6974–6977.
[36] J. Chan, T. F. Jamison, *J. Am. Chem. Soc.* **2004**, *126*, 10682–10691.
[37] a) B. M. Trost, J. L. Belletire, S. Godleski, P. G. McDougal, J. M. Balkovec, J. J. Baldwin, M. E. Christy, G. S. Ponticello, S. L. Varga, J. P. Springer, *J. Org. Chem.* **1986**, *51*, 2370–2374; b) J. M. Seco, E. Quiñoá, R. Riguera, *Chem. Rev.* **2004**, *104*, 17–117.
[38] a) G. E. Keck, D. E. Abbott, *Tetrahedron Lett.* **1984**, *25*, 1883–1886; b) Y. Yamamoto, H. Yatagai, Y. Ishihara, N. Maeda, K. Maruyama, *Tetrahedron* **1984**, *40*, 2239–2246; c) G. E. Keck, K. A. Savin, E. N. K. Cressman, D. E. Abbott, *J. Org. Chem.* **1994**, *59*, 7889–7896.
[39] a) H. C. Brown, K. S. Bhat, *J. Am. Chem. Soc.* **1986**, *108*, 5919–5923; b) H. C. Brown, K. S. Bhat, R. S. Randad, *J. Org. Chem.* **1989**, *54*, 1570–1576.
[40] J. Mulzer, H. M. Kirstein, J. Buschmann, C. Lehmann, P. Luger, *J. Am. Chem. Soc.* **1991**, *113*, 910–923.
[41] S. D. Rychnovsky, D. J. Skalitzky, *Tetrahedron Lett.* **1990**, *31*, 945–948.
[42] H. Normant, *Bull. Soc. Chim. Fr.* **1957**, 728–733.
[43] T. H. Black, T. S. McDermott, G. A. Brown, *Tetrahedron Lett.* **1991**, *32*, 6501–6502.
[44] a) H. Neumann, D. Seebach, *Tetrahedron Lett.* **1976**, *17*, 4839–4842; b) W. F. Bailey, J. J. Patricia, *J. Organomet. Chem.* **1988**, *352*, 1–46; c) M. E. Jung, J. A. Hagenah, *J. Org. Chem.* **1987**, *52*, 1889–1902.
[45] a) B. Kang, S. Chang, *Tetrahedron* **2004**, *60*, 7353–7359; b) H. Takahata, Y. Banba, H. Ouchi, H. Nemoto, *Org. Lett.* **2003**, *5*, 2527–2529.
[46] S.-I. Murahashi, *J. Organomet. Chem.* **2002**, *653*, 27–33.
[47] a) P. J. Garegg, B. Samuelsson, *J. Chem. Soc. Perkin Trans. 1* **1980**, 2866–2869; b) E. J. Corey, S. G. Pyne, W.-G. Su, *Tetrahedron Lett.* **1983**, *24*, 4883–4886.
[48] K. B. Sharpless, R. C. Michaelson, *J. Am. Chem. Soc.* **1973**, *95*, 6136–6137.
[49] A. H. Hoveyda, D. A. Evans, G. C. Fu, *Chem. Rev.* **1993**, *93*, 1307–1370.
[50] B. H. Lipshutz, J. Kozlowski, R. S. Wilhelm, *J. Am. Chem. Soc.* **1982**, *104*, 2305–2307.
[51] J. Cossy, S. BouzBouz, A. H. Hoveyda, *J. Organomet. Chem.* **2001**, *634*, 216–221; T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18–29. S.J. Connon, S. Blechert, *Angew. Chem.* **2003**, *115*, 1944–1968; *Angew. Chem. Int. Ed.* **2003**, *42*, 1900–1923.
[52] a) P. Kocienski, N. J. Dixon, *Synlett* **1989**, 52–54; b) R. W. Hoffmann, V. Giesen, M. Fuest, *Liebigs Ann. Chem.* **1993**, 629–639.
[53] D. A. Evans, J. A. Gauchet-Prunet, *J. Org. Chem.* **1993**, *58*, 2446–2453.
[54] D. A. Evans, B. W. Trotter, P. J. Coleman, B. Côté, L. C. Dias, H. A. Rajapakse, A. N. Tyler, *Tetrahedron* **1999**, *55*, 8671–8726.
[55] a) A. Mengel, O. Reiser, *Chem. Rev.* **1999**, *99*, 1191–1223; b) M. T. Reetz, K. Kesseler, A. Jung, *Tetrahedron Lett.* **1984**, *25*, 729–732; c) D. A. Evans, J. L. Duffy, M. J. Dart, *Tetrahedron Lett.* **1994**, *35*, 8537–8540.
[56] R. G. Jones, H. Gilman, *Org. React.* **1951**, *6*, 339–366.
[57] a) E. J. Corey, R. K. Bakshi, S. Shibata, *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553; b) E. J. Corey, C. J. Helal, *Angew. Chem.* **1998**, *110*, 2092–2118; *Angew. Chem. Int. Ed.* **1998**, *37*, 1986–2012; c) B. M. Trost, J. L. Gunzner, O. Dirat, Y. H. Rhee, *J. Am. Chem. Soc.* **2002**, *124*, 10396–10415.
[58] J. A. Marshall, G. M. Schaaf, *J. Org. Chem.* **2003**, *68*, 7428–7432.
[59] P. Kocovský, *Tetrahedron Lett.* **1986**, *27*, 5521–5524.

Received: July 21, 2008
Published online: October 30, 2008

