Multi-Step Application of Immobilized Reagents and Scavengers: A Total Synthesis of Epothilone C

R. Ian Storer,[a] Toshiyasu Takemoto,[a] Philip S. Jackson,[a] Dearg S. Brown,[b] Ian R. Baxendale,[a] and Steven V. Ley*[a]

Abstract: The total synthesis of the cytotoxic antitumour natural product epothilone C has provided a stage for the exploitation and further development of immobilized reagent methods. A stereoselective convergent synthetic strategy was applied, incorporating polymer-supported reagents, catalysts, scavengers and catch-and-release techniques to avoid frequent aqueous work-up and chromatographic purification.

Keywords: aldol reaction · antitumor agents · immobilized reagents · polyketides · polymers

Introduction

Developments in high-throughput screening and automated technologies have revolutionised both pharmaceutical and agrochemical research. The capacity to design and test thousands of compounds per day has resulted in an increasing burden on synthetic chemists to construct an unprecedented number of new molecules that possess wide structural diversity. Consequently, methods have been sought to allow efficient, multi-parallel synthesis and offer a practical simplicity that is readily applicable to both automation and scale-up.[1,2]

Investigations into solid phase organic synthesis heralded the birth of combinatorial chemistry, offering conceptual compatibility with parallel and automated approaches.[3] However, despite the advantages this technology continues to suffer from inherent limitations that have catalyzed the search for superior alternatives.[4] Arguably the most promising of these advances has been the application of immobilized reagents, catalysts and scavengers.[1,2]

Although there have been numerous applications of supported reagents during the past fifty years,[5] it was only during the last decade that chemists have begun to exploit them to their full capacity.[2,6] During this period we have started to explore the combined application of immobilized reagents and scavengers for the parallel syntheses of drug compound collections and natural products.[7,8] This has proven to be a versatile means for molecular conversion and impurity elimination, offering the opportunity to omit conventional labour intensive approaches to reaction quenching, extraction and purification.

Epothilones A and B (Figure 1) were discovered by Höfle, Reichenbach and their co-workers in the early 1990s.[9] In 1995 widespread interest was triggered when the epothilones were found to be potent inhibitors of tumor cell proliferation inducing mitotic arrest by the same mechanism as Taxol.[10] Accordingly, significant advances in both synthetic chemistry and biology have emerged from the resulting studies that may ultimately result in the development of new and more effective chemotherapeutic agents for the treatment of cancers.[11]

There have been many total syntheses of both natural and designed epothilones reported since the disclosure of their full structural assignments.[12–27] However, these conventional syntheses all required extensive silica gel chromatography to provide material free from contaminating by-products. While this is generally accepted in the research laboratory, such processes are not ideal for larger scale production, nor are they appropriate for the high-throughput synthesis of libraries of analogues.

Recently we reported the application of immobilized reagent techniques to the total synthesis of epothilone C and concurrent formal synthesis of epothilone A.[7] Herein these results are further discussed in context with several alternative approaches that were also investigated to elucidate this technology as an advancing concept within complex molecular assembly.

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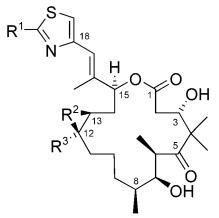


	R^1	R^2	R^3
A	Me	O	H
B	Me	O	Me
C	Me	alkene	H
D	Me	alkene	Me
E	CH_2OH	O	H
F	CH_2OH	O	Me

Figure 1. The natural epothilones.

Synthetic plan: Previous synthetic routes to the epothilone 16-membered macrocycle commonly involved convergent strategies, connecting fragments by a stereoselective C6–C7 aldol coupling, prior to either C1–C15 macrolactonization or C12–C13 ring-closing metathesis.[17,18,28]

Accordingly, our route incorporated the enantioselective preparation of three fragments 1 (**3**), 2 (**4**), and 3 (**5**), and their subsequent diastereoselective coupling to provide a convergent approach to epothilone C (**2**) (Figure 2). The synthesis included some well-established chemistry whilst integrating existing and newly devised immobilized reagent methodologies.

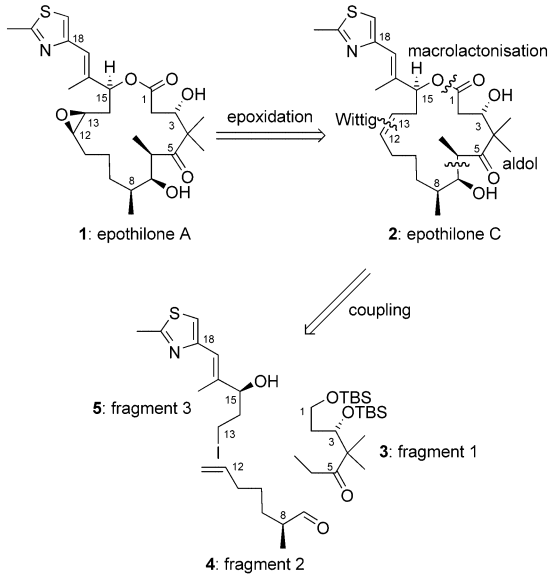


Figure 2. Synthetic plan.

The stereoselective union of fragments 1 (**3**) and 2 (**4**) by C6–C7 lithium aldol was followed by a C12–C13 Wittig reaction to incorporate fragment 3 (**5**). Ring closure by C1–C15 macrolactonization subsequently provided the natural product epothilone C (**2**), from which there is precedent for epoxidation to epothilone A (**1**) (Figure 2).[13]

Three independent methods were simultaneously investigated to construct fragment 1 (**3**): The first incorporated stereochemistry available from the application of pantolactone **6**;[24,29] the second applied Oppolzer's sultam chiral auxiliary to induce the desired asymmetry;[30] while the final approach utilised Kiyooka's chiral borane Lewis acid methodology[31] to install the C3 chiral centre via an asymmetric Mukaiyama aldol reaction.[21,22]

Fragment 2 (**4**) was generated from a commercially available Roche ester derivative to provide the C8 stereochemistry.

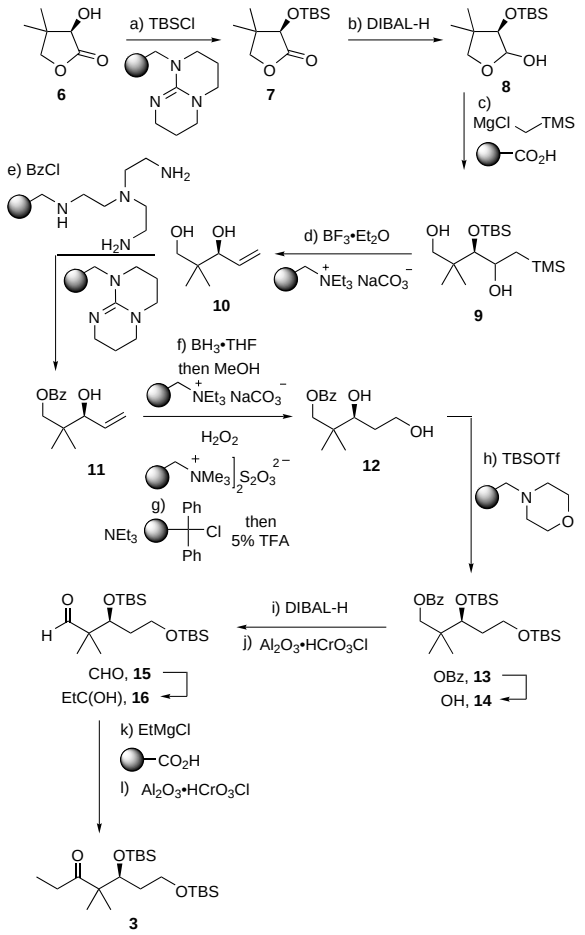
Fragment 3 (**5**) was obtained by two independent methods: Initially the C15 stereocentre was installed using a Brown allylation in conjunction with a catch-and-release method to isolate the resulting allyl alcohol;[17] while the second method incorporated a commercially available asymmetric α-hydroxylactone derivative of malic acid to introduce the C15 stereocentre.[14,15,21]

Results and Discussion

Ketone fragment 1: It was initially planned to derive fragment 1 (**3**) from pantolactone **6**, readily available as a single enantiomer with the requisite geminal dimethyl group in place.[24] Pantolactone **6** was TBS-protected using *tert*-butyldimethylsilylchloride in conjunction with a supported guanidine base (TBD), followed by reduction by treatment with DIBAL-H (Scheme 1). The reduction was quenched using sodium sulfate decahydrate to precipitate the aluminium salts, necessitating only filtration and concentration to provide lactol **8**. Successful transformation to olefin **10** was carried out via a Peterson olefination, involving the addition of (trimethylsilylmethyl)magnesium chloride followed by a scavenger quench using Amberlite IRC-50 immobilized carboxylic acid. Subsequent treatment with Lewis acid, quenched using a polymeric carbonate then affected the elimination to provide alkene **10**. The primary alcohol of diol **10** was selectively protected as the benzoate ester **11**, followed by a hydroboration–oxidation sequence to generate diol **12**. The derived material **12** was then purified by its covalent attachment to a trityl functionalized resin; this permitted extensive washing to remove contaminating by-products prior to its cleavage from the resin. A double TBS protection, followed by selective removal of the benzoate group of **13** using DIBAL-H provided alcohol **14**. Oxidation of the primary alcohol **14** using pyridinium chlorochromate (PCC) on alumina, extracting the product by filtration through Florisil, furnished aldehyde **15** which was further homologated to the desired ketone **3** via an ethylmagnesium chloride addition–oxidation sequence. Work-up of intermediate alcohol **16** was smoothly facilitated by polymer-supported acid quench (Amberlite IRC-50). Subsequent oxidation using PCC on basic alumina afforded the target fragment **3** in 12 steps.

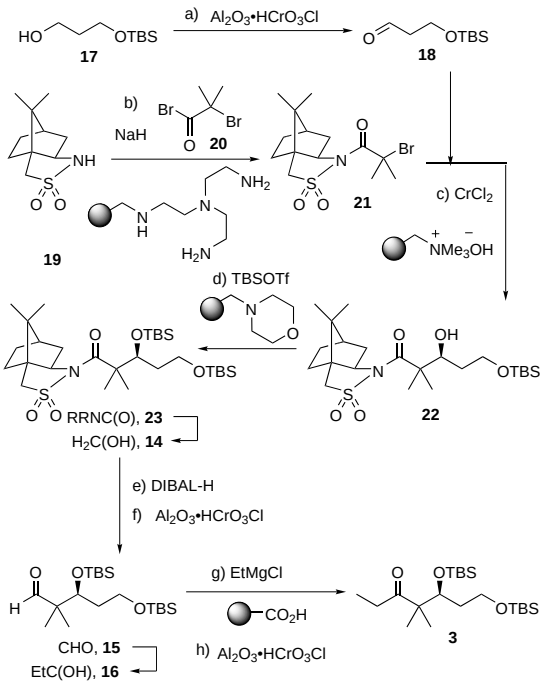
Although this route provided the desired fragment 1 (**3**) in high enantiopurity, the synthesis was somewhat lengthy. In an attempt to develop a more efficient route, several alternative strategies were investigated. It was decided that methods to selectively construct the stereocentre would offer improved synthetic efficiency.

Asymmetric aldol reaction using Oppolzer's chiral auxiliary **19** was employed to establish a more efficient route for the synthesis of the fragment **3** (Scheme 2). Sultam **19** was acylated with excess 2-bromoisobutyryl bromide **20** in the presence of sodium hydride. Excess acyl bromide **20** was efficiently scavenged using polymer-supported-trisamine to



Scheme 1. Pantolactone route to fragment 1. a) TBSCl (2.0 equiv), PS-TBD (5.0 equiv, 2.6 mmol g^{-1}), CH_2Cl_2, RT, 10 h, then MeOH, 96%; b) DIBAL-H (1.3 equiv, 1.0 M in PhMe), PhMe, −78 °C, 30 min, then $Na_2SO_4 \cdot 10H_2O$, RT, 99%; c) $TMSCH_2MgCl$ (4.0 equiv, 1.0 M in Et_2O), THF, 60 °C, 10 h, then Amberlite IRC-50 (28 equiv, 10 mmol g^{-1}), RT, 94%; d) $BF_3 \cdot Et_2O$ (1.0 equiv), RT, 15 h, then MeOH, PS-carbonate (5.0 equiv, 3.2 mmol g^{-1}), RT, 5 h, 98%; e) benzoyl chloride (1.2 equiv), PS-TBD (3.0 equiv, 2.6 mmol g^{-1}), CH_2Cl_2, RT, 5 h, then PS-trisamine (1.0 equiv, 4.27 mmol g^{-1}), RT, 73%; f) $BH_3 \cdot THF$ (3.0 equiv, 1.0 M in THF), THF, 0 °C, 20 h, then MeOH, PS-carbonate (15.0 equiv, 3.23 mmol g^{-1}), 30% H_2O_2, PS-thiosulfate (4.0 equiv, 2.0 mmol g^{-1}), then silica gel (Et_2O), 68%; g) Et_3N (3.0 equiv), PS-tritylchloride (2.0 equiv, 1.23 mmol g^{-1}), CH_2Cl_2, RT, 4 h, then CH_2Cl_2, 5% TFA, RT, 1 h, 88%; h) TBS triflate (3.0 equiv), PS-NMM (10 equiv, 3.5 mmol g^{-1}), CH_2Cl_2, 0 °C → RT, 20 h, then MeOH, 98%; i) DIBAL-H (3 equiv, 1 M in hexanes), THF, −78 °C, 1 h, then $Na_2SO_4 \cdot 10H_2O$, RT, then silica gel (hexane/EtOAc 10:1), 77%; j) PCC on basic alumina (4.0 equiv, 1.0 mmol g^{-1}), CH_2Cl_2, RT, 20 h, then silica gel (Et_2O), 100%; k) EtMgBr (2.0 equiv, 2.0 M in Et_2O), THF, −78 °C, 2 h, then Amberlite IRC-50, then silica gel (hexane/EtOAc 5:1), 98%; l) PCC on basic alumina (3.0 equiv, 1.0 mmol g^{-1}), CH_2Cl_2, RT, 20 h, then silica gel (Et_2O), 98%.[32]

isolate amide **21**. The chromium enolate of amide **21** was coupled with aldehyde **18** and quenched using polymer-supported-ammonium hydroxide to hydrolyze both the intermediate chromium complex and precipitate the unwanted chromium salts. Filtration of the subsequent suspension through a bond elute silica gel pad yielded Reformatsky adduct **22**. Secondary alcohol **22** was silylated and the chiral auxiliary removed by DIBAL-H reduction of amide **23** to produce the corresponding alcohol **14**. The final three steps from alcohol **14** were carried out as previously described

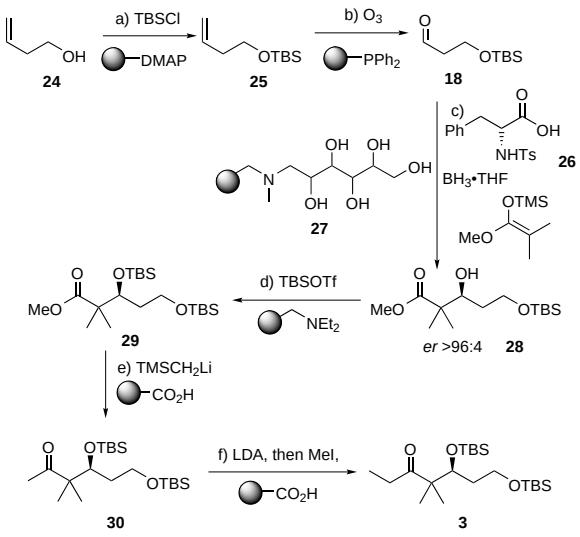


Scheme 2. Auxiliary route to fragment 1. a) PCC on basic alumina (3.0 equiv, 1.0 mmol g^{-1}), CH_2Cl_2, RT, 1 h, then silica gel (Et_2O), 87%; b) NaH (1.2 equiv, 60% dispersion), PhMe, 0 °C → RT, 1 h, then **20** (1.5 equiv), 0 °C → RT, 1 h, then PS-trisamine (3.0 equiv, 3.4 mmol g^{-1}), then silica gel (Et_2O), 92%; c) $CrCl_2$ (4.0 equiv), LiI (0.1 equiv), **18** (2.0 equiv), THF, RT, 1 h, then Ambersep 900 (OH^- form) (19.5 equiv, 3.2 mmol g^{-1}), then silica gel (hexane/EtOAc 10:1), 92%; d) TBS triflate (1.5 equiv), PS-NMM (5.0 equiv, 3.5 mmol g^{-1}), HCH_2Cl_2, 0 °C, 1 h, then MeOH, then silica gel (hexane/EtOAc 10:1), 89%; e) DIBAL-H (2.5 equiv, 1.0 M in CH_2Cl_2), CH_2Cl_2, −78 °C, 1 h, then $Na_2SO_4 \cdot 10H_2O$, RT, then silica gel (hexane/EtOAc 10:1), 90%; f) PCC on basic alumina (4.0 equiv, 1.0 mmol g^{-1}), CH_2Cl_2, RT, 20 h, then silica gel (Et_2O), 100%; g) EtMgBr (2.0 equiv, 2.0 M in Et_2O), THF, −78 °C, 2 h, then Amberlite IRC-50, then silica gel (hexane/EtOAc 5:1), 98%; h) PCC on basic alumina (3.0 equiv, 1.0 mmol g^{-1}), CH_2Cl_2, RT, 20 h, then silica gel (Et_2O), 98%.[32]

(Scheme 1) to afford fragment 1 (**3**) in a total of eight steps (>95% *de*).

A final method to construct fragment 1 (**3**) was investigated in an attempt to provide an even more efficient route to the desired molecule. This route is similar to those illustrated in the syntheses of Mulzer and Taylor.[21,22] As it offered both the shortest synthetic sequence and proved readily scalable, this method was subsequently adopted for the total synthesis. Formation of the C3–C4 bond proceeded with concomitant introduction of the desired C3 stereocentre by application of the asymmetric Mukaiyama aldol reaction developed by Kiyooka (Scheme 3).[33]

Aldol reaction, mediated by a complex of borane with *N*-tosyl-phenylalanine **26**, provided the desired product **28** in 92% enantiomeric excess.[34] Work-up necessitated addition of water and Amberlite IRA-743 **27**, a boron selective scavenger to quench the reaction and additionally remove contaminating boric acid. Filtration and solvent removal yielded a suspension of amino acid in aldol product **28**. The insolubility of the N-protected amino acid **26** in non-polar organic solvents permitted selective dissolution of the product **28**. Subsequent filtration enabled the amino acid residue to be



Scheme 3. Final synthesis of fragment 1. a) TBSCl (1.4 equiv), PS-DMAP (2.0 equiv, 1.49 mmol g^{-1}), CH_2Cl_2, RT, 2 h 30 min, 96%; b) O_3, CH_2Cl_2, −78°C, 20 min, then PS-triphenylphosphine (1.5 equiv, 3.3 mmol g^{-1}), −78°C→RT, 14 h, 93%; c) *N*-Ts-D-phenylalanine (1.2 equiv), BH_3•THF (1.05 equiv, 1.5 M in THF), CH_2Cl_2, 0°C→RT, 30 min, then aldehyde **18** (1.0 equiv), −96°C, 15 min, then 1-methoxy-2-methyl-1-trimethylsilyloxy-propene (1.0 equiv), −96°C→−78°C, 1 h 45 min, then H_2O (5 equiv), Amberlite IRA-743 (1.2 equiv, 1.0 mmol g^{-1}), −78°C→RT, 6 h, 92%, 92% *ee* (92% of *N*-Ts-D-phenylalanine recovered); d) TBS triflate (2.0 equiv), diethylaminomethylpolystyrene (5.0 equiv, 3.2 mmol g^{-1}), CH_2Cl_2, 0°C→RT, 2 h 45 min, then MeOH (25 equiv), RT, 1 h, 100%; e) $TMSCH_2Li$ (2.2 equiv, 1.0 M in pentane), pentane, 0°C, 3 h 15 min, then MeOH (50 equiv), 0°C→RT, 5 h, then Amberlite IRC-50 (25.5 equiv, 10.0 mmol g^{-1}), RT, 1 h 30 min, 100%; f) LDA (2.3 equiv), THF, −78°C→−15°C, 25 min, then MeI (3.1 equiv), −78°C→−40°C, 2 h, then Amberlite IRC-50 (25 equiv, 10.0 mmol g^{-1}), RT, 2 h, 94%.[32]

recovered and recycled whilst concentration of the filtrate allowed isolation of adduct **28**.

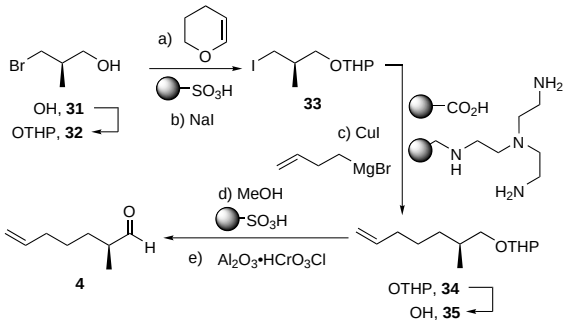
Protection of aldol adduct **28** proceeded using polymer-supported-triethylamine equivalent and excess TBS triflate to provide **29**. Any residual TBS triflate was quenched by the addition of methanol and the triflic acid retained within the basic polymer, necessitating only simple filtration and concentration to isolate the product **29**.

A successful method for conversion of methyl ester **29** to methyl ketone **30** had been demonstrated by Mulzer using (trimethylsilylmethyl)lithium.[21] Application of this method in combination with a scavenger-quench using a carboxylic acid resin, yielded ketone **30** (Scheme 3).

Methyl alkylation of **30** was achieved by treatment of the corresponding lithium enolate with iodomethane followed by a polymer-supported acid quench to provide ethyl ketone fragment 1 (**3**) in six steps.[21]

Fragment 2: Commercially available (*R*)-(−)-3-bromo-2-methyl-1-propanol **31**, derived from the (*R*)-Roche ester, was used as starting material for the synthesis of fragment 2 (**4**) (Scheme 4). Initial protection to form the tetrahydropyranyl ether **32** proceeded smoothly under acid catalysis using a polymeric sulfonic acid.

A Finkelstein halide exchange reaction then allowed conversion of primary bromide **32** to the corresponding iodide



Scheme 4. Synthesis of fragment 2. a) 3,4-Dihydro-2*H*-pyran (1.02 equiv), PS-TsOH (0.05 equiv, 4.2 mmol g^{-1}), neat, 30 min, 98%; b) NaI (3 equiv), 2-butanone, 75°C, 1 h, then silica gel filtration (Et_2O), 96%; c) CuI (1.0 equiv), 3-butenylmagnesium bromide (4.0 equiv, 0.5 M in THF), THF, −10°C→0°C, 2 h 15 min, then Amberlite IRC-50 (15 equiv, 10.0 mmol g^{-1}) and PS-trisamine (3.0 equiv, 4.36 mmol g^{-1}), RT, 24 h, 97%; d) MP-TsOH (0.04 equiv, 4.2 mmol g^{-1}), MeOH, RT, 7 h 30 min, 97%; e) PCC on basic alumina (3.0 equiv, 1.0 mmol g^{-1}), CH_2Cl_2, RT, 3 h 30 min, 80%.[32]

33. Work-up required the addition of Et_2O to precipitate the sodium salts, followed by slurring the mixture with silica gel; filtration and solvent removal then yielded the iodide **33** as a yellow oil.

Displacement of iodide **33** with the cuprate derived from 3-butenylmagnesium bromide gave the required alkene **34** (Scheme 4). Addition of carboxylic acid resin and trisamine resin quenched the reaction and scavenged dissolved copper salts. The resulting mixtures of dark precipitate and green copper-chelated resins were removed by filtration through a pad of silica gel followed by solvent removal to provide alkene **34** as a pale yellow oil.

Hydrolysis of tetrahydropyran(THP)-acetal **34** was affected using catalytic sulfonic acid resin in methanol. The volatility of the methoxy tetrahydropyran by-product allowed straightforward purification of desired alcohol product **35**.

Although a number of oxidative procedures proceeded to completion, including tetrapropylammonium perruthenate (TPAP)/NMO and Dess–Martin reagent, PCC on basic alumina was employed as the most expedient reagent provide aldehyde fragment 2 (**4**) in five steps.

Fragment 3: Two methods were used to construct fragment 3 (**5**). Although attempts were made to generate the C15 stereocentre by an asymmetric reduction using polymer-supported ligands, these proceeded with only low enantioselectivities. As a result, a conventional boron allylation strategy was successfully applied to provide a route to the desired fragment 3 (**5**). A shorter alternative method was also developed that incorporated a commercially available enantiopure lactone **47** (Scheme 6).

The initial route to fragment 3 (**5**) applied a Hantzsch thiazole synthesis between dibromoacetone and thioacetamide in dioxane to yield hydrobromide salt **36** as a precipitate (Scheme 5). The free base **37** was obtained by treatment of the salt with a polymer-supported carbonate, followed by refluxing with polymer-supported triphenylphosphine to form the polymer-supported-phosphonium bromide **38**. Treatment of the phosphonium salt **38** with an excess of

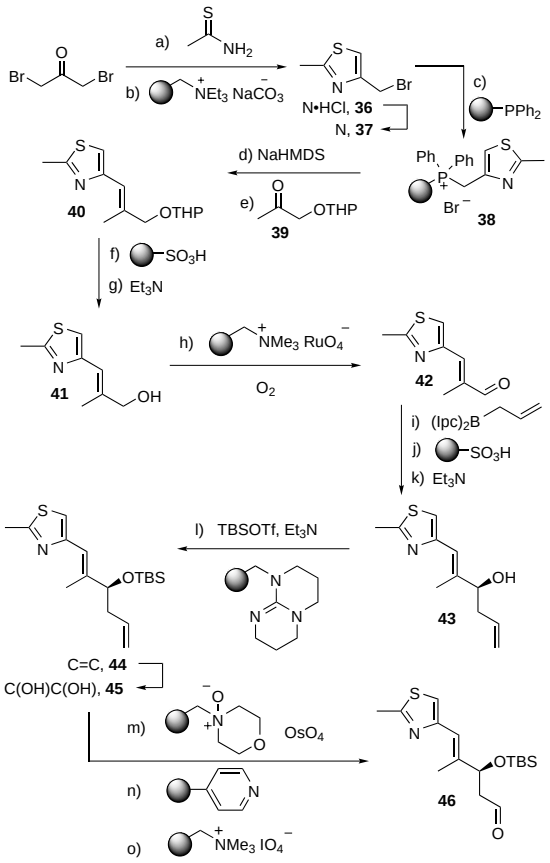
sodium bis(trimethylsilyl)amide followed by resin washing permitted the isolation of the immobilized ylide.[35] The ylide was treated with THP protected α-hydroxyacetone **39** to yield the desired Wittig product **40** with a 10:1 *E*:*Z* ratio. The corresponding triphenylphosphine oxide and unreacted ylide remained bound to the polymer support and were removed by simple filtration. Treatment of the resulting THP-ether **40** with acidic Dowex-50X8 resin deprotected the alcohol and captured the thiazole via the basic nitrogen. Washing of the resin conveniently removed contaminants and subsequent treatment with a solution of triethylamine in methanol released the alcohol **41** from the resin support. Oxidation of the primary alcohol to the required aldehyde **42** was achieved using catalytic polymer-supported perruthenate at reflux under an atmosphere of oxygen.[36,37] The key part of this route was the installation of the C15 chiral centre in alcohol **43**. A precedented route using Brown's (+)-diisopinocamphenylallyborane gave the best results,[13] followed by an acid resin catch-and-release purification to yield the desired alcohol **43** in 92% *ee*. Alcohol **43** was protected as the TBS ether **44**, followed by conversion of alkene **44** to aldehyde **46** via a dihydroxylation–oxidative cleavage sequence. It was initially envisaged that these reactions could be achieved sequentially in a single reaction vessel, however, it proved impossible to carry out both reactions in the same solvent so a conventional two-step process was applied. Dihydroxylation was achieved using catalytic osmium tetroxide and polymer-supported *N*-methylmorpholine oxide as the co-oxidant. Polyvinyl pyridine was later added to scavenge the osmium tetroxide from solution, and the diol **45** was cleaved using polymer-supported periodate with a simple filtration yielding fragment precursor aldehyde **46** in 12 steps.

As an alternative, it was chosen to adapt the methods first described by Mulzer in which the C15 stereocentre was installed from commercially available (*S*)-α-hydroxy-γ-lactone **47** (Scheme 6).[21,38]

Hydroxy lactone **47** was protected using TBSCl with polymer-supported DMAP, followed by addition of methyllithium, which was quenched with a carboxylic acid resin to produce hemiketal **49**. This could be protected as the double TBS ether ketone **50**.

Phosphonate **53** was formed from thiazole chloride **52** (prepared from commercially available **51**) by heating in excess neat triethylphosphite. Most residual phosphite was later removed under reduced pressure, although some phosphorus by-products remained and were carried through subsequent steps. It was anticipated that the final formation of polymer-supported phosphonium salt **56** for Wittig fragment coupling would permit a catch-and-release purification, allowing these residual impurities to be removed at this latter stage.[35]

Phosphonate **53** was deprotonated and reacted with ketone **50** (Scheme 6). An excess phosphonate anion was used and later scavenged using a polymer-supported aldehyde, and addition of silica gel to bind any phosphorus by-products. Although attempts were made to develop a supported version of this phosphonate, these proved to give only poor loadings, and so were not applied.[39]

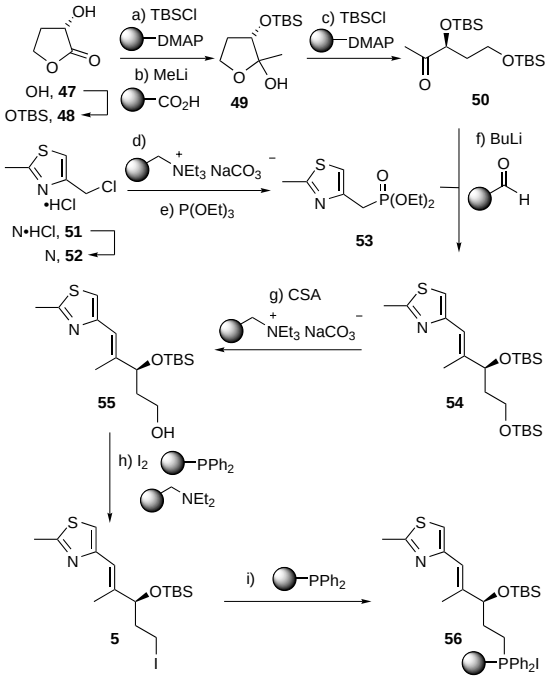


Scheme 5. Asymmetric allylation route to fragment 3. a) Thioacetamide (0.9 equiv), dioxane, reflux, 30 min, 82%; b) PS-carbonate (2.5 equiv, 4.5 mmol g^{-1}), MeOH, RT, 3 h, 96%; c) PS-triphenylphosphine (0.78 equiv, 3.0 mmol g^{-1}), PhMe, 90 °C, 5 h; d) NaHMDS (6 equiv, 1.0 M in THF), THF, RT, 45 min; e) **39** (0.33 equiv), THF, RT, 15 h, 94%; f) Dowex 50X8, MeOH, RT, 5 h; g) Et_3N (10 equiv), MeOH, RT, 4 h, 92%; h) PS-perruthenate (0.2 equiv, 0.5 mmol g^{-1}), PhMe, O_2, reflux, 16 h, 60%; i) (+)-diisopinocamphenylallylborane (1.5 equiv), Et_2O, −100 °C, 3 h; j) Dowex 50X8, MeOH, RT, 5 h; k) Et_3N (10 equiv), MeOH, RT, 4 h, 89%; l) TBS triflate (1.2 equiv), Et_3N (1.5 equiv), PS-TBD (3.4 equiv, 2.2 mmol g^{-1}), CH_2Cl_2, RT, 16 h, 97%; m) PS-NMO (8.5 equiv, ≈3.0 mmol g^{-1}), OsO_4 (0.7 equiv), acetone/H_2O 9:1, 40 °C, 16 h; n) polyvinylpyridine (6.8 equiv, ≈9.5 mmol g^{-1}), 97%; o) PS-periodinate, methanol/H_2O 5:1, RT, 24 h, 95%.[32]

Selective mono-deprotection of bis-silyl protected thiazole **54** was affected using camphorsulfonic acid (CSA) in methanol. The resulting mixture was scavenger-quenched by the use of carbonate on support to provide the corresponding alcohol **55**.

Conversion of primary alcohol **55** to iodide **5** proceeded using iodine with polymer-supported triphenylphosphine and a polymer-supported triethylamine equivalents to yield the fragment in a total of nine steps (seven steps longest linear sequence) (Scheme 6).

Iodide **5** was converted to phosphonium salt **56** by heating with polymer-supported triphenylphosphine in toluene. This provided a supported phosphonium salt **56** with a loading of 0.9 mmol g^{-1}. The efficiency of the loading procedure was enhanced by the recovery of any unloaded iodide **5** for subsequent reuse.



Scheme 6. Final synthesis of fragment 3. a) TBSCl (1.4 equiv), PS-DMAP (2.0 equiv, 1.49 mmol g^{-1}), CH_2Cl_2, RT, 1 h 30 min, 97%; b) MeLi (1.05 equiv), THF, −78°C, 40 min, then Amberlite IRC-50 (21 equiv, ~10 mmol g^{-1}), RT, 45 min, 98%; c) TBSCl (1.48 equiv), PS-DMAP (2.0 equiv, 1.49 mmol g^{-1}), CH_2Cl_2, RT, 2 h 30 min, 98%; d) PS-carbonate (2 equiv, 3.5 mmol g^{-1}), MeOH, RT, 45 min, 98%; e) triethylphosphite (1.2 equiv), neat, 160°C, 3 h, 84%; f) **53** (3.5 equiv), *n*BuLi (3.5 equiv, 1.6 M in hexanes), THF, −78°C, then **50** (1.0 equiv), −78°C→RT, 1.5 h, then PS-benzaldehyde (5.0 equiv, 1.2 mmol g^{-1}), RT, 30 min, then silica gel (Et_2O), 105%; g) CSA (1.5 equiv), MeOH/CH_2Cl_2 (1:1), 0°C, 2 h 30 min, then PS-carbonate (2.2 equiv, 3.5 mmol g^{-1}), 2 h, 104%; h) iodine (4.0 equiv), PS-triphenylphosphine (5.0 equiv, 3.3 mmol g^{-1}), MeCN/Et_2O 3:1, then diethylaminomethylpolystyrene (8.0 equiv, 3.2 mmol g^{-1}), RT, 19 h, 73%; i) PS-triphenylphosphine (1.0 equiv, 3.3 mmol g^{-1}), PhMe, 90°C, 18 h.[32]

The final steps: Coupling at C6–C7 has been extensively investigated using a wide variety of substrates, and shown to be highly sensitive to proximal and remote functionality in both fragments.[20,40] Our approach, although bearing close analogy to those already published, incorporated a novel fragment combination of ketone **3** and aldehyde **4**. This coupling proceeded with high diastereoselectivity (>13:1) using lithium diisopropylamide (LDA) as base (Scheme 7).[41] Attempts to apply an immobilized acid quench resulted in a destructive retro-aldol reaction. For this reason, acetic acid was used since it permitted a lower temperature quench and alleviated product decomposition. Excess acetic acid and aldehyde **4** were subsequently removed from the mixture using a diamine functionalized polymer. Simple filtration then allowed isolation of the secondary alcohol aldol product **57**.

The TBS protection of adduct **57** was successfully completed using TBS triflate with a polymeric triethylamine equivalent. Methanol was added after completion of the reaction to consume excess TBS triflate. Filtration, followed by concentration under reduced pressure, allowed isolation of the desired product **58**.

The C12 alkene was cleaved by ozonolysis, quenching the ozonide with polymer-supported triphenylphosphine to successfully yield aldehyde **59** for application in a Wittig fragment coupling (Scheme 7).[42]

Resin-bound phosphonium salt **56** of fragment 3 was treated with an excess of sodium hexamethyldisilazide (NaHMDS), followed by washing with dry THF. This permitted isolation of the corresponding salt-free ylide which was coupled with aldehyde **59** to install the required C12–C13 *cis*-olefin **60**. An excess of the polymer-supported salt **56** was used in order to ensure good conversion with respect to the aldehyde fragment **59**. Isolation of alkene intermediate **60** then required only filtration and concentration.

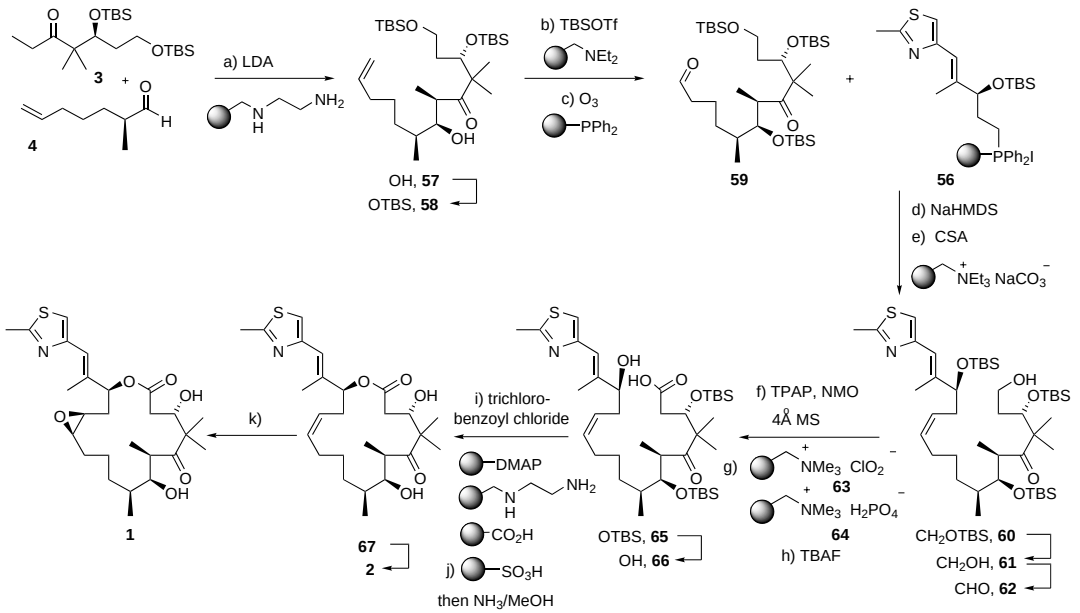
Although polymer-supported sulfonic acids efficiently removed the C1 protecting group in **60** some double C1/15 deprotection occurred. Furthermore, protonation of the thiazole ring caused unwanted sequestration by the polymer. To circumvent this problem, a dilute solution of camphorsulfonic acid in methanol was used to selectively remove the primary TBS group of compound **60**. A polymeric carbonate base was added following the reaction to quench and scavenge the acid with the volatile MeOTBS by-product being removed under reduced pressure.

Oxidation of the resulting primary alcohol **61** to aldehyde **62** was successful using TPAP/NMO, applying filtration through silica gel to remove the morpholine and ruthenium by-products.[37,43]

Further oxidation of aldehyde **62** to the corresponding carboxylic acid **65** was achieved by application of a modified Pinnick oxidation using a polymer-supported chlorite reagent **63**.

The selective deprotection of the C15 secondary allylic TBS ether **65** proved to be difficult. Although precedented conditions using tetrabutylammonium fluoride (TBAF) solution effected clean conversion to alcohol **66**, they required aqueous work-up to remove excess fluoride reagent. Alternative conditions, applying a polymer-supported or solution-phase sulfonic acids were tested to avoid the work-up, but proved unsuccessful resulting in complex mixtures of starting material and mono-, di- and tri-deprotected products.[44] A polymer-supported fluoride and polyvinylpyridine (PVP)·HF were investigated, but also proved ineffective. Consequently, it was deemed necessary to adopt the original TBAF reaction applying aqueous extraction, although no further purification was undertaken (Scheme 7).

A Yamaguchi macrolactonisation using polymer-supported DMAP successfully cyclized **66** to macrolactone **67**.[18,25] Although treatment with a mixture of weakly acidic and weakly basic polymers was sufficient to remove most impurities following reaction, the product was still contaminated. Product capture via the thiazole was therefore undertaken using a polymeric sulfonic acid resin. The loaded polymer was washed to remove all unbound impurities followed by treatment with a solution of ammonia or triethylamine in methanol to release the product from the resin. The washings were concentrated to provide an oil which was identified as epothilone C (**2**). Therefore, not only was the capture and release effective, but the necessary double deprotection to cleave the final TBS ethers occurred. A single chromatog-



Scheme 7. Fragment coupling and cyclization. a) LDA (1.6 equiv), THF, −78 °C→−40 °C, 1 h 30 min, then aldehyde **4** (1.5 equiv), −78 °C, 20 min, then AcOH (5 equiv), −78 °C→RT, 30 min, then PS-diamine (4.8 equiv, 3.0 mmol g^{-1}), RT, 2 h, 100 % (13.5:1); b) TBS triflate (1.5 equiv), diethylaminomethylpolystyrene (3.0 equiv, 3.2 mmol g^{-1}), CH_2Cl_2, 0 °C→RT, 3 h 25 min, then MeOH (3.0 equiv), RT, 2 h, 99 %; c) O_3, CH_2Cl_2, −78 °C, 20 min, then PS-triphenylphosphine (5.0 equiv, 3.3 mmol g^{-1}), −78 °C→RT, 15 h, 100 %; d) phosphonium salt **56** (2.5 equiv, 0.8 mmol g^{-1}), NaHMDS (10.0 equiv, 1 M in THF), THF, RT, 10 min, then THF wash, then aldehyde **59** (1.0 equiv), −78 °C, 10 min, 93 %; e) CSA (1.0 equiv), MeOH/CH_2Cl_2 1:1, 0 °C, 4 h, then CH_2Cl_2, PS-carbonate (4 equiv, 2.8 mmol g^{-1}), 2 h, RT, 99 %; f) TPAP (0.05 equiv), NMO (1.5 equiv), 4 Å MS, CH_2Cl_2, 0 °C→RT, 3 h 10 min, then silica gel (Et_2O), 93 %; g) PS-chlorite **63** (2 equiv, ~0.5 mmol g^{-1}), PS-dihydrogenphosphate **64** (3 equiv, ~0.5 mmol g^{-1}), 2,3-dimethyl-2-butene (5 equiv, 2 M THF), *t*BuOH/H_2O 1:2, RT, 6 h, 99 %; h) TBAF (6 equiv, 1 M THF), THF, RT, 4 h, 100 %; i) 2,4,6-trichlorobenzoylchloride (10.0 equiv), Et_3N (12 equiv), RT, 50 min, then added to PS-DMAP (20 equiv, 1.48 mmol g^{-1}), THF/toluene (1:25), 80 °C, 2 h 30 min, then PS-diamine (63 equiv, 3.8 mmol g^{-1}), Amberlite IRC-50 (333 equiv, 10.0 mmol g^{-1}), 2 h, RT; j) PS-TsOH (12 equiv, 1.5 mmol g^{-1}), CH_2Cl_2, 1 h, then wash CH_2Cl_2 and Et_2O, then wash release NH_3 (2 M in MeOH), 81 % (2 steps), k) ref. [13].[32]

raphy column was run on this final material to remove both residual impurities and small quantities of minor diastereoisomers that had been carried through the synthesis.

Conclusion

In summary, by the synthesis of epothilone C we have demonstrated the scope and utility of supported reagents and scavenging techniques within a stereocontrolled multi-step natural product synthesis. The high selectivity and overall efficiency was comparable with the best of the previous conventional syntheses, preparing the target molecule in 29 steps with a longest linear sequence of only 17 steps from readily available materials. As epothilone C is the most challenging target that has been accomplished using solid-phase reagent and scavenging techniques, we hope that this will encourage their future integration alongside conventional methods for application within general synthesis programs.[45]

Experimental Section

General: All reactions were carried out under an atmosphere of argon, and those not involving aqueous reagents were carried out in oven-dried (200 °C) glassware, cooled under vacuum. All reagents were used as supplied or purified using standard procedures, as necessary. Ether (Et_2O) and tetrahydrofuran (THF) were distilled over sodium/benzophenone; dichloromethane (CH_2Cl_2), acetonitrile (MeCN), methanol (MeOH), benzene and toluene (PhMe) were distilled from calcium hydride; triethylamine (Et_3N), diisopropylethylamine (DIPEA) and diisopropylamine (DIPA) were distilled from potassium hydroxide. All other solvents and reagents were used as supplied unless otherwise stated. Ozonolyses were carried out using a Peak Scientific ozone generator. Flash column chromatography was carried out using Merck 60 Kieselgel (230–400 mesh) under pressure unless otherwise stated. Analytical thin-layer chromatography (TLC) was performed on glass plates pre-coated with Merck Kieselgel 60 F254, and visualised by UV irradiation (254 nm), or by staining with aqueous acidic ammonium molybdate, or aqueous acidic potassium permanganate solutions as appropriate. Melting points were measured on a Reichert hot stage apparatus, and are uncorrected. Optical rotations were measured on an Perkin–Elmer Model 343 polarimeter, and $[\alpha]_D$ values are reported in 10^{-1} deg cm^2 g^{-1}; concentration (c) is in g 100 mL^{-1}. IR spectra were obtained on a Spectrum One FT-IR ATR (Attenuated Total Reflectance) spectrometer, from a thin film deposited onto the ATR. Microanalyses were performed in the microanalytical laboratories at the Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge using a CE-440 Elemental Analyser. Mass spectra and accurate mass data were obtained on a Micromass Platform LC-MS, Kratos MS890 MS, Kratos Concept IH, Micromass Q-TOF, or Bruker BIOAPEX 4.7 T FTICR spectrometer, by electron ionisation, chemical ionisation or fast atom/ion bombardment techniques at the Department of Chemistry, Uniiversity of Cambridge, Lensfield Road, Cambridge. ^1H NMR spectra were recorded at ambient temperature on Bruker DPX-400, DRX-400, DRX-500 or Bruker-DRX-600 spectrometers, at 200, 400, 500 or 600 MHz, with residual protic solvent as the internal reference ($CHCl_3$ $\delta_H = 7.26$ ppm; MeOH $\delta_H = 3.30$ ppm); chemical shifts (δ) are given in parts per million (ppm), and coupling constants (J) are given in Hertz (Hz). The proton spectra are reported as follows δ ppm^{-1} (multiplicity, coupling constant J Hz^{-1}, number of protons, assignment). Assignments of numbered protons are made according to the numbering of the

natural product epothilone C, as shown. ^{13}C NMR spectra were recorded at ambient temperature on the same spectrometers at 50, 100 or 150 MHz, with the central peak of $CHCl_3$ as the internal reference (δ_C = 77.0 ppm). Assignments of numbered carbons are made according to the numbering of the natural product epothilone C, as shown. DEPT135 and two-dimensional (COSY, HMQC, HMBC) NMR spectroscopy were used where appropriate, to aid in the assignment of signals in the ^1H and ^{13}C NMR spectra. Where coincident coupling constants have been observed in the NMR spectrum, the apparent multiplicity of the proton resonance concerned has been reported.

Preparation of the polymer-supported (PS) reagents

Fluka triphenylphosphine, polymer bound: Washed using MeOH (3×), CH_2Cl_2 (3×), Et_2O (3×), then dried to constant mass under reduced pressure at room temperature before use.

Fluka carbonate on polymer support: Used directly as supplied.

Fluka diethylaminomethyl-polystyrene: Washed using MeOH (3×), CH_2Cl_2 (3×), Et_2O (3×), then dried to constant mass under reduced pressure at room temperature before use.

Fluka DMAP on polystyrene: Washed using MeOH (3×), CH_2Cl_2 (3×), Et_2O (3×), then dried to constant mass under reduced pressure at 50–60 °C before use.

Fluka bromopolystyrene: Washed using MeOH (3×), then used directly.

Argonaut DMAP on polystyrene: *For silyl protections*: Used directly as supplied.

For macrocyclisation: Washed using MeOH (3×), CH_2Cl_2 (3×), Et_2O (3×), then dried to constant mass under reduced pressure at 50–60 °C before use.

Argonaut polymer-supported benzaldehyde: Used directly as supplied.

Argonaut MP-TsOH(I), (II) or Amberlyst-15 (MP: macroporous polymer): *For reactions when used as an acid catalyst*: Used directly as supplied.

For final multi-stoichiometric catch-and-release: Washed using MeOH (3×), CH_2Cl_2 (3×), Et_2O (3×), then dried to constant mass under reduced pressure at room temperature before use.

NovaBiochem tris-(2-aminoethyl)amine polystyrene (trisamine): Used directly as supplied.

NovaBiochem *N*-(2-aminoethyl)aminomethyl polystyrene (diamine): Used directly as supplied.

NovaBiochem dibutylphenylphosphine on polystyrene: Used directly as supplied.

NovaBiochem (polystyrylmethyl)trimethylammonium perruthenate: Used directly as supplied.

NovaBiochem morpholinomethyl polystyrene: Used directly as supplied.

Amberlite IRC-50 carboxylic acid polymer: Washed using MeOH (3×), CH_2Cl_2 (3×), Et_2O (3×), then dried to constant mass under reduced pressure at room temperature before use.

Amberlite IRA-743 boron scavenger: Washed using MeOH (3×), CH_2Cl_2 (3×), Et_2O (3×), then dried to constant mass under reduced pressure at room temperature before use.

Aldrich pyridinium chlorochromate on basic alumina: Used directly as supplied.

Fragment 1

(3*R*)-3-(*tert*-Butyldimethylsilyloxy)-4,4-dimethyldihydrofuran-2-one (7):[46] Polymer-supported-1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) (82 g, 2.6 mmol g^{-1}) and TBSCl (12.9 g, 85.4 mmol) were added to a solution of (*R*)-pantolactone **6** (5.6 g, 42.7 mmol) in CH_2Cl_2 (600 mL) at RT. After stirring for 10 h, MeOH (10 mL) was added. The mixture was filtered and concentrated under reduced pressure. The residue was dissolved in MeOH and concentrated three times to yield lactone **7** as a white solid (10 g, 96 %). M.p. 93–94 °C; $[\alpha]_D^{25} = +30.6$ (c = 1.45, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 3.98 (s, 1H, C*H*OTBS), 3.97 (d, ^3J(H,H) = 8.8 Hz, 1H, C*H*HO), 3.86 (d, ^3J(H,H) = 8.8 Hz, 1H, CH*H*O), 1.13 (s, 3H, CH_3CCH_3), 1.04 (s, 3H, CH_3CCH_3), 0.93 (s, 9H, SiC(CH_3)$_3$), 0.19 (s, 3H, SiCH_3), 0.12 (s, 3H, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.8, 75.8, 40.9, 25.6, 23.1, 19.1, 18.3, −4.5, −5.4; IR (film): $\tilde{\nu}$ = 2953, 2929, 1792, 1764, 1460, 1246, 1246, 1210, 1133, 1008, 861, 834, 778 cm^{-1}; MS (EI): *m*/*z*: calcd for $C_{12}H_{24}O_3SiNa$: 267.1392; found: 267.1398 $[M+Na]^+$.

(3*R*)-3-(*tert*-Butyldimethylsilyloxy)-4,4-dimethyltetrahydro-furan-2-ol (8):[46] A solution of DIBAL-H (53.3 mL, 1.0 M in toluene) was added to furanone **7** (10 g, 41.0 mmol) in toluene (200 mL) at −78 °C. The mixture was stirred for 30 min at −78 °C then Et_2O and ground sodium sulfate decahydrate were added to the mixture followed by gradual warming to RT. Filtration and concentration under reduced pressure yielded alcohol **8** as a white solid (9.9 g, 99 %). M.p. 50–52 °C; $[\alpha]_D^{25} = +29.7$ (c = 1.30, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 5.16 (d, ^3J(H,H) = 3.1 Hz, 1H, OC*H*OH), 3.78 (d, ^3J(H,H) = 8.3 Hz, 1H, C*H*HOH), 3.67 (d, ^3J(H,H) = 3.1 Hz, 1H, C*H*OTBS), 3.64 (d, ^3J(H,H) = 8.3 Hz, 1H, CH*H*OH), 3.12 (br s, 1H, O*H*), 1.06 (s, 3H, CH_3CCH_3), 1.01 (s, 3H, CH_3CCH_3), 0.91 (s, 9H, SiC(CH_3)$_3$), 0.09 (s, 3H, SiCH_3), 0.07 (s, 3H, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 104.6, 85.4, 78.5, 42.3, 25.8, 23.7, 20.2, 18.1, −4.5, −5.0; IR (film): $\tilde{\nu}$ = 3290, 2953, 2930, 1461, 1249, 1123, 1009, 985, 864, 835, 776 cm^{-1}; MS (EI): *m*/*z*: calcd for $C_{12}H_{26}O_3SiNa$: 269.1549; found: 269.1545 $[M+Na]^+$.

(3*R*)-3-(*tert*-Butyldimethylsilyloxy)-2,2-dimethyl-5-trimethylsilylpentane-1,4-diol (9): A solution of trimethylsilylmethylmagnesium chloride (35.6 mL, 1.0 M in Et_2O) was added to furanol **8** (2.18 g, 8.90 mmol) in THF (35 mL) at RT. The mixture was heated at 60 °C for 10 h, then cooled to RT and polymer-supported-COOH (Amberlite IRC-50, 25 g, 250 mmol, 10 mmol g^{-1}) was added. The mixture was filtered and concentrated under reduced pressure to afford the diol **9** as a white solid (2.8 g, 94 %). The two diastereoisomers were separated by flash chromatography (hexane/Et_2O 15:1).

Major isomer: m.p. 79–80 °C; $[\alpha]_D^{25} = +3.5$ (c = 0.82, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 4.05 (dd, ^3J(H,H) = 9.8, 4.8 Hz, 1H, C*H*OH), 3.86 (br s, 1H, O*H*), 3.66 (d, ^3J(H,H) = 11.6 Hz, 1H, C*H*HOH), 3.25 (s, 1H, C*H*OTBS), 3.04 (d, ^3J(H,H) = 11.6 Hz, 1H, CH*H*OH), 2.76 (br s, 1H, O*H*), 1.02 (dd, ^3J(H,H) = 14.5, 9.8 Hz, 1H, C*H*HSi(CH_3)$_3$), 0.97 (s, 3H, CH_3CCH_3), 0.95 (s, 9H, SiC(CH_3)$_3$), 0.84 (s, 3H, CH_3CCH_3), 0.64 (dd, ^3J(H,H) = 14.5, 4.8 Hz, 1H, CH*H*Si(CH_3)$_3$), 0.16 (s, 3H, SiCH_3), 0.14 (s, 3H, SiCH_3), 0.04 (s, 9H, Si(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 83.7, 66.9, 66.5, 40.0, 26.4, 26.1, 25.4, 21.9, 18.8, −0.86, −3.00, −3.52; IR (film): $\tilde{\nu}$ = 3123, 2956, 2854, 1472, 1245, 1205, 1060, 1032, 862, 832, 772, 691, 670 cm^{-1}; MS (EI): *m*/*z*: calcd for $C_{16}H_{38}O_3Si_2Na$: 357.2257; found: 357.2248 $[M+Na]^+$.

Minor isomer: m.p. 79–80 °C; $[\alpha]_D^{25} = -5.1$ (c = 0.74, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 3.98 (ddd, ^3J(H,H) = 6.0, 2.4, 2.2 Hz, 1H, C*H*OH), 3.47 (d, ^3J(H,H) = 2.4 Hz, 1H, C*H*OTBS), 3.46 (d, ^3J(H,H) = 11.3 Hz, 1H, C*H*HOH), 3.34 (d, ^3J(H,H) = 11.3 Hz, 1H, CH*H*OH), 2.19 (br s, 1H, O*H*), 1.68 (br s, 1H, O*H*), 1.04 (dd, ^3J(H,H) = 14.8, 6.0 Hz, 1H, C*H*HSi(CH_3)$_3$), 0.98 (s, 3H, CH_3CCH_3), 0.94 (s, 3H, CH_3CCH_3), 0.93 (s, 9H, SiC(CH_3)$_3$), 0.79 (dd, ^3J(H,H) = 14.8, 2.2 Hz, 1H, CH*H*Si(CH_3)$_3$), 0.11 (s, 3H, SiCH_3), 0.10 (s, 3H, SiCH_3), 0.05 (s, 9H, Si(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 84.0, 72.2, 68.7, 39.9, 26.1, 24.9, 22.9, 20.7, 18.4, −0.87, −3.55, −4.62; IR (film): $\tilde{\nu}$ = 3114, 2951, 2855, 1472, 1386, 1247, 1081, 1048, 854, 832, 772, 672 cm^{-1}; MS (EI): *m*/*z*: calcd for $C_{16}H_{38}O_3Si_2Na$: 357.2257; found: 357.2251 $[M+Na]^+$.

(3*S*)-2,2-Dimethylpent-4-ene-1,3-diol (10): $BF_3{\cdot}Et_2O$ (0.964 mL, 7.84 mmol) was added to a solution of diol **9** (2.6 g, 7.84 mmol) in CH_2Cl_2 (15 mL) at RT. The mixture was stirred for 15 h, then MeOH (25 mL) and polymer-supported-carbonate (12 g, 3.23 mmol g^{-1}) were added. The suspension was stirred for 5 h then filtered. The filtrate was concentrated under reduced pressure to afford alkene **10** as a pale yellow oil (1.0 g, 98 %). $[\alpha]_D^{25} = -20.5$ (c = 0.74, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 5.96 (ddd, ^3J(H,H) = 17.2, 10.5, 6.7 Hz, 1H, C*H*=CH$_2$), 5.27 (dd, ^3J(H,H) = 17.2, 1.1 Hz, 1H, CH=C*H*$_{cis}$H$_{trans}$), 5.22 (dd, ^3J(H,H) = 10.5, 1.1 Hz, 1H, CH=CH$_{cis}$*H*$_{trans}$), 4.02 (dd, ^3J(H,H) = 6.7, 3.3 Hz, 1H, C*H*OH), 3.58 (dd, ^3J(H,H) = 10.8, 5.6 Hz, 1H, C*H*HOH), 3.47 (dd, ^3J(H,H) = 10.8, 4.8 Hz, 1H, CH*H*OH), 2.46 (dd, ^3J(H,H) = 5.6, 4.8 Hz, 1H, (C1)O*H*), 2.39 (d, ^3J(H,H) = 3.3 Hz, 1H, (C3)OH), 0.93 (s, 3H, CH_3CCH_3), 0.89 (s, 3H, CH_3CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.5, 116.6, 80.6, 71.6, 38.2, 22.3, 18.9; IR (film): $\tilde{\nu}$ = 3334, 2960, 2875, 1473, 1425, 1390, 1366, 1250, 1118, 1039, 992, 923 cm^{-1}; MS (EI): *m*/*z*: calcd for $C_7H_{14}O_2Na$: 153.0891; found: 153.0883 $[M+Na]^+$.

(3*S*)-3-Hydroxy-2,2-dimethylpent-4-enyl benzoate (11): Polymer-supported-TBD (8.9 g, 2.6 mmol g^{-1}) and BzCl (1.07 mL, 9.25 mmol) was added to a solution of diol **10** (1.0 g, 7.71 mmol) in CH_2Cl_2 (100 mL) at RT. After stirring for 5 h, polymer-supported-trisamine (1.8 g, 4.27 mmol g^{-1})

was added then the suspension was filtered and concentrated under reduced pressure. The residue was filtered through a silica gel pad eluting with Et_2O to obtain benzoate **11** as a pale yellow oil (1.32 g, 73%). $[\alpha]_D^{25} = -21.5$ ($c = 0.84$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.04$ (dd, $^3J(H,H) = 7.5$, 1.2 Hz, 2H, *m*-Ph), 7.56 (dd, $^3J(H,H) = 7.4$, 1.2 Hz, 1H, *p*-Ph), 7.45 (dd, $^3J(H,H) = 7.5$, 7.4 Hz, 2H, *m*-Ph), 5.96 (ddd, $^3J(H,H) = 17.2$, 10.5, 6.7 Hz, 1H, C*H*=CH_2), 5.29 (dd, $^3J(H,H) = 17.2$, 0.8 Hz, 1H, CH=C$H_{cis}H_{trans}$), 5.21 (dd, $^3J(H,H) = 10.5$, 0.8 Hz, 1H, CH=C$H_{cis}H_{trans}$), 4.36 (d, $^3J(H,H) = 11.0$ Hz, 1H, BzOC*H*H), 4.08 (d, $^3J(H,H) = 11.0$ Hz, 1H, BzOCH*H*), 4.04 (d, $^3J(H,H) = 6.7$ Hz, 1H, C*H*OH), 1.03 (s, 3H, CH_3CCH_3), 1.02 (s, 3H, CH_3CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 166.8, 136.9, 133.0, 130.2, 130.1, 129.6, 128.4, 117.1, 70.8, 38.7, 21.4, 19.6; IR (film): $\tilde{\nu} = 3466$, 2966, 1703, 1602, 1451, 1371, 1315, 1272, 1177, 1115, 992, 927, 711 cm^{-1}; MS (EI): *m*/*z*: calcd for $C_{14}H_{18}O_3Na$: 257.1154; found: 257.1154 $[M+Na]^+$.

(3*S*)-3,5-Dihydroxy-2,2-dimethylpentyl benzoate (12): A solution of BH_3·THF complex (16.9 mL, 1.0 M in THF) was added to a solution of benzoate **11** (1.32 g, 5.63 mmol) in THF (10 mL) at 0 °C. The mixture was stirred at RT for 20 h then MeOH (50 mL) was added to the mixture at 0 °C, followed by successive additions of polymer-supported carbonate (26 g, 3.23 mmol g^{-1}), 30% aq. H_2O_2 (2.0 mL) and polymer-supported-$S_2O_3^{2-}$ (10 g, 2.0 mmol g^{-1}). The suspension was filtered and concentrated under reduced pressure. The residue was filtered through a silica gel pad eluting with Et_2O to afford diol **12** (970 mg, 68%). Diol **12** and Et_3N (1.62 mL, 11.6 mmol) were dissolved in CH_2Cl_2 (30 mL). PS-TrCl (9.3 g, 1.23 mmol g^{-1}) was added at RT and stirred for 4 h, then filtered. The resin was washed with CH_2Cl_2 and the filtrate was concentrated under reduced pressure. The residue was suspended in CH_2Cl_2 (30 mL) and 5% TFA in CH_2Cl_2 (5.0 mL) was added and the mixture was stirred for 1 h then filtered. The filtrate was concentrated under reduced pressure to obtain the diol **12** as a colourless oil (850 mg, 88%). $[\alpha]_D^{25} = -2.3$ ($c = 1.50$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.04$ (dd, $^3J(H,H) = 7.5$, 1.2 Hz, 2H, *o*-Ph), 7.58 (dd, $^3J(H,H) = 7.4$, 1.2 Hz, 1H, *p*-Ph), 7.45 (dd, $^3J(H,H) = 7.5$, 7.4 Hz, 2H, *m*-Ph), 4.51 (d, $^3J(H,H) = 11.1$ Hz, 1H, BzOC*H*H), 3.94 (d, $^3J(H,H) = 11.1$ Hz, 1H, BzOCH*H*), 3.92–3.78 (m, 2H, CH_2OH), 3.73–3.62 (m, 1H, C*H*OH), 3.28 (br s, 1H, O*H*), 2.61 (br s, 1H, O*H*), 1.78–1.66 (m, 2H, CH_2CH_2OH), 1.02 (s, 3H, CH_3CCH_3), 1.00 (s, 3H, CH_3CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 167.2$, 133.2, 129.9, 129.7, 128.5, 75.6, 70.9, 62.5, 39.0, 32.2, 21.8, 19.0; IR (film): $\tilde{\nu} = 3371$, 2965, 2878, 1724, 1700, 1602, 1473, 1451, 1371, 1315, 1272, 1177, 1115, 1069, 1054, 1026, 709 cm^{-1}; MS (EI): *m*/*z*: calcd for $C_{14}H_{20}O_4Na$: 275.1259; found: 275.1269 $[M+Na]^+$.

(3*S*)-3,5-Bis-(*tert*-butyldimethylsilyloxy)-2,2-dimethylpentyl benzoate (13): Polymer-supported-NMM (9.6 g, 3.5 mmol g^{-1}) was added to a solution of diol **12** (850 mg, 3.37 mmol) in CH_2Cl_2 (30 mL) at RT. Following a slow addition of TBSOTf (2.32 mL, 10.1 mmol) to the solution at 0 °C the mixture was stirred at RT for 20 h. Excess of TBSOTf was quenched by addition of MeOH. The mixture was filtered and concentrated under reduced pressure to obtain benzoate **13** as a colourless oil (1.58 g, 98%). $[\alpha]_D^{25} = -9.2$ ($c = 0.79$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.04$ (dd, $^3J(H,H) = 7.8$, 1.2 Hz, 2H, *o*-Ph), 7.56 (dd, $^3J(H,H) = 7.5$, 1.2 Hz, 1H, *p*-Ph), 7.44 (dd, $^3J(H,H) = 7.8$, 7.5 Hz, 2H, *m*-Ph), 4.13 (s, 2H, BzOCH_2), 3.86 (dd, $^3J(H,H) = 7.5$, 2.8 Hz, 1H, C*H*OTBS), 3.77–3.63 (m, 2H, CH_2OTBS), 1.92–1.81 (m, 1H, C*H*HCH_2OTBS), 1.65–1.54 (m, 1H, CH*H*CH_2OTBS), 0.99 (s, 3H, CH_3CCH_3), 0.98 (s, 3H, CH_3CCH_3), 0.89 (s, 18H, 2×SiC$(CH_3)_3$), 0.09 (s, 3H, SiCH_3), 0.05 (s, 3H, SiCH_3), 0.04 (s, 3H, SiCH_3), 0.02 (s, 3H, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 166.6$, 132.8, 130.5, 129.5, 128.4, 72.7, 71.1, 60.4, 39.3, 36.1, 26.1, 25.9, 22.2, 19.7, 18.4, 18.2, −3.83, −4.35, −5.25, 5.28; IR (film): $\tilde{\nu} = 2955$, 2929, 1724, 1472, 1271, 1252, 1092, 1069, 833, 774, 709 cm^{-1}; MS (EI): *m*/*z*: calcd for $C_{26}H_{48}O_4Si_2Na$: 503.2989; found: 503.3008 $[M+Na]^+$.

(3*S*)-3,5-Bis-(*tert*-butyldimethylsilyloxy)-2,2-dimethylpentan-1-ol (14)[21]

*From sultam **23***: A solution of diisobutylaluminum hydride (4.7 mL, 1.0 M in CH_2Cl_2) was added to a solution of sultam **23** (1.05 g, 1.88 mmol) in CH_2Cl_2 (20 mL) at −78 °C. The mixture was stirred for 1 h, then quenched by addition of Et_2O and powdered sodium sulfate decahydrate. The mixture was filtered and concentrated under reduced pressure. The residue was filtered through a bond elute silica gel cartridge eluting with hexane/EtOAc (10:1) to obtain alcohol **14** as a colourless oil (640 mg, 90%).

*From benzoate **13***: A solution of diisobutylaluminum hydride (8.7 mL, 1.0 M in hexane) was added to a solution of benzoate **13** (1.4 g, 2.91 mmol) in THF (30 mL) at −78 °C. The mixture was stirred for 1 h before addition of sodium sulfate decahydrate and Et_2O. The mixture was filtered and concentrated under reduced pressure. The residue was filtered through a silica gel pad eluting with hexane and EtOAc (10:1) to obtain alcohol **14** as a colourless oil (850 mg, 77%). $[\alpha]_D^{25} = -14.8$ ($c = 0.77$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.78$–3.61 (m, 4H, CH_2OTBS, C*H*OTBS, C*H*HOH), 3.29 (dd, $^3J(H,H) = 10.9$, 7.4 Hz, 1H, CH*H*OH), 2.95 (dd, $^3J(H,H) = 7.4$, 3.8 Hz, 1H, O*H*), 1.98–1.86 (m, 1H, C*H*HCH_2OTBS), 1.72–1.59 (m, 1H, CH*H*CH_2OTBS), 1.01 (s, 3H, CH_3CCH_3), 0.90 (s, 9H, SiC$(CH_3)_3$), 0.89 (s, 9H, SiC$(CH_3)_3$), 0.80 (s, 3H, CH_3CCH_3), 0.11 (s, 3H, SiCH_3), 0.10 (s, 3H, SiCH_3), 0.06 (s, 6H, 2×SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 76.9$, 70.2, 60.7, 39.3, 36.4, 26.0, 25.9, 22.9, 22.1, 18.3, 18.2, −4.01, −4.25, −5.28, 5.32; IR (film): $\tilde{\nu} = 3440$, 2955, 2929, 2857, 1472, 1252, 1090, 1041, 833, 772 cm^{-1}; MS (EI): *m*/*z*: calcd for $C_{19}H_{44}O_3Si_2Na$: 399.2727; found: 399.2730 $[M+Na]^+$.

(3*S*)-3,5-Bis-(*tert*-butyldimethylsilyloxy)-2,2-dimethylpentanal (15):[47] Supported-PCC (6.0 g, 5.56 mmol, 20% on basic alumina) was added to a solution of alcohol **14** (524 mg, 1.39 mmol) in CH_2Cl_2 (30 mL) at RT. The mixture was stirred for 20 h then filtered through a silica gel pad eluting with Et_2O to afford the aldehyde **15** as a colourless oil (520 mg, 100%). $[\alpha]_D^{25} = -14.6$ ($c = 0.84$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.56$ (s, 1H, C*H*O), 3.98 (dd, $^3J(H,H) = 7.4$, 4.3 Hz, 1H, C*H*OTBS), 3.69–3.58 (m, 2H, CH_2OTBS), 1.77–1.66 (m, 1H, C*H*HCH_2OTBS), 1.64–1.53 (m, 1H, CH*H*CH_2OTBS), 1.06 (s, 3H, CH_3CCH_3), 1.00 (s, 3H, CH_3CCH_3), 0.89 (s, 9H, SiC$(CH_3)_3$), 0.86 (s, 9H, SiC$(CH_3)_3$), 0.09 (s, 3H, SiCH_3), 0.04 (s, 9H, 3×SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 206.3$, 72.8, 59.7, 51.2, 36.5, 25.94, 25.88, 19.0, 18.22, 18.20, 17.5, −3.93, −4.29, −5.32, 5.34; IR (film): $\tilde{\nu} = 2956$, 2929, 2853, 1728, 1472, 1361, 1253, 1093, 834, 774 cm^{-1}; MS (EI): *m*/*z*: calcd for $C_{19}H_{42}O_3Si_2Na$: 397.2570; found: 397.2564 $[M+Na]^+$.

(5*S*)-5,7-Bis-(*tert*-butyldimethylsilyloxy)-4,4-dimethylheptan-3-ol (16):[21,26] A solution of EtMgBr (1.33 mL, 2.0 M in Et_2O) was added dropwise to a solution of aldehyde **15** (500 mg, 1.33 mmol) in THF (6.0 mL) at −78 °C. After stirring for 2 h, polymer-supported-COOH (2.6 g, 26 mmol, 10 mmol g^{-1}) was added to the mixture to quench the excess of Grignard reagent. The reaction mixture was filtered through a silica gel pad eluting with hexane and EtOAc (5:1) and concentrated under reduced pressure to obtain alcohol **16** as a pale yellow oil (530 mg, 98%). The two diastereoisomers were separated by flash chromatography (hexane/Et_2O 20:1).

Major isomer: $[\alpha]_D^{25} = -36.6$ ($c = 0.35$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.26$ (s, 1H, O*H*), 3.77–3.58 (m, 4H, CH_2OTBS, C*H*OTBS, C*H*OH), 1.98–1.89 (m, 1H, C*H*HCH_2OTBS), 1.78–1.67 (m, 1H, CH*H*CH_2OTBS), 1.45–1.23 (m, 2H, CH_3CH_2), 1.11 (t, $^3J(H,H) = 7.3$ Hz, 3H, CH_3CH_2), 0.97 (s, 3H, CH_3CCH_3), 0.90 (s, 9H, SiC$(CH_3)_3$), 0.89 (s, 9H, SiC$(CH_3)_3$), 0.74 (s, 3H, CH_3CCH_3), 0.12 (s, 6H, 2×SiCH_3), 0.05 (s, 6H, 2×SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 80.5$, 77.4, 60.1, 40.7, 36.0, 26.1, 25.9, 24.5, 23.5, 20.5, 18.2, 11.3, −3.93, −4.34, −5.28, 5.32; IR (film): $\tilde{\nu} = 3498$, 2956, 2929, 1472, 1389, 1362, 1253, 1079, 833, 774 cm^{-1}; MS (EI): *m*/*z*: calcd for $C_{21}H_{48}O_3Si_2Na$: 427.3040; found: 427.3048 $[M+Na]^+$.

Minor isomer: $[\alpha]_D^{25} = -4.5$ ($c = 0.45$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.78$–3.63 (m, 3H, CH_2OTBS, C*H*OTBS), 3.37–3.28 (m, 1H, C*H*OH), 2.73 (br s, 1H, O*H*), 2.07–1.96 (m, 1H, C*H*HCH_2OTBS), 1.54–1.45 (m, 2H, CH*H*CH_2OTBS, CH_3CH*H*), 1.38–1.22 (m, 1H, CH_3CH*H*), 0.99 (t, $^3J(H,H) = 7.3$ Hz, 3H, CH_3CH_2), 0.91 (s, 9H, SiC$(CH_3)_3$), 0.89 (s, 9H, SiC$(CH_3)_3$), 0.86 (s, 3H, CH_3CCH_3), 0.75 (s, 3H, CH_3CCH_3), 0.07 (s, 6H, 2×SiCH_3), 0.08 (s, 6H, 2×SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 78.0, 75.5, 61.9, 42.8, 36.5, 26.1, 25.9, 24.2, 18.7, 18.5, 18.4, 18.3, 11.7, −3.57, −4.38, −5.39; IR (film): $\tilde{\nu} = 3497$, 2956, 2930, 1472, 1388, 1361, 1253, 1087, 1004, 937, 832, 772 cm^{-1}; MS (EI): *m*/*z*: calcd for $C_{21}H_{48}O_3Si_2Na$: 427.3040; found: 427.3043 $[M+Na]^+$.

(*S*)-*N*-[2-Bromo-2-methylpropanoyl]bornane-10,2-sultam (21): Sodium hydride (444 mg, 11.1 mmol, ca. 60% dispersion with mineral oil) was added to a solution of camphorsultam **19** (2.0 g, 9.29 mmol) in toluene (40 mL) at 0 °C. The reaction mixture was stirred at RT for 1 h before addition of 2-bromo-2-methylpropanoyl bromide (**20**; 1.8 mL, 14.9 mmol) at 0 °C. After the mixture had been stirred for a further 1 h at RT, CH_2Cl_2

(200 mL) and polymer-supported trisamine (8.8 g, 29.8 mmol, 3.4 mmol g^{-1}) were added to the mixture. The suspension was filtered through a bond elute cartridge and concentrated to obtain a white solid which was washed with Et_2O and dried under reduced pressure to afford sultam **21** (3.11 g, 92%). M.p. 177–179°C; $[\alpha]_D^{25} = -42.0$ ($c = 1.29$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.08$ (dd, ^3J(H,H) = 7.2, 3.7 Hz, 1H, C*H*N), 3.51 (d, ^3J(H,H) = 13.6 Hz, 1H, C*H*HSO$_2$), 3.47 (d, ^3J(H,H) = 13.6 Hz, 1H, CH*H*SO$_2$), 2.12 (s, 3H, BrCC*H*$_3$), 2.04 (s, 3H, BrCC*H*$_3$), 2.04–1.97 (m, 1H, CH), 1.93–1.82 (m, 4H, 2×CH$_2$), 1.52–1.33 (m, 2H, CH$_2$), 1.20 (s, 3H, C*H*$_3$CCH$_3$), 0.97 (s, 3H, CH$_3$CC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 172.2$, 68.1, 59.0, 54.2, 48.6, 48.3, 44.6, 38.6, 33.2, 32.5, 31.1, 27.0, 20.9, 20.3; IR (film): $\tilde{\nu} = 2959$, 1698, 1456, 1330, 1266, 1241, 1171, 1157, 1128, 1096, 1054; MS (EI): *m*/*z*: calcd for $C_{14}H_{22}BrNO_3SNa$: 386.0401; found: 386.0422 $[M+Na]^+$.

(*S*)-*N*-[5-*tert*-Butyldimethylsilyloxy-(3*S*)-hydroxy-2,2-dimethylpentanoyl]-bornane-10,2-sultam (22): Sultam **21** (1.50 g, 4.12 mmol), $CrCl_2$ (2.03 g, 16.5 mmol) and LiI (54.9 mg, 0.41 mmol) were suspended in THF (15 mL). Dropwise addition of aldehyde **18** (1.55 g, 8.24 mmol) in THF (15 mL) was made at 20°C and the mixture stirred for 1 h. Additions of CH_2Cl_2 (200 mL) and polymer-supported hydroxide (25 g, 3.2 mmol g^{-1}, Ambersep 900 OH) were made and the mixture was filtered and concentrated under reduced pressure. The crude product was filtered through a bond elut silica gel cartridge eluting with hexane/EtOAc (10:1) to obtain sultam **22** as a colourless oil (1.80 g, 92%). $[\alpha]_D^{25} = -28.6$ ($c = 0.44$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.24$ (ddd, ^3J(H,H) = 9.7, 4.6, 1.8 Hz, 1H, C*H*OH), 4.06 (dd, ^3J(H,H) = 7.6, 4.8 Hz, 1H, C*H*N), 3.82 (ddd, ^3J(H,H) = 5.9, 5.8, 1.6 Hz, 2H, C*H*$_2$OTBS), 3.50 (d, ^3J(H,H) = 13.6 Hz, 1H, C*H*HSO$_2$), 3.44 (d, ^3J(H,H) = 13.6 Hz, 1H, CH*H*SO$_2$), 3.15 (d, ^3J(H,H) = 4.6 Hz, 1H, CH), 2.01 (dd, ^3J(H,H) = 13.6, 7.7 Hz, 1H, CH), 1.96–1.72 (m, 4H, 4×CH), 1.67–1.56 (m, 2H, C*H*$_2$CH$_2$OTBS), 1.48–1.41 (m, 1H, CH), 1.38–1.32 (m, 1H, CH), 1.34 (s, 3H, C(O)CC*H*$_3$), 1.32 (s, 3H, C(O)CC*H*$_3$), 1.16 (s, 3H, CC*H*$_3$), 0.96 (s, 3H, CC*H*$_3$), 0.90 (s, 9H, SiC(C*H*$_3$)$_3$), 0.08 (s, 6H, 2×SiC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 179.1, 67.6, 61.7, 54.0, 50.9, 48.0, 47.7, 44.4, 38.9, 34.0, 32.9, 26.6, 25.9, 20.68, 20.64, 20.58, 20.39, 19.9, −5.43, −5.48; IR (film): $\tilde{\nu} = 3529$, 2957, 2885, 2857, 1684, 1472, 1410, 1387, 1332, 1251, 1172, 1150, 1094, 1052, 837, 776 cm^{-1}; MS (EI): *m*/*z*: calcd for $C_{23}H_{43}NO_5SiNa$: 496.2532; found: 496.2529 $[M+Na]^+$.

(*S*)-*N*-[(3*S*),5-Bis-*tert*-butyldimethylsilyloxy-2,2-dimethylpentanoyl]-bornane-10,2-sultam (23): Polymer-supported-NMM (4.09 g, 14.3 mmol, 3.5 mmol g^{-1}) was added to a solution of sultam **22** (1.35 g, 2.85 mmol) in CH_2Cl_2 (120 mL). The mixture was cooled to 0°C and TBSOTf (0.98 mL, 4.28 mmol) added and stirred for 1 h. Methanol (1 mL) was added to quench the excess of TBSOTf and the suspension was filtered and concentrated under reduced pressure. The product was filtered through a bond elute silica gel cartridge eluting with hexane/Et_2O (10:1) to yield the bis-TBS ether **23** as a white solid (1.42 g, 89%). M.p. 78–80°C; $[\alpha]_D^{25} = -19.1$ ($c = 0.44$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.35$ (dd, ^3J(H,H) = 8.5, 2.0 Hz, 1H, C*H*OTBS), 4.01 (dd, ^3J(H,H) = 7.7, 4.5 Hz, 1H, C*H*N), 3.75 (ddd, ^3J(H,H) = 15.4, 10.0, 5.3 Hz, 1H, C*H*HSO$_2$), 3.52 (ddd, ^3J(H,H) = 15.6, 10.0, 5.7 Hz, 1H, CH*H*SO$_2$), 3.44 (m, 2H, C*H*$_2$OTBS), 2.01 (dd, ^3J(H,H) = 12.2, 6.7 Hz, 1H), 1.94–1.78 (m, 4H), 1.74–1.61 (m, 1H), 1.53–1.42 (m, 2H), 1.38–1.29 (m, 1H), 1.33 (s, 3H, C(O)C(C*H*$_3$)$_2$), 1.24 (s, 3H, C(O)C(C*H*$_3$)$_2$), 1.14 (s, 3H, C(C*H*$_3$)$_2$), 0.95 (s, 3H, C(C*H*$_3$)$_2$), 0.89 (s, 9H, SiC(C*H*$_3$)$_3$), 0.88 (s, 9H, SiC(C*H*$_3$)$_3$), 0.08 (s, 3H, Si(C*H*$_3$)$_2$), 0.07 (s, 3H, Si(C*H*$_3$)$_2$), 0.02 (s, 6H, 2×Si(C*H*$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 177.7$, 72.0, 67.7, 61.7, 53.9, 51.8, 47.8, 47.7, 44.3, 38.8, 37.8, 32.9, 26.6, 26.0, 25.9, 22.8, 20.4, 19.9, 19.4, 18.3, 18.2, −3.5, −4.1, −5.2, −5.3; IR (film): $\tilde{\nu} = 2956$, 2880, 1729, 1473, 1393, 1337, 1299, 1259, 1138, 1080, 838, 776 cm^{-1}; MS (EI): *m*/*z*: calcd for $C_{29}H_{57}NO_5Si_2Na$: 610.3394; found: 610.3371 $[M+Na]^+$.

4-(*tert*-Butyldimethylsilyloxy)-but-1-ene (25):[48] Alcohol **24** (1.60 g, 22.2 mmol) and polymer-supported DMAP (Argonaut, 1.49 mmol g^{-1}, 29.8 g, 44.4 mmol) were suspended in CH_2Cl_2 (150 mL) at RT. Solid TBSCl (4.69 g, 31.1 mmol) was added portionwise to the reaction mixture and stirred at RT for 2.5 h. The reaction mixture was filtered and concentrated under reduced pressure to give the TBS ether product **25** as a colourless oil (3.97 g, 96%). The bulk of the material was used in subsequent reactions without further purification. A portion of the product was purified by chromatography (silica gel, EtOAc/petrol 1:20). $R_f = 0.74$ (petrol/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.88$–5.77 (ddt, ^3J(H,H) = 17.3, 10.4, 6.8 Hz, 1H, *H*-2), 5.10–5.06 (dd, ^3J(H,H) = 17.3 Hz, ^2J(H,H) = 1.4 Hz, 1H, CH$_{trans}H_{cis}$=CH), 5.06–5.02 (d, ^3J(H,H) = 10.4 Hz, 1H, C*H*$_{trans}$H$_{cis}$=CH), 3.67 (t, ^3J(H,H) = 6.8 Hz, 2H, *H*-4), 2.28 (app. q, ^3J(H,H) = 6.8 Hz, 2H, *H*-3), 0.90 (s, 9H, SiC(C*H*$_3$)$_3$), 0.06 (s, 6H, Si(C*H*$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 135.4$ (CH$_2$=*C*H), 116.3 (*C*H$_2$=CH), 62.8 (*C*-4), 37.5 (*C*-3), 25.9 (SiC(*C*H$_3$)$_3$), 18.0 (Si*C*(CH$_3$)$_3$), −5.6 (Si(*C*H$_3$)$_2$); IR (film): $\tilde{\nu} = 2956$, 2930, 2896, 2858, 1473, 1255, 1096, 909, 833, 773 cm^{-1}; MS (+EI): *m*/*z*: calcd for $C_6H_{13}OSi$: 129.0736; found: 129.0743 $[M-t\text{Bu}]^+$.

3-(*tert*-Butyldimethylsilyloxy)-propanal 18:[21]

*From alcohol **17***: PCC on basic alumina (51.1 g, 51.1 mmol, ~1 mmol g^{-1}) was added to a solution of alcohol **17** (3.0 g, 15.8 mmol) in CH_2Cl_2 (350 mL) at RT. The reaction mixture was stirred for 1 h then Et_2O (500 mL) was added. The resulting suspension was filtered through a bond elute silica gel pad and concentrated under reduced pressure to yield aldehyde **18** (2.58 g, 87%).

*From alkene **25***: Alkene **25** (3.0 g, 16.1 mmol) was dissolved in CH_2Cl_2 (100 mL) and cooled to −78°C. Ozone was bubbled through the solution for 10 min until the reaction mixture turned blue. Polymer-supported triphenylphosphine (Fluka, 3.0 mmol g^{-1}, 8.06 g, 24.2 mmol) was added at −78°C and the suspension allowed to warm to RT and stirred for 14 h. Filtration, washing the resin with Et_2O, followed by concentration of the filtrate under reduced pressure yielded aldehyde **18** as a pale yellow oil (2.80 g, 93%). The bulk of the material was used in subsequent reactions without further purification. A portion of the product was purified by chromatography (silica gel, EtOAc/petrol 1:10). $R_f = 0.61$ (petrol/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.79$ (s, 1H, C*H*O), 3.98 (t, ^3J(H,H) = 6.0 Hz, 2H, *H*-3), 2.58 (td, ^3J(H,H) = 6.0, 1.9 Hz, 2H, *H*-2), 0.87 (s, 9H, SiC(C*H*$_3$)$_3$), 0.05 (s, 6H, Si(C*H*$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 202.0$ (*C*HO), 57.3 (*C*-3), 46.5 (C-*2*), 25.7 (SiC(*C*H$_3$)$_3$), 18.2 (Si*C*(CH$_3$)$_3$), −5.5 (Si(*C*H$_3$)$_2$); IR (film): $\tilde{\nu} = 2956$, 2930, 2887, 2858, 1727, 1473, 1254, 1095, 833, 775 cm^{-1}; MS (+EI): *m*/*z*: calcd for $C_9H_{20}NaO_2Si$: 211.1130; found: 211.1120 $[M+Na]^+$.

(3*S*)-Methyl-5-(*tert*-butyldimethylsilyloxy)-3-hydroxy-2,2-dimethylpentanoate (28):[21]

Racemic method: A solution of aldehyde **18** (481 mg, 2.56 mmol) in THF (5 mL) was cooled to −78°C before addition of BF_3·THF (376 mg, 2.69 mmol). 1-Methoxy-2-methyl-1-trimethylsiloxy-1-propene (468 mg, 2.69 mmol) was added dropwise and the mixture warmed to RT. After stirring at RT for 15 min the reaction was diluted with Et_2O (20 mL) and quenched with water (20 mL). The aqueous phase was extracted using Et_2O (3×10 mL), and the combined organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a colourless crude oil. Purification by flash column chromatography (silica gel, petrol/EtOAc 5:1) yielded racemic alcohol **28** as a colourless oil (571 mg, 77%).

Asymmetric procedure: A suspension of *N*-tosyl-D-phenylalanine (**26**; 2.53 g, 7.91 mmol) in CH_2Cl_2 (58 mL) was cooled to 0°C over 15 min before addition of a solution of BH_3·THF (1.5 M in THF, 4.61 mL, 6.91 mmol) over 4 min. The mixture was allowed to warm to RT over 10 min and stirred at RT for 30 min. The reaction was cooled to −96°C over 15 min, then a pre-cooled (−78°C) solution of aldehyde **18** (1.30 g, 6.91 mmol) in CH_2Cl_2 (6 mL) was added dropwise over 10 min, followed by the addition of a pre-cooled (−78°C) solution of 1-methoxy-2-methyl-1-trimethylsiloxy-1-propene (1.15 g, 6.59 mmol) in CH_2Cl_2 (6 mL) over 10 min. The reaction mixture was warmed slowly to −78°C over 1.5 h and quenched by addition of Amberlite IRA-743 **27** (1 mmol g^{-1}, 8.17 g, 13.2 mmol) and water (0.6 mL) with stirring. The quenched mixture was warmed slowly to RT over 2 h (resin turned yellow) and stirred for a further 4 h. Filtration, washing the resin with Et_2O, followed by solvent removal yielded a suspension of white solid (amino acid **26**) suspended in oil. The residue was diluted using petroleum ether 40–60 (10 mL) and re-filtered. The residual amino acid **26** was collected as a white solid (2.33 g, 93%) and the filtrate was concentrated under reduced pressure to provide the aldol adduct **28** as a colourless oil (1.78 g, 93%). The enantiomeric excess (92% *ee*) was measured by ^{1}H NMR (C_6D_6) analysis of MTPA-OCH$_3$ signals of both (*R*) and (*S*) Mosher's esters and compared with those of the racemic aldol adduct. The bulk of the material was used in subsequent reactions without further purification. A portion of the product **28** was purified by chromatography (silica gel, EtOAc/petrol 1:5). $R_f = 0.35$ (petrol/EtOAc 5:1); $[\alpha]_D^{25} = +0.34$ ($c = 3.26$, $CHCl_3$)

(lit. $[\alpha]_D^{20} = +0.30$ ($c = 1.88$, $CHCl_3$)); ^1H NMR (400 MHz, $CDCl_3$): $\delta =$ 3.93–3.77 (m, 3H, *H*-3, *H*-5), 3.67 (s, 3H, OCH_3), 3.35 (d, $^3J(H,H) =$ 3.2 Hz, 1H, O*H*), 1.57 (ddd, $^3J(H,H) = 11.0$, 5.5, 1.0 Hz, 2H, *H*-2), 1.18 (s, 3H, CH_3CCH_3), 1.15 (s, 3H, CH_3CCH_3), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.06 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 177.7$ (*C*-1), 75.9 (*C*-3), 62.5 (*C*-5), 51.7 (OCH_3), 47.0 (*C*-2), 33.7 (*C*-4), 25.8 ($SiC(CH_3)_3$), 21.2 (CH_3), 20.5 (CH_3), 18.1 ($SiC(CH_3)_3$), −5.5 ($Si(CH_3)_2$); IR (film): $\tilde{\nu} =$ 3528, 2956, 2954, 2887, 2858, 1733, 1472, 1256, 1086, 836, 776 cm^{-1}; MS (+ESI): *m*/*z*: calcd for $C_{14}H_{30}O_4SiNa$: 313.1811; found: 313.1809 $[M+Na]^+$.

(−)-(3*S*)-Methyl-3,5-bis(*tert*-butyldimethylsilyloxy)-2,2-dimethylpentanoate (29):[21] A suspension of alcohol **28** (900 mg, 3.10 mmol) and diethylamino-polystyrene resin (Fluka, 3.2 mmol g^{-1}, 4.84 g, 15.5 mmol) in CH_2Cl_2 (30 mL) was cooled to 0 °C before dropwise addition of TBSOTf (1.42 mL, 6.20 mmol). The resin changed colour from yellow to deep orange and the reaction was stirred at 0 °C for 2.5 h before MeOH (2.5 mL) was added. The mixture was warmed to RT and stirring continued for 1 h. Filtration, washing the resin with alternate CH_2Cl_2 (3×5 mL) and Et_2O (3×5 mL), and concentration under reduced pressure yielded the product **29** as a yellow oil (1.26 g, 100 %). The bulk of the material was used in subsequent reactions without further purification. A portion of the product **29** was purified by chromatography (silica gel, EtOAc/petrol 1:20). $R_f = 0.30$ (petrol/EtOAc 10:1) viewed: moly dip; $[\alpha]_D^{25} = -5.4$ ($c = 1.03$, $CHCl_3$) (lit. $[\alpha]_D^{20} = -6.0$ ($c = 3.91$, $CHCl_3$)); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.05$ (dd, $^3J(H,H) = 7.6$, 3.0 Hz, 1H, *H*-3), 3.64 (s, 3H, OCH_3), 3.69–3.57 (m, 2H, *H*-5), 1.66–1.51 (m, 2H, *H*-4), 1.16 (s, 3H, CH_3CCH_3), 1.09 (s, 3H, CH_3CCH_3), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.082 (s, 3H, $Si(CH_3)_2$, 0.043 (s, 3H, $Si(CH_3)_2$, 0.038 (s, 3H, $Si(CH_3)_2$), 0.03 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 177.5$ (*C*-5), 73.3 (*C*-3), 60.3 (*C*-3), 51.6 (OCH_3), 48.3 (*C*-2), 36.8 (*C*-4), 26.0 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 21.7 (CH_3), 20.3 (CH_3), 18.3 ($SiC(CH_3)_3$), 18.2 ($SiC(CH_3)_3$), −4.0 ($SiCH_3$), −4.3 ($SiCH_3$), −5.28 ($SiCH_3$), −5.29 ($SiCH_3$); IR (film): $\tilde{\nu} =$ 2954, 2929, 2886, 2857, 1734, 1472, 1464, 1253, 1095, 833, 776 cm^{-1}; MS (+ESI): *m*/*z*: calcd for $C_{20}H_{44}O_4Si_2Na$: 427.2670; found: 427.2670 $[M+Na]^+$.

(4*S*)-4,6-Bis(*tert*-butyldimethylsilyloxy)-3,3-dimethylhexan-2-one (30):[21] A solution of methyl ester **29** (555 mg, 1.37 mmol) in pentane (6.0 mL) was cooled to 0 °C. A solution of trimethylsilylmethyllithium (1.0 M solution in pentane, 3.0 mL, 3.0 mmol) was added dropwise at 0 °C and the reaction stirred for 3.5 h before the addition of MeOH (2.5 mL). The mixture was warmed to RT and stirred for 5 h then Amberlite IRC-50 carboxylic acid resin (3.5 g, 35 mmol g^{-1}, 10 mmol g^{-1}) was added and stirred for 1.5 h. Filtration and concentration under reduced pressure yielded methyl ketone **30** as a pale yellow oil (534 mg, 100 %). The bulk of the material was used in subsequent reactions without further purification. A portion of the product **30** was purified by chromatography (silica gel, EtOAc/petrol 1:20). $R_f = 0.40$ (petrol/EtOAc 20:1); $[\alpha]_D^{25} = -13.3$ ($c =$ 2.0, $CHCl_3$) (lit. $[\alpha]_D^{20} = -11.5$ ($c = 0.71$, $CHCl_3$)); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.05$ (dd, $^3J(H,H) = 7.8$, 2.7 Hz, 1H, *H*-4), 3.68–3.58 (m, 2H, *H*-6), 2.15 (s, 3H, *H*-1), 1.59–1.44 (m, 2H, *H*-5), 1.11 (s, 3H, CCH_3), 1.06 (s, 3H, CCH_3), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.10 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$), 0.04 (s, 3H, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 213.4$ (*C*-5), 73.3 (*C*-3), 59.9 (*C*-6), 53.4 (*C*-3), 37.2 (*C*-5), 26.8 (*C*-1), 26.0 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 21.9 (CH_3), 19.9 (CH_3), 18.3 ($SiC(CH_3)_3$), 18.2 ($SiC(CH_3)_3$), −4.0 ($SiCH_3$), −4.1 ($SiCH_3$), −5.3 ($SiCH_3$), −5.4 ($SiCH_3$); IR (film): $\tilde{\nu} =$ 2956, 2929, 2887, 2857, 1706, 1472, 1464, 1388, 1361, 1252, 1092, 833, 774 cm^{-1}; MS (+ESI): *m*/*z*: calcd for $C_{20}H_{44}NaO_3Si_2$: 411.2727; found: 411.2729 $[M+Na]^+$.

Fragment 1—(−)-(5*S*)-5,7-Bis(*tert*-butyldimethylsilyloxy)-4,4-dimethylheptan-3-one (3):[21,26,49]

From alcohol ***16***: PCC on basic alumina (3.85 g, 3.85 mmol, ~1 mmol g^{-1}) was added to a solution of alcohol **16** (480 mg, 1.19 mmol) in CH_2Cl_2 (30 mL) at RT. The mixture was stirred for 20 h and filtered through a silica gel pad eluting with ether to afford ketone **3** as a colourless oil (471 mg, 98 %).

From methyl ketone ***30***: A solution of LDA was prepared: *n*BuLi (1.24 mL, 2.3 M solution in hexanes, 2.40 mmol) was added to diisopropylamine (243 mg, 0.34 mL, 2.40 mmol) in THF (10 mL) at −78 °C, warmed to 0 °C over 15 min, then cooled back to −78 °C to give a colourless solution.

A solution of ketone **30** (402 mg, 1.04 mmol) in THF (10 mL) was added to the solution of freshly prepared LDA at −78 °C with stirring, causing a colour change from colourless to yellow. The solution was warmed to −15 °C for 10 min, then cooled back to −78 °C for 15 min before addition of MeI (0.25 mL, 4 mmol). The reaction mixture was warmed to −40 °C for 2 h, quenched by the addition of Amberlite IRC-50 carboxylic acid resin (2.6 g, 26 mmol, 10 mmol g^{-1}) and warmed to RT. After 2 h the mixture was filtered and the resin washed with Et_2O (3×10 mL). The filtrate was concentrated under reduced pressure to give ethyl ketone **3** as yellow oil (394 mg, 94 %). The bulk of the material was used in subsequent reactions without further purification. A portion of the product was purified by chromatography (silica gel, EtOAc/petrol 1:20). $R_f =$ 0.50 (petrol/EtOAc 20:1); $[\alpha]_D^{25} = -9.4$ ($c = 1.23$, $CHCl_3$) (lit. $[\alpha]_D^{20} =$ −8.3 ($c = 2.10$, $CHCl_3$)); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.07$ (dd, $^3J(H,H) = 7.7$, 2.8 Hz, 1H, *H*-5), 3.66–3.59 (m, 2H, *H*-7), 2.60–2.51 (dq, $^3J(H,H) = 11.2$, 7.2 Hz, 1H, H_a-2), 2.50–2.44 (dq, $^3J(H,H) = 11.2$, 7.2 Hz, 1H, H_b-2), 1.58–1.45 (m, 2H, *H*-6), 1.12 (s, 3H, 4-CH_3), 1.06 (s, 3H, 4-CH_3), 1.01 (t, $^3J(H,H) = 7.2$ Hz, 3H, *H*-1), 0.90 (s, 9H, $SiC(CH_3)_3$), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.10 (s, 3H, $SiCH_3$), 0.052 (s, 3H, $SiCH_3$), 0.046 (s, 3H, $SiCH_3$), 0.037 (s, 3H, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 215.6$ (*C*-3), 73.5 (*C*-5), 60.1 (*C*-7), 53.0 (*C*-4), 37.3 (*C*-6), 31.5 (*C*-2), 26.0 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 22.1 (CH_3), 20.0 (CH_3), 18.3 ($SiC(CH_3)_3$), 18.2 ($SiC(CH_3)_3$), 7.7 (CH_3CH_2), −4.0 ($SiCH_3$), −4.1 ($SiCH_3$), −5.3 ($SiCH_3$), −5.4 ($SiCH_3$); IR (film): $\tilde{\nu} =$ 2957, 2930, 2887, 2858, 1707, 1472, 1464, 1388, 1361, 1253, 1091, 833, 773 cm^{-1}; MS (+ESI): *m*/*z*: calcd for $C_{21}H_{46}O_3Si_2Na$: 425.2883; found: 425.2898 $[M+Na]^+$.

***N*-(4-Methylbenzenesulfonyl)-D-phenylalanine (26)**:[50] A solution of TsCl (8.65 g, 45.4 mmol) in Et_2O (150 mL) was added to a stirred solution of D-phenylalanine (6.25 g, 37.8 mmol) dissolved in an aqueous solution of NaOH (1.5 M, 63 mL, 94.6 mmol) at RT. After 6 h of stirring, concentrated HCl was added to the viscous white suspension until it was homogeneous and acidified. The organic phase was separated and the aqueous layer extracted twice with Et_2O (2×100 mL). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was isolated as a white solid (9.73 g, 81 %) and recrystallized from Et_2O to yield amino acid **26** as a white solid. M.p. 166–167 °C (lit. 164–165 °C recrystallised from EtOH); $R_f = 0.39$ ($CHCl_3$/MeOH 9:1); $[\alpha]_D^{25} = -3.0$ ($c = 1.64$, EtOH) (lit. $[\alpha]_D^{19} = -2.4$ ($c = 7.50$, acetone)); ^1H NMR (400 MHz, CD_3OD): $\delta = 7.53$ (d, $^3J(H,H) = 8.2$ Hz, 2H, CH_{meta}), 7.22 (d, $^3J(H,H) = 8.1$ Hz, 2H, CH_{ortho}), 7.23–7.09 (m, 5H, Ph), 3.99 (dd, $^3J(H,H) = 8.2$, 5.7 Hz, 1H, *CH*NH), 3.01 (dd, $^3J(H,H) = 13.7$, 5.6 Hz, 1H, PhC*H*H), 2.82 (dd, $^3J(H,H) = 13.7$, 8.3 Hz, 1H, PhCH*H*), 2.37 (s, 3H, CCH_3); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 174.4$ (CO_2H), 144.4 (CCH_3), 139.1 (CCH_2), 137.8 (SO_2C), 130.5 (Ar), 130.4 (Ar), 129.4 (Ar), 128.0 (Ar), 127.7 (Ar), 58.8 (*C*HNH), 39.9 ($PhCH_2$), 21.4 (CCH_3); IR (film): $\tilde{\nu} =$ 3283, 3031, 1729, 1671, 1426, 1335, 1210, 1155, 1073, 924, 906, 829, 813, 746, 701, 674, 655 cm^{-1}; MS (+ESI): *m*/*z*: calcd for $C_{16}H_{17}NO_4SNa$: 342.0776; found: 342.0769 $[M+Na]^+$.

Fragment 2

(2*R*)-1-Bromo-2-methyl-3-(tetrahydropyranyloxy)-propane (32):[51] Neat 3,4-dihydro-2*H*-pyran (7.56 g, 89.9 mmol) was added to a stirred RT suspension of polymer-supported sulfonic acid resin (Argonaut MP-TsOH(I), 1.4 mmol g^{-1}, 1.53 g, 2.1 mmol) and bromide **31** (13.1 g, 85.6 mmol). The resulting suspension was stirred at RT for 30 min. The reaction mixture was then filtered and concentrated under reduced pressure to yield the THP protected product **32** as a colourless oil (19.9 g, 98 %), characterised as a mixture of diastereoisomers. The bulk of the material was used in subsequent reactions without further purification. A portion of the product was purified by chromatography (silica gel, EtOAc/petrol 1:10). Analysed as a mixture of diastereoisomers: $R_f =$ 0.59 (petrol/EtOAc 2:1) viewed: moly dip; $[\alpha]_D^{25} = -11.6$ ($c = 0.60$, $CHCl_3$) (lit. $[\alpha]_D^{21} = -13.5$ ($c = 1.04$, $CHCl_3$)); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.61$–4.57 (m, 1H, OC*H*O), 3.88–3.83 (m, 1H, OCHOC*H*H), 3.71–3.64, 3.55–3.41 (m, 1H, H_a-3), 3.34–3.33 (m, 3H, OCHOCH*H*, *H*-1), 3.31–3.21 (m, 1H, H_b-3), 2.16–2.01 (m, 1H, *H*-2), 1.84–1.74 (m, 1H, C*H*HCH$_2$CHOO), 1.69–1.60 (m, 1H, C*H*HCHOO), 1.59–1.40 (m, 4H, CH*H*CHOO, CH*H*CH$_2$CHOO, $CH_2CH_2CH_2CHOO$), 1.04 (t, 3H, $^3J(H,H) = 6.5$ Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 99.3/98.6$ (O*C*HO), 70.1/69.7 (*C*-7), 62.3/62.0 (OCHO*C*H$_2$), 38.2/38.0 (*C*-9), 35.7/

35.6 (*C*-8), 30.6/30.5 (CH_2CHOO), 25.5/25.4 ($CH_2CH_2CH_2CHOO$), 19.5/19.3 ($CH_2CH_2CH_2CHOO$), 15.9/15.8 (CH_3); IR (film): $\tilde{\nu}$ = 2941, 2872, 1121, 1064, 1032, 975, 904, 869 cm^{-1}; MS (+ESI): *m*/*z*: calcd for $C_9H_{16}BrO_2$: 235.0334; found: 235.0342 $[M-H]^+$.

(2*R*)-1-Iodo-2-methyl-3-tetrahydropyranyloxypropane (33):[52] Bromide **32** (19.7 g, 83.0 mmol) was dissolved in butanone (200 mL) before addition of NaI (37.5 g, 250 mmol). The reaction was heated at 75 °C for 1 h, then cooled to RT. The mixture was diluted with Et_2O (50 mL) and silica gel (50 g) was added. The suspension was filtered and the filtrate was concentrated under reduced pressure to yield the iodide **33** as a yellow oil (22.7 g, 96 %). The bulk of the material was used in subsequent reactions without further purification. A portion of the product was purified by chromatography (silica gel, EtOAc/petrol 1:10); analysed as a mixture of diastereoisomers: R_f = 0.59 (petrol/EtOAc 2:1) viewed: UV (254 nm) or moly dip; $[\alpha]_D^{25}$ = −10.2 (*c* = 4.87, $CHCl_3$) (lit. $[\alpha]_D^{22}$ = −11.0 (*c* = 1.16, $CHCl_3$)); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.58–4.55 (dt, ^3J(H,H) = 10.5, 3.3 Hz, 1H, OC*H*O), 3.86–3.80 (m, 1H, C*H*HOCHO), 3.64–3.61/3.56–3.53 (m, 1H, H_a-3), 3.50–3.47 (m, 1H, CH*H*OCHO), 3.33–3.15 (m, 3H, H_b-3, *H*-1), 1.81–1.64 (m, 3H, *H*-2, C*H*HCHOO, CH_2CHHCH_2CHOO), 1.58–1.48 (m, 4H, CH*H*CHOO, CH_2CHHCH_2CHOO, $CH_2CH_2CH_2CHOO$), 0.98/0.96 (d, ^3J(H,H) = 6.7 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 99.2/98.5 (O*C*HO), 71.4/71.0 (*C*-3), 62.3/62.0 (CH_2OCHO), 35.3/35.1 (*C*-2), 30.6/30.5 (CH_2CHOO), 25.4/25.4 ($CH_2CH_2CH_2CHOO$), 19.5/19.3 ($CH_2CH_2CH_2CHOO$), 17.8/17.6 (CH_3), 14.0/13.5 (*C*-1); IR (film): $\tilde{\nu}$ = 2940, 2869, 1454, 1200, 1120, 1063, 1032, 975, 904, 869 cm^{-1}; MS (+EI): *m*/*z*: calcd for $C_9H_{17}O_2I$: 284.0273; found: 284.0264 $[M]^+$.

(6*R*)-6-Methyl-7-tetrahydropyranyloxyhept-1-ene (34): Iodide **33** (8.10 g, 28.3 mmol) was dissolved in THF (50 mL) and copper iodide (5.5 g, 28.3 mmol) was added. The suspension was cooled to −10 °C under a strict Ar atmosphere. A solution of 3-butenylmagnesium bromide (0.5 M solution in THF, 226 mL, 113 mmol) was added dropwise with stirring over 15 min. The reaction mixture was allowed to warm slowly to 0 °C and stirred for 2 h before being quenched by addition of a polymer-supported carboxylic acid (Amberlite IRC-50, 43 g, 430 mmol, 10 mmol g^{-1}) and polymer-supported trisamine (NovaBiochem, ~4.36 mmol g^{-1}, 20 g, 106 mmol). The suspension was shaken at RT for 24 h, then filtered through silica using Et_2O and concentrated under reduced pressure to yield **34** as a yellow oil (5.8 g, 97 %). The bulk of the material was used in subsequent reactions without further purification. A portion of the product was purified by chromatography (silica gel, EtOAc/petrol 1:20). Analysed as a mixture of diastereoisomers: R_f = 0.67 (petrol/EtOAc 2:1); $[\alpha]_D^{25}$ = −3.4 (*c* = 0.41, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.84–5.78 (m, 1H, C*H*=CH_2), 4.99 (dd, ^3J(H,H) = 7.1, 1.5 Hz, 1H, CH=CH_{cis}H), 4.93 (d, ^3J(H,H) = 10.0 Hz, 1H, CH=CHH_{trans}), 4.57–4.55 (m, 1H, OC*H*O), 3.87–3.83 (m, 1H, C*H*HOCHO), 3.60–3.59/3.51–3.49 (m, 2H, OCH*H*CHCH$_3$, CH*H*OCHO), 3.25–3.22/3.15–3.15 (m, 1H, OCH*H*CHCH$_3$), 2.07–2.01 (m, 2H, CH_2CH=CH_2), 1.84–1.75 (m, 1H, CH_2CHHCH_2CHOO), 1.74–1.62 (m, 2H, C*H*HCHOO, C*H*CH$_3$), 1.60–1.30 (m, 7H, CH(CH$_3$)CH_2CH_2, CH*H*CHOO, CH(CH)$_3$C*H*H, CH_2CHHCH_2CHOO, $CH_2CH_2CH_2CHOO$), 1.16–1.10 (m, 1H, CH(CH$_3$)CH*H*), 0.93/0.91 (d, ^3J(H,H) = 6.7 Hz, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 139.03/139.01 (*C*H=CH_2), 114.20/114.18 (CH=*C*H_2), 99.0/98.8 (O*C*HO), 73.1/72.9 (*C*-7), 62.2/62.0 (CH_2OCHO), 34.01/34.00 (*C*-3), 33.32/33.27 (*C*-6), 33.20/33.16 (*C*-5), 30.70 (CH_2CHOO), 26.29 ($CH_2CH_2CH_2CHOO$), 25.52 (*C*-4), 19.58/19.52 ($CH_2CH_2CH_2CHOO$), 17.15/17.07 (CH_3); IR (film): $\tilde{\nu}$ = 2927, 1641, 1454, 1201, 1120, 1063, 1032, 977, 905, 869 cm^{-1}; MS (+EI): *m*/*z*: calcd for $C_{13}H_{24}O_2$: 212.1776; found: 212.1772 $[M-H]^+$.

(*S*)-2-Methyl-6-hepten-1-ol (35):[14,16] Tetrahydropyranyl acetal **34** (5.30 g, 25 mmol) was dissolved in MeOH (20 mL). Polymer-supported sulfonic acid (Argonaut, MP-TsOH(II) ~4.2 mmol g^{-1}, 240 mg, 1.00 mmol) was added at RT and the mixture stirred for 7.5 h. Filtration, followed by concentration under reduced pressure yielded alcohol **35** as a yellow oil (3.10 g, 97 %). The bulk of the material was used in subsequent reactions without further purification. A portion of the product was purified by chromatography (silica gel, EtOAc/petrol 1:5). R_f = 0.36 (petrol/EtOAc 2:1) viewed: moly dip or $KMnO_4$; $[\alpha]_D^{25}$ = −12.8 (*c* = 0.50, $CHCl_3$) (lit. $[\alpha]_D^{20}$ = −12.5 (*c* = 1.03, $CHCl_3$)); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.87–5.77 (m, 1H, *H*-6), 4.99 (d, ^3J(H,H) = 18.1 Hz, 1H, CH=CH_{cis}H$_{trans}$), 4.97 (d, ^3J(H,H) = 10.1 Hz, 1H, CH=CH$_{cis}H_{trans}$), 3.54–3.48 (dd, ^3J(H,H) = 10.3, 6.2 Hz, 1H, H_a-1), 3.45–3.41 (dd, ^3J(H,H) = 10.5, 6.5 Hz, 1H, H_b-1), 2.07–2.01 (m, 2H, *H*-5), 1.67–1.60 (m, 1H, *H*-2), 1.53–1.34 (m, 3H, H_a-3, H_{ab}-4), 1.19–1.08 (m, 1H, H_b-3), 0.92 (d, ^3J(H,H) = 6.5 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.9 (*C*-6), 114.4 (*C*-7), 68.3 (*C*-1), 35.7 (*C*-2), 34.0 (CH_2), 32.6 (CH_2), 26.3 (CH_2), 16.5 (CH_3); IR (film): $\tilde{\nu}$ = 3316, 2927, 2858, 1641 cm^{-1}; MS (+EI): *m*/*z*: calcd for $C_8H_{16}O$: 128.1201; found: 128.1207 $[M]^+$.

Fragment 2—(*S*)-2-Methyl-6-heptenal (4):[14,16] Pyridinium chlorochromate (PCC) on basic alumina (11.7 g, ~1.0 mmol g^{-1}, 11.7 mmol) was added at RT to a stirred solution of alcohol **35** (500 mg, 3.9 mmol) in CH_2Cl_2 (20 mL). The reaction was stirred for 3.5 h at RT until oxidation was complete. The mixture was filtered through Florisil, washing through with 10:1 petroleum ether 30–40/Et_2O dried over $MgSO_4$, refiltered and concentrated under reduced pressure to yield aldehyde **4** as a pale yellow oil (398 mg, 80 %). The bulk of the material was used in subsequent reactions without further purification. A portion of the product was purified by chromatography (silica gel, EtOAc/petrol 1:10). R_f = 0.47 (petrol/EtOAc 2:1) viewed: $KMnO_4$; $[\alpha]_D^{25}$ = +23.0 (*c* = 0.7, $CHCl_3$) (lit. $[\alpha]_D^{20}$ = +25.7 (*c* = 1.00, $CHCl_3$), (lit. $[\alpha]_D^{25}$ = +19.4 (*c* = 0.75, $CHCl_3$)); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.62 (d, ^3J(H,H) = 1.9 Hz, 1H, *H*-1), 5.85–5.75 (m, 1H, *H*-6), 5.00 (dd, ^3J(H,H) = 17.2, 1.6 Hz, 1H, CH=CH_{cis}H$_{trans}$), 4.97 (d, ^3J(H,H) = 10.2 Hz, 1H, CH=CH$_{cis}H_{trans}$), 2.39–2.32 (d of sextets, ^3J(H,H) = 6.9, 1.8 Hz, 1H, *H*-2), 2.11–2.06 (m, 2H, *H*-5), 1.77–1.66 (m, 1H, H_a-3), 1.50–1.34 (m, 3H, H_b-3, *H*-4), 1.10 (d, ^3J(H,H) = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.1 (*C*-1), 138.2 (*C*-6), 114.9 (*C*-7), 46.2 (*C*-2), 33.6 (CH_2), 29.9 (CH_2), 26.2 (CH_2), 13.3 (CH_3); IR (film): $\tilde{\nu}$ = 2932, 2864, 1704, 1641, 1464, 1236, 910 cm^{-1}; MS (+EI): *m*/*z*: calcd for $C_8H_{15}O$ 127.2041; found: 127.1123 $[M+H]^+$.

Fragment 3

1-(Tetrahydropyran-2-yloxy)propan-2-one (39): 1-Hydroxypropan-2-one (7.5 mL, 0.11 mol) and 3,4-dihydro-2*H*-pyran (20.1 mL, 0.22 mol) were added to a suspension of polyvinylpyridine-hydrochloride (2.0 g) in CH_2Cl_2 (40 mL). The reaction mixture was heated at reflux for 16 h. After cooling to RT the mixture was filtered and the filtrate concentrated under reduced pressure to yield the ketone **39** (16.8 g, 97 %) as a colourless oil. The bulk of the material was used in subsequent reactions without further purification. A portion of the product was purified by chromatography (silica gel, EtOAc/petrol 20:80). R_f = 0.16 (EtOAc/petrol 20:80); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.64 (t, ^3J(H,H) = 3.5 Hz, 1H, OC*H*O), 4.24 (d, ^3J(H,H) = 17.3 Hz, 1H, H_a-1), 4.11 (d, ^3J(H,H) = 17.3 Hz, 1H, H_b-1), 3.84 (td, ^3J(H,H) = 11.3 Hz, 3.2 Hz, 1H, OC*H*H), 3.51 (m, 1H, OCH*H*), 2.18 (s, 3H, *H*-3), 1.53–1.91 (m, 6H, 3×CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.7 (*C*-2), 98.7, 72.3 (*C*-1), 62.3, 30.2, 26.4 (*C*-3), 25.2, 19.1, IR (film): $\tilde{\nu}$ = 2943, 2871, 1719, 1442, 1387, 1354 cm^{-1}; MS (+EI): *m*/*z*: calcd for $C_8H_{14}O_3Na$: 181.0841; found: 181.0833 $[M+Na]^+$.

(4-Bromomethyl-2-methyl)thiazole hydrobromide (36): Thioacetamide (5.0 g, 66.7 mmol) was added portionwise over 10 min to a solution of 1,3-dibromoacetone (15.8 g, 73.4 mmol) in dioxane (200 mL). After stirring for 5 min at RT a white precipitate formed. The reaction was heated at reflux for 30 min. On reaching reflux the white precipitate dissolved to give a yellow solution. On standing for 10 min a dark yellow oil separated from the mixture which, on cooling, solidified to give thiazole salt **36** (14.9 g, 82 %) as a pale brown, granular solid. M.p. decomposed at >160 °C; ^{1}H NMR (400 MHz, CD_3OD): δ = 7.93 (s, 1H, *H*-5), 4.73 (s, 2H, CH_2Br), 2.94 (s, 3H, 2-CH_3); ^{13}C NMR (100 MHz, CD_3OD, 25 °C): δ = 174.2 (*C*-2), 144.6 (*C*-4), 121.0 (*C*-5), 20.3 (CH_2), 15.4 (CH_3); IR (solid): $\tilde{\nu}$ = 2470, 1790, 1581, 1491, 1411, 1381, 1293, 1238 cm^{-1}; elemental analysis calcd (%) for $C_5H_7NSBr_2$: C 22.00, H 2.58, N 5.13; found C 22.30, H 2.56, N 5.03; MS (+EI): *m*/*z*: calcd for C_5H_6NSBr: 190.9404; found: 190.9402 $[M-HBr]^+$.

(4-Bromomethyl-2-methyl)thiazole (37): Hydrobromide salt **36** (20 mg, 73.2 μmol) was dissolved in MeOH (3 mL) and polymer supported carbonate (40 mg, 4.5 mmol g^{-1}, 0.18 mmol, 2 % 4-divinylbenzene, DVB) was added. The reaction mixture was shaken at RT for 3 h. The mixture was filtered and the filtrate concentrated under reduced pressure to yield the thiazole bromide free base **37** as a colourless oil (13.5 mg, 96 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.12 (s, 1H, *H*-5), 4.53 (s, 2H, CH_2Br), 2.70 (s, 3H, 2-CH_3); ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 166.9 (*C*-2), 151.7 (*C*-4), 117.2 (*C*-5), 27.1 (CH_2), 19.2 (CH_3); IR (film): $\tilde{\nu}$ = 1517,

1485, 1423, 1375, 1324, 1214 cm^{-1}; MS (+EI): *m/z*: calcd for C_5H_6NSBr: 192.9385; found: 192.9383 $[M]^+$.

(2-Methylthiazol-4-ylmethyl)triphenylphosphonium bromide, polymer-supported 38: Pre-washed polymer-supported triphenylphosphine (5.20 g, 15.6 mmol, 3 mmol g^{-1}) was added to a solution of 4-bromomethyl-2-methylthiazole (**37**; 3.85 g, 20.0 mmol) in PhMe (80 mL). The reaction was heated at 90 °C for 5 h. The resin was recovered by filtration and washed with alternating aliquots of CH_2Cl_2 (3×100 mL) and Et_2O (3×100 mL) to give the product salt **38** as a yellowy brown solid (7.9 g, ~1.75 mmol g^{-1} loading). Remaining unloaded thiazole bromide **37** was recovered as yellow oil (1.13 g). IR (solid): $\tilde{\nu}$ = 2924, 2854, 2217, 1597, 1515, 1484, 1439, 1409, 1322, 1189 cm^{-1}; elemental analysis found: N 2.31 (loading 1.65 mmol g^{-1}).

2-Methyl-4-(2′-methyl-3′-[tetrahydropyran-2′-yloxy]propenyl)thiazole (40): NaHMDS (3.6 mL, 1 M solution in THF, 3.60 mmol) was added to a suspension of polymer-supported (2-methylthiazol-4-ylmethyl)triphenylphosphonium bromide **38** (200 mg, ~0.60 mmol) in THF (2 mL). The reaction was shaken at RT for 45 min. The mixture was filtered under argon and the resin washed with alternating aliquots of THF (3×10 mL) and Et_2O (3×10 mL). The resin was re-suspended in THF (2 mL) and ketone **39** (26 mg, 0.20 mmol) was added as a solution in THF (0.5 mL). The reaction mixture was shaken at RT for 15 h. The mixture was filtered and the filtrate concentrated under reduced pressure to give the product alkenes **40** as a yellow oil (47 mg, 94%, 43:4 *E*:*Z*). The bulk of the material was used in subsequent reactions without further purification. A portion of the product was purified by chromatography (silica gel, EtOAc/petrol 20:80).

2-Methyl-4-([*E*]-2′-methyl-3′-[tetrahydropyran-2′-yloxy]-propenyl)thiazole (40): R_f = 0.24 (EtOAc/petrol 20:80); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.97 (s, 1H, *H*-5), 6.57 (s, 1H, *H*-1′), 4.68 (t, ^3J(H,H) = 3.4 Hz, 1H, OC*H*O), 4.27 (d, ^3J(H,H) = 13.0 Hz, 1H, H_a-3′), 4.08 (d, ^3J(H,H) = 13.0 Hz, 1H, H_b-3′), 3.90 (td, ^3J(H,H) = 11.3 Hz, 3.1 Hz, 1H, OC*H*H), 3.53 (m, 1H, OCH*H*), 2.70 (s, 3H, 2-CH_3), 2.06 (s, 3H, 2′-CH_3), 1.89–1.52 (m, 6H, 3×CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.2 (*C*-2), 153.0 (*C*-4), 136.8 (*C*-2′), 119.5 (*C*-1′), 115.3 (*C*-5), 97.7, 72.4 (*C*-3′), 62.1, 30.7, 25.5, 19.4, 19.2 (2-*C*H_3), 16.2 (2′-*C*H_3); IR (film): $\tilde{\nu}$ = 2914, 2164, 1505, 1439, 1354, 1261 cm^{-1}; MS (+EI): *m/z*: calcd for $C_{13}H_{19}NO_2S$: 253.1136; found: 253.1139 $[M]^+$.

2-Methyl-4-([*Z*]-2′-methyl-3′-[tetrahydropyran-2′-yloxy]-propenyl)thiazole: R_f = (*Z*) 0.28 (EtOAc/petrol 20:80); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.98 (s, 1H, *H*-5), 6.43 (s, 1H, *H*-1′), 4.66 (t, ^3J(H,H) = 3.5 Hz, 1H, OC*H*O), 4.49 (t, ^3J(H,H) = 12.0 Hz, 2H, *H*-3′), 3.90 (td, ^3J(H,H) = 11.1 Hz, 3.2 Hz, 1H, C*H*HO), 3.50 (m, 1H, CH*H*O), 2.68 (s, 3H, 2-CH_3), 1.99 (s, 3H, 2-CH_3), 1.88–1.74 (m, 6H, 3×CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.6 (*C*-2), 152.2 (*C*-4), 137.6 (*C*-2′), 122.0 (*C*-1′), 115.3 (*C*-5), 98.3, 66.8 (*C*-3′), 62.2, 30.7, 25.5, 22.5 (2′-*C*H_3), 19.5, 19.1 (2-*C*H_3); IR (film): $\tilde{\nu}$ = 2914.3, 1736.1, 1505.6, 1373.4, 1319.7, 1257.2, 1181.5 cm^{-1}; MS (+EI): *m/z*: calcd for $C_{13}H_{19}NO_2S$: 253.1136; found: 253.1134 $[M]^+$.

2-Methyl-4-([*E*]-2′-methylprop-1′-en-3′-ol)thiazole (41): Thiazole **40** (353 mg, 1.56 mmol) was dissolved in MeOH (10 mL) and Dowex 50X8 (4 g, 20% DVB) was added. The reaction mixture was shaken at RT for 5 h. The reaction mixture was filtered and the resin washed with MeOH (20 mL). The resin was re-suspended in MeOH (10 mL) and Et_3N (2 mL) was added. The reaction mixture was shaken at RT for 4 h. The reaction mixture was filtered and the resin washed with MeOH (30 mL). The filtrate was concentrated under reduced pressure to give alcohol **41** (208 mg, 92%) as a yellow oil. The bulk of the material was used in subsequent reactions without further purification. A portion of the product was purified by chromatography (silica gel, EtOAc/petrol 40:60). R_f = 0.28 (EtOAc/petrol 40:60); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.94 (s, 1H, *H*-5), 6.55 (s, 1H, *H*-1′), 4.19 (s, 2H, *H*-3′), 2.71 (s, 3H, 2-CH_3), 2.07 (s, 3H, 2′CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): 164.7 (*C*-2), 152.9 (*C*-5), 140.1 (*C*-2′), 117.7 (*C*-1′), 115.0 (*C*-5), 68.0 (*C*-3′), 19.1 (2-*C*H_3), 15.8 (2′-*C*H_3); IR (film): $\tilde{\nu}$ = 3276, 2922, 2856, 1665, 1506, 1440, 1375, 1270, 1189 cm^{-1}; MS (+EI): *m/z*: calcd for $C_8H_{11}NOS$: 169.0561; found: 169.0557 $[M]^+$.

2-Methyl-4-([*E*]-2′-methylpropen-2′-al)thiazole (42): Alcohol **41** (196 mg, 1.17 mmol) was dissolved in toluene (10 mL) and oxygen was bubbled through the solution for 5 min. Polymer-supported perruthenate (430 mg, 0.5 mmol g^{-1}, 0.23 mmol, 20% DVB) was added and the reaction mixture heated at reflux under an atmosphere of oxygen for 16 h. The reaction mixture was filtered and the filtrate concentrated under reduced pressure, to give aldehyde **42** (116 mg, 60%) as a yellow oil which, on standing at RT for 1 h, crystallised to give yellow needles. The bulk of the material was used in subsequent reactions without further purification. A portion of the product was purified by chromatography (silica gel, EtOAc/petrol 20:80). R_f = 0.18 (EtOAc/petrol 20:80); m.p. 57 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.54 (s, 1H, *H*-3′), 7.43 (s, 1H, *H*-5), 7.23 (s, 1H, *H*-1′), 2.75 (s, 3H, 2-CH_3), 2.19 (s, 3H, 2′-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.3 (*C*-3′), 165.9 (*C*-2), 151.6 (*C*-5), 141.0 (*C*-1′), 138.5 (*C*-2′), 122.7 (*C*-5), 19.3 (2-*C*H_3), 11.0 (2′-*C*H_3); IR (film): $\tilde{\nu}$ = 3091, 2917, 2818, 2718, 1675, 1624, 1573, 1435, 1334, 1193 cm^{-1}; MS (+EI): *m/z*: calcd for C_8H_9NOS: 167.0405; found: 167.0399 $[M]^+$.

(*S*)-2-Methyl-4-([1*E*]-2′-methylhexa-1′,5′-dien-3′-ol)thiazole (43): (+)-Diisopinocamphenylallylborane (5.7 mL, 0.63 M in pentane, 3.6 mmol) was added dropwise at −100 °C to a solution of 2-methyl-4-([1*E*]-2-methylpropenal)-thiazole (**42**; 0.40 g, 2.4 mmol) in Et_2O (10 mL). The mixture was stirred at −100 °C for 3 h. The reaction was diluted with MeOH (10 mL) and Dowex 50X8 (3 g, 20% DVB) was added. The reaction mixture was shaken at RT for 5 h and then filtered. The resin was washed with MeOH (20 mL) and the resin re-suspended in MeOH (10 mL). Triethylamine (2 mL) was added and the reaction mixture shaken at RT for 4 h. The mixture was filtered and the resin washed with MeOH (3×10 mL). The filtrate was concentrated under reduced pressure to give alcohol **43** as a yellow oil (449 mg, 89%). The bulk of the material was used in subsequent reactions without further purification. A portion of the product was purified by chromatography (silica gel, EtOAc/petrol 40:60). R_f = 0.21 (EtOAc/petrol 40:60); HPLC (Chiracel OD, MeCN/hexane 25:75) indicated 93% *ee*; $[\alpha]_D^{25}$ = −19.8 (*c* = 0.97 in $CHCl_3$). R_f = 0.21 (EtOAc/petrol 40:60; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.94 (s, 1H, *H*-5), 6.55 (s, 1H, *H*-1′), 5.87–5.77 (m, 1H, *H*-5′), 5.15 (d, ^3J(H,H) = 17.2 Hz, 1H, H_a-6′), 5.11 (d, ^3J(H,H) = 10.2 Hz, 1H, H_b-6′), 4.21 (t, ^3J(H,H) = 5.8 Hz, 1H, *H*-3′), 2.70 (s, 3H, 2-CH_3), 2.45–2.33 (m, 2H, *H*-4′), 2.04 (s, 3H, 2′-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 164.6 (*C*-2), 152.8 (*C*-4), 141.3 (*C*-2′), 134.5 (*C*-5′), 119.1 (*C*-1′), 118.1 (*C*-6′), 115.6 (*C*-5), 76.4 (*C*-3′), 40.0 (*C*-4′), 19.2 (2-*C*H_3), 14.4 (2′-*C*H_3); IR (film): $\tilde{\nu}$ = 3340, 2923, 2105, 1640, 1506, 1435, 1377, 1271, 1188 cm^{-1}; MS (+EI): *m/z*: calcd for $C_{11}H_{15}NOSNa$: 232.0772; found: 232.0769 $[M+Na]^+$.

(*S*)-2-Methyl-4-([*E*]-2′-methyl-3′-(*tert*-butyldimethylsilanyloxy)hexa-1′,5′-dienyl)thiazole (44): TBSOTf (26 μL, 115 μmol) and Et_3N (0.02 mL, 143 μmol) were added to a solution of alkene **43** (20 mg, 96 μmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred at RT for 30 min. Polymer-supported-TBD (150 mg, 2.2 mmol g^{-1}, 330 μmol, 2% DVB) was added and the reaction mixture shaken at RT for 16 h. The mixture was filtered and the filtrate concentrated under reduced pressure to yield TBS ether **44** as a yellow oil (30 mg, 97%). The bulk of the material was used in subsequent reactions without further purification. A portion of the product was purified by chromatography (silica gel, EtOAc/petrol 20:80). R_f = 0.55 (EtOAc/petrol 20:80); $[\alpha]_D^{25}$ = +1.46 (*c* = 0.97 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.92 (s, 1H, *H*-5), 6.46 (s, 1H, *H*-1′), 5.84–5.73 (m, 1H, *H*-5′), 5.04 (d, ^3J(H,H) = 17.4 Hz, 1H, H_a-6′), 5.00 (d, ^3J(H,H) = 10.4 Hz, 1H, H_b-6′), 4.16 (t, ^3J(H,H) = 6.5 Hz, 1H, *H*-3′), 2.67 (s, 3H, 2-CH_3), 2.38–2.28 (m, 2H, *H*-4′), 1.93 (s, 3H, 2-CH_3), 0.87 (s, 9H, SiC(CH_3)$_2$), 0.10 (s, 3H, SiCH_3), 0.01 (s, 3H, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.3 (*C*-2), 153.2 (*C*-4), 142.0 (*C*-2′), 135.3 (*C*-5′), 118.9 (*C*-1′), 116.5 (*C*-6′), 115.1 (*C*-5), 78.5 (*C*-3′), 41.4 (*C*-4′), 25.7 (SiC(*C*H_3)$_3$), 19.2 (Si*C*(CH$_3$)$_3$), 18.2 (2-*C*H_3), 13.9 (2′-*C*H_3), −3.8 (Si*C*H_3), −4.6 (Si*C*H_3); IR (film): $\tilde{\nu}$ = 2927, 1504, 1471, 1251, 1181, 1071 cm^{-1}; MS (+EI): *m/z*: calcd for $C_{17}H_{29}NOSSiNa$: 380.1692; found: 380.1675 $[M+Na]^+$.

2-Methyl-4-([*E*]-2′-methyl-3′-(*S*)-(*tert*-butyldimethylsilanyloxy)hex-1′-en-5′,6′-diol)thiazole (45): Alkene **44** (23 mg, 71 μmol) and OsO_4 (0.06 mL, 2.5 wt% in *t*BuOH, 5 μmol) was added to a suspension of polymer-supported 4-methylmorpholine-*N*-oxide[55] (200 mg) in acetone/H_2O (2 mL, 9:1). The reaction mixture was heated at 40 °C for 16 h. Polyvinylpyridine (50 mg, 0.48 mmol, ≈9.5 mmol g^{-1}) was added and the mixture stirred at RT for 4 h. The reaction was filtered and the filtrate concentrated under reduced pressure to yield diol **45** as a dark brown oil (25 mg, 97%, 5*R*:5*S* 1:1). The bulk of the material was used in subsequent reactions without further purification. A portion of the product was purified by chromatography (silica gel, EtOAc). R_f = 0.49 (EtOAc); ^{1}H NMR (400 MHz,

$CDCl_3$): $\delta = 6.94$, 6.92 (s, 1H, *H*-5), 6.58, 6.50 (s, 1H, *H*-1′), 4.50–4.43 (m, 1H, *H*-3′), 3.95–3.89 (m, 1H, *H*-5′), 3.63–3.59 (m, 1H, H_a-6′), 3.50–3.43 (m, 1H, H_b-6′), 2.71 (s, 3H, 2-CH_3), 2.03, 2.02 (s, 3H, 2-CH_3), 1.89–1.82 (m, 1H, H_a-4′), 1.70–1.60 (m, 1H, H_b-4′), 0.93, 0.92 (s, 9H, SiC(CH_3)$_3$), 0.08, 0.04 (2×s, 3H, 2×SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 164.7$/164.6 (*C*-2), 153.0, 152.6 (*C*-4), 141.4 and 141.0 (*C*-2′), 119.5/118.7 (*C*-1′), 115.6, 115.5 (*C*-5), 77.3 and 75.8 (*C*-3′), 71.1/69.0 (*C*-5′), 66.8, 66.5 (*C*-6′), 39.0/38.3 (*C*-4′), 25.8 (SiC(*C*H$_3$)$_3$), 19.3, 19.2 (Si*C*(CH$_3$)$_3$), 18.2, 18.0 (2-*C*H$_3$), 15.1, 13.8 (2′-*C*H$_3$), −4.8 (Si*C*H$_3$), −4.4 (SiC*C*H$_3$), −5.3 (Si*C*H$_3$), −5.2 (Si*C*H$_3$); IR (film): $\tilde{\nu}$ = 3346, 2921, 1501, 1436, 1357, 1251, 1067 cm^{-1}.

2-Methyl-4-([*E*]-2-methyl-3-[*S*]-(*tert*-butyldimethylsilanyloxy)hex-1-ene-5-al)-thiazole (46): Amberlyst A27 (periodate form) (200 mg, 0.4 mmol, 2 mmol g^{-1}) was added to a solution of diol **45** (45 mg, 0.13 mmol) in MeOH/H_2O (3 mL, 5:1). The mixture was shaken at RT for 1 d. The reaction was filtered and the resin washed with MeOH (10 mL) and the filtrate concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (2 mL) and the mixture filtered. The filtrate was concentrated under reduced pressure to yield aldehyde **46** as a brown oil (39 mg, 95%). A portion of the product was purified by chromatography (silica gel, EtOAc/petrol 50:50). R_f = 0.45 (EtOAc/petrol 50:50); $[\alpha]_D^{25} = -15.6$ (c = 3.58, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.78$ (t, ^3J(H,H) = 2.5 Hz, 1H, *H*-5′), 6.94 (s, 1H, *H*-5), 6.55 (s, 1H, *H*-1′), 4.68 (dd, ^3J(H,H) = 8.2 Hz, 4.0 Hz, 1H, *H*-3′), 2.73 (ddd, ^3J(H,H) = 15.5 Hz, 8.3 Hz, 2.9 Hz, 1H, H_a-4′), 2.69 (s, 3H, 2-CH_3), 2.50 (ddd, ^3J(H,H) = 15.6, 4.0, 2.1 Hz, 1H, H_b-4′), 2.03 (s, 3H, 2′-CH_3), 0.87 (s, 9H, SiCCH_3), 0.07 (s, 3H, SiCH_3), 0.02 (s, 3H, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 201.6 (*C*-5′), 164.7 (*C*-2), 152.6 (*C*-4), 140.4 (*C*-2′), 119.3 (*C*-1′), 115.9 (*C*-5), 73.9 (*C*-3′), 50.1 (*C*-4′), 25.7 (SiC(*C*H$_3$)$_3$), 19.2 (Si*C*(CH$_3$)$_3$), 18.1 (2-*C*H$_3$), 14.1 (2′-*C*H$_3$), −5.6 (Si*C*H$_3$), −5.2 (Si*C*H$_3$); IR (film): $\tilde{\nu}$ = 2954, 2928, 1725, 1501, 1436, 1252, 1077 cm^{-1}; MS (+EI): m/z: calcd for $C_{16}H_{27}NO_2SSi$: 325.1532; found: 325.1537 $[M]^+$.

4-Chloromethyl-2-methyl-thiazole (52):[53] Thiazole chloride hydrochloride salt **51** (12.70 g, 68.9 mmol) was dissolved in methanol (150 mL) and polymer supported carbonate (Fluka, 39.3 g, 3.50 mmol g^{-1}, 138 mmol) was added. The reaction mixture was shaken at RT for 30 min. The mixture was filtered and the filtrate concentrated under reduced pressure to yield thiazole free base **52** as a brown oil (10.0 g, 98%). The product was used in the subsequent reaction without further purification. R_f = 0.67 (CH_2Cl_2/MeOH 19:1); ^{1}H NMR (400 MHz; $CDCl_3$): δ = 7.12 (s, 1H, *H*-5), 4.65 (s, 2H, CH_2), 2.71 (s, 3H, CH_3).

(2-Methyl-thiazol-4-ylmethyl)-phosphonic acid diethyl ester (53):[15] Triethyl phosphite (13.23 g, 79.6 mmol) was added to thiazole chloride **52** and heated to 160°C for 3 h. A colour change from colourless to deep red occurred. The reaction was cooled to RT and excess triethyl phosphite removed under reduced pressure at 60°C to yield phosphonate **53** as a red oil (15.43 g, 84%). The bulk of the material was used in subsequent reactions without further purification. A portion of the product was purified by chromatography (silica gel, Et_2O/MeOH 19:1). R_f = 0.21 (CH_2Cl_2/MeOH 19:1) viewed: UV (254 nm) or $KMnO_4$; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.83$ (d, 1H, ^3J(H,H) = 3.5 Hz, *H*-5), 3.86 (q, ^3J(H,H) = 7.4 Hz, 4H, 2×OCH_2), 3.12 (d, ^3J(H,H) = 11.0 Hz, 2H, CH_2), 2.45 (s, 3H, 2-CH_3), 1.06 (t, ^3J(H,H) = 7.4 Hz, 6H, 2×CH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 164.7$ (d, ^4J(C,P) = 1.1 Hz, *C*-2), 145.5 (d, ^2J = 8.2 Hz, *C*-4), 115.1 (d, ^3J(C,P) = 7.6 Hz, *C*-5), 61.6 (d, ^2J = 6.6 Hz, O*C*H$_2$), 28.9 (d, ^1J(C,P) = 140 Hz, *C*H$_2$), 18.5 (s, 2-*C*H$_3$), 15.8 (d, ^3J = 6.0, CH$_2$*C*H$_3$); IR (film): $\tilde{\nu}$ = 2980, 2237, 1519, 1247, 1054, 1024, 952, 925, 726 cm^{-1}; MS (+ESI): m/z: calcd for $C_9H_{16}NO_3PSNa$: 272.0486; found: 272.0489 $[M+Na]^+$.

(−)-(3*S*)-3-(*tert*-Butyldimethylsilyloxy)dihydrofuran-2-one (48):[15,21] Hydroxy lactone **47** (2.05 g, 19.6 mmol) was dissolved in CH_2Cl_2 (80 mL). Polymer-supported DMAP (Argonaut, 1.49 mmol g^{-1}, 26.30 g, 39.2 mmol) was added to the mixture at RT before addition of TBSCl (4.13 g, 27.4 mmol). The reaction was stirred for 1.5 h at RT then filtered and concentrated under reduced pressure to yield lactone **48** as a pale yellow oil (3.92 g, 93%) that crystallised on standing at −10°C. The bulk of the material was used in subsequent reactions without further purification. A portion of the product was purified by chromatography (silica gel, EtOAc/petrol 1:5). M.p. 17–18°C; R_f = 0.31 (petrol/EtOAc 5:1); $[\alpha]_D^{25} = -32.5$ (c = 1.72, $CHCl_3$) (lit. $[\alpha]_D^{20} = -30.5$ (c = 5.82, $CHCl_3$)); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.41$ (app. t, ^3J(H,H) = 8.4 Hz, 1H, *H*-3), 4.37 (td, ^3J(H,H) = 8.8, 3.2 Hz, 1H, H_a-5), 4.19 (td, ^3J(H,H) = 9.0, 6.4 Hz, 1H, H_b-5), 2.50–2.43 (m, 1H, H_a-4), 2.22 (m, 1H, H_b-4), 0.91 (s, 9H, SiC(CH_3)$_3$), 0.017 (s, 3H, Si(CH_3)$_2$), 1.014 (s, 3H, Si(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 175.9$ (*C*-2), 68.2 (*C*-3), 64.7 (*C*-5), 32.3 (*C*-4), 25.6 (SiC(*C*H$_3$)$_3$), 18.2 (Si*C*(CH$_3$)$_3$), −4.8 (Si*C*H$_3$), −5.3 (Si*C*H$_3$); IR (film): $\tilde{\nu}$ = 2955, 2930, 2858, 1783, 1473, 1361, 1252, 1219, 1148, 1107, 1020, 998, 836, 778 cm^{-1}; HRMS (+ESI): m/z: calcd for $C_{10}H_{20}O_3SiNa$: 239.1079; found: 239.1065 $[M+Na]^+$.

(−)-(3*S*)-3-(*tert*-Butyldimethylsilyloxy)-5-hydroxypentan-2-one (49):[15] A solution of MeLi (1.6 M in Et_2O, 10.6 mL, 17.0 mmol) was added dropwise to a stirred solution of lactone **48** (3.5 g, 16.2 mmol) in THF (55 mL) at −78°C over 10 min to provide a yellow solution. The mixture was stirred at −78°C for 30 min before quenching the reaction by the addition of a polymer-supported carboxylic acid (Amberlite IRC-50, 34 g, 340 mmol, 10 mmol g^{-1}). The reaction was allowed to warm to RT, stirred for 45 min before filtration and concentration under reduced pressure to yield a yellow oil. On standing at RT this oil crystallised as a pale yellow solid **49** (3.68 g, 98%). The bulk of the material was used in subsequent reactions without further purification. A portion of the product was purified by chromatography (silica gel, EtOAc/petrol 1:3). Analysed as an equilibrium mixture of lactol and ring opened isomer; m.p. 54–55°C (lit. 53–60°C); R_f = 0.34 (petrol/EtOAc 5:3); $[\alpha]_D^{25} = +24.76$ (c = 2.2, $CHCl_3$); ^{1}H and ^{13}C NMR spectra were both complex due to being a mixture of three isomers; IR (film): $\tilde{\nu}$ = 3412, 2955, 2930, 2859, 1472, 1251, 1139, 1021, 867, 836, 776, 671 cm^{-1}; MS (+ESI): m/z: calcd for $C_{10}H_{20}O_3SiNa$: 239.1079; found: 255.1408 $[M+Na]^+$.

(−)-(3*S*)-3,5-Bis-(*tert*-butyldimethylsilyloxy)-pentan-2-one (50):[14,15] Lactol **49** (3.0 g, 12.9 mmol) and polymer-supported DMAP (Argonaut, 1.49 mmol g^{-1}, 17.3 g, 2.6 mmol) were suspended in CH_2Cl_2 (50 mL) at RT before the portionwise addition of TBSCl (2.72 g, 18.1 mmol). The mixture was stirred for 2.5 h at RT, then filtered and concentrated under reduced pressure to yield ketone **50** as a pale yellow oil (3.68 g, 98%). The bulk of the material was used in subsequent reactions without further purification. A portion of the product was purified by chromatography (silica gel, EtOAc/petrol 1:10). R_f = 0.73 (petrol/EtOAc 5:2) viewed: moly dip; $[\alpha]_D^{25} = -12.2$ (c = 3.4, $CHCl_3$) (lit. $[\alpha]_D^{20} = -12.9$ (c = 1.00, $CHCl_3$)); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.15$ (dd, ^3J(H,H) = 6.3, 5.6 Hz, 1H, *H*-3), 3.74–3.63 (m, 2H, *H*-5), 2.15 (s, 3H, *H*-1), 1.86–1.74 (m, 2H, *H*-4), 0.91 (s, 9H, SiC(CH_3)$_3$), 0.86 (s, 9H, SiC(CH_3)$_3$), 0.05 (s, 3H, Si*C*H$_3$), 0.05 (s, 3H, Si*C*H$_3$), 0.023 (s, 3H, Si*C*H$_3$), 0.019 (s, 3H, Si(*C*H$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 212.1$ (*C*-2), 75.7 (*C*-3), 58.3 (*C*-5), 37.7 (*C*-1), 25.9 (SiC(*C*H$_3$)$_3$), 25.7 (SiC(*C*H$_3$)$_3$), 25.6 (*C*-4), 18.2 (Si*C*(CH$_3$)$_3$), 18.1 (Si*C*(CH$_3$)$_3$), −3.6 (Si*C*H$_3$), −5.0 (Si*C*H$_3$), −5.48 (Si*C*H$_3$), −5.5 (Si*C*H$_3$); IR (film): $\tilde{\nu}$ = 2955, 2929, 2885, 2858, 1718, 1472, 1464, 1361, 1253, 1101, 1005, 833, 774 cm^{-1}; MS (+ESI): m/z: calcd for $C_{17}H_{38}O_3Si_2Na$ 369.2257; found: 369.2257 $[M+Na]^+$.

(3*S*)-4-[(*E*)-3,5-Bis-(*tert*-butyldimethylsilyloxy)-2′-methylpent-1-enyl]-2-methylthiazole (54):[14] A solution of *n*BuLi (25.3 mL, 1.6 M solution in hexanes, 40.5 mmol) was added to a stirred solution of phosphonate **53** (11.20 g, 40.5 mmol) in THF (32 mL) at −78°C over 7 min. A colour change occurred from pale red to dark red/brown. The reaction mixture was stirred at −78°C for 10 min before addition of ketone **50** (4.00 g, 11.6 mmol) over 5 min at −78°C. The mixture was stirred for 5 min at −78°C, then allowed to warm slowly to RT and stirred for 45 min. Polymer-supported benzaldehyde (Argonaut, 1.2 mmol g^{-1}, 48.30 g, 58.0 mmol) was added and the mixture diluted with Et_2O (100 mL) and stirred at RT for 30 min. Silica gel (200 mL dry) and Et_2O (200 mL) were added causing a colour change from deep red to pale yellow. The suspension was filtered and washed using Et_2O. The filtrate was concentrated, then dissolved in Et_2O (50 mL) and silica gel (50 mL dry) was added. The mixture was filtered and concentrated under reduced pressure to yield **54** as a yellow oil (5.36 g, 105%). The bulk of the material was used in subsequent reactions without further purification. A portion of the product was purified by chromatography (silica gel). R_f = 0.40 (CH_2Cl_2) viewed: UV (254 nm) or moly dip; $[\alpha]_D^{25} = -1.0$ (c = 5.0, $CHCl_3$) (lit. $[\alpha]_D^{20} = -0.7$ (c = 0.46, $CHCl_3$)); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 6.90$ (s, 1H, *H*-5), 6.48 (s, 1H, *H*-1′), 4.33 (dd, 1H, ^3J(H,H) = 7.7, 4.7 Hz, *H*-3′), 3.73–3.62 (m, 2H, *H*-4′), 2.70 (s, 3H, 2-CH_3), 2.00 (s, 3H, 2′-CH_3), 1.81–1.71 (m, 2H, *H*-5′), 0.902 (s, 9H, SiC(CH_3)$_3$), 0.900 (s, 9H, SiC(CH_3)$_3$), 0.08 (s, 3H, Si*C*H$_3$), 0.04 (s, 6H, Si*C*H$_3$), 0.01 (s, 3H, Si(*C*H$_3$)$_2$); ^{1}H NMR (150 MHz, $CDCl_3$): $\delta = 164.2$ (*C*-2), 153.3 (*C*-4),

142.5 (*C*-2′), 118.6 (*C*-5), 114.9 (*C*-1′), 75.1 (*C*-3′), 59.6 (*C*-5′), 39.9 (2′-*C*H$_3$), 25.9 (SiC(*C*H$_3$)$_3$), 25.8 (SiC(*C*H$_3$)$_3$), 19.1 (*C*-14), 18.22 (Si*C*(CH$_3$)$_3$), 18.21 (Si*C*(CH$_3$)$_3$), 13.8 (*C*-21), −4.6 (Si*C*H$_3$), −5.1 (Si*C*H$_3$), −5.3 (Si*C*H$_3$), −5.4 (Si*C*H$_3$); IR (film): $\tilde{\nu}$ = 2953, 2928, 2856, 1472, 1463, 1251, 1183, 1083, 1005, 832, 774 cm^{-1}; MS (+ESI): *m*/*z*: calcd for $C_{22}H_{43}NO_2S$-Si_2Na: 464.2451; found: 464.2466 [*M*+Na]$^+$.

(*E*)-3*S*-(*tert*-Butyldimethylsilyloxy)-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-en-1-ol (55):[14,19,21,27] A solution of CSA (3.80 g, 16.4 mmol) in MeOH (200 mL) was added to a solution of di-silyl ether **54** (4.80 g, 10.9 mmol) in MeOH/CH_2Cl_2 (1:1, 200 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2.5 h before the addition of polymer-supported carbonate and the mixture was allowed to warm to RT. Filtration and solvent removal under reduced pressure yielded mono-silyl ether **55** as a pale yellow viscous oil (3.70 g, 104 %). The bulk of the material was used in subsequent reactions without further purification. A portion of the product was purified by chromatography (silica gel, MeOH/CH_2Cl_2 1:30). R_f = 0.46 (CH_2Cl_2/MeOH 19:1) viewed: UV (254 nm) or moly dip; $[\alpha]_D^{25}$ = −34.1 (*c* = 0.595, $CHCl_3$) (lit. $[\alpha]_D^{20}$ = −31.5 (*c* = 2.81, $CHCl_3$)); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.93 (s, 1H, *H*-5′), 6.53 (s, 1H, *H*-5), 4.39 (dd, ^3J(H,H) = 7.3, 4.6 Hz, 1H, *H*-3), 3.79–3.72 (m, 2H, *H*-1), 2.72 (s, 3H, 2′-C*H*$_3$), 2.30 (br s, 1H, O*H*), 2.03 (d, ^3J(H,H) = 0.6 Hz, 3H, 4-C*H*$_3$), 1.93–1.87 (m, 1H, H_a-2), 1.84–1.72 (m, 1H, H_b-2), 0.92 (s, 9H, SiC(C*H*$_3$)$_3$), 0.12 (s, 3H, Si*CH*$_3$), 0.05 (s, 3H, Si*CH*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.5 (*C*-2′), 153.0 (*C*-1), 141.6 (*C*-4), 118.8 (*C*-4′), 115.4 (*C*-5), 77.5 (*C*-3), 60.4 (*C*-1), 38.2 (2′-*C*H$_3$), 25.8 (SiC(*C*H$_3$)$_3$), 19.2 (*C*-4′), 18.1 (SiC(*C*H$_3$)$_3$), 14.4 (2-*C*H$_3$), −4.6 (Si*C*H$_3$), −5.2 (Si*C*H$_3$); IR (film): $\tilde{\nu}$ = 3403, 2928, 2857, 1472, 1253, 1185, 1074, 837, 777 cm^{-1}; MS (+EI): *m*/*z*: calcd for $C_{16}H_{29}NO_2SSi$: 327.1688; found: 327.1675 [*M*]$^+$.

Fragment 3—4-[(*E*)-3*S*-(*tert*-Butyldimethylsilyloxy)-5-iodo-2-methylpent-1-enyl]-2-methylthiazole (5):[19] Iodine (1.55 g, 6.12 mmol) was added to a suspension of alcohol **55** (500 mg, 1.53 mmol) diethylaminomethylpolystyrene (Fluka, 3.2 mmol g^{-1}, 2.87 g, 9.17 mmol) with polymer-supported triphenylphosphine (Fluka, 3.3 mmol g^{-1}, 2.32 g, 7.65 mmol) in MeCN/Et_2O (3:1, 13.5 mL) at RT. The reaction mixture was stirred at RT for 19 h before filtration and concentration under reduced pressure to yield the iodide **5** as a yellow oil (489 mg, 73 %). The bulk of the material was used in subsequent reactions without further purification. A portion of the product was purified by chromatography (silica gel, EtOAc/petrol 1:5). R_f = 0.58 (petrol/EtOAc 3:1); $[\alpha]_D^{25}$ = +12.8 (*c* = 0.76, $CHCl_3$) (lit. $[\alpha]_D^{20}$ = +11.0 (*c* = 1.00, $CHCl_3$)); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.94 (s, 1H, *H*-5), 6.52 (s, 1H, *H*-1′), 4.23 (dd, ^3J(H,H) = 7.4, 4.5 Hz, 1H, *H*-3′), 3.21 (t, ^3J(H,H) = 7.2 Hz, 2H, *H*-5′), 2.72 (s, 3H, 2-C*H*$_3$), 2.14–2.06 (m, 1H, H_a-4′), 2.05–2.00 (m, 1H, H_b-4′), 2.01 (d, ^3J(H,H) = 0.6 Hz, 3H, 2-C*H*$_3$), 0.91 (s, 9H, SiC(C*H*$_3$)$_3$), 0.13 (s, 3H, Si*CH*$_3$), 0.04 (s, 3H, Si*CH*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.5 (*C*-2), 152.9 (*C*-4), 141.0 (*C*-2′), 119.5 (*C*-5), 115.5 (*C*-1′), 78.1 (*C*-3′), 40.4 (2′-*C*H$_3$), 25.8 (SiC(*C*H$_3$)$_3$), 19.2 (*C*-4′), 18.1 (SiC(*C*H$_3$)$_3$), 13.9 (2-*C*H$_3$), 3.0 (*C*-5′), −4.6 (Si*C*H$_3$), −4.9 (Si*C*H$_3$); IR (film): $\tilde{\nu}$ = 2928, 2857, 1471, 1252, 1080, 935, 834, 775 cm^{-1}; MS (+EI): *m*/*z*: calcd for $C_{16}H_{28}INOSSi$: 437.0706; found: 437.0708 [*M*]$^+$.

(−)-(3*S*,4*E*)-3-(*tert*-Butyldimethylsilyloxy)-4-(methyl-5-(2-methyl-1,3-thiazol-4-yl)pent-4-enyl)-triphenylphosphonium iodide on polystyrene (56):[19] Polymer-supported triphenylphosphine (Fluka, 3.3 mmol g^{-1}, 518 mg, 1.71 mmol) was added to iodide **5** (490 mg, 1.12 mmol) in PhMe (2 mL) and the mixture was heated to 90 °C for 18 h without stirring. The reaction was cooled to RT, filtered and the resin washed using CH_2Cl_2 (3 × 5 mL), then Et_2O (3 × 5 mL). The polymer was dried under reduced pressure to yield the immobilized phosphonium salt **56** as a yellow solid (870 mg, 0.90 mmol g^{-1} calculated based on mass increase of polymer and recovered iodide). The unloaded iodide **5** was recovered as yellow oil (172 mg) from the washings and recycled. The product was used in the subsequent reaction without further purification. IR (solid): $\tilde{\nu}$ = 2930, 1586, 1435, 1253, 1180, 1110 cm^{-1}; elemental analysis found: P 5.34 (loading 1.72 mmol g^{-1}), N 1.10 (loading: 0.8 mmol g^{-1}).

Fragment coupling and cyclisation (compound numbering is based on epothilone structure)

1,3-Bis-(*tert*-butyldimethylsilyloxy)-7-hydroxy-4,4,6,8-tetramethyl-12-tridecen-5-one (57): A solution of LDA was prepared: *n*BuLi (0.63 mL, 1.6 M solution in hexanes, 1.00 mmol) was added to DIPA (101 mg, 1.00 mmol) in THF (3 mL) at −78 °C, warmed to 0 °C over 10 min, then cooled back to −78 °C to give a colourless solution.

A solution of ketone **3** (250 mg, 0.62 mmol) in THF (1.0 mL) was added dropwise over 5 min to the freshly prepared solution of LDA at −78 °C. After being stirred for 20 min at −78 °C, the pale yellow solution was slowly warmed to −40 °C and after 30 min it was cooled back to −78 °C (colourless solution). A solution of aldehyde **4** (118 mg, 0.93 mmol) in THF (1 mL) was added dropwise at −78 °C over 10 min down the side of the cooled reaction vessel, and the resulting mixture was stirred for 25 min and then quenched at −78 °C by slow addition of glacial acetic acid (0.5 mL). The reaction mixture was warmed to RT and diluted with Et_2O before diamine resin (NovaBiochem, 1.0 g, 3.0 mmol g^{-1}, 3.0 mmol) was added. The mixture was stirred for 2 h, filtered and the filtrate was concentrated under reduced pressure to yield **57** as a colourless oil (333 mg, 100 %, 13:1 mix of diastereoisomers). The bulk of the material was used in subsequent reactions without further purification. A portion of the product was purified by chromatography (silica gel, EtOAc/petrol 1:20).

(3S,6R,7S,8S)-Major diastereoisomer ***57***: R_f = 0.22 (petrol 40–60/EtOAc 20:1); $[\alpha]_D^{25}$ = −54.1 (*c* = 0.75, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.85–5.78 (m, 1H, *H*-12), 4.99 (d, ^3J(H,H) = 17.1 Hz, 1H, CH=CH$_{trans}$C*H*$_{cis}$), 4.92 (d, ^3J(H,H) = 10.0 Hz, 1H, CH=C*H*$_{trans}$CH$_{cis}$), 3.90 (dd, ^3J(H,H) = 7.4, 2.6 Hz, 1H, *H*-3), 3.69–3.65 (m, 1H, H_a-1), 3.62–3.57 (m, 1H, H_b-1), 3.48 (s, 1H, O*H*), 3.32–3.27 (m, 2H, *H*-6, *H*-7), 2.08–2.02 (m, 2H, *H*-11), 1.82–1.77 (m, 1H, H_a-2), 1.64–1.61 (m, 1H, H_b-2), 1.61–1.42 (m, 4H, H_a-9, *H*-8, *H*-10), 1.20 (s, 3H, *H*-22), 1.10–1.09 (m, 1H, H_b-9), 1.09 (s, 3H, *H*-23), 1.02 (d, ^3J(H,H) = 6.8 Hz, 3H, *H*-24), 0.90 (s, 9H, SiC(C*H*$_3$)$_3$), 0.88 (s, 9H, SiC(C*H*$_3$)$_3$), 0.82 (d, ^3J(H,H) = 6.8 Hz, 3H, *H*-17), 0.10 (s, 3H, Si(C*H*$_3$)$_2$), 0.08 (s, 3H, Si(C*H*$_3$)$_2$), 0.03 (s, 6H, 2 × Si(C*H*$_3$)$_2$); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 218.1 (*C*-5), 139.1 (*C*-12), 114.2 (*C*-13), 74.8 (*C*-7), 74.1 (*C*-3), 60.5 (*C*-1), 54.0 (*C*-4), 41.3 (*C*-6), 37.9 (*C*-2), 35.5 (*C*-8), 34.2 (*C*-11), 32.4 (*C*-9), 26.1 (*C*-10), 26.1 (SiC(*C*H$_3$)$_3$), 25.9 (SiC(*C*H$_3$)$_3$), 22.8 (*C*-22), 20.4 (*C*-23), 18.3 (Si*C*(CH$_3$)$_3$), 18.2 (Si*C*(CH$_3$)$_3$), 15.3 (*C*-25), 9.59 (*C*-24), −3.8 (Si(*C*H$_3$)$_2$), −4.1 (Si(*C*H$_3$)$_2$), −5.3 (Si(*C*H$_3$)$_2$), −5.30 (Si(*C*H$_3$)$_2$); IR (film): $\tilde{\nu}$ = 3506 (br), 2956, 2929, 2857, 1682, 1472, 1254, 1090, 994, 834, 774 cm^{-1}; HRMS (+ESI): *m*/*z*: calcd for $C_{29}H_{60}O_4Si_2Na$: 551.3928; found: 551.3923 [*M*+Na]$^+$.

(3S,6S,7R,8S)-Minor diastereoisomer ***57***: R_f = 0.15 (petrol 40–60/EtOAc 20:1) viewed: moly dip; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.84–5.81 (m, 1H, *H*-12), 5.03 (d, ^3J(H,H) = 17.1 Hz, 1H, CH=CH$_{trans}$C*H*$_{cis}$), 4.97 (d, ^3J(H,H) = 10.2 Hz, 1H, CH=C*H*$_{trans}$CH$_{cis}$), 4.06 (dd, 7.0, 3.3 Hz, 1H, *H*-3), 3.69–3.65 (m, 1H, H_a-1), 3.65–3.57 (m, 1H, H_b-1), 3.44 (s, 1H, O*H*), 3.32–3.20 (m, 2H, *H*-6, *H*-7), 2.08–2.00 (m, 2H, *H*-11), 1.82–1.77 (m, 1H, H_a-2), 1.64–1.61 (m, 1H, H_b-2), 1.61–1.42 (m, 4H, H_a-9, *H*-8, *H*-10), 1.16 (s, 3H, *H*-22), 1.10–1.09 (m, 1H, H_b-9), 1.12 (s, 3H, *H*-23), 1.00 (d, 3H, ^3J(H,H) = 6.8 Hz, *H*-24), 0.92 (d, ^3J(H,H) = 6.8 Hz, 3H, *H*-25), 0.90 (s, 9H, SiC(C*H*$_3$)$_3$), 0.88 (s, 9H, SiC(C*H*$_3$)$_3$), 0.10 (s, 3H, Si(C*H*$_3$)$_2$), 0.08 (s, 3H, Si(C*H*$_3$)$_2$), 0.03 (m, 6H, 2 × Si(C*H*$_3$)$_2$); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 222.1 (*C*-5), 138.7 (*C*-12), 114.6 (*C*-13), 75.1 (*C*-7), 72.8 (*C*-3), 60.2 (*C*-1), 54.4 (*C*-4), 41.4 (*C*-6), 37.8 (*C*-2), 35.3 (*C*-8), 33.9 (*C*-11), 32.2 (*C*-9), 26.2 (*C*-10), 26.15 (SiC(*C*H$_3$)$_3$), 26.11 (SiC(*C*H$_3$)$_3$), 22.9 (*C*-22), 19.5 (*C*-23), 18.3 (Si*C*(CH$_3$)$_3$), 18.2 (Si*C*(CH$_3$)$_3$), 15.6 (*C*-25), 10.8 (*C*-24), −3.80 (Si(*C*H$_3$)$_2$), −4.10 (Si(*C*H$_3$)$_2$), −5.29 (Si(*C*H$_3$)$_2$), −5.30 (Si(*C*H$_3$)$_2$); IR (film): $\tilde{\nu}$ = 3506 (br), 2956, 2929, 2857, 1682, 1472, 1254, 1090, 994, 834, 774 cm^{-1}.

(3*S*,6*R*,7*S*,8*S*)-1,3,7-Tris-(*tert*-butyldimethylsilyloxy)-4,4,6,8-tetramethyl-12-tridecen-5-one (58): Aldol adduct **57** (600 mg, 1.14 mmol) was dissolved in CH_2Cl_2 (12 mL) and treated at 0 °C with diethylaminomethylpolystyrene (1.07 g, 3.2 mmol g^{-1}, 3.40 mmol) and TBSOTf (450 mg, 1.7 mmol). After stirring for 3.5 h (reaction complete by TLC), the reaction was quenched by the addition methanol (0.2 mL), warmed to RT and stirred for 2 h. The mixture was filtered and the filtrate concentrated under reduced pressure to yield the tris-*tert*-butyldimethylsilyl ether product **58** (728 mg, 99 %) as pale yellow oil. The bulk of the material was used in subsequent reactions without further purification. A portion of the product was purified by chromatography (silica gel, EtOAc/petrol 1:20). R_f = 0.45 (petrol/EtOAc 20:1) viewed: moly dip; $[\alpha]_D^{25}$ = −32.8 (*c* = 0.81, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.82–5.77 (m, 1H, *H*-12), 4.97 (d, ^3J(H,H) = 17.1 Hz, 1H, CH=CH$_{trans}$C*H*$_{cis}$), 4.94 (d, ^3J(H,H) = 10.0 Hz, 1H, CH=C*H*$_{trans}$CH$_{cis}$), 3.90 (dd, 5.0, 2.5 Hz, 1H, *H*-3), 3.77 (dd, ^3J(H,H) = 4.9, 2.5 Hz, 1H, *H*-7), 3.68–3.64 (app. qn, ^3J(H,H) =

6.8 Hz, 1H, H_a-1), 3.60–3.56 (m, 1H, H_b-1), 3.15–3.13 (m, 1H, *H*-6), 2.03 (m, 2H, *H*-11), 1.65–1.55 (m, 1H, H_a-2), 1.50–1.34 (m, 4H, H_b-2, *H*-8, *H*-10), 1.26–1.21 (m, 1H, H_a-9), 1.22 (s, 3H, *H*-22), 1.20–1.09 (m, 1H, H_b-9), 1.05 (d, ^3J(H,H) = 6.8 Hz, 3H, *H*-24), 1.03 (s, 3H, *H*-23), 0.92 (d, ^3J(H,H) = 6.8 Hz, 3H, *H*-25), 0.91 (s, 9H, SiC(CH_3)$_3$), 0.90 (s, 9H, SiC(CH_3)$_3$), 0.88 (s, 9H, SiC(CH_3)$_3$), 0.092 (s, 3H, Si(CH_3)$_2$), 0.066 (s, 3H, Si(CH_3)$_2$), 0.060 (s, 3H, Si(CH_3)$_2$), 0.030 (s, 3H, Si(CH_3)$_2$), 0.028 (s, 3H, Si(CH_3)$_2$), 0.016 (s, 3H, Si(CH_3)$_2$); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 218.1 (*C*-5), 138.9 (*C*-12), 114.4 (*C*-13), 77.4 (*C*-7), 74.0 (*C*-3), 60.9 (*C*-1), 53.7 (*C*-4), 45.0 (*C*-6), 38.9 (*C*-8), 38.1 (*C*-2), 34.3 (*C*-11), 30.5 (*C*-9), 27.1 (*C*-10), 26.2 (SiC(CH_3)$_3$), 26.1 (SiC(CH_3)$_3$), 25.9 (SiC(CH_3)$_3$), 24.5 (*C*-22), 19.4 (*C*-23), 18.5 (Si*C*(CH_3)$_3$), 18.3 (Si*C*(CH_3)$_3$), 18.2 (Si*C*(CH_3)$_3$), 17.4 (*C*-25), 15.1 (*C*-24), −3.72 (Si(CH_3)$_2$), −3.8 (Si(CH_3)$_2$), −3.9 (Si(CH_3)$_2$), −4.0 (Si(CH_3)$_2$), −5.27 (Si(CH_3)$_2$), −5.30 (Si(CH_3)$_2$); IR (film): $\tilde{\nu}$ = 2955, 2929, 2857, 1696, 1472, 1463, 1253, 1093, 985, 833, 773 cm^{-1}; MS (+ESI): *m*/*z*: calcd for $C_{35}H_{74}O_4Si_3Na$: 665.4793; found: 665.4812 [*M*+Na]$^+$.

(3*S*,6*R*,7*S*,8*S*,12*Z*,15*S*,16*E*)-6,10,12-Tris-(*tert*-butyldimethylsilyloxy)-5,7,9,9-tetramethyl-8-oxo-dodecanal (59): Tris-*tert*-butyldimethylsilyl ether **58** (300 mg, 0.47 mmol) was dissolved in CH_2Cl_2 (12.0 mL) and cooled to −78 °C. The mixture was treated with O_3 for 7 min until all starting material had been consumed (by TLC) and solution turned blue. Polymer-supported triphenylphosphine (Fluka, 780 mg, 3.0 mmol g^{-1}, 2.3 mmol) was added at −78 °C and allowed to warm slowly to RT and shaken for 15 h. The suspension was filtered and the filtrate concentrated under reduced pressure to yield the corresponding aldehyde **59** as colourless oil (300 mg, 100 %). The bulk of the material was used in subsequent reactions without further purification. A portion of the product was purified by chromatography (silica gel, EtOAc/petrol 1:20). R_f = 0.25 (petrol/EtOAc 20:1) viewed: moly dip; $[\alpha]_D^{25}$ = −34.9 (*c* = 0.49, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.72 (s, 1H, *H*-12), 3.87 (dd, ^3J(H,H) = 7.4, 2.4 Hz, 1H, *H*-3), 3.75 (dd, ^3J(H,H) = 6.7, 2.0 Hz, 1H, *H*-7), 3.64–3.62 (m, 1H, H_a-1), 3.56–3.54 (m, 1H, H_b-1), 3.10 (app. qn, ^3J(H,H) = 6.8 Hz, 1H, *H*-6), 2.37 (dd, m, 2H, *H*-11), 1.73–1.64 (m, 1H, H_a-10), 1.58–1.50 (m, 1H, H_a-2), 1.47–1.37 (m, 4H, H_b-10, *H*-8, H_a-9, H_b-2), 1.19 (s, 3H, *H*-22), 1.18–1.08 (m, 1H, H_b-9), 1.02 (d, ^3J(H,H) = 6.9, 3H, *H*-24), 1.00 (s, 3H, *H*-23), 0.91 (d, ^3J(H,H) = 6.8 Hz, 3H, *H*-25), 0.87 (s, 9H, SiC(CH_3)$_3$), 0.86 (s, 9H, SiC(CH_3)$_3$), 0.85 (s, 9H, SiC(CH_3)$_3$), 0.06 (s, 3H, SiCH_3), 0.037 (s, 3H, SiCH_3), 0.034 (s, 3H, SiCH_3), 0.029 (s, 3H, SiCH_3), −0.002 (s, 3H, SiCH_3), −0.006 (s, 3H, Si(CH_3)$_2$); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 217.9 (*C*-5), 202.1 (*C*-12), 77.4 (*C*-7), 73.9 (*C*-3), 60.8 (*C*-1), 53.6 (*C*-4), 45.2 (*C*-6), 44.3 (*C*-11), 38.7 (*C*-8), 38.1 (*C*-2), 30.5 (*C*-9), 26.2 ((Si*C*(CH_3)$_3$), 26.1 ((SiC(*C*H_3)$_3$), 25.9 ((SiC(*C*H_3)$_3$), 24.4 (*C*-22), 20.3 (*C*-10), 19.4 (*C*-23), 18.5 (SiC(*C*H_3)$_3$), 18.3 (Si*C*(CH_3)$_3$), 18.2 (Si*C*(CH_3)$_3$), 17.5 (*C*-25), 15.2 (*C*-24), −3.7 (Si(*C*H_3)$_2$), −3.75 (Si*C*H_3), −3.8 (Si*C*H_3), −4.0 (Si*C*H_3), −5.28 (Si*C*H_3), −5.31 (Si*C*H_3); IR (film): $\tilde{\nu}$ = 2955, 2929, 2857, 1730, 1693, 1473, 1256, 1101, 986, 836, 775 cm^{-1}; MS (+ESI): *m*/*z*: calcd for $C_{34}H_{72}O_5Si_3Na$: 667.4585; found: 667.45710 [*M*+Na]$^+$.

(3*S*,6*R*,7*S*,8*S*,12*Z*,15*S*,16*E*)-1,3,7,15-Tetrakis(*tert*-butyldimethylsilyloxy)-4,4,6,8,16-pentamethyl-17-(2-methyl-1,3-thiazol-4-yl)heptadeca-12,16-dien-5-one (60): Polymer-supported phosphonium salt **56** (430 mg, 0.8 mmol g^{-1}, 0.34 mmol) was dried by PhMe azeotrope before being washed using dry CH_2Cl_2 (5 × 1 mL), then THF (5 × 1 mL) in a fritted tube. The resin was suspended in THF (2 mL) and NaHMDS (1 M solution in THF, 1.6 mL, 1.6 mmol) was slowly added at RT (colour change from light brown to black). The mixture was stirred at RT for 10 min, then filtered under Ar, washed with THF (5 × 2 mL) and the ylide resuspended in THF (2 mL). The reaction mixture was cooled to −78 °C and a solution of aldehyde **59** (100 mg, 0.16 mmol) was added slowly over 1 min. The mixture was stirred at −78 °C for 10 min then filtered through celite and concentrated under reduced pressure to yield alkene adduct **60** as a pale yellow oil (135 mg, 93 %). The bulk of the material was used in subsequent reactions without further purification. A portion of the product was purified by chromatography (silica gel, EtOAc/petrol 1:15). R_f = 0.45 (petrol/EtOAc 10:1) viewed: UV (254 nm) or moly dip; $[\alpha]_D^{25}$ = −31.0 (*c* = 0.40, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.91 (s, 1H, *H*-19), 6.45 (s, 1H, *H*-17), 5.40–5.37 (m, 2H, *H*-12, *H*-13), 4.12 (dd, ^3J(H,H) = 6.3, 6.2 Hz, 1H, *H*-15), 3.89 (d, ^3J(H,H) = 5.5 Hz, 1H, *H*-3), 3.76 (d, ^3J(H,H) = 5.5 Hz, 1H, *H*-7), 3.66 (m, 1H, H_a-1), 3.57 (m, 1H, H_b-1), 3.14 (app. qn, ^3J(H,H) = 6.8 Hz, 1H, *H*-6), 2.70 (s, 3H, *H*-21), 2.33–2.29 (m, 2H, *H*-14), 2.10–1.90 (m, 2H, *H*-11), 2.00 (s, 3H, *H*-26), 1.57 (m, 1H, H_a-2), 1.49 (m, 1H, H_b-2), 1.40–1.34 (m, 3H, *H*-9, *H*-8), 1.22 (s, 3H, *H*-22), 1.20–1.05 (m, 2H, *H*-10), 1.04 (d, ^3J(H,H) = 6.9 Hz, 3H, *H*-24), 1.02 (s, 3H, *H*-23), 0.90 (m, 12H, SiC(CH_3)$_3$, *H*-25), 0.88 (s, 9H, SiC(CH_3)$_3$), 0.875 (s, 9H, SiC(CH_3)$_3$), 0.87 (s, 9H, SiC(CH_3)$_3$), 0.086 (s, 3H, SiCH_3), 0.058 (s, 9H, 3 × SiCH_3), 0.027 (s, 9H, 3 × SiCH_3), 0.022 (s, 3H, SiCH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 218.2 (*C*-8), 164.3 (*C*-20), 153.2 (*C*-18), 142.1 (*C*-16), 131.2 (*C*-12), 125.9 (*C*-13), 118.9 (*C*-17), 115.0 (*C*-19), 78.6 (*C*-15), 77.4 (*C*-7), 74.0 (*C*-3), 61.0 (*C*-1), 53.7 (*C*-4), 45.0 (*C*-6), 39.0 (*C*-8), 38.1 (*C*-2), 34.7 (*C*-14), 30.8 (*C*-9), 28.0 (*C*-11), 27.9 (*C*-10), 26.2 (Si*C*(CH_3)$_3$), 26.1 (SiC(*C*H_3)$_3$), 25.9 (SiC(*C*H_3)$_3$), 25.8 (SiC(CH_3)$_3$), 24.5 (*C*-22), 19.2 (*C*-23), 19.1 (*C*-21), 18.5 (Si*C*(CH_3)$_3$), 18.4 (Si*C*(CH_3)$_3$), 18.3 (Si*C*(CH_3)$_3$), 18.2 (Si*C*(CH_3)$_3$), 17.5 (*C*-25), 15.1 (*C*-24), 13.8 (*C*-26), −3.7 (Si*C*H_3), −3.8 (Si*C*H_3), −4.0 (Si*C*H_3), −4.7 (Si*C*H_3), −4.9 (Si*C*H_3), −5.26 (Si*C*H_3), −5.28 (Si*C*H_3), −5.31 (Si*C*H_3); IR (film): $\tilde{\nu}$ = 2955, 2929, 2885, 2857, 1695, 1472, 1253, 1088, 985, 834, 774 cm^{-1}; MS (+ESI): *m*/*z*: calcd for $C_{50}H_{99}NO_5SSi_4Na$: 960.6213; found: 960.6186 [*M*+Na]$^+$.

(3*S*,6*R*,7*S*,8*S*,12*Z*,15*S*,16*E*)-3,7,15-Tris(*tert*-butyldimethylsilyloxy)-1-hydroxy-4,4,6,8,16-pentamethyl-17-(2-methyl-1,3-thiazol-4-yl)heptadeca-12,16-dien-5-one (61): A solution of tetra-(*tert*-butyl(dimethyl)silyl ether **60** (94 mg, 0.10 mmol) in MeOH/CH_2Cl_2 (1:1, 4.4 mL) was cooled to 0 °C. Camphorsulfonic acid (48.0 mg, 0.20 mmol) was added portionwise and the mixture stirred at 0 °C for 4 h. Upon completion of reaction, the mixture was diluted with CH_2Cl_2 (5 mL), quenched and scavenged by the addition of polymer-supported carbonate (Argonaut, 143 mg, 2.8 mmol g^{-1}, 0.40 mmol) and stirred for 2 h at RT. The mixture was filtered and concentrated under reduced pressure to yield colourless oil **61** (82.7 mg, 99 %). The bulk of the material was used in subsequent reactions without further purification. A portion of the product was purified by chromatography (silica gel, EtOAc/petrol 1:10). R_f = 0.14 (petrol/EtOAc 10:1) viewed: moly dip; $[\alpha]_D^{25}$ = −18.5 (*c* = 0.475, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.91 (s, 1H, *H*-19), 6.45 (s, 1H, *H*-17), 5.42–5.36 (m, 2H, *H*-12, *H*-13), 4.12 (app. t, ^3J(H,H) = 6.4 Hz, 1H, *H*-15), 4.06 (dd, ^3J(H,H) = 6.3, 3.9 Hz, 1H, *H*-3), 3.79 (dd, ^3J(H,H) = 7.1, 2.5 Hz, 1H, *H*-7), 3.64 (d, ^3J(H,H) = 5.5 Hz, 2H, *H*-1), 3.12 (app. qn, ^3J(H,H) = 7.0 Hz, 1H, *H*-6), 2.70 (s, 3H, *H*-21), 2.33–2.27 (m, 2H, *H*-14), 2.04–1.92 (m, 2H, *H*-11), 1.99 (s, 3H, *H*-26), 1.92 (brs, 1H, O*H*), 1.60–1.56 (m, 2H, *H*-2), 1.42–1.38 (m, 2H, *H*-10), 1.32 (m, 1H, *H*-8), 1.22 (s, 3H, *H*-22), 1.19–1.14 (m, 2H, *H*-9), 1.06 (s, 3H, *H*-23), 1.06 (d, ^3J(H,H) = 6.6 Hz, 3H, *H*-24), 0.91 (d, ^3J(H,H) = 6.5 Hz, 3H, *H*-25), 0.90 (s, 9H, SiC(CH_3)$_3$), 0.89 (s, 9H, SiC(CH_3)$_3$), 0.88 (s, 9H, SiC(CH_3)$_3$), 0.10 (s, 3H, SiCH_3), 0.067 (s, 3H, SiCH_3), 0.063 (s, 3H, SiCH_3), 0.056 (s, 3H, SiCH_3), 0.04 (s, 3H, SiCH_3), 0.01 (s, 3H, SiCH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 218.0 (*C*-8), 164.3 (*C*-20), 153.2 (*C*-18), 142.2 (*C*-16), 131.2 (*C*-12), 126.0 (*C*-13), 118.8 (*C*-17), 115.0 (*C*-19), 78.6 (*C*-15), 77.5 (*C*-7), 73.1 (*C*-3), 60.2 (*C*-1), 53.8 (*C*-4), 45.0 (*C*-6), 38.8 (*C*-8), 38.4 (*C*-2), 34.7 (*C*-14), 30.5 (*C*-9), 28.0 (*C*-11), 27.8 (*C*-10), 26.2 (SiC(*C*H_3)$_3$), 26.0 (SiC(*C*H_3)$_3$), 25.8 (SiC(CH_3)$_3$), 24.9 (*C*-22), 19.2 (*C*-21), 18.5 (Si*C*(CH_3)$_3$), 18.24 (SiC(CH_3)$_3$), 18.19 (SiC(CH_3)$_3$), 17.7 (*C*-23), 17.6 (*C*-25), 15.6 (*C*-24), 13.8 (*C*-26), −3.7 (Si*C*H_3), −3.8 (Si*C*H_3), −3.9 (Si*C*H_3), −4.0 (Si*C*H_3), −4.7 (Si*C*H_3), −4.9 (Si*C*H_3); IR (film): $\tilde{\nu}$ = 3395, 2955, 2929, 2857, 1693, 1472, 1254, 1081, 986, 836, 775 cm^{-1}; MS: *m*/*z*: calcd for $C_{44}H_{86}NO_5SSi_3$: 824.5534; found: 824.55210 [*M*+H]$^+$.

(3*S*,6*R*,7*S*,8*S*,12*Z*,15*S*,16*E*)-3,7,15-Tris-(*tert*-Butyldimethylsilyloxy)-4,4,6,8,16-pentamethyl-17-(2-methyl-thiazol-4-yl)-5-oxo-heptadeca-12,16-dienal (62): Powdered 4 Å molecular sieves, NMO (16.5 mg, 0.14 mmol), and TPAP (1.65 mg, 0.005 mmol) were added at 0 °C to a solution of alcohol **61** (75 mg, 0.094 mmol) in CH_2Cl_2 (2 mL). The mixture was allowed to warm to RT and stirred for 3 h 10 min. The reaction was loaded onto silica and filtered through using petroleum ether 40–60/EtOAc 10:1 until all aldehyde had been collected. Concentration under reduced pressure yielded the aldehyde product **62** as a colourless oil (67 mg, 93 %). The bulk of the material was used in subsequent reactions without further purification. A portion of the product was purified by chromatography (silica gel, EtOAc/petrol 1:20). R_f = 0.45 (petrol/EtOAc 10:1); $[\alpha]_D^{25}$ = −15.1 (*c* = 1.04, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.75 (s, 1H, *H*-1), 6.90 (s, 1H, *H*-19), 6.45 (s, 1H, *H*-17), 5.42–5.34 (m, 2H, *H*-12, *H*-13), 4.47 (app. t, ^3J(H,H) = 5.0 Hz, 1H, *H*-3), 4.12 (app. t, ^3J(H,H) = 6.4 Hz, 1H, *H*-15), 3.76 (dd, ^3J(H,H) = 6.6, 2.0 Hz, 1H, *H*-7), 3.11 (app. qn, ^3J(H,H) = 7.0 Hz, 1H, *H*-6), 2.69 (s, 3H, *H*-21), 2.51 (ddd, ^3J(H,H) = 16.9, 3.4, 1.6 Hz, 1H, H_a-2), 2.39 (ddd, ^3J(H,H) = 16.9, 5.4, 2.7 Hz, 1H, H_b-2), 2.35–2.25 (m, 2H, *H*-14), 2.01–1.99 (m, 2H, *H*-11), 1.99 (s, 3H, *H*-26), 1.42–1.30 (m, 2H, *H*-10), 1.29–1.25 (m, 1H, *H*-8), 1.23 (s, 3H, *H*-22),

1.19–1.10 (m, 2H, *H*-9), 1.07 (s, 3H, *H*-23), 1.03 (d, ^3J(H,H) = 6.9 Hz, 3H, *H*-24), 0.90–0.87 (m, 30H, *H*-25, 3×SiC(CH_3)$_3$), 0.09 (s, 3H, SiCH_3), 0.051 (s, 3H, SiCH_3), 0.050 (s, 3H, SiCH_3), 0.049 (s, 3H, SiCH_3), 0.03 (s, 3H, SiCH_3), 0.003 (s, 3H, SiCH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 218.0 (*C*-5), 201.0 (*C*-1), 164.3 (*C*-20), 153.2 (*C*-18), 142.1 (*C*-16), 131.2 (*C*-12), 126.0 (*C*-13), 118.9 (*C*-17), 115.0 (*C*-19), 78.6 (*C*-15), 77.5 (*C*-7), 73.3 (*C*-3), 53.4 (*C*-4), 49.5 (*C*-2), 45.1 (*C*-6), 38.8 (*C*-8), 34.7 (*C*-14), 30.6 (*C*-9), 28.0 (*C*-11), 27.9 (*C*-10), 26.2 (SiC(CH_3)$_3$), 25.9 (SiC(CH_3)$_3$), 25.85 (SiC(CH_3)$_3$), 24.1 (*C*-22), 19.2 (*C*-21), 18.8 (*C*-23), 18.5 (Si*C*(CH$_3$)$_3$), 18.2 (Si*C*(CH$_3$)$_3$), 18.1 (Si*C*(CH$_3$)$_3$), 17.7 (*C*-25), 15.5 (*C*-24), 13.9 (*C*-26), −3.7 (Si*C*H$_3$), −3.8 (Si*C*H$_3$), −4.1 (Si*C*H$_3$), −4.5 (Si*C*H$_3$), −4.7 (SiCH$_3$), −4.9 (SiCH$_3$); IR (film): $\tilde{\nu}$ = 2955, 2930, 2857, 1729, 1693, 1472, 1255, 1083, 988, 836, 775 cm^{-1}; MS (+ESI): *m*/*z*: calcd for $C_{44}H_{83}NO_5SSi_3$: 822.5378; found: 822.5372 $[M]^+$.

Polymer-supported chlorite 63:[54] Amberlite IRA 900 (Cl^- form) polystyrene resin (Fluka, 4.0 mmol g^{-1} containing 10% H_2O, 10.0 g, 36.0 mmol) was washed with H_2O (2×50 mL). The resin was suspended in a solution of sodium chlorite (18.1 g, 0.20 mol) in water (100 mL). The mixture was shaken at RT for 24 h before filtration. The polymer was washed with H_2O (4×50 mL), MeCN (4×50 mL) and Et_2O (2×50 mL), then dried under reduced pressure at room temperature to give a yellow solid resin **63** (16.9 g, estimated 2.1 mmol g^{-1} of ClO_2). The polymer was stored under argon at −20 °C and used within a month. IR (solid): $\tilde{\nu}$ = 3378 (br), 3025, 2929, 1636, 1613, 1482, 1476, 1420, 1379, 1219, 1090, 973, 920, 889, 858, 825, 707 cm^{-1}.

Polymer-supported dihydrogenphosphate 64:[54] Amberlite IRA 900 (Cl^- form) polystyrene resin (Fluka, 4.0 mmol g^{-1} containing 10% H_2O, 10.0 g, 36.0 mmol) was washed with H_2O (2×50 mL). The resin was suspended in a solution of potassium dihydrogen phosphate (27.2 g, 200 mmol) in H_2O (100 mL). The mixture was shaken at RT for 24 h before filtration. The polymer was washed with water (4×50 mL), and ether (2×50 mL), then dried under reduced pressure at RT to give a yellow solid resin **64** (18.5 g, estimated 2.0 mmol g^{-1} of H_2PO_4). IR (solid): $\tilde{\nu}$ = 3338 (br), 1639, 1485, 1476, 1135, 1071, 928, 855, 822 cm^{-1}.

(3*S*,6*R*,7*S*,8*S*,12*Z*,15*S*,16*E*)-3,7,15-Tris-(*tert*-butyldimethylsilyloxy)-4,4,6,8,16-pentamethyl-17-(2-methyl-thiazol-4-yl)-5-oxo-heptadeca-12,16-dienoic acid (65):[19] A mixture of polymer-supported chlorite **63** (229 mg, ~0.5 mmol g^{-1}, 0.11 mmol) and polymer-supported dihydrogenphosphate **64** (343 mg, ~0.5 mmol g^{-1}, 0.17 mmol) resins was added to a solution of aldehyde **62** (47 mg, 0.057 mmol) in *tert*-butyl alcohol (3 mL), water (0.6 mL), and 2,3-dimethylbut-2-ene (0.14 mL, 2 M solution in THF, 0.29 mmol). The mixture was stirred for 6 h until all material had been oxidised, then filtered using Et_2O to wash the resins. The filtrate was collected and concentrated under reduced pressure to yield carboxylic acid **65** as a colourless oil (47.4 mg, 99%). The bulk of the material was used in subsequent reactions without further purification. A portion of the product was purified by chromatography (silica gel, EtOAc/petrol 1:10, then 1:5, then 1:3). R_f = 0.07 (petrol 40–60/EtOAc 10:1) viewed: UV (254 nm) or moly dip; $[\alpha]_D^{25}$ = −15.5 (*c* = 3.77, $CHCl_3$) (lit. $[\alpha]_D^{22}$ = −8.8 (*c* = 0.80, $CHCl_3$)); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.92 (s, 1H, *H*-19), 6.52 (s, 1H, *H*-17), 5.43–5.36 (m, 2H, *H*-12, *H*-13), 4.39 (dd, ^3J(H,H) = 6.5, 3.1 Hz, 1H, *H*-3), 4.15 (app. t, ^3J(H,H) = 6.5 Hz, 1H, *H*-15), 3.77 (dd, ^3J(H,H) = 7.4, 1.5 Hz, 1H, *H*-7), 3.14 (app. qn, ^3J(H,H) = 6.8 Hz, 1H, *H*-6), 2.71 (s, 3H, *H*-21), 2.48 (dd, ^3J(H,H) = 16.4, 3.0 Hz, 1H, H_a-2), 2.32 (dd, ^3J(H,H) = 14.9, 6.9 Hz, 1H, H_b-2), 2.33–2.26 (m, 2H, *H*-14), 2.07–2.02 (m, 1H, H_a-11), 2.02–1.94 (m, 1H, H_b-11), 1.97 (s, 3H, *H*-26), 1.43–1.36 (m, 5H, *H*-8, *H*-9, *H*-10), 1.21 (s, 3H, *H*-22), 1.11 (s, 3H, *H*-23), 1.05 (d, ^3J(H,H) = 6.8 Hz, 3H, *H*-25), 0.90–0.88 (m, 30H, *H*-24, 3×SiC(CH_3)$_3$), 0.10 (s, 3H, SiCH_3), 0.062 (s, 3H, SiCH_3), 0.060 (s, 3H, SiCH_3), 0.056 (s, 3H, SiCH_3), 0.05 (s, 3H, SiCH_3), 0.01 (s, 3H, SiCH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 218.0 (*C*-5), 176.5 (*C*-1), 164.8 (*C*-20), 152.9 (*C*-18), 142.7 (*C*-16), 131.4 (*C*-12), 126.0 (*C*-13), 118.6 (*C*-17), 114.7 (*C*-19), 78.7 (*C*-15), 77.3 (*C*-7), 73.5 (*C*-3), 53.6 (*C*-4), 44.9 (*C*-6), 40.1 (*C*-2), 39.0 (*C*-8), 34.7 (*C*-14), 30.8 (*C*-9), 28.0 (*C*-11), 27.8 (*C*-10), 26.2 (SiC(CH_3)$_3$), 26.0 (SiC(CH_3)$_3$), 25.8 (SiC(CH_3)$_3$), 23.6 (*C*-22), 19.2 (*C*-21), 18.9 (*C*-23), 18.5 (Si*C*(CH$_3$)$_3$), 18.19 (Si*C*(CH$_3$)$_3$), 18.18 (Si*C*(CH$_3$)$_3$), 17.3 (*C*-25), 15.7 (*C*-24), 13.8 (*C*-26), −3.8 (Si*C*H$_3$), −3.9 (Si*C*H$_3$), −4.2 (Si*C*H$_3$), −4.6 (Si*C*H$_3$), −4.7 (Si*C*H$_3$), −4.9 (Si*C*H$_3$); IR (film): $\tilde{\nu}$ = 2954, 2930, 2857, 1713, 1472, 1252, 1081, 988, 836, 775 cm^{-1}; MS (+ESI): *m*/*z*: calcd for $C_{44}H_{83}NO_6SSi_3Na$: 860.5147; found: 860.5124 $[M+Na]^+$.

(3*S*,6*R*,7*S*,8*S*,12*Z*,15*S*,16*E*)-3,7-Bis-(*tert*-butyldimethylsilyloxy)-15-hydroxy-4,4,6,8,16-pentamethyl-17-(2-methyl-thiazol-4-yl)-5-oxo-heptadeca-12,16-dienoic acid (66):[13,19] A solution of tris-silyl ether **65** (36.5 mg, 0.044 mmol) in THF (0.8 mL) at RT was treated with TBAF (0.26 mL, 1 M solution in THF, 0.25 mmol)). After being stirred for 4 h, the reaction mixture was diluted with Et_2O (5 mL) and H_2O (2.5 mL) washed with aqueous HCl (5 mL, 1 M solution). The aqueous phase was extracted with Et_2O (3×5 mL), and the combined organic phase was washed with brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure to yield hydroxy acid **66** as pale yellow oil (31.5 mg, 100%). The bulk of the material was used in subsequent reactions without further purification. A portion of the product was purified by chromatography (silica gel, MeOH/CH_2Cl_2 1:19). R_f = 0.20 (CH_2Cl_2/MeOH 19:1) viewed: UV (254 nm) or moly dip; $[\alpha]_D^{25}$ = −19.1 (*c* = 0.56, $CHCl_3$) (lit. $[\alpha]_D^{22}$ = −19.2 (*c* = 0.1, $CHCl_3$)); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.96 (s, 1H, *H*-19), 6.65 (s, 1H, *H*-17), 5.60–5.54 (m, 1H, *H*-12), 5.46–5.39 (m, 1H, *H*-13), 4.41 (dd, ^3J(H,H) = 6.1, 3.5 Hz, 1H, *H*-3), 4.20 (dd, ^3J(H,H) = 6.9, 6.0 Hz, 1H, *H*-15), 3.80 (dd, ^3J(H,H) = 6.5, 1.1 Hz, 1H, *H*-7), 3.14 (app. qn, ^3J(H,H) = 6.8 Hz, 1H, *H*-6), 2.72 (s, 3H, *H*-21), 2.51 (dd, ^3J(H,H) = 16.4, 3.4 Hz, 2H, *H*-2), 2.46–2.23 (m, 2H, *H*-14), 2.38 (dd, ^3J(H,H) = 16.4, 6.4 Hz, 2H, *H*-2), 2.18–2.11 (m, 1H, H_a-11), 2.03 (s, 3H, *H*-26), 2.10–1.95 (m, 1H, H_b-11), 1.48–1.32 (m, 5H, *H*-8, 2×CH_2, *H*-9/*H*-10), 1.23 (s, 3H, *H*-22), 1.14 (s, 3H, *H*-23), 1.07 (d, 3H, ^3J(H,H) = 6.8 Hz, *H*-24), 0.91–0.84 (m, 21H, *H*-25, 2×SiC(CH_3)$_3$), 0.11 (s, 3H, SiCH_3), 0.08 (s, 3H, SiCH_3), 0.07 (s, 3H, SiCH_3), 0.06 (s, 3H, SiCH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 218.0 (*C*-5), 175.1 (*C*-1), 165.1 (*C*-20), 152.5 (*C*-18), 141.8 (*C*-16), 133.4 (*C*-12), 125.0 (*C*-13), 118.8 (*C*-17), 115.2 (*C*-19), 77.3 (*C*-7), 76.8 (*C*-15), 73.5 (*C*-3), 53.7 (*C*-4), 44.8 (*C*-6), 40.0 (*C*-2), 39.0 (*C*-8), 33.4 (*C*-14), 30.9 (*C*-9), 28.0 (*C*-11), 27.9 (*C*-10), 26.2 (SiC(CH_3)$_3$), 26.0 (SiC(CH_3)$_3$), 23.5 (*C*-22), 19.2 (*C*-21), 18.8 (*C*-23), 18.5 (Si*C*(CH$_3$)$_3$), 18.2 (Si*C*(CH$_3$)$_3$), 17.1 (*C*-25), 16.0 (*C*-24), 14.5 (*C*-26), −3.8 (Si*C*H$_3$), −3.9 (Si*C*H$_3$), −4.2 (SiCH$_3$), −4.6 (SiCH$_3$); IR (film): $\tilde{\nu}$ = 3299 (br), 2952, 2929, 2856, 1712, 1695, 1472, 1460, 1384, 1361, 1252, 1085, 988, 836, 775 cm^{-1}; MS (+ESI): *m*/*z*: calcd for $C_{44}H_{83}NO_6SSi_3Na$: 860.5147; found: 860.5124 $[M+Na]^+$.

(4*S*,7*R*,8*S*,9*S*,16*S*)-4,8-Bis-(*tert*-butyldimethylsilyloxy)-5,5,7,9-tetramethyl-16-[(*E*)-1-methyl-2-(2-methyl-1,3-thiazol-4-yl)-1-vinyl]-(13*Z*)-1-oxacyclohexadec-13-ene-2,6-dione (67):[13,14,19,23] A solution of hydroxy acid **66** (10.9 mg, 0.015 mmol) in THF (0.9 mL) was treated at RT with Et_3N (17.6 mg, 0.024 mL, 0.17 mmol) and 2,4,6-trichlorobenzoyl chloride (37.6 mg, 0.024 mL, 0.15 mmol). The reaction mixture was stirred at RT for 50 min, then diluted with PhMe (4.0 mL) and added slowly over 40 min to a solution of polymer-supported DMAP (210 mg, 0.31 mmol, 1.48 mmol g^{-1}) in PhMe (20 mL) at 80 °C and stirred at that temperature for 2 h. The reaction mixture was cooled to RT and polymer-supported diamine resin (NovaBiochem, 250 mg, 3.8 mmol g^{-1}, 0.95 mmol) and Amberlite IRC-50 carboxylic acid resin (500 mg, 5 mmol, 10 mmol g^{-1}) were added. The suspension was shaken at RT for 2 h, then filtered and concentrated under reduced pressure. The resulting crude oil **67** (19 mg) was contaminated with reagent by-products. The bulk of the material was used in subsequent reactions without further purification. A portion of the product was purified by chromatography (silica gel, Et_2O/petrol 1:7). R_f = 0.24 (petrol/Et_2O 7:1) sviewed: UV (254 nm) or moly dip; $[\alpha]_D^{25}$ = −25.5 (*c* = 0.29, $CHCl_3$) (lit. $[\alpha]_D^{22}$ = −22.9 (*c* = 0.30, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.96 (s, 1H, *H*-19), 6.57 (s, 1H, *H*-17), 5.57–5.48 (m, 1H, *H*-12), 5.42–5.34 (m, 1H, *H*-13), 5.01 (d, ^3J(H,H) = 10.3 Hz, 1H, *H*-15), 4.04 (d, ^3J(H,H) = 10.1 Hz, 1H, *H*-3), 3.90 (d, ^3J(H,H) = 8.6 Hz, 1H, *H*-7), 3.01 (app. qn, ^3J(H,H) = 7.3 Hz, 1H, *H*-6), 2.82 (d, ^3J(H,H) = 16.3 Hz, 1H, H_a-2), 2.80–2.70 (m, 1H, H_a-14), 2.71 (s, 3H, *H*-21), 2.67 (dd, ^3J(H,H) = 16.5, 10.5 Hz, 1H, H_a-2), 2.41–2.31 (m, 1H, H_a-11), 2.12 (s, 3H, *H*-26), 2.16–2.06 (m, 1H, H_b-14), 1.92–1.82 (m, 1H, H_b-11), 1.63–1.46 (m, 3H, *H*-8, H_a-9, H_a-10), 1.19–1.00 (m, 2H, H_b-9, H_b-10), 1.19 (s, 3H, *H*-22), 1.15 (s, 3H, *H*-23), 1.10 (d, ^3J(H,H) = 6.7 Hz, 3H, *H*-24), 0.96 (d, ^3J(H,H) = 7.0 Hz, 3H, *H*-25), 0.94 (s, 9H, SiC(CH_3)$_3$), 0.85 (s, 9H, SiC(CH_3)$_3$), 0.12 (s, 3H, SiCH_3), 0.10 (s, 3H, SiCH_3), 0.08 (s, 3H, SiCH_3), −0.09 (s, 3H, SiCH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 215.0 (*C*-5), 171.3 (*C*-1), 164.6 (*C*-20), 152.5 (*C*-18), 138.6 (*C*-16), 135.0 (*C*-12), 122.8 (*C*-13), 119.5 (*C*-17), 116.0 (*C*-19), 79.5 (*C*-15), 79.2 (*C*-7), 76.4 (*C*-3), 53.4 (*C*-4), 47.9 (*C*-6), 38.9 (*C*-2), 37.9 (*C*-8), 31.8 (*C*-14), 31.4 (*C*-9), 29.1 (*C*-11), 28.4 (*C*-10), 26.3 (SiC(CH_3)$_3$), 26.1 (SiC(CH_3)$_3$), 24.9 (*C*-22), 24.2 (*C*-23), 19.2 (*C*-21), 19.0 (*C*-24), 18.7 (Si*C*(CH$_3$)$_3$), 18.6 (Si*C*(CH$_3$)$_3$), 17.6 (*C*-25), 15.2 (*C*-26), −3.2 (Si*C*H$_3$), −3.4 (Si*C*H$_3$), −3.7 (Si*C*H$_3$), −5.7 (Si*C*H$_3$); IR

(film): $\tilde{\nu}$ = 2946, 2929, 2856, 1741, 1697, 1465, 1463, 1380, 1255, 1183, 1160, 1095, 1062, 1019, 984, 937, 875, 836, 775 cm^{-1}; MS (+ESI): *m/z*: calcd for $C_{38}H_{67}NO_5SSi_2Na$: 728.4176; found: 728.4199 $[M+Na]^+$.

Epothilone C

(4*S*,7*R*,8*S*,9*S*,16*S*)-4,8-Dihydroxy-5,5,7,9-tetramethyl-16-[(*E*)-1-methyl-2-(2-methyl-1,3-thiazol-4-yl)-1-vinyl]-(13*Z*)-1-oxacyclohexadec-13-ene-2,6-dione (2): Crude bis-TBS-epothilone C macrolactone **67** was dissolved in CH_2Cl_2 (2.0 mL) at RT. Polymer-supported sulfonic acid resin (Argonaut MP-TsOH(I), ~1.5 mmol g^{-1}, 116 mg, 0.18 mmol) was added and the mixture shaken at RT for 1 h. Analysis by TLC showed complete capture of the macrolactone. The resin was filtered and washed using CH_2Cl_2 (3 mL), then Et_2O (3 mL), then MeOH (3 mL), to remove all unbound impurities. The product was released using a solution of NH_3 in MeOH (3 mL, 2 M solution). The filtrate was concentrated under reduced pressure to give epothilone C (**2**) as a yellow oil (5.8 mg, 81 % over 2 steps). The product (2.9 mg) was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH 99:1) to yield epothilone C (2.2 mg, 76 %) as a colourless foam. R_f = 0.51 (CH_2Cl_2/MeOH 95:5); $[\alpha]_D^{25} = -80.6$ (*c* = 0.17, $CHCl_3$) (lit. $[\alpha]_D^{22} = -80.2$ (*c* = 1.70, $CHCl_3$)); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.96 (s, 1H, *H*-19), 6.59 (br s, 1H, *H*-17), 5.46–5.43 (td, ^3J(H,H) = 10.3, 4.3 Hz, 1H, *H*-12), 5.41–5.37 (td, ^3J(H,H) = 9.7, 4.5 Hz, 1H, *H*-13), 5.29 (dd, ^3J(H,H) = 9.8, 1.7 Hz, 1H, *H*-15), 4.23 (dd, ^3J(H,H) = 11.4, 2.2 Hz, 1H, *H*-3), 3.74–3.73 (m, 1H, *H*-7), 3.25 (br s, 1H, C(3)HOH), 3.14 (dq, ^3J(H,H) = 6.8, 2.0 Hz, 1H, *H*-6), 3.00 (br s, 1H, C(7)HOH), 2.71–2.66 (m, 1H, H_a-14), 2.70 (s, 3H, *H*-21), 2.49 (dd, ^3J(H,H) = 15.1, 11.4, 1H, H_a-2), 2.36 (dd, ^3J(H,H) = 15.1, 2.4 Hz, 1H, H_b-2), 2.30–2.24 (m, 1H, H_b-14), 2.24–2.17 (m, 1H, H_a-11), 2.09 (br s, 3H, *H*-26), 2.04–1.97 (m, 1H, H_b-11), 1.79–1.74 (m, 1H, *H*-8), 1.74–1.55 (m, 1H, H_a-10), 1.40–1.28 (m, 1H, H_a-9), 1.33 (s, 3H, *H*-22), 1.26–1.14 (m, 2H, H_b-9, H_b-10), 1.18 (d, ^3J(H,H) = 6.8 Hz, 3H, *H*-24), 1.09 (s, 3H, *H*-23), 1.00 (d, ^3J(H,H) = 6.9 Hz, 3H, *H*-25); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 220.5 (*C*-5), 170.4 (*C*-1), 165.0 (*C*-20), 151.9 (*C*-18), 138.7 (*C*-16), 133.4 (*C*-12), 125.0 (*C*-13), 119.4 (*C*-17), 115.8 (*C*-19), 78.4 (*C*-15), 74.1 (*C*-7), 72.3 (*C*-3), 53.3 (C-4), 41.7 (*C*-6), 39.2 (*C*-2), 38.5 (*C*-8), 32.4 (*C*-14), 31.8 (*C*-9), 27.6 (*C*-11), 27.5 (*C*-10), 22.7 (*C*-22), 19.0 (*C*-21), 18.6 (*C*-23), 15.9 (*C*-24), 15.5 (*C*-25), 13.5 (*C*-26); IR (film): $\tilde{\nu}$ = 3450, 2934, 1735, 1686, 1462, 1292, 1250, 1183, 1146, 1043, 1004, 975, 730 cm^{-1}; MS: *m/z*: calcd for $C_{26}H_{39}NO_5SNa$: 500.2447; found: 500.2449 $[M+Na]^+$.

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