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Synthetic studies toward cytostatin, a natural product inhibitor of protein phosphatase 2A

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This article is dedicated to the memory of Dr. Patrice Siret

ABSTRACT

Synthetic approaches toward the natural product cytostatin, an inhibitor of protein phosphatase 2A possessing cytotoxic and antimetastatic activities, have been investigated. A formal synthesis of cytostatin has been achieved according to a strategy relying on the formation of the C8–C9 bond by a nucleophilic addition of a functionalized organolithium (C1–C8 subunit) to an aldehyde (C9–C13 subunit).

1. Introduction

The natural product cytostatin was isolated in 1994 from cultures of *Streptomyces* sp. MJ654-NF4.[1] Cytostatin was found to exhibit cytotoxic activity against several cancer cell lines at submicromolar concentrations,[1] to induce apoptosis and to inhibit metastasis of B16-BL6 melanoma cells in mice.[2] The mode of action of this antitumor agent derives from a remarkably selective inhibition of serine–threonine phosphatase 2A (PP2A), an enzyme implicated in the regulation of many crucial biological events including cell division.[3,4] The identification of the structural features in natural products leading to selective inhibition of PP2A may be important for the development of small molecule-based inhibitors that could potentially be used in an alternative approach to cancer therapy.[4]

Cytostatin is a polyketide natural product with an 18-carbon backbone containing an α,β-unsaturated δ-lactone (C1–C5), two *syn*,*anti*-stereotriads (C4–C6 and C9–C11), a phosphate group at C9, and a (*Z*,*Z*,*E*)-conjugated triene (C12–C17) (Fig. 1). The basic structure of cytostatin was readily established by NMR experiments but its absolute and relative configurations were not initially assigned.[1] In 2002, Waldmann and Bialy reported the first total synthesis of the (4*S*,5*S*,6*S*,9*S*,10*S*,11*S*)-stereoisomer of cytostatin according to a linear approach.[5] The configurations of the stereocenters were selected on the basis of the structural analogy between cytostatin and fostriecin[6] or the phoslactomycins[7] as well as additional NMR studies on model diasteromeric α,β-unsaturated δ-lactones incorporating the C4–C6 stereotriad.[8] The spectroscopic data of the synthetic material, which was found to inhibit PP2A at a level comparable to cytostatin, were in agreement with those reported for the natural product. The optical rotations were different but this was attributed to the contamination of the natural product sample by an impurity.[5]

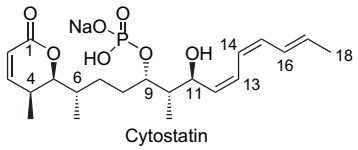

Figure 1. Structure of cytostatin.

The preparation of a C3–C13 precursor of cytostatin was subsequently reported by Marshall and Ellis.[9] The second total synthesis of cytostatin and its C10,C11 diastereomers, according to a convergent approach, was disclosed by Boger et al. in 2006.[10] Recently, cytostatin and three stereoisomers were synthesized by Curran et al. using fluorous mixture synthesis.[11]

Herein, we would like to report our studies on the development of convergent approaches toward cytostatin[12] that include the synthesis of a C3–C13 fragment and a C1–C13 advanced intermediate accounting for a formal synthesis of the natural product.

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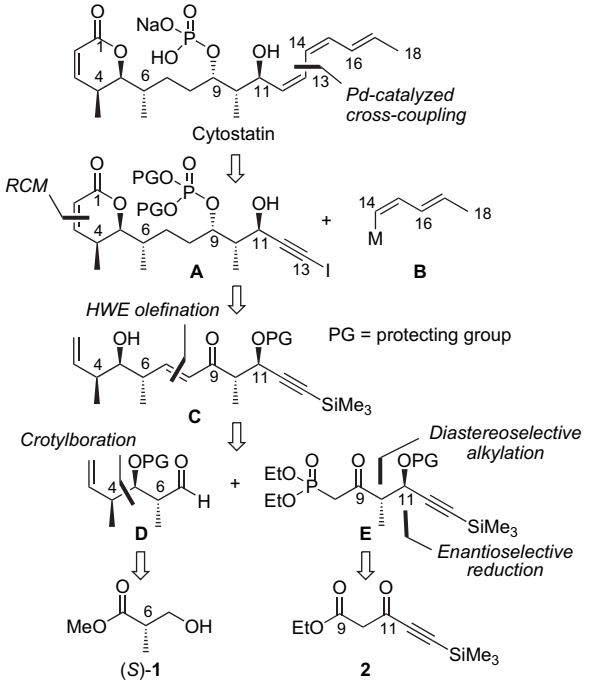
2. First approach: formation of the C7–C8 bond by Horner–Wadsworth–Emmons olefination

2.1. Retrosynthetic analysis

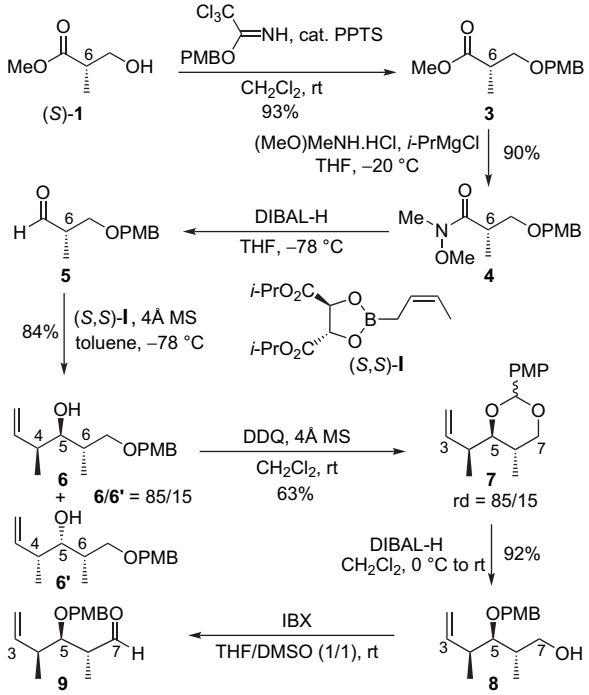
In our retrosynthetic analysis of cytostatin, the formation of the C13–C14 bond was envisaged by using a palladium-catalyzed cross-coupling between a (*Z*)-vinylic iodide, generated from the acetylenic iodide **A** (C1–C13 fragment), and a (*Z*,*E*)-dienyl organometallic reagent **B** (C14–C18 fragment). The formation of the triene unit has been successfully achieved by a Stille coupling in two of the three reported total syntheses of cytostatin.[5,11] The α,β-unsaturated δ-lactone would be constructed by ring-closing metathesis (RCM) of the acrylate derived from the homoallylic alcohol **C**. In this approach, a second key disconnection was considered at the C7–C8 bond whose formation would be achieved by a Horner–Wadsworth–Emmons (HWE) olefination involving aldehyde **D** and the β-ketophosphonate **E**, followed by chemoselective hydrogenation of the C7–C8 alkene. The control of the configuration at C5 and C6 would rely on a diastereoselective crotylboration of an optically active aldehyde derived from the Roche ester (*S*)-**1** that contains the C6 stereocenter of cytostatin. An enantioselective reduction of the acetylenic β-ketoester **2** followed by a diastereoselective alkylation of the resulting β-hydroxyester would allow the installation of the C11 and C10 stereocenters, respectively (Scheme 1).



Scheme 1. First retrosynthetic analysis of cytostatin.

2.2. Synthesis of the C3–C7 subunit

The preparation of the C3–C7 subunit started with the protection of (*S*)-**1** by treatment with (*p*-methoxybenzyl) trichloroacetimidate (cat. PPTS, CH_2Cl_2, rt) to afford the *p*-methoxybenzyl ether **3** (93%).[13] This latter compound was converted to the Weinreb amide **4** (*i*-PrMgCl, (MeO)MeNH·HCl, THF, −20 °C, 90%)[14,15] and subsequent reduction (DIBAL-H, THF, −78 °C) led to aldehyde **5**, which was not purified to avoid racemization.[15,16] To introduce the C4 and C5 stereocenters, aldehyde **5** was then treated with the optically active (*Z*)-crotylboronate (*S*,*S*)-**I** derived from (*S*,*S*)-diisopropyl tartrate (4 Å MS, toluene, −78 °C) and the diastereomeric secondary alcohols **6** and **6′** were obtained in an 85:15 ratio (84%, two steps from **4**) (Scheme 2).[17,18]



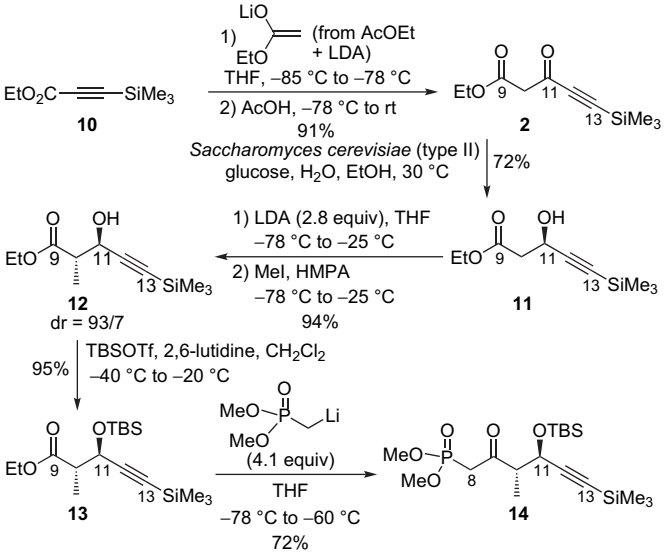
Scheme 2. Synthesis of the C3–C7 subunit.

The use of a (*Z*)-crotylboronate entails a *syn* relative orientation of the C4 methyl and the C5 hydroxyl groups and a predominant anti-Felkin addition mode (*anti* relationship between the C5 hydroxyl and the C6 methyl groups in the major diastereomer **6**). This addition mode is reinforced by the chiral ligand on boron in a double stereodifferentiating reaction proceeding in the matched manifold.[17,19] To synthesize the C3–C7 aldehyde of type **D** having the secondary hydroxyl group protected at C5, alcohol **6** was treated with DDQ (4 Å MS, CH_2Cl_2, rt)[20] and the *p*-methoxybenzylidene acetal **7** (85:15 mixture of epimers, 63%) was regioselectively reduced (DIBAL-H, CH_2Cl_2, 0 °C to rt) to the primary alcohol **8** (92%).[21,22] Subsequent oxidation [IBX, THF/DMSO (1:1), rt][23] led to aldehyde **9**, which was not purified to avoid epimerization (Scheme 2). Aldehyde **9** constitutes the C3–C7 subunit of cytostatin and has been prepared in seven steps from (*S*)-**1** with an overall yield of 41%.

2.3. Synthesis of the C8–C13 subunit

The synthesis of the β-ketophosphonate of type **E** was carried out from the acetylenic ester **10**. Condensation of the lithium enolate generated from ethyl acetate (LDA, THF, −78 °C) with the acetylenic ester **10** (THF, −85 °C to −78 °C) afforded the β-ketoester **2** (91%).[24,25] Quenching the reaction with AcOH before hydrolytic work-up avoided partial loss of the base-sensitive acetylenic TMS group.[25] To create the C11 asymmetric carbon, β-ketoester **2** underwent an enantioselective reduction in the presence of *Saccharomyces cerevisiae* (type II) (glucose, H_2O/EtOH, 30 °C) to provide the β-hydroxyester **11** (72%) with an enantiomeric excess of 92%.[26] The methyl group at C10, which is *anti* to the hydroxyl group at C11, was then introduced by a Frater–Seebach diastereoselective alkylation of the β-hydroxyester **11** [LDA (2.8 equiv), THF, −78 °C to −25 °C then MeI, HMPA, −78 °C to −25 °C] that led to the *anti*-α-methyl-β-hydroxyester **12** (dr=93:7, 94%).[27] The hydroxyl group at C11 was protected as a *tert*-butyldimethylsilyl ether (TBSOTf,

2,6-lutidine, CH_2Cl_2, −40 °C to −20 °C) to provide compound **13** (95%) and subsequent Claisen condensation with lithiated methyl dimethylphosphonate [(4.1 equiv), generated by addition of $(MeO)_2P(=O)Me$ to *n*-BuLi, THF, −78 °C to −60 °C][28] afforded β-ketophosphonate **14** (72%) (Scheme 3).

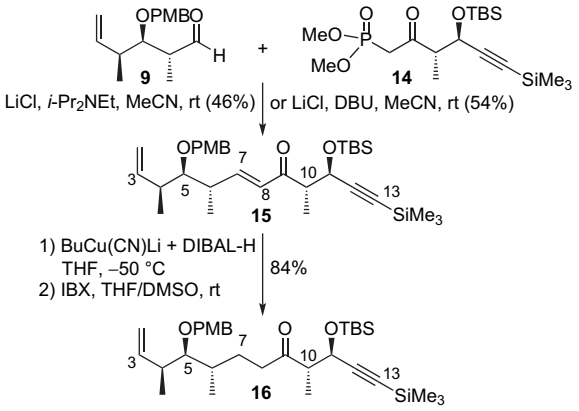


Scheme 3. Synthesis of the C8–C13 subunit.

The β-ketophosphonate **14** corresponds to the C8–C13 subunit of cytostatin and has been prepared in six steps from ethyl trimethylsilylpropiolate **10** (41% overall yield). The coupling of the C3–C7 and C8–C13 subunits by a Horner–Wadsworth–Emmons (HWE) reaction was then investigated.

2.4. Coupling of the C3–C7 and C8–C13 subunits by Horner–Wadsworth–Emmons olefination

β-Ketophosphonate **14** was treated with LiCl and a tertiary amine such as *i*-Pr_2NEt or DBU and aldehyde **9** was added (MeCN, rt).[29] The desired (*E*)-α,β-unsaturated ketone **15** was obtained in moderate yields (46% or 54%, respectively) in the course of initial attempts carried out on a small scale (typically 0.5 mmol). Subsequent reduction of the C7–C8 alkene was accomplished chemoselectively by treatment with an hydridocuprate generated in situ from *n*-BuCu(CN)Li and DIBAL-H (THF, −50 °C).[30] The corresponding ketone **16** was formed but reduction of its C9 carbonyl group also took place to a small extent (15%). Therefore, the crude material was oxidized [IBX, THF/DMSO (1:1), rt][23] to afford ketone **16** as the single product (84%, two steps from enone **15**) (Scheme 4).



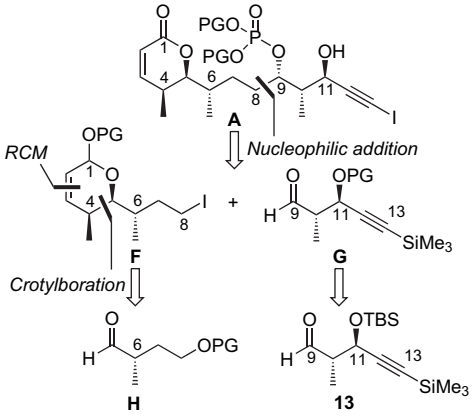
Scheme 4. Synthesis of the C3–C13 fragment.

However, subsequent attempts to carry out the HWE reaction between aldehyde **9** and β-ketophosphonate **14** on larger scale led to non-reproducible results and extensive decomposition took place. Although alternative conditions could have been used,[15] our initial synthetic plan was revised. With the aim of improving the convergency of the synthesis, a second approach relying on the formation of the C8–C9 bond by addition of an organolithium to an aldehyde was examined.

3. Second approach: formation of the C8–C9 bond by addition of an organolithium to an aldehyde

3.1. Retrosynthetic analysis

A key disconnection at the C8–C9 bond was envisaged in our second synthetic approach. The acetylenic iodide intermediate **A** would be obtained by nucleophilic addition of an organolithium derived from the primary alkyl iodide **F** to aldehyde **G**. The six-membered ring acetal (C1–C5), precursor of the α,β-unsaturated lactone, would be constructed by RCM and a crotylboration of the optically active aldehyde **H** would install the C4 and C5 stereocenters. On the other hand, the preparation of aldehyde **G** would be achieved from the protected β-hydroxyester **13** synthesized during the course of our first approach toward cytostatin (Scheme 5).

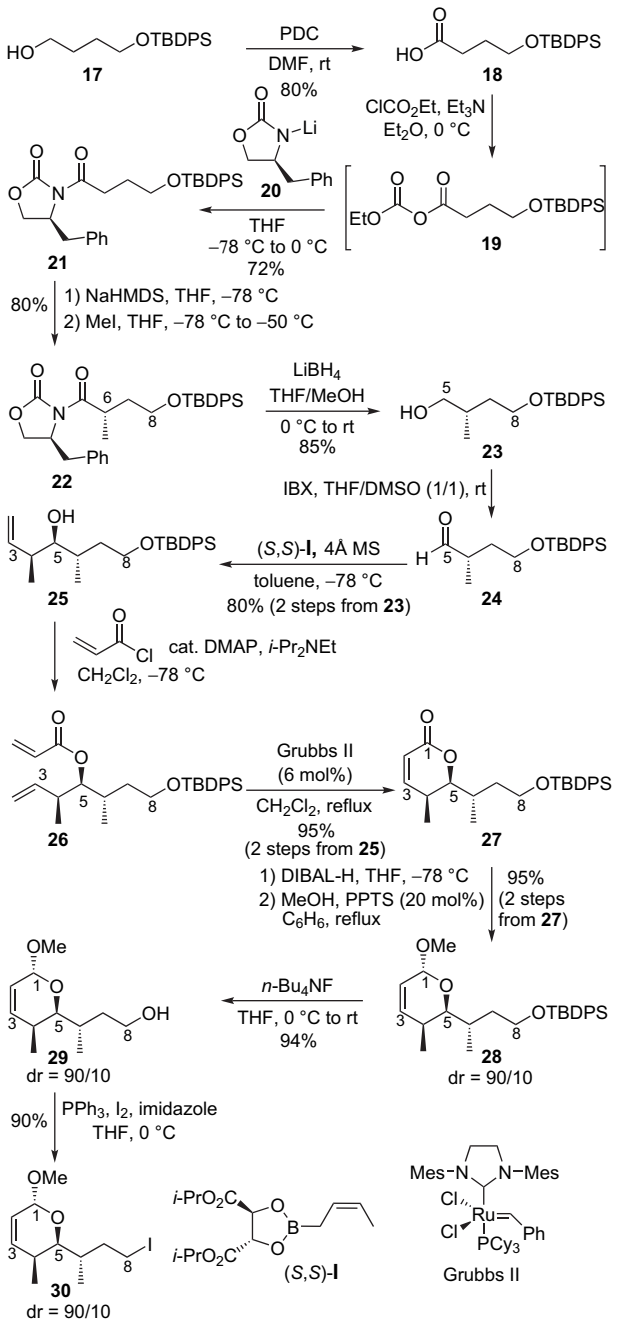


Scheme 5. Second retrosynthetic analysis of cytostatin.

3.2. Synthesis of the C1–C8 subunit

The creation of the C6 methyl-substituted stereocenter was first achieved by an Evans diastereoselective alkylation. Thus, the monoprotected butane-1,4-diol derivative **17** was oxidized to the corresponding carboxylic acid **18** (PDC, DMF, rt, 80%).[31] The latter acid was activated by reaction with $ClCO_2Et$ (Et_3N, Et_2O, 0 °C) and subsequent addition of the lithium amide **20** (generated from (4*S*)-4-benzyloxazolidin-2-one, *n*-BuLi, THF, −78 °C) to the mixed anhydride **19** (THF, −78 °C) afforded the corresponding *N*-acyloxazolidinone **21** (72%).[32] Enolization of compound **21** (NaHMDS, THF, −78 °C) and alkylation of the resulting sodium enolate with MeI (THF, −78 °C) proceeded with high diastereoselectivity (dr>96:4) and led to the alkylated compound **22** (80%).[32,33] Reduction of **22** with $LiBH_4$ (THF/MeOH, 0 °C to rt) produced the primary alcohol **23**[33] (85%) and subsequent oxidation [IBX, DMSO/THF (1:1), rt][26] afforded aldehyde **24**, which was not purified to avoid racemization (Scheme 6).

The next stage was the installation of the C4 and C5 stereocenters and the use of a crotylboration was considered. The stereochemical outcome of the crotylation of protected derivatives of



Scheme 6. Synthesis of the C1–C8 subunit.

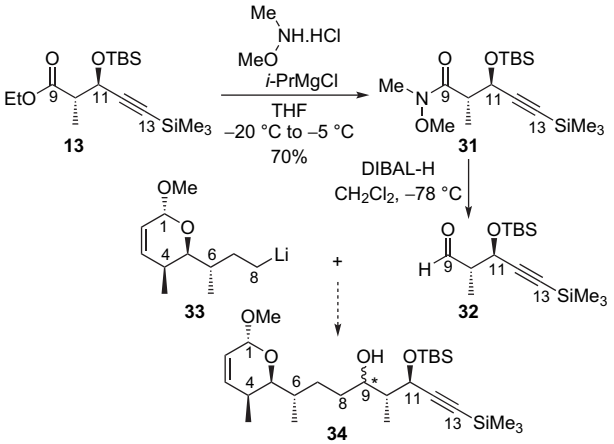
2-methyl-4-hydroxybutanal is not well-documented compared to protected 2-methyl-3-hydroxypropanal (Roche ester derivatives). Despite the smaller steric difference that exists between methyl and 2-alkoxyethyl groups compared to methyl and alkoxymethyl substituents, addition of the optically active (*Z*)-crotylboronate (*S*,*S*)-**I** to aldehyde **24** proceeded with a remarkably high diastereoselectivity (dr>96:4) and provided the *anti*,*syn*-homoallylic alcohol **25** in 80% yield (two steps from **23**). The secondary alcohol **25** was then acylated with acryloyl chloride [*i*-Pr_2NEt, DMAP (30 mol %), CH_2Cl_2, −78 °C] and the resulting acrylate **26** underwent RCM in the presence of Grubbs' second generation catalyst[34] (6 mol %, CH_2Cl_2, reflux) to afford the α,β-unsaturated δ-lactone **27** in high yield (95%, two steps from **25**). As an organolithium will have to be generated at C8 in the key coupling reaction, the carbonyl group of lactone **27** was temporarily masked by reduction to the lactol (DIBAL-H, THF, −78 °C) and formation of the corresponding methyl acetal [MeOH, PPTS (20 mol %), C_6H_6, reflux] to deliver compound **28** (dr=90:10, 95%, two steps from **27**).[35] The hydroxyl group at C8 was then deprotected (TBAF, THF, 0 °C to rt) and the resulting alcohol **29** (94%) was transformed to the primary alkyl iodide **30** (90%) under standard conditions (PPh_3, I_2, imidazole, THF, 0 °C) (Scheme 6).[36]

The primary alkyl iodide **30** constitutes the C1–C8 subunit of cytostatin and has been obtained in 10 steps from alcohol **17** with an overall yield of 22%.

3.3. Synthesis of the C9–C13 subunit and diastereoselectivity of a nucleophilic addition to aldehyde 32

3.3.1. Preparation of the C9–C13 aldehyde

The previously prepared protected β-hydroxyester **13** was converted to the Weinreb amide **31** (Me(OMe)NH·HCl, *i*-PrMgCl, THF, −20 °C)[14] and subsequent reduction (DIBAL-H, THF, −78 °C) led to the corresponding aldehyde **32** (C9–C13 subunit), which was not purified to prevent epimerization. In agreement with our synthetic plan, the next task was to achieve the formation of the C8–C9 bond by nucleophilic addition of the organolithium **33** derived from the primary alkyl iodide **30** (C1–C8 subunit). This operation would lead to alcohol **34**, a C1–C13 precursor of cytostatin, and create a stereocenter at C9 (Scheme 7).



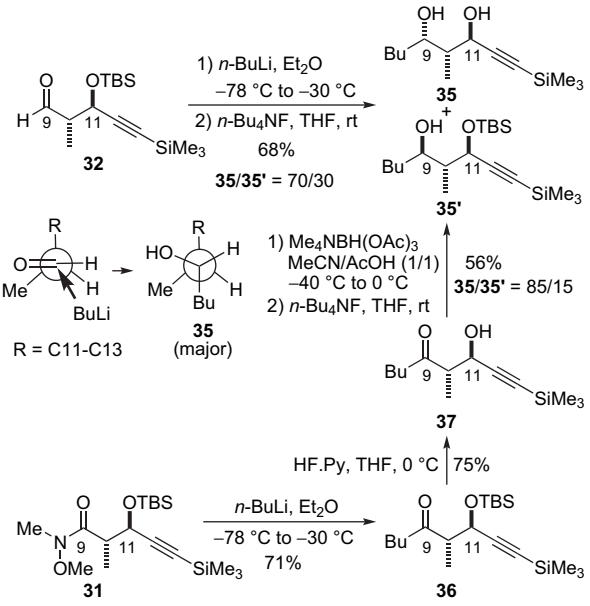
Scheme 7. Synthesis of the C9–C13 subunit.

Thus, preliminary experiments were carried out to investigate the diastereoselectivity of a nucleophilic addition to aldehyde **32**.

3.3.2. Diastereoselectivity of a nucleophilic addition to aldehyde 32

The C10 methyl-substituted stereocenter in aldehyde **32** was anticipated to control the diastereoselectivity of nucleophilic additions to the carbonyl group at C9. According to the Felkin–Anh model, a *syn* relationship between the hydroxyl group at C9 and the methyl group at C10 was expected in the major diasteromeric adduct.[19] To check if this was indeed the case, the addition of a primary organolithium such as *n*-BuLi to aldehyde *rac*-**32**[37] was investigated. Thus, treatment of compound *rac*-**32** with *n*-BuLi (Et_2O, −78 °C to −50 °C) afforded a 70:30 mixture of the corresponding epimeric secondary alcohols, which underwent desilylation (*n*-Bu_4NF, THF, rt) to produce a mixture of the diastereomeric 1,3-diols **35** and **35′** in a 70:30 ratio (68%, two steps from *rac*-**32**). On the other hand, Weinreb amide *rac*-**31** was converted to the corresponding butylketone **36** (*n*-BuLi, Et_2O, −78 °C, 71%). Deprotection of the alcohol (HF·Py, THF, 0 °C) led to the β-hydroxyketone **37** (75%), which underwent reduction with $Me_4NBH(OAc)_3$ (MeCN/AcOH, −40 °C to 0 °C) to afford, after desilylation of the alkyne

(TBAF, THF, rt), a mixture of the epimeric 1,3-diols **35** and **35′** in an 85:15 ratio (56%). As it is known that β-hydroxyketones are reduced to anti-1,3-diols with $Me_4NBH(OAc)_3$,[38] this latter result indicated that the relative orientation of the methyl group at C9 and the hydroxyl group at C10 was *syn* in the major 1,3-diol **35**. Thus, the major diastereomer obtained during the nucleophilic addition of an organolithium to aldehyde **32** is indeed controlled by the C10 stereocenter and corresponds to a Felkin–Anh addition mode (Scheme 8).



Scheme 8.

The coupling of the C1–C8 and C9–C13 subunits was then investigated.

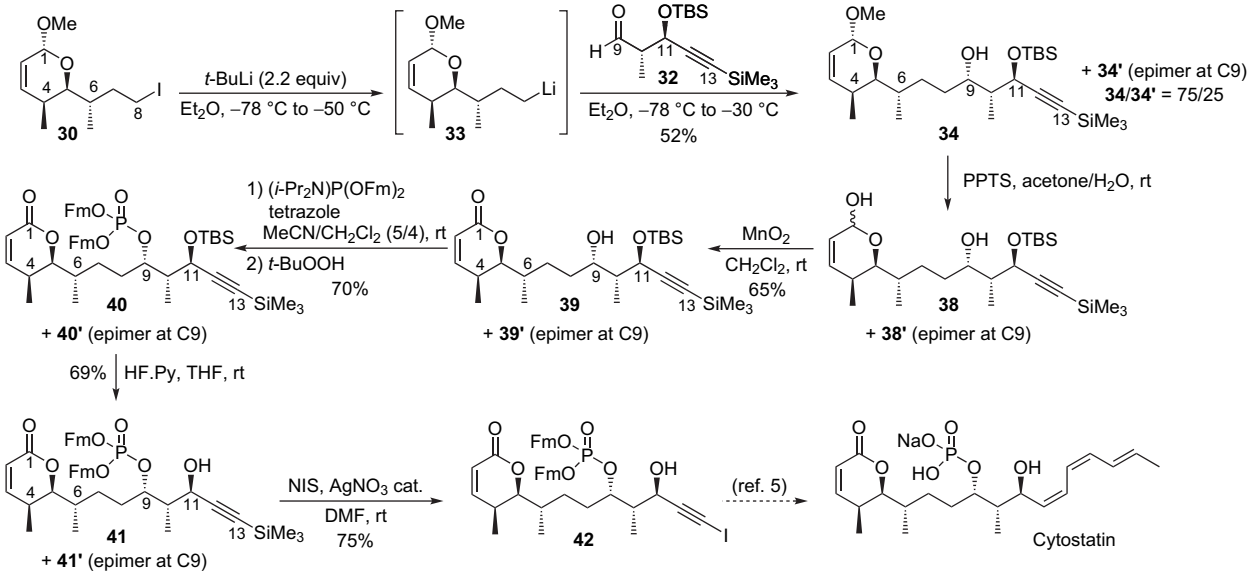
3.4. Synthesis of the C1–C13 fragment: formal synthesis of cytostatin

The primary alkyl iodide **30** underwent lithium–iodine exchange by treatment with *t*-BuLi (2.2 equiv) (Et_2O, −78 °C to −50 °C)[39] and the resulting alkyllithium **33** reacted with aldehyde **32** to afford a mixture of the two epimeric secondary alcohols **34** and **34′** in a 75:25 ratio (52%). The diastereomeric ratio was somewhat difficult to evaluate at that stage due to partial equilibration of the acetal center at C1. The mixture of the epimeric alcohols **34** and **34′** underwent hydrolysis of the methyl acetal (PPTS, acetone/H_2O, rt) to afford the corresponding lactols **38**/**38′**, which were chemoselectively oxidized with MnO_2 and provided a 75:25 mixture of the epimeric secondary alcohols **39** and **39′** (65%, two steps from **34**/**34′**). Although the diastereomers could be separated at this stage, the separation turned out to be easier later in the synthesis. Phosphorylation of the hydroxyl group at C9 was accomplished, by treatment with the phosphoramidite $(i\text{-}Pr_2N)P(OFm)_2$ [tetrazole, $MeCN/CH_2Cl_2$ (5:4), rt][40] but subsequent oxidation of the phosphorus atom was best carried out with TBHP instead of *m*-CPBA or I_2.[5,40] The corresponding diasteromeric mixture of phosphates **40**/**40′** was obtained in 70% yield. Deprotection of the alcohol at C11 was achieved by treatment with HF·Py (THF, rt) and the alkynylsilanes **41**/**41′** underwent iododesilylation (NIS, cat. $AgNO_3$, DMF, rt) to afford the alkynyl iodide **42** (75%) after separation of the minor epimer at C9 (Scheme 9).

The physical and spectroscopic data of compound **42** matched with those reported by Waldmann and Bialy[5] who described the preparation of this compound according to a linear approach (24 steps) and successfully completed the first total synthesis of cytostatin in three steps from this intermediate. Indeed, transformation of the acetylenic iodide **42** to the natural product was previously achieved by reduction to the corresponding (*Z*)-alkenyl iodide with diimide, Stille coupling with a (*Z*,*E*)-dienylstannane to form the C13–C14 of the triene, and finally phosphate deprotection.[5]

4. Conclusion

We have reported two synthetic approaches toward cytostatin. A first route involving the formation of the C7–C8 bond by a Horner–Wadsworth–Emmons reaction between an aldehyde (C3–C7 subunit) and a β-ketophosphonate (C8–C13 subunit) enabled the synthesis of a C3–C13 fragment containing five of the six stereocenters of the natural product. The second route relied on the nucleophilic addition of a functionalized alkyllithium (C1–C8 subunit), containing a cyclic methyl acetal as a precursor of the δ-lactone, to an aldehyde (C9–C13 subunit). A C1–C13 known precursor of the natural product was prepared according to this strategy in



Scheme 9. Formal synthesis of cytostatin.

16 steps for the longest linear sequence (3% overall yield), thereby accounting for a formal synthesis of cytostatin. Other key step features the installation of the C6 stereocenter by an Evans alkylation, a diastereoselective crotylboration to introduce the C4 and C5 stereocenters, a Baker's yeast enantioselective reduction of an acetylenic β-ketoester, and a Frater–Seebach diastereoselective alkylation to create the C11 and C10 asymmetric carbons.

5. Experimental section

5.1. General procedures

Infrared (IR) spectra were recorded on a Bruker Tensor 27 (IR-FT), wavenumbers are indicated in cm^{-1}. ^1H NMR spectra were recorded on a Bruker AC300 (300 MHz) or a Bruker Avance 400 (400 MHz) and data are reported as follows: chemical shift in parts per million from tetramethylsilane as an internal standard, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet or overlap of non-equivalent resonances), integration. ^{13}C NMR spectra were recorded at 75 or 100 MHz and data are reported as follows: chemical shift in parts per million from tetramethylsilane with the solvent as an internal indicator ($CDCl_3$, δ 77.0 ppm), multiplicity with respect to proton (deduced from DEPT experiments, s=quaternary C, d=CH, t=CH_2, q=CH_3). Mass spectra with electronic impact (MS-EI) were recorded from a Hewlett-Packard tandem 5890A GC (12 m capillary column)—5971 MS (70 eV). THF and diethyl ether were distilled from sodium/benzophenone. CH_2Cl_2, CH_3CN, toluene, Et_3N, *i*-Pr_2NH, 2,6-lutidine, and DMF were distilled from CaH_2. Anhydrous EtOAc was obtained by distillation from P_2O_5. Other reagents were obtained from commercial suppliers and used as received. TLC was performed on silica gel plates and visualized either with a UV lamp (254 nm), or by using solutions of *p*-anisaldehyde/H_2SO_4/AcOH in EtOH or $KMnO_4/K_2CO_3$ in water followed by heating. Flash chromatography was performed on silica gel (230–400 mesh).

5.2. First approach: formation of the C7–C8 bond by Horner–Wadsworth–Emmons olefination

5.2.1. Synthesis of the C3–C7 fragment

*5.2.1.1. Methyl (S)-3-(4-methoxybenzyloxy)-2-methylpropanoate (**3**).*[13] To a mixture of freshly prepared 4-methoxybenzyl 2,2,2-trichloroacetimidate (8.40 g, 29.7 mmol, 1.75 equiv) and Roche ester (*S*)-**1** (2.00 g, 16.9 mmol, 1 equiv) in CH_2Cl_2 (30 mL) at rt was added PPTS (254 mg, 1.01 mmol, 0.06 equiv). After 15 h at rt, the reaction mixture was poured into a saturated aqueous solution of $NaHCO_3$, the layers were separated, and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was taken-up in hexanes (20 mL) at 0 °C and the precipitate of trichloroacetamide was removed by filtration through Celite (hexanes). The filtrate was evaporated under reduced pressure and the residue was purified by flash chromatography (petroleum ether/EtOAc gradient: 90:10–80:20) to provide 3.77 g (93%) of **3** as a colorless oil ($C_{13}H_{18}O_4$, MW=238.28 g mol^{-1}). $[\alpha]_D^{20}$ +4.2 (*c* 1.47, $CHCl_3$); IR 1735, 1612, 1512, 1244, 1199, 1173, 1085, 1033, 872, 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (br d, *J*=8.5 Hz, 2H), 6.87 (d, *J*=8.5 Hz, 2H), 4.45 (s, 2H), 3.79 (s, 3H), 3.68 (s, 3H), 3.63 (dd, *J*=9.0, 7.5 Hz, 1H), 3.46 (dd, *J*=9.0, 6.0 Hz, 1H), 2.81–2.72 (m, 1H), 1.16 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2 (s), 159.1 (s), 130.2 (s), 129.1 (d, 2C), 113.7 (d, 2C), 72.7 (t), 71.6 (t), 55.2 (q), 51.6 (q), 40.1 (d), 13.9 (q); MS-EI *m*/*z* (relative intensity) 238 (M^+, 1), 138 (9), 137 (100), 136 (9), 122 (11), 121 (97), 109 (11), 101 (4), 91 (7), 78 (13), 77 (15), 59 (5).

*5.2.1.2. Methyl (S)-N-methyl-N-methoxy-3-(4-methoxybenzyloxy)-2-methylpropanoate (**4**).*[14,15] To a mixture of ester **3** (377 g, 15.8 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (2.32 g, 23.7 mmol, 1.5 equiv) in THF (30 mL) at −20 °C was added dropwise *i*-PrMgCl (24.0 mL, 2 M in THF, 48.0 mmol, 3 equiv). After 1 h at −20 °C, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl, the layers were separated, and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/Et_2O gradient: 85:15–60:40) and 3.80 g (90%) of **4** was obtained as a yellow oil ($C_{14}H_{21}NO_4$, MW=267.32 g mol^{-1}). $[\alpha]_D^{20}$ +2.6 (*c* 2.5, $CHCl_3$); IR 1655, 1612, 1512, 1462, 1244, 1173, 1094, 1032, 991, 818 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, *J*=8.7 Hz, 2H), 6.86 (d, *J*=8.7 Hz, 2H), 4.48 (d, AB syst, *J*=11.7 Hz, 1H), 4.40 (d, AB syst, *J*=11.7 Hz, 1H), 3.79 (s, 3H), 3.69 (s, 3H), 3.71–3.65 (m, 1H), 3.39 (dd, *J*=8.7, 5.7 Hz, 1H), 3.25–3.19 (m, 1H), 3.20 (s, 3H), 1.10 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8 (s, weak intensity), 159.1 (s), 130.6 (s), 129.1 (d, 2C), 113.7 (d, 2C), 72.9 (t), 72.3 (t), 61.5 (q), 55.2 (q), 35.9 (d), 32.4 (q, weak intensity), 14.2 (q); MS-EI *m*/*z* (relative intensity) 267 (M^+, 1), 236 (7), 131 (8), 122 (10), 121 (100), 100 (26), 78 (8), 77 (9).

*5.2.1.3. (S)-3-(4-Methoxybenzyloxy)-2-methylpropanal (**5**).*[16b] To a solution of Weinreb amide **4** (168 g, 6.28 mmol) in THF (15 mL) at −78 °C was added dropwise a solution of DIBAL-H (6.90 mL, 1 M in hexanes, 6.90 mmol, 1.1 equiv). After 45 min at −78 °C, the cold reaction mixture was poured into a saturated aqueous solution of sodium potassium tartrate (15 mL). The resulting mixture was diluted with Et_2O (15 mL) and vigorously stirred for 1 h. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The last traces of water were removed by azeotropic evaporation with toluene to obtain 1.33 g (quantitative) of aldehyde **5** as a pale yellow oil, which was directly engaged in the next step ($C_{12}H_{16}O_3$, MW=208.25 g mol^{-1}). ^1H NMR (300 MHz, $CDCl_3$) δ 9.71 (d, *J*=1.5 Hz, 1H), 7.24 (d, *J*=8.6 Hz, 2H), 6.88 (d, *J*=8.7 Hz, 2H), 4.45 (s, 2H), 3.80 (s, 3H), 3.65–3.61 (m, 2H), 2.66–2.63 (m, 1H), 1.13 (d, *J*=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.0 (d), 159.2 (s), 130.0 (s), 129.2 (d, 2C), 113.8 (d, 2C), 73.0 (t), 69.7 (t), 55.2 (q), 46.8 (d), 10.7 (q).

*5.2.1.4. (2S,3R,4S)-1-(4-Methoxybenzyloxy)-2,4-dimethylhex-5-en-3-ol (**6**).* A solution of aldehyde **5** (1.33 g, 6.28 mmol) in toluene (9 mL) was added dropwise to a mixture of crotylboronate (*S*,*S*)-**I** (13.5 mL, 0.79 M stock solution in toluene, 10.6 mmol, 1.7 equiv)[17] and powdered activated 4 Å MS (250 mg) in toluene (9 mL) at −78 °C. After 15 h at −78 °C, the reaction mixture was poured into a 1 M aqueous solution of NaOH. After 1.5 h stirring at 0 °C, the layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried over K_2CO_3, filtered, and concentrated under reduced pressure. Analysis of the ^1H NMR spectrum of the crude material indicated the formation of an 85:15 diastereomeric mixture of homoallylic alcohols **6** and **6′**. The residue was purified by flash chromatography (toluene/EtOAc: 98:2, 96:4) to afford 400 mg (24%) of **6** and 993 mg (60%) of a mixture of **6** and **6′** (dr≥95:5) as colorless oils ($C_{16}H_{24}O_3$, MW=264.36 g mol^{-1}). $[\alpha]_D^{20}$ +5.2 (*c* 1.3, $CHCl_3$); IR 3484, 1612, 1512, 1456, 1245, 1079, 1034, 912, 819 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, *J*=8.7 Hz, 2H), 6.87 (d, *J*=8.7 Hz, 2H), 5.91–5.79 (m, 1H), 5.07–4.99 (m, 2H), 4.44 (s, 2H), 3.80 (s, 3H), 3.63 (dd, *J*=9.1, 4.2 Hz, 1H), 3.46 (dd, *J*=9.1, 6.4 Hz, 1H), 3.42–3.36 (m, 1H), 3.25 (d, *J*=4.1 Hz, 1H, OH), 2.36–2.25 (m, 1H), 1.99–1.86 (m, 1H), 1.03 (d, *J*=6.8 Hz, 3H), 0.94 (d, *J*=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1 (s), 142.4 (d), 129.9 (s), 129.3 (d, 2C), 114.0 (t), 113.8 (d, 2C), 79.1 (d), 74.5 (t), 73.2 (t), 55.3 (q), 41.0 (d), 35.6 (d), 14.4 (q), 13.2 (q); MS-EI *m*/*z*

(relative intensity) 264 (M^+, 1), 137 (20), 121 (100), 91 (32), 78 (5), 77 (3).

*5.2.1.5. (2RS,4R,5S)-2-(4-Methoxyphenyl)-5-methyl-4-((S)-1-methylallyl)-[1,3]dioxane (**7**).*[22] To a mixture of alcohol **6** (502 mg, 191 mmol) and powdered activated 4 Å molecular sieves (400 mg) in CH_2Cl_2 (8 mL) at rt was added DDQ (516 mg, 2.28 mmol, 1.2 equiv). After 0.5 h, a saturated aqueous solution of Na_2SO_3 (5 mL) and Et_2O (15 mL) were successively added. The reaction mixture was stirred for 1 h and then filtered through Celite (Et_2O). The pH of the aqueous layer was adjusted to 8 by addition of a saturated aqueous solution of $NaHCO_3$, the layers were then separated, and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/Et_2O: 90:10, 80:20, and 50:50) to afford 316 mg (63%) of **7** as an 85:15 inseparable mixture of epimers and a colorless oil ($C_{16}H_{22}O_3$, MW=262.34 g mol^{-1}). $[\alpha]_D^{20}$ +5.2 (*c* 1.3, $CHCl_3$); IR 1615, 1517, 1460, 1390, 1370, 1301, 1247, 1170, 1114, 1077, 1032, 911, 825, 732 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) *only the signals corresponding to the major epimer can be unambiguously described*: δ 7.41 (d, *J*=8.7 Hz, 2H), 6.89 (d, *J*=8.7 Hz, 2H), 6.03 (ddd, *J*=17.3, 10.2, 7.6 Hz 1H), 5.42 (s, 1H), 5.08 (br d, *J*=17.3 Hz, 1H), 5.00 (br d, *J*=10.2 Hz, 1H), 4.08 (dd, *J*=11.0, 4.7 Hz, 1H), 3.79 (s, 3H), 3.48 (dd, apparent t, *J*=10.9 Hz, 1H), 3.44 (dd, *J*=10.2, 2.4 Hz, 1H), 2.53–2.44 (m, 1H), 2.10–1.95 (m, 1H), 1.10 (d, *J*=7.1 Hz, 3H), 0.78 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8 (s), 142.4 (d), 131.5 (s), 127.3 (d, 2C), 113.6 (t), 113.5 (d, 2C), 100.9 (d), 86.0 (d), 73.1 (t), 55.3 (q), 39.0 (d), 30.9 (d), 13.2 (q), 12.2 (q); MS-EI *m*/*z* (relative intensity) 262 (M^+, 14), 261 (10), 208 (14), 207 (100), 137 (68), 136 (42), 135 (78), 121 (22), 109 (25), 77 (17), 67 (8), 55 (11). Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.26; H, 8.54.

*5.2.1.6. (2S,3R,4S)-3-(4-Methoxybenzyloxy)-2,4-dimethylhex-5-en-1-ol (**8**).*[22] To a solution of acetal **7** (262 mg, 100 mmol) in CH_2Cl_2 (8 mL) at 0 °C was added dropwise DIBAL-H (2.50 mL, 1 M in hexanes, 2.50 mmol, 2.5 equiv). After 3 h at rt, the reaction mixture was poured into a saturated aqueous solution of sodium potassium tartrate (10 mL) and Et_2O (20 mL) was added. After 40 min of vigorous stirring, the layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/Et_2O: 80:20, 70:30) to afford 242 mg (92%) of alcohol **8** as a colorless oil ($C_{16}H_{24}O_3$, MW=264.36 g mol^{-1}). $[\alpha]_D^{20}$ −31.7 (*c* 0.82, $CHCl_3$); IR 3424, 1612, 1513, 1457, 1301, 1246, 1173, 1032, 911, 820, 731 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J*=8.7 Hz, 2H), 6.87 (d, *J*=8.7 Hz, 2H), 5.90 (ddd, *J*=17.3, 10.2, 7.4 Hz, 1H), 5.09 (br d, *J*=17.3 Hz, 1H), 5.04 (br d, *J*=10.2 Hz, 1H), 4.60 (d, AB syst, *J*=10.6 Hz, 1H), 4.45 (d, AB syst, *J*=10.6 Hz, 1H), 3.80 (s, 3H), 3.70 (m, 1H), 3.57 (m, 1H), 3.30 (dd, apparent t, *J*=5.6 Hz, 1H), 2.73 (br s, 1H, OH), 2.58–2.47 (m, 1H), 1.94–1.87 (m, 1H), 1.11 (d, *J*=6.8 Hz, 3H), 1.00 (d, *J*=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3 (s), 142.1 (d), 130.3 (s), 129.5 (d, 2C), 114.4 (t), 113.9 (d, 2C), 88.4 (d), 74.7 (t), 66.1 (t), 55.3 (q), 40.9 (d), 37.3 (d), 15.6 (q), 14.7 (q). Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.63; H, 9.34.

*5.2.1.7. (2R,3R,4S)-3-(4-Methoxybenzyloxy)-2.4-dimethylhex-5-enal (**9**).* To a solution of alcohol **8** (251 mg, 0.949 mmol, 1 equiv) in DMSO/THF (1:1, 8 mL) at 0 °C was added IBX (400 mg, 1.42 mmol, 1.5 equiv). After 1 h at rt, H_2O (15 mL) was added and the resulting mixture was filtered through Celite (Et_2O). The layers of the filtrate were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 285 mg (quantitative) of aldehyde **9** as a colorless oil, which was directly engaged in the next step ($C_{16}H_{22}O_3$, MW=262.34 g mol^{-1}). IR 1721, 1612, 1513, 1457, 1394, 1346, 1302, 1246, 1173, 1033, 1000, 951, 917, 820, 756 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.73 (d, *J*=1.9 Hz, 1H), 7.24 (d, *J*=8.7 Hz, 2H), 6.87 (d, *J*=8.7 Hz, 2H), 5.77 (ddd, *J*=17.3, 10.2, 7.9 Hz, 1H), 5.11 (br d, *J*=17.3 Hz, 1H), 5.08 (br d, *J*=10.2 Hz, 1H), 4.54 (d, AB syst, *J*=10.7 Hz, 1H), 4.48 (d, AB syst, *J*=10.7 Hz, 1H), 3.80 (s, 3H), 3.54 (dd, *J*=6.5, 5.1 Hz, 1H), 2.73–2.64 (m, 1H), 2.60–2.51 (m, 1H), 1.13 (d, *J*=6.8 Hz, 3H), 1.00 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.4 (d), 159.2 (s), 140.7 (d), 130.2 (s), 129.3 (d, 2C), 115.8 (t), 113.7 (d, 2C), 84.2 (d), 73.4 (t), 55.2 (q), 48.6 (d), 40.7 (d), 15.5 (q), 11.1 (q).

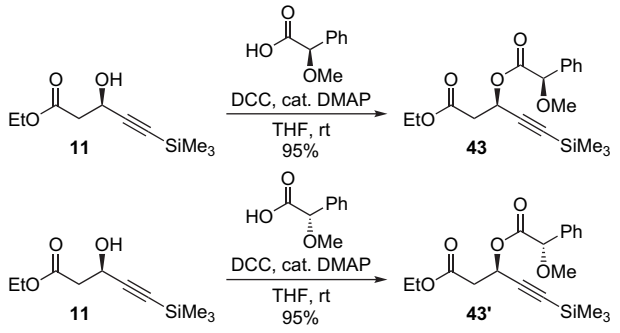
5.2.2. Synthesis of the C8–C13 fragment

*5.2.2.1. Ethyl 3-oxo-5-trimethylsilylpent-4-ynoate (**2**).*[25] To a solution of *i*-Pr_2NH (109 mL, 78.0 mmol, 2.6 equiv) in THF (70 mL) at −50 °C was added dropwise *n*-BuLi (30.6 mL, 2.5 M in hexanes, 76.5 mmol, 2.55 equiv). After 20 min between −50 °C and −10 °C, the resulting solution of LDA was cooled to −78 °C and freshly distilled anhydrous EtOAc (7.3 mL, 75.0 mmol, 2.5 equiv) was added dropwise within 15 min. The reaction mixture was then cooled to −85 °C and a solution of ethyl trimethylsilylpropynoate (5.05 g, 30.0 mmol, 1 equiv) in THF (10 mL) was added dropwise at such a rate that the internal temperature did not exceed −78 °C. After 1 h stirring at −78 °C, AcOH (5.15 mL, 90.0 mmol) was added to the reaction mixture, which was then warmed to 0 °C and gradually poured into ice-cold water whilst the aqueous layer was maintained to pH 3 by addition of a 3 M aqueous solution of hydrochloric acid. After extraction with Et_2O, the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (hexanes/Et_2O gradient: 96:4–90:10) to afford 5.83 g (91%) of β-ketoester **2** as a yellow oil ($C_{10}H_{16}O_3Si$, MW=212.32 g mol^{-1}). IR 1745, 1682, 1650, 1607, 1234, 1145, 1097, 1033, 939, 841, 805, 760 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) (65:35 mixture of ketone/enol tautomers) ketone form: δ 4.25–4.19 (m, 2H), 3.58 (s, 2H), 1.28 (t, *J*=7.2 Hz, 3H), 0.24 (s, 9H); enol form: δ 11.8 (s, 1H, OH), 5.37 (s, 1H), 4.25–4.19 (m, 2H), 1.29 (t, *J*=7.2 Hz, 3H), 0.24 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) ketone form: δ 178.5 (s), 165.9 (s), 101.0 (s), 100.4 (s), 61.6 (t), 51.1 (t), 14.0 (q), −0.95 (q, 3C); enol form: δ 172.0 (s), 154.4 (s), 100.4 (s), 97.9 (s), 97.6 (d), 60.6 (t), 14.1 (q), −0.69 (q, 3C); MS-EI *m*/*z* (relative intensity) 212 (M^+, 4), 197 ($M-Me^+$, 28), 169 (17), 151 (18), 141 (14), 127 (31), 125 (100), 113 (10), 99 (12), 97 (35), 83 (10), 75 (19), 73 (18).

*5.2.2.2. Ethyl (R)-3-hydroxy-5-trimethylsilylpent-4-ynoate (**11**).*[25] A mixture of *S cerevisiae* (type II) (10.5 g) and glucose (34 g) in water (previously boiled and cooled) (500 mL) was stirred at 30 °C for 0.5 h and a solution of β-ketoester **2** (1.00 g, 4.71 mmol) in 95% EtOH (3 mL) was added. After 15 h at 30 °C, the reaction mixture was cooled to 0 °C and Celite (4 g) was added. The resulting mixture was stirred for 1 h at 0–5 °C and filtered through Celite (EtOAc). The filtrate was saturated by addition of solid NaCl (with moderate stirring). The layers were separated and the aqueous phase was extracted with EtOAc (5×200 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/EtOAc: 80:20) to afford 730 mg (72%) of β-hydroxyester **11** (ee=92%) as a colorless oil ($C_{10}H_{18}O_3Si$, MW=214.33 g mol^{-1}). $[\alpha]_D^{20}$ +22.5 (*c* 1.0, $CHCl_3$); IR 3427, 1720, 1372, 1346, 1249, 1162, 1055, 1024, 839, 759 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73 (ddd, apparent br q, *J*=6.0 Hz, 1H), 4.19–4.12 (m, 2H), 3.23 (d, *J*=6.0 Hz, 1H, OH), 2.75–2.65 (m, 2H), 1.25 (t, *J*=7.2 Hz, 3H), 0.13 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1 (s),

104.5 (s), 89.7 (s), 60.9 (t), 59.0 (d), 42.0 (t), 14.1 (q), −0.30 (q, 3C); MS-EI *m*/*z* (relative intensity) 199 (M−Me$^+$, 70), 185 (15), 171 (17), 169 (13), 157 (38), 153 (46), 141 (13), 140 (13), 129 (51), 127 (44), 125 (33), 117 (30), 111 (60), 109 (28), 105 (13), 101 (28), 99 (52), 97 (14), 88 (13), 83 (24), 77 (24), 75 (100), 73 (50).

*5.2.2.3. Determination of the enantiomeric excess of β-hydroxyester **11**.* To a solution of β-hydroxyester **11** (54 mg, 0.25 mmol) in THF (2 mL) at rt were added (*R*)- or (*S*)-methoxyphenylacetic acid (44 mg, 0.26 mmol, 1.05 equiv), one small crystal of DMAP and DCC (60 mg, 0.29 mmol, 1.15 equiv). After 15 h at rt, the reaction mixture was diluted with Et_2O, filtered through Celite (Et_2O), and the filtrate was evaporated under reduced pressure. Comparative analysis of the ^1H NMR spectra of the corresponding crude mandelates **43** and **43′**, respectively, showed that the minor diastereomer was in each case at the limit of detection (dr≥96:4) thus indicating an ee≥92% for β-hydroxyester **11**.



After purification by flash chromatography (petroleum ether/Et_2O: 98:2), 86 mg (95%) of mandelate **43** or 87 mg (95%) of mandelate **43′**, respectively, was obtained as colorless oil.

*5.2.2.3.1. Ethyl (R)-3-((R)-2-methoxy-2-phenylacetoxy)-5-trimethylsilylpent-4-ynoate (**43**).* $C_{19}H_{26}O_5Si$, MW=362.49 g mol^{-1}; $[\alpha]_D^{20}$ +22.6 (*c* 1.0, $CHCl_3$); IR 2183, 1739, 1250, 1162, 1102, 1039, 997, 841, 760, 731, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45–7.42 (m, 2H), 7.38–7.30 (m, 3H), 5.80 (dd, *J*=8.7, 5.2 Hz, 1H), 4.78 (s, 1H), 4.14–4.02 (m, 2H), 3.44 (s, 3H), 2.86 (dd, *J*=16.1, 8.7 Hz, 1H), 2.77 (dd, *J*=16.1, 5.1 Hz, 1H), 1.20 (t, *J*=7.1 Hz, 3H), 0.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2 (s), 168.5 (s), 135.6 (s), 128.7 (d), 128.5 (d, 2C), 127.3 (d, 2C), 100.1 (s), 91.5 (s), 82.3 (d), 61.1 (d), 60.9 (t), 57.4 (q), 39.8 (t), 14.1 (q), −0.50 (q, 3C); MS-EI *m*/*z* (relative intensity) 347 (M−Me$^+$, 1), 181 (3), 139 (2), 121 (100), 109 (5), 91 (6), 77 (8).

*5.2.2.3.2. Ethyl (R)-3-((S)-2-methoxy-2-phenylacetoxy)-5-trimethylsilylpent-4-ynoate (**43′**).* $C_{19}H_{26}O_5Si$, MW=362.49 g mol^{-1}; $[\alpha]_D^{20}$ +87.8 (*c* 1.0, $CHCl_3$); IR 2183, 1739, 1250, 1160, 1104, 1040, 991, 841, 760, 733, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43–7.40 (m, 2H), 7.36–7.31 (m, 3H), 5.78 (dd, *J*=8.8, 5.3 Hz, 1H), 4.79 (s, 1H), 3.96–3.88 (m, 1H), 3.86–3.78 (m, 1H), 3.41 (s, 3H), 2.75 (dd, *J*=16.1, 8.8 Hz, 1H), 2.67 (dd, *J*=16.1, 5.3 Hz, 1H), 1.08 (t, *J*=7.1 Hz, 3H), 0.14 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1 (s), 168.2 (s), 135.8 (s), 128.7 (d), 128.5 (d, 2C), 127.2 (d, 2C), 100.4 (s), 91.6 (s), 82.2 (d), 61.0 (d), 60.8 (t), 57.3 (q), 39.9 (t), 13.9 (q), −0.4 (q, 3C); MS-EI *m*/*z* (relative intensity) 347 (M−Me$^+$, 1), 181 (3), 139 (2), 121 (100), 109 (4), 91 (6), 77 (8).

*5.2.2.4. Ethyl (2S,3R)-3-hydroxy-2-methyl-5-trimethylsilylpent-4-ynoate (**12**).* To a solution of *i*-Pr_2NH (0.60 mL, 4.30 mmol, 3 equiv) in THF (10 mL) at −30 °C was added dropwise *n*-BuLi (1.60 mL, 2.5 M in hexanes, 4.00 mmol, 2.8 equiv). After 25 min between −30 °C and 0 °C, the resulting solution of LDA was cooled to −78 °C and a solution of β-hydroxyester **11** (302 mg, 1.42 mmol, 1 equiv) in THF (5 mL) was added dropwise. The reaction mixture was stirred for 20 min at −78 °C, warmed to −25 °C, and stirred at that temperature for 20 min before being cooled again to −78 °C. A solution of MeI (0.15 mL, 2.40 mmol, 1.7 equiv) and HMPA (0.40 mL, 2.30 mmol, 1.6 equiv) in THF (5 mL) was then added dropwise. After 1.5 h at −78 °C and 0.5 h at −25 °C, the cold reaction mixture was poured into a 1 M aqueous solution of hydrochloric acid (40 mL). The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/Et_2O: 80:20) to afford 305 mg (94%) of **12** as a yellow oil and as a 93:7 mixture of *anti*/*syn* diastereomers ($C_{11}H_{20}O_3Si$, MW=228.36 g mol^{-1}). $[\alpha]_D^{20}$ +5.0 (*c* 0.2, $CHCl_3$); IR 3453, 2174, 1719, 1249, 1180, 1038, 839, 759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.48 (apparent t, *J*=7.1 Hz, 1H), 4.23–4.13 (m, 2H), 2.90 (d, *J*=6.7 Hz, 1H, OH), 2.73 (apparent quintet, *J*=7.2 Hz, 1H), 1.28 (t, *J*=7.1 Hz, 3H), 1.27 (d, *J*=7.2 Hz, 3H), 0.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6 (s), 104.1 (s), 90.7 (s), 64.7 (d), 60.8 (t), 46.3 (d), 14.1 (q), 13.8 (q), −0.30 (q, 3C); MS-EI *m*/*z* (relative intensity) 228 (M$^+$, 1), 213 (M−Me$^+$, 9), 195 (4), 185 (3), 167 (11), 139 (8), 127 (14), 111 (12), 102 (100), 99 (22), 83 (10), 75 (37), 74 (38), 73 (22), 56 (9), 55 (4).

*5.2.2.5. Ethyl (2S,3R)-3-(tert-butyldimethylsilyloxy)-2-methyl-5-trimethylsilylpent-4-ynoate (**13**).* To a solution of β-hydroxyester **12** (1.05 g, 4.60 mmol) in CH_2Cl_2 (30 mL) at −40 °C were successively added 2,6-lutidine (1.35 mL, 11.6 mmol, 2.5 equiv) and TBSOTf (2.12 mL, 9.24 mmol, 2 equiv). After 2 h from −40 °C to −20 °C, the reaction mixture was poured into a saturated aqueous solution of $NaHCO_3$ and extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/Et_2O: 95:5, 90:10) to afford 1.49 g (95%) of **13** as a colorless oil ($C_{17}H_{34}O_3Si_2$, MW=342.62 g mol^{-1}). $[\alpha]_D^{20}$ +64.4 (*c* 1.0, $CHCl_3$); IR 1737, 1250, 1178, 1091, 1052, 1024, 835, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.52 (d, *J*=9.0 Hz, 1H), 4.21–4.04 (m, 2H), 2.68 (dq, *J*=9.0, 7.2 Hz, 1H), 1.26 (t, *J*=7.2 Hz, 3H), 1.21 (d, *J*=7.2 Hz, 3H), 0.88 (s, 9H), 0.16 (s, 9H), 0.15 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1 (s), 105.9 (s), 90.7 (s), 65.8 (d), 60.4 (t), 47.7 (d), 25.7 (q, 3C), 18.1 (s), 14.2 (q), 13.6 (q), −0.3 (q, 3C), −4.5 (q), −5.2 (q); MS-EI *m*/*z* (relative intensity) 327 (M−Me$^+$, 4), 286 (26), 285 (M−*t*-Bu$^+$, 100), 241 (20), 157 (8), 155 (7), 147 (68), 133 (11), 115 (13), 103 (21), 75 (25), 73 (40).

*5.2.2.6. Dimethyl (3S,4R)-4-(tert-butyldimethylsilyloxy)-3-methyl-2-oxo-6-trimethylsilylhex-5-ynyl-phosphonate (**14**).* To a solution of *n*-BuLi (1.91 mL, 2.5 M in hexanes, 4.7 mmol, 4.1 equiv) in THF (15 mL) at −78 °C was added freshly distilled dimethyl methylphosphonate (0.640 mL, 5.84 mmol, 5 equiv). After 15 min at −60 °C, a solution of ester **13** (400 mg, 1.17 mmol, 1 equiv) in THF (5 mL) was added slowly (internal temperature≤−60 °C). After 15 min at −60 °C, the cold reaction mixture was poured into a saturated aqueous solution of NH_4Cl, the layers were separated, and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/Et_2O gradient: 80:20, 70:30, and 50:50) to afford 354 mg (72%) of phosphonate **14** as a colorless oil ($C_{18}H_{37}O_5PSi_2$, MW=420.63 g mol^{-1}); $[\alpha]_D^{20}$ +143 (*c* 1.0, $CHCl_3$); IR 1716, 1250, 1182, 1028, 834, 778, 760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.38 (d, *J*=9.0 Hz, 1H), 3.80 (d, J^3_{H-P}=4.9 Hz, 3H), 3.76 (d, J^3_{H-P}=4.9 Hz, 3H), 3.40 (dd, J^2_{H-P}=22.6 Hz, *J*=13.9 Hz, 1H), 3.16–3.06 (m, 1H), 3.05 (dd, J^2_{H-P}=22.6 Hz, *J*=13.9 Hz, 1H), 1.13 (d, *J*=6.8 Hz, 3H), 0.85 (s, 9H), 0.16 (s, 9H), 0.12 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.3 (s, J^2_{C-P}=6.5 Hz), 105.2 (s), 91.3 (s), 66.8 (d), 53.2 (d), 53.0 (q, J^2_{C-P}=6.5 Hz), 52.9 (q, J^2_{C-P}=6.4 Hz), 43.2 (t, J^1_{C-P}=128 Hz), 25.7 (q, 3C), 18.1 (s), 13.5 (q), −0.3 (q, 3C), −4.6 (q),

−5.3 (q); MS-EI *m*/*z* (relative intensity) 420 (M^+, 1), 405 (M−Me^+, 3), 364 (22), 363 (M−*t*-Bu^+, 68), 238 (21), 237 (100), 151 (6), 109 (8), 89 (7), 75 (17), 73 (19). Anal. Calcd for $C_{18}H_{37}O_5PSi_2$: C, 51.40; H, 8.87. Found: C, 51.42; H, 8.65.

5.2.3. Synthesis of the C3–C13 subunit by HWE olefination

*5.2.3.1. (E)-[(3R,4S,8S,9R,10S)-3-(tert-Butyldimethylsilyloxy)-9-(4-methoxybenzyloxy)-4,8,10-trimethyl-1-trimethylsilyldodeca-6,11-dien-1-yn-5-one (**15**).* To a degassed solution of phosphonate **14** (267 mg, 0.645 mmol, 1.2 equiv) in MeCN (4 mL) (argon bubbling, 10 min) were successively added, at rt, anhydrous LiCl (41 mg, 0.97 mmol, 1.8 equiv) and DBU (0.12 mL, 0.78 mmol, 1.45 equiv). After 0.5 h, a solution of aldehyde **9** (138 mg, 0.530 mmol, 1 equiv) in MeCN (2 mL) was added dropwise within 15 min. After 72 h at rt, the reaction mixture was hydrolyzed with H_2O (3 mL) and evaporated under reduced pressure. The residue was partitioned between H_2O and Et_2O, the layers were separated, and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/Et_2O: 90:10, 80:20) to afford 159 mg (54%) of **15** as a viscous colorless oil ($C_{32}H_{52}O_4Si_2$, MW=556.92 g mol^{-1}). IR 1697, 1671, 1624, 1455, 1361, 1249, 1084, 1006, 836, 779, 732, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (br d, *J*=8.7 Hz, 2H), 6.94 (dd, *J*=15.8, 8.3 Hz, 1H), 6.88 (d, *J*=8.7 Hz, 2H), 6.08 (dd, *J*=15.8, 0.8 Hz, 1H), 5.65 (ddd, *J*=17.3, 10.2, 7.9 Hz, 1H), 5.05–4.96 (m, 2H), 4.58–4.44 (m, 3H), 3.80 (s, 3H), 3.24–3.14 (m, 2H), 2.70–2.59 (m, 1H), 2.44–2.32 (m, 1H), 1.11 (d, *J*=6.8 Hz, 3H), 1.09 (d, *J*=6.8 Hz, 3H), 1.07 (d, *J*=6.8 Hz, 3H), 0.82 (s, 9H), 0.17 (s, 9H), 0.11 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.1 (s), 159.2 (s), 150.0 (d), 141.3 (d), 130.8 (d), 130.6 (s), 129.4 (d, 2C), 114.8 (t), 113.8 (d, 2C), 106.0 (s), 90.6 (s), 86.4 (d), 74.6 (t), 66.1 (d), 55.3 (q), 49.0 (d), 41.7 (d), 40.3 (d), 25.7 (q, 3C), 18.1 (s), 17.4 (q), 15.9 (q), 14.4 (q), −0.23 (q, 3C), −4.7 (q), −5.3 (q).

*5.2.3.2. (3R,4S,8S,9S,10S)-3-(tert-Butyldimethylsilyloxy)-9-(4-methoxybenzyloxy)-4,8,10-trimethyl-1-trimethylsilyldodeca-11-en-1-yn-5-one (**16**).* To a suspension of CuCN (40 mg, 0.44 mmol, 4.5 equiv) in THF (2.2 mL) at −20 °C was added dropwise *n*-BuLi (0.17 mL, 2.5 M in hexanes, 0.43 mmol, 4.4 equiv). After 0.5 h at −20 °C, the reaction mixture was cooled to −50 °C and DIBAL-H (0.86 mL, 1 M in hexanes, 0.86 mmol, 8 equiv) was added dropwise. After 1 h at −50 °C, a portion of the resulting hydridocuprate [HBu-Cu(CN)Li(Al*i*-Bu_2)] solution (1.6 mL, ca. 0.21 mmol, ca. 2.2 equiv) was added rapidly, via a syringe, to a solution of enone **15** (54 mg, 0.097 mmol, 1 equiv) in THF (1.5 mL) at −50 °C. After 0.5 h at −50 °C, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl that had been adjusted to pH 7 by addition of a 20% aqueous solution of NH_4OH. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by rapid filtration through silica gel (Et_2O), the filtrate was evaporated under reduced pressure, and the residue was dissolved in DMSO/THF (1:1, 2 mL). To the resulting solution at rt, was added IBX (30 mg, 0.10 mmol, 1.1 equiv) and after 1 h, the reaction mixture was hydrolyzed with H_2O (5 mL). The resulting mixture was filtered through Celite (Et_2O), the layers of the filtrate were separated, and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/Et_2O: 90:10) to afford 46 mg (84%, two steps from enone **15**) of ketone **16** as a colorless oil ($C_{32}H_{54}O_4Si_2$, MW=558.94 g mol^{-1}). $[\alpha]_D^{20}$ +59.8 (*c* 0.85, $CHCl_3$); IR 1717, 1613, 1514, 1461, 1249, 1078, 1037, 909, 850, 778, 760, 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J*=8.5 Hz, 2H), 6.85 (d, *J*=8.5 Hz, 2H), 5.76 (ddd, *J*=17.0, 10.1, 8.0 Hz 1H), 5.03 (br d, *J*=17.0 Hz, 1H), 4.96 (dd, *J*=10.1, 1.5 Hz 1H), 4.55–4.47 (m, 2H), 4.45 (d, *J*=9.0 Hz, 1H), 3.79 (s, 3H), 3.08 (dd, *J*=7.0, 3.5 Hz, 1H), 2.84 (qd, *J*=9.0, 7.0 Hz, 1H), 2.63–2.55 (m, 1H), 2.48–2.40 (m, 1H), 1.76–1.47 (m, 4H), 1.08 (d, *J*=6.5 Hz, 3H), 1.07 (d, *J*=7.0 Hz, 3H), 0.90 (d, *J*=6.5 Hz, 3H), 0.84 (s, 9H), 0.16 (s, 9H), 0.12 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.4 (s), 159.0 (s), 142.1 (d), 131.1 (s), 129.1 (d, 2C), 114.0 (t), 113.7 (d, 2C), 105.7 (s), 90.8 (s), 86.8 (d), 74.7 (t), 66.2 (d), 55.2 (q), 52.4 (d), 42.4 (t), 41.3 (d), 35.6 (d), 29.7 (t), 27.9 (q), 25.7 (q, 3C), 18.0 (s), 16.4 (q), 13.8 (q), −0.27 (q, 3C), −4.7 (q), −5.3 (q).

5.3. Second approach: formation of the C8–C9 bond by addition of an organolithium to an aldehyde

5.3.1. Synthesis of the C1–C8 subunit

*5.3.1.1. 4-(tert-Butyldiphenylsilyloxy)butanoic acid (**18**).*[31] To a solution of alcohol **17** (105 g, 32.0 mmol) in DMF (80 mL) at rt was added portionwise PDC (42.1 g, 112 mmol, 3.5 equiv). After 15 h at rt, Celite (20 g) was added and the reaction mixture was successively diluted with H_2O (300 mL) and Et_2O (150 mL) (while cooling to 5 °C). After stirring for 45 min at rt, the resulting mixture was filtered through Celite (Et_2O). The layers of the filtrate were separated and the aqueous phase was extracted with Et_2O (3×100 mL). The combined organic extracts were successively washed with a 1 M aqueous solution of HCl and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/EtOAc: 95:5–80:20) to afford 8.77 g (80%) of carboxylic acid **18** as a colorless oil ($C_{20}H_{26}O_3Si$, MW=342.50 g mol^{-1}). IR 3000 (br), 1703, 1427, 1294, 1258, 1093, 1032, 971, 825, 758, 736, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, *J*=7.5, 1.5 Hz, 4H), 7.43–7.35 (m, 6H), 3.70 (t, *J*=6.0 Hz, 2H), 2.51 (t, *J*=7.5 Hz, 2H), 1.92–1.85 (m, 2H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.3 (s), 135.6 (d, 4C), 133.7 (s, 2C), 129.8 (d, 2C), 127.7 (d, 4C), 62.8 (t), 30.8 (t), 27.5 (t), 26.9 (q, 3C), 19.2 (s).

*5.3.1.2. (S)-4-Benzyl-3-[4-(tert-butyldiphenylsilyloxy)butanoyl]-oxazolidin-2-one (**21**).* To a solution of carboxylic acid **18** (3.17 g, 9.25 mmol) in Et_2O (100 mL) at rt was added Et_3N (1.29 mL, 9.25 mmol, 1 equiv). After 15 min at rt, the reaction mixture was cooled to 0 °C and freshly distilled $ClCO_2Et$ (0.880 mL, 9.25 mmol, 1 equiv) was added dropwise. After 1 h at rt, the reaction mixture containing the mixed anhydride **19** was cooled to −78 °C and cannulated into a solution of the lithium salt **20** generated from (*S*)-4-benzyloxazolidin-2-one (1.64 g, 9.25 mmol, 1 equiv) and *n*-BuLi (3.70 mL, 2.5 M in hexanes, 9.25 mmol, 1 equiv) in THF (35 mL) (−78 °C, 15 min). After 0.5 h at −78 °C and 1 h at 0 °C, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/EtOAc: 90:10, 80:20) to afford 3.34 g (72%) of **21** as a colorless oil ($C_{30}H_{35}NO_4Si$, MW=501.69 g mol^{-1}). $[\alpha]_D^{20}$ +36.1 (*c* 1.63, $CHCl_3$); IR 1780, 1699, 1384, 1351, 1210, 1105, 822, 737, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.65 (m, 4H), 7.44–7.25 (m, 9H), 7.21–7.18 (m, 2H), 4.66–4.60 (m, 1H), 4.18–4.13 (m, 2H), 3.75 (t, *J*=6.5 Hz, 2H), 3.27 (dd, *J*=13.6, 3.5 Hz, 1H), 3.07 (t, *J*=7.5 Hz, 2H), 2.72 (dd, *J*=13.6, 9.5 Hz, 1H), 2.00–1.93 (m, 2H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1 (s), 153.4 (s), 135.6 (d, 4C), 135.4 (s), 133.8 (s, 2C), 129.7 (d), 129.6 (d), 129.4 (d, 2C), 129.0 (d, 2C), 127.7 (d, 2C), 127.6 (d, 2C), 127.3 (d), 66.2 (t), 62.9 (t), 55.2 (d), 37.9 (t), 32.2 (t), 27.0 (t), 26.9 (q, 3C), 19.2 (s).

*5.3.1.3. (S)-4-Benzyl-3-[(S)-4-(tert-butyldiphenylsilyloxy)butanoyl]-oxazolidin-2-one (**22**).* To a solution of NaHMDS (3.95 mL, 2 M in THF, 7.90 mmol, 1.2 equiv) in THF (12 mL) at −78 °C was added dropwise a solution of oxazolidinone **21** (3.30 g, 6.58 mmol) in THF (3 mL). After 0.5 h at −78 °C, MeI (0.615 mL, 9.87 mmol, 1.5 equiv) was added. The reaction mixture was stirred for 2 h between −60 °C and −50 °C and then poured into a saturated aqueous solution of NH_4Cl. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/EtOAc gradient: 96:4–90:10 then 70:30) to afford 2.71 g (80%) of **22** as a colorless oil (dr>96:4) ($C_{31}H_{37}NO_4Si$, MW=515.17 g mol^{-1}). $[\alpha]_D^{20}$ +39.5 (*c* 0.96, $CHCl_3$); IR 1778, 1697, 1382, 1206, 1105, 822, 737, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.63 (m, 4H), 7.43–7.25 (m, 9H), 7.21–7.18 (m, 2H), 4.59–4.53 (m, 1H), 4.10 (dd, *J*=9.0, 2.5 Hz, 1H), 4.04–4.00 (m, 1H), 3.98–3.88 (m, 1H), 3.76–3.67 (m, 2H), 3.24 (dd, *J*=13.6, 3.5 Hz, 1H), 2.74 (dd, *J*=13.6, 9.5 Hz, 1H), 2.18–2.09 (m, 1H), 1.71–1.63 (m, 1H), 1.23 (d, *J*=7.0 Hz, 3H), 1.03 (s, 9H); ^{13}C NMR δ 176.9 (s), 152.9 (s), 135.6 (d, 2C), 135.5 (d, 2C), 135.5 (s), 133.8 (s, 2C), 129.6 (d, 2C), 129.4 (d, 2C), 128.9 (d, 2C), 127.6 (d, 4C), 127.3 (d), 65.9 (t), 61.9 (t), 55.3 (d), 37.9 (t), 35.6 (t), 34.8 (d), 26.8 (q, 3C), 19.2 (s), 18.0 (q).

*5.3.1.4. (S)-2-Methyl-4-(tert-butyldiphenylsilyloxy)butanol (**23**).*[41] To a solution of **22** (100 g, 1.94 mmol) in THF/MeOH (10:1, 11 mL) at 0 °C was added dropwise a suspension of $LiBH_4$ (6.0 mL, 1.6 M in THF, 9.6 mmol, 5 equiv). After 2 h at rt, the reaction mixture was cautiously poured into a cold 0.5 M aqueous solution of sodium potassium tartrate (15 mL). The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/EtOAc: 80:20, 60:40) to afford 565 mg (85%) of alcohol **23** as a colorless oil and 282 mg (82%) of (4*S*)-4-benzyloxazolidin-2-one was also recovered ($C_{21}H_{30}O_2Si$, MW=342.55 g mol^{-1}). $[\alpha]_D^{20}$ −5.3 (*c* 0.95, $CHCl_3$); IR 3346, 1471, 1427, 1389, 1107, 1085, 1040, 996, 822, 736, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.66 (m, 4H), 7.46–7.36 (m, 6H), 3.79–3.67 (m, 2H), 3.52 (dd, *J*=10.5, 5.5 Hz, 1H), 3.47 (dd, *J*=10.5, 6.5 Hz, 1H), 2.43 (br s, 1H, OH), 1.90–1.79 (m, 1H), 1.67–1.59 (m, 1H), 1.53–1.45 (m, 1H), 1.05 (s, 9H), 0.90 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6 (d, 4C), 133.5 (s, 2C), 129.7 (d, 2C), 127.7 (d, 4C), 68.3 (t), 62.5 (t), 36.8 (t), 33.9 (d), 26.8 (q, 3C), 19.1 (s), 17.2 (q); MS-EI *m*/*z* (relative intensity) 285 (M−*t*-Bu$^+$, 3), 267 (3), 229 (31), 200 (19), 199 (100), 181 (9), 139 (9), 69 (9).

*5.3.1.5. (S)-2-Methyl-4-(tert-butyldiphenylsilyloxy)butanal (**24**).* To a solution of alcohol **23** (410 mg, 1.20 mmol) in DMSO/THF (1:1, 10 mL) at rt was added IBX (670 mg, 2.40 mmol, 1 equiv). After 2 h, H_2O (10 mL) and Et_2O (20 mL) were added, the resulting mixture was then vigorously stirred for 10 min, and filtered through Celite (Et_2O). The layers of the filtrate were separated and the aqueous phase was extracted with Et_2O (3×20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Traces of water were removed by azeotropic evaporation with toluene and the viscous residue was dried under high vacuum (0.1 mmHg) for 2 h to afford 415 mg (quantitative) of aldehyde **24**, which was directly engaged in the next step ($C_{21}H_{28}O_2Si$, MW=340.53 g mol^{-1}). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (d, *J*=1.5 Hz, 1H), 7.67–7.64 (m, 4H), 7.46–7.37 (m, 6H), 3.78–3.66 (m, 2H), 2.63–2.54 (m, 1H), 2.06–1.97 (m, 1H), 1.66–1.58 (m, 1H), 1.09 (d, *J*=7.0 Hz, 3H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9 (d), 135.6 (d, 4C), 133.5 (s, 2C), 129.7 (d, 2C), 127.7 (d, 4C), 61.1 (t), 43.5 (d), 33.4 (t), 26.8 (q, 3C), 19.2 (s), 13.1 (q).

*5.3.1.6. (3S,4S,5S)-7-(tert-Butyldiphenylsilyloxy)-3,5-dimethylhept-1-en-4-ol (**25**).* A solution of crude aldehyde **24** (415 mg, 1.20 mmol) in toluene (4 mL) was added to a mixture of crotylboronate (*S*,*S*)-**I**[17] (1.50 mL, 0.8 M in toluene, 1.20 mmol, 1 equiv) and powdered activated 4 Å MS (50 mg) in toluene (4 mL) at −78 °C. After 15 h at −78 °C, an additional quantity of crotylboronate (*S*,*S*)-**I** (1.50 mL, 0.8 M in toluene, 1.20 mmol, 1 equiv) was added and 6 h later, the reaction mixture was poured into a 1 M aqueous solution of NaOH. After 1.5 h stirring at 0 °C, the layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried over K_2CO_3, filtered, and concentrated under reduced pressure. Analysis of the ^{1}H NMR spectrum of the crude material indicated the formation of the desired alcohol with high diastereoselectivity (dr≥96:4). The residue was purified by flash chromatography (petroleum ether/Et_2O: 98:2, 95:5) to afford 381 mg (80%, two steps from **22**) of alcohol **25** as a colorless oil ($C_{25}H_{36}O_2Si$, MW=396.64 g mol^{-1}). $[\alpha]_D^{20}$ −7.8 (*c* 1.65, $CHCl_3$); IR 3424, 1461, 1427, 1107, 1085, 994, 908, 822, 734, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.67 (m, 4H), 7.46–7.37 (m, 6H), 5.82 (ddd, *J*=17.6, 10.0, 7.5 Hz, 1H), 5.08–5.01 (m, 2H), 3.81–3.75 (m, 1H), 3.70–3.64 (m, 1H), 3.27–3.23 (m, 1H), 2.44–2.35 (m, 1H+OH), 1.92–1.76 (m, 2H), 1.59–1.51 (m, 1H), 1.06 (s, 9H), 1.06 (d, *J*=7.0 Hz, 3H), 0.91 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2 (d), 135.6 (d, 4C), 133.5 (s, 2C), 129.7 (d, 2C), 127.7 (d, 4C), 114.3 (t), 78.9 (d), 61.9 (t), 40.9 (d), 33.9 (t), 33.2 (d), 26.8 (q, 3C), 19.1 (s), 16.9 (q), 14.1 (q); MS-EI *m*/*z* (relative intensity) 339 (M−*t*-Bu$^+$, 2), 337 (2), 321 (2), 283 (6), 229 (5), 205 (7), 100 (18), 199 (100), 197 (12), 183 (10), 181 (12), 139 (11), 135 (13), 123 (53), 85 (23), 81 (25), 67 (7), 55 (10).

*5.3.1.7. (5S,6S)-6-[(S)-3-(tert-Butyldiphenylsilyloxy)-1-methylpropyl]-5-methyl-5,6-dihydro-pyran-2-one (**27**).* To a solution of alcohol **25** (715 mg, 1.80 mmol), DMAP (66 mg, 0.54 mmol, 0.30 equiv), and *i*-Pr_2NEt (0.75 mL, 4.32 mmol, 2.4 equiv) in CH_2Cl_2 (10 mL) at −78 °C was added dropwise acryloyl chloride (1.08 mL, 1.80 mmol, 1 equiv). After 1 h at −78 °C, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was filtered through a short pad of silica gel (Et_2O) and the filtrate was evaporated under reduced pressure. The resulting acrylate **26** was dissolved in CH_2Cl_2 (30 mL) and to the resulting degassed solution (argon bubbling, 10 min) was added Grubbs' second generation catalyst (92 mg, 0.11 mmol, 0.06 equiv) (in three portions at 1 h interval). After heating at reflux for a total duration of 4 h, the reaction mixture was cooled to rt and evaporated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/EtOAc: 95:5, 90:10, and 80:20) to afford 723 mg (95%, two steps from **25**) of lactone **27** as a pale brown oil ($C_{26}H_{34}O_3Si$, MW=422.63 g mol^{-1}). $[\alpha]_D^{20}$ +42.6 (*c* 0.53, $CHCl_3$); IR 1719, 1461, 1427, 1376, 1249, 1106, 1049, 988, 822, 733, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.59 (m, 4H), 7.37–7.29 (m, 6H), 6.89 (dd, *J*=9.5, 6.5 Hz, 1H), 5.89 (d, *J*=9.5 Hz, 1H), 3.96 (dd, *J*=10.0, 3.0 Hz, 1H), 3.75–3.65 (m, 2H), 2.41–2.34 (m, 1H), 2.21–2.13 (m, 1H), 2.01–1.91 (m, 1H), 1.34–1.26 (m, 1H), 0.97 (s, 9H), 0.94 (d, *J*=7.0 Hz, 3H), 0.78 (d, *J*=6.5 Hz, 3H). The ^{1}H NMR spectrum of **27** was also recorded in CD_3OD for comparison with data reported for structurally related lactones:[8,10] ^{1}H NMR (400 MHz, CD_3OD) δ 7.69–7.66 (m, 4H), 7.43–7.37 (m, 6H), 7.13 (dd, *J*=9.6, 6.5 Hz, 1H), 5.92 (dd, *J*=9.6, 0.7 Hz, 1H), 4.11 (dd, *J*=10.5, 3.1 Hz, 1H), 3.86–3.74 (m, 2H), 2.59–2.51 (m, 1H), 2.22–2.14 (m, 1H), 2.10–2.00 (m, 1H), 1.42–1.33 (m, 1H), 1.03 (s, 9H), 0.98 (d, *J*=7.1 Hz, 3H), 0.84 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8 (s), 151.8 (d), 135.6 (d, 4C), 133.9 (s, 2C), 129.7 (d, 2C), 127.7 (d, 4C), 120.0 (d), 83.8 (d), 61.7 (t), 34.7 (t), 31.1 (d), 30.4 (d), 26.9 (q, 3C), 19.2 (s), 14.8 (q), 10.7 (q); MS-EI *m*/*z* (relative intensity) 366 (M−$C_4H_8^+$, 22), 365 (M−*t*-Bu$^+$, 73), 287 (43),

225 (22), 200 (17), 199 (100), 197 (15), 183 (24), 181 (20), 175 (18), 149 (23), 139 (18), 135 (13), 121 (13), 105 (11), 77 (11). Anal. Calcd for $C_{26}H_{34}O_3Si$: C, 73.89; H, 8.11. Found: C, 73.55; H, 8.15.

*5.3.1.8. tert-Butyl-[(S)-3-((2S,3S,6R)-6-methoxy-3-methyl-3,6-dihydro-2H-pyran-2-yl)butoxy]-diphenylsilane (**28**).* To a solution of lactone **27** (340 mg, 0.804 mmol) in THF (7 mL) at −78 °C was added dropwise DIBAL-H (0.88 mL, 1 M in hexanes, 0.88 mmol, 1.1 equiv). After 1 h at −78 °C, the reaction mixture was poured into a saturated aqueous solution of sodium potassium tartrate (10 mL). After 1 h of vigorous stirring, the layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude lactol was dissolved in a mixture of C_6H_6 (5 mL) and MeOH (2.25 mL) and PPTS (40 mg, 0.16 mmol, 0.2 equiv) was then added. After 1.5 h at reflux, the reaction mixture was evaporated under reduced pressure and the residue was partitioned between EtOAc and a saturated aqueous solution of $NaHCO_3$ (10 mL). The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/EtOAc: 90:10, 80:20) to afford 334 mg (95%, two steps from **27**) of acetal **28** as mixture of epimers at C1 (dr=90:10) ($C_{27}H_{38}O_3Si$, MW=438.67 g mol^{-1}). IR 1658, 1461, 1427, 1389, 1184, 1105, 1076, 1040, 987, 960, 822, 734, 700, 612 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *only the signals corresponding to the major epimer can be described unambiguously:* δ 7.70–7.66 (m, 4H), 7.44–7.35 (m, 6H), 6.03 (ddd, *J*=10.0, 6.0, 1.0 Hz, 1H), 5.64 (ddd, *J*=10.0, 2.7, 1.0 Hz, 1H), 4.80 (br d, *J*=2.7 Hz, 1H), 3.84–3.71 (m, 2H), 3.49 (dd, *J*=10.0, 2.5 Hz, 1H), 3.38 (s, 3H), 2.27–2.19 (m, 1H), 2.10–2.02 (m, 1H), 1.82–1.71 (m, 1H), 1.37–1.25 (m, 1H), 1.05 (s, 9H), 0.89 (d, *J*=7.0 Hz, 3H), 0.79 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1 (d), 135.6 (d, 4C), 134.2 (s, 2C), 129.5 (d, 2C), 127.6 (d, 4C), 124.0 (d), 96.4 (d), 73.7 (d), 62.4 (t), 55.4 (q), 36.0 (t), 31.0 (d), 30.2 (d), 26.9 (q, 3C), 19.2 (s), 15.4 (q), 11.7 (q); MS-EI *m*/*z* (relative intensity) 349 (M−MeOH−*t*-Bu$^+$, 12), 284 (21), 283 (86), 253 (8), 227 (7), 213 (29), 205 (30), 200 (13), 199 (66), 197 (11), 183 (23), 181 (17), 175 (21), 151 (12), 139 (15), 135 (19), 133 (12), 123 (11), 106 (15), 98 (30), 97 (13), 95 (29), 91 (15), 79 (13), 78 (100), 77 (37), 56 (13), 55 (14), 52 (15), 51 (17); HRMS calcd for $C_{27}H_{38}O_3NaSi$ (M+Na$^+$): 461.24824, found: 461.24803.

*5.3.1.9. (S)-3-((2S,3S,6R)-6-Methoxy-3-methyl-3,6-dihydro-2H-pyran-2-yl)butan-1-ol (**29**).* To a solution of silyl ether **28** (120 mg, 0.273 mmol) in THF (5 mL) at 0 °C was added *n*-Bu_4NF (0.68 mL, 1 M in THF, 0.68 mmol, 2.5 equiv). After 1 h at rt, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl, the layers were separated, and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/EtOAc: 70:30) to afford 51 mg (94%) of **29** as a colorless oil and a mixture of epimers at C1 (dr=90:10) ($C_{11}H_{20}O_3$, MW=200.27 g mol^{-1}). IR 3442, 1455, 1379, 1334, 1241, 1184, 1103, 1074, 1038, 960, 891, 734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *only the signals corresponding to the major epimer can be described unambiguously:* δ 6.05 (dd, *J*=10.0, 6.0 Hz, 1H), 5.66 (dd, *J*=10.0, 3.0 Hz, 1H), 4.84 (apparent br d, *J*=2.0 Hz, 1H), 3.83–3.76 (m, 1H), 3.73–3.64 (m, 1H), 3.55 (dd, *J*=10.5, 2.7 Hz, 1H), 3.46 (s, 3H), 2.20–2.06 (m, 2H+OH), 1.82–1.72 (m, 1H), 1.47–1.38 (m, 1H), 0.92 (d, *J*=6.5 Hz, 3H), 0.90 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0 (d), 123.9 (d), 96.3 (d), 73.9 (d), 60.9 (t), 55.6 (q), 36.7 (t), 31.0 (d), 30.2 (d), 16.0 (q), 11.7 (q); MS-EI *m*/*z* (relative intensity) 169 (M−OMe$^+$, 21), 105 (17), 98 (21), 97 (19), 95 (34), 94 (20), 91 (24), 85 (100), 84 (24), 83 (24), 81 (21), 79 (24), 69 (18), 68 (27), 67 (31), 55 (38), 53 (27); HRMS calcd for $C_{11}H_{20}O_3Na$ (M+Na$^+$): 223.13047, found: 223.13011.

*5.3.1.10. (2S,3S,6R)-2-((S)-3-Iodo-1-methylpropyl)-6-methoxy-3-methyl-3,6-dihydro-2H-pyran (**30**).* To a solution of alcohol **29** (340 mg, 1.70 mmol) in THF (15 mL) at 0 °C were successively added imidazole (277 mg, 4.08 mmol, 2.4 equiv), PPh_3 (535 mg, 2.04 mmol, 1.2 equiv), and I_2 (518 mg, 2.04 mmol, 1.2 equiv). After 15 min at 0 °C, the reaction mixture was poured into a mixture of a saturated aqueous solution of $NaHCO_3$ and a saturated aqueous solution of $Na_2S_2O_3$ (1:1, 10 mL) and extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/Et_2O: 99:1, 95:5) to afford 480 mg (90%) of iodide **30** as a colorless oil and a mixture of epimers at C1 (dr=90:10) ($C_{11}H_{19}IO_2$, MW=310.17 g mol^{-1}). IR 1658, 1454, 1398, 1381, 1334, 1233, 1183, 1104, 1076, 1040, 988, 958, 890, 733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *only the signals corresponding to the major epimer can be described unambiguously*: δ 6.04 (ddd, *J*=10.0, 6.0, 1.0 Hz, 1H), 5.66 (ddd, *J*=10.0, 3.0, 1.0 Hz, 1H), 4.82 (d, *J*=3.0 Hz, 1H), 3.57 (dd, *J*=10.0, 3.0 Hz, 1H), 3.44 (s, 3H), 3.39–3.32 (m, 1H), 3.26–3.19 (m, 1H), 2.46–2.38 (m, 1H), 2.11–2.03 (m, 1H), 1.81–1.67 (m, 2H), 0.92 (d, *J*=7.0 Hz, 3H), 0.86 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9 (d), 124.0 (d), 96.4 (d), 73.1 (d), 55.6 (q), 38.1 (t), 35.3 (d), 30.2 (d), 14.6 (q), 11.7 (q), 4.3 (t); MS-EI *m*/*z* (relative intensity) 310 (M$^+$, 0.5), 309 (1), 279 (M−OMe$^+$, 13), 199 (2), 183 (3), 167 (4), 151 (18), 123 (6), 99 (11), 98 (100), 97 (41), 95 (61), 86 (33), 83 (10), 81 (9), 69 (10), 67 (24), 55 (21); HRMS calcd for $C_{11}H_{19}O_2INa$ (M+Na$^+$): 333.03219, found: 333.03182.

5.3.2. Synthesis of the C9–C13 subunit

*5.3.2.1. (2S,3R)-N-Methyl-N-methoxy-3-(tert-butyldimethylsilyloxy)-2-methyl-5-trimethylsilylpent-4-ynamide (**31**).* To a mixture of ethyl ester **13** (1.49 g, 4.35 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (680 mg, 6.96 mmol, 1.6 equiv) in THF (10 mL) at −20 °C was added dropwise a solution of *i*-PrMgCl (5.45 mL, 2 M in THF, 10.9 mmol, 2.2 equiv). After 1.5 h at −5 °C, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl, the layers were separated, and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/Et_2O: 95:5) to afford 1.09 g (70%) of Weinreb amide **31** as a pale yellow oil and 403 mg (27%) of the starting material **13** were recovered ($C_{17}H_{35}NO_3Si_2$, MW=357.63 g mol^{-1}). $[\alpha]_D^{20}$ +145.0 (*c* 1.0, $CHCl_3$); IR 1662, 1250, 1086, 1024, 993, 835, 778, 760, 733 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.53 (d, *J*=10.0 Hz, 1H), 3.71 (s, 3H), 3.16 (br s+m, 3H+1H), 1.14 (d, *J*=7.0 Hz, 3H), 0.85 (s, 9H), 0.16 (s, 9H), 0.11 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9 (s), 106.0 (s), 90.4 (s), 66.2 (q), 61.6 (d), 42.5 (d), 31.9 (q), 25.6 (q, 3C), 18.1 (s), 14.3 (q), −0.2 (q, 3C), −4.7 (q), −5.3 (q); MS-EI *m*/*z* (relative intensity) 357 (M$^+$, 1), 342 (M−Me$^+$, 9), 326 (7), 301 (26), 300 (M−*t*-Bu$^+$, 100), 241 (10), 143 (12), 142 (20), 123 (11), 115 (18), 89 (31), 75 (17), 73 (6), 68 (11). Anal. Calcd for $C_{17}H_{35}NO_3Si_2$: C, 57.09; H, 9.86. Found: C, 56.93; H, 9.86.

*5.3.2.2. (2S,3R)-3-(tert-Butyldimethylsilyloxy)-2-methyl-5-trimethylsilylpent-4-ynal (**32**).* To a solution of Weinreb amide **31** (980 mg, 2.74 mmol) in THF (18 mL) at −78 °C was added dropwise DIBAL-H (3.0 mL, 1 M in hexanes, 3.0 mmol, 1.1 equiv). After 1 h at −78 °C, the reaction mixture was poured into a saturated aqueous solution of sodium potassium tartrate (20 mL). After addition of Et_2O (20 mL) and 0.5 h of vigorous stirring at rt, the layers were separated and the aqueous phase was extracted with Et_2O. The

combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residual traces of water were removed by azeotropic evaporation with toluene and the residue was dried under vacuum (0.1 mmHg) during 1.5 h to afford 818 mg (quantitative) of aldehyde **32**. This compound was directly engaged in the next step without further purification ($C_{15}H_{30}O_2Si_2$, MW=298.57 g mol^{-1}). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (d, J=1.5 Hz, 1H), 4.54 (d, J=6.0 Hz, 1H), 2.63–2.56 (m, 1H), 1.12 (d, J=7.0 Hz, 3H), 0.87 (s, 9H), 0.16 (s, 9H), 0.15 (s, 3H), 0.10 (s, 3H).

5.3.3. Diastereoselectivity of a nucleophilic addition to aldehyde **32**

5.3.3.1. (3R,4S*)-3-(tert-Butyldimethylsilyloxy)-4-methyl-1-trimethylsilylnon-1-yn-5-one (**36**).* To a solution of the Weinreb amide *rac*-**31** (263 mg, 0.735 mmol) in Et_2O (5 mL) at −78 °C was added dropwise *n*-BuLi (0.588 mL, 2.5 M in hexanes, 1.47 mmol, 2 equiv). After 2 h at −30 °C, the cold reaction mixture was poured into a saturated aqueous solution of NH_4Cl, the layers were separated, and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/Et_2O: 96:4) to afford 185 mg (71%) of ketone **36** as a colorless oil ($C_{19}H_{38}O_2Si_2$, MW=354.67 g mol^{-1}). IR 2170, 1719, 1461, 1362, 1250, 1078, 1012, 834, 778, 760 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 (d, J=9.2 Hz, 1H), 2.85 (dq, J=9.2, 7.0 Hz, 1H), 2.51–2.47 (m, 2H), 1.57–1.48 (m, 2H), 1.36–1.26 (m, 2H), 1.08 (d, J=7.0 Hz, 3H), 0.90 (t, J=7.3 Hz, 3H), 0.86 (s, 9H), 0.16 (s, 9H), 0.13 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.6 (s), 105.8 (s), 90.7 (s), 66.2 (d), 52.3 (d), 43.9 (t), 25.7 (q, 3C), 25.2 (t), 22.3 (t), 18.1 (s), 13.9 (q), 13.8 (q), −0.3 (q, 3C), −4.7 (q), −5.3 (q); MS-EI m/z (relative intensity) 354 (M^+, 1), 339 (M−Me^+, 4), 298 (M−$C_4H_8^+$, 27), 297 (M−t-Bu^+, 100), 241 (15), 223 (13), 211 (9), 199 (8), 171 (40), 147 (54), 133 (14), 75 (56), 73 (55), 57 (11); HRMS (FAB) calcd for $C_{19}H_{38}NaO_2Si_2$ (M+Na^+): 377.2302, found: 377.2307.

5.3.3.2. (3R,4S*)-3-Hydroxy-4-methyl-1-trimethylsilylnon-1-yn-5-one (**37**).* To a solution of ketone **36** (112 mg, 0.316 mmol) in THF (6 mL) at 0 °C (polyethylene vessel) was added dropwise HF·Py complex (70% HF, 1.0 mL). After 8 h at rt, the reaction mixture was cooled to 0 °C and a saturated aqueous solution of $NaHCO_3$ (5 mL) was cautiously added dropwise followed by neutralization by portionwise addition of solid $NaHCO_3$. After extraction with EtOAc, the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/Et_2O: 98:2) to afford 57 mg (75%) of β-hydroxyketone **37** as a colorless oil ($C_{13}H_{24}O_2Si$, MW=240.41 g mol^{-1}). IR 3424, 2173, 1707, 1457, 1375, 1249, 1022, 998, 840, 759, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.48 (dd, apparent t, J=6.9 Hz, 1H), 2.90–2.83 (m, 1H), 2.58–2.45 (m, 2H), 1.62–1.54 (m, 2H), 1.38–1.28 (apparent sextet, J=7.4 Hz, 2H), 1.20 (d, J=7.2 Hz, 3H), 0.92 (t, J=7.4 Hz, 3H), 0.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.4 (s), 104.7 (s), 90.6 (s), 64.8 (d), 51.5 (d), 42.7 (t), 25.4 (t), 22.3 (t), 14.0 (q), 13.8 (q), −0.2 (q, 3C); MS-EI m/z (relative intensity) 225 (M−Me^+, 10), 207 (9), 183 (42), 167 (M−$SiMe_3^+$, 17), 165 (22), 138 (13), 123 (100), 114 (24), 111 (93), 99 (25), 97 (50), 85 (42), 83 (28), 75 (50), 73 (30), 72 (57), 57 (80), 55 (20).

5.3.3.3. (3R,4S*,5R*)-4-Methylnon-1-yn-3,5-diol (**35**)*

*5.3.3.3.1. By nucleophilic addition of n-BuLi to aldehyde **32**.* To a solution of aldehyde *rac*-**32** (50 mg, 0.16 mmol) in Et_2O (5 mL) at −78 °C was added *n*-BuLi (0.10 mL, 2.5 M in hexanes, 0.25 mmol, 1.5 equiv). After 2 h from −78 °C to −30 °C, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was dissolved in THF (5 mL) and a solution of *n*-Bu_4NF (0.40 mL, 1 M in THF, 0.40 mmol, 2.5 equiv) was added. After 20 min at rt, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (petroleum ether/Et_2O: 75:35) to afford 18 mg (68%) of a 70:30 mixture of the diastereomeric alcohols *anti*- and *syn*-1,3-diols **35** and **35′**.

*5.3.3.3.2. By reduction of β-hydroxyketone **37**.* To a solution of $Me_4NBH(OAc)_3$ (264 mg, 1.12 mmol, 8 equiv) in CH_3CN/AcOH (1:1, 1.6 mL) at −40 °C was added dropwise a solution of ketone **37** (35 mg, 0.146 mmol) in CH_3CN/AcOH (1:1, 1.6 mL). After 5 h stirring at −40 °C, 5 h at −20 °C, and 12 h at 0 °C, the reaction mixture was poured into a saturated aqueous solution of sodium potassium tartrate (10 mL). After 2 h of vigorous stirring, the layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were successively washed with a saturated aqueous solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was dissolved in THF (2 mL) and a solution of *n*-Bu_4NF (0.17 mL, 1 M in THF, 0.17 mmol, 1.15 equiv) was added to the resulting solution at 0 °C. After 20 min, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/Et_2O: 70:30) to afford 14 mg (56%) of an 85:15 mixture of the *anti*- and *syn*-1,3-diols **35** and **35′**.

*Compound (**35**).* $C_{10}H_{18}O_2$, MW=170.25 g mol^{-1}; IR 3310 (br), 1459, 1379, 1251, 1117, 1075, 1024, 964 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.42 (m, 1H), 4.24–4.19 (m, 1H), 3.16 (apparent br s, 1H, OH), 2.52 (d, J=2.1 Hz, 1H), 2.10–1.96 (br m, 1H, OH), 1.85–1.78 (m, 1H), 1.60–1.50 (m, 2H), 1.48–1.28 (m, 4H), 1.06 (d, J=7.1 Hz, 3H), 0.92 (t, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 84.4 (s), 73.8 (d), 72.3 (d), 66.6 (d), 42.4 (d), 34.3 (t), 28.2 (t), 22.6 (t), 14.0 (q), 9.9 (q).

5.3.4. Formal synthesis of cytostatin

*5.3.4.1. (3R,4R,5S,8S)-3-(tert-Butyldimethylsilyloxy)-8-((2S,3S,6R)-6-methoxy-3-methyl-3,6-dihydro-2H-pyran-2-yl)-4-methyl-1-trimethylsilylnon-1-yn-5-ol (**34**) and (3R,4R,5R,8S)-3-(tert-butyldimethylsilyloxy)-8-((2S,3S,6R)-6-methoxy-3-methyl-3,6-dihydro-2H-pyran-2-yl)-4-methyl-1-trimethylsilylnon-1-yn-5-ol (**34′**).* To a solution of alkyl iodide **30** (566 mg, 1.82 mmol, 1 equiv) in Et_2O (10 mL) at −78 °C was added a solution of *t*-BuLi (2.35 mL, 1.7 M in pentane, 4.00 mmol, 2.2 equiv). After 10 min at −78 °C and 15 min at −30 °C, the resulting organolithium **33** solution was cooled to −78 °C and a solution of aldehyde **32** (818 mg, 2.74 mmol, 1.5 equiv) in Et_2O (10 mL) was added dropwise within 20 min. After 1.5 h at −78 °C and 2 h at −30 °C, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/Et_2O gradient: 98:2–80:20) to afford 389 mg (52%) of a diastereomeric mixture of alcohols **34** and **34′** in a 75:25 ratio and as a colorless oil ($C_{26}H_{50}O_4Si_2$, MW=482.84 g mol^{-1}). IR 3471, 2171, 1659, 1462, 1249, 1184, 1075, 1042, 962, 835, 777, 760, 734 cm^{-1}; major epimer (**34**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.05 (dd, J=9.8, 5.9 Hz, 1H), 5.65 (dd, J=9.8, 1.3 Hz, 1H), 4.83 (apparent br s, 1H), 4.41 (d, J=3.9 Hz, 1H), 4.23 (m, 1H), 3.62–3.49 (m, 1H), 3.44 (s, 3H), 2.13–1.87 (m, 1H), 1.75–1.58 (m, 2H), 1.40–1.22 (m, 4H), 1.01 (d, J=7.0 Hz, 3H), 0.98 (d, J=6.9 Hz, 3H), 0.91 (s, 9H), 0.90–0.85 (m, 3H), 0.17 (s, 3H), 0.15 (s,

9H), 0.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1 (d), 123.9 (d), 106.2 (s), 94.4 (d), 90.7 (s), 73.7 (d), 71.7 (d), 68.8 (d), 55.5 (q), 43.3 (d), 34.0 (d), 31.9 (t), 30.2 (d), 29.7 (t), 25.7 (q, 3C), 18.1 (s), 15.1 (q), 11.8 (q), 10.1 (q), −0.3 (q, 3C), −4.6 (q), −5.4 (q); minor epimer (**34′**): ^{1}H NMR (400 MHz, $CDCl_3$) *some signals cannot be accurately described due to overlap*: δ 6.05 (dd, J=9.8, 5.9 Hz, 1H), 5.65 (dd, J=9.8, 1.3 Hz, 1H), 4.83 (br s, 1H), 4.49 (d, J=6.1 Hz, 1H), 3.62–3.49 (m, 2H), 3.44 (s, 3H), 2.13–1.87 (m, 1H), 1.84–1.78 (m, 1H), 1.75–1.58 (m, 1H), 1.40–1.22 (m, 4H), 1.04–0.85 (9H), 0.91 (s, 9H), 0.17–0.15 (15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1 (d), 123.9 (d), 106.3 (s), 94.4 (d), 90.6 (s), 74.7 (d), 73.3 (d), 66.9 (d), 55.5 (q), 45.4 (d), 34.1 (d), 31.1 (t), 30.2 (d), 28.5 (t), 25.8 (q, 3C), 18.1 (s), 15.3 (q), 12.4 (q), 11.7 (q), −0.3 (q, 3C), −4.3 (q), −5.0 (q).

*5.3.4.2. (3R,4R,5S,8S)-3-(tert-Butyldimethylsilyloxy)-8-((2S,3S,6R)-6-methoxy-3-methyl-3,6-dihydro-2H-pyran-2-yl)-4-methyl-1-trimethylsilylnon-1-yn-5-ol (**39**).* To mixture of epimeric alcohols **34** and **34′** (300 mg, 0.621 mmol, 1 equiv, 75:25 ratio) in acetone (15 mL) and H_2O (1 mL) was added PPTS (47 mg, 0.19 mmol, 0.3 equiv). After 12 h and 18 h at rt, additional quantities of PPTS (47 mg, 0.19 mmol, 0.3 equiv) were added. After a further 6 h, the reaction mixture was neutralized by addition of an aqueous solution of $NaHCO_3$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture of the lactols **38**/**38′** was dissolved in CH_2Cl_2 (18 mL) and MnO_2 (1.36 g, 15.6 mmol, 25 equiv) was added. After 15 h at rt, a second portion of MnO_2 (1.36 g, 15.6 mmol, 25 equiv) was added and 12 h later the reaction mixture was filtered through Celite (CH_2Cl_2). The filtrate was evaporated under reduced pressure and the residue was purified by flash chromatography (petroleum ether/EtOAc: 90:10, 80:20, and 60:40) to afford 188 mg (65%) of a mixture of epimeric alcohols **39** and **39′** (75:25 ratio) as a colorless oil ($C_{25}H_{46}O_4Si_2$, MW=466.80 g mol^{-1}). $[\alpha]_D^{20}$ +95.0 (*c* 0.4, $CHCl_3$); IR 3436, 2170, 1719, 1462, 1378, 1249, 1073, 1006, 990, 840, 778, 760 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *only the signals corresponding to the major epimer could be unambiguously assigned*: δ 6.99 (dd, J=9.5, 6.5 Hz, 1H), 5.97 (d, J=9.5 Hz, 1H), 4.42 (d, J=4.0 Hz, 1H), 4.22–4.18 (m, 1H), 4.02 (dd, J=10.5, 3.2 Hz, 1H), 3.00 (br s, 1H, OH), 2.52–2.44 (m, 1H), 2.01–1.94 (m, 1H), 1.89–1.63 (m, 3H), 1.33–1.23 (m, 2H), 1.03 (d, J=6.5 Hz, 3H), 1.01 (d, J=6.8 Hz, 3H), 0.92 (d, J=6.5 Hz, 3H), 0.91 (s, 9H), 0.17 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8 (s), 151.8 (d), 119.9 (d), 106.0 (s), 90.9 (s), 84.1 (d), 71.6 (d), 68.7 (d), 42.9 (d), 34.0 (d), 31.8 (t), 30.9 (d), 28.9 (t), 25.6 (q, 3C), 18.0 (s), 14.5 (q), 10.7 (q), 10.1 (q), −0.3 (q, 3C), −4.6 (q), −5.4 (q); HRMS (FAB) calcd for $C_{25}H_{46}NaO_4Si_2$ (M+Na$^+$): 489.2827, found: 489.2826.

*5.3.4.3. Bis-(9H-fluoren-9-ylmethyl) (1S,2S,3R)-3-(tert-butyldimethylsilyloxy)-2-methyl-1-[(S)-3-((2S,3S)-3-methyl-6-oxo-3,6-dihydro-2H-pyran-2-yl)butyl]-5-trimethylsilylpent-4-ynylphosphate (**40**).* To a solution of the mixture of epimeric alcohols **39** and **39′** (75:25 ratio) (43 mg, 0.092 mmol, 1 equiv) in CH_3CN/CH_2Cl_2 (5:4, 5 mL) at rt, in a screw cap tube protected from light, at 0 °C were added tetrazole (22 mg, 0.32 mmol, 3.5 equiv) and bis-(9-fluorenylmethyl)diisopropylphosphoramidite[5,40] (120 mg, 0.230 mmol, 2.5 equiv). After 5 h at rt with exclusion of light, additional quantities of tetrazole (22 mg, 0.32 mmol, 3.5 equiv) and phosphoramidite (120 mg, 0.230 mmol, 2.5 equiv) were added. After 3 h at rt, the reaction mixture was cooled to 0 °C and *t*-BuOOH (0.12 mL, 5.5 M in decane, 0.66 mmol, 7 equiv) was added dropwise. The resulting mixture was stirred for 1 h at rt and hydrolyzed with a mixture of a saturated aqueous solution of $NaHCO_3$ (1 mL) and a 1 M aqueous solution of $Na_2S_2O_3$ (1.5 mL). After extraction with EtOAc, the combined organic extracts were washed with a 1 M aqueous solution of KH_2PO_4, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/EtOAc: 40:60, 50:50 then 60:40) to separate the excess of phosphorus reagents and 9-fluorenylmethanol and then by chromatography on preparative TLC plate (petroleum ether/EtOAc: 70:30) to afford 58 mg (70%) of a mixture of diastereomeric phosphates **40** and **40′** (75:25 ratio) as a colorless oil ($C_{53}H_{67}O_7PSi_2$, MW=902.41 g mol^{-1}). IR 1717, 1449, 1249, 1103, 1070, 987, 908, 837, 757, 728 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *only the signals corresponding to the major epimer could be unambiguously assigned*: δ 7.78–7.19 (m, 16H), 6.95 (dd, J=9.5, 6.5 Hz, 1H), 5.93 (d, J=9.5 Hz, 1H), 4.64–4.56 (m, 1H), 4.34–4.08 (m, 6H), 3.90 (dd, J=10.3, 2.8 Hz, 1H), 2.44–2.38 (m, 1H), 1.90–1.56 (m, 6H), 0.99 (d, J=7.0 Hz, 3H), 0.97 (d, J=6.9 Hz, 3H), 0.86 (s, 9H), 0.82 (d, J=6.7 Hz, 3H), 0.15 (s, 9H), 0.13 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5 (s), 151.6 (d), 143.9 (s), 143.6 (s), 143.2 (s), 143.0 (s), 141.4 (s), 141.3 (s, 2C), 141.2 (s), 127.8 (d), 127.7 (d, 2C), 127.6 (d), 127.0 (d, 2C), 126.9 (d, 2C), 125.1 (d, 2C), 125.0 (d, 2C), 124.9 (d), 120.0 (d), 119.9 (d, 2C), 119.8 (d), 106.3 (s), 90.9 (s), 83.7 (d), 79.9 (d, J^2_{C-P}=6.3 Hz), 69.0 (t, J^3_{C-P}=5.9 Hz), 67.2 (t, J^3_{C-P}=5.5 Hz), 64.2 (d), 48.2 (d, J^3_{C-P}=8.5 Hz), 47.9 (d, J^3_{C-P}=8.4 Hz), 43.6 (d, J^3_{C-P}=4.9 Hz), 33.9 (d), 30.3 (d), 30.1 (t), 28.0 (t), 25.7 (q, 3C), 18.1 (s), 14.5 (q), 10.7 (q), 10.1 (q), −0.3 (q, 3C), −4.1 (q), −4.8 (q); HRMS (FAB) calcd for $C_{53}H_{67}O_7NaPSi_2$ (M+Na$^+$): 925.4055, found: 925.4053.

*5.3.4.4. Bis-(9H-fluoren-9-ylmethyl) (1S,2S,3R)-3-hydroxy-2-methyl-1-[(S)-3-((2S,3S)-3-methyl-6-oxo-3,6-dihydro-2H-pyran-2-yl)butyl]-5-trimethylsilylpent-4-ynylphosphate (**41**).* To a solution of the mixture of phosphates **40** and **40′** (75:25 ratio, 60 mg, 0.066 mmol, 1 equiv) in THF (4 mL) at 0 °C (polyethylene vessel) was added HF·Py (70% HF, 0.6 mL). After 15 h at rt, more HF·Py (0.2 mL) was added and, 6 h later, the reaction mixture was cautiously neutralized at 0 °C by dropwise addition of a saturated aqueous solution of $NaHCO_3$ (5 mL) and then solid $NaHCO_3$. After extraction with EtOAc, the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on a preparative TLC plate (petroleum ether/EtOAc: 50:50) to afford 36 mg (69%) of a mixture of the diastereomeric propargylic alcohols **41** and **41′** (75:25 ratio) as a colorless oil ($C_{47}H_{53}O_7PSi$, MW=788.98 g mol^{-1}). IR 3370, 2172, 1717, 1449, 1379, 1248, 1106, 986, 841, 757, 738 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *only the signals corresponding to the major epimer could be unambiguously assigned*: δ 7.74–7.68 (m, 4H), 7.56–7.45 (m, 4H), 7.41–7.22 (m, 8H), 6.95 (dd, J=9.6, 6.5 Hz, 1H), 5.94 (d, J=9.6 Hz, 1H), 4.73–4.67 (m, 1H), 4.36–4.30 (m, 1H), 4.26–4.09 (m, 6H), 3.86 (dd, J=10.3, 2.9 Hz, 1H), 2.45–2.38 (m, 1H), 1.85–1.58 (m, 4H), 1.60–1.50 (m, 1H), 1.25–1.15 (m, 1H), 0.98 (d, J=7.0 Hz, 3H), 0.91 (d, J=6.9 Hz, 3H), 0.79 (d, J=6.7 Hz, 3H), 0.19 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5 (s), 151.6 (d), 143.2 (s), 142.9 (s), 142.8 (s, 2C), 141.4 (s, 2C), 141.3 (s, 2C), 127.9 (d, 2C), 127.8 (d, 2C), 127.2 (d), 127.1 (d, 3C), 125.0 (d, 4C), 120.05 (d, 2C), 120.0 (d, 2C), 119.9 (d), 106.0 (s), 89.4 (s), 83.6 (d), 78.5 (d, J^2_{C-P}=5.9 Hz), 69.4 (t, J^3_{C-P}=6.4 Hz), 69.3 (t, J^3_{C-P}=6.4 Hz), 63.9 (d), 47.9 (d, J^3_{C-P}=8.6 Hz), 47.8 (d, J^3_{C-P}=8.4 Hz), 43.7 (d, J^3_{C-P}=3.8 Hz), 33.8 (d), 30.5 (t, J^3_{C-P}=4.7 Hz), 30.3 (d), 28.5 (t), 14.7 (q), 10.7 (q), 9.2 (q), −0.1 (q, 3C); HRMS (FAB) calcd for $C_{47}H_{53}O_7NaPSi$ (M+Na$^+$): 811.31904, found: 811.3189.

*5.3.4.5. Bis-(9H-fluoren-9-ylmethyl) (1S,2S,3R)-3-hydroxy-5-iodo-2-methyl-1-[(S)-3-((2S,3S)-3-methyl-6-oxo-3,6-dihydro-2H-pyran-2-yl)-butyl]pent-4-ynylphosphate (**42**).* To a mixture of compounds **41** and **41′** (**41**/**41′**=75/25) (10 mg, 0.013 mmol) in DMF (1.5 mL) at 0 °C were successively added $AgNO_3$ (0.3 mg, 0.002 mmol, 0.15 equiv) and NIS (4.3 mg, 0.020 mmol, 1.5 equiv). After 1.5 h at rt, the reaction mixture was diluted with H_2O (2 mL) and extracted with EtOAc. The combined extracts were washed with an aqueous solution of NaCl, dried over $MgSO_4$, filtered, and concentrated under

reduced pressure. The residue was purified by chromatography on a silica gel preparative TLC plate (petroleum ether/EtOAc: 40:60) to afford 8 mg (75%) of **42** as a white solid; mp 112 °C (lit.[5] mp 117 °C) ($C_{44}H_{44}IO_7P$, MW=842.69 g mol^{-1}). $[\alpha]_D^{20}$ +46.5 (*c* 0.40, $CHCl_3$) [lit.[5] +41.5 (*c* 0.50, $CHCl_3$)]; IR 3353, 2360, 1714, 1449, 1380, 1250, 1106, 1070, 987, 739 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75–7.67 (m, 4H), 7.54–7.41 (m, 4H), 7.41–7.20 (m, 8H), 6.95 (dd, *J*=9.5, 6.5 Hz, 1H), 5.93 (d, *J*=9.5 Hz, 1H), 4.69–4.61 (m, 1H), 4.36–4.07 (m, 7H), 3.86 (dd, *J*=10.3, 2.4 Hz, 1H), 2.40 (m, 1H), 1.83–1.58 (m, 4H), 1.51–1.41 (m, 1H), 1.15–1.05 (m, 1H), 0.98 (d, *J*=7.0 Hz, 3H), 0.89 (d, *J*=6.9 Hz, 3H), 0.78 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4 (s), 151.6 (d), 143.1 (s, 2C), 142.9 (s), 142.8 (s), 141.3 (s, 4C), 127.9 (d), 127.8 (d), 127.7 (d, 2C), 127.2 (d, 2C), 127.1 (d, 2C), 125.0 (d, 4C), 120.0 (d), 119.9 (d, 4C), 94.8 (s), 83.5 (d), 78.4 (d, J^2_{C-P}=5.8 Hz), 69.4 (t, J^3_{C-P}=4.0 Hz), 69.3 (t, J^3_{C-P}=4.3 Hz), 65.1 (d), 47.9 (d, J^3_{C-P}=8.4 Hz), 47.8 (d, J^3_{C-P}=8.7 Hz), 43.9 (d, J^3_{C-P}=3.6 Hz), 33.8 (d), 30.6 (t, J^3_{C-P}=4.1 Hz), 30.3 (d), 28.4 (t), 14.7 (q), 10.7 (q), 9.1 (q), 1.1 (s).

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