Total Synthesis and Biological Evaluation of the Protein Phosphatase 2A Inhibitor Cytostatin and Analogues

Laurent Bialy[a, b] and Herbert Waldmann*[a, b]

Abstract: The total synthesis of the natural product cytostatin is described which inhibits protein phosphatase 2A. Cytostatin has anti-metastatic properties and induces apoptosis. On the basis of this synthesis the relative and absolute configuration of cytostatin could be assigned. Key structural elements of cytostatin are an α,β-unsaturated lactone group and a side chain embodying a phosphate and a rather unstable (*Z*,*Z*,*E*)-triene subunit. In addition, the natural product carries six stereocenters. For the construction of the stereocenters reagent-controlled transformations were used in order to ensure maximum stereochemical flexibility. The Evans *syn*-aldol reaction was chosen to establish the stereochemistry at C-4, C-5, C-9 and C-10; C-6 was introduced by means of the Evans asymmetric alkylation. In all cases the same chiral auxiliary was employed as stereodirecting group. The stereocenter at C-11 was established by an asymmetric reduction using CBS-oxazaborolidine. Temporary protection of the phosphate group was achieved best by using the base-labile 9-fluorenylmethyl group, which could be cleanly cleaved by an excess of triethylamine; this reaction yielded analytically pure phosphates after a simple aqueous work-up. The (*Z*,*Z*,*E*)-triene embodied in cytostatin was synthesized by means of a Stille coupling as key transformation. The synthesis sequence established in this way readily gave access to a series of analogues with simplified structure. Initial biological testing of these analogues proved that the α,β-unsaturated lactone, the C-11-hydroxy group and a fully deprotected phosphate moiety at C-9 are essential for the PP2A-inhibitory activity of cytostatin. The rather unstable triene moiety in the side chain can be replaced by other lipophilic residues with only moderate decrease of biological activity. Other phosphatases, that is, PP1, VHR, PTP1B, CD45, were not inhibited by cytostatin or any of the analogues, demonstrating the high selectivity of this compound. These findings will be useful for the design and synthesis of cytostatin-derived chemical tools for the study of biological processes influenced by PP2A.

Keywords: cytostatin · natural products · phosphorylation · protein phosphatases · total synthesis

Introduction

The reversible phosphorylation of proteins is employed by living organisms for the regulation of innumerable cellular processes, and aberrant protein phosphorylation contributes to the development of many human diseases, including cancer and diabetes.[1] Protein kinases (PKs) catalyze protein phosphorylation, whereas protein phosphatases (PPs) are responsible for dephosphoshorylation. PKs are established targets of drug discovery.[2] However, the development of small-molecule inhibitors of PPs is emerging only recently as a very rapidly growing area of investigation in clinical biology and medicinal chemistry.[3] Natural products, which have widely been used to antagonize PP action in biological experiments, can serve as invaluable starting points in structural space for the development of potent and selective PP inhibitors.[4] The serine-threonine phosphatase 2A (PP2A) is one of the most important and abundant phosphatases and is involved in the regulation of many crucial biological programs such as signal transduction cascades and the cell cycle. Several toxic and biologically active natural products have been identified as nanomolar PP2A inhibitors, in particular the diarrhetic shellfish poisoning toxin okadaic acid,[5] the microcystins[6] and calyculin.[7] However, the most selective PP2A inhibitors belong to the fostriecin family.[8–11] They show an unprecedented discrimination between the highly homologous serine-threonine phosphatases PP2A

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(IC_{50} 3.2 nM–3.7 μM) and PP1 (IC_{50} > 100 μM),[8d,9d,10c] accompanied by interesting biological activities such as anti-cancer[8f–i,9b] and thrombopoietic activity.[10d]

Cytostatin **1** was isolated from a new *Streptomyces* strain by Ishizuka et al.[9a] and belongs to the fostriecin family. It inhibits PP2A with an IC_{50} value of 210 nM,[9d] blocks the adhesion of B16 melanoma cells to components of the extracellular matrix (laminin and collagen),[9a] displays anti-metastatic and cytotoxic activity,[9] and induces apoptosis of B16 melanoma cells at submicromolecular concentrations.[9d] Ishizuka et al. determined the constitution of the natural product, but not its relative and absolute configuration.[9e] In order to develop chemical tools for the study of the biological phenomena influenced by PP2A we embarked on a total synthesis of cytostatin to prove the stereochemistry of the natural product, get access to a variety of more stable analogues and establish an initial structure–activity relationship (SAR).[12] Herein we disclose a full account of this synthesis, the assignment of the relative and absolute configuration of cytostatin **1** and the synthesis and biological evaluation of analogues of the natural product. These results demonstrate which structural features of cytostatin are required for PP2A inhibition.

Results and Discussion

Retrosynthesic analysis: In planning the synthesis, we drew from the structurally related fostriecin **2** and the phoslactomycins **3**, whose absolute configurations have been determined by NMR spectroscopy[8e,10b] and total synthesis (Figure 1).[13] Based on the assumption that these natural

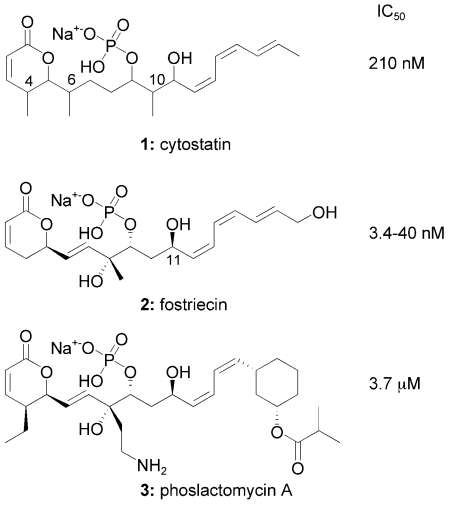


Figure 1. Members of the fostriecin class and IC_{50} values for the inhibition of protein phosphatase 2A (PP2A).

products might have been synthesized via similar biosynthetic pathways, the configuration of stereocenters 4, 5, 9, and 11 of cytostatin was chosen by analogy. The configuration of stereocenter 10 was chosen based on the reported coupling constant ($^3J = 9.4$ Hz) between H-10 and H-11.[9e] Assuming that an intramolecular hydrogen bond between O-9 and OH-11 is formed,[8e] one can deduce an *anti*-configuration between H-10 and H-11 based on the Karplus relationship (Figure 2). The configuration of stereocenter 6 was determined by synthesis of a short substructure of cytostatin.[14] The unknown configuration of cytostatin prompted us to design the synthesis with a high degree of flexibility to allow rapid and reliable variation of absolute and relative configuration if desired. Therefore, we chose to employ the asymmetric Evans aldol methodology (which gives access to *syn*- and *anti*-aldol products in both enantiomeric forms[15,16]), the asymmetric Evans alkylation,[17] and the enantioselective reduction of an acetylenic ketone (for which efficient reagent-controlled processes that give rise to both possible stereoisomers are known[18]) as synthesis methods for the generation of the stereocenters.

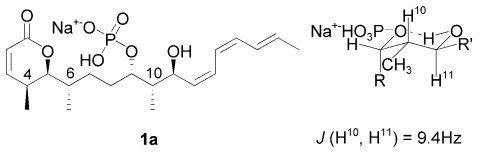


Figure 2. Proposed configuration of cytostatin.

Initial retrosynthesic analysis of (2*S*,3*S*,4*S*,9*S*,10*S*,11*S*)-cytostatin (**1a**) traced the molecule back to enediyne **4**, from which it should be accessible via partial hydrogenation (Figure 3). The enediyne can be dissected into alkyne **5** and alkynylhalide **6** (retro yne–yne coupling). The α,β-unsaturated lactone **5** was traced back to β-hydroxy aldehyde **7**, from which it should be accessible via Still–Gennari olefination[19] and subsequent lactonization. It was planned to generate both *syn*-diols (corresponding to C-4/C-5 and C-9 and C-10 in the natural product) by means of an asymmetric aldol reaction employing *N*-propionyloxazolidinone (**8**) and the chiral aldehyde **9**, which in turn is accessible by asymmetric alkylation of **8**.[17] Conversion of the double bond into an aldehyde group and a second aldol reaction employing again **8** as chiral auxiliary would then be carried out. Finally, transformation of the N-acyl group into an alkynyl ketone using trimethylsilylacetylene (**10**) as nucleophile followed by asymmetric reduction of the ketone would yield **7**.

Synthesis of the (*Z*,*Z*,*E*)-triene unit—model studies: The feasibility of the planned partial reduction of enediyne **4** was investigated employing a model analogue. Partial reduction of diynes has been carried out mainly by hydrogenation with the Lindlar catalyst[20] and zinc reduction.[21] Pent-1-yn-3-ol (**11**) was protected as *p*-methoxybenzyl ether **12** (Scheme 1). Trimethylsilylacetylene (**10**) and (*E*)-1-bromo-1-propene (**13**) were coupled in a Sonogashira reaction to yield trimethylsilylenyne **14**,[22] which was converted to bromoenyne **15**[23] by means of the Isobe protocol.[24] The attempted synthesis of the more reactive iodoalkyne led to formation of substantial amounts of the undesired (*Z*)-isomer. Enediyne **16a** was then generated by palladium-catalyzed coupling employing conditions previously described

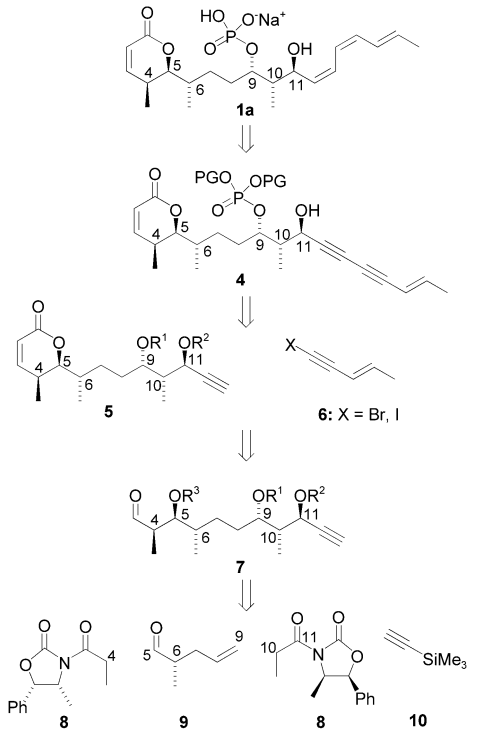
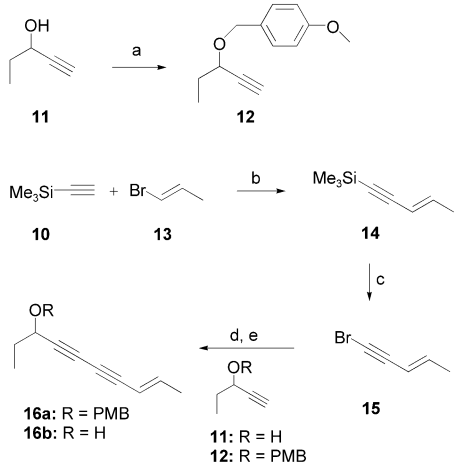


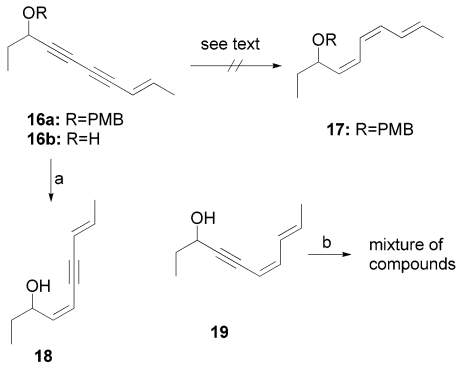
Figure 3. Retrosynthesic analysis of (2*S*,3*S*,4*S*,9*S*,10*S*,11*S*)-cytostatin **1a**.



Scheme 1. Synthesis of the model diynes **16a/b**: a) 1.1 equiv NaHMDS, THF, DMF, 0 °C, 30 min; 1.2 equiv PMBCl, 0.05 equiv $Bu_4N^+I^-$, room temperature, 16 h, 67 %; b) 0.05 equiv $[Pd(PPh_3)_4]$, 2 equiv NEt_3, 0.1 equiv CuI, THF, RT, 18 h, 69 %; c) 1.25 equiv NBS, 0.25 equiv $AgNO_3$, DMF, 0 °C→RT, 4 h; ca. 50 %; d) 0.03 equiv $[Pd_2(dba)_3]$, 0.25 equiv CuI, 0.2 equiv LiI, 4.2 equiv 1,2,2,6,6-pentamethylpiperidine, DMSO, room temperature, 0.66 equiv **11**, 19 h, 50 % (based upon **11**); e) 0.03 equiv $[Pd_2(dba)_3]$, 0.25 equiv CuI, 0.2 equiv LiI, 4.2 equiv 1,2,2,6,6-pentamethylpiperidine, DMSO, room temperature, 0.66 equiv **12**, 18 h, 56 % (based upon **12**).

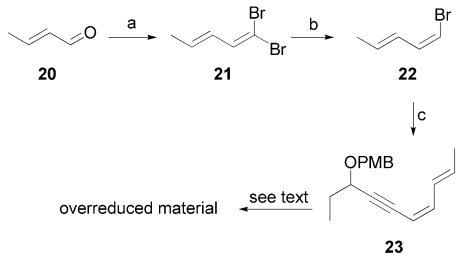
by Vasella et al.[25] The corresponding unprotected enediyne **16b** was synthesized similarly from **11** and **14**.

Unfortunately, all attempts to generate the corresponding (*Z*,*Z*,*E*)-triene **17** from **16** failed. Different reaction conditions using the Lindlar catalyst (palladium on charcoal, lead-poisoned),[26a] the Rosenmund catalyst (palladium on barium sulfate),[26b] freshly prepared Zn/Ag/Cu[27] and Zn with potassium cyanide[28] were examined and led to overreduction and isomerization of **16a** and **16b** to yield complex mixtures of compounds. In one case (with Zn/Cu/Ag), two products **18** and **19** generated from addition of one molecule H_2 were identified as main products by ^1H NMR and GC-MS (Scheme 2). However, further treatment of the mixture with fresh reagent and heating up led to a mixture of different reduced products which could not be further separated.



Scheme 2. Attempted partial reduction of the endiynes **16a,b** to the (*Z*,*Z*,*E*)-trienes: a) Zn/Cu/Ag, MeOH, RT, 14 h; b) Zn/Cu/Ag, MeOH, 55 °C, 24 h.

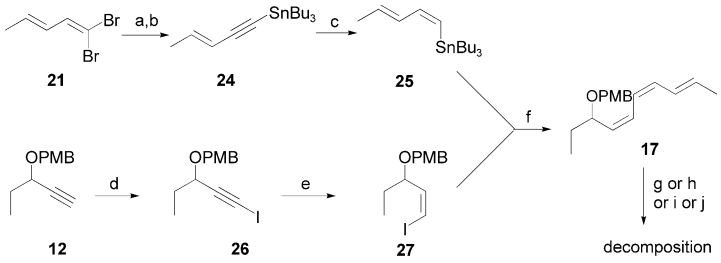
As alternative starting material for the hydrogenation dienyne **23** was investigated (Scheme 3). (*E*)-Crotonic aldehyde (**20**) was transformed to dibromoalkene **21** following



Scheme 3. Synthesis and attempted partial reduction of the dienyne **23** to the (*Z*,*Z*,*E*)-triene **17**: a) 2 equiv CBr_4, 4 equiv PPh_3, CH_2Cl_2, 0 °C, 8 min, 87 %; b) 0.04 equiv $[Pd(PPh_3)_4]$, 1.07 equiv Bu_3SnH, THF, room temperature, 2 h; c) 0.2 equiv **12**, 0.11 equiv CuI, DIPEA, THF, RT, 16 h, 36 % (based upon **12**).

the Corey–Fuchs protocol.[29] Selective reduction to (*Z*)-bromoalkene **22** and subsequent Sonogashira reaction with alkyne **12** yielded the desired dienyne **23**. This compound could not be selectively hydrogenated to triene **17**. Rather overreduced compounds were formed under all reaction conditions investigated. Similar difficulties were encountered in an early synthetic study towards fostriecin, although no detailed description of the results was given.[30]

At this stage we anticipated that a Stille coupling strategy,[31] which already had been successfully used to build up similar trienes,[32] would be a more promising methodology. For this purpose the dibromoalkene **21** was converted into the alkynylstannane **24** by the Corey–Fuchs protocol

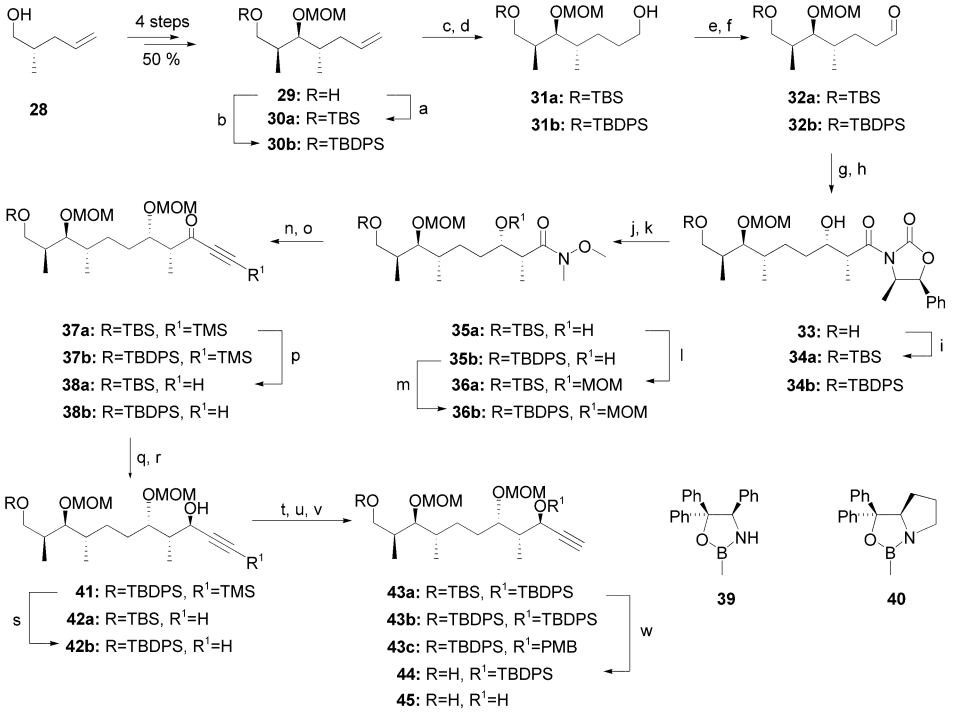


Scheme 4. Synthesis and attempted deprotection of the triene **17**: a) 2 equiv *n*BuLi, THF, −78 °C, 1 h, RT, 70 min; b) 1.05 equiv Bu_3SnCl, THF, −78 °C→RT, 15 h, 50 % over 2 steps; c) 2.25 equiv Cp_2ZrHCl, THF, RT, 30 min, silica gel, 99 %; d) 0.20 equiv $AgNO_3$, 1.25 equiv NIS, acetone, 4 h; 71 %; e) 1.88 equiv potassium azodicarboxylate, 4.32 equiv pyridine, 3.75 equiv HOAc in two portions, methanol, RT, 20 h, 92 %; f) 0.05 equiv $[Pd(CH_3CN)_2Cl_2]$, DMF/THF 28:1, RT, 16 h, 74 %; g) 2.4 equiv DDQ, CH_2Cl_2/H_2O 20:1, RT, 30 min; h) 2 equiv cerium ammonium nitrate, CH_3CN/H_2O 9:1, 0 °C, 45 min; i) 2 equiv $Ph_3C^+BF_4^-$, DCM/H_2O 5:1, 0 °C, 5 min; j) CH_2Cl_2/TFA/thioanisol 43:1:1, −15 °C, 30 min.

(Scheme 4). Reduction of stannane **24** to (*Z*)-alkenylstannane **25** was achieved by treatment with zirconocene hydrochloride (Schwartz's reagent).[33] Subsequent hydrolysis of the zirconium species was best carried out by filtration through silica gel. Aqueous work-up with saturated ammonium chloride solution led to substantial isomerization to the (*E*,*E*)-isomer. Alkynyliodide **26** was obtained by silver catalyzed iodination of alkyne **12**. Subsequent diimide reduction[34] yielded (*Z*)-alkenyl iodide **27**. Overreduction to the alkyl iodide could be largely suppressed by adding the reagents (potassium azodicarboxylate, acetic acid and pyridine) in two portions, careful monitoring of the reaction by GC-MS, and termination of the conversion when the amounts of alkinyl iodide and alkyl iodide present were comparable. The Stille coupling between **25** and **27** was effected under ligand-free conditions as described before[31] and yielded the desired (*Z*,*Z*,*E*)-triene **17** in high yield and stereoselectively. For this reaction, the addition of a small amount of THF as cosolvent proved to be necessary since stannane **25** is not soluble in DMF. Interestingly, the corresponding (*Z*)-bromoalkene did not react at all with stannane **25** (not shown).

The *p*-methoxybenzyl group could serve as a potential phosphate protecting group in the course of the synthesis.[35] Therefore, deprotection of triene **17** was investigated in order to find conditions for its removal which are compatible with the sensitivity of the triene moiety. Unfortunately acidic and oxidative conditions examined led to extensive decomposition of the material, probably by polymerization of the triene. These results suggest that an acidic cleavage of protecting groups should be avoided after installation of the triene moiety.

Synthesis of the C1–C13 fragment of (2*S*,3*S*,4*S*,9*S*,10*S*,11*S*)-cytostatin: After the general methodology for the synthesis of the triene moiety had been established the construction of the C1–C13 fragment was investigated (Scheme 5). Starting from the known alcohol **28** which was obtained by asym-



Scheme 5. Synthesis of the C3–C13 fragment with all stereocenters of (all-*S*)-cytostatin implemented: a) 1.3 equiv TBSCl, 3 equiv imidazole, DMF, room temperature, 15 h, 100 %; b) 1.2 equiv TBDPSCl, 2 equiv imidazole, DMF, RT, 17 h, 97 %; c) 1.1 equiv 9-BBN, THF, 0 °C, RT, 15 h, 3.5 equiv NaOH, H_2O_2, 24 h, RT, 83 % (**31a** from **30a**); d) 1.1 equiv 9-BBN, THF, RT, 19.5 h, 3.5 equiv NaOH, H_2O_2, RT, 24 h, 100 % (**31b** from **30b**); e) 2.6 equiv $(COCl)_2$, 6 equiv DMSO, CH_2Cl_2, −78 °C, 150 min, 7.5 equiv NEt_3, −78→0 °C (**32a** from **31a**); f) 1.5 equiv DMP, 11.5 equiv $NaHCO_3$, CH_2Cl_2, 1 h (**32b** from **31b**); g) 1.18 equiv Bu_2BOTf, 1.36 equiv $(iPr)_2NEt$, CH_2Cl_2, 0 °C, 1 h, −78 °C, **8**, 50 min, RT, 130 min, pH 7, H_2O, 0 °C, methanol, H_2O_2, H_2O, RT, 90 min, 89 % over 2 steps (**33** from **32a**); h) 1.2 equiv Bu_2BOTf, 1.35 equiv $(iPr)_2NEt$, CH_2Cl_2, 0 °C, 45 min, −78 °C, **8**, RT, 90 min, H_2O_2, pH 7, 43 % over 2 steps (**34b** from **31b**); i) 2 equiv TBSCl, 4 equiv NEt_3, 0.1 equiv DMAP, CH_2Cl_2, 0 °C, 30 min, RT, 15 h, 97 %; j) 4.6 equiv Me_3Al, 5 equiv $Cl^-{}^+H_2N(Me)OMe$, THF, −20→0 °C, 15 h, 84 % (**35a** from **34a**); k) 5 equiv Me_3Al, 5 equiv $Cl^-{}^+H_2N(Me)OMe$, THF, −10→0 °C, 15 h (**35b** from **34b**); l) 10 equiv MOMCl, 13 equiv $(iPr)_2NEt$, CH_2Cl_2, 0 °C, 1 h, RT, 18 h, 94 %; m) 10 equiv MOMCl, 13 equiv $(iPr)_2NEt$, CH_2Cl_2, 0 °C, 1 h, RT, 19 h, 86 % over 2 steps; n) 3 equiv BuLi, 6 equiv $Me_3SiC{\equiv}CH$, THF, −78→−10 °C, 75 min (**37a** from **36a**); o) 3 equiv BuLi, 6 equiv $Me_3SiC{\equiv}CH$, THF, −78→−10 °C, 45 min, 84 % (**37b** from **36b**); p) 0.01 equiv $Na_2B_4O_7$/methanol 5:1, −10 °C→RT, 70 min, 95 % over 2 steps; q) 2 equiv **40**, 5 equiv $BH_3{\cdot}Me_2S$, THF, −30 °C, 1 h, 84 % (**42a** from **38a**); r) 1 equiv **39**, 1.2 equiv $BH_3{\cdot}Me_2S$, THF, 0 °C, 40 min, 71 % (**41** from **38b**); s) 1.1 equiv K_2CO_3, MeOH, 22 h, 84 %; t) 1.35 equiv TBDPSCl, 2.5 equiv Imidazole, DMF, 15 h, RT (**43a** from **42a**); u) 1.5 equiv TBDPSCl, 2.5 equiv imidazole, DMF, 21 h, 86 % (**43b** from **42b**); v) 1.1 equiv NaHMDS, DMF, 0 °C, 30 min, 1.2 equiv PMBCl, 0.05 equiv $Bu_4N^+I^-$, RT, 24 h, 30 %; w) 70 % HF/py/THF 1:10, room temperature, 40 min, 88 % over 2 steps.

metric Evans alkylation followed by reduction,[17] alcohol **29** was synthesized by oxidation to the corresponding aldehyde, Evans aldol reaction with **8**, MOM protection of the aldol product and reduction of the acyloxazolidinone.[14] For protection of the primary hydroxy function, initially the TBDPS (*tert*-butyldiphenylsilyl) group was examined. However, further progression of the synthesis prompted us to use TBS (*tert*-butyldimethylsilyl) group instead (see below). Therefore, the synthesis of both the TBS and TBDPS protected compounds is described together to allow for a better comparison of the results. Protection of alcohol **29** as silyl ether to give **30a** (TBS ether) and **30b** (TBDPS ether) turned out to be straightforward. After hydroboration with 9-BBN followed by oxidative work-up, alcohols **31a** and **31b** were oxidized by the Swern method[36] (for **32a**) or with the Dess–Martin periodinane[37] (for **32b**). In our hands this hypervalent iodine compound gave a higher yield than the tetrapropylammonium perruthenate catalyzed oxidation developed by Ley et al.[38] Next, a *syn*-selective Evans aldol reaction with freshly distilled dibutylboryl triflate and Hünig's base was carried out. The commercially available solutions of dibutylboryl triflate gave unreproducible results. Surprisingly, the TBS group was cleaved off in the course of the reaction (yielding diol **33**), whereas this was not the case for the TBDPS compound; **34b** was obtained in high yield and with complete stereoselectivity. Fortunately, selective reprotection of the primary hydroxy group was possible using TBSCl, triethylamine and catalytic amounts of DMAP (*N*,*N*-dimethylaminopyridine) in dichloromethane to give the desired silyl ether **34a** in high yield. Standard procedures were used for the conversion of the oxazolidinones **34a,b** to the Weinreb amides[17,39] **35a,b** and the MOM ethers **36a,b**. The Weinreb amides were then converted to alkynyl ketones which were suitable for an asymmetric reduction to the corresponding alkynols. Initial attempts with commercial bromomagnesium acetylide were unsuccessful. Upon treatment with lithium trimethylsilyl acetylide, prepared in situ from *n*-butyllithium and trimethylsilylacetylene (**10**), the TMS-protected alkynones **37a**,**b** were obtained in high yields. However, varying amounts of the terminal alkynones **38a** and **38b** were detected. These compounds are probably generated through TMS cleavage by impurities in the butyllithium solutions used. For example, lithium hydroxide could cleave the TMS group from **37a**,**b**.

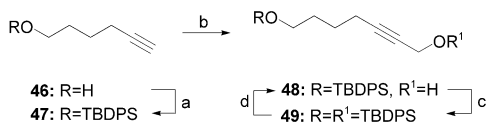
We therefore searched for a method to convert the mixtures of protected and deprotected alkynones to the deprotected alkynes. Treatment with potassium carbonate in methanol led to rapid decomposition of alkynone **37a**. Exposure of alkynone **37a** to catalytic amounts of borax (sodium tetraborate) in aqueous methanol[40] at room temperature surprisingly led to substantial decomposition (up to 50%) via β-elimination of the MOM-protected hydroxy group. Finally, it was discovered that slow addition of the aqueous borax solution to a solution of alkynol **37a** in methanol precooled to −10°C followed by warming to room temperature, yielded deprotected alkynol **38a** in very high yield and purity. This modified procedure may be generally useful for deprotection of TMS-alkynones prone to β-elimination.

Next the asymmetric reduction of the ketone at C-11 was investigated. In initial experiments with Midland's Alpine borane[18a] no conversion of alkynone **37a** was observed, which is probably due to steric hindrance. Reduction with (*R*)-phenylglycine-derived oxazaborolidine **39**, which has been reported to reduce TMS-alkynones with high stereoselectivity,[18e] gave varying yields of alkynol **41** (71% in the best case). However, problems were encountered in the purification of the product, especially since **41** could hardly be separated from the chiral ligand by column chromatography. Fortunately, Corey's methyl CBS oxazaborolidine **40**[18c,d] gave good yields of alkynol **42a** with complete stereoselectivity. The C-13 epimer could not be detected by ^{1}H NMR spectroscopy. The TBDPS-analogue **42b** could be obtained via deprotection of TMS-protected alkynol **41** with potassium carbonate in methanol.

Next, the protection of the C-11-hydroxy group was investigated. The protecting group should be orthogonally stable to the silyl protecting group of the primary alcohol and resist the planned acidic deprotection of the MOM groups. The first candidate which was examined was the PMB group, which should be more stable under acidic conditions than the MOM groups.[41] However, deprotonation of the alcohol with a strong base such as sodium hexamethyldisilazide (NaHMDS) and subsequent treatment with *p*-methoxybenzyl chloride in the presence of catalytic amounts of tetrabutylammonium iodide[42] gave PMB ether **43c** in only poor yield (30%). Under those conditions, migration and cleavage of the TBDPS group by the intermediate alcoholate probably occurred, leading to a mixture of compounds. Protection with PMB-trichloroacetimidate under various acidic conditions (0.02 equiv triflic acid in diethyl ether, 0.1 equiv camphorsulfonic acid in dichloromethane or 0.05 equiv $BF_3{\cdot}Et_2O$ complex in dichloromethane) was only sluggish. Under forced conditions, the starting compound decomposed. An alternative protecting group would be the *p*-methoxyphenyl group.[43] However, no reaction was observed when alcohol **42b** was treated with 4-methoxyphenol under Mitsunobu conditions (PPh_3, DEAD, THF, 90°C). Next, silyl protecting groups were examined. The TIPS (triisopropylsilyl) group should be more stable than the TBDPS group under basic deprotection conditions[44] and than the MOM protecting groups under acidic conditions. Unfortunately, the attempted protection of the C-11 OH group in **42b** by treatment with TIPSCl and imidazole in DMF was not successful even at 90°C. A further possibility was offered by the TBDPS group, which should be more stable at the C-11 position than the primary TBDPS-group at C-3 due to steric hindrance. Gratifyingly and—in the light of the difficulties encountered with the other protecting groups examined—quite surprisingly, treatment of **42b** with TBDPSCl and imidazole in DMF gave the bis-silyl ether **43b** in 86% yield.

The selective mono-deprotection of the bis(TBDPS)-ether **43b** turned out to be problematic. Upon treatment with TBAF, no selectivity was observed. A low selectivity for the desired TBDPS ether **44** was observed with the HF/pyridine complex. Surprisingly, a reversed selectivity was observed with ammonium fluoride in methanol: the secondary

TBDPS group was cleaved off *faster* than the primary silyl ether. This result may be due to the propargylic character of the C-11-OTBDPS group. To test this hypothesis a diol with two primary TBDPS-protected hydroxy groups was synthesized (Scheme 6). Hex-5-yn-1-ol (**46**) was protected as

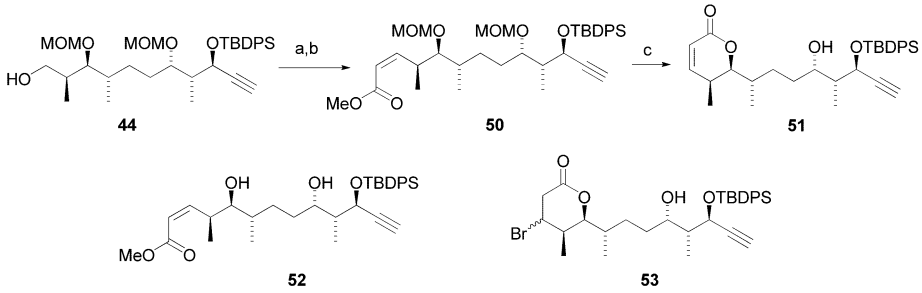


Scheme 6. Selective deprotection of a propargylic silyl ether: a) 1.2 equiv TBDPSCl, 3 equiv imidazole, DMF, room temperature, 48 h, 95%; b) 1.2 equiv BuLi, THF, −40°C, 1 h, 3 equiv $1/x(HCHO)_x$, −78°C→RT, 5 h, 70%; c) 1.2 equiv TBDPSCl, 3 equiv imidazole, DMF, room temperature, 15 h, 90%; d) 10 equiv NH_4F, MeOH, room temperature, 8 h, 82%.

TBDPS-ether **47**, then hydroxymethylated to alcohol **48** which was protected to give the bis(TBDPS)-ether **49**. Treatment of **49** with ammonium fluoride in methanol yielded the expected alcohol **48** in a non-optimized yield of 82%. These results are in accordance with previous observations showing that allylic silyl-protected alcohols can be deprotected selectively in the presence of other silyl-protected alcohols.[45]

Application of neutral alumina,[46] which has been reported to deprotect primary silyl ethers selectively, was tested but failed to deprotect **43b**. Finally, it was decided to change the silyl protecting group at C-3 to the more labile TBS group. Gratifyingly, the TBS group of compound **43a** could be removed in a highly selective manner by treatment with HF/pyridine for 40 min with a yield of 88% (over two steps from **42a**).

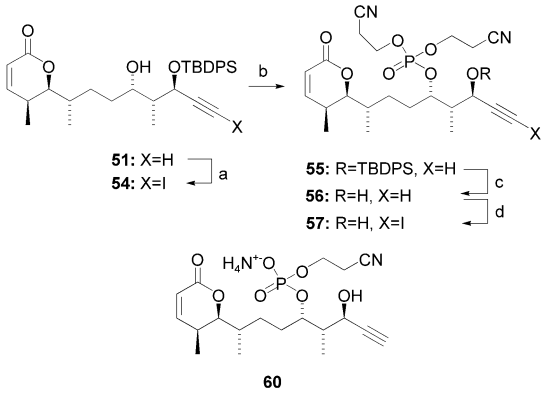
The synthesis of the lactone fragment of the natural product is depicted in Scheme 7. Alcohol **44** was oxidized with the Dess–Martin periodinane. The resulting aldehyde was submitted to a (*Z*)-selective Still–Gennari olefination to yield ester **50** in high yield and complete stereoselectivity. No (*E*)-isomer was detected. It was planned to synthesize lactone **51** by selective acid-mediated cleavage of the MOM-protecting groups and concomitant ring closure. While treating ester **50** with TMS-bromide for 1 h at −30°C in dichloromethane yielded deprotected ester **52** along with starting material, treatment of this mixture with TMS-bromide again at 0°C for 40 min gave a 40:60 epimeric mixture of the bromides **53**, probably resulting from a Michael addition of bromide ion to the unsaturated lactone **51**. In contrast, heating ester **50** with tetrabromomethane in 2-propanol[47] led to a clean reaction and a high yield of the desired lactone **51**. In this transformation probably HBr is generated slowly thereby establishing conditions mild enough to deprotect MOM groups in the presence of the TBDPS-ether.



Scheme 7. Synthesis of the lactone **51**: a) 1.5 equiv DMP, 11.5 equiv $NaHCO_3$, CH_2Cl_2, RT, 85 min; b) 2 equiv $(CF_3CH_2O)_2P(O)CH_2C(O)OMe$, 4 equiv [18]crown-6, 1.5 equiv KHMDS, THF, −78°C, 35 min, aldehyde, −78°C, 260 min, 86% over 2 steps; c) 0.5 equiv CBr_4, 2-propanol, 82°C, 14 h, 83%.

Completion of the synthesis—Choice of the right phosphate protecting group: For completion of the synthesis the transformation of the alkyne moiety in **51** into a (*Z*)-alkenyl iodide suitable for the planned Stille coupling, the deprotection and phosphorylation of the C-11-hydroxy group, and the Stille coupling were considered the major problems to be solved. It was planned to assemble the triene at a late stage and to deprotect the phosphotriester at C-11 in the final step to allow for facile purification of the intermediates. Since acid-mediated deprotection of model triene **17** led to extensive decomposition of the compound, an acid-labile phosphate protecting group was ruled out. A Pd^0 labile protecting group such as the allyl group[48] would not be compatible with the Stille coupling. A protecting group sensitive to hydrogenation such as the benzyl group would also not be a good choice due to the presence of the triene unit. Therefore, base-labile protecting groups were investigated which should be compatible to all structural features of the molecule (for a detailed discussion see below). The first choice was the well-established β-cyanoethyl group.[49]

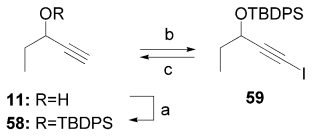
Iodination of alkyne **51** to alkynyl iodide **54** (Scheme 8) could not be effected by treatment of **51** with *N*-iodosuccinimide and catalytic amounts of silver nitrate probably due to steric hindrance by the adjacent TBDPS group. In contrast,



Scheme 8. Synthesis of the phosphorylated alkynyl iodide **57**: a) I_2, 5 equiv 15 equiv DMAP, toluene, 50°C, 3 h, 76%; b) 6.1 equiv $(\beta\text{-CE})_2P\text{-N}i\text{Pr}_2$, 4.45 equiv tetrazole, CH_3CN, 0°C→RT, 105 min; 6.1 equiv I_2, THF/pyridine/H_2O 7:2:1, RT, 5 min, quantitative (starting from **51**); c) 70% HF·pyridine/THF 17:83, RT, 24 h, 84%; d) 1.5 equiv NIS, 0.15 equiv $AgNO_3$, DMF, RT, 90 min, 88%.

treatment with iodine and morpholine in toluene at 50 °C for 2.5 h (60 % yield) or with iodine and DMAP (76 %) was successful.

At this stage of the synthesis it was decided to introduce the phosphate in order to get access to diverse phosphorylated analogues for biological screening. For this purpose phosphoramidite chemistry was employed.[51] However, upon treatment of alcohol **54** with $(NCCH_2CH_2O)_2PN(iPr)_2$ and tetrazole in acetonitrile and subsequent oxidation with hydrogen peroxide, surprisingly the *deiodinated*, phosphorylated compound **55** was isolated. Changing the oxidant to iodine in a pyridine/water solution, also resulted in a clean conversion to **55** (71 % yield). Thus, we speculate that the phosphoramidite, a phosphorous(III) reagent, had reduced the iodoalkyne to the terminal alkyne in the presence of an acid (in this case tetrazole). To test this hypothesis, a simple alkynyl iodide was synthesized and exposed to an excess of triphenylphosphine in the presence of tetrazole in acetonitrile. The corresponding terminal alkyne was obtained in quantitative yield. To our knowledge, this is the first report on the reduction of a iodoalkyne by phosphorous reagents such as triphenylphosphine (Scheme 9).



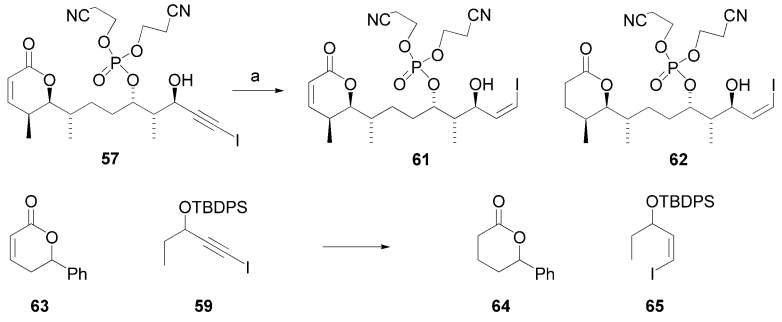
Scheme 9. Reduction of a iodoalkyne with triphenylphosphine: a) 1.2 equiv TBDPSCl, 2 equiv imidazole, DMF, RT, 77 %; b) 1.25 equiv NIS, 0.2 equiv $AgNO_3$, acetone, RT, 4.5 h; 96 %; c) PPh_3, tetrazole, CH_3CN, quantitative.

Consequently the reaction sequence was reversed and alkyne **51** was treated with phosphoramidite $(\beta\text{-CE})_2PNiPr_2$ and subsequently oxidized to phosphotriester **55**. Because of the base lability of the β-cyanoethyl group, the conditions established for the synthesis of alkynyliodide **54** could not be adopted. The C-13-OTBDPS group was removed before iodination to reduce the steric hindrance. To avoid simultaneous cleavage of the base-labile phosphate protecting group, acidic conditions had to be used. Ammonium fluoride in methanol led to the removal of one β-cyanoethyl group, to give phosphodiester **60** (Scheme 8). Treatment of **55** with tetrabutylammonium fluoride (TBAF) in the presence of an excess (400 equivalents) of acetic acid[52] resulted in no conversion. Finally, the use of the HF/pyridine complex (70 % HF) in THF led to a high yield of the desired alcohol **56**. Iodination of alkyne **56** with *N*-iodosuccinimide in the presence of catalytic amounts of silver nitrate gave a high yield of the desired iodoalkyne **57**.

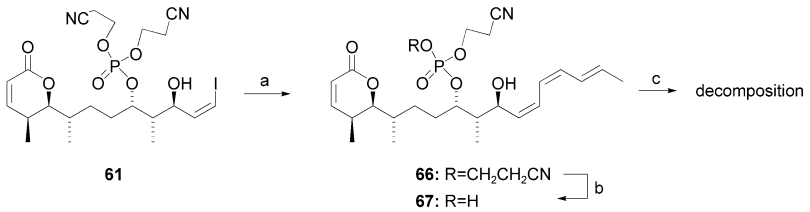
With iodoalkyne **57** at hand, the diimide reduction to the (*Z*)-iodoalkene was investigated. Treatment with diazodicarboxylate, acetic acid and pyridine in methanol led to a very low yield along with extensive decomposition of the starting compound (not shown). This was traced back to reduction of the lactone double-bond, giving the saturated lactone **62** and probably to nucleophilic attack of hydrazine, which can be formed by disproportionation of diimide,[26c] to the α,β-unsaturated lactone. This would lead to water-soluble compounds. The last reaction was thought to be the main side reaction, as considerable loss of material was observed during diimide reduction of **57**. Conditions for the diimide reduction were optimized employing a mixture of model compounds **59** and **63**,[53] and after variation of the solvent (CH_3CN, DMSO, dioxane, 2-propanol), equivalents of HOAc and azodicarboxylate added and reaction time conditions were found under which the desired vinyl iodide **61** was obtained in 44 % isolated yield (Scheme 10).

(*Z*)-Alkenyliodide **61** was then subjected to reaction conditions developed for the synthesis of the model triene **17** (Scheme 11), and bis(β-cyanoethyl)protected cytostatin **66** was obtained in 40 % yield by Stille coupling with stannane **25** in the presence of catalytic amounts of tris(dibenzylideneacetone)dipalladium.

For the final deprotection of bis-cyanoethyl cytostatin problems were expected since phosphotriesters are readily cleaved to phosphodiesters under basic conditions followed by a much slower cleavage of the second phosphoester

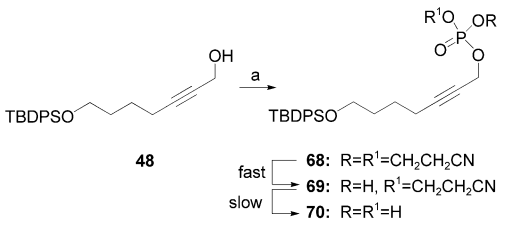


Scheme 10. Reduction of alkynyl iodide **57** to vinyl iodide **61**: a) 2 equiv $K^+{}^-OOC{-}N{=}N{-}COO^-{}^+K$, 4 equiv HOAc, 2-propanol, RT, 24 h, 44 % (**61**) and 9 % (**62**).



Scheme 11. Stille coupling and attempted deprotection of β-cyanoethyl protected (all-*S*) cytostatin: a) 1.3 equiv **25**, 0.05 equiv $[Pd_2(dba)_3{\cdot}CHCl_3]$, DMF/THF 20:1, RT, 14 h, 40 %; b) 8 equiv DBU, 4 equiv TMSCl, CH_2Cl_2, room temperature, 8 h; c) (*N,O*)-bis-trimethylsilyl-acetamide, CH_2Cl_2, $h\tilde{\nu}$, 12 equiv DBU, CH_2Cl_2.

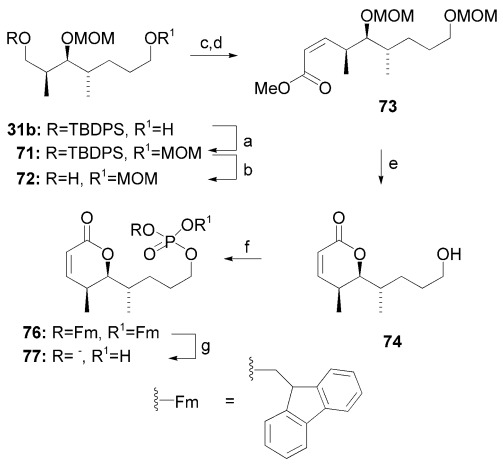
group.[54] Indeed, conditions for the complete deprotection of both cyanoethyl esters are harsh[55] and competing attack at the unsaturated lactone was feared. To find conditions compatible with this structural element, model compound **68** was synthesized and exposed to a variety of different conditions (Scheme 12). However, use of different amines



Scheme 12. Model reactions for the deprotection of bis(β-cyanoethyl) phosphate triesters under non-nucleophilic conditions: a) 2 equiv tetrazole, 2 equiv $(NCCH_2CH_2O)_2PN(iPr)_2$, CH_3CN, 3 h, room temperature; 2 equiv I_2, pyridine/H_2O/THF, 5 min, room temperature, 74%.

(Me_2NEt, $tBuNH_2$) in different solvents (CH_3OH, 2-propanol, DMF, neat, pyridine, acetonitrile) led to formation of diester **69**. Application of Me_2NEt/H_2O 1:1 for five days gave the desired phophate **70** in quantitative yield but exposure of **51** to these reaction conditions resulted in conjugate addition of hydroxide to the enoate and ring opening. Finally, the use of a base (NEt_3, DBU) together with TMSCl (to temporarily mask the intermediary formed phosphodiester) developed by Evans et al. in the synthesis of calyculin[54] was investigated. Indeed, **68** was converted to **70** when DBU/TMSCl was applied but under these conditions bis-cyanoethyl cytostatin **66** was only deprotected once. In the light of these findings the use of the cyanoethyl phosphate protecting groups had to be abandoned.

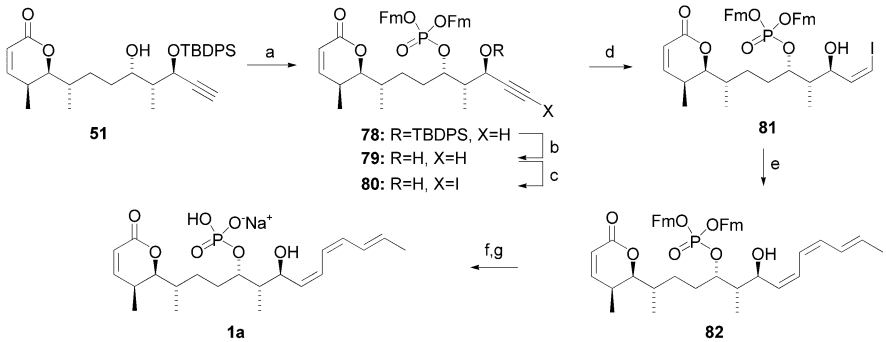
The 9-fluorenylmethyl group was demonstrated by Watanabe et al. to be an efficient base-labile phosphomonoester protecting group, allowing for complete deprotection of bis(9-fluorenylmethyl) protected phosphotriesters by means of an excess of triethylamine under anhydrous conditions.[56] The suitability of this protecting group for the completion of the cytostatin synthesis was investigated with a truncated, C1–C9 fragment of cytostatin (Scheme 13). To this end, alcohol **31b** was protected as MOM ether protected to give **71**. After cleavage of the TBDPS group, the alcohol **72** obtained was oxidized to the corresponding aldehyde which was immediately subjected to a Still–Gennari olefination to yield the (*Z*)-configured unsaturated ester **73**. Upon heating in aqueous HCl and THF, lactone **74** was formed. Phosphorylation with phosphoramidite $(FmO)_2PNiPr_2$ (**75**) and subsequent oxidation with *m*-chloroperbenzoic acid (*m*CPBA)



Scheme 13. Investigation of the 9-fluorenylmethyl group on a C1–C9 fragment of cytostatin: a) 10 equiv MOMCl, 13 equiv $(iPr)_2NEt$, CH_2Cl_2, 0°C, 1 h, room temperature, 13 h; b) 1.2 equiv TBAF, THF, room temperature, 15 h, 90% over 2 steps; c) 1.5 equiv Dess–Martin periodinane, 11.5 equiv $NaHCO_3$, CH_2Cl_2, room temperature, 90 min; d) 2 equiv $(CF_3CH_2O)_2P(O)CH_2C(O)Me$, 4 equiv 18-crown-6, 1.5 equiv KHMDS, THF, −78°C, 35 min, aldehyde, −78°C, 3 h, 80% over 2 steps; e) 1 N HCl, H_2O, THF, 15 h, 60°C, 88%; f) 4 equiv $(iPr_2)NP(OFm)_2$ (**75**), 3 equiv tetrazole, CH_2Cl_2, 270 min, 10 equiv m-CPBA, −78°C, 0°C, 90 min; 88%; g) NEt_3/CH_3CN 1:4.8 *v/v*, room temperature, 18 h, 75%.

gave the desired phosphotriester **76**. Gratifyingly, treatment of **76** with an excess of triethylamine in acetonitrile gave completely deprotected compound **77** in high yield.

Encouraged by these results, the reaction sequence developed for the synthesis of cytostatin was carried out by analogy (Scheme 14). Phosphorylation of alcohol **51** with phosphoramidite **75** had to be performed in a mixture of dichloromethane and acetonitrile. Phosphoramidite **75** is only very poorly soluble in acetonitrile, but in CH_2Cl_2 no conversion was observed. TBDPS deprotection of phosphotriester **78** could be effected in high yield by using a higher concentration of HF/pyridine in THF and longer reaction times in comparison to the β-cyanoethyl protected phosphotriester **55**. This lower reactivity is probably due to higher steric hindrance due to the presence of the larger neighboring 9-fluo-

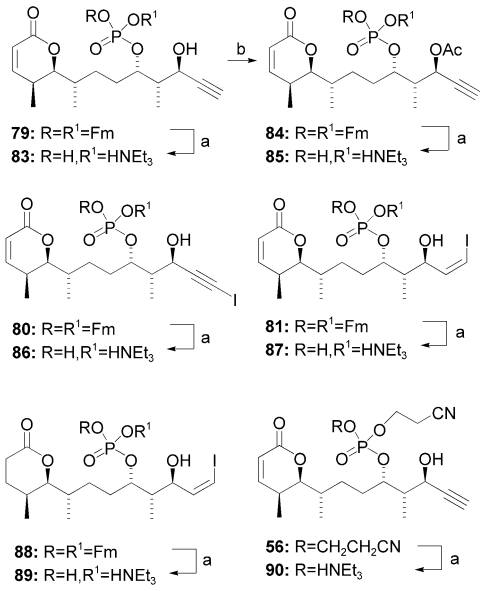


Scheme 14. Final steps of the total synthesis: a) 3 equiv $(iPr)_2NP(OFm)_2$, 2.7 equiv tetrazole, CH_3CN/CH_2Cl_2 5:4 *v/v*, RT, 330 min, 3 equiv I_2, THF/pyridine/H_2O 7:2:1 (v/v), 5 min, 95%; b) HF/py/THF 1:4.75 *v/v*, RT, 24 h, then 1:2.4, room temperature, 8 h, 82%; c) 1.5 equiv NIS, 0.15 equiv $AgNO_3$, DMF, 90 min, 100%; d) 1.73 equiv $K^+(^-OOCN{=}NCOO^-)^+K$, 3.47 equiv HOAc, 2-propanol/dioxane 11:1 *v/v*, 870 min, 63% (**81**), (and 21% **80**); e) 4.3 equiv $(iPr_2)NP(OFm)_2$ (**75**), 0.24 equiv $[PdCl_2(CH_3CN)_2]$, DMF/THF 17:1 *v/v*, RT, 20.5 h, 62%; f) NEt_3/CH_3CN 2:9 *v/v*, RT, 20 h, quantitative; g) Na^+-Dowex, MeOH/H_2O 1:1 *v/v*, 85%.

renylmethyl groups. The synthesis of iodoalkyne **80** by reaction of **79** with *N*-iodosuccinimide (NIS) and a catalytic amount of silver nitrate in DMF was straightforward. The diimide reduction could not be effected in 2-propanol as developed for the β-cyanoethyl protected compound **57** due to the insolubility of iodoalkyne **80** in the solvent. However, this problem was readily solved by addition of a small amount of dioxane as cosolvent. Use of 2-propanol/dioxane (11:1) gave a 63% yield of (*Z*)-iodoalkene **81** if the reaction was stopped before the entire starting material had been consumed (21% **80** recovered). The Stille coupling was performed under ligand-free conditions with stannane **25** and a catalytic amount of bis(acetonitrile)palladium(II) chloride and triene **82** was isolated in 62% yield after reversed-phase HPLC. Gratifyingly, deprotection of the triester **82** proceeded smoothly under the conditions developed for the truncated compound **76**, that is, with an excess of triethylamine in acetonitrile. The obtained monotriethylammonium salt was converted to the sodium salt **1a** by ion-exchange filtration over Dowex resin.

To verify that the relative configuration of (2*S*,3*S*,4*S*,9*S*,10*S*,11*S*)-cytostatin **1a** was chosen correctly, we made a direct NMR comparison of **1a** with a sample of the isolated natural product[57] by mixing synthetic and natural cytostatin in equimolar amounts. ^{1}H NMR, ^{31}P NMR and ^{13}C NMR spectroscopic (determined by HSQC) examination in CD_3OD proved spectroscopic identity of the two compounds. Unfortunately, the sample of the isolated material provided by Ishizuka was seriously contaminated with impurities which could not be removed by reversed-phase HPLC. The optical rotation of the isolated sample ($[\alpha]_D^{20} = +20$ ($c = 0.265$, methanol)) was lower than the value recorded for synthetic **1a** ($[\alpha]_D^{20} = +46$ ($c = 0.265$, methanol)). However, in the light of the NMR spectroscopic identity of the compounds and the fact that the specific rotation is positive for both samples we propose that the absolute configuration of natural cytostatin is (4*S*,5*S*,6*S*,9*S*,10*S*,11*S*).

Synthesis of cytostatin analogues: After successful completion of the total synthesis a set of analogues of the natural product was prepared in order to unravel the decisive structural parameters of cytostatin. To this end, several synthesis intermediates and model compounds were deprotected. Since the phosphate moiety of the natural product is indispensable for inhibition of PP2A,[9d] it was decided to investigate only phosphorylated analogues. The C1–C9 fragment of cytostatin **77** was synthesized as shown in Scheme 13. The synthesis of the other derivatives is depicted in Scheme 15. All fluorenylmethyl-deprotection reactions were carried out under the conditions described above, that is, with an excess of triethylamine in acetonitrile and yielded analytically pure compounds after simple aqueous work up. Alkyne **79**, iodoalkyne **80** and (*Z*)-iodoalkene **81** were converted to compounds **83**, **86** and **87** in very high yields. To evaluate the importance of the C-11-hydroxy function, alcohol **79** was acetylated with acetic anhydride in the presence of catalytic amounts of DMAP in pyridine to give acetate **84**. Deprotection yielded compound **85** acetylated at C-11. The saturated lactone **88** was formed in small amounts as by-product in



Scheme 15. Synthesis of cytostatin analogues: a) NEt_3/CH_3CN 1:4.6 *v*/*v*, room temperature, 15 h, 98% (**83**), 49% (**85**), quantitative (**86**, **87**), 92% (**89**), 85% (**90**); b) Ac_2O, pyridine, cat. DMAP, 1 h, 60%.

the course of the diimide reduction of **80**. It was deprotected to give compound **89** in order to shed light on the importance of the electrophilic double bond in the lactone moiety of the natural product. Finally, the bis(β-cyanoethyl) protected compound **56** was selectively monodeprotected to diester **90** by treatment with an excess of triethylamine in acetonitrile. Investigation of this compound would show if the phosphate needs to be fully deprotected in order to ensure PP2A inhibitory activity.

Biological evaluation of cytostatin analogues: The cytostatin analogues were evaluated by means of in vitro inhibition assays of the serine-threonine phosphatases of type 2A (PP2A) and 1 (PP1). These are of particular interest because cytostatin has been described as a highly selective PP2A-, but not PP1 inhibitor.[9d] In addition, the inhibition of protein tyrosine phosphatases PTP1B (which is considered as a potential target for diabetes therapy[58]) and CD45 (a positive regulator of T-cell activation and therefore a potential target for treatment of autoimmune diseases and suppression of graft rejection[59]), and the dual-specifity phosphatase VHR (which dephosphorylates ERK, a member of the ras signal transduction pathway[60]) was examined. The enzymatic activity was determined by hydrolysis of *p*-nitrophenyl phosphate (*p*-NPP) in standard buffers for PP2A1, PP1, VHR, PTP1B, and a commercially available peptide for CD45 (see the Experimental Section).

Under the conditions described by Ishizuka et al.,[9d] only low enzymatic activity of PP2A in the hydrolysis of *p*-NPP was observed. A much higher activity could be obtained by using a different buffer at a higher pH value (8.1).[61] The inhibition curves determined for the inhibition of $PP2A_1$ are shown in Figure 4, the determined IC_{50} values are given in Table 1. Synthetic cytostatin **1a** displays an IC_{50} value of 33 nM which is about seven times smaller than the value re-

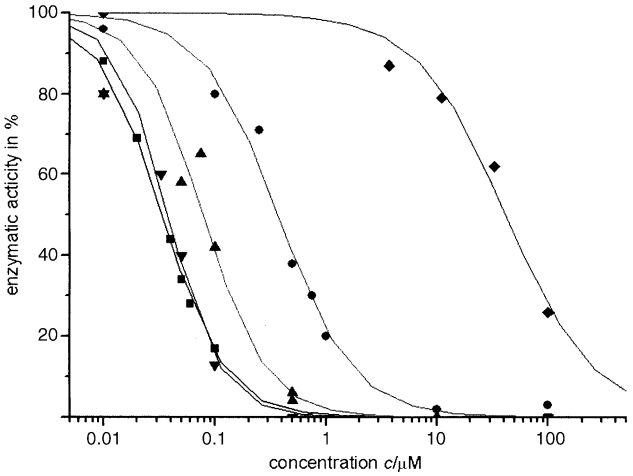


Figure 4. $PP2A_1$ inhibition by cytostatin analogues **1a** (■), **83** (●), **86** (▲), **89** (▼), and **90** (◆).

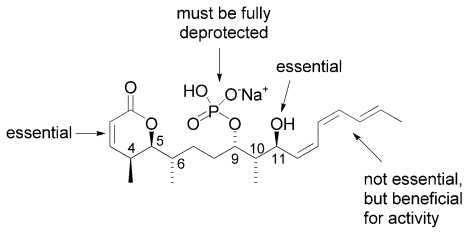


Figure 5. Structure–activity relationship for cytostatin ($PP2A_1$ inhibition).

Table 1. IC_{50} values [μM] for inhibition of different phosphatases with cytostatin analogues.[c]

Entry	Compound	$PP2A_1$	PP1	VHR	PTP1B	CD45
1	**1a**	0.033 ± 0.003	>20[a]	>20[a]	>20[a]	>20[a]
2	**77**	>100[a]	>100[a]	>100[a]	>100[a]	>100[a]
3	**83**	0.37 ± 0.05	>100[a]	>100[a]	>100[a]	>100[a]
4	**85**	>100[a]	>100[a]	>100[a]	>100[a]	n.i.[b]
5	**86**	0.079 ± 0.009	>100[a]	>100[a]	>100[a]	n.i.[b]
6	**87**	0.039 ± 0.004	>100[a]	>100[a]	>100[a]	n.i.[b]
7	**89**	ca. 100	>100[a]	>100[a]	>100[a]	n.i.[b]
8	**90**	42 ± 7	>100[a]	>100[a]	>100[a]	n.i.[b]

[a] Highest concentration investigated. [b] Not investigated. [c] IC_{50} values were calculated on the basis of at least three determinations.

ported for the isolated compound. Two reasons can be invoked to explain this deviation: 1) We used an enzyme from a different source than Ishizuka et al. (see Experimental Section), 2) we used different assay conditions (buffer, pH value) than Ishizuka et al. The truncated cytostatin analogue **77** (C1–C9) is totally inactive (entry 2). The shortened fragments of the natural product show a lower activity against PP2A, albeit still in the submicromolecular range. It is interesting to note that alkyne **83** is less active than the more hydrophobic iodoalkyne **86**. This analogue in turn is less active than the (*Z*)-iodoalkene **87** which is nearly as potent as the natural product itself (entries 3, 5 and 6). The acetylated derivative **85** is totally inactive (entry 4), while saturated lactone **89** and phosphodiester **90** show very weak activities with IC_{50} values in the high micromolar range.

From these results, the basic structure–activity relationship shown in Figure 5 can be derived. The unsaturated lactone is necessary for the biological activity of the natural product. It is prudent to speculate that covalent modification of the enzyme may take place, for example by nucleophilic attack of a cysteine residue in a Michael-type reaction. Furthermore, the phosphate group must be fully deprotected, suggesting that a very tight interaction of the phosphate with the enzyme is required for inhibition. The C-11-hydroxy group seems to be essential for activity, as suggested by the lack of inhibition by the truncated compound **77** and the acetylated compound **85**. The triene moiety is not essential for PP2A inhibition. The presence of a (*Z*)-configured double bond with a hydrophobic group attached (here an iodine) seems to be sufficient for high PP2A-inhibitory activity.

Clinical phase I trials of fostriecin have been stopped by the NCI due to impurities in the natural product samples.[62] Most probably the triene moiety in fostriecin and cytostatin is responsible for the instability of the natural products upon storage. Thus, the finding that it may be replaced by simpler structural elements without loss of biological activity is of particular importance for the design of more stable but still active analogues.

Notably protein phosphatase 1 (PP1) was not inhibited by any of the cytostatin analogues in a *p*-NPP based assay identical to the PP2A assay (Table 1). This demonstrates that variation of the structure of the natural product can be carried out without compromising the high selectivity described for the natural products of the fostriecin class. Furthermore VHR, PTP1B and CD45 were also not inhibited by any of the analogues. Thus, biological probes derived from cytostatin promise to be highly selective tools for biological investigations, for example in chemical proteomics studies.

Conclusion

We accomplished the first total synthesis of the PP2A-inhibitor cytostatin, thereby establishing its relative and absolute stereochemistry. The natural product was obtained in a 24-step sequence with an overall yield of 4.1% starting from the known and easily accessible alcohol **28**. The synthesis sequence was employed successfully to generate several analogues of the natural product. Assaying the phosphatase-inhibiting activity of these analogues revealed the importance of the unsaturated C-2,C-3 double bond, the phosphate, and the C-11-hydroxy group for biological activity of cytostatin, whereas the triene moiety could be replaced by other lipophilic groups. Our results demonstrate that highly selective phosphatase inhibitors with enhanced properties are likely to emerge from the synthesis of analogues of the natural products of the fostriecin class. Such compounds could serve as new molecular tools for the study of cellular phosphorylation processes.

Experimental Section

General: All reactions were carried out under an argon atmosphere. All solvents were distilled using standard procedures before use. THF was distilled under argon from molten potassium. Diethyl ether was distilled under argon from molten Na/K alloy. CH_2Cl_2 was distilled under argon from CaH_2. Dibutylboryltriflate was synthesized as previously described.[64] All other chemicals were purchased from commercial sources and used without further purification. Yields refer to isolated and pure compounds unless otherwise stated. ^1H and ^{13}C NMR data were recorded on a Varian Mercury 400 spectrometer. The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, m = multiplet, brs = broad signal. FAB and EI measurements were taken with a Jeol SX 102A using a 3-nitrobenzyl alcohol (3-NBA) matrix. GC-MS analysis was performed on a Hewlett–Packard HP 5890-Series II gaschromatograph with a HP 5972-series mass selective detector. HPLC purifications were performed using a Varian Pro Star machine with a Varian detector model 340. Optical rotations were measured with a Perkin–Elmer Polarimeter 341. Flash chromatography was performed using silica gel from Merck (silica gel 60). TLC was performed with aluminium-backed silica gel 60 F_{254} plates (Merck) using UV as a visualizing agent and a 0.5% aqueous potassium permanganate solution or an ethanolic solution of phosphomolybdic acid and heat as developing agents. Melting points were recorded on a Büchi B-540 apparatus and are uncorrected. Enzymatic assays were measured on a dynatech MR 5000 photometer with Roth polysterene microtiter plates. The enzymes were purchased from Calbiochem ($PP2A_1$ (bovine kidney), PP1 (α-isoform, rabbit muscle, recombinant)), Biomol (CD45 (human, recombinant) tyrosine phosphatase assay kit, PTP1B (human, recombinant), VHR (human, recombinant)). Merck silica gel (60, partical size 40–63 μM) and Merck aluminium oxide (type 506C) were used for flash column chromatography.

1-(1-Ethyl-prop-2-ynyloxymethyl)-4-methoxy-benzene (12): A 1 M NaHMDS solution in THF (1.31 mL, 1.31 mmol) was added dropwise at 0 °C to a solution of pent-1-yn-3-ol (100 mg, 1.19 mmol) in DMF (2 mL) and the mixture was stirred for 30 min at 0 °C. 4-Methoxybenzylchloride (0.194 mL, 1.43 mmol) and tetrabutylammonium iodide (22 mg, 0.06 mmol) were added at 0 °C and the mixture was stirred for 16 h at room temperature. The reaction mixture was quenched with 1 M aqueous KH_2PO_4 (10 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine (10 mL), then dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, pentane/diethyl ether 40:1 to 25:1) to give PMB-ether **12** (163 mg, 67%) as a colourless oil. $R_f = 0.86$ (pentane/diethyl ether 5:1); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.30 (d, $J = 8.6$ Hz, 2H), 6.89 (d, $J = 8.6$ Hz, 2H), 4.74 (d, $J = 11.4$ Hz, 1H), 4.46 (d, $J = 11.4$, 1H), 4.00 (dt, $J = 2.0$, 6.5 Hz, 1H), 3.81 (s, 3H), 2.47 (d, $J = 2.0$ Hz, 1H), 1.81–1.72 (m, 2H), 1.02 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4, 130.1, 129.8, 113.9, 83.0, 73.9, 70.2, 69.5, 55.4, 28.9, 9.7; HRMS (EI): calcd for $C_{13}H_{16}O_2$: 204.1150; found: 204.1134 $[M]^+$.

(*E*)-Trimethyl-pent-3-en-1-ynyl-silane (14): $[Pd(PPh_4)]$ (578 mg, 0.5 mmol) and copper iodide (190 mg, 1 mmol) were added at 0 °C to a solution of (*E*)-2-bromopropene (0.86 mL, 10 mmol), triethylamine (2.78 mL, 20 mmol), trimethylsilylacetylene (2.08 mL, 15 mmol), in degassed THF (100 mL). The mixture was stirred for 15 h at 0 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with diethyl ether (2 × 50 mL). The combined organic layers were washed with brine (40 mL), then dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, pentane) and distilled (30 mbar, 80 °C) to give TMS-alkyne **14** (960 mg, 69%) as a colourless oil. $R_f = 0.72$ (pentane); ^1H NMR (400 MHz, $CDCl_3$): δ = 6.22 (dq, $J = 16.1$, 7.0 Hz, 1H), 5.51 (dq, $J = 16.1$, 2.0 Hz, 1H), 1.78 (dd, $J = 7.0$, 2.0 Hz, 3H), 0.17 (s, 9H); MS (EI, 70 meV): *m*/*z* (%): 138 (18) $[M]^+$, 123 (100) $[M-CH_3]^+$. The analytical data are in agreement with the literature.[63]

(*E*)-1-Bromopent-3-en-1-yne (15): Recrystallized *N*-bromosuccinimide (70 mg, 0.39 mmol) and $AgNO_3$ (6 mg, 35 μmol) were added at 0 °C to a solution of TMS-alkyne **14** (50 mg, 0.36 mmol) in DMF (2.5 mL) and the mixture was stirred at 0 °C for 2 h and room temperature for 1 h. A second portion of recrystallized *N*-bromosuccinimide (10 mg, 0.06 mmol) and $AgNO_3$ (10 mg, 58 μmol) were added and the mixture was stirred at room temperature for 2 h. The reaction mixture was quenched by addition of ice-cold water (10 mL) and extracted with pentane (10 mL). The combined organic layers were washed with brine (5 mL), then dried (Na_2SO_4) and concentrated (500 mbar) to yield crude bromoalkyne (26 mg) as a slightly yellow oil which was used immediately in the next step without purification. $R_f = 0.9$ (pentane); ^1H NMR (400 MHz, $CDCl_3$): δ = 6.21 (dq, $J = 16.1$, 7.0 Hz, 1H), 5.46 (dq, $J = 16.1$, 2.0 Hz, 1H), 1.77 (dd, $J = 7.0$, 2.0 Hz, 3H); MS (EI, 70 meV): *m*/*z* (%): 146, 144 (100) $[M]^+$, 65 (89) $[M-Br]^+$.

1-[(*E*)-1-Ethyl-oct-6-ene-2,4-diynyloxymethyl]-4-methoxy-benzene (16a): A solution of alkyne **12** (56 mg, 0.28 mmol) and bromoalkyne **15** (60 mg, 0.41 mmol) in degassed DMSO (3 mL, and 2 × 0.5 mL washings) and 1,2,2,6,6-pentamethylpiperidine (0.21 mL, 1.18 mmol) were added to a mixture of CuI (14 mg, 0.07 mmol), LiI (8 mg, 0.06 mmol) and di-palladium-tris-(dibenzylideneacetone)-chloroform complex (9 mg, 9 μmol). The reaction mixture was stirred in the dark for 17 h at room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with diethyl ether (2 × 10 mL). The combined organic layers were washed with water (2 × 5 mL), brine (2 × 5 mL), then dried (Na_2SO_4), filtered through a short pad of silica gel and concentrated. The residue was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 1:1) to give endiyne **16a** (40 mg, 56%) as a yellow oil. $R_f = 0.26$ (cyclohexane/ethyl acetate 40:1); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, $J = 8.8$ Hz, 2H), 6.88 (d, $J = 8.8$ Hz, 2H), 6.35 (dq, $J = 15.8$, 7.0 Hz, 1H), 5.55 (dqd, $J = 15.8$, 1.8, 0.8 Hz, 1H), 4.72 (d, $J = 11.3$ Hz, 1H), 4.43 (d, $J = 11.3$ Hz, 1H), 4.08 (t, $J = 6.5$ Hz, 1H), 3.80 (s, 3H), 1.83 (dd, $J = 6.8$, 2.0 Hz, 3H), 1.82–1.70 (m, 2H), 1.00 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4, 144.1, 130.0, 129.8, 113.9, 109.8, 81.1, 72.0, 71.2, 70.7, 70.5, 70.2, 55.4, 29.0, 19.1, 9.9; HRMS (FAB, 3-NBA): *m*/*z*: calcd for $C_{18}H_{20}O_2$: 268.1463, found 268.1473 $[M]^+$.

(*E*)-Dec-8-ene-4,6-diyn-3-ol (16b): Endiyne **16b** was synthesized by analogy to **16a** starting from pent-1-yn-3-ol (**11**) (49 μL, 0.57 mmol) to yield a brown oil (42 mg, 0.28 mmol). $R_f = 0.4$ (pentane/diethyl ether 5:1); ^1H NMR (400 MHz, $CDCl_3$): δ = 6.33 (dq, $J = 15.8$, 7.0 Hz, 1H), 5.53 (dqd, $J = 15.8$, 1.8, 0.8 Hz, 1H), 4.41 (t, $J = 6.3$ Hz, 1H), 1.82 (dd, $J = 6.8$, 1.8 Hz, 3H), 1.79–1.70 (m, 2H), 1.01 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.3, 109.7, 82.2, 77.9, 71.7, 69.9, 64.4, 30.9, 19.0, 9.5; HRMS (EI, 70 meV): *m*/*z*: calcd for $C_{10}H_{12}O$: 148.0888; found: 148.0880 $[M+H]^+$.

(*E*)-1,1-Dibromopenta-1,3-diene (21): The reaction was carried out in the dark. $CDCl_3$ was filtered through a layer of basic alumium oxide before use. To a solution of (*E*)-crotonic aldehyde (**20**) (0.41 mL, 5 mmol) and tetrabromomethane (3.32 g, 10 mmol) in CH_2Cl_2 was added PPh_3 (5.24 g, 20 mmol) in five portions at 0 °C over a period of 3 min and the bright orange mixture was stirred for 8 min at 0 °C. The reaction mixture was diluted with pentane (100 mL), filtered through a layer of neutral aluminium oxide and carefully concentrated (100 mbar, room temperature). The residue was purified by flash chromatography (neutral aluminium oxide, pentane) to give dibromoalkene **21** (980 mg, 87%) as a yellow oil which was immediately used for the next step due to its pronounced lability. $R_f = 0.9$ (pentane); ^1H NMR (400 MHz, $CDCl_3$): δ = 6.89 (d, $J = 10.0$ Hz, 1H), 6.14–6.07 (m, 1H), 5.92 (dq, $J = 15.1$, 6.7 Hz, 1H), 1.77 (dd, $J = 1.5$, 6.7 Hz, 3H). The analytical data are in agreement with the literature.[22]

1-[(4*Z*,6*E*)-1-Ethylocta-4,6-dien-2-ynyloxymethyl]-4-methoxy-benzene (23): Tri-*n*-butylstannane (2.0 mL, 7.7 mmol) was added dropwise to a solution of dibromoalkene **22** (1.65 g, 7.3 mmol) and tetrakis-(triphenylphosphine)-palladium (337 mg, 0.29 mmol) in degassed THF (70 mL) and the reaction mixture was stirred for 1 h at room temperature. Another portion of tri-*n*-butylstannane (0.1 mL, 0.385 mmol) was added dropwise and the reaction solution was stirred for 1 h at room temperature. The reaction progress was carefully monitored by GC-MS. To the reaction solution were added a solution of alkyne **12** (298 mg, 1.46 mmol) in degassed THF (2 mL), degassed Et*N*iPr_2 (7.5 mL) and CuI (150 mg, 0.79 mmol) and the mixture was stirred for 16 h at room temperature. The mixture was quenched with saturated NH_4Cl (250 mL) and extracted with diethyl ether (300 mL). The combined organic layers were washed with brine (2 × 50 mL), then dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, pentane to pentane/diethyl ether 10:1) to give dienyne **23** (142 mg, 36% over 2 steps) as a yellow oil. R_f = 0.30 (pentane); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.32 (d, $J = 8.8$ Hz,

2H), 6.89 (d, J=8.8 Hz, 2H), 6.66–6.58 (m, 1H), 6.37 (t, J=10.6 Hz, 1H), 5.92 (dq, J=15.1, 7.0 Hz, 1H), 5.38 (d, J=10.8 Hz, 1H), 4.77 (d, J=11.4 Hz, 1H), 4.49 (d, J=11.4 Hz, 1H), 4.20 (dt, J=1.8, 6.5 Hz, 1H), 3.81 (s, 3H), 1.86–1.78 (m, 5H), 1.04 (t, J=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 140.5, 133.6, 130.4, 129.7, 129.2, 113.9, 106.3, 94.0, 83.2, 70.4, 70.2, 55.4, 29.2, 18.6, 10.0; HRMS (FAB, 3-NBA): m/z: calcd for $C_{16}H_{17}O_2$: 241.1229, found 241.1268 $[M-C_2H_5]^+$.

(*E*)-Tributyl-pent-3-en-1-ynyl-stannane (24): $CDCl_3$ was filtered through a layer of basic alumium oxide before use. Silica gel was pretreated with acetone/pyridine 1:1 and air-dried before use. A 2.5 M BuLi solution in hexanes (3.31 mL, 8.28 mmol) was added at −78 °C over a period of 45 min to a solution of dibromoalkene **21** (936 mg, 4.14 mmol) in THF (20 mL). The mixture was stirred for 1 h at −78 °C and for 70 min at room temperature. The mixture was recooled to −78 °C, tributylchlorostannane (1.18 mL, 4.35 mmol) was added dropwise at −78 °C and the mixture was stirred for 15 h at room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl and the mixture was extracted with pentane (50 mL). The combined organic layers were washed with brine (50 mL), then dried (Na_2SO_4) and concentrated at room temperature. The residue was purified by flash chromatography (silica gel, cyclohexane) to alkinylstannane **24** (729 mg, 50 %) as a colourless oil. R_f=0.95 (pentane/diethyl ether 10:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.15 (dq, J=15.8, 6.8 Hz, 1H), 5.53 (dq, J=15.8, 2.0 Hz, 1H), 1.76 (dd, J=6.8, 2.0 Hz, 1H), 1.60–1.52 (m, 6H), 1.33 (sext, J=7.8 Hz, 6H), 1.01–0.97 (m, 6H), 0.90 (t, J=7.4 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.6, 111.6, 109.0, 91.3, 29.0, 27.1, 18.6, 13.8, 11.2; HRMS (FAB, 3-NBA): m/z: calcd for $C_{14}H_{23}Sn$: 299.0822; found: 299.0808 $[M-C_4H_9]^+$.

(1*Z*,3*E*)-Tributyl-penta-1,3-dienyl-stannane (25): The reaction was carried out in the dark. $CDCl_3$ was filtered through a layer of basic alumium oxide before use. A solution of alkinylstannane **24** (40 mg. 0.113 mmol) in THF (0.5 mL, and 0.5 mL washing) was added to a mixture of zirconocene hydrochloride (65 mg, 0.254 mmol) in THF (0.75 mL). The orange mixture was stirred for 30 min at room temperature, diluted with pentane (5 mL), stirred for another 35 min at room temperature, filtered (silica gel, 7 cm high pad, pentane/diethyl ether 30:1) and concentrated at room temperature to yield crude alkenylstannane **25** (40 mg, 99 %) as a slightly yellow oil. Compound **25** was immediately used in the next step because of its marked lability. R_f=0.95 (pentane/diethyl ether 10:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02 (dd, J=12.8, 10.4 Hz, 1H), 6.01–5.93 (m, 1H), 5.90 (dd, J=12.8, 0.6 Hz, 1H), 5.72 (dq, J=14.9, 6.6 Hz, 1H), 1.78 (dd, J=6.6, 1.6 Hz, 1H), 1.55–1.47 (m, 6H), 1.32 (sext, J=7.4, 6H), 0.96–0.92 (m, 6H), 0.89 (t, J=7.2 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.7, 134.7, 131.2, 130.8, 29.3, 27.4, 18.4, 13.8, 10.6; MS (EI, 70 meV): m/z (%): 357.0 (73) $[M-H]^+$, 301 (100) $[M-C(CH_3)_3]^+$, 245 (27) $[M-C_8H_{17}]^+$, 187 (26) $[M-C_{12}H_{27}]^+$.

1-(1-Ethyl-3-iodo-prop-2-ynyloxymethyl)-4-methoxy-benzene (26): $AgNO_3$ (166 mg, 0.98 mmol) was added in the dark to a solution of alkyne **13** (1.00 g, 4.90 mmol) and *N*-iodosuccinimide (1.38 g, 6.12 mmol) in acetone (40 mL) and the mixture was stirred for 4 h at room temperature. The reaction mixture was quenched with ice-cold water (100 mL) and extracted with ethyl acetate (3×150 mL). The combined organic layers were washed with brine (100 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 100:1 to 30:1) to give iodoalkyne **26** (1.43 mg, 71 %) as a yellow oil. R_f=0.77 (cyclohexane/ethyl acetate 30:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, J=8.6 Hz, 2H), 6.88 (d, J=8.6 Hz, 2H), 4.72 (d, J=11.3 Hz, 1H), 4.43 (d, J=11.3 Hz, 1H), 4.12 (dt, J=6.5 Hz, 1H), 3.81 (s, 3H), 1.78–1.71 (m, 2H), 0.99 (t, J=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2, 129.8, 129.6, 113.8, 94.1, 71.0, 70.3, 55.3, 28.9, 9.7, 1.4; HRMS (FAB, 3-NBA): m/z: calcd for $C_{13}H_{15}INaO_2$: 353.0014; found: 352.9987 $[M+Na]^+$.

1-[(*Z*)-1-Ethyl-3-iodo-allyloxymethyl]-4-methoxy-benzene (27): Acetic acid (0.27 mL, 4.73 mmol) over a period of 1 h was added to a mixture of alkynyl iodide **26** (624 mg, 1.89 mmol), potassium azodicarboxylate (459 mg, 2.36 mmol) and pyridine (0.45 mL, 5.44 mmol) in methanol (7.9 mL) and the mixture was stirred for 5 h at room temperature. Another portion of potassium azodicarboxylate (230 mg, 1. 8 mmol) and acetic acid (0.14 mL, 2.36 mmol) were added and the mixture was stirred for further 15 h at room temperature. The pH of the reaction mixture was adjusted to pH 3 with 1 M aqueous HCl and the solution was extracted with diethyl ether (3×30 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (30 mL), brine (30 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 30:1) to give alkenyliodide **27** (576 mg, 92 %) as a yellow oil. R_f=0.30 (cyclohexane/ethyl acetate 30:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, J=8.7 Hz, 2H), 6.87 (d, J=8.7 Hz, 2H), 6.47 (dd, J=7.8, 1.0 Hz, 1H), 6.19 (t, J=7.8 Hz, 1H), 4.51 (d, J=11.3 Hz, 1H), 4.34 (d, J=11.3 Hz, 1H), 4.05 (ddt, J=7.2, 1.0, 7.0 Hz, 1H), 3.81 (s, 3H), 1.75–1.53 (m, 2H), 0.95 (t, J=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.1, 142.1, 130.6, 129.5, 113.8, 84.0, 82.0, 70.5, 55.5, 27.8, 9.9; HRMS (FAB, 3-NBA): m/z: calcd for $C_{13}H_{17}IO_2$: 332.0273, found 332.0285 $[M]^+$.

1-[(2*Z*,4*Z*,6*E*)-1-Ethylocta-2,4,6-trienyloxymethyl]-4-methoxy-benzene (17): The reaction was carried out in the dark. $CDCl_3$ was filtered through a layer of basic alumium oxide before use. To a solution of alkenyliodide **27** (137 mg, 0.412 mmol) and alkenylstannane **25** (294 mg, 0.824 mmol) in degassed DMF (7 mL) and degassed THF (0.25 mL) was added bis(acetonitrile)-palladium(II)chloride (10 mg) and the mixture was stirred for 16 h at room temperature. The reaction mixture was quenched with 10 % aqueous NH_3 (5 mL) and water (25 mL) and extracted with diethyl ether (3×30 mL). The combined organic layers were washed with saturated aqueous 1 M aqueous KH_2PO_4 (20 mL), brine (20 mL), then dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, pentane/diethyl ether 50:1 to 10:1) to give triene **17** (83 mg, 74 %) as a yellow oil. R_f=0.28 (cyclohexane/ethyl acetate 30:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, J=8.6 Hz, 2H), 6.86 (d, J=8.6 Hz, 2H), 6.67 (t, J=10.6 Hz, 1H), 6.60–6.52 (m, 1H), 6.08–5.97 (m, 2H), 5.80 (dq, J=14.7, 6.8 Hz, 1H), 5.38 (t, J=9.6 Hz, 1H), 4.51 (d, J=11.5 Hz, 1H), 4.27 (d, J=11.5 Hz, 1H), 4.18 (q, J=6.8 Hz, 1H), 3.80 (s, 3H, OCH_3), 1.83 (dd, J=6.8 Hz, J=1.4 Hz, 1H), 1.78–1.43 (m, 2H), 0.89 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2, 132.7, 132.0, 131.1, 131.1, 129.5, 126.8, 126.7, 121.8, 113.8, 75.1, 69.8, 55.4, 28.8, 18.6, 10.0; MS (EI, 70 meV): m/z (%): 272 (2) $[M]^+$, 121 (100) $[C_8H_9O]^+$.

***tert*-Butyl-[(2*S*,3*S*,4*S*)-3-methoxymethoxy-2,4-dimethyl-hept-6-enyloxy]-dimethylsilane (30a)**: *tert*-Butylchlorodimethylsilane (4.26 g, 28.3 mmol) was added to a solution of alcohol **29** (4.09 g, 20.2 mmol) and imidazole (4.26 g, 28.3 mmol) in DMF (25 mL) and the mixture was stirred for 15 h at room temperature. The reaction mixture was quenched with brine (150 mL) and extracted with diethyl ether (3×300 mL). The combined organic layers were washed with brine (100 mL), then dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, pentane/diethyl ether 50:1 to 10:1) to give TBS ether **30a** (6.46 g, quantitative) as a colourless oil. R_f=0.50 (pentane/diethyl ether 50:1); $[\alpha]_D^{20}$=+7.65 (c=1.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.79 (dddd, J=17.2, 10.2, 8.0, 6.1 Hz, 1H), 5.05–4.98 (m, 2H), 4.68 (d, J=6.5 Hz, 1H), 4.62 (d, J=6.5 Hz, 1H), 3.50 (dd, J=9.9, 6.3 Hz, 1H), 3.45 (dd, J=9.9, 7.8 Hz, 1H), 3.40 (dd, J=7.4, 2.7 Hz, 1H), 3.39 (s, 3H), 2.43–2.36 (m, 1H), 1.90–1.80 (m, 2H), 1.80–1.70 (m, 1H), 0.89 (s, 9H), 0.86 (d, J=6.8 Hz, 3H), 0.86 (d, J=6.6 Hz, 3H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.9, 115.9, 98.6, 83.2, 66.0, 56.1, 37.8, 37.6, 36.0, 26.1, 18.4, 16.1, 10.9, −5.2, −5.3; HRMS (FAB, 3-NBA): m/z: calcd for $C_{17}H_{37}O_3Si$: 317.2512; found: 317.2521 $[M+H]^+$.

(2*S*,3*S*,4*S*)-7-(*tert*-Butyldimethylsilyloxy)-5-methoxymethoxy-4,6-dimethylheptan-1-ol (31a): A 0.5 M solution of 9-BBN in THF (44.9 mL, 22.5 mmol) was added dropwise to a solution of alkene **30a** (6.46 g, 20.4 mmol) in THF (67 mL) and the mixture was stirred for 15 h at room temperature. The mixture was cooled to 0 °C, 3 M aqueous NaOH (24 mL, 72 mmol) was added dropwise and the mixture was stirred for 24 h at room temperature. The reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (3×160 mL). The combined organic layers were washed with brine (100 mL), then dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 5:2) to give alcohol **31a** (5.67 g, 83 %) as a colourless oil. R_f=0.45 (cyclohexane/ethyl acetate 2:1); $[\alpha]_D^{20}$=−4.9 (c=0.59, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.67 (d, J=6.5 Hz, 1H), 4.62 (d, J=6.5 Hz, 1H), 3.66–3.60 (m, 2H), 3.50–3.39 (m, 3H), 3.38 (s, 3H), 1.88–1.79 (m, 1H), 1.73–1.57 (m, 4H), 1.55–1.45 (m, 1H), 1.23–1.14 (m, 1H), 0.88 (s, 9H), 0.88 (d, J=6.8 Hz, 3H), 0.84 (d, J=6.8 Hz, 3H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 98.6, 83.3, 66.1, 63.4, 56.1, 37.6, 35.8, 30.5, 28.9, 26.0, 18.4, 16.4, 11.0, −5.2, −5.3; HRMS (FAB, 3-NBA): m/z: calcd for $C_{17}H_{38}NaO_4Si$: 357.2437; found: 357.2435 $[M+Na]^+$.

***tert*-Butyl-[(2*S*,3*S*,4*S*)-3-methoxymethoxy-2,4-diphenyl-hept-6-enyloxy]-dimethyl-silane (30b)**: TBDPS ether **30b** was synthesized by analogy to **30a** starting from alcohol **28** (1.06 g, 5.54 mmol) to yield a colourless oil (2.02 g, 97%). R_f=0.28 (cyclohexane/ethyl acetate 40:1); $[\alpha]_D^{20}$=+10.0 (c=0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.66 (m, 4H), 7.46–7.36 (m, 6H), 5.79 (dddd, J=16.6, 10.0, 8.0, 6.0 Hz, 1H), 5.06–5.00 (m, 2H), 4.71 (d, J=6.5 Hz, 1H), 4.63 (d, J=6.5 Hz, 1H), 3.61 (dd, J=10.0, 8.0 Hz, 1H), 3.54–3.49 (m, 2H), 3.34 (s, 3H), 2.44–2.37 (m, 1H), 1.96–1.82 (m, 2H), 1.82–1.71 (m, 1H), 1.08 (s, 9H), 0.88 (d, J=6.5 Hz, 3H), 0.86 (d, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.7, 135.6, 133.9, 129.6, 127.6, 115.9, 98.5, 83.2, 66.8, 56.1, 37.7, 37.7, 36.0, 27.1, 19.6, 16.3, 11.0; HRMS (FAB, 3-NBA): m/z: calcd for $C_{27}H_{40}NaO_3Si$: 463.2644; found: 463.2623 $[M+Na]^+$.

***tert*-Butyl-[(2*S*,3*S*,4*S*)-3-methoxymethoxy-2,4-diphenyl-hept-6-enyloxy]-dimethyl-silane (31b)**: Alcohol **31b** was synthesized by analogy to **31a** starting from alcohol **30b** (1.87 g, 4.25 mmol) to yield a colourless oil (1.67 g, 86%). R_f=0.33 (cyclohexane/ethyl acetate 2:1); $[\alpha]_D^{20}$=−1.6 (c=0.32, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.64 (m, 4H), 7.45–7.36 (m, 6H), 4.69 (d, J=6.5 Hz, 1H), 4.62 (d, J=6.5 Hz, 1H), 3.65–3.47 (m, 5H), 3.33 (s, 3H), 1.90 (dsext, J=6.5, 2.5 Hz, 1H), 1.73–1.55 (m, 4H), 1.52–1.43 (m, 1H), 1.22–1.14 (m, 1H), 1.06 (s, 9H), 0.89 (d, J=7.0 Hz, 3H), 0.84 (d, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.7, 133.9, 129.7, 127.7, 98.5, 83.3, 66.7, 63.4, 56.0, 37.5, 35.7, 30.4, 28.8, 27.0, 19.4, 16.4, 11.0; HRMS (FAB, 3-NBA): m/z: calcd for $C_{27}H_{42}NaO_4Si$: 481.2750; found: 481.2722 $[M+Na]^+$.

(4*R*,5*S*)-3-[(2*R*,3*S*,6*S*,7*S*,8*S*)-9-(*tert*-Butyldimethylsilyloxy)-3-hydroxy-7-methoxymethoxy-2,6,8-trimethyl-nonanoyl]-4-methyl-5-phenyl-oxazolidin-2-one (34a): A solution of DMSO (7.1 mL, 99.4 mmol) in CH_2Cl_2 (38 mL) was added dropwise at −78°C to a solution of oxalylchloride (3.64 mL, 42.4 mmol) in CH_2Cl_2 (250 mL) and the mixture was stirred for 1 h at −78°C. A solution of alcohol **31a** (5.57 g, 16.6 mmol) in CH_2Cl_2 (49 mL) was added dropwise at −78°C and the mixture was stirred for 2.5 h at −78°C. Triethylamine (17.3 mL, 124 mmol) was added dropwise at −78°C and the mixture was warmed to 0°C. The reaction mixture was quenched with 1 M aqueous KH_2PO_4 (200 mL) and extracted with CH_2Cl_2 (3×200 mL). The combined organic layers were washed with brine (100 mL), water (2×100 mL), then dried (Na_2SO_4) and concentrated to give crude aldehyde **32a** (6.35 g) as a pale yellow oil which was immediately used in the next step without purification. **32a**: R_f=0.77 (cyclohexane/ethyl acetate 2:1).

Et*N*iPr_2 (4.26 g, 18.3 mmol) and freshly distilled dibutylboryltriflate (5.5 mL, 21.6 mmol) were added at 0°C to a solution of *N*-propionyloxazolidinone (**8**; 4.26 g, 18.3 mmol) in CH_2Cl_2 (75 mL) and the solution was stirred for 1 h at 0°C. The solution was cooled to −78°C and a solution of aldehyde **33** in CH_2Cl_2 (20 mL) was added dropwise. The mixture was stirred for 50 min at −78°C and for 130 min at room temperature. The reaction mixture was cooled to 0°C, quenched with 0.1 M phosphate buffer (pH 7, 200 mL) and extracted with CH_2Cl_2 (300 mL). The organic layer were concentrated, the residue was redissolved in methanol (40 mL), 30% aqueous H_2O_2 (47 mL) was added dropwise at 0°C and the mixture was stirred at room temperature for 90 min. The mixture was diluted with brine (400 mL) and extracted with CH_2Cl_2 (3×800 mL). The combined organic layers were washed with brine (400 mL), then dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 3:1 to 2:1) to give diol **33** (6.64 g, 89%) as a colourless oil, which was immediately used in the next step without further characterization. R_f=0.32 (cyclohexane/ethyl acetate 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.35 (m, 3H), 7.31–7.28 (m, 2H), 5.68 (d, J=7.2 Hz, 1H), 4.79 (dq, J=7.2, 6.6 Hz, 1H), 4.72 (d, J=6.8 Hz, 1H), 4.70 (d, J=6.8 Hz, 1H), 3.96–3.91 (m, 1H), 3.80 (dq, J=2.7, 6.8 Hz, 1H), 3.53–3.43 (m, 3H), 3.43 (s, 3H), 2.96 (t, J=6.6 Hz, 1H), 2.88 (d, J=3.1 Hz, 1H), 2.01–1.92 (m, 1H), 1.78–1.60 (m, 3H), 1.40–1.25 (m, 2H), 1.24 (d, J=7.2 Hz, 3H), 0.89 (d, J=6.6 Hz, 3H), 0.87 (d, J=6.8 Hz, 3H), 0.80 (d, J=7.0 Hz, 3H).

To a mixture of alcohol **33** (6.17 g, 13.7 mmol), *N*,*N*-dimethylaminopyridine (167 mg, 1.37 mmol) and triethylamine (7.6 mL, 54.6 mmol) in CH_2Cl_2 (70 mL) was added dropwise a solution of *tert*-butylchlorodimethylsilane in CH_2Cl_2 (30 mL) at 0°C. The reaction mixture was stirred for 30 min at 0°C, for 15 h at room temperature, quenched with 1 M aqueous KH_2PO_4 (200 mL) and extracted with ethyl acetate (3×200 mL). The combined organic layers were washed with brine (100 mL), then dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 5:2 to 3:2) to give TBS ether **34a** (7.46 g, 97%) as a pale yellow oil. R_f=0.20 (cyclohexane/ethyl acetate 4:1); $[\alpha]_D^{20}$=+ 8.7 (c=0.515, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.35 (m, 3H), 7.31–7.29 (m, 2H), 5.68 (d, J=7.1 Hz, 1H), 4.79 (quint, J=7.1 Hz, 1H), 4.69 (d, J=6.5 Hz, 1H), 4.64 (d, J=6.5 Hz, 1H), 3.96–3.91 (m, 1H), 3.78 (dq, J=2.9, 7.0 Hz, 1H), 3.51–3.36 (m, 3H), 3.40 (s, 3H), 2.92 (d, J=3.3 Hz, 1H), 1.90–1.80 (m, 1H), 1.74–1.61 (m, 3H), 1.41–1.34 (m, 2H), 1.24 (d, J=7.0 Hz, 3H), 0.89 (d, J=6.8 Hz, 3H), 0.89 (d, J=6.8 Hz, 3H), 0.89 (s, 9H), 0.85 (d, J=6.8 Hz, 3H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.3, 152.7, 133.3, 128.9, 125.8, 98.7, 83.3, 79.0, 72.0, 66.1, 56.1, 54.9, 42.7, 37.7, 35.8, 31.6, 29.2, 26.1, 18.4, 16.3, 14.5, 10.8, 10.5, −5.2, −5.3; HRMS (FAB, 3-NBA): m/z: calcd for $C_{30}H_{51}NNaO_7Si$: 588.3332, found 588.3325 $[M+Na]^+$.

(4*R*,5*S*)-3-[(2*R*,3*S*,6*S*,7*S*,8*S*)-(*tert*-Butyldiphenylsilyloxy)-3-hydroxy-7-methoxymethoxy-2,6,8-trimethyl-nonanoyl]-4-methyl-5-phenyl-oxazolidin-2-one (34b): TBDPS ether **34b** was synthesized by analogy to **34a** starting from alcohol **31b** (753 mg, 1.64 mmol) to yield a colourless oil (486 mg, 43% over 2 steps). R_f=0.33 (cyclohexane/ethyl acetate 2:1); $[\alpha]_D^{20}$=−1.6 (c=0.32, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.64 (m, 4H), 7.45–7.35 (m, 9H), 7.32–7.29 (m, 2H), 5.67 (d, J=7.2 Hz, 1H), 4.79 (quint, J=7.0 Hz, 1H), 4.69 (d, J=6.5 Hz, 1H), 4.62 (d, J=6.5 Hz, 1H), 3.95–3.90 (m, 1H), 3.78 (dq, J=2.9, 7.0 Hz, 1H), 3.59 (dd, J=10.0, 8.0 Hz, 1H), 3.53–3.48 (m, 2H), 3.33 (s, 3H), 1.94–1.88 (m, 1H), 1.73–1.61 (m, 3H), 1.39–1.34 (m, 2H), 1.24 (d, J=7.0 Hz, 3H), 1.06 (s, 9H), 0.89 (d, J=6.6 Hz, 3H), 0.89 (d, J=6.6 Hz, 3H), 0.83 (d, J=6.8 Hz, 3H); ^{13}C (100.6 MHz, $CDCl_3$): δ = 177.3, 152.8, 135.8, 134.0, 133.3, 129.7, 128.9, 127.8, 125.8, 98.7, 83.4, 79.0, 72.0, 66.8, 56.1, 54.9, 42.8, 37.6, 35.7, 31.5, 29.2, 27.0, 19.4, 16.4, 14.3, 10.9, 10.6.

(2*R*,3*S*,7*S*,8*S*,9*S*)-9-(*tert*-Butyldimethylsilyloxy)-3-hydroxy-*N*-methoxy-7-methoxymethoxy-*N*-2,6,8-tetramethyl-nonanoic acid amide (35a): A 2 M solution of trimethylaluminium in toluene (30 mL, 60 mmol) was added dropwise at 0°C to a mixture of *N*,*O*-dimethylhydroxylamine hydrochloride (6.34 g, 65.0 mmol) in THF (50 mL) and the mixture was stirred for 30 min at room temperature. The solution was cooled to −20°C and a solution of oxazolidinone **34a** (7.36 g, 13.0 mmol) in THF (25 mL) was added dropwise at −20°C. The mixture was warmed to 0°C over a period of 30 min and stirred for 15 h at 0°C. The reaction mixture was poured into a well-stirred mixture of 1 M aqueous HCl (430 mL) and chloroform (500 mL) at 0°C. The pH of the aqueous layer should be 4–5. The layers were separated and the aqueous layer was extracted with $CHCl_3$ (3×400 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (200 mL), brine (200 mL), then dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, pentane/diethyl ether 1:3 to 1:8) to give Weinreb amide **35a** (4.89 g, 84%) as a pale yellow oil. R_f=0.50 (pentane/diethyl ether 1:4); $[\alpha]_D^{20}$=−6.4 (c=0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.67 (d, J=6.5 Hz, 1H), 4.63 (d, J=6.5 Hz, 1H), 3.85–3.80 (m, 1H), 3.71 (br s, 1H), 3.69 (s, 3H), 3.51–3.38 (m, 3H), 3.38 (s, 3H), 3.19 (s, 3H), 2.85–2.80 (m, 1H), 1.89–1.80 (m, 1H), 1.70–1.60 (m, 3H), 1.32–1.27 (m, 2H), 1.17 (d, J=7.0 Hz, 3H), 0.89 (d, J=6.5 Hz, 3H), 0.88 (s, 9H), 0.84 (d, J=7.0 Hz, 3H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.5, 98.6, 83.3, 72.0, 66.1, 61.7, 56.1, 39.0, 37.6, 36.1, 32.1, 31.8, 29.3, 26.1, 18.4, 16.3, 10.9, 10.4, −5.2, −5.3; HRMS (FAB, 3-NBA): m/z: calcd for $C_{22}H_{48}NO_6Si$: 450.3251, found: 450.3241 $[M+H]^+$.

(2*R*,3*S*,7*S*,8*S*,9*S*)-9-(*tert*-Butyldiphenylsilyloxy)-3-hydroxy-*N*-methoxy-3,7-bis-methoxymethoxy-*N*-2,6,8-tetramethyl-nonanoic acid amide (36a): Chloromethyl methyl ether (8.1 mL, 107 mmol) at 0°C was added dropwise to a solution of alcohol **35a** (4.79 g, 10. 7 mmol) in CH_2Cl_2 (120 mL) and Et*N*iPr_2 (23.7 mL, 138.5 mmol). The solution was stirred for 1 h at 0°C and for 18 h at room temperature. The orange solution was quenched 1 M KH_2PO_4 (170 mL) and extracted with CH_2Cl_2 (3×500 mL). The combined organic layers were washed with water (100 mL), brine (100 mL), then dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, pentane/diethyl ether 1:2) to give MOM ether **36a** (4.97 g, 94%) as a pale yellow oil. R_f=0.40 (pentane/diethyl ether 1:2); $[\alpha]_D^{20}$=−7.0 (c=0.63, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.68–4.59 (m, 4H), 3.78 (q, J=5.6 Hz, 1H), 3.69 (s, 3H), 3.50 (dd, J=9.6, 7.6 Hz, 1H), 3.43 (dd, J=9.6, 6.3 Hz, 1H), 3.38 (s, 6H), 3.35 (dd, J=6.8, 2.0 Hz, 1H), 3.18 (s, 3H), 3.10–3.02 (m, 1H), 1.88–1.79 (m, 1H), 1.69–1.59 (m, 3H), 1.50–1.44 (m, 1H), 1.21–1.14 (m,

1H), 1.19 (d, $J=7.0$ Hz, 3H), 0.88 (s, 9H), 0.86 (d, $J=6.8$ Hz, 3H), 0.84 (d, $J=6.8$ Hz, 3H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.0, 98.4, 96.7, 83.5, 79.7, 66.2, 61.5, 56.1, 56.1, 39.6, 37.7, 36.3, 32.4, 30.9, 28.4, 26.1, 18.4, 16.2, 13.7, 11.1, −5.2, −5.3; HRMS (FAB, 3-NBA): m/z: calcd for $C_{24}H_{52}NO_7Si$: 494.3513, found 494.3521 $[M+H]^+$.

(2*R*,3*S*,7*S*,8*S*,9*S*)-9-(*tert*-Butyldiphenylsilyloxy)-3-hydroxy-*N*-methoxy-3,7-bis-methoxymethoxy-*N*-2,6,8-tetramethyl-nonanoic acid amide (36b): Weinreb amide **35b** was synthesized by analogy to **35a** starting from alcohol **34b** (221 mg, 0.320 mmol) to yield a colourless oil (241 mg). Compound **35b** was used without chromatographic purification in the next step. **35b**: $R_f=0.40$ (cyclohexane/ethyl acetate 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.63 (m, 4H), 7.43–7.34 (m, 6H), 4.68 (d, $J=6.4$ Hz, 1H), 4.62 (d, $J=6.4$ Hz, 1H), 3.84–3.79 (m, 1H; CHOH), 3.66 (s, 3H; CH_3ON), 3.59 (dd, $J=10.0$, 8.0 Hz, 1H), 3.52–3.47 (m, 2H), 3.31 (s, 3H), 3.19 (s, 3H), 2.93–2.81 (brs, 1H), 1.96–1.87 (m, 1H), 1.72–1.55 (m, 3H), 1.33–1.25 (m, 2H), 1.17 (d, $J=7.2$ Hz, 3H), 1.05 (s, 9H), 0.89 (d, $J=6.8$ Hz, 3H), 0.83 (d, $J=6.8$ Hz, 3H); ^{13}C (100.6 MHz, $CDCl_3$): δ = 178.4, 135.7, 134.0, 129.7, 127.7, 98.5, 83.2, 72.0, 66.8, 61.6, 56.0, 39.0, 37.5, 36.1, 32.1, 31.8, 29.3, 27.0, 19.4, 16.3, 10.9, 10.4.

MOM ether **36b** was synthesized by analogy to **36a** starting from alcohol **35b** to yield a colourless oil (171 mg, 86% over two steps). **36b**: $R_f=0.40$ (cyclohexane/ethyl acetate 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.63 (m, 4H), 7.44–7.35 (m, 6H), 4.67–4.52 (m, 3H), 4.60 (d, J=6.4 Hz, 1H), 3.80–3.76 (m, 1H), 3.67 (CH_3ON), 3.59 (dd, J=10.1, 7.9 Hz, 1H), 3.50–3.45 (m, 2H), 3.37 (s, 3H), 3.30 (s, 3H), 3.18 (s, 3H), 3.12–3.02 (m, 1H), 1.90 (dsext, $J=7.5$, 2.6 Hz, 1H), 1.70–1.60 (m, 3H), 1.49–1.41 (m, 1H), 1.19 (d, $J=7.1$ Hz, 3H), 1.22–1.12 (m, 1H), 1.05 (s, 9H), 0.85 (d, $J=6.7$ Hz, 3H), 0.84 (d, $J=6.7$ Hz, 3H); ^{13}C (100.6 MHz, $CDCl_3$): δ = 176.2, 135.7, 134.0, 129.7, 127.7, 98.5, 96.7, 83.5, 79.6, 66.9, 61.5, 56.0, 56.0, 39.6, 37.7, 36.2, 32.4, 30.8, 28.3, 27.0, 19.4, 16.3, 13.7, 11.0; MS (ESI-MS): m/z: 640.6 $[M+Na]^+$.

(3*R*,4*S*,5*S*,8*S*,9*S*,10*S*)-11-(*tert*-Butyldiphenylsilyloxy)-5,9-bis-methoxymethoxy-4,8,10-trimethyl-1-trimethylsilyl-undec-1-yn-3-one (37b): TMS-alkynone **37b** was synthesized by analogy to **37a** starting from Weinreb amide **36a** (18 mg, 0.029 mmol) to yield a colourless oil (16 mg, 84%). $R_f=0.46$ (cyclohexane/ethyl acetate 10:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.63 (m, 4H), 7.44–7.35 (m, 6H), 4.68 (d, $J=6.5$ Hz, 1H), 4.64–4.60 (m, 3H), 4.15–4.08 (m, 1H), 3.58 (dd, $J=10.1$, 7.9 Hz, 1H), 3.52–3.47 (m, 2H), 3.33 (s, 3H), 3.32 (s, 3H), 3.25 (dq, $J=3.7$, 6.7 Hz, 1H), 1.90 (dsext, $J=2.7$, 6.7 Hz, 1H), 1.82–1.74 (m, 1H), 1.70–1.62 (m, 1H), 1.61–1.53 (m, 1H), 1.44–1.37 (m, 1H), 1.23–1.15 (m, 1H), 1.17 (d, $J=6.7$ Hz, 3H), 1.05 (s, 9H), 0.89 (d, $J=6.7$ Hz, 3H), 0.83 (d, $J=7.1$ Hz, 3H), 0.25 (s, 9H); ^{13}C (100.6 MHz, $CDCl_3$): δ = 189.7, 135.8, 134.0, 129.8, 127.8, 101.9, 99.0, 98.5, 96.4, 83.3, 78.4, 66.8, 56.1, 55.9, 51.8, 37.6, 36.2, 30.4, 28.7, 27.0, 19.4, 16.4, 11.0, 9.7, −0.6.

(3*R*,4*S*,5*S*,8*S*,9*S*,10*S*)-11-(*tert*-Butyldimethylsilyloxy)-5,9-bis-methoxymethoxy-4,8,10-trimethyl-undec-1-yn-3-one (38a): A solution of *n*-butyllithium in hexanes at −78°C was added dropwise to a solution of trimethylsilylacetylene (5.16 mL, 36.5 mmol) in THF (30 mL) and the reaction mixture was stirred for 1 h at −78°C and 15 min at room temperature. This lithium trimethylsilyacetylide solution was added dropwise to a solution of Weinreb amide **36a** (3.00 g, 6.08 mmol) in THF (120 mL) and the mixture was warmed to −10°C over a period of 20 min. The mixture was stirred for 75 min at −10°C, recooled to −78°C, quenched with saturated aqueous NH_4Cl (200 mL), diluted with diethyl ether (200 mL) and warmed to room temperature. The mixture was diluted with water (200 mL) and extracted with diethyl ether (3×300 mL). The combined organic layers were washed with brine (100 mL), then dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 7:1 to 5:1) to give a mixture of TMS-alkynone **37a** and alkynone **38a** (3.28 g) which was used in the next step without separation. **37a**: $R_f=0.78$ (cyclohexane/ethyl acetate 2:1).

A solution of disodium tetraborate (Borax, 12.6 mg) in water (120 mL) at −10°C was added dropwise to a solution of the mixture of **37a** and **38a** in methanol (600 mL) and the mixture was stirred for 10 min at −10°C, then for 70 min at room temperature. The reaction progress is carefully monitored by TLC. The reaction mixture was quenched with 1M aqueous KH_2PO_4 (100 mL), diluted with brine (400 mL) and extracted with diethyl ether (3×500 mL). The combined organic layers were washed with brine (300 mL), then dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 5:1) to give alkynone **38a** (2.64 g, 95% over 2 steps) as a colourless oil. $R_f=0.68$ (cyclohexane/ethyl acetate 2:1); $[\alpha]_D^{20}=-11.2$ ($c=1.09$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.68 (d, $J=6.5$ Hz, 1H), 4.66 (d, $J=6.8$ Hz, 1H), 4.62 (d, $J=6.5$ Hz, 1H), 4.61 (d, $J=6.8$ Hz, 1H), 4.15 (dt, $J=3.7$, 6.6 Hz, 1H), 3.49 (dd, $J=9.8$, 7.8 Hz, 1H), 3.44 (dd, $J=9.8$, 6.1 Hz, 1H), 3.41 (dd, $J=7.2$, 2.5 Hz, 1H), 3.39 (s, 3H), 3.33 (s, 3H), 3.25 (s, 1H), 2.74 (dq, $J=3.7$, 6.8 Hz, 1H), 1.89–1.75 (m, 2H), 1.71–1.64 (m, 1H), 1.55–1.63 (m, 1H), 1.50–1.39 (m, 1H), 1.26–1.15 (m, 1H), 1.19 (d, $J=7.0$ Hz, 3H), 0.90 (d, $J=7.0$ Hz, 3H), 0.89 (s, 9H), 0.85 (d, $J=6.8$ Hz, 3H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.2, 98.5, 96.4, 83.1, 81.2, 79.3, 78.3, 66.0, 56.1, 56.0, 52.1, 37.7, 36.2, 30.5, 28.9, 26.0, 18.4, 16.4, 11.0, 9.3, −5.2, −5.3; HRMS (FAB, 3-NBA): m/z: calcd for $C_{24}H_{46}NaO_6Si$: 481.2961, found 481.2979 $[M+Na]^+$.

(3*R*,4*S*,5*S*,8*S*,9*S*,10*S*)-11-(*tert*-Butyldiphenylsilyloxy)-5,9-bis-methoxymethoxy-4,8,10-trimethyl-1-trimethylsilyl-undec-1-yn-3-ol (41): THF (0.2 mL) and a solution of TMS-alkynone **37b** (73 mg, 0.111 mmol) in THF (0.2 mL) were added dropwise at 0°C to a 0.4M solution of oxazaborolidine **39**[18e] in toluene (0.28 mL, 0.133 mmol) and a 2M solution of $BH_3{\cdot}Me_2S$ in THF (67 μL, 0.134 mmol). The reaction mixture was stirred for 40 min at 0°C. The reaction was quenched by slow addition of methanol (0.25 mL) at 0°C. The mixture was stirred for 20 min at room temperature and concentrated. The residue was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 5:1 to 2:1) to give TMS-alkynol **41** (52 mg, 71%) as a colourless oil. $R_f=0.24$ (cyclohexane/ethyl acetate 6:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67–7.63 (m, 4H), 7.44–7.36 (m, 6H), 4.69–4.65 (m, 3H), 4.60 (d, $J=6.5$ Hz, 1H), 4.30 (d, $J=8.5$ Hz, 1H), 3.88 (dt, $J=2.5$, 7.0 Hz, 1H), 3.57 (dd, $J=10.0$, 8.0 Hz, 1H), 3.52–3.46 (m, 2H), 3.40 (s, 3H), 3.32 (s, 3H), 1.92–1.84 (m, 2H), 1.78–1.62 (m, 2H), 1.57–1.49 (m, 1H), 1.42–1.31 (m, 1H), 1.18–1.09 (m, 1H), 1.05 (s, 9H), 0.99 (d, $J=7.0$ Hz, 3H), 0.88 (d, $J=7.0$ Hz, 3H), 0.83 (d, $J=7.0$ Hz, 3H), 0.17 (s, 9H); MS (MALDI-TOF): m/z: 679.6 $[M+Na]^+$.

(3*R*,4*S*,5*S*,8*S*,9*S*,10*S*)-11-(*tert*-Butyldimethylsilyloxy)-5,9-bis-methoxymethoxy-4,8,10-trimethyl-undec-1-yn-3-ol (42a): A 1M solution of (*R*)-2-methyl-CBS-oxazolidinone **40** in toluene (11.2 mL, 11.2 mmol) was evaporated to dryness. To the residue was added a solution of alkynone **38a** (2.56 g, 5.58 mmol) in THF (70 mL) and the solution was cooled to −30°C. To this solution was added a 2M solution of $BH_3{\cdot}Me_2S$ in THF (14.0 mL, 28.0 mmol) and the mixture was stirred for 1 h at −30°C. To the reaction mixture was added dropwise methanol (22.5 mL) at −30°C. The mixture is diluted with saturated aqueous NH_4Cl (100 mL) and extracted with ethyl acetate (3×170 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL), then dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 5:1) to give alkynol **42a** (2.30 g, 89%) as a colourless oil. $R_f=0.35$ (cyclohexane/ethyl acetate 3:1); $[\alpha]_D^{20}=+$ 29.1 ($c=0.23$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.70 (d, $J=6.5$ Hz, 1H), 4.67 (d, $J=6.5$ Hz, 1H), 4.67 (d, $J=6.5$ Hz, 1H), 4.62 (d, $J=6.5$ Hz, 1H), 4.31 (ddd, $J=8.0$, 5.8, 2.2 Hz, 1H), 3.90 (dt, $J=2.7$, 7.0 Hz, 1H), 3.70 (d, $J=5.8$ Hz, 1H), 3.50–3.40 (m, 3H), 3.41 (s, 3H), 3.38 (s, 3H), 2.45 (d, $J=2.2$ Hz, 1H), 1.94–1.86 (m, 1H), 1.86–1.63 (m, 3H), 1.59–1.50 (m, 1H), 1.43–1.34 (m, 1H), 1.20–1.09 (m, 1H), 1.02 (d, $J=7.0$ Hz, 3H), 0.89 (d, $J=6.8$ Hz, 3H), 0.89 (s, 9H), 0.84 (d, $J=7.0$ Hz, 3H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 98.5, 97.0, 84.8, 83.0, 79.4, 73.1, 66.0, 65.2, 56.1, 56.1, 42.5, 37.6, 36.2, 29.5, 29.1, 26.1, 18.4, 16.4, 10.9, 10.7, −5.2, −5.3; HRMS (FAB, 3-NBA): m/z: calcd for $C_{24}H_{48}NaO_6Si$: 483.3118, found 483.3128 $[M+Na]^+$.

(3*R*,4*S*,5*S*,8*S*,9*S*,10*S*)-11-(*tert*-Butyldiphenylsilyloxy)-5,9-bis-methoxymethoxy-4,8,10-trimethylundec-1-yn-3-ol (42b): K_2CO_3 (22 mg, 0.159 mmol) was added to a solution of TMS-alkynone **41** (92 mg, 0.140 mmol) in methanol (5 mL) and the mixture was stirred for 15 h at room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl (20 mL), diluted with brine (100 mL) and extracted with diethyl ether (3×200 mL). The combined organic layers were concentrated. The residue was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 5:1 to 3:1) to give alkynol **42b** (67 mg, 82%) as a colourless oil. $R_f=0.15$ (cyclohexane/ethyl acetate 5:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.63 (m, 4H), 7.45–7.35 (m, 6H), 4.70–4.65 (m, 3H), 4.60 (d, $J=6.5$ Hz, 1H), 4.31 (dd, $J=8.2$, 2.0 Hz, 1H), 3.90 (dt, $J=2.7$, 7.0 Hz, 1H), 3.58 (dd, $J=10.0$, 8.0 Hz, 1H), 3.52–3.46 (m, 2H), 3.41 (s, 3H), 3.32 (s, 3H), 2.45 (d, $J=2.0$ Hz, 1H), 1.93–1.85 (m, 2H), 1.80–1.63 (m, 2H),

1.58–1.48 (m, 1H), 1.40–1.30 (m, 1H), 1.22–1.09 (m, 1H), 1.06 (s, 9H), 1.00 (d, J=7.0 Hz, 3H), 0.89 (d, J=6.8 Hz, 3H), 0.83 (d, J=6.8 Hz, 3H); MS (MALDI-TOF): m/z: 607.7 $[M+Na]^+$.

(3*R*,4*R*,5*S*,8*S*,9*S*,10*S*)-11-(*tert*-Butyldimethylsilyloxy)-3-(*tert*-butyldiphenylsilyloxy)-5,9-bis-methoxymethoxy-4,8,10-trimethylundec-1-yne (43a): *tert*-Butylchlorodiphenylsilane (1.70 mL, 6.53 mmol) was added dropwise to a solution of alcohol **42a** (2.23 g, 4.84 mmol) and imidazole (824 mg, 12.1 mmol) in DMF (10 mL) and the mixture was stirred for 15 h at room temperature. The reaction mixture was diluted with brine (100 mL) and extracted with diethyl ether (3×100 mL). The combined organic layers were washed with brine (50 mL), then dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 20:1 to 10:1) to give alkynol **43a** (4.25 g) as a colourless oil. The product was not totally pure and was used as such in the next step. An analytical sample was obtained for characterization. R_f= 0.34 (cyclohexane/ethyl acetate 15:1); $[\alpha]_D^{20}$=+17.2 (c=0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76–7.70 (m, 4H), 7.45–7.34 (m, 6H), 4.64 (d, J=6.5 Hz, 1H), 4.58 (d, J=6.5 Hz, 1H), 4.51 (d, J=6.5 Hz, 1H), 4.49 (d, J=6.5 Hz, 1H), 4.40 (dd, J=5.9, 2.2 Hz, 1H), 3.59 (q, J=5.5 Hz, 1H), 3.51 (dd, J=9.9, 7.8 Hz, 1H), 3.43 (dd, J=9.9, 6.4 Hz, 1H), 3.36 (s, 3H), 3.31 (dd, J=7.2, 2.3 Hz, 1H), 3.30 (s, 3H), 2.26 (d, J=2.2 Hz, 1H), 1.95–1.86 (m, 1H), 1.85–1.77 (m, 1H), 1.59–1.48 (m, 3H), 1.37–1.26 (m, 1H), 1.12 (d, J=6.8 Hz, 3H), 1.11–1.07 (m, 1H), 1.08 (s, 9H), 0.91 (s, 9H), 0.84 (d, J=6.8 Hz, 3H), 0.75 (d, J=6.8 Hz, 3H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.2, 136.0, 133.8, 133.6, 129.9, 129.7, 127.8, 127.4, 98.4, 96.6, 83.5, 83.3, 79.2, 74.8, 66.2, 65.2, 56.0, 55.8, 43.6, 37.6, 36.5, 30.2, 28.3, 27.1, 26.1, 19.5, 18.4, 16.1, 10.9, 10.5, −5.2, −5.2; HRMS (FAB, 3-NBA): m/z: calcd for $C_{40}H_{66}NaO_6Si_2$: 721.4296, found 721.4294 $[M+Na]^+$.

(3*R*,4*R*,5*S*,8*S*,9*S*,10*S*)-Bis-3,11-(*tert*-Butyldiphenylsilyloxy)-5,9-bis-methoxymethoxy-4,8,10-trimethyl-undec-1-yne (43b): TBDPS ether **43b** was synthesized by analogy to **43a** starting from alcohol **42a** (39 mg, 0.067 mmol) to yield a colourless oil (47 mg, 85%). R_f=0.22 (cyclohexane/ethyl acetate 20:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75–7.64 (m, 8H), 7.44–7.33 (m, 12H), 4.62 (d, J=6.5 Hz, 1H), 4.55 (d, J=6.5 Hz, 1H), 4.49 (d, J=6.5 Hz, 1H), 4.46 (d, J=6.5 Hz, 1H), 4.40 (dd, J=5.7, 2.2 Hz, 1H), 3.61–3.55 (m, 2H), 3.47 (dd, J=10.0, 6.3 Hz, 1H), 3.38 (dd, J=7.4, 2.5 Hz, 1H), 3.28 (s, 3H), 3.27 (s, 3H), 2.25 (d, J=2.2 Hz, 1H), 1.92–1.84 (m, 2H), 1.56–1.50 (m, 3H), 1.35–1.21 (m, 1H), 1.11 (d, J= 6.8 Hz, 3H), 1.08–1.05 (m, 1H), 1.07 (s, 9H), 1.06 (s, 9H), 0.82 (d, J= 6.8 Hz, 3H), 0.74 (d, J=6.7 Hz, 3H); MS (MALDI-TOF): 845.7 $[M+Na]^+$.

(2*S*,3*S*,4*S*,7*S*,8*S*,9*R*)-*tert*-Butyl-[9-(4-methoxybenzyloxy)-3,7-bis-methoxymethoxy-2,4,8-trimethyl-undec-10-ynyloxy]-diphenyl-silane (43c): A 1M solution of sodium hexamethyldisilazide (68 μL, 68 μmol) in THF at 0°C was added dropwise to a solution of alcohol **42a** (36 mg, 62 μmol) in DMF (0.85 mL) and the mixture was stirred for 30 min at 0°C. 4-Methoxybenzylchloride (15 μL, 111 μmol) and tetrabutylammoniumiodide (1 mg, 3 μmol) were added at 0°C and the mixture was stirred for 24 h at room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with diethyl ether (3×10 mL). The combined organic layers were washed with brine (5 mL), then dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 50:1 to 1:1) to give PMB ether **43c** (13 mg, 30%) as a colourless oil and the starting compound **42a** (4 mg, 11%). **43c**: R_f=0.42 (cyclohexane/ethyl acetate 5:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.63 (m, 4H), 7.44–7.34 (m, 6H), 7.29 (d, J=8.8 Hz, 2H), 6.87 (d, J=8.8 Hz, 2H), 4.74 (d, J=10.9 Hz, 1H), 4.65 (d, J=6.5 Hz, 1H), 4.59 (d, J=6.5 Hz, 1H), 4.56 (d, J=6.6 Hz, 1H), 4.54 (d, J=6.6 Hz, 1H), 4.41 (d, J=10.9 Hz, 1H), 4.07 (dd, J=8.4, 2.2 Hz, 1H), 3.79 (s, 3H), 3.81–3.75 (m, 1H), 3.58 (dd, J=10.0, 8.0 Hz, 1H), 3.50–3.44 (m, 2H), 3.32 (s, 3H), 3.29 (s, 3H), 2.48 (d, J=2.0 Hz, 1H), 1.98–1.84 (m, 2H), 1.75–1.45 (m, 3H), 1.40–1.30 (m, 1H), 1.15–1.03 (m, 4H), 1.05 (s, 9H), 0.85 (d, J=6.8 Hz, 3H), 0.83 (d, J=6.8 Hz, 3H).

(2*S*,3*S*,4*S*,7*S*,8*R*,9*R*)-9-(*tert*-Butyldiphenylsilyloxy)-3,7-bis-methoxymethoxy-2,4,8-trimethyl-undec-10-yn-1-ol (44): The reaction was performed in a teflon vessel. HF/py (11 mL) was added to a solution of TBS ether **43a** in THF (110 mL) and the solution was stirred for 40 min at room temperature. The reaction was carefully monitored by TLC. The mixture was diluted with ethyl acetate (150 mL) and saturated aqueous $NaHCO_3$ was carefully added until no more CO_2 formation was observed (pH>7). The mixture was extracted with ethyl acetate (3×300 mL), the combined organic layers were washed with brine (100 mL), then dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 2:1 to 1:1) to give alkynol **44** (2.43 g, 88% over two steps) as a colourless oil. R_f=0.32 (cyclohexane/ethyl acetate 2:1); $[\alpha]_D^{20}$=+77.1 (c=0.55, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75–7.68 (m, 4H), 7.46–7.35 (m, 6H), 4.61 (d, J=6.6 Hz, 1H), 4.59 (d, J=6.6 Hz, 1H), 4.51 (d, J=6.8 Hz, 1H), 4.49 (d, J=6.8 Hz, 1H), 4.38 (dd, J=5.7, 2.2 Hz, 1H), 3.54 (q, J=5.9 Hz, 1H), 3.51–3.45 (m, 2H), 3.41 (s, 3H), 3.30 (s, 3H), 3.32–3.28 (m, 1H), 3.06 (t, J=6.5 Hz, 1H), 2.30 (d, J=2.2 Hz, 1H), 1.95–1.82 (m, 2H), 1.58–1.44 (m, 3H), 1.37–1.25 (m, 1H), 1.14 (d, J=6.8 Hz, 3H), 1.09–1.07 (m, 1H), 1.08 (s, 9H), 0.75 (d, J=7.0 Hz, 3H), 0.68 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.2, 136.0, 133.7, 133.6, 130.0, 129.8, 127.8, 127.5, 99.2, 96.5, 83.9, 83.3, 79.3, 74.8, 65.2, 65.0, 56.3, 55.8, 43.5, 36.7, 36.5, 29.8, 27.9, 27.1, 19.5, 15.5, 10.6, 9.8; HRMS (FAB, 3-NBA): m/z: calcd for $C_{34}H_{52}NaO_6Si$: 607.3431, found 607.3405 $[M+Na]^+$.

1,7-Bis(*tert*-butyldiphenylsilyloxy)hept-2-yne (49): *tert*-Butyldiphenylsilyl chloride (86 μL, 0.326 mmol) *tert*-Butyldiphenylsilyl chloride (86 μL, 0.326 mmol) to a solution of alcohol **48**[64] (100 mg, 0.272 mmol) and imidazole (56 mg, 0.816 mmol) in DMF (0.4 mL) and the mixture was stirred for 15 h at room temperature. The mixture was quenched with brine (10 mL) and extracted with diethyl ether (3×20 mL). The combined organic layers were washed with brine (10 mL), then dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 150:1) to give TBDPS ether **49** (149 mg, 91%) as a colourless oil. R_f=0.83 (cyclohexane/ethyl acetate 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72–7.64 (m, 8H), 7.43–7.34 (m, 12H), 4.30 (t, J=2.0 Hz, 2H), 3.65 (t, J=6.1 Hz, 2H), 2.15 (dt, J=6.6, 2.0 Hz, 2H), 1.65–1.52 (m, 4H), 1.67–1.60 (m, 4H), 1.05 (s, 9H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.8, 135.7, 134.1, 133.5, 129.8, 129.7, 127.8 (2×C), 85.8, 78.7, 63.5, 53.1, 31.8, 27.0, 26.9, 25.1, 19.4, 19.3, 18.7; HRMS (FAB, 3-NBA): m/z: calcd for $C_{32}H_{43}NaO_4Si$: 627.3091, found 627.3110 $[M+Na]^+$.

7-(*tert*-Butyldiphenylsilyloxy)-hept-2-yn-1-ol (48): NH_4F (30 mg, 0.83 mmol) was added to a solution of the TBDPS ether **48** (50 mg, 83 μmol) in methanol (5 mL) and the mixture was stirred for 8 h at room temperature. The mixture was quenched with a 1M aqueous phosphate buffer (pH 7) (10 mL), diluted with brine (10 mL) and extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with brine (10 mL), then dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 10:1) to give the alcohol **48** (25 mg, 82%) as a colourless oil. R_f=0.28 (cyclohexane/ethyl acetate 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.65 (m, 4H), 7.45–7.36 (m, 6H), 4.23 (t, J=2.2 Hz, 2H), 3.68 (t, J= 5.9 Hz, 2H), 2.22 (tt, J=6.6, 2.2 Hz, 2H), 1.70–1.57 (m, 4H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.7, 134.1, 129.7, 127.8, 86.6, 78.6, 63.5, 51.6, 31.8, 27.0, 25.2, 19.4, 18.7.

The spectroscopical data are in accordance with the literature.[63]

Methyl (4*S*,5*S*,6*S*,9*S*,10*S*,11*R*)-11-(*tert*-butyldiphenylsilyloxy)-5,9-bis-methoxymethoxy-4,6,10-trimethyl-tridec-2-en-12-ynoate (50): A solution of 15% (by weight) Dess–Martin periodinane in CH_2Cl_2 (0.24 mL, 0.11 mmol) was added dropwise at room temperature to a mixture of the alcohol **44** (43 mg, 74 μmol) and $NaHCO_3$ (71 mg, 0.85 mmol) in CH_2Cl_2 (1.7 mL) and the mixture was stirred for 85 min at room temperature. The mixture was added to a well-stirred mixture of saturated aqueous NaS_2O_3 (5 mL), saturated aqueous $NaHCO_3$ (5 mL) and diethyl ether (10 mL). The mixture was stirred for 1 h at room temperature, diluted with saturated aqueous $NaHCO_3$ (10 mL) and extracted with diethyl ether (3×30 mL). The combined organic layers were washed with brine (2×20 mL), then dried (Na_2SO_4) and concentrated at room temperature. The residue was purified by flash chromatography (silica gel, pentane/diethyl ether 1:1 to 0:1) to give the aldehyde (40 mg, 93%) as a colourless oil which was directly used in the next step. R_f=0.50 (cyclohexane/ethyl acetate 3:1).

A 0.5M solution of potassium hexamethyldisilazide in toluene (10.4 mL, 5.2 mmol) at −78°C was added dropwise to a solution of [18]crown-6 (3.65 g, 13.8 mmol) and *O*,*O*′-bis(2,2,2-trifluoroethyl)-phosphono-acetic acid methyl ester (1.46 mL, 6.90 mmol) in THF (65 mL) and the solution was stirred at −78°C for 35 min. A solution of the aldehyde synthesized

as described above (2.01 g, 3.45 mmol) in THF (12 mL) was added dropwise over a period of 45 min at −78 °C and the mixture was stirred for 260 min at −78 °C. The mixture was quenched with saturated aqueous NH_4Cl (100 mL) and extracted with diethyl ether (3×500 mL). The combined organic layers were washed with brine (100 mL), then dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 5:1 to 2:1) to give ester **50** (2.05 g, 92% over 2 steps) as a colourless oil. R_f=0.71 (cyclohexane/ethyl acetate 2:1); $[\alpha]_D^{20}$=+53.2 (c=0.52, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75–7.69 (m, 4H), 7.44–7.34 (m, 6H), 6.18 (dd, J=11.5, 10.2 Hz, 1H), 5.73 (dd, J=11.5, 0.8 Hz, 1H), 4.60 (d, J=6.8 Hz, 1H), 4.57 (d, J=6.8 Hz, 1H), 4.49 (d, J=6.8 Hz, 1H), 4.46 (d, J=6.8 Hz, 1H), 4.38 (dd, J=5.9, 2.2 Hz, 1H), 3.85–3.75 (m, 1H), 3.69 (s, 3H), 3.56 (q, J=5.3 Hz, 1H), 3.37 (s, 3H), 3.28 (s, 3H), 3.12 (dd, J=6.1, 5.1 Hz, 1H), 2.26 (d, J=2.2 Hz, 1H), 1.92–1.84 (m, 1H), 1.60–1.42 (m, 3H), 1.31–1.22 (m, 1H), 1.10 (d, J=6.8 Hz, 3H), 1.09–1.06 (m, 1H), 1.07 (s, 9H), 1.02 (d, J=6.6 Hz, 3H), 0.83 (d, J=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6, 154.1, 136.2, 136.0, 133.8, 133.6, 129.9, 129.7, 127.8, 127.4, 118.0, 98.5, 96.5, 87.4, 83.5, 79.1, 74.8, 65.2, 56.2, 55.8, 51.2, 43.6, 36.8, 34.9, 30.3, 27.7, 27.1, 19.5, 16.3, 14.9, 10.4; HRMS (FAB, 3-NBA): m/z: calcd for $C_{37}H_{54}NaO_7Si$: 661.3536, found 661.3549 $[M+Na]^+$.

(5*S*,6*S*)-6-[(1*S*,4*S*,5*R*,6*R*)-6-(*tert*-Butyldiphenylsilyloxy)-4-hydroxy-1,5-dimethyl-oct-7-ynyl]-5-methyl-5,6-dihydro-pyran-2-one (51): A solution of the ester **50** (1.97 g, 3.08 mmol) and CBr_4 (510 mg, 1.54 mmol) in 2-propanol (136 mL) was heated for 15 h to 82 °C, then concentrated. The residue was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 2:1 to 3:2) to give the lactone **51** (1.33 g, 83%) as a colourless oil. R_f=0.6 (cyclohexane/ethyl acetate 1:1); $[\alpha]_D^{20}$=+115 (c=0.56, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76–7.69 (m, 4H), 7.47–7.36 (m, 6H), 6.98 (dd, J=9.6, 6.5 Hz, 1H), 5.97 (d, J=9.6 Hz, 1H), 4.35 (dd, J=4.1, 2.2 Hz, 1H), 4.18–4.13 (m, 1H), 3.98 (dd, J=10.4, 2.9 Hz, 1H), 2.62 (br s, 1H), 2.46 (dquint, J=3.1, 7.0 Hz, 1H), 2.33 (d, J=2.2 Hz, 1H), 1.98–1.90 (m, 1H), 1.80–1.56 (m, 3H), 1.26–1.20 (m, 2H), 1.09 (s, 9H), 1.03 (d, J=6.5 Hz, 3H), 1.01 (d, J=6.6 Hz, 3H), 0.89 (d, J=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.0, 152.0, 136.4, 136.2, 132.9, 132.5, 130.2, 130.0, 127.9, 127.5, 120.2, 84.2, 83.6, 75.2, 71.8, 68.6, 44.1, 34.3, 32.2, 30.6, 29.2, 27.1, 19.5, 14.7, 10.9, 10.0; HRMS (FAB, 3-NBA): m/z: calcd for $C_{32}H_{43}O_4Si$: 519.2930, found 519.2888 $[M+H]^+$.

(5*S*,6*S*)-6-[(1*S*,4*S*,5*R*,6*R*)-6-(*tert*-Butyldiphenylsilyloxy)-4-hydroxy-8-iodo-1,5-dimethyl-oct-7-ynyl]-5-methyl-5,6-dihydro-pyran-2-one (54): A solution of iodine (49 mg, 0.193 mmol) and *N*,*N*-dimethylaminopyridine (71 mg, 58 μmol) in toluene (1.5 mL) was stirred in the dark for 1 h at room temperature. To the dark brown mixture was added a solution of the alkyne **51** (20 mg, 39 μmol) in toluene (3 mL) and the mixture was heated for 3 h to 50 °C in the dark. The reaction mixture was cooled to room temperature, diluted with 0.4 M aqueous $Na_2S_2O_3$ (8 mL), 1 M aqueous KH_2PO_4 (16 mL) and brine (30 mL). The mixture was extracted with ethyl acetate (3×40 mL), the combined organic layers were washed with brine (30 mL), then dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 5:1 to 3:1) to give the lactone iodoalkyne **54** (19 mg, 76%) as a colourless oil. R_f=0.37 (cyclohexane/ethyl acetate 2:1); $[\alpha]_D^{20}$=+131 (c=0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73–7.68 (m, 4H), 7.46–7.38 (m, 6H), 6.98 (dd, J=9.6, 6.5 Hz, 1H), 5.97 (dd, J=9.6, 0.6 Hz, 1H), 4.45 (d, J=4.5 Hz, 1H), 4.17–4.12 (m, 1H), 3.99 (dd, J=10.4, 2.9 Hz, 1H), 2.46 (dquint, J=3.1, 7.2 Hz, 1H), 2.00–1.92 (m, 1H), 1.83–1.57 (m, 3H), 1.29–1.22 (m, 2H), 1.08 (s, 9H), 1.02 (d, J=7.0 Hz, 3H), 1.01 (d, J=7.0 Hz, 3H), 0.90 (d, J=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.0, 152.0, 136.3, 136.2, 132.8, 132.4, 130.3, 129.9, 127.9, 127.6, 120.2, 94.5, 84.2, 71.7, 70.2, 44.2, 34.3, 32.1, 30.6, 29.1, 27.1, 19.5, 14.7, 10.9, 10.0, 4.7; HRMS (FAB, 3-NBA): m/z: calcd for $C_{32}H_{42}O_4SiI$: 645.1897, found 645.1880 $[M+H]^+$.

{(1*S*,2*S*,3*R*)-3-(*tert*-Butyldiphenylsilyloxy)-2-methyl-1-[(3*S*,4*S*)-3-((3*S*)-3-methyl-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)-butyl]-pent-4-ynyl}-bis(2-cyanoethyl) phosphate (55): A solution of the phosphoramidite $(NCCH_2CH_2O)_2PNiPr_2$[65] in acetonitrile (0.75 mL) at 0 °C was added dropwise to a solution of the alcohol **51** (36 mg, 69 μmol) and tetrazol (22 mg, 0.31 mmol) in acetonitrile (2.2 mL) and the mixture was stirred for 105 min at room temperature and a 0.1 M solution of iodine in pyridine/THF/H_2O 2:7:1 (4.2 mL, 0.42 mmol) was added dropwise over 1 min. The mixture was stirred for 5 min at room temperature, then poured into a well-stirred mixture of saturated aqueous $NaHCO_3$ (5.3 mL), 0.1 M $Na_2S_2O_3$ (5.3 mL) and ethyl acetate (30 mL). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (2×30 mL). The combined organic layers were washed with 1 M aqueous KH_2PO_4 (25 mL), brine (20 mL), then dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, CH_2Cl_2/ethanol 30:1) to give the phosphotriester **55** (49 mg, quantitative) as a colourless oil. R_f=0.31 (CH_2Cl_2/ethanol 30:1); $[\alpha]_D^{20}$=+76.6 (c=0.27, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75–7.68 (m, 4H), 7.45–7.35 (m, 6H), 6.99 (dd, J=9.6, 6.5 Hz, 1H), 5.95 (d, J=9.6 Hz, 1H), 4.50–4.43 (m, 1H), 4.34–4.15 (m, 5H), 3.85 (dd, J=10.4, 2.9 Hz, 1H), 2.78 (t, J=6.1 Hz, 2H), 2.70 (t, J=6.1 Hz, 2H), 2.41 (dquint, J=2.9, 7.0 Hz, 1H), 2.36 (d, J=2.2 Hz, 1H), 2.04–1.54 (m, 6H), 1.23 (d, J=6.8 Hz, 3H), 1.08 (s, 9H), 0.98 (d, J=7.0 Hz, 3H), 0.66 (d, J=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.8, 152.2, 136.2, 136.0, 133.3, 133.2, 130.0, 129.9, 127.9, 127.6, 120.0, 117.1, 116.7, 83.5, 82.3 (d, $J(^{13}C,^{31}P)$=6.9 Hz), 81.9, 75.5, 64.1, 62.5 (d, $J(^{13}C,^{31}P)$=5.4 Hz), 62.3 (d, $J(^{13}C,^{31}P)$=5.4 Hz), 43.4 (d, $J(^{13}C,^{31}P)$=6.2 Hz), 33.9, 30.4, 29.6 (d, $J(^{13}C,^{31}P)$=2.3 Hz), 26.9, 26.2, 19.8 (d, $J(^{13}C,^{31}P)$=8.5 Hz), 19.7 (d, $J(^{13}C,^{31}P)$=7.7 Hz), 19.5, 14.3, 10.9, 10.9; ^{31}P NMR (162 MHz, $CDCl_3$): δ = −2.07; HRMS (FAB, 3-NBA): m/z: calcd for $C_{38}H_{49}N_2NaO_7PSi$: 727.2944, found 727.2914 $[M+Na]^+$.

Bis(cyanoethyl)-{(1*S*,2*S*,3*R*)-3-hydroxy-2-methyl-1-[(3*S*,4*S*)-3-((3*S*)-3-methyl-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)-butyl]-pent-4-ynyl} phosphate (56): The reaction was carried out in a teflon vessel. 70% HF/py (0.54 mL) was added to a solution of TBDPS ether **55** (49 mg, 69 μmol) in THF (2.6 mL) and the solution was stirred for 24 h at room temperature. The reaction mixture was added to a well-stirred mixture of saturated aqueous $NaHCO_3$ (10 mL) and ethyl acetate (30 mL), the combined organic layers were washed with 1 M aqueous KH_2PO_4 (6 mL), brine (6 mL), then dried (Na_2SO_4), diluted with toluene (5 mL) and concentrated at room temperature. The residue was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 1:8, then CH_2Cl_2/ethanol 10:1) to give the alcohol **56** (27 mg, 84%) as a colourless oil. R_f=0.16 (cyclohexane/ethyl acetate 1:8); $[\alpha]_D^{20}$=+88.0 (c=0.57, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.99 (dd, J=9.6, 6.5 Hz, 1H), 5.95 (d, J=9.8 Hz, 1H), 4.91–4.85 (m, 1H), 4.40–4.26 (m, 4H), 4.25 (dd, J=9.2, 2.2 Hz, 1H), 4.08 (dd, J=10.6, 3.1 Hz, 1H), 2.92–2.75 (m, 4H), 2.48 (dquint, J=2.9, 7.0 Hz, 1H), 2.48 (d, J=2.2 Hz, 1H), 1.95–1.85 (m, 4H), 1.56–1.41 (m, 2H), 1.07 (d, J=6.8 Hz, 3H), 1.03 (d, J=7.0 Hz, 3H), 0.91 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.9, 152.1, 120.0, 117.0, 116.7, 84.0, 83.4, 79.9 (d, $J(^{13}C,^{31}P)$=6.2 Hz), 63.6, 62.9 (d, $J(^{13}C,^{31}P)$=4.6 Hz), 62.8 (d, $J(^{13}C,^{31}P)$=6.2 Hz), 44.5 (d, $J(^{13}C,^{31}P)$=3.8 Hz), 33.4, 30.4, 30.1 (d, $J(^{13}C,^{31}P)$=3.8 Hz), 28.4, 19.9 (d, $J(^{13}C,^{31}P)$=8.5 Hz), 19.8 (d, $J(^{13}C,^{31}P)$=7.7 Hz), 14.5, 10.9, 9.6; ^{31}P NMR (162 MHz, $CDCl_3$): δ = −0.29; HRMS (FAB, 3-NBA): m/z: calcd for $C_{22}H_{32}N_2O_7P$: 467.1947, found 467.1943 $[M+H]^+$.

Bis(cyanoethyl)-{(1*S*,2*S*,3*R*)-3-hydroxy-5-iodo-2-methyl-1-[(3*S*,4*S*)-3-((3*S*)-3-methyl-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)-butyl]-pent-4-ynyl} phosphate (57): Iodoalkyne **57** was synthesized by analogy to iodoalkyne **80** starting from alkyne **56** (11.0 mg, 23.6 μmol). The residue was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 1:15 to 0:1) to give iodoalkyne **57** (15.6 mg, 84%) as a colourless oil. R_f=0.38 (cyclohexane/ethyl acetate 1:16); $[\alpha]_D^{20}$=+65 (c=0.135, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.98 (dd, J=9.6, 6.5 Hz, 1H), 5.94 (dd, J=9.6, 0.6 Hz, 1H), 4.86–4.80 (m, 1H), 4.40–4.27 (m, 5H), 4.07 (dd, J=10.6, 3.1 Hz, 1H), 2.91–2.75 (m, 4H), 2.45 (dquint, J=3.1, 7.0 Hz, 1H), 1.95–1.84 (m, 4H), 1.56–1.40 (m, 2H), 1.05 (d, J=6.8 Hz, 3H), 1.02 (d, J=7.0 Hz, 3H), 0.91 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.9, 152.1, 120.0, 117.0, 116.7, 94.7, 83.4, 79.9 (d, $J(^{13}C,^{31}P)$=6.2 Hz), 65.3, 62.9 (d, $J(^{13}C,^{31}P)$=5.4 Hz), 62.8 (d, $J(^{13}C,^{31}P)$=5.4 Hz), 44.7 (d, $J(^{13}C,^{31}P)$=3.8 Hz), 33.4, 30.4, 30.0 (d, $J(^{13}C,^{31}P)$=4.6 Hz), 28.4, 19.9 (d, $J(^{13}C,^{31}P)$=7.7 Hz), 19.8 (d, $J(^{13}C,^{31}P)$=7.7 Hz), 14.5, 10.9, 9.7, 2.0; ^{31}P NMR (162 MHz, $CDCl_3$): δ = −0.35; HRMS (FAB, 3-NBA): m/z: calcd for $C_{22}H_{31}IN_2O_7P$: 593.0914, found 593.0931 $[M+H]^+$.

***tert*-Butyl-(1-ethyl-prop-2-ynyloxy)-diphenylsilane (58)**: *tert*-Butyldiphenylsilyl chloride (1.86 mL, 7.12 mmol) was added dropwise to a solution of pent-1-yn-3-ol (11, 500 mg, 5.94 mmol) and imidazole (809 mg, 11.9 mmol) in DMF (5 mL) and the mixture was stirred for 19.5 h at room temperature. The reaction mixture was quenched with brine (50 mL) and extracted with diethyl ether (3×50 mL). The combined or-

ganic layers were washed with brine (50 mL), then dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 100:1) to give the TBDPS ether **58** (1.48 g, 77%) as a colourless oil. R_f=0.7 (cyclohexane/ethyl acetate 50:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77–7.68 (m, 4H), 7.46–7.35 (m, 4H), 4.31 (ddd, J=6.8, 5.5, 2.2 Hz, 1H), 2.31 (d, J=2.2 Hz, 1H), 1.74–1.62 (m, 2H), 1.09 (s, 9H), 0.96 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.0, 135.8, 133.7, 133.6, 129.7, 129.6, 127.6, 127.4, 85.0, 72.7, 65.0, 31.6, 27.2, 19.6, 9.4; HRMS (FAB, 3-NBA): m/z: calcd for $C_{21}H_{27}OSi$: 323.1831, found 323.1863 $[M+H]^+$.

***tert*-Butyl-(1-ethyl-3-iodo-prop-2-ynyloxy)-diphenylsilane (59)**: Iodoalkyne **59** was synthesized by analogy to iodoalkyne **26** starting from alkyne **58** (750 mg, 2.3 mmol) to give a colourless oil (990 mg, 96%). R_f=0.36 (cyclohexane/ethyl acetate 100:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75–7.66 (m, 4H), 7.46–7.36 (m, 6H), 4.41 (dd, J=6.5, 5.7 Hz, 1H), 1.74–1.63 (m, 2H), 1.08 (s, 9H); 0.95 (t, J=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.0, 135.8, 133.5, 133.5, 129.7, 129.6, 127.6, 127.4, 95.9, 66.7, 31.8, 27.2, 19.6, 9.5, 1.4; HRMS (FAB, 3-NBA): m/z: calcd for $C_{21}H_{25}IOSi$: 448.0719, found 448.0742 $[M]^+$.

Bis(cyanoethyl)-{(1*S*,2*S*,3*R*,4*Z*)-3-hydroxy-5-iodo-2-methyl-1-[(3*S*,4*S*)-3-((3*S*)-3-methyl-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)-butyl]-pent-4-enyl} phosphate (61): A solution of acetic acid (2.8 μL, 48 μmol) in 2-propanol (38 μL) over a period of 45 min was added to a mixture of iodoalkyne **57** (7.1 mg, 12.0 μmol) and potassium azodicarboxylate (4.7 mg, 24 μmol) in 2-propanol (88 μL) and the mixture was stirred for 24 h at room temperature. The reaction mixture was quenched with a 0.1 M phosphate buffer (1.5 mL) and extracted with ethyl acetate (3×5 mL). The combined organic layers were washed with brine (1 mL), then dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 2:3 to 1:3) to give (*Z*)-iodoalkene **61** (3.9 mg, 44%) as a colourless oil which was contaminated with saturated the lactone **62** (0.8 mg) and used in the next step without further purification. R_f=0.31 (CH_2Cl_2/ethanol 20:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.99 (dd, J=9.6, 6.5 Hz, 1H), 6.47 (dd, J=7.4, 0.6 Hz, 1H), 6.23 (dd, J=8.2, 7.6 Hz, 1H), 5.96 (dd, J=9.6, 0.6 Hz, 1H), 4.98–4.90 (m, 1H), 4.44–4.24 (m, 4H), 4.11–4.06 (m, 2H), 2.88–2.76 (m, 4H), 2.52–2.44 (m, 1H), 1.98–1.74 (m, 3H), 1.57–1.37 (m, 2H), 1.03 (d, J=7.2 Hz, 3H), 0.92 (d, J=7.0 Hz, 6H); ^{31}P NMR (162 MHz, $CDCl_3$): δ = −0.35.

***tert*-Butyl-(1-ethyl-3-iodo-allyloxy)-diphenylsilane (65)**: (*Z*)-Iodoalkene **65** was synthesized by analogy to (*Z*)-iodoalkene **27** starting from iodoalkyne **59** (848 mg, 1.88 mmol) to give a colourless oil (785 mg, 93%). R_f= 0.35 (cyclohexane/ethyl acetate 150:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.64 (m, 4H), 7.45–7.33 (m, 6H), 6.26 (t, J=7.6 Hz, 1H), 6.09 (dd, J=7.6, 1.0 Hz, 1H), 4.42–4.37 (m, 1H), 1.64–1.50 (m, 2H), 1.07 (s, 9H), 0.88 (t, J=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.6, 135.9, 135.9, 134.1, 134.1, 129.6, 129.5, 127.6, 127.5, 80.4, 77.2, 30.2, 27.3, 19.6, 9.3; HRMS (FAB, 3-NBA): m/z: calcd for $C_{17}H_{18}IOSi$: 393.0172, found 393.0187 $[M-C(CH_3)_3]^+$.

Bis(2-cyanoethyl)-{(1*S*,2*S*,3*R*,4*Z*,6*Z*,8*Z*)-3-hydroxy-2-methyl-1-[(3*S*,4*S*)-3-((3*S*)-3-methyl-3,6-dihydro-2*H*-hydropyran-2-yl)-butyl]-deca-4,6,8-trienyl} phosphate (66): The reaction was carried out in the dark. To a solution of the (*Z*)-alkenyl iodide **61** (3.3 mg, 5.55 μmol) was added a solution of the freshly prepared (*Z*)-alkenylstannane **25** (2.6 mg, 7.2 mmol) in degassed DMF (0.10 mL) and degassed THF (6 μL), then a solution of [Pd_2dba_3·$CHCl_3$] (0.3 mg) in degassed DMF (20 μL) at 0 °C. The mixture was stirred for 14 h at room temperature, diluted simultaneously with ethyl acetate (1 mL) and saturated aqueous $NaHCO_3$ (1 mL), and extracted with ethyl acetate (3×5 mL). The combined organic layers were washed with 0.1 M pH 7 phosphate buffer (1 mL), brine (1 mL), then dried (Na_2SO_4) and concentrated at room temperature. The residue was purified by flash chromatography (silica gel, CH_2Cl_2/ethanol/pyridine 100:5:1 to 90:9:1), then preparative reversed-phase HPLC (VP 250/10 NUCLEOSIL 100-5 C18 HD, flow rate 2.5 mL min^{-1}, t=0 min, 30% CH_3CN, 70% H_2O → t=19 min, 80% CH_3CN, 20% H_2O → t=34 min, 80% CH_3CN, 20% H_2O → t=35 min, 99% CH_3CN, 1% H_2O, t_R= 21.5 min, UV detection 210 nm) to give triene **66** (1.2 mg, 40%) as a colourless oil. R_f=0.31 (CH_2Cl_2/ethanol 20:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.99 (dd, J=9.6, 6.1 Hz, 1H), 6.60 (t, J=11.3 Hz, 1H), 6.57–6.49 (m, 1H), 6.12 (t, J=11.3 Hz, 1H), 6.05 (t, J=10.8 Hz, 1H), 5.96 (d, J=9.6 Hz, 1H), 5.80 (dq, J=14.9, 6.8 Hz, 1H), 5.42 (t, J=9.8 Hz, 1H), 5.00–4.92 (m, 1H), 4.47 (t, J=9.8 Hz, 1H), 4.41–4.31 (m, 4H), 4.08 (dd, J=10.4, 2.9 Hz, 1H), 2.92–2.77 (m, 4H), 2.50–2.44 (m, 1H), 1.82 (dd, J=6.8, 1.4 Hz, 1H), 1.98–1.75 (m, 3H), 1.68–1.45 (m, 2H), 1.30–1.22 (m, 1H), 1.03 (d, J=7.2 Hz, 3H), 0.92 (d, J=6.8 Hz, 3H), 0.85 (d, J=7.0 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$): δ = −0.33; MS (ESI): m/z (%): 557.1 (19) $[M+Na]^+$, 313.2 (100) $[C_{21}H_{29}O_2]^+$.

[7-(*tert*-Butyl-diphenylsilyloxy)-hept-2-ynyl]-bis(2-cyano-ethyl) phosphate (68): A solution of $(NCCH_2CH_2O)_2PN(iPr)_2$ (64 mg, 0.175 mmol) in CH_3CN (1 mL) at 0 °C was added to a solution of the alcohol **48** (64 mg, 0.175 mmol) and tetrazole (25 mg, 0.35 mmol) in CH_3CN (0.75 mL) and the mixture was stirred for 3 h at room temperature. To the reaction mixture was added dropwise a 0.1 M solution of iodine in pyridine/THF/H_2O 2:7:1 (4.2 mL, 0.42 mmol) over 1 min and the mixture was stirred for 5 min at room temperature. The reaction mixture was poured onto a well-stirred mixture of saturated aqueous $NaHCO_3$ (4.4 mL), 0.1 M aqueous $Na_2S_2O_3$ (4.4 mL) and ethyl acetate (30 mL). The mixture was extracted with ethyl acetate (2×30 mL), the combined organic layers were washed with 1 M aqueous KH_2PO_4 (30 mL), then dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 1:3 to 1:8) to give the phosphotriester **68** (72 mg, 74%) as a colourless oil. R_f=0.30 (cyclohexane/ethyl acetate 1:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67–7.64 (m, 4H), 7.45–7.36 (m, 6H), 4.73 (dt, J=10.6, 2.2 Hz, 2H), 4.35–4.24 (m, 4H), 3.70–3.66 (m, 2H), 2.76 (t, J=6.3 Hz, 4H), 2.28–2.23 (m, 2H), 1.67–1.60 (m, 4H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.7, 134.0, 129.7, 127.8, 116.3, 89.9, 73.7 (d, $J(^{13}C,^{31}P)$=6.9 Hz), 64.0, 62.4 (d, $J(^{13}C,^{31}P)$=4.6 Hz), 57.1 (d, $J(^{13}C,^{31}P)$=5.4 Hz), 31.8, 27.0, 24.9, 19.8 (d, $^3J(^{13}C,^{31}P)$=6.9 Hz), 19.4, 18.7; ^{31}P NMR (162 MHz, $CDCl_3$): δ = −0.33; HRMS (FAB, 3-NBA): m/z: calcd for $C_{29}H_{37}N_2NaO_5PSi$: 575.2107, found 575.2091 $[M+Na]^+$.

(2*S*,3*S*,4*S*)-7-Bis-methoxymethoxy-2,4-dimethyl-heptan-1-ol (72): MOM-ether **71** was synthesized by analogy to MOM-ether **36a** starting from alcohol **31b** (208 mg, 0.453 mmol) to give a colourless oil after aqueous work-up which was immediately used in the next step without purification.

To a solution of TBDPS-ether **71** was added dropwise a 1 M solution of tetrabutylammonium fluoride in THF (0.54 mL, 0.54 mmol) at 0 °C and the solution was stirred for 15 h at room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and H_2O (10 mL), and extracted with ethyl acetate (3×25 mL). The combined organic layers were washed with brine (2×10 mL), then dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 2:1) to give the alcohol **72** (108 mg, 90%) as a colourless oil. R_f=0.28 (cyclohexane/ethyl acetate 2:1); $[\alpha]_D^{20}$= +73.8 (c=0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.66 (s, 2H), 4.60 (s, 2H), 3.54–3.47 (m, 4H), 3.41 (s, 3H), 3.41–3.37 (m, 1H), 3.34 (s, 3H), 2.83–2.72 (br s, 1H), 1.99–1.90 (m, 1H), 1.78–1.60 (m, 3H), 1.55–1.45 (m, 1H), 1.17–1.08 (m, 1H), 0.85 (d, J=6.8 Hz, 3H), 0.78 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 99.1, 96.5, 84.0, 68.2, 65.2, 56.3, 55.2, 36.8, 36.0, 29.5, 27.5, 15.8, 10.0; HRMS (FAB, 3-NBA): m/z: calcd for $C_{13}H_{29}O_5$: 265.2015, found 265.2026 $[M+H]^+$.

Methyl (2*Z*,4*S*,5*S*,6*S*)-5,9-bis-methoxymethoxy-4,6-dimethyl-non-2-enoate (73): A solution of 15% (by weight) Dess–Martin periodinane in CH_2Cl_2 (1.9 mL, 0.891 mmol) was added dropwise at room temperature to a mixture of alcohol **72** (157 mg, 0.594 mmol) and $NaHCO_3$ (574 mg, 6.83 mmol) in CH_2Cl_2 (13.5 mL) and the mixture was stirred for 90 min at room temperature. The mixture was added to a well-stirred mixture of saturated aqueous NaS_2O_3 (15 mL), saturated aqueous $NaHCO_3$ (15 mL) and diethyl ether (30 mL). The mixture was stirred for 1 h at room temperature and extracted with diethyl ether (2×50 mL). The combined organic layers were washed with brine (20 mL), then dried (Na_2SO_4) and concentrated at room temperature. The crude aldehyde was immediately used in the next step without purification.

A 0.5 M solution of potassium hexamethyldisilazide in toluene (1.78 mL, 0.89 mmol) over 15 min at −78 °C was added dropwise to a solution of [18]crown-6 (630 mg, 2.38 mmol) and *O*,*O*′-bis(2,2,2-trifluoroethyl)-phosphono-acetic acid methyl ester (0.25 mL, 1.19 mmol) in THF (13 mL) and the solution was stirred at −78 °C for 35 min. A solution of the aldehyde synthesized as described above in THF (1 mL, and 2×0.5 mL washings) was added dropwise over a period of 45 min at −78 °C and the mixture was stirred for 3 h at −78 °C. The mixture was quenched with satu-

rated aqueous NH_4Cl (15 mL), warmed to room temperature, diluted with water (15 mL) and extracted with diethyl ether (3×100 mL). The combined organic layers were washed with brine (40 mL), then dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 3:1) to give the ester **73** (151 mg, 80% over 2 steps) as a colourless oil. R_f=0.37 (cyclohexane/ethyl acetate 3:1); $[\alpha]_D^{20}$=+ 64 (c=0.16, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.16 (dd, J=11.7, 10.4 Hz, 1H), 5.73 (dd, J=11.5, 1.0 Hz, 1H), 4.65–4.61 (m, 2H), 4.60 (s, 2H), 3.86–3.78 (m, 1H), 3.70 (s, 3H), 3.51–3.47 (m, 2H), 3.39 (s, 3H), 3.35 (s, 3H), 3.21 (t, J=5.5 Hz, 1H), 1.75–1.57 (m, 4H), 1.52–1.42 (m, 1H), 1.21–1.10 (m, 1H), 1.04 (d, J= 6.8 Hz, 3H), 0.97 (d, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.7, 153.8, 118.2, 98.5, 96.5, 87.4, 68.3, 56.2, 55.2, 51.2, 36.5, 35.1, 28.6, 27.8, 16.5, 15.3; HRMS (FAB, 3-NBA): m/z: calcd for $C_{16}H_{31}O_6$: 341.1940, found 341.1957 $[M+Na]^+$.

(5*S*,6*S*)-6-((1*S*)-4-Hydroxy-1-methylbutyl)-5-methyl-5,6-dihydro-pyran-2-one (74): 1 M aqueous HCl (7.5 mL) was added to a solution of ester **73** (151 mg, 0.475 mmol) in THF (15 mL) and the mixture was stirred for 15 h at 60 °C. The mixture was cooled to room temperature, quenched with saturated aqueous $NaHCO_3$, extracted with diethyl ether (3× 30 mL). The combined organic layers were washed with brine (20 mL), then dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 2:5) to give lactone **74** (83 mg, 88%) as a colourless oil. R_f=0.25 (cyclohexane/ethyl acetate 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.98 (dd, J=9.6, 6.5 Hz, 1H), 5.94 (dd, J=9.6, 0.5 Hz, 1H), 3.99 (dd, J=10.4, 3.1 Hz, 1H), 3.69–3.60 (m, 2H), 2.46 (dquint, J=3.1, 6.6 Hz, 1H), 1.96–1.79 (m, 2H), 1.75–1.69 (m, 1H), 1.58–1.47 (m, 1H), 1.27–1.16 (m, 1H), 1.01 (d, J=7.0 Hz, 3H), 0.90 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.0, 152.1, 120.0, 84.0, 63.1, 33.8, 30.5, 29.7, 28.6, 14.7, 10.9; HRMS (FAB, 3-NBA): m/z: calcd for $C_{11}H_{19}O_3$: 199.1334, found 199.1322 $[M+H]^+$.

Bis(9*H*-fluoren-9-ylmethyl)-diisopropylamidophosphite (75):[56] $CDCl_3$ was filtered through a layer of basic alumium oxide before use. Diisopropylaminophosphodichloridite (2.28 g, 11.3 mmol) at 0 °C Diisopropylaminophosphodichloridite (2.28 g, 11.3 mmol) at 0 °C to a solution of 9-fluorenylmethanol (4.44 g, 22.6 mmol) and Et*N*i*Pr*$_2$ (5.88 mL, 41.6 mmol) in THF (25 mL). The mixture was stirred for 1 h at room temperature, then filtered, and diluted with a 1 M pH 7 buffer (pH of aqueous phase should be 7 after shaking!) and ethyl acetate (200 mL). The mixture was extracted with ethyl acetate (3×150 mL), then dried (Na_2SO_4) and concentrated. The residue (5.9 g, quantitative) was further purified by flash chromatography (silica gel, cyclohexane/ethyl acetate/dimethylethylamine 20:1:0.2) to give the phosphoramidite **75** (551 mg starting from 1.0 g of crude product, 53%) as a pale yellow oil. R_f=0.6 (cyclohexane/ethyl acetate/dimethylethylamine 20:1:0.2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (t, J=6.8 Hz, 4H), 7.66–7.62 (m, 4H), 7.40–7.34 (m, 4H), 7.28 (dq, J= 7.6, 1.2 Hz, 4H), 4.17 (t, J=7.0 Hz, 2H), 4.00 (dt, J=10.0, 6.6 Hz, 2H), 3.80 (dt, J=10.0, 7.2 Hz, 2H), 3.70–3.60 (m, 2H), 1.15 (d, J=6.8 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.8, 144.5, 141.3, 141.1, 127.3, 127.3, 126.8, 126.7, 125.4, 125.1, 119.8, 119.7, 66.0 (d, $^2J(^{13}C,^{31}P)$= 16.9 Hz), 49.3 (d, $^3J(^{13}C,^{31}P)$=7.7 Hz), 43.2 (d, $J(^{13}C,^{31}P)$=12.3 Hz, 24.8 (d, $J(^{13}C,^{31}P)$=6.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 147.3.

Bis(9*H*-fluoren-9-ylmethyl)-{(4*S*)-4-[(2*S*,3*S*)-3-methyl-6-oxo-3,6-dihydro-2*H*-pyran-2-yl]-pentyl} phosphate (76): A solution of the phosphoramidite **75** (209 mg, 0.400 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added to a solution of the alcohol **74** (20 mg, 0.1 mmol) and tetrazole (21 mg, 0.3 mmol) in CH_2Cl_2 (2 mL) and the mixture was stirred for 4.5 h at room temperature. The reaction was cooled to −78 °C and 4-chloroperbenzoic acid (247 mg, 70% purity by weight, 1 mmol) was added. The mixture was stirred for 90 min at 0 °C, then quenched with 10% aqueous sodium sulfite (15 mL), and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were washed with 1 M aqueous KH_2PO_4 (8 mL), saturated aqueous $NaHCO_3$ (20 mL), brine (2×10 mL), then dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 2:1 to 2:3) to give the phosphotriester **76** (56 mg, 88%) as a pale yellow oil. R_f=0.19 (cyclohexane/ethyl acetate 2:3); $[\alpha]_D^{20}$=+ 44.8 (c=0.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (t, J=7.6 Hz, 4H), 7.56 (d, J=7.6 Hz, 2H), 7.50 (d, J= 7.6 Hz, 4H), 7.41–7.23 (m, 8H), 6.97 (dd, J=9.4, 6.5 Hz, 1H), 5.96 (d, J=9.4 Hz, 1H), 4.31–4.22 (m, 4H), 4.17–4.13 (m, 2H), 3.94 (dd, J=10.6, 3.2 Hz, 1H), 3.93–3.84 (m, 2H), 2.43 (dquint, J=2.9, 6.7 Hz, 1H), 1.90–1.65 (m, 3H), 1.60–1.49 (m, 1H), 1.21–1.09 (m, 1H), 1.00 (d, J=7.0 Hz, 3H), 0.83 (d, J=6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.7, 151.9, 143.3, 143.2, 143.2, 141.5, 128.0, 128.0, 127.2, 127.2, 125.2, 120.1, 120.1, 120.1, 83.7, 69.2 (d, $J(^{13}C,^{31}P)$=6.2 Hz), 68.2 (d, $J(^{13}C,^{31}P)$=6.2 Hz), 48.1 (d, $J(^{13}C,^{31}P)$=8.0 Hz), 33.7, 30.5, 28.6, 27.4 (d, $J(^{13}C,^{31}P)$=6.9 Hz), 14.6, 10.9; ^{31}P NMR (162 MHz, $CDCl_3$): δ = −0.50; HRMS (FAB, 3-NBA): m/z: calcd for $C_{39}H_{39}NaO_6P$: 657.2382, found 657.2393 $[M+Na]^+$.

(Triethylammonium)-monohydrogen-{(4*S*)-4-[(2*S*,3*S*)-3-methyl-6-oxo-3,6-dihydro-2*H*-pyran-2-yl]-pentyl} phosphate (77): NEt_3 (0.84 mL, 6.04 mL) was added dropwise at 0 °C to a solution of the phosphotriester **76** (96 mg, 0.151 mmol) in CH_3CN (4 mL) and the solution was stirred for 18 h at room temperature. The solution was diluted with toluene (2 mL) and concentrated at room temperature. The residue was diluted with water (10 mL) and diethyl ether (5 mL). After separation from the organic layer, the aqueous layer was washed (no shaking!) with small portions of diethyl ether (5 mL) until no UV-detectable material (TLC, R_f ca. 1, ethyl acetate) was present in the aqueous layer. The aqueous layer was lyophilized to yield the phosphate **77** as colourless oil (43 mg, 75%). R_f=0 (ethyl acetate); $[\alpha]_D^{20}$=+104 (c=0.45, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ = 7.16 (dd, J=9.6, 6.5 Hz, 1H), 5.93 (dd, J=9.6, 0.8 Hz, 1H), 4.08 (dd, J=10.4, 2.9 Hz, 1H), 3.90 (q, J=6.5 Hz, 2H), 3.18 (q, J=7.2 Hz, 6H), 2.59 (dquint, J=3.1, 6.8 Hz, 1H), 2.00–1.75 (m, 3H), 1.69–1.57 (m, 1H), 1.32–1.23 (m, 1H), 1.31 (t, J=7.4 Hz, 9H), 1.01 (d, J=7.0 Hz, 3H), 0.95 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.2, 155.0, 120.0, 85.5, 66.6 (d, $J(^{13}C,P)$=5.4 Hz), 47.5, 34.9, 31.6, 29.8, 28.9 (d, $^3J(^{13}C,P)$=7.7 Hz), 14.8, 10.9, 9.1; ^{13}C NMR (100 MHz, CD_3OD): δ = 167.2, 155.0, 120.0, 85.5, 66.6 (d, $^2J(^{13}C,P)$=5.4 Hz), 47.5, 34.9, 31.6, 29.8, 28.9 (d, $^3J(^{13}C,P)$=7.7 Hz), 14.8, 10.9, 9.1; ^{31}P NMR (162 MHz, CD_3OD): δ = 1.86; HRMS (FAB, 3-NBA): m/z: calcd for $C_{11}H_{20}O_6P$: 279.0998, found 279.1009 $[M+H]^+$.

{(1*S*,2*S*,3*R*)-3-(*tert*-Butyldiphenylsilyloxy)-2-methyl-1-[(3*S*,4*S*)-3-((3*S*)-3-methyl-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)-butyl]-pent-4-ynyl}-bis(9*H*-fluoren-9-ylmethyl) phosphate (78): A solution of phosphoramidite **75** (905 mg, 1.73 mmol) in CH_2Cl_2 (7.2 mL) at 0 °C was added to a solution of alcohol **51** (300 mg, 0.58 mmol) and tetrazole (109 mg, 1.56 mmol) in CH_3CN (9 mL) and the mixture was stirred for 5.5 h at room temperature. To the reaction mixture was added a 0.1 M solution of iodine in pyridine/THF/H_2O 2:7:1 (17.4 mL, 1.74 mmol) over 1 min and the mixture was stirred for 5 min at room temperature. The reaction mixture was poured to a well-stirred mixture of saturated aqueous $NaHCO_3$ (30 mL), 0.1 M aqueous $Na_2S_2O_3$ (30 mL) and ethyl acetate (150 mL). The mixture was extracted with ethyl acetate (2×150 mL), the combined organic layers were washed with 1 M aqueous KH_2PO_4 (60 mL), then dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 1:1 to 3:2) to give phosphotriester **78** (542 mg, 95%) as a colourless oil. R_f=0.49 (cyclohexane/ethyl acetate 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79–7.76 (m, 8H), 7.56–7.16 (m, 18H), 6.95 (dd, J=9.6, 6.5 Hz, 1H), 5.97 (d, J=9.6 Hz, 1H), 4.38–4.03 (m, 8H), 3.73 (dd, J=10.4, 3.1 Hz, 1H), 2.35 (dquint, J=3.1, 6.8 Hz, 1H), 2.25 (d, J=2.2 Hz, 1H), 2.00–1.93 (m, 1H), 1.89–1.79 (m, 1H), 1.39–1.60 (m, 3H), 1.15 (d, J=6.6 Hz, 1H), 1.10–1.05 (m, 1H), 0.90 (d, J=7.0 Hz, 3H), 0.60 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.6, 151.7, 143.5, 143.4, 143.3, 143.3, 141.5, 141.5, 141.4, 136.2, 136.0, 133.5, 133.4, 129.9, 129.8, 127.9, 127.8, 127.8, 127.6, 127.2, 127.2, 127.2, 125.4, 125.4, 125.3, 120.3, 120.0, 120.0, 120.0, 83.7, 82.2, 81.2 (d, $J(^{13}C,^{31}P)$=6.2 Hz), 75.3, 69.2 (d, $J(^{13}C,^{31}P)$=6.2 Hz), 69.0 (d, $J(^{13}C,^{31}P)$=5.8 Hz), 64.4, 48.1 (d, $J(^{13}C,^{31}P)$=8.5 Hz), 48.1 (d, $J(^{13}C,^{31}P)$= 8.1 Hz), 43.2 (d, $J(^{13}C,^{31}P)$=6.5 Hz), 34.2, 30.4, 29.8 (d, $J(^{13}C,^{31}P)$= 2.3 Hz), 27.0, 26.3, 19.5, 14.3, 10.9, 10.6; ^{31}P NMR (162 MHz, $CDCl_3$): δ = −1.15; HRMS (FAB, 3-NBA): m/z: calcd for $C_{60}H_{64}O_7PSi$: 955.4159, found 955.4144 $[M+H]^+$.

Bis(9*H*-fluoren-9-ylmethyl)-{(1*S*,2*S*,3*R*)-3-Hydroxy-2-methyl-1-[(3*S*,4*S*)-3-((3*S*)-3-methyl-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)-butyl]-pent-4-ynyl} phosphate (79): The reaction was performed in a teflon vessel. 70% HF/py (1.2 mL) and the solution was stirred for 24 h at room temperature was added to a solution of the TBDPS-ether **78** (145 mg, 0.152 mmol) in THF (5.7 mL). Another portion of 70% HF/py (1.2 mL) was added and the solution was stirred for another 8 h at room temperature. The reaction mixture was carefully (!) added to a well-stirred mixture of ethyl acetate (100 mL) and saturated aqueous $NaHCO_3$ (100 mL). The mixture was extracted with ethyl acetate (3×100 mL). The combined organic

layers were washed with brine (75 mL), then dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 2:1 to 1:1) to give alcohol **79** (89 mg, 82%) as a white solid. $R_f = 0.16$ (cyclohexane/ethyl acetate 1:1); $[\alpha]_D^{20} = +54.6$ ($c = 0.46$, $CHCl_3$); m.p. 79°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74–7.68 (m, 4H), 7.57–7.44 (m, 4H), 7.41–7.22 (m, 8H), 6.95 (dd, $J = 9.6$, 6.5 Hz, 1H), 5.93 (dd, $J = 9.6$, 0.4 Hz, 1H), 4.74–4.67 (m, 1H), 4.35 (dt, $J = 9.8$, 6.3 Hz, 1H), 4.27–4.08 (m, 6H), 3.86 (dd, $J = 10.4$, 2.9 Hz, 1H), 2.43 (d, $J = 2.2$ Hz, 1H), 2.40 (dquint, $J = 2.8$, 6.9 Hz, 1H), 1.85–1.65 (m, 4H), 1.55–1.45 (m, 1H), 1.16–1.08 (m, 1H), 0.98 (d, $J = 7.0$ Hz, 3H), 0.93 (d, $J = 7.0$ Hz, 3H), 0.79 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.5, 151.7, 143.3, 143.0, 143.0, 141.5, 141.5, 141.4, 141.4, 128.0, 128.0, 128.0, 127.3, 127.2, 127.2, 125.2, 125.1, 120.2, 120.1, 120.1, 84.3, 83.7, 78.6 (d, $J(^{13}C,^{31}P) = 6.2$ Hz), 73.1, 69.5 (d, $J(^{13}C,^{31}P) = 6.9$ Hz), 69.4 (d, $J(^{13}C,^{31}P) = 6.2$ Hz), 63.6, 48.0 (d, $J(^{13}C,^{31}P) = 9.2$ Hz), 47.9 (d, $J(^{13}C,^{31}P) = 8.5$ Hz), 43.8 (d, $J(^{13}C,^{31}P) = 3.8$ Hz), 33.9, 30.7 (d, $J(^{13}C,^{31}P) = 4.6$ Hz), 30.4, 28.6, 14.8, 10.8, 9.2; ^{31}P NMR (162 MHz, $CDCl_3$): $\delta = 0.96$; HRMS (FAB, 3-NBA): m/z: calcd for $C_{44}H_{46}O_7P$: 717.2981, found 717.2996 $[M+H]^+$.

Bis(9*H*-fluoren-9-ylmethyl)-{(1*S*,2*S*,3*R*)-3-Hydroxy-5-iodo-2-methyl-1-[(3*S*,4*S*)-3-((3*S*)-3-methyl-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)-butyl]-pent-4-ynyl} phosphate (80): A solution of $AgNO_3$ (7.5 mg, 44 μmol) in DMF (0.23 mL) was added to a solution of the alkyne **79** (210 mg, 0.293 mmol) and *N*-iodosuccinimide (99 mg, 0.440 mmol) in DMF (3.3 mL) and the mixture was stirred for 90 min at room temperature. The reaction mixture was quenched by addition of ice-cold water (50 mL) and extracted with ethyl acetate (3×100 mL). The combined organic layers were washed with brine (50 mL), then dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 1:1 to 2:3) to give the iodoalkyne **80** (247 mg, quantitative) as an off-white solid. $R_f = 0.30$ (cyclohexane/ethyl acetate 2:3); $[\alpha]_D^{20} = +41.4$ ($c = 0.5$, $CHCl_3$); m.p. 117°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74–7.68 (m, 4H), 7.56–7.43 (m, 4H), 7.41–7.21 (m, 8H), 6.95 (dd, $J = 9.6$, 6.5 Hz, 1H), 5.93 (dd, $J = 9.6$, 0.6 Hz, 1H), 4.68–4.62 (m, 1H), 4.36–4.07 (m, 7H), 3.86 (dd, $J = 10.4$, 3.1 Hz, 1H), 2.40 (dquint, $J = 3.1$, 7.0 Hz, 1H), 1.85–1.67 (m, 4H), 1.52–1.43 (m, 1H), 1.15–1.06 (m, 1H), 0.98 (d, $J = 7.0$ Hz, 3H), 0.90 (d, $J = 6.8$ Hz, 3H), 0.78 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.5, 151.7, 143.3, 143.1, 143.0, 141.5, 141.5, 141.4, 128.1, 128.0, 128.0, 127.3, 127.3, 127.3, 125.2, 125.2, 125.1, 120.2, 120.2, 120.1, 120.1, 95.0, 83.7, 78.6 (d, $J(^{13}C,^{31}P) = 6.2$ Hz), 69.5, 69.4, 65.3, 48.0 (d, $J(^{13}C,^{31}P) = 8.3$ Hz), 48.0 (d, $J(^{13}C,^{31}P) = 8.2$ Hz), 44.1 (d, $J(^{13}C,^{31}P) = 3.8$ Hz), 34.0, 30.8 (d, $J(^{13}C,^{31}P) = 4.6$ Hz), 30.5, 28.6, 14.9, 10.9, 9.3, 1.3; ^{31}P NMR (162 MHz, $CDCl_3$): $\delta = 0.80$; HRMS (FAB, 3-NBA): m/z: calcd for $C_{44}H_{45}IO_7P$: 843.1948, found 843.1944 $[M+H]^+$.

Bis(9*H*-fluoren-9-ylmethyl)-{(1*S*,2*S*,3*R*,4*Z*)-3-hydroxy-5-iodo-2-methyl-1-[(3*S*,4*S*)-3-((3*S*)-3-methyl-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)-butyl]-pent-4-enyl} phosphate (81): A solution of acetic acid (0.36 mL, 0.864 mmol) in 2-propanol (4.6 mL) was added dropwise over a period of 1 h to a mixture of iodoalkyne **80** (210 mg, 0.249 mmol) and potassium azodicarboxylate (84 mg, 0.432 mmol) in 2-propanol (1.56 mL) and 1,4-dioxane (0.21 mL) and the mixture was stirred for 14.5 h at room temperature. The reaction mixture was quenched with a 0.1 M phosphate buffer (50 mL) and extracted with ethyl acetate (3×100 mL). The combined organic layers were washed with brine (30 mL), then dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 2:3 to 1:3) to give (*Z*)-iodoalkene **81** (139 mg, 63%) as a white solid which was contaminated with saturated lactone **88** (7 mg) and used in the next step without further purification. Residual starting compound **80** (45 mg, 21%) could be reisolated after chromatography. $R_f = 0.15$ (cyclohexane/ethyl acetate 2:3); $[\alpha]_D^{20} = +49$ ($c = 0.235$, $CHCl_3$); m.p. 77°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75–7.67 (m, 4H), 7.61–7.50 (m, 4H), 7.41–7.20 (m, 8H), 6.95 (dd, $J = 9.6$, 6.5 Hz, 1H), 6.39 (d, $J = 7.6$ Hz, 1H), 6.16 (dd, $J = 8.4$, 7.6 Hz, 1H), 5.94 (dd, $J = 9.6$, 0.6 Hz, 1H), 4.82–4.76 (m, 1H), 4.45–4.23 (m, 4H), 4.21–4.13 (m, 3H), 3.87 (dd, $J = 10.4$, 2.9 Hz, 1H), 2.41 (dquint, $J = 2.9$, 6.8 Hz, 1H), 1.85–1.64 (m, 4H), 1.56–1.47 (m, 1H), 1.18–1.10 (m, 1H), 0.99 (d, $J = 7.0$ Hz, 3H), 0.81 (d, $J = 6.7$ Hz, 3H), 0.78 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.6, 151.7, 143.5, 143.2, 143.1, 142.0, 141.5, 141.5, 128.1, 128.0, 127.3, 125.5, 125.4, 125.3, 120.2, 120.2, 120.2, 120.1, 84.6, 83.8, 78.9, 74.2, 70.0, 69.8, 48.1, 42.7, 34.1, 30.7, 30.5, 28.7, 14.9, 10.9, 8.4; ^{31}P NMR (162 MHz, $CDCl_3$): δ = 1.29; HRMS (FAB, 3-NBA): m/z: calcd for $C_{44}H_{47}IO_7P$: 845.2104, found 845.2109 $[M+H]^+$.

Bis(9*H*-fluoren-9-ylmethyl)-{(1*S*,2*S*,3*R*,4*Z*,6*Z*,8*Z*)-3-hydroxy-2-methyl-1-[(3*S*,4*S*)-3-((3*S*)-3-methyl-3,6-dihydro-2*H*-hydropyran-2-yl)-butyl]-deca-4,6,8-trienyl} phosphate (82): All operations were done under exclusion of slightly. To a solution of (*Z*)-alkenyliodide **81** (7.0 mg, 8.3 μmol) was added a solution of the freshly prepared (*Z*)-alkenylstannane **25** (12.7 mg, 35.6 μmol) in degassed DMF (0.10 mL) and degassed THF (7 μL), then a 0.1 M solution of $Pd(CH_3CN)_2Cl_2$ in degassed DMF (20 μL, 2 μmol) was added at 0°C. The mixture was stirred for 20.5 h at room temperature, a total of 10 μL (8%) of the reaction solution was taken to monitor reaction progress. The solution was diluted simultaneously with ethyl acetate (5 mL) and saturated aqueous $NaHCO_3$ (5 mL), and extracted with ethyl acetate (3×10 mL). The combined organic layers were washed a 0.1 M pH 7 phosphate buffer (3 mL), brine (3 mL), then dried (Na_2SO_4) and concentrated at room temperature. The residue was purified by a SEPAK cartridge (C4-reversed phase material, H_2O to methanol), then reversed-phase HPLC (VP 250/10 NUCLEOSIL 100-5 C18 HD, flow rate 2.5 mL min^{-1}, $t = 0$ min, 50% CH_3CN, 50% $H_2O \rightarrow t =$ 20 min, 90% CH_3CN, 10% $H_2O \rightarrow t = 45$ min, 90% CH_3CN, 10% $H_2O \rightarrow t = 50$ min, 99% CH_3CN, 1% H_2O, $t_R = 34.7$ min, UV detection 300 nm) to give triene **82** (3.7 mg, 57%; 62% after 10% correction) as a colourless oil. $R_f = 0.30$ (acetonitrile/water 3:1, RP-C8-TLC); $[\alpha]_D^{20} = +49$ ($c = 0.235$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75–7.68 (m, 4H), 7.59–7.51 (m, 3H), 7.48–7.45 (m, 1H), 7.41–7.19 (m, 8H), 6.95 (dd, $J = 9.6$, 6.6 Hz, 1H), 6.54 (t, $J = 11.4$ Hz, 1H), 6.54–6.46 (m, 1H), 5.94 (dd, $J = 9.6$, 0.6 Hz, 1H), 5.91 (t, $J = 11.3$ Hz, 1H), 5.83 (t, $J = 11.0$ Hz, 1H), 5.75 (dq, $J = 14.9$, 6.8 Hz, 1H), 5.37 (t, $J = 10.6$ Hz, 1H), 4.85–4.78 (m, 1H; CHOP), 4.35–4.21 (m, 5H), 4.17–4.11 (m, 2H), 3.88 (dd, $J = 10.4$, 2.9 Hz, 1H), 2.80–2.67 (brs, 1H, OH), 2.41 (dquint, $J = 2.9$, 7.0 Hz, 1H), 1.81 (dd, $J = 6.8$, 1.0 Hz, 1H), 1.80–1.67 (m, 3H), 1.62–1.47 (m, 2H), 1.19–1.09 (m, 1H), 0.99 (d, $J = 7.0$ Hz, 3H), 0.80 (d, $J = 6.8$ Hz, 3H), 0.72 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.6, 151.8, 143.2, 143.1, 143.1, 141.5, 141.5, 141.5, 141.5, 132.3, 132.0, 131.3, 128.0, 128.0, 128.0, 127.3, 127.3, 126.9, 125.7, 125.3, 125.2, 125.2, 121.9, 120.2, 120.1, 120.1, 120.1, 83.8, 79.5 (d, $J(^{13}C,^{31}P) = 6.2$ Hz), 69.6 (d, $J(^{13}C,^{31}P) = 6.2$ Hz), 69.5 (d, $J(^{13}C,^{31}P) = 6.2$ Hz), 67.4 (CHOH), 48.1 (d, $J(^{13}C,^{31}P) = 5.4$ Hz), 48.0 (d, $J(^{13}C,^{31}P) = 5.4$ Hz), 43.1 (d, $J(^{13}C,^{31}P) = 3.8$ Hz), 34.0, 30.8 (d, $J(^{13}C,^{31}P) = 3.8$ Hz), 30.5, 28.7, 18.6, 14.8, 10.9, 8.8; ^{31}P NMR (162 MHz, $CDCl_3$): δ 0.74; HRMS (FAB, 3-NBA): m/z: calcd for $C_{49}H_{54}O_7P$: 785.3607, found 785.3621 $[M+H]^+$.

(4*S*,5*S*,6*S*,9*S*,10*S*,11*S*)-Cytostatin (1a): Only deionized water was used for all operations. To a solution of phosphotriester **82** (11.7 mg, 15 μmol) in CH_3CN (2.5 mL) was added dropwise NEt_3 (0.55 mL) at 0°C and the solution was stirred for 20 h at room temperature. The solution was diluted with toluene (1 mL) and concentrated at room temperature. The residue was diluted with water (10 mL) and diethyl ether (5 mL). After separation from the organic layer, the aqueous layer was washed (no shaking!) with small portions of diethyl ether (5 mL) until no UV-detectable material (TLC, R_f ca. 1, ethyl acetate) was present in the aqueous layer. The aqueous layer was lyophilized to yield the monotriethylammonium phosphate **1a** as colourless oil (8 mg, quantitative). The sodium salt was prepared by chromatography on ion exchange resin (DOWEX 50W2, 50–100 mesh, strongly acidic, 10 cm height, 0.8 cm diameter, methanol/water 1:1; the resin was sequentially washed with methanol/water 1:1, 1.0 M aqueous $NaHCO_3$ (CO_2!), H_2O, methanol/water 1:1 before use) to yield **1a** as an amorphous pale yellow powder. $R_f = 0$ (ethyl acetate); $[\alpha]_D^{20} = +46$ ($c = 0.285$, methanol); ^{1}H NMR (400 MHz, CD_3OD): δ = 7.15 (dd, $J = 9.6$, 6.6 Hz, 1H), 6.59 (t, $J = 11.5$ Hz, 1H), 6.62–6.54 (m, 1H), 6.26 (t, $J = 11.1$ Hz, 1H), 5.99 (t, $J = 11.5$ Hz, 1H), 5.93 (dd, $J = 9.6$, 0.6 Hz, 1H), 5.76 (dq, $J = 14.9$, 6.8 Hz, 1H), 5.41 (t, $J = 10.2$ Hz, 1H), 4.59 (t, $J = 10.0$ Hz, 1H), 4.55–4.48 (m, 1H), 4.11 (dd, $J = 10.2$, 2.9 Hz, 1H), 2.58 (dquint, $J = 3.1$, 7.0 Hz, 1H), 2.05–1.96 (m, 1H), 1.86–1.75 (m, 2H), 1.80 (dd, $J = 6.8$, 1.0 Hz, 3H), 1.58–1.46 (m, 2H), 1.30–1.24 (m, 1H), 1.01 (d, $J = 7.0$ Hz, 3H), 0.97 (d, $J = 6.8$ Hz, 3H), 0.80 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD, determined by HSQC and HMBC): δ = 167.1, 154.9, 133.7, 132.0, 131.5, 127.9, 126.3, 123.3, 119.9, 85.4, 75.2, 68.7, 43.9, 35.2, 31.5, 31.4, 29.2, 18.4, 14.7, 10.9, 9.1; ^{31}P NMR (162 MHz, CD_3OD): δ = 3.96; HRMS (FAB, 3-NBA): m/z: calcd for $C_{21}H_{33}NaO_7P$: 451.1862, found 451.1873 $[M+Na]^+$.

(Triethylammonium)-hydrogen-{(1*S*,2*S*,3*R*,4*Z*)-3-hydroxy-2-methyl-1-{(3*S*)-3-[(2*S*,3*S*)-3-methyl-6-oxo-3,6-dihydro-2*H*-pyran-2-yl]-butyl}-pent-4-ynyl} phosphate (83): Phosphate **83** was synthesized by analogy to monotriethylammonium salt of **1a** starting from phosphotriester **79** (5.0 mg, 7.0 μmol) to give an amorphous white powder (3.2 mg, 98%). $R_f=0$ (ethyl acetate); $[\alpha]_D^{20}=+75.6$ ($c=0.16$, methanol); ^{1}H NMR (400 MHz, CD_3OD): δ = 7.16 (dd, $J=9.6$, 6.5 Hz, 1H), 5.93 (dd, $J=9.6$, 0.6 Hz, 1H), 4.44 (dddd, $J=10.2$, 8.0, 6.3, 2.3 Hz, 1H), 4.32 (dd, $J=9.8$, 2.2 Hz, 1H), 4.11 (dd, $J=10.2$, 2.9 Hz, 1H), 3.20 (q, $J=7.4$ Hz, 6H), 2.73 (d, $J=2.2$ Hz, 1H), 2.59 (dquint, $J=3.1$, 7.0 Hz, 1H), 2.01–1.91 (m, 1H), 1.88–1.74 (m, 3H), 1.53 (ddt, $J=16.8$, 4.5, 8.0 Hz, 1H), 1.31 (t, $J=7.2$ Hz, 9H), 1.34–1.24 (m, 1H), 1.02 (d, $J=6.8$ Hz, 3H), 1.01 (d, $J=7.0$ Hz, 3H), 0.97 (d, $J=6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ = 167.4, 155.1, 120.0, 85.9, 85.6, 74.9 (d, $J(^{13}C,^{31}P)=5.4$ Hz), 73.8, 64.8, 47.8, 44.9 (d, $J(^{13}C,^{31}P)=3.8$ Hz), 35.4, 31.6, 31.6 (d, $J(^{13}C,^{31}P)=3.1$ Hz), 29.4, 14.9, 10.9, 9.6, 9.2; ^{31}P NMR (162 MHz, CD_3OD): δ = 2.96; HRMS (FAB, 3-NBA): *m/z*: calcd for $C_{16}H_{25}NaO_7P$: 383.1236, found 383.1223 $[M+Na]^+$.

{1-[(1*S*,2*S*,5*S*)-2-{Bis(9*H*-fluoren-9-ylmethoxy)-phosphoryloxy}-1-methyl-5-[(2*S*,3*S*)-3-methyl-6-oxo-3,6-dihydro-2*H*-pyran-2-yl]-hexyl}-prop-2-ynyl} ethanoate (84): *N*,*N*-Dimethylaminopyridine (ca. 0.2 mg) and acetanhydride (5 μL) were added to a solution of the alcohol **79** (10 mg, 14 μmol) in pyridine (0.1 mL) and the mixture was stirred for 1 h at room temperature. The reaction mixture was quenched with 1 M aqueous KH_2PO_4 (10 mL) and extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with brine (15 mL), then dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 1:1 to 1:2) to give the ester **84** (6.4 mg, 60%) as a colourless oil. $R_f=0.65$ (cyclohexane/ethyl acetate 1:3); $[\alpha]_D^{20}=+70.3$ ($c=0.32$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73–7.66 (m, 4H), 7.59 (d, $J=7.5$ Hz, 1H), 7.53–7.49 (m, 2H), 7.44 (d, $J=7.5$ Hz, 1H), 7.40–7.19 (m, 8H), 6.96 (dd, $J=9.6$, 6.6 Hz, 1H), 5.94 (d, $J=9.6$ Hz, 1H), 5.26 (dd, $J=8.4$, 2.2 Hz, 1H), 4.56–4.49 (m, 1H), 4.30–4.04 (m, 6H), 3.89 (dd, $J=10.4$, 2.9 Hz, 1H), 2.44 (d, $J=2.2$ Hz, 1H), 2.44–2.38 (m, 1H), 2.16–2.08 (m, 1H), 2.09 (s, 3H), 1.94–1.52 (m, 4H), 1.17–1.07 (m, 1H), 1.05 (d, $J=6.8$ Hz, 3H), 0.98 (d, $J=7.0$ Hz, 3H), 0.79 (d, $J=6.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 164.6, 151.8, 143.4, 143.3, 143.2, 141.4, 128.1, 128.0, 128.0, 127.1, 127.0, 125.3, 125.1, 120.2, 120.0, 83.7, 80.1, 79.0, 74.8, 69.3, 69.2, 64.6, 48.0, 47.9, 40.3, 34.1, 30.3, 29.9, 27.8, 20.9, 14.5, 10.4, 9.6; ^{31}P NMR (162 MHz, $CDCl_3$): δ = −0.77; HRMS (FAB, 3-NBA): *m/z*: calcd for $C_{46}H_{48}O_8P$: 759.3087, found 759.3119 $[M+H]^+$.

Monotriethylammoniumsalt of {1-[(1*S*,2*S*,5*S*)-1-methyl-5-[(2*S*,3*S*)-3-methyl-6-oxo-3,6-dihydro-2*H*-pyran-2-yl]-2-phosphonooxy-hexyl}-prop-2-ynyl}ethanoate (85): Phosphate **85** was synthesized by analogy to the monotriethylammonium salt of **1a** starting from phosphotriester **84** (6.4 mg, 8.4 μmol) to give an amorphous white powder (2.1 mg, 49%). $R_f=0$ (ethyl acetate); $[\alpha]_D^{20}=+118$ ($c=0.10$, methanol); ^{1}H NMR (400 MHz, CD_3OD): δ = 7.16 (dd, $J=9.6$, 6.5 Hz, 1H), 5.93 (d, $J=9.6$, 0.6 Hz, 1H), 5.28 (dd, $J=8.2$, 2.2 Hz, 1H), 4.31 (dddd, $J=10.6$, 7.0, 5.5, 3.7 Hz, 1H), 4.11 (dd, $J=10.2$, 2.9 Hz, 1H), 3.20 (q, $J=7.2$ Hz, 6H), 2.88 (d, $J=2.2$ Hz, 1H), 2.59 (dquint, $J=7.0$, 3.1 Hz, 1H), 2.17–2.10 (m, 1H), 2.07 (s, 3H), 2.03–1.95 (m, 1H), 1.93–1.78 (m, 2H), 1.63 (ddt, $J=16.8$, 4.3, 7.2 Hz, 1H), 1.31 (t, $J=7.2$ Hz, 9H), 1.33–1.24 (m, 1H), 1.13 (d, $J=7.0$ Hz, 3H), 1.01 (d, $J=7.0$ Hz, 3H), 0.97 (d, $J=6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ = 171.7, 167.3, 155.0, 120.0, 85.6, 81.8, 76.0 (d, $J(^{13}C,^{31}P)=6.2$ Hz), 75.9, 66.6, 47.7, 41.4 (d, $J(^{13}C,^{31}P)=6.2$ Hz), 35.5, 31.6, 30.9, 28.9, 21.0, 14.8, 11.0, 10.3, 9.2; ^{31}P NMR (162 MHz, CD_3OD): δ = 1.33; HRMS (FAB, 3-NBA): *m/z*: calcd for $C_{46}H_{48}NaO_8P$: 425.1341, found 425.1328 $[M+Na]^+$.

(Triethylammonium)-hydrogen-{(1*S*,2*S*,3*R*,4*Z*)-3-hydroxy-5-iodo-2-methyl-1-{(3*S*)-3-[(2*S*,3*S*)-3-methyl-6-oxo-3,6-dihydro-2*H*-pyran-2-yl]-butyl}-pent-4-ynyl} phosphate (86): Phosphate **86** was synthesized by analogy to the monotriethylammonium salt of **1a** starting from phosphotriester **80** (5.0 mg, 5.9 μmol) to give an amorphous white powder (3.5 mg, quantitative). $R_f=0$ (ethyl acetate); $[\alpha]_D^{20}=+52.6$ ($c=0.175$, methanol); ^{1}H NMR (400 MHz, CD_3OD): δ = 7.16 (dd, $J=9.6$, 6.6 Hz, 1H), 5.93 (dd, $J=9.6$, 0.6 Hz, 1H), 4.44 (d, $J=9.6$ Hz, 1H), 4.46–4.37 (m, 1H), 4.11 (dd, $J=10.2$, 2.9 Hz, 1H), 3.20 (q, $J=7.4$ Hz, 6H), 2.63–2.54 (m, 1H), 2.00–1.90 (m, 1H), 1.88–1.73 (m, 3H), 1.54–1.47 (m, 1H), 1.32 (t, $J=7.2$ Hz, 9H), 1.34–1.24 (m, 1H), 1.01 (d, $J=6.8$ Hz, 3H), 1.00 (d, $J=6.8$ Hz, 3H), 0.96 (d, $J=6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ = 167.4, 155.1, 120.0, 95.9, 85.6, 74.9 (d, $J(^{13}C,^{31}P)=6.2$ Hz), 65.0, 47.8, 45.2 (d, $J(^{13}C,^{31}P)=4.6$ Hz), 35.4, 31.6, 31.5, 29.4, 14.9, 11.0, 9.7, 9.2, 4.5; ^{31}P NMR (162 MHz, CD_3OD): δ = 2.87; HRMS (FAB, 3-NBA): *m/z*: calcd for $C_{16}H_{24}NaIO_7P$: 509.0202, found 509.0211 $[M+Na]^+$.

(Triethylammonium)-hydrogen-{(1*S*,2*S*,3*R*,4*Z*)-3-hydroxy-5-iodo-2-methyl-1-{(3*S*)-3-[(2*S*,3*S*)-3-methyl-6-oxo-3,6-dihydro-2*H*-pyran-2-yl]-butyl}-pent-4-enyl} phosphate (87): Phosphate **87** was synthesized by analogy to the monotriethylammonium salt of **1a** starting from phosphotriester **81** (5.0 mg, 5.9 μmol) to give an amorphous white powder (3.5 mg, quantitative). $R_f=0$ (ethyl acetate); $[\alpha]_D^{20}=+76.0$ ($c=0.175$, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ = 7.16 (dd, $J=9.6$, 6.5 Hz, 1H), 6.51 (dd, $J=7.7$, 0.8 Hz, 1H), 6.25 (dd, $J=8.4$, 7.7 Hz, 1H), 5.93 (dd, $J=9.6$, 0.8 Hz, 1H), 4.49 (dddd, $J=10.4$, 8.2, 5.9, 2.2 Hz, 1H), 4.37 (t, $J=9.2$ Hz, 1H), 4.10 (dd, $J=10.2$, 2.9 Hz, 1H), 3.20 (q, $J=7.2$ Hz, 6H), 2.62–2.54 (m, 1H), 2.05–1.94 (m, 1H), 1.87–1.67 (m, 3H), 1.53 (ddt, $J=17.2$, 4.5, 8.2 Hz, 1H), 1.32 (t, $J=7.2$ Hz, 9H), 1.34–1.24 (m, 1H), 1.01 (d, $J=7.0$ Hz, 3H), 0.97 (d, $J=6.8$ Hz, 3H), 0.91 (d, $J=6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ = 167.4, 155.0, 143.9, 120.0, 85.5, 83.7, 75.8, 75.2 (d, $J(^{13}C,^{31}P)=5.4$ Hz), 47.8, 43.3 (d, $J(^{13}C,^{31}P)=4.6$ Hz), 35.4, 31.6, 31.6 ($J(^{13}C,^{31}P)=3.1$ Hz), 29.4, 14.9, 10.9, 9.2, 9.1; ^{31}P NMR (162 MHz, CD_3OD): δ = 3.05; HRMS (FAB, 3-NBA): *m/z*: calcd for $C_{16}H_{26}INaO_7P$: 511.0359, found 511.0351 $[M+Na]^+$.

Bis(9*H*-fluoren-9-ylmethyl)-{(1*S*,2*S*,3*R*,4*Z*)-3-hydroxy-5-iod-2-methyl-1-[(3*S*,4*S*)-3-((3*S*)-3-methyl-6-oxo-tetrahydropyran-2-yl)-butyl]-pent-4-enyl} phosphate (88): Reduced lactone **88** was isolated as side-product during the synthesis of **80** and was purified by reversed-phase HPLC (VP 250/10 NUCLEOSIL 100-5 C18 HD, flow rate 2.5 mL min^{-1}, $t=0$ min, 50% CH_3CN, 50% $H_2O \rightarrow t=20$ min, 90% CH_3CN, 10% $H_2O \rightarrow t=45$ min, 90% CH_3CN, 10% $H_2O \rightarrow t=50$ min, 99% CH_3CN, 1% H_2O, $t_R=31.1$ min, UV detection 300 nm) to give a colourless oil (2.2 mg). $R_f=0.3$ (cyclohexane/ethyl acetate 1:2); $[\alpha]_D^{20}=-10.2$ ($c=0.205$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77–7.67 (m, 4H), 7.62–7.50 (m, 4H), 7.42–7.15 (m, 8H), 6.39 (d, $J=7.6$ Hz, 1H), 6.16 (t, $J=8.2$ Hz, 1H), 4.83–4.76 (m, 1H), 4.47–4.40 (m, 1H), 4.37–4.29 (m, 2H), 4.27–4.14 (m, 4H), 4.77–4.73 (dd, $J=10.0$, 2.2 Hz, 1H), 2.48–2.41 (m, 2H), 2.14–2.08 (m, 1H), 2.04–1.95 (m, 1H), 1.88–1.72 (m, 2H), 1.71–1.58 (m, 3H), 1.54–1.45 (m, 1H), 1.18–1.10 (m, 1H), 0.90 (d, $J=7.0$ Hz, 3H), 0.80 (d, $J=6.8$ Hz, 3H), 0.78 (d, $J=7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 143.4, 143.2, 143.1, 142.0, 141.5, 141.5, 128.1, 128.1, 127.3, 127.3, 125.5, 125.4, 120.3, 120.2, 120.1, 86.5, 84.6, 79.1 (d, $J(^{13}C,^{31}P)=6.3$ Hz), 74.3, 70.0 (d, $J(^{13}C,^{31}P)=5.7$ Hz), 69.9 (d, $J(^{13}C,^{31}P)=6.3$ Hz), 48.1 ($J(^{13}C,^{31}P)=8.6$ Hz), 48.0 ($J(^{13}C,^{31}P)=5.7$ Hz), 42.6, 34.9, 30.8, 29.1, 27.0, 26.7, 26.3, 14.9, 11.5, 8.4; ^{31}P NMR (162 MHz, $CDCl_3$): δ 0.97; HRMS (FAB, 3-NBA): *m/z*: calcd for $C_{44}H_{49}O_7PI$: 847.2261, found 847.2256 $[M+H]^+$.

(Triethylammonium)-hydrogen-{(1*S*,2*S*,3*R*,4*Z*)-3-hydroxy-5-iodo-2-methyl-1-{(3*S*)-3-[(2*S*,3*S*)-3-methyl-6-oxo-tetrahydro-pyran-2-yl]-butyl}-pent-4-enyl} phosphate (89): Phosphate **89** was synthesized by analogy to the monotriethylammonium salt of **1a** starting from phosphotriester **81** (2.2 mg, 2.6 μmol) to give an amorphous white powder (1.4 mg, 92%). $R_f=0$ (ethyl acetate); $[\alpha]_D^{20}=+32.9$ ($c=0.07$, methanol); ^{1}H NMR (400 MHz, CD_3OD): δ = 6.51 (dd, $J=7.6$, 0.6 Hz, 1H), 6.24 (dd, $J=8.4$, 7.8 Hz, 1H), 4.48 (dddd, $J=10.6$, 8.2, 5.9, 2.3 Hz, 1H), 4.36 (t, $J=8.8$ Hz, 1H), 4.06 (dd, $J=10.0$, 2.2 Hz, 1H), 3.20 (q, $J=7.2$ Hz, 1H), 2.58 (ddd, $J=17.9$, 8.6, 5.1 Hz, 1H), 2.47 (dt, $J=17.9$, 8.0 Hz, 1H), 2.26–2.18 (m, 1H), 2.18–2.08 (m, 1H), 2.03–1.94 (m, 1H), 1.80–1.60 (m, 4H), 1.57–1.45 (m, 1H), 1.32 (t, $J=17.9$ Hz, 9H), 1.32–1.20 (m, 1H), 0.95 (d, $J=6.6$ Hz, 3H), 0.93 (d, $J=7.0$ Hz, 3H), 0.89 (d, $J=7.0$ Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ = 175.1, 143.8, 87.9, 83.6, 75.8 (d, $J(^{13}C,^{31}P)=10.0$ Hz), 75.1, 47.8, 43.2, 36.2, 31.6, 29.8, 28.2, 27.5, 27.0, 15.1, 11.9, 9.3, 9.2; ^{31}P NMR (162 MHz, CD_3OD): δ = 3.07; = HRMS (FAB, 3-NBA): *m/z*: calcd for $C_{16}H_{28}INaO_7P$: 513.0515, found 513.0502 $[M+Na]^+$.

(Triethylammonium)-(2-cyanoethyl)-{(1*S*,2*S*,3*R*,4*Z*)-3-hydroxy-2-methyl-1-{(3*S*)-3-[(2*S*,3*S*)-3-methyl-6-oxo-3,6-dihydro-2*H*-pyran-2-yl]-butyl}-pent-4-ynyl} phosphate (90): Phosphate **90** was synthesized by analogy to the monotriethylammonium salt of **1a** starting fro phosphotriester **56** (11.3 mg, 24.2 μmol) to give a colourless oil (10.6 mg, 85%). $R_f=0$ (ethyl acetate); $[\alpha]_D^{20}=+76.8$ ($c=0.525$, MeOH).; ^{1}H NMR (400 MHz, CD_3OD): δ = 7.15 (dd, $J=9.6$, 6.5 Hz, 1H), 5.93 (d, $J=9.6$ Hz, 1H), 4.52–4.44 (m, 1H), 4.30 (dd, $J=9.2$, 2.0 Hz, 1H), 4.14 (dd, $J=10.2$, 2.9 Hz, 1H), 4.07 (q, $J=6.6$ Hz, 1H), 3.20 (q, $J=7.2$ Hz, 6H), 2.81–2.76 (m, 3H), 2.58 (dquint, $J=2.9$, 6.6 Hz, 1H), 1.90–1.76 (m, 4H), 1.61–1.51 (m, 1H), 1.39–1.30 (m, 1H), 1.32 (t, $J=7.2$ Hz, 9H), 1.04 (d, $J=6.8$ Hz,

3H), 1.01 (d, J=7.0 Hz, 3H), 0.97 (d, J=6.6 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ = 167.2, 154.9, 120.1, 119.4, 85.6, 85.4, 76.3 (d, $J(^{13}C,^{31}P)$=6.2 Hz), 74.1, 64.6, 61.7 (d, $J(^{13}C,^{31}P)$=5.4 Hz), 47.8, 45.1 (d, $J(^{13}C,^{31}P)$=4.6 Hz), 35.2, 31.6, 31.4 (d, $J(^{13}C,^{31}P)$=3.1 Hz), 29.4, 20.4 (d, $J(^{13}C,^{31}P)$=8.5 Hz), 14.9, 11.0, 9.8, 9.2; ^{31}P NMR (162 MHz, CD_3OD): δ = 1.55; HRMS (FAB, 3-NBA): m/z: calcd for $C_{19}H_{29}NO_7P$: 414.1682, found 414.1720 $[M+H]^+$.

Enzymatic assays—PP2A$_1$ inhibition: The enzyme (0.025 U) was pre-incubated with the inhibitors in a buffer[61] (pH 8.1, 100 μL total assay volume) containing Tris·HCl (40 mM), KCl (20 mM), $MgCl_2{\cdot}6H_2O$ (30 mM), DTT (2 mM) and BSA (0.1%) for 10 min at room temperature. Then *p*-NPP was added (end concentration 5 mM) and the read-out (405 nm) was recorded on a microplate-reader after 10–15 min incubation at room temperature.

Enzymatic assays—PP1 inhibition: The enzyme (0.025 U) was pre-incubated with the inhibitors in a buffer[61] (pH 8.1, 100 μL total assay volume) containing Tris·HCl (40 mM), KCl (20 mM), $MgCl_2{\cdot}6H_2O$ (30 mM) and DTT (2 mM) and BSA (0.1%) for 10 min at room temperature. Then *p*-NPP was added (end concentration 5 mM) and the read-out (405 nm) was recorded on a microplate-reader after 10–15 min incubation at room temperature.

VHR inhibition: The enzyme (0.001 U) was pre-incubated with the inhibitors in a buffer[66] (pH 6.5, 100 μL total assay volume) containing MOPS (25 mM), EDTA (5 mM), NaCl (125 mM), DTT (2 mM) and BSA (0.1%) for 10 min at room temperature. Then *p*-NPP was added (end concentration 5 mM) and the read-out (405 nm) was recorded on a microplate-reader after 1 h incubation at 37 °C.

PTP1B inhibition: The enzyme (0.001 U) was pre-incubated with the inhibitors in a buffer[66] (pH 6.5, 100 μL total assay volume) containing MOPS (25 mM), EDTA (5 mM), NaCl (125 mM), DTT (2 mM) and BSA (0.1%) for 10 min at room temperature. Then *p*-NPP was added (end concentration 5 mM) and the read-out (405 nm) was recorded on a microplate-reader after 10–15 min incubation at room temperature.

CD45 inhibition: The assay was performed using the commercially available Biomol Green CD45 tyrosine phosphatase assay kit.

The enzyme (75 U) was incubated with the inhibitors in a buffer (pH 7.2, 45 μL total assay volume) containing HEPES (50 mM), EDTA (1 mM), DTT (1 mM), 0.05% NP-40 and pp60$^{c\text{-}src}$ peptide (M=1543.7) (0.177 mM end concentration) as substrate for 1 h at 30 °C. Then 100 μL Biomol Green reagent was added and the read-out (690 nm) was recorded on a microplate-reader.

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