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Design, synthesis and biological evaluation of bridged epothilone D analogues†

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Abstract

Six epothilone D analogues with a bridge between the C4-methyl and the C12-methyl carbons were prepared in an attempt to constrain epothilone D to its proposed tubulin-binding conformation. Ring-closing metathesis (RCM) was employed as the key step to build the C4-C26 bridge. In antiproliferative assays in the human ovarian cancer (A2780) and prostate cancer (PC3) cell lines, and also in tubulin assembly assay, all these compounds proved to be less active than epothilone D.

Introduction

The epothilones are a class of macrolide natural products isolated from the soil myxobacterium *Sorangium cellulosum*.¹ Epothilones A (**1**) and B (**2**) (epoA and B) were discovered in 1986 based on their antifungal activity,¹ but they attracted only moderate scientific interest until the report by Bollag *et al.* in 1995 that they had the same mechanism of action as paclitaxel, stabilizing the tubulin polymer and causing apoptotic cell death.² This report triggered a large amount of research on their biology and chemistry, which has been reviewed on several occasions.³ At this time one epothilone derivative, the semisynthetic epoB analogue ixabepilone (**3**), has been approved for clinical use,⁴ and at least six other epothilone analogues are in advanced clinical trials.⁵ EpoB is in phase III trials and EpoD (**4**) is currently in Phase II clinical trials. Additional new and exciting analogues, such as fludelone,⁶ have emerged in recent years.

The nature of the binding of the epothilones to tubulin has been extensively investigated. The early observation that epothilones can displace tubulin-bound paclitaxel suggested that both are bound by the same or overlapping binding sites.⁷ A combined paclitaxel-epothilone hybrid construct has been prepared and shown to promote tubulin assembly 3-fold less effectively than paclitaxel, lending support to the hypothesis that paclitaxel and the epothilones share a common binding site and mechanism of action.⁸ The X-ray structure of epoB has been published,⁹ and two distinct solution conformations have been detected for epoA and epoB,¹⁰ but neither result addressed the conformation of epothilone on the tubulin polymer. A

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conformation of tubulin-bound epothilone has been proposed based on solution NMR spectroscopy.¹¹ The NMR experiments were however performed on unassembled tubulin, and it is uncertain if the conformation of epoA bound to tubulin is the same as its conformation bound to microtubules. Finally, a minireceptor modeling approaches led to 3D QSAR models of epothilone.¹²

Recently one of us proposed an entirely different epothilone A conformation based on crystallographic electron density maps of Zn-stabilized tubulin sheets that diffract to 2.9 Å, molecular modeling, and NMR-NAMFIS treatment.^{13,14} The proposed binding conformation from this study explains most of the SAR studies generated for the epothilones, and also accounts for the drug resistance of mutated cell lines. Analysis of this Nettles *et al.* model for epoA reveals juxtaposition of a C4 methyl carbon and C12-H at a distance of 4.5 Å (Figure 2). The corresponding separation between C4-Me and C12-Me (epoB) is 5.5 Å. To test the proposed binding modes, we designed epoD analogues with built-in conformational restrictions between these positions by introducing a bridge between C4 and C26. Herein, we report the synthesis of six new bridged epothilone analogues and their antiproliferative activities towards human-ovarian (A2780) and prostate cancer (PC3) cell lines, as well as their tubulin-assembly activities.

Results

Synthetic Strategy

The introduction of a bridge between C4-Me and C26 in epothilone D was planned with a ring closing metathesis reaction as the key step, by analogy with our successful synthesis of bridged paclitaxel derivatives.¹⁵ Thus, the synthesis of bridged analogue **5** was designed to proceed from diene precursors **7** or **10** (Scheme 1). The diene precursor **7** could be derived from fragments **8** and **9** in a convergent manner. Fragment **8** has previously been synthesized by us employing Nicolaou's method¹⁶ as an intermediate in the synthesis of fluorescently labeled epothilone analogues.¹⁷ The alternative diene precursor **10** could be synthesized from fragments **9** and **11**.

Synthesis

The synthesis of fragment **8** was carried out as previously described.^{16,17} Ketone **9** was prepared as shown in Scheme 2. Treatment of methyl acetoacetate with benzyl chloromethyl ether provided diketone **12**,¹⁸ which was subjected to catalytic asymmetric reduction to provide hydroxyester **13**.¹⁹ The benzyl group was deprotected and the resulting diol **14a** was selectively protected with tert-butyldimethylsilyl chloride to give ester **14b** in 95% overall yield. Compound **14b** was treated with LDA and allyl iodide to provide an allyl derivative in excellent yield and diastereoselectivity, which was subjected to LDA and methyl iodide to provide compound **15** as the major diastereomer in 53% yield (dr. 3:1).

The configuration of allyl derivative **15** was initially assigned based on literature precedent;¹⁹ this assignment was subsequently established by converting it to the ketal **17**. Selective irradiation of the C4-methyl group (Figure 3) resulted in signal enhancement of the protons H_a-H_c on the adjacent carbons. Irradiation of proton H_a of the (*S*) chiral center gave signal enhancement of the C4-methyl group and the H_b and H_c protons, but not of the CH₂ protons of the allyl group.

These results confirm the (*R*) configuration of the newly introduced center at the C4 carbon. The remaining transformations from **15** to **9** were straightforward and proceeded via alcohol **16** in 52% overall yield for the five steps.

Aldol coupling of aldehyde **8** and ketone **9** using LDA as the base furnished **18** in 85% yield and high diastereoselectivity (11:1). The stereochemistries at the C6 and C7 positions of the major and minor diastereomers were assigned by analogy to literature precedents.²⁰ Presumably this aldol coupling step proceeds via the favoured Cram/Felkin-Ahn transition state leading to a 6*R*,7*S* major diastereomer. Alcohol **18** was converted to hydroxyacid **19e** and then to lactones **20a** and then **21** in seven synthetic steps and 51% overall yield by methods similar to those described previously¹⁶ (Scheme 3).

Having made the advanced C4-allyl-C4-demethyl-triol intermediate **21**, we acylated it separately with acryloyl chloride, 3-butenoyl chloride, and 4-pentenoyl chloride by a known protocol¹⁸ to yield the diene precursors **7**, **22** and **23** in good yields (Scheme 4).

At this point, two options were available for the last two steps of the synthesis. The first was to attach the thiazole unit and then do the ring closing metathesis, while the second reverses the order of these steps. The second option was attractive, since it would generate the macrocyclic iodide building blocks **6**, **24**, or **25** that could be exploited by attaching various side chain units such as pyridine and benzothiazoles, in addition to the parent thiazole unit. Initially, diene **7** was subjected to ring closing metathesis²¹ with either first- or second- or third-generation Grubbs catalyst and also the second-generation Hoveyda-Grubbs catalyst. The reaction was very sluggish, and when the reaction time was prolonged the starting material decomposed and no product **6** was obtained. Similar results were observed for diene **22**. Diene **23**, however, with the longest olefin chain, underwent ring closing metathesis with the second-generation Grubbs catalyst, albeit in low yield, to furnish the desired product **25** (Scheme 4).

The configuration of the double bond in **25** was established as *trans* based on 1D NOE experiments. Selective irradiation of either of its olefinic bridge protons resulted in signal enhancement of the CH₂ protons adjacent to the other side of the double bond, thus confirming the *trans* orientation of double bond. The bridged iodide **25**, on coupling with the thiazolyl stannane **26** in the presence of Pd(MeCN)₂Cl₂, provided the final bridged epothilone D analogue **27** in 70% yield.

At this point we reconsidered option 1, introduction of the thiazole unit on the triol **21** followed by acylation at the C26 position and then ring closing metathesis, with the notion that replacing the iodide with the thiazole unit might bring the ring closing olefinic units together. Treatment of triol **21** with thiazolyl stannane **26** provided the intermediate **28**, which then was acylated with 3-butenoyl chloride to give **29**. Gratifyingly, when **29** was subjected to ring closing metathesis with second-generation Grubbs catalyst, the ring closed epothilone D analogue **30** was obtained, albeit in low yield (Scheme 5). In an effort to make the shorter bridged analogue **5** by this route, diene **31** was likewise prepared from **28**. However, this diene did not undergo normal ring closing metathesis with second-generation Grubbs catalyst to give the expected product **5**. Since conjugation of double bonds with carbonyl groups reduces their reactivity towards ring-closing metathesis, we next investigated cyclization of the diene precursor **33** (Scheme 6) with a C26 allyloxy group instead of a C26 acryloyl group.

The (4*R*)-4-allyl-4-demethyl-epothilone analogue **32** was prepared by selective deprotection of the trityl group of lactone **20** followed by coupling with thiazolyl stannane **26**. Alcohol **32** was then converted to its sodium alkoxide with sodium hydride in THF and allylated with allyl iodide to give diene **33** in 23% yield, together with 55% starting material **32**. The yield could not be improved by prolonging the reaction time, which only led to the formation of elimination byproduct. Diol **34** was prepared by standard desilylation of **33** with HF.Py complex for comparison of its bioactivity with that of the final cyclized product. Happily, ring closing metathesis of **33** with second-generation Grubbs catalyst gave the expected bridged epothilone analogue **35** in 79% yield. Desilylation of **35** with HF.Py complex in THF provided the final

epothilone D analogue **36** in 84% yield, with a 5-atom bridge between C4 and C26. Interestingly, the ^1H NMR spectrum of the TBS ether **35** of the bridged analogue showed only one signal for each type of proton. However, the bridged analogue **36** with two free hydroxyl groups showed pairs of signals for each group of protons in its ^1H NMR spectrum in both CDCl_3 and CD_3CN . We attribute this pairing of signals to the existence of two atropisomers of **36**, and this conclusion was supported by the fact that some pairs of signals collapsed to single signals when the temperature was increased from 22 °C to 50 °C in CDCl_3 .

We also investigated the effect of the stereochemistry at C4 on biological activity by preparing bridged epothilone analogues with the 4*S* stereochemistry. Compound **14b** was treated with LDA and methyl iodide to provide a methyl derivative, which was reacted with LDA and allyl iodide to furnish compound **37** as the major diastereomer in 62% yield. The remaining transformations from **37** to **39** were straightforward and proceeded in 20% overall yield for the five steps (Scheme 7).

To our surprise, aldol coupling of aldehyde **11** and ketone **39** employing LDA as the base furnished the unexpected 6*S*,7*R* diastereoisomer **40** as the major product (46%), as well as two other diastereomers (28%) (Scheme 8).

The indicated stereochemistry of **40** was confirmed by X-ray crystallographic analysis of its derivative **56** described below. Alcohol **40** was converted to hydroxyacid **41d** and thence to lactones **42** and **43** in seven steps and 19% overall yield by methods similar to the preparation of compound **21** (Scheme 8). By the same procedures as used for the preparation of 4*R*,6*R*,7*S* bridged analogue **36**, and in similar yields, the 4*S*,6*S*,7*R* bridged analogue **47** was prepared from compound **43** via intermediates **44** and **46** (Scheme 9). The configuration of the bridging double bond in **47** was established as *cis* based in 1D NOE experiments. Selective irradiation of one of the olefinic bridge protons resulted in signal enhancement of the other olefinic bridge proton. The 4*S*,6*S*,7*R* bridged analogue **47** also exists as a pair of atropisomers, showing paired signals for each group of protons in its proton NMR spectrum in CD_3CN as solvent.

In an additional effort to investigate the effect of the 4*S*,6*S*,7*R* stereochemistry on metathesis of a C26 acryloxyl group, the C26 acryloyl derivative **48** was prepared from **43**. Diene **48** did not undergo ring closing metathesis with second-generation Grubbs catalyst. However, dienes **49** and **50**, with one or two free hydroxyl groups, underwent ring closing metathesis with second-generation Grubbs catalyst to furnish the bridged products **51** (62%) and **53** (93%). The latter compound was contaminated by a minor epothilone impurity which could not be removed by normal chromatography; the major compound was estimated to be 86.5% pure by ^1H NMR spectroscopy (Scheme 9).

Desilylation of **51** with HF.Py complex in THF provided the bridged analogue **52** with the 4*S*,6*S*,7*R* stereochemistry. The configurations of the double bonds in **51** and **52** were established as *cis* based on the coupling constant ($J = 11.5$ Hz) of the olefinic proton adjacent to the carbonyl group of the newly made bridge. The coupling constant ($J = 17.0$ Hz) of the corresponding olefinic proton of **53** indicated that the configuration of its bridged double bond was *trans*.

Assignment of the stereochemistry of the C6 and C7 chiral centers of the 4*S* series of compounds could not readily be achieved by conventional NMR methods, and so the benzoyloxy derivative **56** was prepared from **42** via intermediate **54** and **55** (Scheme 10).

Global deprotection of **42** with HF.Py complex yield triol **54** in 51% yield. Then using the Sharpless conditions [L-(+)-DET, $\text{Ti}(\text{iPrO})_4$, $t\text{BuOOH}$],²² allylic alcohol **54** was converted to 12*β*,13*β*-epoxide **55** (d.e. > 95% as judged by ^1H NMR spectroscopy). The primary hydroxyl group at C26 of triol **55** was selectively acylated with benzoyl chloride to yield the benzoyloxy

derivative **56** as colorless needles from hexanes-acetone. Single crystal X-ray crystallography of **56** confirmed its absolute stereochemistry as C3(*S*), C4(*S*), C6(*S*), C7(*R*), C8(*S*), C12(*S*), C13(*S*) and C15(*S*) (Figure 4).²³

Bioactivity

The in vitro antiproliferative activities of the open and constrained epothilone analogues were determined by employing the A2780 ovarian cancer and PC-3 prostate cancer cell lines (Table 1). The activities of the constrained analogues **27**, **30** and **52** were comparable to those of their respective open chain analogues, but they were significantly less than that of epothilone D. The effect of some of the analogues on tubulin assembly was also investigated. The trend in the ability of the analogue to induce microtubule assembly correlated with the trends in antiproliferative activities (Table 1).

Molecular Modeling and Discussion

The bridged epothilone D analogues **27**, **30** and **36** were docked into the tubulin binding site of epothilone using the Glide docking program.²⁴ Neither **27** nor **30** adopts a docking pose similar to that of epothilone A in the electron crystallographic (EC) binding model.¹³ This is most likely due to the longer and less compatible length of the cross-ring bridges in **27** and **30**. As expected, the shorter bridge in **36** permits the analogue to readily adopt the epothilone A EC binding model in the binding site (Figure 5). In the cell-free tubulin assembly assay, the reduction in EC₅₀ compared to EpoD correlates with bridge length, **36** < **30** < **27**, while the most active analog is only 3-4 fold less active than EpoD (Table 1). One possible explanation for the lack of potency improvement in the bridged series is that the bridge alters the conformational profile of the ligands to introduce a greater degree of global conformational strain relative to the monocyclic standard, thereby decreasing *K_a* and increasing *DG_{bind}*.

The cell-based data shows another activity pattern. That is, the EC₅₀ values for all three compounds in both A2780 and PC3 cytotoxicity assays are 75-390 fold greater than that for EpoD, while the corresponding tubulin polymerization range is 4-15 fold (Table 1). We attribute the differences provisionally to physical property variations associated with membrane permeability.

Two additional observations can be made from the data. The diastereomeric compounds **47**, **52**, and **53** were all significantly less active in the A2780 antiproliferative assay than compounds with the normal epothilone stereochemistry. This finding, while unsurprising, confirms the importance of stereochemistry in the bioactivity of the epothilones. A second observation is that the open chain 4-allyl analogue **34** is the most active of all the analogues prepared, and approaches the activity of epothilone D in the tubulin assembly assay. It is likewise only 2-5 fold less cytotoxic than EpoD (Table 1). Epothilones with additional substitution at C-4 are suggested as a class of analogs that is worth investigating further.

Experimental

General synthetic procedures

Optical rotations were recorded on a Perkin-Elmer 241 Polarimeter. Infrared spectra were measured using a SENSIR ATR on MIDAC M2004 Series spectrometer. NMR spectra were obtained on a JEOL Eclipse 500 or a Varian Unity 400 or Varian Inova 400 spectrometer in CDCl₃ or CD₃CN. The chemical shifts are given in δ (ppm), and coupling constants are reported in Hz. High-resolution FAB mass spectra were obtained on a JEOL HX110 Dual Focusing Mass Spectrometer. THF was distilled from sodium-benzophenone and dichloromethane was distilled from calcium hydride. Other reagents and solvents were purchased from commercial sources and were used without further purification. Silica gel column chromatography was

performed using flash silica gel (32–63 μ). Preparative thin-layer chromatography (PTLC) separations were carried out on 500 or 1000 MICRONS Uniplate thin layer chromatography plates. All reactions were carried out under a nitrogen atmosphere unless otherwise noted.

Methyl (3S)-3-hydroxy-5-(*tert*-butyldimethylsilyloxy)-pentanoate (14b)—Pd-C (10%, 0.6 g) was added to the solution of benzyl ether **13**²⁵ (3.4 g, 14.2 mmol) in CH₃OH (20 mL), and the resulting mixture was hydrogenated in a sealed tube at 35 psi for 4 h. The insoluble material was removed by filtration through a silica gel pad, and the filtrate was concentrated *in vacuo* to give residue, which was subjected to silica gel chromatography with 50% ethyl acetate in hexanes to provide diol **14a** (2.1 g, 100%). [α]_D + 19.13 (*c* 1.8, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 4.20 (m, 1H), 3.90 (br.s, 1H), 3.75 (m, 2H), 3.65 (s, 3H), 3.40 (br.s, 1H), 2.46 (dd, *J* = 5.8, 1.2 Hz, 2H), 1.65 (q, *J* = 5.6 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 173.2, 67.4, 60.5, 51.9, 41.7, 38.1.

To a solution of diol **14a** (1.9 g, 6.75 mmol) in CH₂Cl₂ (15 mL) was sequentially added imidazole (0.69 g, 10 mmol, 1.5eq) and TBSCl (1 g, 6.75 mmol, 1eq), and the reaction was allowed to proceed at 25 °C with stirring for 30 min. A saturated solution of aqueous NaHCO₃ was added to quench the reaction and the mixture was extracted with EtOAc (20 mL $\times$ 3). The combined organic extracts were dried (Na₂SO₄), and the solvent was removed *in vacuo*. The crude product obtained was subjected to silica gel column chromatography eluting with 20–25% EtOAc in hexanes to afford **14b** (1.7 g, 95% yield) as a colorless oil. [α]_D + 9.6 (*c* 0.74, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 4.20 (m, 1H), 3.80 (m, 2H), 3.62 (s, 3H), 3.60 (d, *J* = 1.2 Hz, 1H), 2.44 (m, 2H), 1.63 (m, 2H), 0.82 (s, 9H), 0.01 (s, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 172.8, 67.7, 61.6, 51.7, 41.8, 38.3, 26.0, 18.3, -5.35, -5.37. HRFABMS: calcd for C₁₂H₂₇O₄Si (M+H) 263.1679, found 263.1669.

Methyl (S)-2-((S)-1-hydroxy-3-(*tert*-butyl-dimethylsilyloxy)-propyl)pent-4-enoate—A solution of LDA (2 M, 3.96 mmol, 2.6 eq) in THF was added to a solution of **14b** (0.4 g, 1.52 mmol) in THF (15 mL) at -78 °C, and the resulting solution was allowed to warm to -20 °C and stir for 30 min at -20 °C. Allyl iodide (0.2 mL, 2.28 mmol, 1.5 eq) in HMPA (0.76 mL, 4.27 mmol, 1.08 eq to LDA) was added to the above reaction mixture that was recooled to -78 °C. The subsequent reaction mixture was warmed to -20 °C and the reaction was allowed to proceed at -20 °C with stirring for 1 h prior to being quenched by the addition of saturated NH₄Cl solution (50 mL). The two layers were separated and aqueous phase was extracted with ether (20 $\times$ 3). The combined organic extracts were washed with water and brine, the organic fraction was dried over anhydrous Na₂SO₄, and the solvents were removed under reduced pressure to give the crude mass. Purification of the product by silica gel column chromatography eluting with 10% ethyl acetate in hexanes yielded methyl (S)-2-((S)-1-hydroxy-3-(*tert*-butyl-dimethylsilyloxy)-propyl)pent-4-enoate (0.336 g, 72%). [α]_D + 5.4 (*c* 1, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 5.70 (m, 1H), 5.04 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.96 (dt, *J* = 10.0, 0.8 Hz, 1H), 3.92 (m, 1H), 3.82 (m, 1H), 3.75 (m, 1H), 3.64 (s, 3H), 3.40 (d, *J* = 4.4 Hz, 1H), 2.51 (m, 1H), 2.32 (m, 2H), 1.66 (m, 2H), 0.83 (s, 9H), 0.01 (s, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 174.9, 135.2, 117.1, 71.6, 61.9, 51.7, 51.4, 36.6, 33.2, 26.0, 18.3, -5.3. HRFABMS: calcd for C₁₅H₃₁O₄Si (M+H) 303.1992, found 303.2002.

Methyl (R)-2-((S)-1-hydroxy-3-(*tert*-butyl-dimethylsilyloxy)propyl)-2-methylpen-4-enoate (15)—To a freshly prepared solution of LDA (0.6 M, 15.73 mmol, 2.6 eq) in THF (24 mL), a solution of (S)-2-((S)-1-hydroxy-3-(*tert*-butyl-dimethylsilyloxy)-propyl)pent-4-enoate, obtained from the previous reaction, (1.83 g, 6 mmol) in THF (15 mL) was added at -78 °C, and the resulting solution was warmed to -20 °C and stirred for 4 h at that temperature. Then a solution of methyl iodide (0.6 mL, 9.69 mmol, 1.6 eq) in HMPA (17 mmol, 1.08 eq to LDA) was added to the above reaction mixture that was re-cooled to -78 °C. The subsequent reaction mixture was re-warmed to -20 °C and allowed to stir at that temperature

for 2 h. The reaction was quenched by the addition of saturated ammonium chloride (50 mL). The two layers were separated and aqueous phase was re-extracted with ether (20 mL $\times$ 3). The combined organic phases were washed with water and brine, the organic fraction was dried (Na_2SO_4), and the solvents were removed under reduced pressure. The crude oil obtained was subjected to silica gel column chromatography using 5% ether in hexane as eluent to provide **15** as the major product (1.09 g, 57% yield), together with a minor diastereomeric product (0.35 g, 18% yield). Compound **15**: $[\alpha]_D + 17.4$ (c 1.3, CHCl_3). ^1H NMR (400 MHz, CDCl_3) δ 5.70 (m, 1H), 5.04 (dd, $J = 17.2, 1.6$ Hz, 1H), 3.98 (dd, $J = 10.8, 0.8$ Hz, 1H), 3.93 (br.d, $J = 10.4, 1\text{H}$), 3.85-3.71 (m, 2H), 3.60 (s, 3H), 3.43 (d, $J = 2.4$ Hz, 1H), 2.47 (dd, $J = 13.6, 7.2$ Hz, 1H), 2.26 (dd, $J = 13.6, 7.2$ Hz, 1H), 1.66-1.54 (m, 1H), 1.45 (dt, $J = 12.8, 1.0$ Hz, 1H), 1.19 (s, 3H), 1.08 (s, 9H), 0.8 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 176.2, 134.4, 118.0, 75.7, 63.0, 51.7, 51.3, 40.8, 34.3, 26.0, 18.3, 16.2, -5.3. HRFABMS: calcd for $\text{C}_{16}\text{H}_{33}\text{O}_4\text{Si}$ (M+H) 317.2148, found 317.2166.

Methyl (R)-2-((S)-1,3-bis(tert-butyl dimethylsilyloxy)-propyl)-2-methylpent-4-enoate—To a solution of **15** (1.97 g, 6.23 mmol) in dichloromethane (25 mL) was added 2,6-lutidine (1.15 mL, 9.96 mmol, 1.6 eq) and TBSOTf (2.24 mL, 9.35 mmol, 1.5 eq) at -78°C and the resulting reaction mixture was allowed to stir at -78°C over 6 h. Saturated ammonium chloride (50 mL) was added to quench the reaction. The organic layer was separated and the aqueous phase was re-extracted with dichloromethane (20 mL $\times$ 3). The combined dichloromethane phase was dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure. The crude product obtained was subjected to silica gel chromatography eluting with 5% ether in hexanes to furnish bis-TBS ether (2.22 g, 83%). $[\alpha]_D + 5.1$ (c 1, CHCl_3). ^1H NMR (400 MHz, CDCl_3) δ 5.62 (m, 1H), 4.99-4.95 (m, 2H), 3.98 (dd, $J = 8.0, 3.2$ Hz, 1H), 3.58 (s, 3H), 3.61-3.51 (m, 2H), 2.38 (dd, $J = 13.6, 7.2$ Hz, 1H), 2.22 (dd, $J = 13.6, 7.2$ Hz, 1H), 1.62-1.44 (m, 2H), 1.04 (s, 3H), 0.85 (s, 9H), 0.84 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H), -0.009 (s, 3H), -0.01 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 176.0, 134.5, 117.9, 73.6, 60.0, 52.8, 51.6, 42.3, 37.7, 26.2, 26.0, 18.5, 18.4, 14.8, -3.6, -3.8, -5.1.

(S)-2-((S)-1,3-bis(tert-butyl dimethylsilyloxy)propyl)-2-methylpent-4-en-1-ol (16)—A solution of DIBAL-H (1 M, 17 mmol, 3.5 eq) was added dropwise to a solution of bis-TBS ether (2.08 g, 4.83 mmol), obtained from the above reaction, in dichloromethane (45 mL) at -78°C . The reaction was allowed to proceed at -78°C with stirring for 45 min. Methanol (5 mL) was added and the solution was allowed to warm to 25°C . Then a saturated solution of sodium/potassium tartrates (50 mL) was added to the mixture, which was stirred at 25°C until the two layers were clearly separated. The organic layer was separated and the aqueous phase was re-extracted with dichloromethane (30 mL $\times$ 3). The combined organic extracts were dried over anhydrous Na_2SO_4 , and the solvents was evaporated under reduced pressure. Purification of the crude product obtained by silica gel column chromatography with 3% EtOAc in hexanes as eluent to yield **16** (1.83 g, 94%). $[\alpha]_D -16.9$ (c 0.87, CHCl_3). ^1H NMR (400 MHz, CDCl_3) δ 5.80 (m, 1H), 5.05-5.01 (m, 2H), 3.77-3.63 (m, 4H), 3.32 (dd, $J = 11.2, 6.8$ Hz, 1H), 2.97 (t, $J = 4.4$ Hz, 1H), 2.25-1.91 (m, 3H), 1.67-1.58 (m, 1H), 0.98 (s, 3H), 0.90 (s, 18H), 0.099 (s, 3H), 0.092 (s, 3H), 0.06 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 134.6, 117.8, 76.1, 68.5, 60.8, 42.2, 39.7, 36.2, 26.3, 26.1, 19.4, 18.4, -3.7, -3.9, -5.0, -5.1.

(R)-2-((S)-1,3-bis(tert-butyl dimethylsilyloxy)propyl)-2-methylpent-4-enal—To a solution of **16** (1.8 g, 4.5 mmol) in a 1:1 mixture of CH_2Cl_2 and DMSO (40 mL), was added triethylamine (3.16 mL, 22.7 mmol, 5eq) followed by $\text{SO}_3\cdot\text{Py}$ (3.16 g, 22.78 mmol, 5 eq) at 0°C and the resulting reaction mixture was stirred for 30 min. The reaction was quenched by the addition of saturated NH_4Cl solution (50 mL). Organic layer was separated and the aqueous phase was extracted with dichloromethane (20 mL $\times$ 3). The combined organic phases were dried over anhydrous Na_2SO_4 , and the solvents was removed under reduced pressure. The

crude product was purified *via* silica gel column chromatography eluting with 5 % ether in hexanes to yield (*R*)-2-((*S*)-1,3-bis(*tert*-butyldimethylsilyloxy)propyl)-2-methylpent-4-enal (1.75 g, 97%). $[\alpha]_D -3.8$ (*c* 1.1, CHCl_3). ^1H NMR (400 MHz, CDCl_3) δ 9.60 (s, 1H), 5.65 (m, 1H), 5.08-5.03 (m, 2H), 4.00 (dd, $J = 7.6, 3.2$ Hz, 1H), 3.68-3.56 (m, 2H), 2.50 (dd, $J = 14.2, 6.8$ Hz, 1H), 2.25 (dd, $J = 14.2, 6.8$ Hz, 1H), 1.76-1.66 (m, 1H), 1.65-1.56 (m, 1H), 1.00 (s, 3H), 0.885 (s, 9H), 0.880 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 206.7, 133.7, 118.4, 72.9, 59.7, 54.3, 37.2, 37.0, 26.2, 26.1, 18.5, 18.4, 15.7, -3.6, -4.0, -5.11, -5.13.

(4*S*)-4-((*S*)-1,3-bis(*tert*-butyldimethylsilyloxy)propyl)-4-methylhept-6-en-3-ol—

To a solution of (*R*)-2-((*S*)-1,3-bis(*tert*-butyldimethylsilyloxy)propyl)-2-methylpent-4-enal (1.5 g, 3.75 mmol), obtained from the above reaction, in THF (20 mL) was added ethyl magnesium bromide (1 M, 6.56 mL, 6.56 mmol, 1.7 eq) at 0 °C and the resulting reaction mixture was allowed to stir at 0 °C for 1 h. Saturated NH_4Cl solution (50 mL) was added to quench the reaction. Organic layer was separated and the aqueous phase was re-extracted with dichloromethane (20 mL $\times$ 3). The organic extracts were combined and dried over anhydrous Na_2SO_4 , and the solvents were removed under reduced pressure. The crude product obtained was purified *via* silica gel column chromatography eluting with 2.5 % ether in hexanes to produce the product as a diastereomeric mixture (9:1) (68%) and alcohol **16** as an undesired byproduct (31%). The diastereomeric mixture of (4*S*)-4-((*S*)-1,3-bis(*tert*-butyldimethylsilyloxy)propyl)-4-methylhept-6-en-3-ol was subjected to the next reaction without further purification. HRFABMS: calcd for $\text{C}_{23}\text{H}_{51}\text{O}_3\text{Si}_2$ ($\text{M}+\text{H}$) 431.3371, found 431.3372.

(*R*)-4-((*S*)-1,3-bis(*tert*-butyldimethylsilyloxy)propyl)-4-methylhept-6-en-3-one

(9)—To a solution of (4*S*)-4-((*S*)-1,3-bis(*tert*-butyldimethylsilyloxy)propyl)-4-methylhept-6-en-3-ol (1.545 g, 3.59 mmol) in a 1:1 mixture of CH_2Cl_2 and DMSO (36 mL), was added triethylamine (2.50 mL, 17.97 mmol, 5 eq) followed by $\text{SO}_3\cdot\text{Py}$ complex (2.82 g, 17.96 mmol, 5 eq) at 0 °C. The reaction was allowed to proceed at 0 °C with stirring for 2 h prior to being quenched by the addition of saturated NH_4Cl solution (50 mL). Organic layer was separated and the aqueous phase was extracted with dichloromethane (20 mL $\times$ 3). The combined organic extracts were dried over anhydrous Na_2SO_4 , and the solvent was removed under reduced pressure to give crude product, which was purified *via* silica gel chromatography eluting with 3 % ether in hexanes to give **9** (1.16 g, 75%). $[\alpha]_D -0.0$ (*c* 1.8, CHCl_3). ^1H NMR (400 MHz, CDCl_3) δ 5.60 (m, 1H), 5.00-4.97 (m, 2H), 4.05 (dd, $J = 8.0, 2.8$ Hz, 1H), 3.58 (dd, $J = 8.0, 4.8$ Hz, 2H), 2.55-2.35 (m, 3H), 2.22 (dd, $J = 14.2, 6.8$ Hz, 1H), 1.52-1.35 (m, 2H), 1.09 (s, 3H), 0.98 (t, $J = 7.2$ Hz, 3H), 0.90 (s, 9H), 0.87 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 214.6, 134.3, 117.9, 73.3, 59.8, 57.4, 42.3, 37.8, 32.8, 26.3, 26.0, 18.6, 18.4, 14.9, 7.6, -3.5, -3.6, -5.13, -5.15. HRFABMS: calcd for $\text{C}_{23}\text{H}_{49}\text{O}_3\text{Si}_2$ ($\text{M}+\text{H}$) 429.3220, found 429.3208.

Aldol Product 18—A solution of ketone **9** (1.4 g, 3.27 mmol, 1.8 eq to aldehyde **8**) in THF (8 mL) was added to a solution of freshly prepared LDA (~ 0.6 M, 3.76 mmol, 1.15 eq to **9**) in THF at -78 °C. After stirring for 1 h at -78 °C, the solution was allowed to warm up to -40 °C and stir at that temperature for 30 min. The reaction mixture was then recooled to -78 °C and a cold (-78 °C) solution of aldehyde **8** (1.3 g, 1.81 mmol) in THF (18 mL) was rapidly introduced to the above reaction mixture. Upon completion of the addition, stirring was continued for a further 5 min before the reaction was quenched by the rapid injection of AcOH (0.521 mL, 4.8 eq) as a solution in THF (1.8 mL). The whole reaction mixture was warmed to 25 °C and partitioned between ether and saturated aqueous NH_4Cl solution. The aqueous phase was re-extracted with ether (50 mL $\times$ 3), and the combined organic extracts were dried (Na_2SO_4), and the solvents were removed under reduced pressure. Flash column

chromatography (silica gel, 1.5 to 20% ether in hexanes) of crude product obtained provided **18** (1.77 g, 80%) as a colorless oil. $[\alpha]_D -21.1$ (c 0.55, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.44 (dd, $J = 7.2, 1.6$ Hz, 6H), 7.22 (m, 9H), 6.17 (s, 1H), 5.60 (m, 1H), 5.49 (t, $J = 7.2$ Hz, 1H), 5.00 (d, $J = 10.0$ Hz, 1H), 4.97 (dd, $J = 17.0, 1.6$ Hz, 1H), 4.16 (t, $J = 6.0$ Hz, 1H), 3.80 (dd, $J = 7.8, 2.4$ Hz, 1H), 3.64-3.56 (m, 2H), 3.43 (br.s, 2H), 3.25 (br.s, 1H), 3.16 (m, 2H), 2.42 (dd, $J = 14.0, 6.0$ Hz, 1H), 2.26 (m, 2H), 2.08-1.98 (m, 3H), 1.80 (s, 3H), 1.65 (m, 2H), 1.42 (m, 2H), 1.24 (s, 3H), 0.96 (d, $J = 6.8$ Hz, 3H), 0.86 (2 singlets, 27H), 0.67 (d, $J = 6.8$ Hz, 3H), 0.08 (2 singlets, 6H), 0.02 to -0.02 (3 singlets, 12H); ^{13}C NMR (100 MHz, CDCl_3) δ 219.0, 150.4, 144.5, 138.9, 134.2, 128.8, 127.9, 127.0, 121.4, 118.5, 86.7, 77.7, 77.6, 74.4, 73.8, 67.3, 60.4, 57.7, 42.4, 41.6, 38.0, 35.5, 34.8, 33.2, 29.3, 26.3, 26.1, 25.8, 19.9, 18.6, 18.49, 18.41, 17.3, 15.4, 9.1, -3.4, -3.8, -4.6, -4.7, -5.02, -5.05; HRFABMS: calcd for $\text{C}_{62}\text{H}_{99}\text{O}_6\text{Si}_3\text{INa}$ (M + Na) 1173.5692, found 1173.5741.

Tetrakis-[*tert*-butyldimethylsilyl]-ether 19a—To a solution of **18** (2.8 g, 2.43 mmol) in dichloromethane (35 mL) was added 2,6-lutidine (1.21 mL, 10.5 mmol, 4.3 eq) followed by TBSOTf (1.78 mL, 7.79 mmol, 3.2 eq) at 0 °C and the reaction was allowed to proceed with stirring for 4 h at 0 °C. Saturated NaHCO_3 solution was added to quench the reaction. Two layers were separated and the aqueous layer was re-extracted with dichloromethane (50 mL $\times$ 3). The combined organic extracts were dried (Na_2SO_4), and the solvents were removed under reduced pressure. The crude mass obtained was subjected to column chromatography over silica gel, eluting with 1.5% ether in hexanes, to yield tetrakis-TBS ether **19a** (2.82 g, 94%). $[\alpha]_D -18.0$ (c 1.6, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.46 (dd, $J = 7.2, 1.6$ Hz, 6H), 7.30-7.22 (m, 9H), 6.21 (s, 1H), 5.60 (m, 1H), 5.52 (t, $J = 7.2$ Hz, 1H), 4.98 (d, $J = 10.0$ Hz, 1H), 4.96 (dd, $J = 17.0, 1.6$ Hz, 1H), 4.20 (t, $J = 6.0$ Hz, 1H), 3.79 (dd, $J = 7.8, 2.4$ Hz, 1H), 3.63 (m, 3H), 3.47 (dd, $J = 17.0, 12.0$ Hz, 2H), 3.06 (dd, $J = 6.8, 4.8$ Hz, 1H), 2.42 (dd, $J = 14.0, 6.0$ Hz, 1H), 2.28 (m, 2H), 2.0 (m, 3H), 1.82 (s, 3H), 1.72 (m, 1H), 1.40 (m, 1H), 1.28 (m, 3H), 1.22 (s, 3H), 1.06 (m, 1H), 1.05 (d, $J = 6.8$ Hz, 3H), 0.91 (2 singlets, 36H), 0.81 (d, $J = 6.8$ Hz, 3H), 0.12-0.02 (8 singlets, 24H); ^{13}C NMR (100 MHz, CDCl_3) δ 217.2, 150.4, 144.5, 138.9, 134.6, 128.9, 127.9, 127.0, 121.7, 118.1, 86.7, 77.6, 76.6, 74.7, 67.3, 60.6, 56.9, 45.5, 41.1, 39.9, 37.7, 34.9, 31.7, 29.5, 26.8, 26.44, 26.40, 26.1, 26.0, 19.9, 18.7, 18.6, 18.5, 18.4, 17.2, 14.3, 1.21, -3.3, -3.4, -3.6, -3.8, -4.6, -4.7, -5.0; HRFABMS: calcd for $\text{C}_{68}\text{H}_{113}\text{O}_6\text{Si}_4\text{Li}$ (M+Li) 1271.6820, found 1271.6862.

Tris-[*tert*-butyldimethylsilyl]-ether 19b—To a solution of **19a** (2.8 g, 2.21 mmol) in THF (50 mL) was added a stock solution of HF.Py (this stock solution was prepared by addition of 4 mL HF.Py to 11 mL pyridine in 22 mL THF) at 0 °C. The resulting reaction mixture was warmed to 25 °C by removing the ice-bath and allowed to stir at that temperature for 2 h. Saturated NaHCO_3 solution was added to quench the reaction and two layers were separated. The aqueous layer was extracted with ethyl acetate (50 mL $\times$ 3). The combined organic extracts were dried over anhydrous Na_2SO_4 , and the solvents were removed under reduced pressure. The crude product obtained was subjected to column chromatography over silica gel employing 12% EtOAc in hexanes as eluent to yield the desired primary alcohol **19b** (2.2 g, 86%). $[\alpha]_D -9.1$ (c 0.23, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.45 (dd, $J = 7.2, 1.6$ Hz, 6H), 7.32-7.22 (m, 9H), 6.20 (s, 1H), 5.60 (m, 1H), 5.52 (t, $J = 7.2$ Hz, 1H), 5.00 (d, $J = 10.0$ Hz, 1H), 4.94 (dd, $J = 17.2, 1.6$ Hz, 1H), 4.20 (t, $J = 6.0$ Hz, 1H), 3.98 (m, 1H), 3.72-3.64 (m, 3H), 3.46 (dd, $J = 17.0, 12.0$ Hz, 2H), 3.00 (dd, $J = 7.0, 4.8$ Hz, 1H), 2.45 (dd, $J = 14.0, 6.0$ Hz, 1H), 2.28 (m, 2H), 2.00 (m, 3H), 1.80 (s, 3H), 1.64 (m, 1H), 1.58 (m, 1H), 1.28 (m, 3H), 1.26 (s, 3H), 1.03 (d, $J = 6.8$ Hz, 3H), 0.90 (2 singlets, 27H), 0.80 (d, $J = 6.8$ Hz, 3H), 0.12-0.02 (6 singlets, 18H). ^{13}C NMR (100 MHz, CDCl_3) δ 218.3, 150.4, 144.5, 138.9, 133.8, 128.8, 128.1, 127.9, 127.4, 127.0, 121.7, 118.3, 86.7, 76.2, 73.1, 67.3, 60.4, 57.2, 45.4, 41.0, 39.9, 38.1, 34.9, 31.6, 29.5, 26.7, 26.4, 26.3, 26.0, 25.8, 19.9, 18.7, 18.6, 18.4, 17.6, 17.1, 14.6, -3.5, -3.6, -3.8, -4.6, -4.7; HRFABMS: calcd for $\text{C}_{62}\text{H}_{99}\text{O}_6\text{Si}_3\text{Li}$ (M+Li) 1157.5956, found 1157.5931.

Oxidation of primary alcohol 19b to aldehyde 19c—To a solution of primary alcohol **19b** obtained in the preceding step (2.15 g, 1.86 mmol) in 1:1 mixture of dichloromethane and DMSO (22 mL), was added triethylamine (1.33 mL, 9.34 mmol, 5 eq) followed by SO₃Py (1.5 g, 9.34 mmol, 5 eq) at 0 °C and the reaction was allowed to proceed at 0 °C with stirring for 1 h. Saturated NH₄Cl solution (50 mL) was added to quench the reaction, and the mixture was extracted with dichloromethane (20 mL × 3). The combined organic extracts were dried over anhydrous Na₂SO₄, and the organic solvents were removed under reduced pressure. The crude product obtained was subjected to silica gel column chromatography eluting with 1-2% ether in hexanes to give **19c** (1.87 g, 87%). [α]_D -14.6 (c 0.24, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 9.75 (s, 1H, CHO), 7.45 (dd, *J* = 7.2, 1.6 Hz, 6H), 7.25 (m, 9H), 6.20 (s, 1H), 5.60 (m, 1H), 5.51 (t, *J* = 7.2 Hz, 1H), 5.00 (d, *J* = 10.4 Hz, 1H), 4.95 (d, *J* = 16.8 Hz, 1H), 4.38 (t, *J* = 5.6 Hz, 1H), 4.19 (t, *J* = 6.4 Hz, 1H), 3.63 (dd, *J* = 5.0, 2.4 Hz, 1H), 3.45 (dd, *J* = 17.4, 12.0 Hz, 2H), 3.03 (dd, *J* = 7.0, 5.6 Hz, 1H), 2.64 (dd, *J* = 17.0, 4.4 Hz, 1H), 2.44 (dd, *J* = 5.2, 2.4 Hz, 1H), 2.38-2.23 (m, 3H), 1.97 (m, 3H), 1.80 (s, 3H), 1.25 (s, 3H), 1.01 (d, *J* = 6.4 Hz, 3H), 0.88 (2 singlets, 27H), 0.8 (d, *J* = 6.8 Hz, 3H), 0.11-0.008 (6 singlets, 18H); ¹³C NMR (100 MHz, CDCl₃) δ 217.4, 200.8, 150.4, 144.5, 138.8, 133.4, 128.8, 127.9, 127.0, 121.7, 118.8, 86.7, 77.6, 76.5, 71.3, 67.3, 56.5, 49.3, 45.5, 40.6, 39.8, 34.9, 31.6, 29.4, 26.7, 26.4, 26.1, 26.0, 19.9, 18.7, 18.4, 18.2, 17.2, 14.5, -3.5, -3.7, -3.8, -4.1, -4.6, -4.7; HRFABMS: calcd for C₆₂H₉₇O₆Si₃ILi (M+Li) 1155.5799, found 1155.5792.

Further oxidation of aldehyde 19c to carboxylic acid 19d—To a solution of **19c** (1.87 g, 1.62 mmol) in *t*-BuOH:H₂O (4.5:1, 11 mL) was added sequentially, 2-methyl-2-butene (12 mL, 120 mmol, 75 eq) in THF (33 mL), NaH₂PO₄ (678 mg, 5.7 mmol, 3.5 eq), and NaClO₂ (1 g, 11.4 mmol, 7 eq). The reaction was allowed to proceed with stirring at 25 °C for 1 h, then volatiles were removed under reduced pressure, and the residue was partitioned between ethyl acetate and brine solution. Two layers were separated and aqueous layer was re-extracted with ethyl acetate (30 mL × 3). The combined organic extracts were dried over anhydrous Na₂SO₄, and the organic solvents were removed in vacuo. Purification of the crude product via silica gel column chromatography employing 20% ether in hexanes as eluent furnished **19d** (1.8 g, 98%). [α]_D -22.5 (c 0.24, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.44 (d, *J* = 7.6 Hz, 6H), 7.27 (m, 9H), 6.20 (s, 1H), 5.60 (m, 1H), 5.51 (t, *J* = 7.6 Hz, 1H), 5.00 (d, *J* = 10.4 Hz, 1H), 4.96 (d, *J* = 17.2 Hz, 1H), 4.27 (dd, *J* = 6.8, 2.8 Hz, 1H), 4.19 (t, *J* = 6.0 Hz, 1H), 3.63 (dd, *J* = 5.2, 2.0 Hz, 1H), 3.45 (dd, *J* = 17.4, 12.0 Hz, 2H), 3.05 (dd, *J* = 7.0, 5.6 Hz, 1H), 2.62 (dd, *J* = 17.4, 4.4 Hz, 1H), 2.41 (dd, *J* = 14.4, 6.4 Hz, 1H), 2.31 (m, 3H), 1.99 (m, 3H), 1.81 (s, 3H), 1.28 (m, 3H), 1.24 (s, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 27H), 0.8 (d, *J* = 6.4 Hz, 3H), 0.11-0.01 (6 singlets, 18H); ¹³C NMR (100 MHz, CDCl₃) δ 217.2, 177.8, 150.4, 144.5, 138.8, 133.5, 128.8, 127.9, 127.0, 121.7, 118.8, 86.7, 77.6, 76.7, 73.9, 67.3, 56.6, 45.6, 40.4, 39.8, 39.7, 34.9, 31.5, 29.5, 26.7, 26.4, 26.2, 26.0, 19.9, 18.7, 18.47, 18.41, 17.3, 14.6, -3.4, -3.6, -4.0, -4.3, -4.6, -4.7; HRFABMS: calcd for C₆₂H₉₇O₇Si₃ILi (M+Li) 1171.5748, found 1171.5822.

Hydroxy acid 19e—A solution of the carboxylic acid **19d** (880 mg, 0.757 mmol) in THF (15 mL) at 0 °C was treated with TBAF (4.54 mL, 1 M in THF, 4.54 mmol, 6 eq) and then the mixture was allowed to warm up to 25 °C. The reaction was quenched after being stirred for 20 h at 25 °C by the addition of saturated aqueous NH₄Cl solution (50 mL), and the mixture was extracted with EtOAc (30 mL × 3). The combined organic extracts were dried over anhydrous Na₂SO₄, and the solvents were removed under reduced pressure to give crude product. Column chromatography of this crude product over silica gel, eluting with 40% ethyl acetate in hexanes, yielded hydroxyl acid **19e** (767 mg, 96%). [α]_D -21.0 (c 0.5, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.40 (dd, *J* = 8.0, 0.8 Hz, 6H), 7.27-7.20 (m, 9H), 6.30 (s, 1H), 5.55 (m, 1H), 5.43 (t, *J* = 6.8 Hz, 1H), 4.97 (d, *J* = 9.2 Hz, 1H), 4.93 (d, *J* = 17.2 Hz, 1H), 4.25 (dd, *J* = 6.8, 2.8 Hz, 1H), 4.18 (t, *J* = 6.0 Hz, 1H), 3.61 (d, *J* = 3.2 Hz, 1H), 3.52 (d, *J* = 12.4

Hz, 2H), 3.46 (d, $J = 12.4$ Hz, 1H), 3.00 (m, 1H), 2.54 (dd, $J = 17.0, 1.6$ Hz, 1H), 2.40 (dd, $J = 14.4, 6.4$ Hz, 1H), 2.32 (t, $J = 6.8$ Hz, 2H), 2.24 (dd, $J = 17.2, 6.4$ Hz, 1H), 1.99 (m, 3H), 1.81 (s, 3H), 1.24 (m, 3H), 1.20 (s, 3H), 0.99 (d, $J = 6.8$ Hz, 3H), 0.85 (s, 18H), 0.78 (d, $J = 6.8$ Hz, 3H), 0.07-0.01 (4 singlets, 12H); ^{13}C NMR (100 MHz, CDCl_3) δ 216.9, 176.9, 149.1, 144.1, 140.7, 133.4, 128.6, 127.7, 126.9, 120.1, 118.5, 86.7, 78.4, 77.2, 76.5, 76.0, 73.5, 67.1, 56.5, 45.4, 40.1, 39.6, 39.3, 33.4, 31.2, 29.2, 26.5, 26.1, 25.9, 20.1, 18.4, 18.2, 18.1, 17.2, 14.5, -3.7, -3.9, -4.2, -4.6; HRFABMS: calcd for $\text{C}_{56}\text{H}_{82}\text{O}_7\text{Si}_2\text{I}$ (M+H) 1049.4644, found 1049.4554.

Macrolactone 20a—To a solution of hydroxyl acid **19e** (832 mg, 0.792 mmol) in THF (8.2 mL, 0.1 M) was added triethylamine (0.661 mL, 4.75 mmol, 6 eq), followed by 2,4,6-trichlorobenzoyl chloride (0.3 mL, 1.9 mmol, 2.4 eq) at 0 °C and the resulting reaction mixture was stirred for 1 h at that temperature. The mixture was then added to a solution of DMAP (212 mg, 1.74 mmol, 2.2 eq) in toluene (160 mL, 0.005 M based on **19e**) at 75 °C over 3 h, *via* syringe pump. After addition was complete, the reaction mixture was stirred for an additional 2 h. Toluene was removed under reduced pressure and the residue was filtered through a short plug of silica gel, eluting with 60% ether in hexanes, to give a crude product. Purification of this product by column chromatography over silica gel, eluting with 2% ether in hexanes, furnished lactone **20a** (645 mg, 78%). $[\alpha]_{\text{D}} -10.7$ (c 1.4, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.44 (dd, $J = 7.0, 1.6$ Hz, 6H), 7.30-7.21 (m, 9H), 6.38 (s, 1H), 5.63 (m, 1H), 5.53 (dd, $J = 9.8, 5.6$ Hz, 1H), 5.16 (m, 1H), 5.09 (d, $J = 10.0$ Hz, 1H), 5.04 (d, $J = 17.2$ Hz, 1H), 4.13 (m, 1H), 3.84 (d, $J = 8.0$ Hz, 1H), 3.48, 3.40 (ABq, $J = 11.6$ Hz, 2H), 3.00 (m, 1H), 2.72 (m, 2H), 2.58 (m, 1H), 2.38 (m, 3H), 2.18 (m, 1H), 2.00 (m, 1H), 1.90 (s, 3H), 1.50 (m, 3H), 1.20 (s, 3H), 1.10 (d, $J = 6.8$ Hz, 3H), 1.07 (s, 3H), 0.93 (s, 9H), 0.84 (d, $J = 6.8$ Hz, 3H), 0.72 (s, 9H), 0.08-0.05 (4 singlets, 12H); ^{13}C NMR (100 MHz, CDCl_3) δ 214.2, 170.6, 146.4, 144.3, 133.2, 128.8, 127.9, 127.1, 118.9, 86.6, 79.9, 77.9, 77.4, 74.3, 66.9, 56.9, 41.1, 32.2, 31.2, 28.8, 27.1, 26.6, 26.3, 20.7, 18.8, 18.7, 1.2, -3.0, -3.3; HRFABMS: calcd for $\text{C}_{56}\text{H}_{80}\text{O}_6\text{Si}_2\text{I}$ (M+H) 1031.4531, found 1031.4489.

Macrolactone iodide 21—To a solution of macrolactone **20a** (426 mg, 0.423 mmol) in THF (30 mL) was added HF.Py (70%, 10 mL) at 0 °C. The resulting reaction mixture was allowed to warm up to 25 °C and the reaction was allowed to proceed with stirring at 25 °C for 36 h prior to being quenched by careful portionwise addition into saturated aqueous NaHCO_3 solution with further addition of sufficient solid NaHCO_3 to ensure complete neutralization. The mixture was then extracted with EtOAc (50 mL $\times$ 3), the combined organic extracts were dried (Na_2SO_4), and the solvent was removed under reduced pressure. Purification of the crude product obtained by column chromatography over silica gel eluting with 55% ethyl acetate in hexanes gave **21** (224 mg, 94%). $[\alpha]_{\text{D}} -43$ (c 0.32, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 6.42 (s, 1H), 5.62 (m, 1H), 5.38 (m, 1H), 5.36 (d, $J = 10.0$ Hz, 1H), 5.14 (d, $J = 17.2$ Hz, 1H), 5.12 (d, $J = 10.0$ Hz, 1H), 4.22 (dd, $J = 11.0, 2.4$ Hz, 2H), 4.05, 3.95 (ABq, $J = 13.6$ Hz, 2H), 3.65 (dd, $J = 5.2, 1.6$ Hz, 1H), 3.15 (dq, $J = 7.2, 1.6$ Hz, 1H), 2.68 (m, 1H), 2.52 (m, 4H), 2.38 (m, 1H), 2.20 (m, 2H), 2.00 (m, 2H), 1.88 (s, 3H), 1.76 (m, 1H), 1.60 (m, 1H), 1.38 (m, 2H), 1.12 (d, $J = 6.8$ Hz, 3H), 1.00 (s, 3H), 0.98 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 219.3, 170.1, 146.4, 145.6, 142.5, 133.3, 121.4, 119.5, 80.5, 77.7, 73.5, 72.5, 66.5, 57.2, 42.0, 40.0, 39.5, 37.8, 31.9, 28.1, 25.2, 21.0, 15.9, 15.8, 12.6; HRFABMS: calcd for $\text{C}_{25}\text{H}_{40}\text{O}_6\text{I}$ (M+H) 563.1870, found 563.1881.

26-Acryloyloxy-macrolactone 7—To a solution of triol **21** (28 mg, 0.049 mmol) in dichloromethane (2 mL) was added sequentially Et_3N (35 μL , 0.25 mmol, 5eq), acryloyl chloride (7.2 μL , 0.088 mmol, 1.8eq) and DMAP (2 mg) at 0 °C. The resulting reaction mixture was allowed to stir for 30 min prior to being quenched by addition into saturated aqueous NaHCO_3 solution. The mixture was then extracted with EtOAc (10 mL $\times$ 3), the combined organic extracts were dried (Na_2SO_4), and the solvent was removed under reduced pressure.

Purification of the crude product obtained by preparative thin layer chromatography over silica gel eluting with 18% ethyl acetate in hexanes gave **7** (18 mg, 60%). $[\alpha]_D -50.0$ (*c* 0.32, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 6.41 (t, *J* = 0.8 Hz, 1H), 6.40 (dd, *J* = 17.4, 1.2 Hz, 1H), 6.13 (dd, *J* = 17.2, 10.4 Hz, 1H), 5.84 (dd, *J* = 10.6, 1.2 Hz, 1H), 5.63 (m, 1H), 5.38 (m, 2H), 5.16 (d, *J* = 10.4 Hz, 1H), 5.13 (d, *J* = 17.2 Hz, 1H), 4.60 (d, *J* = 12.8 Hz, 1H), 4.50 (d, *J* = 12.8 Hz, 1H), 4.26 (m, 1H), 3.66 (m, 1H), 3.17 (dq, *J* = 5.8, 2.0 Hz, 1H), 2.94 (d, *J* = 2.0 Hz, 1H), 2.69-2.44 (m, 4H), 2.39 (m, 2H), 2.25 (m, 2H), 2.05 (m, 1H), 1.88 (s, 3H), 1.76 (m, 1H), 1.38-1.24 (m, 3H), 1.14 (d, *J* = 6.8 Hz, 3H), 1.04 (s, 3H), 0.99 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 219.3, 169.9, 166.1, 145.3, 137.3, 133.4, 131.3, 128.4, 124.0, 119.4, 80.3, 73.6, 72.4, 67.5, 57.2, 41.9, 40.0, 39.4, 38.1, 32.0, 31.9, 29.9, 28.3, 25.1, 21.1, 15.9, 15.7, 12.8; HRFABMS: calcd for $\text{C}_{28}\text{H}_{42}\text{O}_7\text{I}$ (M+H) 617.1975, found 617.2003.

26-(3-Butenoyloxy)-macrolactone 22—A similar procedure was employed as that described above for the conversion of **21** to **7** (19 mg, 50%). ^1H NMR (400 MHz, CDCl_3) δ 6.42 (s, 1H), 5.92 (m, 1H), 5.64 (m, 1H), 5.38 (d, *J* = 1.2 Hz, 1H), 5.36 (t, *J* = 6.0 Hz, 1H), 5.18 (dd, *J* = 17.0, 1.2 Hz, 1H), 5.14 (dd, *J* = 10.4, 1.2 Hz, 1H), 5.08 (dd, *J* = 17.2, 10.4 Hz, 1H), 5.02 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.52 (d, *J* = 13.2 Hz, 1H), 4.43 (d, *J* = 13.2 Hz, 1H), 4.25 (dd, *J* = 10.8, 2.4 Hz, 1H), 3.66 (dd, *J* = 4.8, 2.0 Hz, 1H), 3.16 (dq, *J* = 5.8, 2.0 Hz, 1H), 3.11 (dt, *J* = 7.2, 1.2 Hz, 2H), 2.68-2.46 (m, 4H), 2.38 (dd, *J* = 15.2, 2.4 Hz, 1H), 2.20 (m, 2H), 2.00 (m, 1H), 1.88 (s, 3H), 1.78 (m, 1H), 1.64 (m, 1H), 1.38-1.26 (m, 3H), 1.15 (d, *J* = 6.8 Hz, 3H), 1.04 (s, 3H), 1.00 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 219.2, 171.4, 169.9, 145.3, 137.4, 133.4, 130.3, 123.8, 119.4, 119.0, 80.3, 73.6, 72.4, 67.6, 57.2, 41.9, 40.8, 39.4, 39.3, 38.0, 31.96, 31.91, 29.9, 25.0, 21.1, 15.9, 15.7, 12.8; HRFABMS: calcd for $\text{C}_{29}\text{H}_{44}\text{O}_7\text{I}$ (M+H) 631.2132, found 631.2095.

26-(4-Pentenoyloxy)-macrolactone 23—A similar procedure was employed as that described above for the conversion of **21** to **7** (21.7 mg, 75%). ^1H NMR (400 MHz, CDCl_3) δ 6.41 (s, 1H), 5.80 (m, 1H), 5.62 (m, 1H), 5.38 (d, *J* = 1.2 Hz, 1H), 5.35 (t, *J* = 6.0 Hz, 1H), 5.16 (dd, *J* = 17.0, 1.2 Hz, 1H), 5.14 (dd, *J* = 10.4, 1.2 Hz, 1H), 5.05 (dd, *J* = 17.2, 10.4 Hz, 1H), 5.02 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.52 (d, *J* = 12.8 Hz, 1H), 4.42 (d, *J* = 12.8 Hz, 1H), 4.25 (m, 1H), 3.66 (m, 1H), 3.16 (dq, *J* = 5.8, 2.0 Hz, 1H), 2.93 (d, *J* = 2.4 Hz, 1H), 2.68-2.46 (m, 4H), 2.40 (m, 6H), 2.22 (m, 2H), 2.02 (m, 1H), 1.88 (s, 3H), 1.78 (m, 1H), 1.38-1.24 (m, 4H), 1.14 (d, *J* = 6.8 Hz, 3H), 1.04 (s, 3H), 1.00 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 219.2, 172.7, 169.7, 145.1, 137.3, 136.5, 133.1, 123.5, 119.2, 115.2, 80.1, 77.0, 73.3, 72.2, 67.1, 56.9, 41.7, 39.8, 39.2, 37.8, 33.4, 31.74, 31.70, 28.7, 27.9, 24.8, 20.8, 15.7, 15.5, 12.5; HRFABMS: calcd for $\text{C}_{30}\text{H}_{46}\text{O}_7\text{I}$ (M+H) 645.2288, found 645.2258.

Bridged macrolactone iodide 25—To a solution of diene **23** (13 mg, 0.02 mmol) in dichloromethane (3 mL) was added second-generation Grubbs catalyst (6 mg, 0.007 mmol) at room temperature for 3 h and the resulting reaction mixture was stirred for 3 d. The dichloromethane was evaporated to give crude product, which was subjected to preparative thin layer chromatography over silica gel, eluting with 20% ethyl acetate in hexanes, to furnish **25** (3.7 mg, 30%). $[\alpha]_D -68.6$ (*c* 0.035, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 6.44 (s, 1H), 6.00 (m, 1H), 5.82 (m, 1H), 5.43 (s, 1H), 5.42 (t, *J* = 6.0 Hz, 1H), 5.00 (d, *J* = 14.0 Hz, 1H), 4.40 (m, 1H), 4.07 (d, *J* = 14.0 Hz, 1H), 3.49 (d, *J* = 2.4 Hz, 1H), 3.18 (dq, *J* = 5.8, 2.4 Hz, 1H), 2.88 (d, *J* = 2.8 Hz, 1H), 2.70-2.58 (m, 3H), 2.50-2.38 (m, 6H), 2.30 (m, 2H), 2.10 (m, 2H), 1.88 (s, 3H), 1.84 (m, 1H), 1.70 (m, 1H), 1.40 (m, 1H), 1.27 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.95 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 220.0, 172.6, 169.1, 143.7, 137.3, 134.4, 128.2, 118.0, 78.2, 77.4, 76.0, 75.6, 67.9, 63.8, 57.0, 42.7, 39.9, 39.1, 38.6, 32.0, 29.9, 29.8, 28.8, 27.7, 26.9, 24.0, 22.8, 16.9, 14.4, 14.3; HRFABMS: calcd for $\text{C}_{28}\text{H}_{42}\text{O}_7\text{I}$ (M+H) 617.1975, found 617.1982.

Bridged epothilone D 27—A solution of iodide **25** (3 mg, 0.0048 mmol), and Pd (MeCN)₂(Cl)₂ (2 mg) were added to a degassed solution of stannane **26** (8 mg, 0.02 mmol, 4 eq) in DMF (0.8 mL) at 25 °C and the resulting solution was stirred over 24 h. The reaction mixture was filtered off through a short plug of silica gel eluting with ethyl acetate. The filtrate was concentrated and the residue was subjected to preparative thin layer chromatography over silica gel, eluting with 25% ethyl acetate in hexanes, to furnish **27** (2 mg, 70%). [α]_D -68.2 (c 0.08, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.00 (s, 1H), 6.59 (s, 1H), 6.06 (m, 1H), 6.00 (m, 1H), 5.67 (t, *J* = 10.8 Hz, 1H), 5.39 (br.s, 1H), 4.88 (d, *J* = 13.6 Hz, 1H), 4.55 (d, *J* = 10.8 Hz, 1H), 4.20 (d, *J* = 13.6 Hz, 1H), 3.54 (br.s, 1H), 3.36 (m, 1H), 3.22 (q, *J* = 6.8 Hz, 1H), 2.99 (br.s, 1H), 2.82 (m, 1H), 2.44 (s, 3H), 2.56-2.42 (m, 6H), 2.28 (m, 2H), 2.16 (m, 2H), 2.06 (s, 3H), 1.88 (m, 2H), 1.38 (m, 2H), 1.27 (d, *J* = 6.8 Hz, 3H), 1.25 (s, 3H), 0.99 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 221.0, 173.0, 169.6, 164.8, 152.1, 136.5, 133.8, 128.3, 120.1, 119.5, 115.2, 77.4, 75.8, 75.7, 67.2, 64.9, 57.4, 42.5, 40.0, 39.2, 38.8, 32.0, 30.1, 29.9, 28.7, 28.1, 26.5, 24.2, 19.1, 17.1, 16.9, 14.4, 14.1; HRFABMS: calcd for C₃₂H₄₆NO₇S (M+H) 588.2995, found 588.2960.

(4R)-4-Allyl-4-demethyl-26-hydroxyepothilone 28—Iodide **21** was converted to **28** (33 mg, 89%) by a similar procedure to that described previously for the conversion of **25** to **27**. [α]_D -79 (c 0.6, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 6.94 (s, 1H), 6.62 (s, 1H), 5.63 (m, 1H), 5.44 (dd, *J* = 9.8, 4.8 Hz, 1H), 5.30 (d, *J* = 8.4 Hz, 1H), 5.13 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.10 (dd, *J* = 10.4, 1.6 Hz, 1H), 4.45 (d, *J* = 11.2 Hz, 1H), 4.06 (d, *J* = 13.2 Hz, 1H), 4.00 (d, *J* = 13.2 Hz, 1H), 3.90 (br.s, 1H), 3.66 (d, *J* = 6.0 Hz, 1H), 3.22 (qt, *J* = 6.8, 1.2 Hz, 1H), 3.13 (br.s, 1H), 2.67 (s, 3H), 2.60 (m, 3H), 2.50 (m, 1H), 2.38-2.30 (m, 3H), 2.05 (s, 3H), 1.96 (m, 3H), 1.80 (m, 1H), 1.62 (m, 2H), 1.45 (m, 2H), 1.30 (m, 2H), 1.17 (d, *J* = 6.8 Hz, 3H), 1.02 (s, 3H), 1.00 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 220.0, 170.5, 165.3, 152.0, 142.1, 139.2, 133.5, 122.2, 119.2, 119.1, 115.8, 78.5, 73.3, 71.6, 66.5, 58.0, 41.5, 40.2, 39.8, 37.4, 31.6, 28.2, 27.0, 24.7, 17.7, 15.7, 14.5, 13.8; HRFABMS: calcd for C₂₉H₄₄NO₆S (M+H) 534.2889, found 534.2925.

(4R)-4-Allyl-4-demethyl-26-(3-butenoyloxy)epothilone D 29—Epothilone derivative **28** was acylated to provide **29** (10 mg, 50%) by a similar procedure to that described for the conversion of **21** to **22**. ¹H NMR (400 MHz, CDCl₃) δ 6.95 (s, 1H), 6.58 (s, 1H), 5.90 (m, 1H), 5.66 (m, 1H), 5.46 (dd, *J* = 10.2, 5.2 Hz, 1H), 5.30 (d, *J* = 9.6 Hz, 1H), 5.17 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.15 (dd, *J* = 10.4, 1.2 Hz, 1H), 5.14 (dd, *J* = 17.2, 10.4 Hz, 1H), 5.12 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.55 (dd, *J* = 12.4 Hz, 1H), 4.46 (d, *J* = 12.4 Hz, 1H), 4.44 (m, 1H), 3.67 (d, *J* = 5.6 Hz, 1H), 3.62 (d, *J* = 5.2 Hz, 1H), 3.20 (q, *J* = 5.6 Hz, 1H), 3.12 (d, *J* = 7.2 Hz, 1H), 3.09 (dt, *J* = 7.2, 1.2 Hz, 1H), 2.69 (s, 3H), 2.62-2.42 (m, 3H), 2.40-2.22 (m, 3H), 2.06 (s, 3H), 2.02 (m, 1H), 1.80 (m, 1H), 1.64 (m, 1H), 1.42 (m, 2H), 1.30 (m, 2H), 1.14 (d, *J* = 6.8 Hz, 3H), 1.03 (s, 3H), 1.00 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 219.8, 170.4, 165.4, 152.0, 139.0, 137.1, 133.5, 130.3, 125.3, 119.4, 119.1, 118.9, 115.9, 78.2, 73.4, 71.7, 67.9, 57.9, 41.4, 40.2, 39.8, 39.3, 37.7, 32.5, 31.6, 28.3, 24.7, 19.2, 16.1, 15.7, 14.6, 12.2; HRFABMS: calcd for C₃₃H₄₈NO₇S (M+H) 602.3152, found 602.3141.

Bridged epothilone D 30—A similar procedure was employed to prepare bridged epothilone D (3 mg, 25%) as that described previously for the conversion of **23** to **25**. ¹H NMR (400 MHz, CDCl₃) δ 7.07 (s, 1H), 6.89 (s, 1H), 5.90 (m, 1H), 5.68 (t, *J* = 10.8 Hz, 1H), 5.32 (d, *J* = 4.8 Hz, 1H), 4.78 (d, *J* = 11.2 Hz, 1H), 4.48 (d, *J* = 10.8 Hz, 1H), 4.20 (d, *J* = 11.2 Hz, 1H), 3.46 (br.s, 1H), 3.36 (m, 1H), 3.00 (m, 2H), 2.90 (br.s, 1H), 2.80 (m, 1H), 2.62-2.45 (m, 3H), 2.30 (d, *J* = 15.6 Hz, 1H), 2.17-2.00 (s, 3H), 2.10 (s, 3H), 1.96 (s, 3H), 1.81 (m, 2H), 1.65 (m, 1H), 1.22 (m, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.99 (s, 3H), 0.86 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 221.1, 171.0, 170.4, 169.5, 145.2, 144.3, 137.0, 129.1, 126.6, 125.4, 114.7, 112.8, 74.5, 74.1, 71.3, 66.1, 57.7, 42.8, 39.0, 38.9, 38.4, 38.3, 31.8, 30.4, 29.7, 28.9,

25.9, 17.2, 16.4, 15.2, 13.6; HRFABMS: calcd for $C_{31}H_{44}NO_7S$ (M+H) 574.2838, found 574.2848.

(4R)-4-Allyl-4-demethyl-26-(acryloyloxy)epothilone D 31—Epothilone derivative **31** was prepared (20 mg, 60%) by a similar procedure to that described above for the conversion of **21** to **22**. 1H NMR (400 MHz, $CDCl_3$) δ 6.92 (s, 1H), 6.55 (s, 1H), 6.36 (dd, $J = 17.2, 1.6$ Hz, 1H), 6.09 (dd, $J = 17.2, 10.4$ Hz, 1H), 5.80 (dd, $J = 10.6, 1.2$ Hz, 1H), 5.60 (m, 1H), 5.45 (dd, $J = 10.2, 4.8$ Hz, 1H), 5.27 (d, $J = 8.0$ Hz, 1H), 5.11 (dd, $J = 17.2, 1.6$ Hz, 1H), 5.07 (dd, $J = 10.4, 1.6$ Hz, 1H), 4.58 (d, $J = 12.8$ Hz, 1H), 4.49 (d, $J = 12.8$ Hz, 1H), 4.41 (dd, $J = 11.0, 3.2$ Hz, 1H), 3.64 (d, $J = 5.6$ Hz, 1H), 3.49 (br.s, 1H), 3.19 (qd, $J = 5.6, 1.2$ Hz, 1H), 3.08 (d, $J = 1.6$ Hz, 1H), 2.66 (m, 1H), 2.65 (s, 3H), 2.60–2.42 (m, 3H), 2.38–2.26 (m, 3H), 2.04 (s, 1H), 2.03 (s, 3H), 1.77 (m, 2H), 1.63 (m, 1H), 1.40 (m, 1H), 1.28 (m, 1H), 1.11 (d, $J = 7.2$ Hz, 3H), 1.00 (s, 3H), 0.99 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 219.6, 170.2, 165.9, 151.7, 138.9, 137.0, 133.4, 131.0, 128.4, 125.3, 119.2, 118.9, 115.8, 78.2, 73.3, 71.6, 67.6, 57.7, 41.4, 40.1, 39.6, 37.6, 32.4, 31.5, 28.3, 24.6, 19.0, 16.0, 15.5, 14.6, 12.1; HRFABMS: calcd for $C_{32}H_{46}NO_7S$ (M+H) 588.2995, found 588.3007.

(4R)-4-Allyl-4-demethyl-26-hydroxyepothilone D bis-TBS ether (32)—To a solution of macrolactone **20a** (28 mg, 0.027 mmol) in ether (0.56 mL) at $-5^\circ C$ was added formic acid (0.56 mL) and the reaction was allowed to proceed with stirring for 5 h at $-5^\circ C$. Water (10 mL) and then solid $NaHCO_3$ were sequentially added until cessation of effervescence. The mixture was extracted with ether (10 mL $\times$ 3), the combined organic extracts were dried (Na_2SO_4), and the solvents were removed *in vacuo*. Purification of the crude product *via* preparative thin layer chromatography eluting with 50% ether in hexanes to yield lactone iodide **20b** (15 mg, 71%). $[\alpha]_D -21.6$ (c 0.7, $CHCl_3$); 1H NMR (400 MHz, $CDCl_3$) δ 7.26 (s, 1H), 6.39 (s, 1H), 5.69–5.59 (m, 1H), 5.43 (dd, $J = 9.6, 6.0$ Hz, 1H), 5.17–5.05 (overlap, 1H), 5.10 (d, $J = 10.4$ Hz, 1H), 5.05 (d, $J = 17.2$ Hz, 1H), 4.17 (d, $J = 8.8$ Hz, 1H), 4.09 (br.d, $J = 12.4$ Hz, 1H), 3.96 (d, $J = 13.2$ Hz, 1H), 3.89 (d, $J = 8.8$ Hz, 1H), 3.09–3.05 (m, 1H), 2.75–2.56 (m, 3H), 2.48–2.28 (m, 3H), 2.15–1.92 (m, 2H), 1.88 (s, 3H), 1.76–1.62 (m, 1H), 1.56–1.43 (m, 1H), 1.32–1.15 (m, 7H), 1.12 (d, $J = 6.8$ Hz, 3H), 1.11 (s, 3H), 0.96 (d, $J = 6.8$ Hz, 3H), 0.93 (s, 9H), 0.83 (s, 9H), 0.09 (two singlet, 9H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.0, 170.4, 146.0, 132.9, 118.7, 79.8, 77.7, 74.1, 66.3, 56.7, 40.9, 31.9, 31.1, 29.6, 28.1, 27.1, 26.3, 26.1, 20.5, 18.6, 18.5, -3.3, -3.5, -3.6, -5.3. HRFABMS: calcd for $C_{37}H_{68}O_6Si_2I$ (M+H) 791.3599, found 791.3676. Iodide **20b** was converted to **32** by a similar procedure to that described previously for the conversion of **25** to **27**. 1H NMR (400 MHz, $CDCl_3$) δ 6.93 (s, 1H), 6.51 (s, 1H), 5.58 (m, 1H), 5.43 (m, 1H), 5.00–4.97 (m, 3H), 3.94 (dd, $J = 13.2, 4.4$ Hz, 1H), 4.10–4.05 (m, 2H), 3.86 (dd, $J = 8.4, 4.8$ Hz, 1H), 3.04 (m, 1H), 2.76–2.53 (m, 3H), 2.67 (s, 3H), 2.46–2.20 (m, 3H), 2.18–1.92 (m, 3H), 2.08 (s, 3H), 1.75–1.55 (m, 4H), 1.06 (s, 3H), 0.89 (s, 9H), 1.20–0.74 (m, 7H), 0.77 (s, 9H), 0.03 (s, 9H), -0.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.4, 171.0, 164.8, 152.5, 143.9, 138.5, 133.0, 120.7, 119.6, 118.9, 116.2, 79.5, 74.6, 66.7, 60.7, 57.0, 48.2, 41.0, 39.2, 37.8, 32.6, 31.5, 28.3, 27.4, 26.6, 26.4, 19.6, 19.4, 18.9, 15.5, 14.4, -3.0, -3.25, -3.4, -5.3; HRFABMS: calcd for $C_{41}H_{72}NO_6SSi_2$ (M+H) 762.4619, found 762.4654.

(4R)-4-Allyl-4-demethyl-26-(allyloxy)epothilone D bis-TBS ether 33—To a solution of **32** (20 mg, 0.026 mmol) in THF (1.5 mL) was added sodium hydride (6.3 mg, 60%, 0.158 mmol) at $0^\circ C$, and the resultant mixture was allowed to stir at $25^\circ C$ for 30 min. Allyl iodide (48 μ L, 0.525 mmol) was added to the above reaction mixture, and the reaction was allowed to proceed at $25^\circ C$ for additional 1.5 h. The reaction mixture was filtered off *via* a pad of silica gel eluting with ether to provide crude product, which was subjected to preparative thin layer chromatography over silica gel, eluting with 30% ether in hexanes, to furnish allyl ether **33** (4.84 mg, 23%) and starting material (11 mg, 55%). Compound **33** was obtained as a colorless

oil; ^1H NMR (500 MHz, CDCl_3) δ 6.96 (s, 1H), 6.54 (s, 1H), 5.94–5.85 (m, 1H), 5.66–5.58 (m, 1H), 5.46 (dd, $J = 6.8, 5.5$ Hz, 1H), 5.26 (d, $J = 13.6$ Hz, 1H), 5.17 (d, $J = 8.3$ Hz, 1H), 5.04–5.01 (m, 3H), 4.16–4.08 (m, 1H), 4.04 (d, $J = 9.4$ Hz, 1H), 3.99–3.85 (m, 3H), 3.72 (d, $J = 9.4$ Hz, 1H), 3.10–3.04 (m, 1H), 2.85–2.64 (m, 3H), 2.70 (s, 3H), 2.45–2.31 (m, 3H), 2.19–1.98 (m, 3H), 2.11 (s, 3H), 1.83–1.76 (m, 1H), 1.32–1.02 (m, 2H), 1.11 (d, $J = 6.8$ Hz, 3H), 1.10 (s, 3H), 1.02–0.80 (m, 1H), 0.96 (d, $J = 6.8$ Hz, 3H), 0.95 (s, 9H), 0.82 (s, 9H), 0.10 (s, 3H), 0.07 (s, 6H), -0.15 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 214.8, 171.3, 165.1, 152.9, 138.9, 135.3, 133.4, 124.2, 119.8, 119.2, 117.5, 116.5, 79.8, 77.7, 74.9, 73.9, 71.3, 57.2, 48.7, 41.3, 40.2, 39.8, 37.8, 32.9, 31.8, 30.2, 28.7, 27.6, 26.8, 26.6, 19.7, 19.1, 19.0, 15.8, 0.49, -2.7, -2.96, -3.18, -5.00; HRFABMS: calcd for $\text{C}_{44}\text{H}_{76}\text{NO}_6\text{SSi}_2$ (M+H) 802.4932, found 802.4968.

(4R)-4-Allyl-4-demethyl-26-(allyloxy)epothilone D 34—A similar procedure was employed to prepare **34** (2.39 mg, 83%, colorless oil) as that described previously for the conversion of **20a** to **21**. ^1H NMR (500 MHz, CDCl_3) δ 6.96 (s, 1H), 6.58 (s, 1H), 5.93–5.85 (m, 1H), 5.68–5.59 (m, 1H), 5.43 (dd, $J = 10.4, 4.4$ Hz, 1H), 5.34 (d, $J = 9.9$ Hz, 1H), 5.25 (dt, $J = 17.0, 1.6$ Hz, 1H), 5.16 (br.d, $J = 10.7$ Hz, 1H), 5.13 (br.d, $J = 17.9$ Hz, 1H), 5.10 (br.d, $J = 10.4$ Hz, 1H), 4.44 (d, $J = 10.4$ Hz, 1H), 3.95–3.86 (m, 3H), 3.78 (d, $J = 11.8$ Hz, 1H), 3.66 (m, 2H), 3.21 (q, $J = 6.8$ Hz, 1H), 3.14 (br.s, 1H), 2.73–2.47 (m, 4H), 2.68 (s, 3H), 2.34–2.23 (m, 3H), 2.09–2.03 (m, 1H), 2.06 (s, 3H), 1.83–1.76 (m, 1H), 1.70–1.62 (m, 1H), 1.48–1.37 (m, 2H), 1.32–1.24 (m, 2H), 1.14 (d, $J = 6.6$ Hz, 3H), 1.02 (s, 3H), 1.01 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 218.0, 170.5, 165.4, 152.0, 139.4, 134.9, 133.5, 124.2, 119.3, 119.1, 117.2, 115.8, 78.6, 73.7, 73.4, 71.8, 71.2, 57.9, 41.4, 40.2, 39.8, 37.8, 32.6, 31.8, 28.3, 24.7, 19.2, 16.1, 15.7, 14.7, 12.2; HRFABMS: calcd for $\text{C}_{32}\text{H}_{48}\text{NO}_6\text{S}$ (M+H) 574.3202, found 574.3188.

Bridged epothilone D 35—To a solution of diene **33** (1.1 mg, 0.00137 mmol) in dichloromethane (3 mL) was added second-generation Grubbs catalyst (0.41 mg, 0.00048 mmol, 0.35 eq) in dichloromethane (2 mL) for a period of 1.5 h *via* syringe pump under N_2 . The resulting reaction mixture was allowed to stir for 0.5 h at 25 °C, and then the dichloromethane was removed under reduced pressure. The residue obtained was subjected to preparative thin layer chromatography over silica gel, eluting with 30% ether in hexanes, to furnish **35** (0.84 mg, 79%) as a pale yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 6.88 (s, 1H), 6.46 (s, 1H), 5.62 (br.t, $J = 10.4$ Hz, 1H), 5.56–5.48 (m, 1H), 5.44 (br.s, 1H), 5.29 (d, $J = 4.4$ Hz, 1H), 4.61 (br.s, 2H), 4.49 (br.s, 2H), 4.23 (dd, $J = 10.4, 2.5$ Hz, 1H), 3.73 (d, $J = 6.3$ Hz, 1H), 3.32–3.26 (m, 1H), 3.10–3.04 (m, 1H), 2.71 (s, 3H), 2.70–2.65 (m, 1H), 2.54–2.45 (m, 2H), 2.16–2.03 (m, 4H), 2.15 (s, 3H), 1.70–1.62 (m, 1H), 1.46 (s, 3H), 1.42–1.26 (m, 2H), 1.26 (s, 3H), 1.14–1.02 (m, 1H), 1.07 (d, $J = 6.8$ Hz, 3H), 0.91, 0.87 (each s, 18H), 0.86 (overlap, 3H), 0.174 (s, 3H), 0.170 (s, 3H), 0.05 (s, 3H), 0.02 (s, 3H); HRFABMS: calcd for $\text{C}_{42}\text{H}_{72}\text{NO}_6\text{SSi}_2$ (M+H) 774.4619, found 774.4644.

Bridged epothilone 36—The epothilone D bridged analogue **36** was obtained from bridged epothilone D bis-TBS ether (**35**), according to the procedure described previously for the preparation of **21**, as a colorless oil in 84.5% yield. ^1H NMR (500 MHz, CDCl_3) δ 7.01, 7.00 (s, 1H), 6.67, 6.57 (s, 1H), 5.77–5.70 (m, 1H), 5.62–5.36 (m, 3H), 4.64 (br.s, 2H), 4.53 (br.s, 2H), 4.54–4.0, 4.15–4.11 (m, 1H), 3.65, 3.20 (br.s, 1H), 3.55, 3.39 (d, $J = 9.5$ Hz, 1H), 3.40–3.31 (m, 2H), 3.10–3.04 (m, ~0.5 H), 2.93 (br.d, $J = 13.5$ Hz, ~0.5H), 2.78, 2.71 (br.s, 1H), 2.74 (s, 3H), 2.75–2.46 (m, 3H), 2.25–2.06 (m, 3H), 2.15 (s, 3H), 1.85–1.80 (m, 1H), 1.51–1.40 (m, 4H), 1.26, 1.16 (s, 3H), 1.20, 1.11 (d, $J = 6.5$ Hz, 3H), 0.89, 0.86 (d, $J = 7.5$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 218.0, 170.2, 165.4, 152.3, 140.7, 132.0, 125.8, 119.2, 118.9, 116.6, 116.3, 77.4, 77.2, 76.2, 73.2, 72.6, 58.4, 44.3, 41.2, 35.6, 33.0, 32.8, 27.7, 25.0, 19.4, 16.9, 15.9, 15.79, 15.70; HRFABMS: calcd for $\text{C}_{30}\text{H}_{44}\text{NO}_6\text{S}$ (M+H) 546.2889, found 546.2914.

Methyl (R)-2-((S)-1-hydroxy-3-(*t*-butyl-dimethylsilyloxy) propyl)-2-methylpen-4-enoate **37**—A solution of LDA (~0.6 M, 69.7 mmol, 2.6 eq) in THF was added to a solution of **14b** (7.02 g, 26.8 mmol) in THF (55 mL) at -78 °C, and the resulting solution was allowed to warm to -20 °C and stir for 30 min at -20 °C. Methyl iodide (2.5 mL, 40.2 mmol, 1.5 eq) in HMPA (13 mL, 75.04 mmol, 1.08 eq to LDA) was added to the above reaction mixture that was recooled to -78 °C. The subsequent reaction mixture was warmed to -20 °C and the reaction was allowed to proceed at -20 °C with stirring for 1 h prior to being quenched by the addition of saturated NH₄Cl solution (200 mL). The two layers were separated and aqueous phase was extracted with ether (100 × 3). The combined organic extracts were washed with water and brine, the organic fraction was dried over anhydrous Na₂SO₄, and the solvents were removed under reduced pressure to give the crude mass. Purification of the product by silica gel column chromatography eluting with 10% ethyl acetate in hexanes yielded methyl-2-(*R*)-methyl-3-(*S*)-hydroxy-5-*O*-*t*-butyldimethylsilyloxy pentanoate (3.5 g, 47%). ¹H NMR (400 MHz, CDCl₃) δ 3.91-3.70 (m, 2H), 3.70-3.50 (m, 2H), 3.66 (s, 3H), 2.59-2.48 (m, 1H), 1.71-1.55 (m, 2H), 1.11 (d, *J* = 7.2 Hz, 3H), 0.84 (s, 9H), 0.02 (s, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 176.0, 73.0, 62.1, 51.8, 45.7, 35.8, 26.0, 18.3, 13.6, -5.34, -5.35. HRFABMS: calcd for C₁₃H₂₉O₄Si (M+H) 277.1835, found 277.1818.

To a freshly prepared solution of LDA (0.6 M, 27.3 mmol, 2.6 eq) in THF (50 mL), a solution of methyl-2-methyl-3-hydroxy-5-*O*-*t*-butyldimethylsilyloxy pentanoate, obtained from the above reaction, (2.90 g, 10.51 mmol) in THF (20 mL) was added at -78 °C, and the resulting solution was warmed to -20 °C and stirred for 2 h at that temperature. Then a solution of allyl iodide (1.45 mL, 15.76 mmol, 1.5 eq) in HMPA (29.53 mmol, 1.08 eq to LDA) was added to the above reaction mixture that was re-cooled to -78 °C. The subsequent reaction mixture was re-warmed to -20 °C and allowed to stir at that temperature for 2 h. The reaction was quenched by the addition of saturated ammonium chloride (150 mL). The two layers were separated and aqueous phase was re-extracted with ether (100 mL × 3). The combined organic phases were washed with water and brine, the organic fraction was dried (Na₂SO₄), and the solvents were removed under reduced pressure. The crude oil obtained was subjected to silica gel column chromatography using 10% ethyl acetate in hexanes as eluent to provide **37** (2.07 g, 62.3% yield): ¹H NMR (400 MHz, CDCl₃) δ 5.75-5.64 (m, 1H), 5.05 (d, *J* = 18.4 Hz, 1H), 5.03 (d, *J* = 10.0 Hz, 1H), 3.92 (d, *J* = 10.4, 1H), 3.88-3.79 (m, 2H), 3.68 (s, 3H), 3.32 (br.s, 1H), 2.43 (dd, *J* = 13.6, 7.2 Hz, 1H), 2.18 (dd, *J* = 13.6, 7.6 Hz, 1H), 1.68-1.48 (m, 2H), 1.13 (s, 3H), 0.88 (s, 9H), 0.05 (s, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 176.8, 133.8, 118.4, 75.4, 62.4, 52.0, 51.2, 40.6, 33.7, 26.1, 18.4, 17.0, -5.2.

(R)-2-((S)-1,3-bis(*tert*-butyldimethylsilyloxy)propyl)-2-methylpen-4-en-1-ol (38**)**

—To a solution of **37** (2.35 g, 7.43 mmol) in dichloromethane (37 mL) was added 2,6-lutidine (1.38 mL, 11.90 mmol, 1.6 eq) and TBSOTf (2.58 mL, 11.15 mmol, 1.5 eq) at -78 °C and the resulting reaction mixture was allowed to warm to -20 °C over 6 h. Saturated ammonium chloride (60 mL) was added to quench the reaction. The organic layer was separated and the aqueous phase was re-extracted with dichloromethane (30 mL × 3). The combined dichloromethane phase was dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure. The crude product obtained was subjected to silica gel chromatography eluting with 5% ether in hexanes to furnish methyl (S)-2-((S)-1,3-bis(*tert*-butyldimethylsilyloxy) propyl)-2-methylpen-4-enoate (3.08 g, 96%). ¹H NMR (400 MHz, CDCl₃) δ 5.78-5.60 (m, 1H), 5.00 (d, *J* = 18.0 Hz, 1H), 4.99 (d, *J* = 12.0 Hz, 1H), 4.11 (dd, *J* = 8.0, 2.8 Hz, 1H), 3.72-3.56 (m, 2H), 3.61 (s, 3H), 2.37 (dd, *J* = 16.5, 8.5 Hz, 1H), 2.08-2.02 (m, 1H), 1.78-1.64 (m, 1H), 1.59-1.50 (m, 1H), 1.12 (s, 3H), 0.90 (s, 9H), 0.85 (s, 9H), 0.07 (s, 3H), 0.04 (s, 6H), -0.006 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 176.2, 134.3, 117.9, 73.9, 60.5, 52.7, 51.6, 40.5, 36.4, 26.1, 18.5, 18.4, 16.4, -3.7, -4.3, -5.0.

A solution of DIBAL-H (1 M, 25 mmol, 3.5 eq) was added dropwise to a solution of methyl (S)-2-((S)-1,3-bis(tert-butyldimethylsilyloxy) propyl)-2-methylpent-4-enoate (3.08 g, 7.16 mmol), obtained from the above reaction, in dichloromethane (72 mL) at -78 °C. The reaction was allowed to proceed at -78 °C with stirring for 1 h. Methanol (8 mL) was added and the solution was allowed to warm to 25 °C. Then a saturated solution of sodium/potassium tartrates (80 mL) was added to the mixture, which was stirred at 25 °C until the two layers were clearly separated. The organic layer was separated and the aqueous phase was re-extracted with dichloromethane (50 mL × 3). The combined organic extracts were dried over anhydrous Na₂SO₄, and the solvents were evaporated under reduced pressure. Purification of the crude product obtained by silica gel column chromatography with 3 % EtOAc in hexanes as eluent to yield **38** (2.66 g, 92%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 5.89-5.80 (m, 1H), 5.08 (d, *J* = 16.8 Hz, 1H), 5.06 (d, *J* = 10.1 Hz, 1H), 3.77-3.60 (m, 4H), 4.33 (dd, *J* = 11.2, 8.5 Hz, 1H), 3.03 (dd, *J* = 8.0, 3.3 Hz, 1H), 2.38 (dd, *J* = 13.7, 7.7 Hz, 1H), 2.06 (dd, *J* = 13.5, 7.4 Hz, 1H), 1.98-1.90 (m, 1H), 1.70-1.62 (m, 1H), 0.88 (s, 18H), 0.71 (s, 3H), 0.10 (s, 6H), 0.04 (s, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 135.0, 117.6, 76.4, 67.5, 60.7, 42.0, 39.2, 36.3, 26.1, 25.9, 18.7, 18.3, -4.2, -5.21, -5.24.

(S)-4-((S)-1,3-bis(tert-butyldimethylsilyloxy)propyl)-4-methylhept-6-en-3-one (39)—To a solution of **38** (2.64 g, 6.57 mmol) in a 1:1 mixture of CH₂Cl₂ and DMSO (66 mL), was added triethylamine (4.6 mL, 32.8 mmol, 5eq) followed by SO₃·Py (5.22 g, 32.8 mmol, 5 eq) at 0 °C and the resulting reaction mixture was stirred for 30 min. The reaction was quenched by the addition of saturated NH₄Cl solution (100 mL). Organic layer was separated and the aqueous phase was extracted with ethyl ether (50 mL × 3). The combined organic phases were dried over anhydrous Na₂SO₄, and the solvents were removed under reduced pressure. The crude product was purified via silica gel column chromatography eluting with 5 % ethyl acetate in hexanes to yield (S)-2-((S)-1,3-bis(tert-butyldimethylsilyloxy)propyl)-2-methylpent-4-enal (2.47 g, 94%). ¹H NMR (400 MHz, CDCl₃) δ 9.54 (s, 1H), 5.65-5.55 (m, 1H), 5.00 (d, *J* = 17.2 Hz, 1H), 4.98 (d, *J* = 13.6 Hz, 1H), 4.02 (dd, *J* = 7.6, 2.8 Hz, 1H), 3.64-3.59 (m, 2H), 2.38 (dd, *J* = 14.0, 6.8 Hz, 1H), 2.10 (dd, *J* = 14.4, 8.0 Hz, 1H), 1.76-1.71 (m, 1H), 1.58-1.53 (m, 1H), 0.97 (s, 3H), 0.85 (s, 9H), 0.82 (s, 9H), 0.03 (s, 3H), 0.005 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 206.3, 132.9, 118.3, 72.3, 59.5, 54.2, 37.9, 36.1, 25.9, 25.8, 18.2, 18.1, 14.2, -3.9, -4.3, -5.3.

To a solution of (S)-2-((S)-1,3-bis(tert-butyldimethylsilyloxy)propyl)-2-methylpent-4-enal (1.55 g, 3.87 mmol), obtained from the above reaction, in THF (39 mL) was added ethyl magnesium bromide (1 M, 11.6 mL, 11.6 mmol, 2.5 eq) at 0 °C and the resulting reaction mixture was allowed to stir at 0 °C for 20 min. Saturated NH₄Cl solution (100 mL) was added to quench the reaction. Organic layer was separated and the aqueous phase was re-extracted with dichloromethane (50 mL × 3). The organic extracts were combined and dried over anhydrous Na₂SO₄, and the solvents were removed under reduced pressure. The crude product obtained was purified via silica gel column chromatography eluting with 3 % ether in hexanes and 10 % ethyl acetate in hexanes to produce the product as a diastereomeric mixture (9:1) (660 mg, 39%), together with alcohol **38** (480 mg, 31%) as an undesired byproduct (31%) and starting material (420 mg, 27%). The diastereomeric mixture of (4R)-4-((S)-1,3-bis(tert-butyldimethylsilyloxy)propyl)-4-methylhept-6-en-3-ol was subjected to the next reaction without further purification.

To a solution of (4R)-4-((S)-1,3-bis(tert-butyldimethylsilyloxy)propyl)-4-methylhept-6-en-3-ol (1.6 g, 3.72 mmol) in a 1:1 mixture of CH₂Cl₂ and DMSO (38 mL), was added triethylamine (2.60 mL, 18.6 mmol, 5 eq) followed by SO₃·Py complex (2.96 g, 18.6 mmol, 5 eq) at 0 °C. The reaction was allowed to proceed at 0 °C with stirring for 2 h prior to being quenched by the addition of saturated NH₄Cl solution (60 mL). Organic layer was separated and the aqueous phase was extracted with ethyl ether (30 mL × 3). The combined organic extracts were washed

with brine and dried over anhydrous Na_2SO_4 , and the solvent was removed under reduced pressure to give crude product, which was purified via silica gel chromatography eluting with 2 % ether in hexanes to give **39** (1.05 g, 63%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 5.65-5.50 (m, 1H), 4.99 (d, J = 16.4 Hz, 1H), 4.98 (d, J = 10.8 Hz, 1H), 4.05 (dd, J = 7.6, 2.4 Hz, 1H), 3.70-3.52 (m, 2H), 2.56-2.36 (m, 3H), 2.00 (q, J = 6.8 Hz, 1H), 1.72-1.60 (m, 1H), 1.49-1.42 (m, 1H), 1.10 (s, 3H), 0.96 (t, J = 6.8 Hz, 3H), 0.87 (s, 9H), 0.86 (s, 9H), 0.08 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), 0.005 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 215.0, 134.3, 117.9, 74.2, 60.2, 56.5, 40.3, 36.8, 33.4, 26.2, 26.1, 18.5, 18.4, 17.4, 7.6, -3.92, -3.96, -5.10. HRFABMS: calcd for $\text{C}_{23}\text{H}_{49}\text{O}_3\text{Si}_2$ (M+H) 429.3220, found 429.3194.

Aldol product 40—The 4*S*, 6*S*, 7*R* aldol product **40** was obtained from the aldol reaction of ketone **39** and aldehyde **11**, according to the procedure described previously for the synthesis of aldol product **18**, as a major product (680 mg, 46%, colorless oil), together with other two minor products (28% total yield for both). Compound **40**: ^1H NMR (500 MHz, CDCl_3) δ 7.45 (d, J = 7.1 Hz, 6H), 7.27 (t, J = 7.1 Hz, 6H), 7.20 (t, J = 7.1 Hz, 3H), 6.89 (s, 1H), 6.50 (s, 1H), 5.62-5.53 (m, 2H), 4.99 (d, J = 10.4 Hz, 1H), 4.98 (d, J = 16.4 Hz, 1H), 4.17 (t, J = 6.8 Hz, 1H), 3.68-3.59 (m, 3H), 3.47 (br.s, 2H), 3.33 (d, J = 8.2 Hz, 1H), 3.13 (q, J = 6.9 Hz, 1H), 2.69 (s, 3H), 2.43-2.31 (m, 3H), 2.13 (dd, J = 14.0, 7.7 Hz, 1H), 2.03-1.99 (m, 1H), 2.03 (s, 3H), 1.82-1.78 (m, 1H), 1.66-1.60 (m, 1H), 1.54-1.38 (m, 2H), 1.15 (s, 3H), 1.00 (d, J = 6.9 Hz, 3H), 0.90 (s, 9H), 0.89-0.87 (overlap, 21H), 0.12 (s, 3H), 0.10 (s, 3H), 0.036 (s, 3H), 0.030 (s, 3H), 0.027 (s, 3H), 0.024 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 220.5, 164.4, 153.2, 144.4, 142.4, 138.1, 133.9, 128.7, 127.7, 126.9, 122.9, 118.9, 118.1, 115.2, 86.6, 78.7, 74.9, 72.1, 67.4, 60.1, 57.8, 41.6, 39.2, 36.9, 35.4, 35.2, 32.9, 29.0, 26.2, 26.0, 25.9, 19.2, 18.5, 18.4, 18.35, 18.32, 15.5, 14.1, 10.2, -3.5, -4.0, -4.5, -4.7, -5.1; HRFABMS: calcd for $\text{C}_{66}\text{H}_{104}\text{NO}_6\text{SSi}_3$ (M+Na) 1122.6892, found 1122.6927.

Tetrakis-[tert-butyldimethylsilyl]-ether 41a—4*S*, 6*S*, 7*R* tetrakis-TBS ether **41a** was prepared (510 mg, 94%) as a colorless oil by a silimar procedure to that described above for the conversion of **18** to **19a**. ^1H NMR (500 MHz, CDCl_3) δ 7.43 (d, J = 8.0 Hz, 6H), 7.25 (t, J = 8.2 Hz, 6H), 7.21 (t, J = 7.4 Hz, 3H), 6.89 (s, 1H), 6.50 (s, 1H), 5.62-5.54 (m, 2H), 4.92 (d, J = 17.0 Hz, 1H), 4.87 (d, J = 10.1 Hz, 1H), 4.18 (t, J = 6.9 Hz, 1H), 4.10 (d, J = 8.8 Hz, 1H), 3.74 (d, J = 7.4 Hz, 1H), 3.66-3.58 (m, 2H), 3.46, 3.42 (ABq, J = 11.8 Hz, 2H), 3.05-2.98 (m, 1H), 2.69 (s, 3H), 2.48-2.27 (m, 3H), 2.99 (dd, J = 14.3, 7.7 Hz, 1H), 2.04 (s, 3H), 2.03-1.95 (m, 1H), 1.91-1.82 (m, 1H), 1.74-1.69 (m, 1H), 1.62-1.46 (m, 4H), 1.19-1.11 (m, 2H), 1.01 (d, J = 6.9 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.83 (s, 18H), 0.73 (d, J = 6.8 Hz, 3H), 0.11 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.038 (s, 3H), 0.031 (s, 3H), 0.026 (s, 3H), -0.02 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 215.8, 164.3, 153.3, 144.4, 142.4, 138.1, 134.8, 128.7, 127.7, 126.8, 122.5, 118.8, 117.4, 115.2, 86.5, 78.7, 76.9, 71.7, 67.3, 60.1, 57.5, 45.2, 38.3, 36.9, 36.2, 35.2, 35.1, 34.7, 31.6, 29.0, 26.6, 26.3, 26.2, 26.0, 25.9, 22.7, 20.7, 19.9, 19.2, 18.66, 18.60, 18.38, 18.31, 16.2, 14.2, 14.0, 13.5, 11.5, -3.2, -3.3, -3.6, -3.9, -4.5, -4.7, -4.9, -5.0; HRFABMS: calcd for $\text{C}_{72}\text{H}_{118}\text{NO}_6\text{SSi}_4$ (M+H) 1236.7757, found 1236.7793.

Tris-[tert-butyldimethylsilyl]-ether 41b—4*S*, 6*S*, 7*R* tris-TBS ether **41b** was prepared (390 mg, 87%) as a colorless oil from tetrakis-TBS ether **41a** using a silimar procedure as described previously for the conversion of **19a** to **19b**. ^1H NMR (500 MHz, CDCl_3) δ 7.43 (d, J = 7.9 Hz, 6H), 7.28-7.22 (m, 6H), 7.19 (t, J = 7.9 Hz, 3H), 6.88 (s, 1H), 6.49 (s, 1H), 5.64-5.52 (m, 2H), 4.94 (d, J = 17.0 Hz, 1H), 4.89 (d, J = 10.1 Hz, 1H), 4.17 (t, J = 5.5 Hz, 1H), 4.11 (d, J = 8.0 Hz, 1H), 3.74 (d, J = 7.4 Hz, 1H), 3.73-3.58 (m, 2H), 3.45, 3.41 (ABq, J = 11.8 Hz, 2H), 3.06-3.00 (m, 1H), 2.68 (s, 3H), 2.41-2.27 (m, 3H), 2.15 (dd, J = 14.3, 7.1 Hz, 1H), 2.03 (s, 3H), 2.00-1.94 (m, 3H), 1.72-1.52 (m, 4H), 1.18 (s, 3H), 1.15-1.05 (m, 3H), 1.00 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.86 (s, 9H), 0.73 (d, J = 6.4 Hz, 3H), 0.11

(s, 3H), 0.08 (s, 3H), 0.03 (s, 3H), 0.028 (s, 3H), 0.022 (s, 3H), -0.03 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 216.1, 164.3, 153.2, 144.4, 142.5, 138.1, 134.4, 128.7, 127.7, 126.8, 122.5, 118.8, 117.6, 115.1, 86.5, 78.7, 71.7, 67.4, 59.9, 57.2, 45.2, 38.4, 37.2, 36.2, 35.2, 35.1, 29.0, 26.6, 26.3, 26.2, 25.9, 19.8, 19.2, 18.6, 18.5, 18.3, 16.1, 14.1, 13.6, -3.3, -3.6, -4.1, -4.5, -4.7; HRFABMS: calcd for $\text{C}_{66}\text{H}_{104}\text{NO}_6\text{SSi}_3$ (M+H) 1122.6892, found 1122.6949.

Oxidation of 41b to aldehyde 41c—A similar procedure was employed to prepare aldehyde **41c** (353.5 mg, 90%, colorless oil) as that described previously for the conversion of **19b** to **19c**. ^1H NMR (500 MHz, CDCl_3) δ 9.76 (s, 1H), 7.42 (d, J = 7.1 Hz, 6H), 7.25 (t, J = 7.1 Hz, 6H), 7.17 (t, J = 7.1 Hz, 3H), 6.88 (s, 1H), 6.50 (s, 1H), 5.59 (t, J = 7.1 Hz, 1H), 5.57-5.48 (m, 1H), 4.93 (d, J = 14.8 Hz, 1H), 4.91 (d, J = 8.2 Hz, 1H), 4.64 (dd, J = 6.0, 3.8 Hz, 1H), 4.18 (t, J = 6.6 Hz, 1H), 3.74 (d, J = 7.7 Hz, 1H), 3.45, 3.41 (ABq, J = 11.5 Hz, 2H), 3.05-2.97 (m, 1H), 2.69 (s, 3H), 2.56-2.50 (m, 2H), 2.38-2.25 (m, 3H), 2.14 (dd, J = 14.5, 6.6 Hz, 1H), 2.03 (s, 3H), 1.99-1.93 (m, 1H), 1.21 (s, 3H), 1.15-0.98 (m, 4H), 0.96 (d, J = 6.8 Hz, 3H), 0.88 (s, 9H), 0.86 (s, 9H), 0.84 (s, 9H), 0.72 (d, J = 6.3 Hz, 3H), 0.11 (s, 3H), 0.06 (s, 3H), 0.027 (s, 6H), 0.021 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 215.6, 201.3, 164.3, 153.3, 144.4, 142.4, 138.1, 133.4, 128.7, 127.7, 126.8, 122.6, 118.9, 118.3, 115.2, 86.5, 78.7, 76.6, 69.3, 67.4, 56.9, 47.9, 45.3, 38.4, 37.6, 35.19, 35.15, 29.0, 26.6, 26.3, 26.0, 25.9, 19.2, 19.0, 18.6, 18.3, 16.0, 14.1, 13.5, -3.3, -3.6, -4.1, -4.2, -4.5, -4.7; HRFABMS: calcd for $\text{C}_{66}\text{H}_{100}\text{NO}_6\text{SSi}_3$ (M-H) 1118.6579, found 1118.6549.

Hydroxy acid 41d—A similar procedure was employed to prepare hydroxy acid **41d** (300 mg, 91% for two steps, colorless oil) from aldehyde **41c** as previously described for the conversion of **19c** to **19e**. ^1H NMR (500 MHz, CDCl_3) δ 7.42 (d, J = 7.4 Hz, 6H), 7.21 (t, J = 7.4 Hz, 6H), 7.19 (t, J = 7.4 Hz, 3H), 6.91 (s, 1H), 6.60 (s, 1H), 5.69-5.57 (m, 1H), 5.56 (t, J = 7.1 Hz, 1H), 4.97 (d, J = 18.6 Hz, 1H), 4.94 (d, J = 10.4 Hz, 1H), 4.48 (dd, J = 7.4, 2.2 Hz, 1H), 4.18 (t, J = 6.6 Hz, 1H), 3.76 (d, J = 7.1 Hz, 1H), 3.53, 3.49 (ABq, J = 12.1 Hz, 2H), 3.15-3.09 (m, 1H), 2.71 (s, 3H), 2.47-2.29 (m, 4H), 2.23-2.15 (m, 1H), 2.03 (s, 3H), 2.05-1.99 (m, 1H), 1.16 (s, 3H), 1.02 (d, J = 6.9 Hz, 3H), 0.87 (s, 9H), 0.86 (s, 9H), 0.76 (d, J = 6.6 Hz, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), -0.02 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 216.9, 175.6, 165.2, 152.5, 144.3, 142.1, 140.3, 134.1, 128.7, 127.8, 126.9, 121.5, 118.6, 117.9, 115.3, 86.8, 77.0, 76.6, 72.5, 67.5, 57.1, 45.9, 39.2, 38.7, 37.1, 35.3, 33.9, 28.9, 26.7, 26.3, 26.1, 19.9, 18.8, 18.6, 18.3, 16.2, 14.8, 13.6, -3.4, -3.6, -4.1, -4.5. HRFABMS: calcd for $\text{C}_{60}\text{H}_{88}\text{NO}_7\text{SSi}_2$ (M+H) 1022.5820, found 1022.5824.

Macrolactone 42—4*S*, 6*S*, 7*R* macrolactone **42** was prepared (135 mg, 46.6%) as a colorless oil from hydroxy acid **41d** by a similar procedure as described previously for the synthesis of macrolactone **20a**. ^1H NMR (500 MHz, CDCl_3) δ 7.43-7.38 (m, 6H), 7.26-7.13 (m, 9H), 6.83 (s, 1H), 6.38 (s, 1H), 5.73-5.60 (m, 1H), 5.59 (t, J = 7.6 Hz, 1H), 5.22 (br.s, 1H), 5.08 (d, J = 14.0 Hz, 1H), 5.07 (d, J = 7.9 Hz, 1H), 4.17 (br.d, J = 7.4 Hz, 1H), 3.90 (br.s, 1H), 3.48, 3.40 (ABq, 2H), 2.70-2.64 (m, 1H), 2.68 (s, 3H), 2.58-2.45 (m, 3H), 2.25-2.12 (m, 2H), 2.18 (s, 3H), 1.76-1.70 (m, 1H), 1.55-1.45 (m, 1H), 1.38-1.32 (m, 2H), 1.05 (d, J = 6.8 Hz, 3H), 0.95 (s, 3H), 0.86 (s, 18 H), 0.79 (d, J = 6.8 Hz, 3H), 0.17 (s, 3H), 0.15 (s, 3H), 0.03 (s, 3H), -0.12 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 220.1, 170.4, 164.4, 152.7, 144.3, 140.4, 136.8, 134.1, 129.1, 127.8, 126.9, 119.1, 118.9, 118.0, 116.4, 86.7, 75.0, 73.6, 67.6, 60.4, 56.5, 48.6, 42.3, 40.0, 38.8, 34.8, 31.0, 29.7, 28.5, 28.0, 26.4, 19.3, 18.8, 18.7, 16.1, 15.9, -3.5, -3.9, -4.5, -4.7. HRFABMS: calcd for $\text{C}_{60}\text{H}_{86}\text{NO}_6\text{SSi}_2$ (M+H) 1004.5714, found 1004.5754.

Primary Alcohol 43—To a solution of macrolactone **42** (132.5 mg, 0.13 mmol) in ether (3 mL) at -5 °C was added formic acid (3 mL) and the reaction was allowed to proceed with stirring for 5 h at -5 °C. Water (20 mL) and then solid NaHCO_3 were sequentially added until cessation of effervescence. The mixture was extracted with ether (20 mL $\times$ 3), the combined

organic extracts were dried (Na_2SO_4), and the solvents were removed in vacuo. Purification of the crude product via preparative thin layer chromatography eluting with 50% ether in hexanes to yield primary alcohol **43** (62 mg, 62%) as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 6.95 (s, 1H), 6.33 (s, 1H), 5.74-5.64 (m, 1H), 5.33 (t, $J = 7.6$ Hz, 1H), 5.17 (br.s, 1H), 5.07 (d, $J = 17.6$ Hz, 1H), 5.06 (d, $J = 9.6$ Hz, 1H), 4.17 (d, $J = 8.8$ Hz, 1H), 4.05-3.91 (m, 2H), 3.98 (br.s, 2H), 3.46-3.36 (m, 1H), 2.72-2.62 (m, 2H), 2.68 (s, 3H), 2.51-2.40 (m, 5H), 2.25-2.19 (m, 2H), 2.09 (s, 3H), 1.92-1.72 (m, 2H), 1.15-1.00 (m, 2H), 1.06 (d, $J = 7.2$ Hz, 3H), 0.95 (s, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.87 (d, $J = 6.0$ Hz, 3H), 0.19 (s, 3H), 0.15 (s, 3H), 0.11 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 214.4, 170.5, 164.7, 152.6, 143.0, 136.7, 134.2, 119.9, 119.4, 118.1, 116.2, 78.5, 75.0, 73.8, 67.5, 56.6, 48.7, 42.3, 40.3, 38.7, 35.0, 30.9, 28.2, 26.5, 26.4, 19.4, 18.9, 18.7, 16.2, 16.1, 14.3, -3.4, -3.8, -4.2, -4.6. HRFABMS: calcd for $\text{C}_{41}\text{H}_{72}\text{NO}_6\text{SSi}_2$ (M+H) 762.4619, found 762.4601.

(4S)-4-Allyl-4-demethyl-26-(allyloxy)-6S,7R-epothilone D bis-TBS ether (44)—

Allyl ether **44** was synthesized as a colorless oil (4.0 mg, 19%), as well as 55% starting material was recovered, from primary alcohol **43** following the procedure described previously for the synthesis of allyl ether **33**. ^1H NMR (400 MHz, CDCl_3) δ 6.96 (s, 1H), 6.33 (s, 1H), 5.91-5.82 (m, 1H), 5.75-5.62 (m, 1H), 5.35 (t, $J = 8.8$ Hz, 1H), 5.24-5.06 (m, 4H), 4.17 (d, $J = 8.8$ Hz, 1H), 3.99 (d, $J = 2.8$ Hz, 1H), 3.93-3.83 (m, 2H), 3.79 (d, $J = 11.6$ Hz, 1H), 3.47-3.35 (m, 1H), 2.70 (s, 3H), 2.65 (t, $J = 6.8$ Hz, 1H), 2.59-2.41 (m, 3H), 2.55-2.19 (m, 1H), 2.12 (s, 3H), 1.98-1.88 (m, 1H), 1.55-1.42 (m, 4H), 1.28-1.24 (m, 2H), 1.07 (d, $J = 7.2$ Hz, 3H), 0.96 (s, 3H), 0.92 (s, 9H), 0.90 (s, 9H), 0.88 (d, $J = 6.4$ Hz, 3H), 0.20 (s, 3H), 0.16 (s, 3H), 0.12 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 214.8, 170.5, 164.7, 152.7, 140.2, 136.7, 135.1, 134.1, 134.2, 122.2, 119.2, 118.1, 117.0, 116.3, 77.4, 75.0, 74.8, 73.8, 70.9, 56.6, 48.7, 42.4, 40.2, 38.9, 34.9, 31.1, 29.9, 28.2, 28.1, 26.5, 26.4, 19.4, 18.9, 18.8, 16.1, 14.3, -3.3, -3.8, -4.2, -4.6; HRFABMS: calcd for $\text{C}_{44}\text{H}_{76}\text{NO}_6\text{SSi}_2$ (M+H) 802.4932, found 802.4903.

(4S)-4-Allyl-4-demethyl-26-(allyloxy)-6S,7R-epothilone D 45—A similar procedure was employed to prepare **45** (0.65 mg, 29%, colorless oil), together with 64% mono-TBS ether, from **44** as that described for the conversion of **20a** to **21**. ^1H NMR (500 MHz, CDCl_3) δ 6.97 (s, 1H), 6.51 (s, 1H), 5.95-5.86 (m, 1H), 5.64-5.57 (m, 2H), 5.47 (dd, $J = 9.9, 3.5$ Hz, 1H), 5.28 (dd, $J = 17.0, 1.6$ Hz, 1H), 5.19 (dd, $J = 10.4, 1.6$ Hz, 1H), 5.12 (d, $J = 11.5$ Hz, 1H), 5.11 (d, $J = 15.4$ Hz, 1H), 4.16 (br.d, $J = 11.0$ Hz, 1H), 3.96-3.94 (m, 2H), 3.91, 3.82 (ABq, $J = 11.8$ Hz, 2H), 3.58-3.50 (m, 2H), 3.31 (br.s, 1H), 2.92 (d, $J = 3.6$ Hz, 1H), 2.74-2.63 (m, 2H), 2.70 (s, 3H), 2.57 (dd, $J = 16.2, 1.9$ Hz, 1H), 2.48-2.20 (m, 4H), 2.09-2.00 (m, 2H), 2.08 (s, 3H), 1.49-1.38 (m, 2H), 1.09 (d, $J = 6.9$ Hz, 3H), 1.02 (d, $J = 6.6$ Hz, 3H), 0.95 (s, 3H), 0.95-0.82 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 222.0, 170.9, 165.1, 152.1, 138.7, 134.8, 132.5, 123.9, 120.3, 119.3, 117.0, 116.6, 78.4, 74.7, 73.1, 72.0, 71.1, 56.1, 42.4, 39.3, 38.6, 35.6, 33.3, 32.5, 29.7, 28.3, 24.2, 19.5, 16.4, 16.0, 15.6, 11.7; HRFABMS: calcd for $\text{C}_{32}\text{H}_{48}\text{NO}_6\text{S}$ (M+H) 574.3202, found 574.3223.

4S, 6S, 7R-Bridged epothilone D bis-TBS ether 46—Bridged analogue **46** was prepared as a colorless oil (2.4 mg, 71%) via ring closing metathesis reaction with second-generation Grubbs catalyst from terminal diene **44**, according to the procedure described previously for the synthesis of bridged compound **35**. ^1H NMR (400 MHz, CDCl_3) δ 6.92 (s, 1H), 6.50 (s, 1H), 5.43 (br.s, 1H), 5.50-5.32 (m, 2H), 5.29 (d, $J = 5.2$ Hz, 1H), 4.75 (dd, $J = 11.2, 4.4$ Hz, 1H), 4.61 (br.s, 2H), 4.48 (br.s, 2H), 3.93 (d, $J = 9.6$ Hz, 1H), 3.13-2.98 (m, 2H), 2.72 (s, 3H), 2.66 (dd, $J = 14.0, 4.0$ Hz, 1H), 2.45, 2.42 (ABq, $J = 11.2$ Hz, 2H), 2.20 (dd, $J = 16.0, 12.0$ Hz, 1H), 2.13 (s, 3H), 2.16-1.99 (m, 2H), 1.79-1.72 (m, 1H), 1.44 (s, 3H), 1.46-1.10 (m, 2H), 1.25 (s, 3H), 0.99 (d, $J = 7.2$ Hz, 3H), 0.90, 0.83 (each s, 18H), 0.80 (d, $J = 6.8$ Hz, 3H), 0.18 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 213.4, 169.9, 165.0, 152.9, 140.5, 135.7, 129.5, 124.2, 119.2, 119.1, 116.5, 77.4, 76.2, 74.7,

70.8, 57.0, 45.2, 40.8, 38.0, 35.3, 32.5, 29.9, 27.3, 26.4, 26.0, 19.5, 18.8, 18.2, 17.4, 16.7, 15.6, 13.0, -3.10, -3.31, -4.00, -5.28; HRFABMS: calcd for $C_{42}H_{72}NO_6SSi_2$ (M+H) 774.4619, found 774.4568.

Bridged epothilone 47—A similar procedure was used to prepare **47** (1.16 mg, 71.6%, colorless oil) from bis-TBS ether **46** based on the previously described method for the conversion of **20** to **21**. 1H NMR (500 MHz, CD_3CN) δ 7.17, 7.15 (s, 1H), 6.61, 6.55 (s, 1H), 5.65-5.27 (m, 4H), 4.62 (dd, J = 10.5, 4.0 Hz, 1H), 4.51 (br.s, 2H), 4.42 (br.s, 2H), 3.60-3.54, 3.40-3.35 (m, 2H), 3.32-3.28, 3.21-3.13 (m, 1H), 2.98-2.92 (m, 1H), 2.76 (dd, J = 10.5, 4.0 Hz, 1H), 2.66 (s, 3H), 2.56, 2.52; 2.41, 2.38 (ABq, J = 11.5 Hz, 2H), 2.27-2.05 (m, 4H), 2.15 (s, 3H), 1.58-1.36 (m, 6H), 1.27, 1.22 (s, 3H), 1.05, 1.04 (d, J = 7.0 Hz, 3H), 0.92, 0.86 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 218.6, 169.7, 165.0, 152.6, 140.7, 135.3, 129.3, 124.3, 119.0, 118.6, 116.7, 76.4, 75.4, 74.6, 74.2, 68.8, 56.8, 42.8, 39.2, 35.4, 33.3, 33.1, 26.9, 26.4, 24.7, 18.3, 16.3, 15.9, 13.5, 12.5; HRFABMS: calcd for $C_{30}H_{44}NO_6S$ (M+H) 546.2889, found 546.2908.

(4S)-4-Allyl-4-demethyl-26-(acryloyloxy)-6S,7R-epothilone D bis-TBS ether 48—Acryloyloxy derivative **48** was synthesized (6 mg, 56%) as a colorless oil from primary alcohol **43**, according to the procedure described previously for the preparation of **7**. 1H NMR (500 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.36 (d, J = 17.3 Hz, 1H), 6.34 (s, 1H), 6.10 (dd, J = 17.3, 10.4 Hz, 1H), 5.77 (d, J = 10.4 Hz, 1H), 5.74-5.65 (m, 1H), 5.42 (t, J = 8.2 Hz, 1H), 5.16 (t, J = 4.1 Hz, 1H), 5.08 (d, J = 18.4 Hz, 1H), 5.07 (d, J = 9.6 Hz, 1H), 4.56, 4.51 (ABq, J = 12.6 Hz, 2H), 4.18 (br.d, J = 8.5 Hz, 1H), 3.98 (d, J = 3.3 Hz, 1H), 3.45-3.38 (m, 1H), 2.69 (s, 3H), 2.65 (dd, J = 14.5, 6.5 Hz, 1H), 2.56-2.43 (m, 4H), 2.25-2.20 (m, 2H), 2.11 (s, 3H), 1.95-1.87 (m, 1H), 1.60-1.44 (m, 5H), 1.07 (d, J = 7.1 Hz, 3H), 0.96 (s, 3H), 0.90 (s, 9H), 0.88 (s, 9H), 0.86 (d, J = 6.3 Hz, 3H), 0.19 (s, 3H), 0.15 (s, 3H), 0.12 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 220.1, 170.4, 166.0, 164.6, 152.5, 137.9, 136.4, 134.1, 130.7, 128.5, 123.6, 119.4, 118.0, 116.3, 77.6, 74.8, 73.8, 68.5, 56.3, 48.6, 42.0, 40.2, 38.6, 34.8, 31.1, 28.3, 27.8, 26.3, 21.1, 19.3, 18.8, 18.6, 16.1, 15.8, 14.3, -3.5, -4.0, -4.3, -4.7; HRFABMS: calcd for $C_{44}H_{74}NO_7SSi_2$ (M+H) 816.4725, found 816.4722.

(4S)-4-Allyl-4-demethyl-26-(acryloyloxy)-6S,7R-epothilone analogues 49 and 50—A similar procedure was employed to prepare mono-TBS ether **49** (3.0 mg, 50%, colorless oil) and diol **50** (2.0 mg, 40%) from bis-TBS ether **48** as previously described for the conversion of **20a** to **21**. Compound **49**: 1H NMR (500 MHz, $CDCl_3$) δ 6.94 (s, 1H), 6.38 (d, J = 17.6 Hz, 1H), 6.33 (s, 1H), 6.10 (dd, J = 17.6, 10.0 Hz, 1H), 5.80 (d, J = 10.4 Hz, 1H), 5.55-5.45 (m, 2H), 5.32 (br.s, 1H), 5.10 (d, J = 9.2 Hz, 1H), 5.07 (d, J = 16.0 Hz, 1H), 4.63, 4.58 (ABq, J = 12.8 Hz, 2H), 4.17 (br.d, J = 8.8 Hz, 1H), 3.78-3.72 (m, 1H), 3.62 (d, J = 8.4 Hz, 1H), 3.54 (br.s, 1H), 2.78 (dd, J = 14.4, 6.4 Hz, 1H), 2.70 (s, 3H), 2.57-2.41 (m, 3H), 2.32-2.02 (m, 3H), 2.07 (s, 3H), 1.66-1.45 (m, 3H), 1.28-1.20 (m, 3H), 1.13 (d, J = 6.8 Hz, 3H), 1.05 (d, J = 6.8 Hz, 3H), 0.94 (s, 9H), 0.20 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 222.4, 170.4, 166.0, 164.8, 152.3, 137.0, 136.3, 132.8, 130.9, 128.4, 124.4, 119.1, 119.0, 116.2, 75.0, 73.8, 68.4, 67.6, 57.3, 44.2, 40.2, 39.5, 35.2, 33.5, 31.1, 29.7, 28.2, 26.4, 23.5, 19.5, 19.3, 18.6, 16.3, 15.7, 11.5, -3.5, -4.5; HRFABMS: calcd for $C_{38}H_{60}NO_7SSi$ (M+H) 702.3860, found 702.3855. Compound **50**: 1H NMR (500 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.51 (s, 1H), 6.43 (d, J = 17.3 Hz, 1H), 6.15 (dd, J = 17.5, 10.4 Hz, 1H), 5.87 (d, J = 10.4 Hz, 1H), 5.62-5.54 (m, 2H), 5.42 (t, J = 6.8 Hz, 1H), 5.13 (d, J = 18.1 Hz, 1H), 5.12 (d, J = 9.3 Hz, 1H), 4.67, 4.54 (ABq, J = 13.2 Hz, 2H), 4.20 (d, J = 11.3 Hz, 1H), 3.58 (q, J = 6.8 Hz, 1H), 3.53 (d, J = 9.3 Hz, 1H), 3.31 (br.s, 1H), 2.93 (d, J = 3.0 Hz, 1H), 2.73-2.66 (m, 1H), 2.70 (s, 3H), 2.55 (d, J = 15.9 Hz, 1H), 2.48 (dd, J = 14.2, 6.3 Hz, 1H), 2.42-2.30 (m, 4H), 2.09-2.00 (m, 1H), 2.07 (s, 3H), 1.66-1.40 (m, 3H), 1.26-1.22 (m, 1H), 1.09 (d, J = 6.6 Hz, 3H), 1.02 (d, J = 6.3 Hz, 3H), 0.95 (s, 3H), 0.97-0.85 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 222.1, 170.7, 166.2, 165.2, 152.1, 136.8,

136.3, 132.5, 131.2, 128.3, 124.6, 120.3, 119.2, 116.7, 78.3, 74.7, 71.9, 70.3, 67.1, 56.2, 42.2, 39.0, 38.5, 35.6, 33.3, 32.6, 28.5, 24.3, 19.3, 16.0, 15.9, 15.5, 11.8; HRFABMS: calcd for $C_{32}H_{46}NO_7S$ (M+H) 588.2995, found 588.3037.

Cis bridged epothilone 51—Compound **51** was prepared as a colorless oil with a *cis* double bond on the newly made bridge (2.8 mg, 62%) *via* ring closing metathesis with second-generation Grubbs catalyst from terminal diene **49**, according to the procedure described previously for the synthesis of bridged compound **35**. 1H NMR (500 MHz, $CDCl_3$) δ 6.97 (s, 1H), 6.58 (s, 1H), 6.09 (dt, J = 12.1, 3.0 Hz, 1H), 5.82 (dd, J = 11.5, 2.2 Hz, 1H), 5.78 (t, J = 6.8 Hz, 1H), 5.76 (d, J = 11.5 Hz, 1H), 4.72 (d, J = 8.5 Hz, 1H), 4.68, 4.33 (ABq, J = 11.8 Hz, 2H), 3.93 (t, J = 13.5 Hz, 1H), 3.42 (q, J = 6.6 Hz, 1H), 3.29 (d, J = 10.4 Hz, 1H), 2.88–2.73 (m, 2H), 2.71 (s, 3H), 2.59 (d, J = 11.0 Hz, 1H), 2.46–2.41 (m, 2H), 2.33 (t, J = 12.6 Hz, 1H), 2.15 (s, 3H), 1.99 (d, J = 14.3 Hz, 1H), 1.79–1.72 (m, 1H), 1.52–1.37 (m, 3H), 1.30–1.17 (m, 2H), 1.21 (s, 3H), 1.08 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H), 0.83 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 221.5, 169.9, 166.1, 165.1, 152.2, 141.6, 136.9, 136.1, 131.4, 123.1, 121.2, 117.1, 79.7, 74.9, 72.2, 68.1, 59.7, 40.0, 36.3, 32.7, 32.6, 31.1, 29.7, 26.7, 25.8, 19.4, 19.3, 18.2, 15.0, 10.4, 1.11, 0.09, -2.6, -3.8; HRFABMS: calcd for $C_{36}H_{56}NO_7SSi$ (M+H) 674.3547, found 674.3593.

Cis bridged epothilone 52—A similar procedure was used to prepare **52** (1.36 mg, 47%, colorless oil) from mono-TBS ether **51** based on the previously described method for the conversion of **20a** to **21**. 1H NMR (500 MHz, $CDCl_3$) δ 6.99 (s, 1H), 6.56 (s, 1H), 6.25–6.15 (m, 1H), 5.90 (dd, J = 11.8, 1.9 Hz, 1H), 5.72 (d, J = 9.3 Hz, 1H), 5.65 (dd, J = 11.5, 1.7 Hz, 1H), 4.64, 4.45 (ABq, J = 11.4 Hz, 2H), 4.52–4.30 (m, 1H), 3.63–3.54 (m, 1H), 3.44–3.34 (m, 4H), 2.81–2.67 (m, 2H), 2.70 (s, 3H), 2.44–2.41 (m, 3H), 2.09 (s, 3H), 1.91–1.82 (m, 1H), 1.71–1.58 (m, 2H), 1.45–1.38 (m, 2H), 1.31–1.19 (m, 2H), 1.25 (s, 3H), 1.07 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 7.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 221.5, 169.9, 166.2, 165.1, 152.0, 141.8, 137.0, 136.8, 130.8, 123.1, 120.7, 116.9, 78.8, 76.8, 70.9, 70.7, 58.2, 41.1, 35.8, 33.2, 32.7, 31.6, 30.9, 29.7, 26.5, 22.7, 19.3, 15.3, 14.2, 10.8; HRFABMS: calcd for $C_{30}H_{42}NO_7S$ (M+H) 561.2760, found 560.2720.

Trans bridged epothilone 53—Ring closing metathesis reaction of terminal diene **50** with second-generation Grubbs catalyst, according to the procedure described previously for the synthesis of bridged compound **35**, produced a mixture (0.86 mg, ~93% total yield) as a colorless oil. This mixture consists of 86.5% of **53** based on the integration of its 1H NMR spectrum. Compound **53**: 1H NMR (500 MHz, $CDCl_3$) δ 6.95 (s, 1H), 6.55 (s, 1H), 5.94 (d, J = 17.0 Hz, 1H), 5.70 (dd, J = 17.0, 9.9 Hz, 1H), 5.46 (dd, J = 12.1, 3.0 Hz, 1H), 4.71 (t, J = 7.4 Hz, 1H), 4.59, 4.52 (ABq, J = 11.3 Hz, 2H), 3.43 (d, J = 10.4 Hz, 1H), 3.25 (q, J = 6.6 Hz, 1H), 2.82–2.71 (m, 1H), 2.70 (s, 3H), 2.55–2.31 (m, 6H), 2.09 (s, 3H), 2.08–2.02 (m, 1H), 1.75–1.65 (m, 1H), 1.50–1.20 (m, 3H), 1.23 (s, 3H), 1.06 (s, 3H), 1.03 (d, J = 6.6 Hz, 3H), 0.95 (d, J = 6.9 Hz, 3H), 0.97–0.85 (m, 1H); HRFABMS: calcd for $C_{30}H_{42}NO_7S$ (M+H) 560.2682, found 560.2593.

(4S)-4-Allyl-4-demethyl-26-hydroxy-6S,7R-epothilone D 54—A similar procedure was used to prepare triol **54** (14.5 mg, 51%, colorless oil), as well as 48% mono-TBS ether, from lactone **42** following the procedure described previously for the conversion of **20a** to **21**. Compound **54**: 1H NMR (500 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.53 (s, 1H), 5.66–5.60 (m, 2H), 5.46 (dd, J = 9.6, 3.0 Hz, 1H), 5.13 (d, J = 16.0 Hz, 1H), 5.12 (d, J = 11.3 Hz, 1H), 4.15–4.11 (m, 1H), 4.05, 4.02 (ABq, J = 13.5 Hz, 2H), 3.65–3.54 (m, 1H), 3.50 (d, J = 9.6 Hz, 1H), 3.45–3.39 (m, 1H), 3.36 (br.s, 1H), 3.31 (d, J = 3.3 Hz, 1H), 2.73–2.66 (m, 1H), 2.69 (s, 3H), 2.55 (dd, J = 15.7, 2.2 Hz, 1H), 2.50 (dd, J = 14.0, 8.2 Hz, 1H), 2.41–2.26 (m, 4H), 2.07 (s, 3H), 2.04–1.94 (m, 1H), 1.70–1.43 (m, 5H), 1.08 (d, J = 6.9 Hz, 3H), 1.02 (d, J = 6.6 Hz, 3H),

0.95 (s, 3H), 0.96-0.91 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 222.2, 171.0, 165.2, 152.7, 141.5, 137.0, 132.5, 122.6, 120.2, 119.4, 116.5, 78.4, 74.7, 72.3, 66.1, 56.1, 43.0, 39.3, 38.5, 35.5, 33.4, 32.5, 28.4, 24.5, 19.2, 17.2, 16.0, 15.5, 11.8.

12 β ,13 β -Epoxide 55—To a solution of allylic alcohol **54** (14.5 mg, 0.027 mmol) and 4 Å molecular sieves (40 mg) in CH_2Cl_2 (0.5 mL) at -20°C was added diethyl-L-tartrate (6.7 mg, 0.0326 mmol, 1.2 eq) in CH_2Cl_2 (0.1 mL) and titanium isopropoxide (7.7 mg, 0.027 mmol, 1.0 eq) in CH_2Cl_2 (0.1 mL). After stirring at that temperature for 1 h, *t*-butyl hydroperoxide (16 μL , 5 M in decane, 0.0081 mmol, 3.0 eq) was added and the resulting reaction mixture was stirred at -20°C for an additional 2 h. The reaction mixture was then filtered through celite into saturated aqueous Na_2SO_4 solution (10 mL), rinsing with EtOAc (10 mL). The subsequent biphasic mixture was stirred for 1 h and two layers were separated. The aqueous phase was re-extracted with EtOAc (10 mL $\times$ 3), and the combined organic extracts were dried over anhydrous Na_2SO_4 , and the solvents were removed *in vacuo* to give a crude oil. Purification of this oil by preparation thin layer chromatography over silica gel using 70% EtOAc in hexanes as eluent furnished β -epoxide triol **55** (8.5 mg, 84%) as a syrup. ^1H NMR (500 MHz, CDCl_3) δ 6.97 (s, 1H), 6.63 (s, 1H), 5.67 (br.s, 1H), 5.52-5.47 (m, 1H), 5.10 (d, J = 9.3 Hz, 1H), 5.09 (d, J = 17.3 Hz, 1H), 4.31-4.28 (m, 2H), 3.74 (d, J = 9.3 Hz, 1H), 3.69 (br.s, 2H), 3.53 (br.s, 1H), 3.45-3.30 (m, 3H), 2.69 (s, 3H), 2.58-2.37 (m, 3H), 2.20-2.18 (m, 2H), 2.13 (s, 3H), 1.97-1.93 (m, 1H), 1.86-1.58 (m, 4H), 1.54-1.40 (m, 2H), 1.11 (d, J = 6.9 Hz, 3H), 1.02 (d, J = 6.8 Hz, 3H), 0.99 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 220.6, 171.5, 164.9, 152.2, 134.7, 132.2, 119.8, 119.2, 116.6, 76.0, 74.0, 73.2, 63.3, 62.3, 57.6, 56.8, 40.7, 39.7, 39.6, 35.9, 34.4, 33.4, 30.1, 28.6, 26.6, 19.3, 16.3, 15.8, 14.2, 11.4.

(4*R*)-4-Allyl-4-demethyl-26-(benzoyloxy)-6*S*,7*R*-epothilone B 56—26-benzoyloxy- β -epoxide **56** was synthesized from β -epoxide triol **55** employing the same procedure as that described for compound **22**. Compound **56** was obtained as a colorless needles from hexanes-acetone in 94% yield. ^1H NMR (500 MHz, CDCl_3) δ 7.95 (d, J = 7.2 Hz, 2H), 7.53 (t, J = 7.4 Hz, 1H), 7.35 (t, J = 7.4 Hz, 2H), 6.93 (s, 1H), 6.65 (s, 1H), 5.65 (br.s, 1H), 5.56-5.48 (m, 1H), 5.15-5.08 (overlap, 1H), 5.10 (d, J = 11.2 Hz, 1H), 5.09 (d, J = 16.0 Hz, 1H), 4.48-4.41 (m, 1H), 4.20 (br.s, 1H), 4.18 (d, J = 12.0 Hz, 1H), 3.79 (d, J = 9.0 Hz, 1H), 3.47 (br.s, 1H), 3.31 (q, J = 7.0 Hz, 1H), 3.25 (dd, J = 9.4, 3.3 Hz, 1H), 2.70 (s, 3H), 2.70-2.68 (m, 1H), 2.56 (d, J = 12.3 Hz, 1H), 2.52 (d, J = 9.1 Hz, 1H), 2.41 (dd, J = 14.3, 5.5 Hz, 1H), 2.25 (dt, J = 15.4, 3.8 Hz, 1H), 2.16 (s, 3H), 1.99-1.86 (m, 1H), 1.73-1.38 (m, 8H), 1.10 (d, J = 6.8 Hz, 3H), 1.02 (d, J = 6.4 Hz, 3H), 1.01 (s, 3H). Colorless needles of compound **56** (0.03 $\times$ 0.03 $\times$ 0.80 mm³) were crystallized from hexanes/acetone at room temperature. The chosen crystal was centered on the goniometer of an Oxford Diffraction Gemini Ultra diffractometer equipped with a Sapphire 3 CCD detector and operating with $\text{CuK}\alpha$ radiation. The data collection routine, unit cell refinement, and data processing were carried out with the program CrysAlis.²⁶ The Laue symmetry and systematic absences were consistent with the orthorhombic space group P212121. Structure solution was performed with the graphical user interface WinGX.²⁷ The structure was solved by direct methods using SIR92²⁸ and refined using SHELXTL-NT.²⁹ The asymmetric unit of the structure comprises one crystallographically independent molecule. The final refinement model involved anisotropic displacement parameters for non-hydrogen atoms and a riding model for all hydrogen atoms. The absolute configuration was established from anomalous dispersion effects (Flack x = 0.01(6)). The configuration of chiral centers were assigned as C3(*S*), C4(*S*), C6(*S*), C7(*R*), C8(*S*), C12(*S*), C13(*S*) and C15(*S*).

Biological data—Tubulin was prepared by two cycles of temperature dependent assembly–disassembly as described by Williams and Lee.³⁰ ED₅₀ values for tubulin assembly were determined as described in Chatterjee et al.³¹

The A2780 ovarian cancer cell line assay was performed at Virginia Polytechnic Institute and State University as previously reported.³² The A2780 cell line is a drug-sensitive ovarian cancer cell line.³³ The MTT assay³⁴ was used at SUNY for PC3 cells.

Molecular Modeling and Design—Structures of bridged epothilone analogues 27, 30 and 36 were constructed in Maestro³⁵ by using the electron crystallographic structure of epo-A as template. The structures were subsequently optimized with the MMFF/GBSA/H₂O force field. The optimized structures of 27, 30 and 36 were separately and flexibly docked into tubulin binding site by using the Glide docking protocol.²⁴ The best docking poses were chosen on the basis of the Emodel scoring function together with visualization to ensure reasonable binding modes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 2.

(a) The Nettles-Snyder proposed epoA model based on EC density with juxtaposition of the C4-methyl and C12-H (methyl for epoB); $r(\text{C} \cdots \text{C}) = 4.5 \text{ \AA}$. (b) MMFF-energy minimized structures of the EC template and the designed bridged epoD analogue **5**. (Overlaid with 3 point selection in PyMol).

Figure 3.
Key NOE correlations of ketal **17**

Figure 4.
Displacement ellipsoid drawing (50%) of compound **56**.

Figure 5.
Docking poses of **1** (yellow) and **36** (cyan) in the EC determined tubulin binding site.

Scheme 1.
Retrosynthetic analysis for bridged epothilone 5

Scheme 2.
Synthesis of ketone **9**

Scheme 3.

Synthesis of lactone **21**. i. LDA, THF, -78 °C to -40 °C, 80%; ii. TBSOTf, 2,6-lutidine, 0 °C, 94%; iii. HF.Py in Py, 0 °C-RT, 86; iv. SO₃.Py, 87%; v. NaClO₂, NaH₂PO₄, 98%; vi. TBAF, THF, 0 °C-RT, 97%; vii. Et₃N, 2,4,6-Trichlorobenzoyl chloride, DMAP, 78%

Scheme 4.
Synthesis of bridged epothilone D analogue **27**

Scheme 5.
Synthesis of bridged epothilone D analog **30**

Scheme 6.
Synthesis of bridged epothilone D analog **36**

Scheme 7. Synthesis of fragment C1-C6 with 4*S* stereochemistry

Scheme 8.
Synthesis of allyl epothilone derivative **43**

Scheme 9. Synthesis of bridged epothilone D analog **47**, **52**, and **53**

Scheme 10.
Synthesis of 4S,6S,7R epothilone D derivative **56**

Table 1

Bioactivity data of epothilone D and its analogues

Cmpd	IC ₅₀ , A2780 (μM)	IC ₅₀ , PC3 (μM)	EC ₅₀ , tubulin assembly (μM)
EpoD	0.04 ± 0.002	0.016 ± 0.001	0.44 ± 0.02
7	19.3 ± 2.5	ND	ND
23	25.6 ± 7.0	ND	ND
25	22.0 ± 1.1	ND	ND
27	15.6 ± 3.0	2.1 ± 0.15	6.9 ± 0.92
28	2.05 ± 1.14	1.2 ± 0.40	1.3 ± 0.07
29	4.7 ± 0.26	1.2 ± 0.13	0.88 ± 0.06
30	3.2 ± 0.1	0.93 ± 0.06	2.4 ± 0.10
31	0.24 ± 0.018	ND	0.583 ± 0.064
34	0.10 ± 0.035	0.077 ± 0.016	0.54 ± 0.07
36	3.91 ± 0.49	1.20 ± 0.25	1.62 ± 0.13
45	6.23 ± 0.75	ND	ND
47	22.9 ± 0.92	ND	ND
50	5.23 ± 0.22	ND	ND
52	4.95 ± 0.30	ND	ND
53	31.17 ± 1.19	ND	ND