Total Synthesis of 16-Desmethylepothilone B, Epothilone B_{10}, Epothilone F, and Related Side Chain Modified Epothilone B Analogues

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Abstract: The macrolactonization-based strategy for the total synthesis of epothilones has been streamlined and improved to a high level of efficiency and stereoselectivity. This strategy has been applied to the construction of vinyl iodide **19** which served as a common intermediate for the synthesis of a series of natural and designed epothilones including an epothilone B_{10} (**3**), epothilone F (**5**), 16-desmethylepothilone B (**14**), pyridine epothilones **57a–57g**, dimeric epothilones **59** and **61**, and benzenoid epothilones **63a–63g**.

Keywords: antitumor agents · designed analogues · epothilone · synthesis · total synthesis

Introduction

Since publication of the full chemical structures of epothilones A and B in July 1996,[1] there has been considerable interest in this series of natural products.[2] Numerous synthetic approaches have been developed[3, 4] and some of these efforts have culminated in total syntheses of the natural epothilones A (**1**),[4a–c, e–i, o, s] B (**2**),[4g–j, l, m, p, u] C (**6**),[4a–i, o, s] D (**7**)[4g–j, l, m, p, q, u] and E (**4**)[5h,k] (Figure 1). Since completion of our own synthesis of epothilones A–D, we have been involved in a program dedicated to the preparation of a large number of analogues[5b, c, e–k] using both solution- and solid-phase techniques. Some of the compounds prepared in these studies have recently been reported[6] as the natural epothilones C_4 (**9**), G_1 (**10**), G_2 (**11**), H_1 (**12**), H_2 (**13**), and I_1 (**8**). In addition, several epothilone derivatives have been synthesized and tested by the Danishefsky[5a,d,l] and Winkler[5m] groups and more recently, a number of analogues have been prepared by degradation and alteration of natural material derived from fermentation.[7] The driving force for all of these synthetic endeavors lies primarily in the biological profile of the epothilones[8] and their potential as anticancer agents. Like the approved cancer treatment paclitaxel,[9] the epothilones have been shown to exert a cytotoxic effect through their interaction with tubulin and the resulting disruption of microtubule dynamics. This event is thought to cause apoptosis (programmed cell death) by preventing correct assembly of the mitotic spindle during cell division. Since the epothilones exhibit increased in vitro potency[2, 8] and are reported to possess considerably higher water solubility[1c] compared with paclitaxel, they are clearly important lead compounds which require further investigation and development. These studies have been aided by the relative chemical simplicity of the epothilones (as compared with paclitaxel) which makes them much more amenable to chemical synthesis and structural modification.

In our previous work, we prepared a number of epothilone analogues[2, 5k] which has provided us with information toward an understanding of the essential structural features needed for tubulin binding. In particular, we have synthesized numerous side chain modified analogues of epothilone C[5h] as well as some analogues of epothilone B possessing a combination of modified side chains and alternative C26 substituents (see Figure 1 for epothilone numbering).[5i, k] These studies have highlighted the importance of these two regions of the epothilone structure and demonstrated that numerous modifications to these positions are tolerated. Although these modifications do not always improve the activity, they do offer the possibility of tailoring these regions and fine-tuning the biological profile. In addition, these changes can be used to adjust the physical properties of the molecules. In fact, because of the high cytotoxicity of

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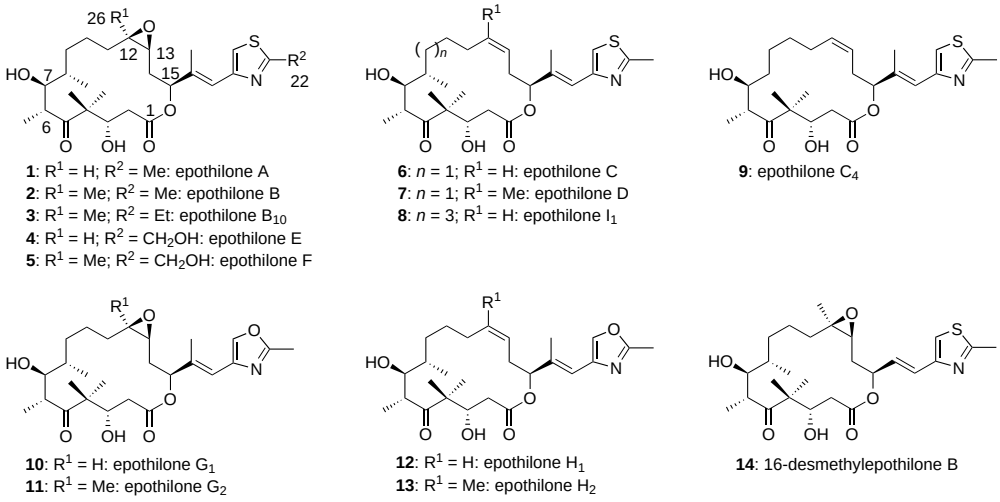

Figure 1. Structures and numbering of selected naturally occurring epothilones and 16-desmethylepothilone B (**14**).

epothilone B, analogues with somewhat reduced cytotoxicity may be optimal, and it is hoped that this can be achieved while simultanously improving the pharmacological properties of the compounds.

Mindful of previous results, we felt that further investigations within these two modification tolerant regions of the epothilone structure were warranted, and this led us first to consider alterations of the portion linking the macrolactone core of the epothilones to the important heteroaromatic group. Towards this end, we recently reported in a preliminary communication[10] the total synthesis of 16-desmethylepothilone B (**14**), which possesses a more flexible C16–C17 olefinic linkage (see Figure 1). In addition to providing material for biological evaluation, this endeavor also enabled us to develop an improved and more convergent macrolactonization route to the epothilones as outlined in Figure 2. At the outset, three facets of the strategy were of particular importance; first, we decided to develop a synthesis of the C7–C22 "top" fragment of the molecule by coupling ylide **15** and aldehyde **16**, thus making the approach more convergent than our previous strategy. In fact, the overall objective was to create a fusion of our highly convergent and modular metathesis approach[4f] which provided epothilone A analogues in a very rapid, albeit moderately selective fashion, with our more selective and efficient macrolactonization route.[4g] Second, we desired to improve the previously troublesome aldol protocol which is used to construct the C6–C7 bond via the union of the C1–C6 and C7–C22 fragments.[4g] Finally, we envisioned the use of a hydroxyl group on C26 to direct a chemo-, regio-, and stereoselective epoxidation of the C12–C13 olefin.[5i] However, since the target compound **14** possessed the natural C12 methyl substituent, we realized that a C26 deoxygenation protocol would need to be developed.

We now wish to report a full account of the synthetic work involved in achieving the objectives described above, and to present an extension of this approach to the synthesis of vinyl iodide **19** and a series of additional epothilone analogues (**18**). As illustrated in Figure 3, it was anticipated that this core structure could be used, by expansion of our previously reported Stille coupling protocol,[5k] to produce a number of epothilone B analogues (**18**) encompassing a wide range of modified side chain substituents. In particular, a series of pyridine analogues was targeted. In addition, we envisaged

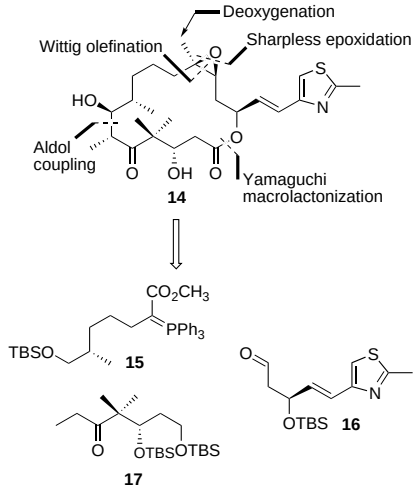

Figure 2. Retrosynthetic analysis and strategy for the total synthesis of 16-desmethylepothilone B (**14**).

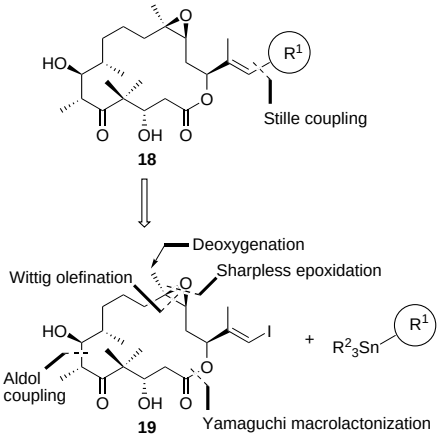

Figure 3. Retrosynthetic analysis and strategy for the total synthesis of side chain analogues (**18**) of epothilone B.

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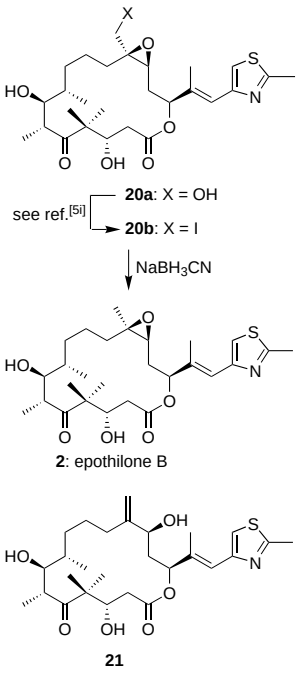
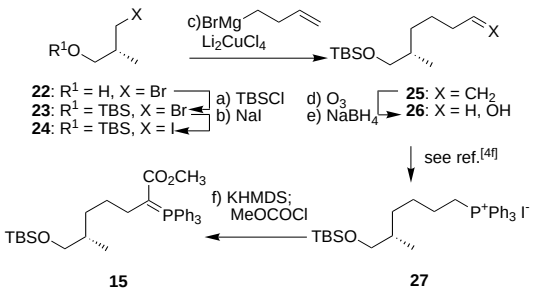
that the pivotal intermediate **19** could be used to complete the first total synthesis of the natural products epothilone B_{10} (**3**)[6] and epothilone F (**5**).[6, 7d]

Results and Discussion

During our previously reported synthesis of C26 modified epothilones,[5i] we discovered that a hydroxyl group at C26 allowed application of the Sharpless asymmetric epoxidation protocol and that this reaction proceeded with complete chemo-, regio-, and stereoselectivity. For several of our newly targeted analogue structures we were concerned about the possibility of competitive heterocycle oxidation and side chain epoxidation (desmethyl analogue **14**), as well as the stereoselectivity problems that we[4f] have previously encountered. Thus, we wished to make use of this highly efficient reaction for the preparation of epothilone B, and related analogues, and therefore we initiated an investigation to uncover a suitable method for deoxygenation at the C26 position after the asymmetric epoxidation; furthermore, we hoped to achieve this goal without relying upon the use of protecting groups. We began by searching for potential methods for the deoxygenation of 26-hydroxyepothilone B (**20a**)[5i] (Scheme 1). We ruled out the possibility of employing the Barton–McCombie or other radical-based methods as such procedures are well documented to cause the rupture of adjacent epoxides.[11] This forced us to focus our attention on the C26-iodo derivative **20b**, which we prepared previously from **20a** by a high-yielding protocol[5i] as shown in Scheme 1. Since reductive deiodination using low-valent metal systems was inapplicable on similar grounds to the radical methods, our options were limited to hydrogenolysis or hydride displacement reactions. Disappointingly, catalytic hydrogenolysis (Pd/C or $Pd(OH)_2$) rapidly promoted reductive epoxide opening to afford **21** (Scheme 1), which was detected by monitoring the reaction by ^{1}H-NMR spectroscopy. Attempted hydride displacement with Super-Hydride (THF, −78 to 0 °C) and sodium borohydride (DMF, 25 °C) caused the decomposition of the macrocycle, presumably due to lactone opening or retro-aldol processes. We eventually discovered that sodium cyanoborohydride in HMPA[12] smoothly effected the deiodination without damaging the unprotected macrocycle. This procedure thus enabled us to produce a relatively large amount of epothilone B (ca. 100 mg) from the 26-hydroxy analogue **20a**, and holds promise as a method for producing [^{3}H]-labeled epothilone B.



Scheme 1. Synthesis of epothilone B (**2**): $NaBH_3CN$ (10.0 equiv), HMPA, 45 °C, 40 h, 70 %. HMPA = hexamethylphosphoramide.

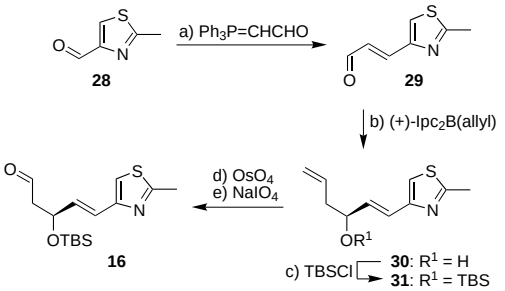


Scheme 2. Synthesis of ylide **15**: a) TBSCl (1.3 equiv), imidazole (1.5 equiv), DMF, 0 to 25 °C, 1 h; b) NaI (3.0 equiv), acetone, reflux, 18 h, 99 % (two steps); c) CH_2=$CHCH_2CH_2MgBr$ (1.4 equiv), Li_2CuCl_4 (1 mol), THF, 0 °C, 1 h, 96 %; d) O_3, CH_2Cl_2, −78 °C; then PPh_3 (3.0 equiv); e) $NaBH_4$ (1.0 equiv), EtOH, 0 °C, 30 min, 91 % (two steps); f) KHMDS (2.0 equiv), THF, 0 °C, 30 min, then MeOCOCl (1.1 equiv), −78 °C, 3 h, (crude). TBS = *tert*-butyldimethylsilyl; DMF = dimethylformamide; THF = tetrahydrofuran; KHMDS = potassium hexamethyldisilazide.

With a method for C26 deoxygenation now available, we were in a position to attempt our synthesis of the 16-desmethyl analogue **14**. As outlined in Figure 2, the convergent approach to the C7−C22 "top fragment" of the molecule required preparation of ylide **15** and thiazole aldehyde **16**.

The synthesis of ylide **15** is outlined in Scheme 2. Initial protection of the commercially available alcohol **22** (TBSCl, imidazole, DMF, 0 to 25 °C) and subsequent Finkelstein reaction (NaI, acetone, reflux) afforded iodide **24** in 99 % overall yield (Scheme 2). The copper-catalyzed coupling reaction[13] between **24** and the commercially available butenyl magnesium bromide (Li_2CuCl_4, THF, 0 °C, 96 %) provided olefin **25** which was transformed into alcohol **26** via ozonolysis (O_3, CH_2Cl_2, −78 °C; then PPh_3) followed by reduction ($NaBH_4$, EtOH, 0 °C, 91 % for two steps). In an identical way to that previously reported,[4g] the alcohol **26** was converted to phosphonium salt **27**. The corresponding ylide was then generated using KHMDS (THF, 0 °C) and quenched with methyl chloroformate[14] at −78 °C to furnish the desired phosphorane **15**, which was used in the Wittig reaction without purification. We noted that maintaining a low solution temperature during the quenching seems essential for obtaining an ylide of good quality.

The preparation of thiazole aldehyde **16** is delineated in Scheme 3, starting with a Wittig reaction between the known aldehyde **28** and Ph_3P=CHCHO (CH_2Cl_2, reflux) to give

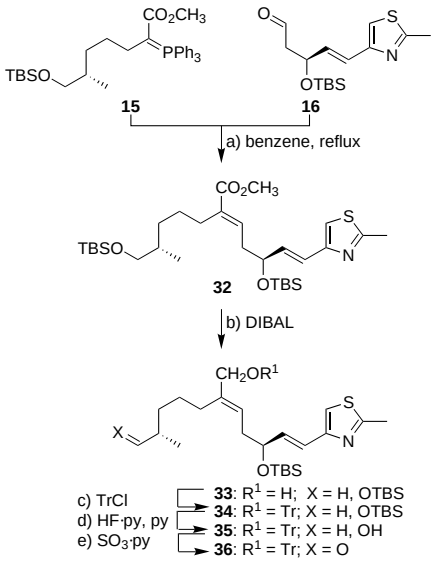


Scheme 3. Synthesis of aldehyde **16**: a) $Ph_3P{=}CHCHO$ (1.15 equiv), CH_2Cl_2, reflux, 12 h, 82%; b) (+)-Ipc_2B(allyl) (2.1 equiv), CH_2Cl_2, Et_2O, pentane, $-100\,^{\circ}C$, 2 h, 96%; c) TBSCl (1.2 equiv), imidazole (1.5 equiv), DMF, 0 to 25 °C, 2 h, 99%; d) OsO_4 (1 mol%), NMO (1.1 equiv), THF/*t*BuOH/H_2O 5:5:1, 0 to 25 °C, 12 h, 68%; e) $NaIO_4$ (6.0 equiv), MeOH/H_2O 2:1, 0 to 25 °C, 1 h, 89%. Ipc = isopinocampheyl; NMO = 4-methylmorpholine *N*-oxide.

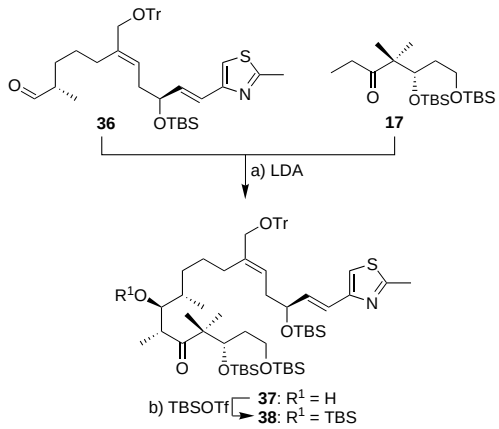
unsaturated aldehyde **29** as a crystalline solid in good yield (82%). As previously described in our total synthesis of epothilones A–E,[4f] the Brown enantioselective allylboration reaction, under salt-free conditions, was employed to introduce the stereogenic center at C15 (for epothilone numbering, see Figure 1). Solubility problems were initially encountered when the usual ether/pentane solvent system was employed. This difficulty was readily overcome by changing to a ternary CH_2Cl_2/Et_2O/pentane system, leading to the preparation of alcohol **30** in high yield and high enantioselectivity (96%, $\geq$97% *ee* by chiral HPLC by comparison to the racemate).[15] Silyl ether formation (TBSCl, imidazole, DMF, 0 to 25 °C, 99%) to give **31** and the ensuing two-step olefin cleavage and oxidation (OsO_4, NMO, THF/*t*BuOH/H_2O, 25 °C; $NaIO_4$, MeOH/H_2O, 0 to 25 °C) afforded the desired aldehyde **16** (61% yield overall). The lower overall yield for this transformation compared with the natural epothilone series is likely the result of the low regioselectivity of the initial dihydroxylation. This diminution in selectivity is almost certainly a consequence of the decreased substitution of the internal olefin compared with the natural series[4g] which possesses an extra methyl substituent.

With the coupling partners **15** and **16** in hand, the Wittig reaction could now be attempted. As illustrated in Scheme 4, heating a mixture of ylide **15** and aldehyde **16** (benzene, reflux) resulted in the formation of the desired C7–C22 fragment **32** in high yield (84%) and with excellent selectivity ($E{:}Z > 30{:}1$). This result was particularly pleasing since initial attempts to construct the C12–C13 bond employing the corresponding phosphonate ester[16] in a Horner–Wadsworth–Emmons coupling had mainly resulted in β-elimination from the sensitive aldehyde with only traces of the desired product being observed as a ca. 1:1 $E{:}Z$ mixture.

With compound **32** in hand, subsequent reduction (DIBAL, THF, $-78\,^{\circ}C$, 93%) and tritylation (TrCl, 4-DMAP, DMF, 70 °C, 82%) were followed by selective deprotection (HF·py in py/THF, 0 to 25 °C, 66%) to furnish primary alcohol **35** which was readily oxidized to aldehyde **36** under mild conditions (SO_3·py, DMSO/CH_2Cl_2, Et_3N, 0 °C, ca. 95%, crude). With this fragment in hand, we could now perform the crucial aldol reaction with ketone **17**[4g] (Scheme 5) to construct the C6–C7 bond and establish absolute stereo-



Scheme 4. Synthesis of aldehyde **36**: a) **15** (1.3 equiv based on **16**), benzene, reflux, 18 h, 84%; b) DIBAL (3.0 equiv), THF, $-78\,^{\circ}C$, 3 h, 93%; c) TrCl (1.2 equiv), 4-DMAP (1.4 equiv), DMF, 80 °C, 24 h, 82%; d) HF·py, py/THF, 25 °C, 4 h, 66%; e) SO_3·py (5.0 equiv), Et_3N (5.0 equiv), DMSO/CH_2Cl_2 1:1, 0 °C, 1 h, ca. 95% (crude). DIBAL = diisobutylaluminiumhydride; 4-DMAP = 4-dimethylaminopyridine; Tr = triphenylmethyl; py = pyridine; DMSO = dimethylsulfoxide.



Scheme 5. Synthesis of advanced intermediate **38**: a) LDA (2.4 equiv), **17** (2.3 equiv), THF, $-78\,^{\circ}C$, 1 h, -78 to $-40\,^{\circ}C$, 30 min, then add **36** (1.0 equiv), THF, $-78\,^{\circ}C$, 2 min, then AcOH (4.8 equiv), -78 to 25 °C, 76%; b) TBSOTf (1.5 equiv), 2,6-lutidine (2.5 equiv), CH_2Cl_2, -78 to 0 °C, 2 h, 95%. LDA = lithium diisopropylamide; Tf = trifluoromethanesulfonyl.

chemistry at these positions. Previous work had shown similar reactions to be somewhat capricious in terms of both yield and stereoselectivity; in order to improve this reaction, we considered modifying our original conditions. Due to the highly reversible nature of ketone-derived lithium enolate aldol reactions,[17] we decided to employ a large excess of the ketone enolate. Since a retro-aldol reaction can potentially cause scrambling of the enolate geometry, these conditions ensured that the (*Z*)-enolate formed initially upon ketone deprotonation would remain in large excess throughout the reaction. To further minimize aldol equilibration, we kept the reaction time as short as possible (which was also facilitated by the use of excess enolate), and employed a rapid low

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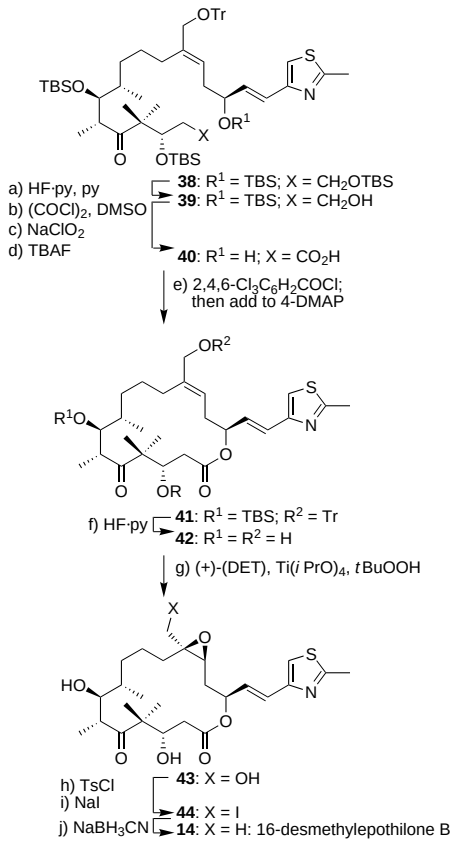
temperature quench with AcOH. Furthermore, in our new synthetic approach we have taken into account the stereochemical lability of intermediate aldehydes such as **36**. The production of α-chiral aldehydes by most common alcohol oxidation procedures is generally considered to be stereochemically secure;[18] previously, related aldehydes were obtained by a more risky nitrile reduction-imine hydrolysis protocol[5k] with potential scrambling of the chiral center. In addition, we have taken steps to avoid any processing or purification of the aldehyde which may compromise stereochemical homogeneity. Thus, the alcohol oxidation was performed immediately prior to the ensuing aldol reaction and the crude aldehyde **36** was used directly without purification. Gratifyingly, we were delighted to find that both TLC and ^{1}H-NMR analysis of the crude reaction mixture showed a very favorable product ratio.[19] Due to overlapping signals in the ^{1}H-NMR spectrum of the crude reaction mixture, however, an accurate determination of the diastereomeric excess could not be made at this stage. Purification by flash chromatography allowed full recovery of the excess ketone **17** which could be utilized in further reactions, as well as facile separation of the aldol stereoisomers. The desired aldol product **37** was isolated in 76% yield as a single stereoisomer. Fractions of all of the other products observed, which contained minor aldol stereoisomers and small amounts of starting aldehyde, were combined, and by mass balance alone the lower limit for the aldol stereoselectivity was at least $\geq$10:1. Subsequent silylation (TBSOTf, 2,6-lutidine, CH_2Cl_2, -78 to 0 °C) provided pure tetrasilyl ether **38** as a single stereoisomer in an excellent 95% yield. These modified conditions were found to be highly reliable and amenable to reactions on a scale of several grams of material.

The transformation of silyl ether **38** into the desired epothilone macrocyclic core is summarized in Scheme 6. Selective removal of the primary silyl ether protecting group (HF·py in py/THF, 0 °C) afforded alcohol **39** (87% after one recycling of over-deprotected material), which was oxidized via a two-step procedure (Swern oxidation;[18c] then $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*BuOH/H_2O, 25 °C). Subsequent removal of the C15 hydroxyl protecting group (TBAF, THF, 0 to 25 °C) provided the desired hydroxy-acid **40** in excellent overall yield (slightly contaminated with Bu_4N^+ salts, 60%, three steps) and laid the foundation for the formation of the epothilone core. The key macrolactonization step was achieved under Yamaguchi conditions[20] (2,4,6-trichlorobenzoylchloride, Et_3N, THF; then add to a solution of 4-DMAP in toluene, 0.005 M, 75 °C) to give the protected intermediate **41** in 73% yield. Global deprotection (HF·py in py/THF, 0 to 25 °C, 78%) completed the synthesis of **42**. The hydroxy functionality at C26 was now utilized to direct a highly chemo-, regio-, and stereoselective epoxidation of the C12–C13 olefin under Sharpless conditions[21] [(+)-DET, Ti(*i*PrO)$_4$, *t*BuOOH, 4 Å molecular sieves, CH_2Cl_2, -30 °C, 67%) to provide epoxide **43** as a single isomer. All that remained to complete the synthesis of **14** was the removal of the now unnecessary C26 hydroxyl group. This transformation was achieved as previously described for epothilone B itself (see Scheme 1) by formation of iodide **44** through an efficient

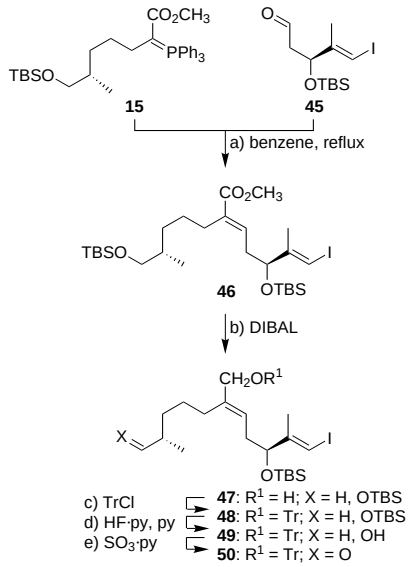


Scheme 6. Synthesis of 16-desmethylepothilone B (**14**): a) HF·py, py/THF, 0 °C, 3 h, 87% (after one recycle); b) $(COCl)_2$ (2.0 equiv), DMSO (4.0 equiv), CH_2Cl_2, -78 °C, 30 min, then Et_3N (6.0 equiv), -78 to 0 °C, 30 min; c) $NaClO_2$ (5.0 equiv), NaH_2PO_4 (2.5 equiv), *t*BuOH/THF/H_2O/2-methyl-2-butene 9:5.2:2:1.6, 25 °C, 2 h; d) TBAF (6.0 equiv), THF, 0 °C, 10 h, 60% (three steps); e) 2,4,6-$Cl_3C_6H_2COCl$ (2.4 equiv), Et_3N (6.0 equiv), THF, 0 °C, 1 h, then add to 4-DMAP (2.2 equiv) in toluene, 75 °C, 1 h, 73%; f) HF·py, THF, 0 to 25 °C, 24 h, 78%; g) (+)-diethyl L-tartrate (0.5 equiv), Ti(*i*PrO)$_4$ (0.4 equiv), *t*BuOOH (2.0 equiv), CH_2Cl_2, 4 Å MS, -30 °C, 2 h, 67%; h) TsCl (1.5 equiv), Et_3N (3.0 equiv), 4-DMAP (1.0 equiv), CH_2Cl_2, 0 to 25 °C, 1 h; i) NaI (3.0 equiv), acetone, 25 °C, 24 h, 91% (two steps); j) $NaBH_3CN$ (10.0 equiv), HMPA, 45 °C, 40 h, 67%. TBAF = tetrabutylammonium fluoride; MS = molecular sieves; Ts = 4-toluenesulfonyl.

two-step procedure via an intermediate tosylate (TsCl, Et_3N, 4-DMAP, CH_2Cl_2, 0 to 25 °C; then NaI, acetone, 25 °C, 91% for two steps) and subsequent reductive deiodination ($NaBH_3CN$, HMPA, 45 °C, 67%). Thus, the desired compound **14** (16-desmethylepothilone B) was prepared in an efficient manner with high stereoselectivity throughout the synthesis.

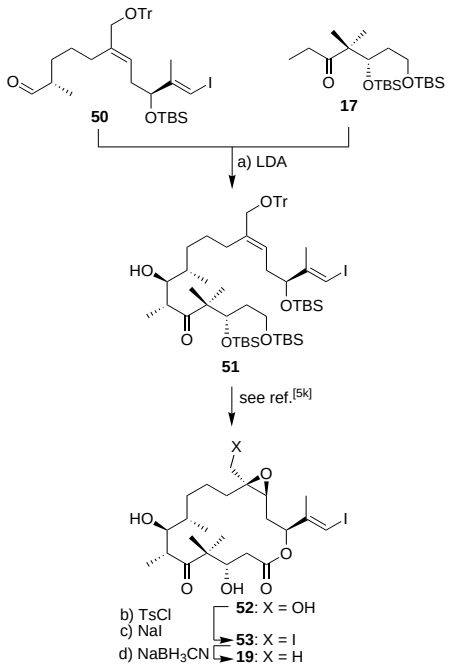
The next objective was to utilize the improved methodology to achieve a synthesis of vinyl iodide **19** (Figure 3). This result would not only assess the generality of the new process, but also would provide rapid access to a series of epothilone B analogues **18** by application of our previously[5k] described Stille coupling technology.[22] The synthesis of **19** commenced with a Wittig reaction between the common intermediate **15** and our previously reported aldehyde **45**[5k] as shown in Scheme 7.

The resulting unsaturated methyl ester **46** was further converted into alcohol **49** by a concise sequence of trans-



Scheme 7. Synthesis of aldehyde **50**: a) **15** (1.3 equiv based on **45**), benzene, reflux, 18 h, 92%; b) DIBAL (3.0 equiv), THF, −78°C, 3 h, 71%; c) TrCl (1.2 equiv), 4-DMAP (1.4 equiv), DMF, 80°C, 24 h, 94%; d) HF·py, py/THF, 0°C, 4 h, 67%; e) SO_3·py (5.0 equiv), Et_3N (5.0 equiv), DMSO/CH_2Cl_2 1:1, 0°C, 1 h, ca. 98% (crude).

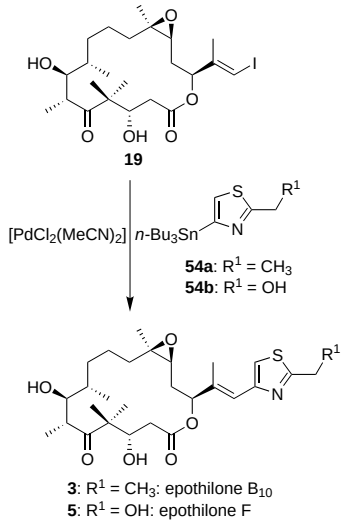
formations similar to those described for the preparation of **32** (Schemes 3 and 4). Once again, the three-step oxidation sequence was employed to deliver aldehyde **50**. Pleasingly, the aldol reaction with the ketone enolate derived from **17** under our newly defined conditions provided the desired aldol product **51** in excellent yield and selectivity (74%, >15:1 *dr*), which was transformed into macrocycle **52** (Scheme 8) using



Scheme 8. Synthesis of vinyl iodide **19**. a) LDA (2.4 equiv), **17** (2.3 equiv), THF, −78 to −40°C, 1 h, then add **50** (1.0 equiv), THF, −78°C, 2 min, then AcOH (4.8 equiv), −78 to 0°C, 74%; b) TsCl (1.5 equiv), Et_3N (3.0 equiv), 4-DMAP (1.0 equiv), CH_2Cl_2, 0 to 25°C, 2 h; c) NaI (4.5 equiv), acetone, 25°C, 12 h, 75% (two steps); d) $NaBH_3CN$ (11.5 equiv), DMPU, 45°C, 24 h, 70%. DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone.

our well-established and reliable route.[5k] To complete the preparation of **19**, removal of C26 hydroxy group was again required and was achieved by the same three-step protocol as described above. In addition to deiodination of aliphatic halides, the $NaBH_3CN$/HMPA combination has been shown to be effective for the dehalogenation of vinylic substrates.[12] We were pleased to find, however, that selective deiodination at the C26 position of **53** in this instance could be achieved in good yield using $NaBH_3CN$/DMPU combination to provide the required vinyl iodide **19**.

We initially used the vinyl iodide **19** to complete the first total syntheses of the naturally occurring metabolites epothilone B_{10} (**3**)[6] and epothilone F (**5**)[6, 7d] (Scheme 9). The thiazole stannanes **54a** and **54b** were obtained from the respective bromides using established procedures,[5k] and the Stille coupling proceeded smoothly under our previously described conditions[5k] {[$PdCl_2(MeCN)_2$], DMF, 25°C}.



Scheme 9. Synthesis of epothilone B_{10} (**3**) and epothilone F (**5**): **54a–b** (2.0 equiv), [$PdCl_2(MeCN)_2$] (0.2 equiv), DMF, 25°C 25 h; **3**: 53%; **5**: 64%.

Wishing to extend this approach to the synthesis of further heterocyclic analogues, we prepared a series of pyridine stannanes **56a–g** from the bromides **55a–g** by metallation and quenching with $n$$Bu_3SnCl$ as shown in Scheme 10. However, application of our standard Stille coupling protocol, which generally required prolonged reaction times of more than 30 h, gradually caused substrate decomposition before any coupling products could be observed. A possible explanation, which accounts for the observation of highly polar material being formed, might be that opening of the macrocycle to generate a Pd-π-allyl complex can compete with the Stille coupling pathway, since Sn/Pd transmetallation as the rate limiting step would be retarded for the electron-poor pyridine stannanes employed. Efforts to overcome this problem involved extensive experimentation with different Pd sources [Pd^{II} and Pd^0 complexes], ligands (PPh_3, $AsPh_3$, and "ligandless" conditions), additives (CuI, $i$$Pr_2NEt$), solvents (THF, DMF, NMP), and temperatures (25 to 90°C).[23] Eventually, the desired coupling could be achieved employing CuI, which was first introduced as a co-catalyst by Liebeskind

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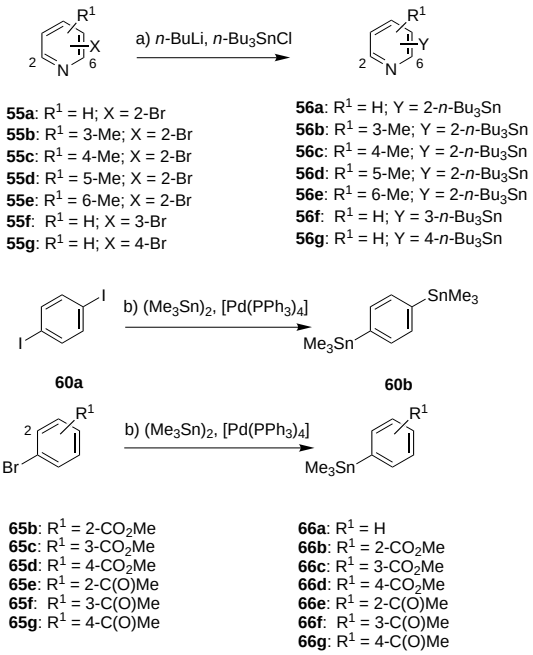
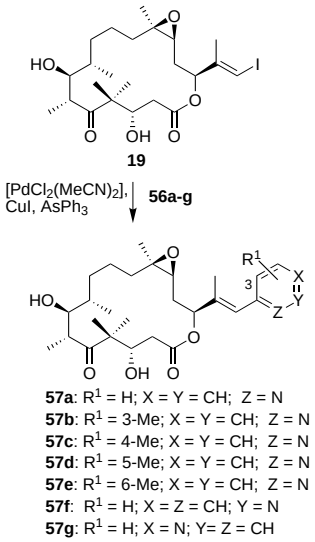


Scheme 10. Synthesis of pyridine stannanes **56a–g**, benzenoid distannane **60b** and benzenoid stannanes **66b–g**: a) *n*-BuLi (1.1 equiv, based on **55a–f**; 2.2 equiv, based on commercially available hydrochloride salt of **55g**), THF, −78 °C, 1 h; then *n*-Bu_3SnCl (1.2 equiv), −78 to 25 °C, 30 min; b) $(Me_3Sn)_2$ (1.2 equiv), $[Pd(PPh_3)_4]$ (0.1 equiv), toluene, reflux, 30 min. **56a–g**: 40 to 89 %; **66a** commercially available; **66b–g**: 50 to 95 %; **60b**: 83 %.

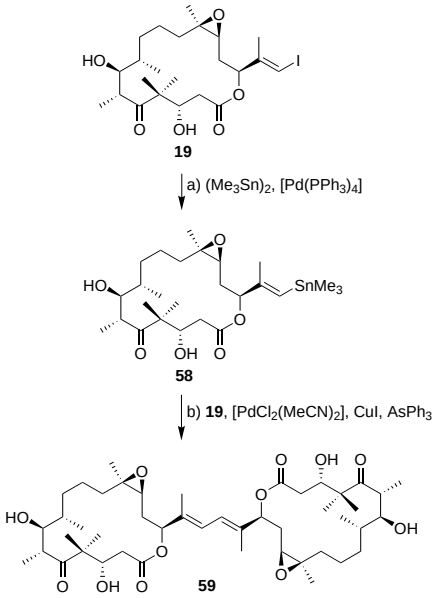
et al.[24] A previous report[25] indicated that with "weak" ligands as $AsPh_3$ in highly dipolar solvents, stannanes may form organocopper intermediates that transmetallate onto Pd more readily than the original tin species. As a crucial factor for the success of this protocol we rigorously ensured the quality of the employed CuI, which had to be freshly purified in a procedure rigorously avoiding exposure to light.[26]

Under these conditions, coupling of the stannanes **56a–g**[28c,e] proceeded rapidly (1 h or less) to give the desired epothilone B pyridine analogues **57a–g** in good yields (Scheme 11). The preliminary biological testing revealed generally high microtubule stabilizing activities for this new class of heterocycle modified epothilone analogues, with the exceptional lack of activity in case of derivative **57b** most likely being attributed to sterical interactions between the two methyl groups at C16 of the vinylic side chain region and in position 3 of the pyridine ring. These pyridine epothilones exhibited interesting biological properties as reported elsewhere.[27] Also noteworthy is the increased polarity and water solubility of the easily ionized pyridine analogues, which became apparent in the course of their synthesis and purification.

As a part of our investigations of the Stille coupling reaction, we also explored the possibility to obtain the above described analogues via the macrocyclic vinyl stannane **58** (Scheme 12). This strategy, although later dismissed, led to an unexpected and very interesting finding: Along with small quantities of the desired products **57a–g**, the dimeric epothilone **59** was obtained in varying amounts as a side product resulting from stannane homocoupling. Subjected to



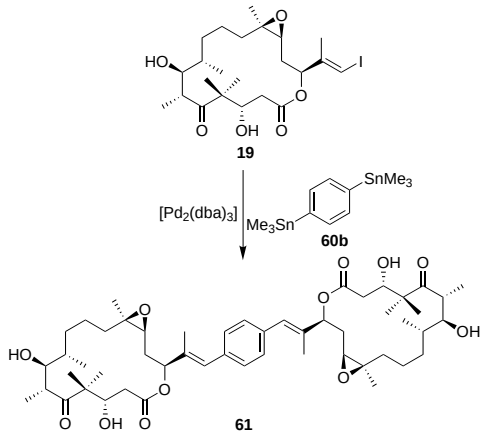
Scheme 11. Synthesis of pyridine analogues **57a–g**: **56a–g** (2.5 equiv), $[PdCl_2(MeCN)_2]$ (0.5 equiv), CuI (2.0 equiv), $AsPh_3$ (1.0 equiv), DMF, 25 °C, 1 h, 52 to 73 %.



Scheme 12. Synthesis of epothilone B dimer **59**: a) $(Me_3Sn)_2$ (5.0 equiv), $[Pd(PPh_3)_4]$ (0.1 equiv), toluene, 85 °C, 30 min, 50 %; b) **19** (1.0 equiv), $[PdCl_2(MeCN)_2]$ (0.5 equiv), CuI (2.0 equiv), $AsPh_3$ (1.0 equiv), DMF, 25 °C, 1 h, 44 %.

our routine tubulin polymerization assay, this unprecedented derivative surprisingly exhibited a remarkable biological activity. To our knowledge, this was the first example of tubulin polymerization properties being maintained in an epothilone derivative lacking a heterocyclic moiety. Thus, this results opened the way for a novel class of side chain modified epothilones (later we discovered other such compounds with good tubulin binding properties, vide infra).

In a first effort to further elucidate this new structural modification, we sought to combine an aromatic subunit, with the dimeric structural motif, by coupling vinyl iodide **19** to the aromatic distannane **60b**[28b,d] (Scheme 10) by preparing the new dimeric analogue **61** (Scheme 13).

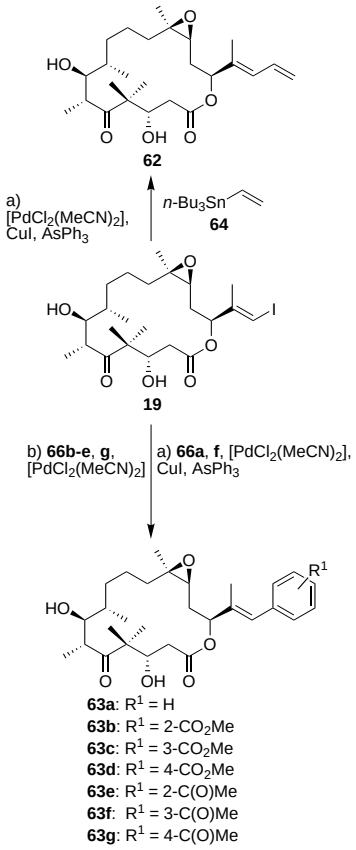


Scheme 13. Synthesis of epothilone B dimer **61**: $[Pd_2(dba)_3]$ (0.1 equiv), **60b** (1.0 equiv), DMF, 60 °C, 3 h, 28 %. dba = dibenzylideneacetone.

In an additional approach, the second epothilone unit of the dimeric compound **59** was replaced by smaller unsaturated residues, as in the unsubstituted vinyl and benzenoid derivatives **62** and **63a**, respectively, which are readily accessible from vinyl iodide **19** and commercially available stannanes **64** and **66a** (Scheme 10 and 14). Since the preliminary biological data[27] appeared to be most promising for the monomeric benzenoid derivative **63a**, this structural type was further modified by employing a series of carbonyl-substituted aromatic stannanes **66b–g**[28a,f] to obtain the corresponding benzenoid epothilone analogues **63b–g** (Scheme 14). Although the reactivity of the stannanes employed in these syntheses generally allowed us to return to the simpler standard coupling protocol omitting the sensitive co-catalyst CuI, the resulting long reaction times on some occasions apparently caused isomerization in the vinylic spacer region, in which cases again the improved, faster procedure yielded better results. Biological screening revealed that the absence of the nitrogen in the side chain was associated with low, if any activity except for the 3-acetyl derivative **63f** which retained considerable biological action. These studies demonstrate a great sensitivity of the side chain domain towards structural changes, and thereby reveal a promising potential for further systematic adjustments for fine-tuning the biological properties of future analogues within the same series.

Conclusion

The chemistry described herein renders our convergent strategy to the epothilones highly stereoselective at each step and allows for the construction of a variety of natural and designed epothilones with novel side chain modifications. Particularly attractive is the ability of vinyl iodide **19** to serve as a common intermediate for accessing a variety of structures through a Stille coupling reaction. The chemical synthesis of the designed epothilones disclosed in this article allowed the investigation of their chemical biology, thus leading to findings regarding the structure–activity relationships within the epothilone family. Of particular importance was the establishment of the nitrogen atom as a crucial element for potent biological action.[29]



Scheme 14. Synthesis of benzenoid analogues **63a–g** and vinyl analogue **62**: **62**, **63a**,**f**: a) **64** or **66a**,**f** (2.0 equiv), $[PdCl_2(MeCN)_2]$ (0.2 equiv), CuI (0.2 equiv), $AsPh_3$ (0.6 equiv), DMF, 25 °C, 1 h. **63b–e** and **63g**: b) **66b–e** or **66g** (5.0 equiv), $[PdCl_2(MeCN)_2]$ (1.0 equiv), DMF, 25 °C, 30 to 68 h. **62**: 46 %; **63a–g**: 38 to 91 %.

Experimental Section

General techniques: All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran (THF) and diethyl ether (ether) were distilled from sodium/benzophenone and methylene chloride (CH_2Cl_2), benzene (PhH), and toluene from calcium hydride. Anhydrous solvents were also obtained by passing them through commercially available activated alumina columns. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. All reagents were purchased at highest commercial quality and used without further purification, unless otherwise stated. All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and 7 % ethanolic phosphomolybdic acid or *p*-anisaldehyde solution and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.25, 0.50, or 1 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker DRX-600, AMX-500, AMX-400, or AC-250 instruments and calibrated using residual undeuterated solvents as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad. IR spectra were recorded on a Perkin–Elmer 1600 series FT-IR specrometer. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter. High resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions and matrix-assisted (MALDI-FTMS) mass spectra were recorded on a PerSeptive Biosystems Voyager IonSpec mass spectrometer. Electrospray (ESI) mass

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spectra were recorded on an API 100 Perkin–Elmer mass spectrometer. Melting points (m.p.) are uncorrected and were recorded on a Thomas-Hoover Unimelt capillary melting point apparatus.

Iodide 24: (*R*)-3-Bromo-2-methylpropanol **22** (6.5 g, 42.4 mmol, 1.0 equiv) was dissolved in DMF (42 mL, 1M), the resulting solution cooled to 0 °C, and *tert*-butyldimethylsilyl chloride (8.3 g, 55.2 mmol, 1.3 equiv) and then imidazole (4.34 g, 63.7 mmol, 1.5 equiv) were added. The reaction mixture was allowed to reach 25 °C and stirred for 45 min before being diluted with ether (200 mL). This solution was poured into a separatory funnel containing hexanes (200 mL) and washed with HCl (1M, 200 mL), and a saturated aqueous NaCl solution (25 mL), and then dried ($MgSO_4$) and evaporated. The crude silyl ether **23** (ca. 11.3 g) was used directly in the next step.

The crude silyl ether **23** from the previous step (ca. 11.3 g, 42.4 mmol, 1.0 equiv) was dissolved in acetone (200 mL) and treated with NaI (19.0 g, 127.2 mmol, 3.0 equiv). The reaction mixture was heated at reflux for 18 h before being diluted with ether (200 mL) and poured into a separatory funnel containing hexanes (200 mL). The organic solution was washed with water (3 × 200 mL), dried ($MgSO_4$), evaporated, and the residue purified by flash column chromatography (silica gel, 0 to 5% ether in hexanes) to afford pure iodide **24** (13.3 g, 99%, two steps). $R_f = 0.92$ (5% ether in hexanes); $[\alpha]_D^{22} = -9.4$ ($c = 1.0$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2954$, 2858, 1465, 1254, 1101, 839, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 3.52$ (dd, $J = 10.0$, 5.0 Hz, 1H, CH_2OSi), 3.39 (dd, $J = 10.0$, 7.0 Hz, 1H, CH_2OSi), 3.30 (dd, $J = 9.5$, 5.0 Hz, 1H, CH_2I), 3.25 (dd, $J = 9.5$, 5.5 Hz, 1H, CH_2I), 1.63 (m, 1H, $CHCH_3$), 0.95 (d, $J = 7.0$ Hz, $CHCH_3$), 0.89 (s, 9H, $(CH_3)_3CSi$), 0.06 (s, 6H, $(CH_3)_2Si$); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 66.5$, 37.2, 25.8, 17.1, 13.7, −5.5.

Olefin 25: To a solution of iodide **24** (6.5 g, 20.7 mmol, 1.0 equiv) in THF (20 mL, 1M) at 0 °C was added 3-butenylmagnesium bromide (58 mL, 0.5M in THF, 29.0 mmol, 1.4 equiv) followed by a solution of Li_2CuCl_4 (21 mL, 0.01M, 0.2 mmol, 0.01 equiv) [prepared by dissolving LiCl (85 mg, 2.0 mmol, 2.0 equiv) and $CuCl_2$ (134 mg, 1.0 mmol, 1.0 equiv) in THF (100 mL, 0.01M)]. The reaction mixture was stirred at 0 °C for 1 h before dilution with ether (300 mL) and quenching with HCl (1M, 200 mL). The organic layer was separated, washed a further time with HCl (1M, 200 mL), then saturated aqueous NaCl solution (200 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography (silica gel, 3% ether in hexanes) to afford the olefin **25** as an oil (4.83 g, 96%). **25**: $R_f = 0.95$ (5% ether in hexanes); $[\alpha]_D^{22} = -3.4$ ($c = 1.0$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2931$, 2858, 1642, 1465, 1254, 1096, 839, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.82$ (ddt, $J = 17.1$, 10.3, 6.8 Hz, 1H, $CH=CH_2$), 5.00 (dd, $J = 17.1$, 1.9 Hz, 1H, $CH=CH_2$), 4.93 (ddt, $J = 10.3$, 2.2, 1.1 Hz, 1H, $CH=CH_2$), 3.44 (dd, $J = 9.9$, 5.9 Hz, 1H, CH_2OSi), 3.36 (dd, $J = 9.9$, 6.6 Hz, 1H, CH_2OSi), 2.06–2.01 (m, 2H, $CH_2CH=CH_2$), 1.57 (m, 1H, $CHCH_3$),1.46–1.34 (m, 4H, CH_2CH_2), 0.90 (s, 9H, $(CH_3)_3CSi$), 0.87 (d, $J = 6.6$ Hz, 3H, CH_3CH), 0.04 (s, 6H, $(CH_3)_2Si$); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 139.0$, 114.1, 68.2, 35.5, 34.0, 32.6, 26.2, 25.8, 16.6, −5.5.

Alcohol 26:[4g] A solution of olefin **25** (19.3 g, 79.4 mmol, 1.0 equiv) in CH_2Cl_2 (800 mL, 0.1M) was cooled to −78 °C and sparged with ozone for ca. 30 min (until a blue color persisted). Oxygen was then passed through the solution for ca. 15 min, causing the blue color to fade, PPh_3 (63.0 g, 240 mmol, 3.0 equiv) was added and the stirred reaction mixture was allowed to warm to 25 °C over 1.5 h. The solvent was removed under reduced pressure and the mixture was dissolved in EtOH (800 mL, 0.1M). After cooling to 0 °C, sodium borohydride (3.0 g, 79.6 mmol, 1.0 equiv) was added portionwise over 15 min, and the resulting solution was stirred at that temperature for 30 min. The reaction mixture was quenched by the cautious addition of saturated aqueous NH_4Cl solution (500 mL) followed by ether (500 mL). The organic layer was separated and the aqueous phase was extracted with ether (2 × 500 mL). The combined organic fractions were dried ($MgSO_4$), evaporated and the residue purified by flash column chromatography (10 to 70% ether in hexanes) to afford the alcohol **26**[4g] as an oil (17.9 g, 91%).

The alcohol **26** was converted to phosphonium salt **27**[4g] by a previously reported procedure.

Ylide 15:[4g] The crude phosphonium salt **27** (46.4 g, ca. 75.0 mmol, 1.0 equiv) was dissolved in THF (375 mL, 0.2M), and the solution was cooled to 0 °C. Potassium bis(trimethylsilyl)amide (300 mL, 0.5M in toluene, 150.0 mmol, 2.0 equiv) was slowly added and the resulting orange solution was stirred for at 0 °C for 30 min. The mixture was then cooled to −78 °C and freshly distilled methyl chloroformate (sparged with Ar for 15 min prior to use) (6.4 mL, 82.5 mmol, 1.1 equiv) was added dropwise. Stirring at −78 °C was continued for another 3 h, the reaction mixture was then quenched with saturated aqueous $NaHCO_3$ solution (50 mL) and the mixture was allowed to warm to 25 °C. The mixture was partitioned between water (750 mL) and CH_2Cl_2 (500 mL) and the organic layer was washed with saturated aqueous NaCl solution (150 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product **15**[4g] (ca. 33.7 g) was used directly in the next reaction without further purification.

Aldehyde 29: $Ph_3P{=}CHCHO$ (51.5 g, 169.0 mmol, 1.15 equiv) was added to a solution of aldehyde **28**[4g] (18.7 g, 147.0 mmol, 1.0 equiv) in CH_2Cl_2 (300 mL, 0.5M) and the mixture was heated at reflux for 12 h. The mixture was then filtered through a short pad of silica gel followed by washing with 2:1 ether/hexanes and the solvents were removed under reduced pressure. The crude product was then purified by crystallization (CH_2Cl_2/hexanes) to afford aldehyde **29** as a solid (18.5 g, 82%); **29**: m.p.: 88–89 °C (CH_2Cl_2/hexanes); $R_f = 0.73$ (ether); IR (thin film): $\tilde{\nu}_{max} = 3066$, 2828, 2741, 1668, 1621, 1505, 1428, 1372, 1330, 1185, 1144, 1118, 968, 738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.70$ (d, $J = 7.7$ Hz, 1H, CHO), 7.43 (s, 1H, SCH=C), 7.38 (d, $J = 15.4$ Hz, 1H,$CH{=}CHCHO$), 6.92 (dd, $J = 15.4$, 7.7 Hz, 1H, $CH{=}CHCHO$), 2.75 (s, 3H, $N{=}C(CH_3)S$); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 193.6$, 167.2, 151.3, 143.4, 130.2, 122.9, 19.4; ES HRMS: *m*/*z*: 154.0326 $[M+H]^+$ calcd for C_7H_7NOS 154.0327.

Alcohol 30: Allylmagnesium bromide (198 mL, 1M in ether, 198.0 mmol, 2.1 equiv) was added dropwise over 30 min to a solution of (−)-$(Ipc)_2BOMe$ (62.5 g, 198.0 mmol, 2.1 equiv) in ether (500 mL, 0.4M) at 0 °C and the resulting pale gray suspension was allowed to warm to 25 °C over 1 h. The ether was removed under reduced pressure and pentane (500 mL) was added to the residual solid. The resulting slurry was stirred at 25 °C for 15 min following which the solids were allowed to settle over 1 h. The clear supernatant was then transferred carefully to a separate flask via filter cannula. This process was repeated four times (with the same quantity of pentane each time) and the resulting solution was reduced to a concentration of ca. 0.2M. This solution was added dropwise, over 30 min, to a solution of aldehyde **29** (14.5 g, 94.6 mmol, 1.0 equiv) in 2:1 CH_2Cl_2/ether (300 mL, 0.3M) at −100 °C. After 2 h at −100 °C, MeOH (50 mL) was added and the mixture was allowed to warm to 25 °C. Aminoethanol (57.8 mL, 0.94 mol, 10.0 equiv) was added and stirring was continued for 15 h. The work up procedure was completed by the addition of saturated aqueous NH_4Cl solution (200 mL) and extraction with EtOAc (3 × 100 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, 10 to 90% ether in hexanes) furnished alcohol **30** (17.7 g, 96%). **30**: colorless oil; $R_f = 0.35$ (60% ether in hexanes); $[\alpha]_D^{22} = -29.4$ ($c = 1.1$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3356$, 3108, 2925, 1640, 1505, 1435, 1323, 1184, 1128, 1034, 969, 915, 734 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.85$ (s, 1H, SCH=C), 6.53 (m, 2H, $CH{=}CH$), 5.82 (dddd, $J = 17.3$, 10.1, 7.1, 7.1 Hz, 1H, $CH{=}CH_2$), 5.12 (dddd, $J = 17.0$, 1.3, 1.3, 1.3 Hz, 1H, $CH=CH_2$), 5.09 (d, $J = 9.9$ Hz, 1H, $CH=CH_2$), 4.31 (m, 1H, CHOSi), 2.66 (s, 3H, $N{=}C(CH_3)S$), 2.41–2.30 (m, 2H, $CH_2CH=CH_2$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 166.1$, 152.9, 134.2, 134.1, 122.6, 118.1, 114.6, 71.1, 41.7, 19.1; FAB HRMS (NBA/NaI): *m*/*z*: 196.0801 $[M+H]^+$ calcd for $C_{10}H_{13}NOS$ 196.0796.

Silyl ether 31: To a solution of alcohol **30** (17.7 g, 91.0 mmol, 1.0 equiv) in DMF (100 mL, 1M) at 0 °C was added imidazole (9.3 g, 136.0 mmol, 1.5 equiv) followed by *tert*-butyldimethylsilyl chloride (16.4 g, 109 mmol, 1.2 equiv). After warming to 25 °C over 2 h, the reaction was quenched by the addition of water (100 mL), 5% ether in hexanes was added (200 mL), and the organic layer separated. The aqueous phase was extracted with hexanes (3 × 100 mL), the combined organic fractions were dried ($NaSO_4$), and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, 0 to 20% ether in hexanes) furnished silyl ether **31** as a colorless oil (27.9 g, 99%). **31**: $R_f =$ 0.68 (40% ether in hexanes); $[\alpha]_D^{22} = -15.0$ ($c = 1.1$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3077$, 2955, 2856, 1641, 1508, 1469, 1436, 1361, 1254, 1179, 1077, 989, 914, 836, 776, 729 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.86$ (s, 1H, SCH=C), 6.52 (m, 2H, $CH{=}CH$), 5.84 (dddd, $J = 17.2$, 10.2, 7.1, 7.1 Hz, 1H, $CH{=}CH_2$), 5.07 (dddd, $J = 16.8$, 1.3, 1.3, 1.3 Hz, 1H, $CH=CH_2$), 5.04 (d, $J = 9.6$ Hz, 1H, $CH=CH_2$), 4.34 (ddd, $J = 6.1$, 6.1, 3.6 Hz, 1H, CHOSi), 2.70 (s, 3H, $N{=}C(CH_3)S$), 2.34 (dd, $J = 6.8$ Hz, 2H, CH_2CH), 0.92 (s, 9H, $(CH_3)_3CSi$), 0.07 (s, 3H, $(CH_3)_2Si$), 0.05 (s, 3H, $(CH_3)_2Si$); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 165.9$,

153.5, 135.1, 134.8, 121.9, 117.1, 114.1, 72.6, 42.9, 25.9, 19.3, −4.4, −4.7; FAB HRMS (NBA/NaI): *m/z*: 310.1671 $[M+H]^+$ calcd for $C_{16}H_{27}NOSSi$ 310.1661.

Aldehyde 16: To a solution of olefin **31** (10.8 g, 34.8 mmol, 1.0 equiv) in a mixture of THF (125 mL), *t*BuOH (125 mL) and H_2O (25 mL) at 0 °C was added 4-methylmorpholine *N*-oxide (4.5 g, 38.4 mmol, 1.1 equiv) followed by OsO_4 (3.5 mL, 2.5% *w/v* in *t*BuOH, 0.001 equiv). The mixture was vigorously stirred for 30 min at 0 °C and then for 12 h at 25 °C before being quenched with saturated aqueous Na_2SO_3 (100 mL). The resulting solution was stirred at 25 °C for 2 h and then partitioned between EtOAc (220 mL) and water (50 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (2 × 100 mL). The combined organic extracts were dried ($MgSO_4$), the solvents were removed under reduced pressure. Flash column chromatography (silica gel, EtOAc) provided the corresponding intermediate diols as a ca. 1:1 mixture of diastereoisomers (ca. 6.64 g).

The crude mixture of diols obtained from above (6.64 g, ca. 19.3 mmol, 1.0 equiv) was dissolved in a mixture of MeOH (100 mL) and water (50 mL) and the solution was cooled to 0 °C. $NaIO_4$ (25.0 g, 116.0 mmol, 6.0 equiv) was then added portionwise over 5 min and the resulting slurry was stirred vigorously for 30 min at 25 °C. After completion of the reaction, the mixture was partitioned between CH_2Cl_2 (150 mL) and water (50 mL) and the organic phase was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were washed with saturated aqueous NaCl solution (1 L), dried ($MgSO_4$), and concentrated under reduced pressure. Flash column chromatography (silica gel, 50% ether in hexanes) provided aldehyde **16** as an oil (5.4 g, 89%). **16**: $R_f = 0.74$ (60% ether in hexanes); $[\alpha]_D^{22} = -51.9$ ($c = 1.0$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3107, 2955, 2929, 2887, 2856, 2722, 1723, 1506, 1469, 1361, 1255, 1180, 1114, 1076, 969, 863, 778\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.79$ (dd, $J = 2.4$, 2.4 Hz, 1H, CHO), 6.90 (s, 1H, SCH=C), 6.56 (m, 2H, CH=CH), 4.83 (ddt, $J = 6.7$, 4.5, 2.2 Hz, 1H, CHOSi), 2.70 (s, 3H, N=C(CH_3)S), 2.68 (ddd, $J = 15.8$, 6.2, 2.9 Hz, 1H, CH_2CHO), 2.59 (ddd, $J = 15.9$, 4.9, 2.3 Hz, 1H, CH_2CHO), 0.89 (s, 9H, (CH_3)$_3$CSi), 0.08 (s, 3H, (CH_3)$_2$Si), 0.06 (s, 3H, (CH_3)$_2$Si); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 201.5$, 166.1, 152.8, 133.6, 122.8, 115.0, 68.6, 51.3, 25.7, 19.3, 18.1, −4.4, −5.0; FAB HRMS (NBA/NaI): *m/z*: 312.1464 $[M+H]^+$ calcd for $C_{15}H_{25}NO_2SSi$ 312.1454.

Unsaturated methyl esters 32 and 46: A mixture of aldehyde **16** (4.76 g, 15.3 mmol, 1.0 equiv) and stabilized ylide **15** (11.0 g, ca. 20.0 mmol, 1.3 equiv) in benzene (150 mL, 0.1M) was heated at reflux for 18 h. After cooling to 25 °C, the mixture was filtered through a pad of silica gel eluting with 60% ether in hexanes and the solvent was removed under reduced pressure. Flash column chromatography (silica gel, 50% ether in hexanes) furnished methylester **32** (7.4 g, 84%). **32**: $R_f = 0.73$ (50% ether in hexanes); $[\alpha]_D^{22} = -7.3$ ($c = 1.0$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2954, 2930, 2890, 2856, 1716, 1646, 1508, 1489, 1436, 1387, 1362, 1287, 1254, 1196, 1894, 1006, 970, 837, 777\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.88$ (s, 1H, SCH=C), 6.82 (t, $J = 7.4$ Hz, 1H, C=CH), 6.52 (m, 2H, CH=CH), 4.39 (td, $J = 6.1$, 1.9 Hz, 1H, CHOSi), 3.71 (s, 3H, CH_3O), 3.41 (dd, $J = 9.7$, 5.7 Hz, 1H, CH_2OSi), 3.32 (dd, $J = 9.6$, 6.6 Hz, 1H, CH_2OSi), 2.70 (s, 3H, N=C(CH_3)S), 2.45 (dd, $J = 6.8$, 6.8 Hz, 2H, CH_2CHOSi), 2.27–2.25 (m, 2H, CH_2C=C), 1.54–1.00 (m, 5H), 0.91 (s, 9H, (CH_3)$_3$CSi), 0.88 (s, 9H, (CH_3)$_3$CSi), 0.83 (d, $J = 6.6$ Hz, 3H, CH_3CH), 0.07 (s, 3H, (CH_3)$_2$Si), 0.05 (s, 3H, (CH_3)$_2$Si), 0.02 (s, 6H, (CH_3)$_2$Si); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta =$ 168.3, 166.0, 153.2, 138.6, 134.7, 133.8, 122.3, 114.5, 72.0, 68.3, 51.6, 37.6, 35.6, 33.1, 27.3, 26.7, 25.9, 25.8, 19.3, 18.3, 18.2, 16.6, −4.4, −4.9, −5.4; FAB HRMS (NBA/CsI): *m/z*: 714.2465 $[M+Cs]^+$ calcd for $C_{30}H_{55}NO_4SSi_2$ 714.2445.

The above reaction was repeated under identical conditions using aldehyde **45** (8.27 g, 23.3 mmol) to afford unsaturated methyl ester **46** (13.41 g, 92%). **46**: $R_f = 0.89$ (25% ether in hexanes); $[\alpha]_D^{22} = -7.5$ ($c = 1.0$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2954, 2928, 2856, 1717, 1462, 1436, 1361, 1274, 1255, 1206, 1089, 836, 776, 674\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.68$ (dd, $J = 7.6$, 7.3 Hz, 1H, C=CHCH$_2$CH(O)), 6.21 (s, 1H, CH=CCH$_3$), 4.20 (dd, $J = 7.3$, 5.4 Hz, 1H, CHOSi), 3.71 (s, 3H, CH_3O), 3.41 (dd, $J = 9.7$, 6.0 Hz, 1H, CH_2OSi), 3.34 (dd, $J = 6.5$, 9.7 Hz, 1H, CH_2OSi), 2.36 (m, 2H, CH_2CHOSi), 2.24 (m, 2H, CH_2C=CH), 1.78 (s, 3H, CH=CCH_3), 1.57 (m, 1H), 1.33 (m, 3H), 1.05 (m, 1H), 0.88 (s, 9H, (CH_3)$_3$CSi), 0.85 (s, 9H, (CH_3)$_3$CSi), 0.84 (d, $J = 7.3$ Hz, 3H, CH_3CH), 0.02 (s, 9H, 2 × (CH_3)$_2$Si), −0.03 (s, 3H, (CH_3)$_2$Si); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 168.1$, 149.6, 138.0, 133.9, 78.1, 68.2, 51.6, 35.7, 35.6, 33.0, 29.7, 27.3, 26.7, 25.9, 25.7, 19.7, 18.3, 18.1, 16.6, −5.0, −5.2, −5.4; FAB HRMS (NBA/CsI): *m/z*: 757.1590 $[M+Cs]^+$ calcd for $C_{27}H_{53}IO_4Si_2$ 757.1582.

Allylic alcohols 33 and 47: To a solution of methyl ester **32** (7.4 g, 12.7 mmol, 1.0 equiv) in THF (63 mL, 0.2M) at −78 °C, DIBAL (38 mL, 1M in CH_2Cl_2, 38.0 mmol, 3.0 equiv) was added dropwise over 30 min. The reaction mixture was stirred for a further 3 h at that temperature, then quenched by very cautious addition of MeOH (10 mL) and allowed to warm slowly to 25 °C. Saturated aqueous sodium/potassium tartrate (12 mL) was added and the resulting mixture was stirred rapidly at 25 °C for 3 h. The organic layer was separated and the aqueous phase was extracted with ether (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography (silica gel, 10 to 60% ether in hexanes) furnished allylic alcohol **33** (6.54 g, 93%). **33**: $R_f = 0.70$ (80% ether in hexanes); $[\alpha]_D^{22} = -2.1$ ($c = 1.0$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3380, 2954, 2929, 2856, 1507, 1489, 1408, 1387, 1362, 1253, 1182, 1095, 836, 777\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.86$ (s, 1H, SCH=C), 6.51 (m, 2H, CH=CH), 5.48 (dd, $J = 7.2$, 7.2 Hz, 1H, C=CHCH$_2$), 4.31 (td, $J = 6.4$, 2.2 Hz, 1H, CHOSi),4.03 (s, 2H, CH_2OH), 3.41 (dd, $J = 9.6$, 5.9 Hz, 1H, CH_2OSi), 3.33 (dd, $J = 9.6$, 6.6 Hz, 1H, CH_2OSi), 2.69 (s, 3H, N=C(CH_3)S), 2.37–2.30 (m, 2H, CH_2CHOSi), 2.06 (t, $J = 7.4$ Hz, 2H, CH_2C=CH), 1.56–1.31 (m, 4H), 0.91 (s, 9H, (CH_3)$_3$CSi), 0.88 (s, 9H, (CH_3)$_3$CSi), 0.83 (d, $J = 6.6$ Hz, 3H, CH_3CH), 0.07 (s, 3H, (CH_3)$_2$Si), 0.05 (s, 3H, (CH_3)$_2$Si), 0.02 (s, 6H, (CH_3)$_2$Si); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 165.9$, 153.4, 141.1, 135.3, 122.4, 121.8, 114.0, 72.7, 68.3, 67.1, 36.6, 35.7, 33.3, 28.6, 25.9, 19.3, 18.3, 18.3, 16.7, −4.4, −4.8, −5.4; FAB HRMS (NBA/CsI): *m/z*: 686.2518 $[M+Cs]^+$ calcd for $C_{29}H_{56}NO_3SSi_2$ 686.2496.

The above reaction was repeated under identical conditions using methyl ester **46** (13.44 g, 21.5 mmol) to afford allylic alcohol **47** (9.11 g, 71%). **47**: $R_f = 0.35$ (25% ether in hexanes); $[\alpha]_D^{22} = -2.2$ ($c = 1.0$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2952, 2927, 2891, 2856, 2360, 2341, 2330, 1472, 1465, 1459, 1387, 1361, 1279, 1252, 1088, 1005, 941, 895, 776\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.13$ (dd, $J = 1.8$, 1.0 Hz, 1H, CH=CCH$_3$), 5.33 (dd, $J = 7.3$, 7.0 Hz, 1H, CH=CCH$_2$OH), 4.13 (dd, $J = 6.2$, 6.2 Hz, 1H, CHOSi), 4.01 (s, 2H, CH_2OH), 3.41 (dd, $J = 9.7$, 5.9 Hz, 1H, CH_2OSi), 3.35 (dd, $J = 9.7$, 6.5 Hz, 1H, CH_2OSi), 2.24 (m, 2H, CH_2CHOSi), 2.04 (m, 2H), 1.77 (s, 3H, CH=CCH_3), 1.57 (m, 1H, CHCH$_3$), 1.37 (m, 3H), 1.05 (m, 1H), 0.88 (s, 9H, (CH_3)$_3$CSi), 0.86 (s, 9H, (CH_3)$_3$CSi), 0.85 (d, $J = 7.0$ Hz, 3H, CH_3CH), 0.02 (s, 6H, (CH_3)$_2$Si),0.01 (s, 3H, (CH_3)$_2$Si), −0.03 (s, 3H, (CH_3)$_2$Si); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 150.1$, 141.2, 122.1, 77.5, 68.3, 67.1, 35.6, 34.5, 33.3, 28.5, 25.9, 25.7, 19.6, 18.2, 16.7, −4.9, −5.1, −5.3; FAB HRMS (NBA/CsI): *m/z*: 729.1615 $[M+Cs]^+$ calcd for $C_{26}H_{53}IO_3Si_2$ 729.1632.

Triphenylmethyl ethers 34 and 48: Allylic alcohol **33** (6.6 g, 11.9 mmol, 1.0 equiv) was dissolved in DMF (50 mL, 0.25M) and 4-DMAP (2.0 g, 16.6 mmol, 1.4 equiv) and trityl chloride (3.98 g, 14.2 mmol, 1.2 equiv) were added. The reaction mixture was stirred at 80 °C for 24 h, then cooled to 25 °C and quenched by the addition of water (12 mL), 50% ether in hexanes was added (50 mL) and the organic layer was separated. The aqueous phase was extracted with the same solvent mixture (3 × 25 mL), the combined organic fractions were dried (Na_2SO_4) and the solvents were removed under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, 5 to 40% ether in hexanes) to afford the required ether **34** as an oil (7.7 g, 82%). **34**: $R_f = 0.70$ (40% ether in hexanes); $[\alpha]_D^{22} = +4.1$ ($c = 1.0$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3059, 2954, 2928, 2856, 1597, 1490, 1469, 1447, 1388, 1362, 1320, 1253, 1179, 1090, 969, 835, 777, 705\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.48–7.20$ (m, 15H, Ph), 6.85 (s, 1H, SCH=C), 6.56 (m, 2H, CH=CH), 5.65 (t, $J = 7.2$ Hz, 1H, C=CHCH$_2$), 4.36 (dt, $J = 6.1$, 4.0 Hz, 1H, CHOSi), 3.48 (s, 2H, CH_2OTr), 3.38 (dd, $J = 9.7$, 5.7 Hz, 1H, CH_2OSi), 3.27 (dd, $J = 9.6$, 6.9 Hz, 1H, CH_2OSi), 2.71 (s, 3H, N=C(CH_3)S), 2.40–2.35 (m, 2H, CH_2CHOSi), 2.03 (t, $J = 7.3$ Hz, 2H, CH_2C=CH), 1.48–1.18 (m, 5H), 0.94 (s, 9H, (CH_3)$_3$CSi), 0.88 (s, 9H, (CH_3)$_3$CSi), 0.78 (d, $J = 6.8$ Hz, 3H, CH_3CH), 0.11 (s, 3H, (CH_3)$_2$Si), 0.08 (s, 3H, (CH_3)$_2$Si), 0.02 (s, 6H, (CH_3)$_2$Si); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 165.8$, 153.6, 144.4, 138.6, 135.5, 128.6, 127.7, 126.8, 122.1, 121.8, 114.0, 86.5, 76.7, 72.9, 68.4, 67.4, 36.6, 35.7, 33.3, 29.0, 25.9, 19.3, 18.3, 16.6, −4.4, −4.7, −5.3; FAB HRMS (NBA/CsI): *m/z*: 928.3621 $[M+Cs]^+$ calcd for $C_{48}H_{69}NO_3SSi_2$ 928.3591.

The reaction was repeated under identical conditions using allylic alcohol **47** (7.71 g, 12.9 mmol) to afford the required ether **48** (10.18 g, 94%). **48**: $R_f = 0.78$ (20% ether in hexanes); $[\alpha]_D^{22} = -1.6$ ($c = 2.0$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2950, 2925, 2855, 2362, 2345, 1483, 1462, 1453, 1387, 1362, 1278,$

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1251, 1084, 1008, 940, 899, 841, 775 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 7.40 (m, 5H, Ph), 7.25 (m, 10H, Ph), 6.19 (s, 1H, C*H*=CCH$_3$), 5.52 (dd, $J =$ 7.3, 7.0 Hz, 1H, C*H*=CCH$_2$), 4.18 (dd, $J = 6.5$, 6.2 Hz, 1H, CHOSi), 3.45 (s, 2H, CH$_2$OTr), 3.37 (dd, $J = 9.7$, 5.7 Hz, 1H, CH$_2$OSi), 3.28 (dd, $J = 9.7$, 6.8 Hz, 1H, CH$_2$OSi), 2.17 (m, 2H, CH$_2$CHOSi), 1.97 (m, 2H, CH_2C=CH), 1.81 (s, 3H, CH=CCH_3), 1.46 (m, 1H, C*H*CH$_3$), 1.21 (m, 3H), 0.97 (m, 1H), 0.87 (s, 18H, (CH$_3$)$_3$CSi), 0.78 (d, $J = 7.3$ Hz, 3H, CH_3CH), 0.05 (s, 3H, (CH$_3$)$_2$Si), 0.01 (s, 9H, (CH$_3$)$_2$Si); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 150.2$, 144.3, 138.8, 128.7, 128.6, 127.7, 126.8 121.3, 86.5, 77.4, 68.3, 67.1, 35.7, 34.6, 33.2, 30.3, 29.7, 29.0, 26.0, 25.8, 19.7, 18.2, 16.6, −4.9, −5.0, −5.3; FAB HRMS (NBA/CsI): *m*/*z*: 971.2743 $[M+Cs]^+$ calcd for $C_{45}H_{67}IO_3Si_2$ 971.2728.

Alcohols 35 and 49: A solution of silyl ether **34** (7.59 g, 9.5 mmol, 1.0 equiv) in THF (95 mL, 0.1M) was cooled to 0 °C before the addition of a solution of HF·py in pyridine/THF mixture (144 mL) [from a stock solution prepared by addition of HF·py (20 mL) to pyridine (56.2 mL) in THF (98 mL)]. The reaction mixture was allowed to reach 25 °C and was stirred for 4 h before being quenched by cautious portionwise addition over 10 min to saturated aqueous $NaHCO_3$ solution (500 mL, adding sufficient solid $NaHCO_3$ to ensure complete neutralization) and EtOAc (250 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 25 mL). The combined organic extracts were washed with saturated aqueous NaCl solution (550 mL), dried and evaporated. Flash column chromatography of the residue (silica gel, 20 to 75% ether in hexanes) afforded alcohol **35** as an oil (4.28 g, 66%). **35**: $R_f = 0.30$ (50% ether in hexanes); $[\alpha]_D^{22} = +3.3$ ($c = 1.2$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3379$, 3058, 2953, 2926, 2856, 1597, 1490, 1448, 1363, 1253, 1181, 1052, 969, 835, 775, 706 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.49-7.21$ (m, 15H, Ph), 6.86 (s, 1H, SCH=C), 6.24 (m, 2H, CH=CH), 5.69 (t, $J = 7.0$ Hz, 1H, C=C*H*CH$_2$), 4.40 (dt, $J = 5.8$, 4.0 Hz 1H, CHOSi), 3.51 (s, 2H, CH$_2$OTr), 3.41 (dd, $J =$ 10.4, 5.8 Hz, 1H, CH_2OH), 3.36 (dd, $J = 10.5$, 6.5 Hz, 1H, CH_2OH), 2.71 (s, 3H, N=C(CH$_3$)S), 2.42–2.35 (m, 2H, CH_2CHOSi), 2.07 (m, 2H), 1.51–0.96 (m, 5H), 0.96 (s, 9H, (CH$_3$)$_3$CSi), 0.83 (d, $J = 6.8$ Hz, 3H, CH_3CH), 0.13 (s, 3H, (CH$_3$)$_2$Si), 0.11 (s, 3H, (CH$_3$)$_2$Si); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 165.9$, 153.4, 144.3, 138.3, 135.5, 128.6, 127.6, 126.7, 122.2, 121.7, 114.0, 86.4, 72.8, 68.0, 67.3, 36.5, 35.5, 33.0, 30.2, 28.8, 25.9, 25.6, 19.2, 18.2, 16.5, −4.4, −4.7; FAB HRMS (NBA/CsI): *m*/*z*: 814.2754 $[M+Cs]^+$ calcd for $C_{42}H_{55}NO_3SSi$ 814.2726.

The reaction was repeated under identical conditions using silyl ether **48** (10.08 g, 12.0 mmol) to furnish alcohol **49** (5.83 g, 67%). **49**: $R_f = 0.20$ (25% ether in hexanes); $[\alpha]_D^{22} = -2.7$ ($c = 1.0$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3358$, 2948, 2923, 2855, 2364, 2347, 1490, 1459, 1448, 1386, 1363, 1276, 1250, 1220, 1076, 938, 835, 775, 764, 745, 707 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 7.48 (m, 5H, Ph), 7.25 (m, 10H, Ph), 6.19 (s, 1H, C*H*=CCH$_3$), 5.51 (dd, $J =$ 7.0, 7.3 Hz, 1H, C=C*H*CH$_2$), 4.18 (dd, $J = 6.2$, 5.9 Hz, 1H, CHOSi), 3.45 (s, 2H, CH$_2$OTr), 3.41 (dd, $J = 10.5$, 6.0 Hz, 1H, CH_2OH), 3.33 (dd, $J = 10.5$, 6.5 Hz, 1H, CH$_2$OH), 2.27 (m, 2H, CH_2CHOSi), 1.99 (m, 2H, CH_2C=CH), 1.80 (s, 3H, CH=CCH_3), 1.48 (m, 1H), 1.22 (m, 3H), 1.00 (m, 1H), 0.87 (s, 9H, (CH$_3$)$_3$CSi), 0.83 (d, $J = 6.8$ Hz, 3H, CH_3CH), 0.05 (s, 3H, (CH$_3$)$_2$Si), 0.00 (s, 3H, (CH$_3$)$_2$Si); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 150.2$, 144.3, 138.6, 128.7, 127.7, 127.6, 126.8, 126.7, 122.4, 121.5, 87.3, 77.4, 68.2, 67.1, 35.6, 34.6, 33.1, 28.9, 25.8, 25.7, 19.7, 18.2, 16.5, −4.9, −5.0; FAB HRMS (NBA/CsI): *m*/*z*: 857.1872 $[M+Cs]^+$ calcd for $C_{39}H_{53}IO_3Si$ 857.1863.

Aldehydes 36 and 50: To a stirred solution of alcohol **35** (4.3 g, 6.3 mmol, 1.0 equiv) in a mixed solvent system of DMSO/CH_2Cl_2 (1:1, 63 mL, 0.1M) at 0 °C, was added Et_3N (4.4 mL, 32.0 mmol, 5.0 equiv) then solid SO_3·py complex (5.09 g, 32 mmol, 5.0 equiv, previously dried under vacuum for 1 h). The reaction mixture was stirred at that temperature for 1 h before being quenched by the addition of saturated aqueous NH_4Cl solution (100 mL) and ether (100 mL). The layers were separated and the aqueous phase was extracted with ether (3 × 100 mL). The combined organic extracts were then washed with saturated aqueous NaCl solution (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. After being dried under high vacuum for 2 h, the crude aldehyde **36** (4.1 g, ca. 95%) was used directly in the subsequent aldol reaction.

The reaction was repeated under identical conditions using alcohol **49** (5.38 g, 7.43 mmol) to furnish aldehyde **50** (5.29 g, ca. 98%) which was used directly in the subsequent aldol reaction.

Aldols 37 and 51: A solution of ketone **17**[4g] (3.4 g, 8.4 mmol, 2.3 equiv) in THF (10 mL) was added dropwise over 2 min to a freshly prepared solution of LDA at −78 °C [*n*-BuLi (5.5 mL, 1.6M in hexanes, 8.8 mmol, 2.4 equiv) was added to a diisopropylamine (1.24 mL, 8.8 mmol, 2.4 equiv) in THF (10 mL) at −78 °C, the solution was allowed to warm to 0 °C and then recooled to −78 °C]. After stirring for 1 h at −78 °C, the solution was allowed to warm up to −40 °C for 30 min. The reaction mixture was then recooled to −78 °C and a cold (−78 °C) solution of aldehyde **36** (2.5 g, 3.7 mmol, 1.0 equiv) in THF (17 mL, 0.1M overall) was added rapidly via cannula, running the solution down the wall of the receiving flask to ensure effective cooling before contact with the enolate solution. Upon completion of the addition, stirring was continued for a further 2 min before the reaction was quenched by the rapid injection of AcOH (1.02 mL, 17.8 mmol, 4.8 equiv) as a solution in THF (3 mL). After stirring for 5 min, the mixture was warmed to 25 °C and partitioned between ether (50 mL) and saturated aqueous NH_4Cl solution (50 mL). The aqueous phase was extracted with ether (3 × 50 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The reaction was repeated using another batch of aldehyde (1.6 g, 2.4 mmol) and the material from the two runs was combined for purification. Flash column chromatography (silica gel, 4 to 20% ether in hexanes) provided first unreacted ketone **17** (3.37 g, ca. 100%), and then the desired aldol product **37** (3.04 g, 76%) followed by more polar side products, including the unwanted diastereoisomer (445 mg, ca. 7%). **37**: $R_f = 0.40$ (20% ether in hexanes); $[\alpha]_D^{22} = -21.6$ ($c = 1.5$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3508$, 3058, 2955, 2884, 2856, 1682, 1597, 1490, 1472, 1449, 1388, 1360, 1256, 1179, 1101, 1004, 971, 910, 836, 775, 734, 707 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.45-7.18$ (m, 15H, Ph), 6.84 (s, 1H, SCH=C), 6.55 (m, 2H, CH=CH), 5.64 (t, $J = 7.2$ Hz, 1H, C=C*H*CH$_2$), 4.35 (ddd, $J = 6.0$, 6.0, 3.8 Hz, 1H, CHOSi), 3.88 (dd, $J = 7.6$, 2.7 Hz, 1H, CHOSi), 3.68 (ddd, $J = 10.0$, 8.0, 4.7 Hz, 1H, CH$_2$OSi), 3.67–3.58 (m, 1H, CH$_2$OSi), 3.47 (s, 2H, CH$_2$OTr), 3.42 (s, 1H, OH), 3.27–3.22 (m, 2H), 2.70 (s, 3H, N=C(CH$_3$)S), 2.40 (m, 2H, CH_2CHOSi), 2.04 (t, $J = 7.8$ Hz, 2H, CH_2C=CHCH$_2$), 1.69–1.27 (m, 4H), 1.20 (s, 3H, C(CH$_3$)$_2$), 1.08 (s, 3H, C(CH$_3$)$_2$), 1.00 (d, $J = 7.0$ Hz, 3H, CH_3CHC(O)), 0.93 (s, 9H, (CH$_3$)$_3$CSi), 0.91 (s, 9H, (CH$_3$)$_3$CSi), 0.89 (s, 9H, (CH$_3$)$_3$CSi), 0.70 (d, $J = 6.8$ Hz, 3H, CH_3CH), 0.11 (s, 3H, (CH$_3$)$_2$Si), 0.10 (s, 3H, (CH$_3$)$_2$Si), 0.09 (s, 3H, (CH$_3$)$_2$Si), 0.08 (s, 3H, (CH$_3$)$_2$Si); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 222.3$, 165.7, 153.6, 144.4, 138.5, 135.6, 128.7, 127.7, 126.7, 122.0, 121.8, 113.9, 86.5, 74.8, 74.1, 72.9, 67.4, 60.4, 53.9, 41.3, 37.8, 36.6, 35.4, 32.9, 29.1, 26.1, 26.0, 25.6, 22.9, 20.4, 19.3, 18.3, 18.3, 9.5, −3.7, −4.1, −4.4, −4.7, −5.3; FAB HRMS (NBA/CsI): *m*/*z*: 1214.5497 $[M+Cs]^+$ calcd for $C_{63}H_{99}NO_6SSi_3$ 1214.5555.

The reaction was repeated under identical conditions using aldehyde **50** (5.29 g, 7.29 mmol) to furnish known aldol **51**[5k] (6.07 g, 74%).

Silyl ether 38: The aldol product **37** (4.96 g, 4.6 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (45 mL, 0.1M), cooled to −78 °C and treated with 2,6-lutidine (1.23 mL, 11.4 mmol, 2.5 equiv) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.82 mL, 6.9 mmol, 1.5 equiv). The mixture was then warmed to 0 °C and stirred for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (50 mL) and the aqueous phase was extracted with ether (3 × 50 mL). The combined organic extracts were washed with saturated aqueous NaCl solution (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Flash column chromatography (silica gel, 2 to 95% ether in hexanes) furnished silyl ether **38** as a colorless oil (5.20 g, 95%). **38**: $R_f = 0.60$ (20% ether in hexanes); $[\alpha]_D^{22} = -17.9$ ($c = 0.9$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3059$, 2955, 2856, 1696, 1597, 1471, 1387, 1360, 1255, 1179, 1101, 986, 836, 775, 706, 632 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.48-7.20$ (m, 15H, Ph), 6.85 (s, 1H, SCH=C), 6.59 (m, 2H, CH=CH), 5.67 (t, $J = 7.0$ Hz, 1H, C=C*H*CH$_2$), 4.39 (ddd, $J = 5.5$, 5.5, 5.5 Hz, 1H, CHOSi), 3.89 (dd, $J = 7.7$, 2.6 Hz, 1H, CHOSi), 3.74 (d, $J = 5.1$ Hz, 1H, CHOSi), 3.69 (ddd, $J = 13.9$, 4.7, 4.7 Hz, 1H, CH$_2$OSi), 3.63–3.57 (m, 1H, CHOSi), 3.46 (s, 2H, CH$_2$OTr), 3.12 (quint, $J = 6.8$ Hz, 1H, CH$_3$C*H*C(O)), 2.71 (s, 3H, N=C(CH$_3$)S), 1.64–1.23 (m, 4H), 1.21 (s, 3H, C(CH$_3$)$_2$), 0.99 (s, 3H, C(CH$_3$)$_2$), 0.96 (d, $J = 7$ Hz, 3H, CH_3CHC(O)), 0.96 (s, 9H, (CH$_3$)$_3$CSi), 0.92 (s, 9H, (CH$_3$)$_3$CSi), 0.91 (s, 18H, 2 × (CH$_3$)$_3$CSi), 0.70 (d, $J = 6.8$ Hz, 3H, CH_3CH), 0.13 (s, 3H, (CH$_3$)$_2$Si), 0.11 (s, 3H, (CH$_3$)$_2$Si), 0.10 (s, 3H, (CH$_3$)$_2$Si), 0.08 (s, 3H, (CH$_3$)$_2$Si), 0.07 (s, 3H, (CH$_3$)$_2$Si), 0.06 (s, 3H, (CH$_3$)$_2$Si), 0.06 (s, 3H, (CH$_3$)$_2$Si), 0.06 (s, 3H, (CH$_3$)$_2$Si); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 218.1$, 165.7, 153.5, 144.3, 138.4, 135.5, 128.6, 127.6, 126.8, 122.2, 121.8, 113.9, 86.5, 74.0, 72.8, 67.4, 60.9, 53.6, 44.9, 38.8, 38.0, 36.6, 31.1, 29.3, 26.4, 26.2, 26.1, 26.0, 24.4, 19.4, 19.3, 18.4, 18.3, 18.2, 17.4, 15.0, −3.7, −3.7, −3.8, −4.0, −4.4, −4.7, −5.3, −5.3; FAB

HRMS (NBA/CsI): *m/z*: 1328.6491 $[M+Cs]^+$ calcd for $C_{69}H_{113}NO_6SSi_4$ 1328.6420.

Alcohol 39: To a solution of silyl ethers **38** (5.23 g, 4.4 mmol, 1.0 equiv) in THF (44 mL, 0.1 M) at 0 °C was added HF·py in pyridine/THF mixture (62 mL) (from a stock solution prepared as for the procedure for alcohol **35**) and the resulting solution was allowed to warm to 25 °C and stirred for 3 h. The reaction mixture was diluted with EtOAc (40 mL) and quenched by careful addition to saturated aqueous $NaHCO_3$ solution (250 mL, adding sufficient solid $NaHCO_3$ to ensure complete neutralization) and the product was extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography (silica gel, 30 % ether in hexanes) furnished alcohol **39** as a pale yellow oil (3.6 g, 71 %), together with more polar side products (1.17 g). These products were resilylated under the same conditions applied for the preparation of silyl ether **38** and the resulting product was desilylated as above to provide a further 0.83 g (16 %) of **39** (87 % combined yield). **39**: $R_f = 0.35$ (60 % ether in hexanes); $[\alpha]_D^{22} = -11.8$ ($c = 1.0$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3420$, 2954, 2856, 1690, 1490, 1472, 1360, 1252, 1180, 1088, 1054, 987, 836, 775, 707 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.49-7.40$ (m, 5H, Ph), 7.30–7.20 (m, 10H, Ph), 6.84 (s, 1H, SCH=C), 6.60–6.58 (m, 2H, CH=CH), 5.68 (dd, $J = 7.1$, 7.1 Hz, 1H, C=C*H*CH_2), 4.42–4.38 (m, 1H, CHOSi), 4.06 (dd, $J = 4.9$, 4.9 Hz, 1H, CHOSi), 3.78 (dd, $J = 7.0$, 1.6 Hz, 1H, CHOSi), 3.66 (m, 2H, C*H*$_2$OH), 3.47 (br s, 2H, CH_2OTr), 3.12 (dq, $J = 6.8$, 6.8 Hz, 1H, CH_3CHC(O)), 2.70 (s, 3H, N=C(CH_3)S), 2.43–2.37 (m, 2H, C*H*$_2$CHOSi), 2.12–2.04 (m, 2H, C*H*$_2$C=CH), 1.62–1.57 (m, 2H, C*H*$_2$$CH_2$OH), 1.32–1.28 (m, 1H), 1.21 (s, 3H, C(CH_3)$_2$), 1.07 (d, $J = 7.0$ Hz, 3H, C*H*$_3$CHC(O)), 1.03 (s, 3H, C(CH_3)$_2$), 0.96 (s, 9H, $(CH_3)_3$CSi), 0.92 (s, 9H, $(CH_3)_3$CSi), 0.91 (s, 9H, $(CH_3)_3$CSi), 0.84 (d, $J = 6.5$ Hz, 3H, C*H*$_3$CH), 0.13 (s, 6H, $(CH_3)_2$Si), 0.11 (s, 3H, $(CH_3)_2$Si), 0.08 (s, 3H, $(CH_3)_2$Si), 0.08 (s, 3H, $(CH_3)_2$Si), 0.06 (s, 3H, $(CH_3)_2$Si); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 219.3$, 165.7, 153.4, 144.2, 138.3, 135.4, 128.5, 127.6, 126.7, 122.2, 121.7, 113.9, 86.4, 73.0, 72.7, 67.3, 59.9, 53.6, 44.9, 38.6, 38.1, 36.5, 30.8, 29.2, 26.3, 26.2, 26.1, 26.1, 26.0, 25.9, 25.8, 24.7, 19.2, 18.4, 18.2, 17.8, 17.5, 15.4, 14.0, −3.7, −3.8, −3.9, −4.0, −4.4, −4.7; FAB HRMS (NBA/CsI): *m/z*: 1214.5614 $[M+Cs]^+$ calcd for $C_{63}H_{99}NO_6SSi_3$ 1214.5555.

Carboxylic acid 40: To a solution of oxalyl chloride (673 μL, 7.7 mmol, 2.0 equiv) in CH_2Cl_2 (10 mL) at −78 °C was added dropwise DMSO (1.10 mL, 15.4 mmol, 4.0 equiv). After stirring for 15 min at −78 °C, a solution of alcohol **39** (4.18 g, 3.9 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL) was added dropwise. The resulting solution was stirred at −78 °C for 30 min and then Et_3N (3.29 mL, 23.2 mmol, 6.0 equiv) was added and the reaction mixture was allowed to warm up to 0 °C over 30 min. Ether (60 mL) was added, followed by saturated aqueous NH_4Cl solution (100 mL), and then the organic layer was separated and the aqueous layer was extracted with ether (3 × 40 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Filtration through a short plug of silica gel (eluting with 30 % ether in hexanes) furnished the intermediate crude aldehyde (ca. 4.18 g) as a colorless oil which was used directly for the next step without further purification.

To a solution of the above aldehyde (4.18 g, ca. 3.9 mmol, 1.0 equiv) in *t*BuOH (180 mL) and H_2O (38 mL) was added 2-methyl-2-butene (31 mL) in THF (100 mL), NaH_2PO_4 (1.16 g, 9.6 mmol, 2.5 equiv) followed by $NaClO_2$ (1.40 g, 80 %, 19.3 mmol, 5.0 equiv) and the resulting mixture was stirred at 25 °C for 2 h. The volatiles were then removed under reduced pressure and the residue was partitioned between EtOAc (100 mL) and saturated aqueous NaCl solution (100 mL) and the layers were separated. The aqueous phase was then extracted with EtOAc (3 × 100 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to furnish the intermediate crude carboxylic acid (ca. 4.24 g)as an oil.

A solution of this crude carboxylic acid (4.24 g, ca. 3.9 mmol, 1.0 equiv) in THF (0.12 M) at 0 °C was treated with TBAF (23.2 mL, 1 M in THF, 23.2 mmol, 6.0 equiv) and the mixture was allowed to warm to 25 °C. The reaction was quenched after being stirred for 10 h by the addition of saturated aqueous NH_4Cl solution (100 mL) and the product was extracted with EtOAc (3 × 60 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography (silica gel, 5 % MeOH in CH_2Cl_2) furnished hydroxy acid **40** as an oil (2.30 g, slightly contaminated with Bu_4N^+ salts, 60 % over three steps). **40**: $R_f = 0.35$ (5 % MeOH in CH_2Cl_2); $[\alpha]_D^{22} = -9.1$ ($c = 1.1$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3369$, 2950, 2853, 1712, 1694, 1466, 1255, 1055, 991, 838, 779, 738, 708 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.44-7.42$ (m, 5H, Ph), 7.27–7.18 (m, 10H, Ph), 6.86 (s, 1H, SCH=C), 6.59 (br s, 2H, CH=CH), 5.59 (dd, $J = 7.0$, 7.0 Hz, 1H, C=C*H*CH_2), 4.38–4.26 (m, 2H, CHOSi, C*H*OH), 3.74 (dd, $J = 7.0$, 7.0 Hz 1H, CHOSi), 3.56–3.49 (br s, 2H, CH_2OTr), 3.16–3.06 (m, 2H, OH, CH_3CHC(O)), 2.69 (s, 3H, N=C(CH_3)S), 2.49–2.40 (m, 2H, C*H*$_2$$CO_2H$, C=CHC*H*$_2$CH(O)), 2.28 (dd, $J = 14.4$, 6.5 Hz, 1H, C*H*$_2$$CO_2H$), 2.14–1.99 (m, 2H, C*H*$_2$C=CH), 1.72–1.64 (m, 1H), 1.90 (s, 3H, C(CH_3)$_2$), 1.04 (s, 3H, C(CH_3)$_2$), 1.03 (d, $J = 7.8$ Hz, 3H, C*H*$_3$CHC(O)), 0.88 (s, 9H, $(CH_3)_3$CSi), 0.86 (s, 9H, $(CH_3)_3$CSi), 0.07 (s, 3H, $(CH_3)_2$Si), 0.05 (s, 6H, $(CH_3)_2$Si), 0.03 (s, 3H, $(CH_3)_2$Si); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 217.9$, 176.1, 166.4, 152.9, 144.1, 140.1, 134.5, 128.5, 127.6, 127.5, 127.5, 127.5, 127.4, 126.7, 122.4, 121.3, 114.5, 86.6, 77.3, 73.6, 72.0, 67.3, 53.4, 52.6, 44.8, 40.0, 38.7, 35.5, 31.2, 29.1, 26.5, 26.1, 25.9, 25.9, 25.5, 25.2, 23.4, 19.8, 19.3, 18.9, 18.3, 18.0, 17.2, 15.7, 13.4, −3.7, −3.8, −3.9, −4.3, −4.7; FAB HRMS (NBA/CsI): *m/z*: 1114.4452 $[M+Cs]^+$ calcd for $C_{57}H_{83}NO_7SSi_2$ 1114.4483.

Macrolactone 41: To a solution of hydroxy acid **40** (6.58 mg, 0.7 mmol, 1.0 equiv) in THF (7.0 mL, 0.1 M) was added Et_3N (0.56 mL, 4.0 mmol, 6.0 equiv) and 2,4,6-trichlorobenzoyl chloride (0.41 mL, 1.6 mmol, 2.4 equiv). The reaction mixture was stirred at 0 °C for 1 h and then added slowly over a period of 2 h via syringe pump to a solution of 4-DMAP (180 mg, 1.5 mmol, 2.2 equiv) in toluene (140 mL, 0.005 M based on **40**) at 75 °C. The mixture was stirred at that temperature for an additional 1 h and was then concentrated under reduced pressure. The resulting residue was filtered through a plug of silica gel eluting with 50 % ether in hexanes. Flash column chromatography (silica gel, 20 % ether in hexanes) furnished macrolactone **41** as a colorless foam (4.7 g, 73 %). **41**: $R_f = 0.25$ (20 % ether in hexanes); $[\alpha]_D^{22} = -9.9$ ($c = 1.0$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2931$, 2865, 1738, 1695, 1472, 1385, 1250, 1152, 1065, 989, 832, 772, 707 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.47-7.45$ (m, 5H, Ph), 7.29–7.19 (m, 10H, Ph), 6.93 (s, 1H, SCH=C), 6.62 (d, $J = 15.7$ Hz, 1H, *CH*=CH), 6.51 (dd, $J = 15.7$, 7.3 Hz, 1H, CH=C*H*), 5.58 (dd, $J = 8.6$, 8.6 Hz, 1H, C=C*H*CH_2), 5.21–5.18 (m, 1H, CH_2CH(O)), 4.00 (d, $J = 8.9$ Hz, 1H, CHOSi), 3.83 (d, $J = 8.6$, 1H, CHOSi), 3.52–3.45 (m, 2H, CH_2OTr), 3.00–2.93 (m, 1H, CH_3CHC(O)), 2.85–2.75 (m, 2H, C=CHC*H*$_2$CH(O), CH_2C(O)), 2.70 (s, 3H, N=C(CH_3)S), 2.56 (m, 1H, CH_2C(O)), 2.43–2.38 (m, 1H, C=CHC*H*$_2$CH(O)), 2.29–2.24 (m, 1H, C*H*$_2$C=CH), 2.07–2.02 (m, 1H, C*H*$_2$C=CH), 1.17 (s, 3H, C(CH_3)$_2$), 1.12 (s, 3H, C(CH_3)$_2$), 1.07 (d, $J = 6.8$ Hz, 3H, C*H*$_3$CHC(O)), 0.94 (s, 9H, $(CH_3)_3$CSi), 0.84 (d, $J = 6.7$ Hz, 3H, C*H*$_3$CHC(O)), 0.73 (s, 9H, $(CH_3)_3$CSi), 0.10 (s, 3H, $(CH_3)_2$CSi), 0.09 (s, 3H, $(CH_3)_2$Si), 0.07 (s, 3H, $(CH_3)_2$Si), −0.28 (s, 3H, $(CH_3)_2$Si); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 215.0$, 171.2, 166.2, 152.5, 144.2, 141.9, 130.0, 128.5, 127.7, 126.9, 125.5, 119.7, 115.9, 86.4, 76.0, 75.3, 66.7, 53.3, 39.3, 37.6, 32.9, 31.5, 28.7, 27.1, 26.4, 26.3, 26.2, 26.1, 24.2, 19.3, 18.6, 18.5, 17.7, −3.3, −3.6, −3.7, −5.7; FAB HRMS (NBA/CsI): *m/z*: 1096.4348 $[M+Cs]^+$ calcd for $C_{57}H_{81}NO_6SSi_2$ 1096.4378.

Triol 42: To a solution of macrolactone **41** (300 mg, 0.3 mmol, 1.0 equiv) in THF (15.5 mL, 0.02 M) at 0 °C was added HF·py in pyridine/THF mixture (25 mL) (from a stock solution prepared as for the procedure for alcohol **35**). The resulting mixture was allowed to warm up to 25 °C and stirred for 24 h. After cooling to 0 °C, the reaction mixture was diluted with EtOAc (50 mL) and quenched by careful, portionwise addition into saturated aqueous $NaHCO_3$ solution (50 mL) with further addition of sufficient solid $NaHCO_3$ to ensure complete neutralization. The product was then extracted with EtOAc (3 × 50 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography (silica gel, 80 % EtOAc in hexanes) furnished triol **42** as a colorless foam (120 mg, 78 %). **42**: $R_f = 0.40$ (80 % ether in hexanes); $[\alpha]_D^{22} = -46.6$ ($c = 1.1$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3384$, 2930, 1732, 1687, 1464, 1372, 1258, 1148, 1071, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta =$ 6.93 (s, 1H, SCH=C), 6.61 (d, $J = 15.8$ Hz, 1H, C*H*=CH), 6.43 (dd, $J = 15.5$, 6.7 Hz, 1H, CH=C*H*), 5.49–5.45 (m, 2H, C=C*H*CH_2, CH_2CH(O)), 4.17 (m, 1H, C*H*OH), 4.05 (d, $J = 12.8$ Hz, 1H, C*H*$_2$OH), 3.98 (d, $J = 13.2$ Hz, 1H, C*H*$_2$OH), 3.81 (br s, 1H, CH_2OH), 3.64 (m, 1H, C*H*OH), 3.11–3.09 (m, 3H, CH_3CHC(O), CH_2OH, CH_2OH), 2.65 (s, 3H, N=C(CH_3)S), 2.69–2.59 (m, 1H), 2.41 (dd, $J = 15.1$, 11.0 Hz, 1H, C*H*$_2$C(O)), 2.34 (dd, $J = 14.3$, 3.0 Hz, 1H, CH_2C(O)), 2.23–2.17 (m, 2H, C*H*$_2$C=CH), 2.10–2.06 (m, 1H, C=CHC*H*$_2$CH(O)), 1.67–1.63 (m, 2H), 1.28 (s, 3H, C(CH_3)$_2$), 1.28–1.24 (m, 3H), 1.14 (d, $J = 7$ Hz, 3H, C*H*$_3$CHC(O)), 1.00 (s, 3H, C(CH_3)$_2$), 0.95 (d, $J = 7.0$ Hz, 3H, C*H*$_3$CH); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 220.5$,

0947-6539/00/0615-2794 $ 17.50+.50/0 *Chem. Eur. J.* **2000**, *6*, No. 15

170.3, 166.6, 152.2, 141.8, 129.7, 124.9, 121.0, 115.9, 74.3, 74.1, 71.8, 65.9, 41.7, 39.5, 38.1, 32.9, 31.5, 27.8, 25.5, 22.5, 19.0, 17.8, 14.0, 13.6; FAB HRMS (NBA/NaI): m/z: 494.2589 $[M+H]^+$ calcd for $C_{26}H_{39}NO_6S$ 494.2576.

Epoxide 43: To a solution of allylic alcohol **42** (119 mg, 0.2 mmol, 1.0 equiv) and 4 Å molecular sieves in CH_2Cl_2 (2.5 mL, 0.1M) at $-30\,^{\circ}C$ was added dropwise (+)-diethyl L-tartrate (25.0 mg, 0.12 mmol, 0.5 equiv), followed by titanium isopropoxide (27.3 mg, 0.1 mmol, 0.4 equiv). After 1 h at this temperature, *tert*-butyl hydroperoxide (0.1 mL, 5M solution in decane, 2.0 equiv) was added and the reaction mixture was stirred at $-30\,^{\circ}C$ for 2 h. The reaction mixture was then filtered through Celite into saturated aqueous Na_2SO_4 solution (10 mL), eluting with EtOAc (10 mL). The resulting biphasic mixture was then stirred for 1 h and the layers were separated. The aqueous phase was extracted with EtOAc (3×10 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 80% EtOAc in hexanes) to afford epoxide **43** (82 mg, 67%). **43**: $R_f=0.48$ (EtOAc); $[\alpha]_D^{22}=-35.1$ ($c=1.0$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}=3418$, 2938, 1732, 1682, 1470, 1373, 1290, 1256, 1147, 1042, 979, 911, 733, 647 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta=6.96$ (s, 1H, SCH=C), 6.62 (d, $J=15.6$ Hz, 1H, C*H*=CH), 6.49 (dd, $J=15.8$, 6.6 Hz, 1H, CH=C*H*), 5.66–5.65 (m, 1H, $CH_2CH(O)$), 4.10–4.06 (m, 1H, C*H*OH), 3.70–3.65 (m, 2H, C*H*OH, CH_2OH), 3.50 (d, $J=12.5$ Hz, 1H, CH_2OH), 3.31 (m, 1H, $CH_3CHC(O)$), 3.18 (dd, $J=6.0$, 6.0 Hz, 1H, C*H*-epoxide), 2.95–2.80 (br s, 3H, CHO*H*, CHO*H*, CH_2OH), 2.67 (s, 3H, N=C(CH_3)S), 2.50 (dd, $J=14.1$, 10.0 Hz, 1H, $CH_2C(O)$), 2.32 (dd, $J=14.2$, 2.9 Hz, 1H, $CH_2C(O)$), 2.06 (ddd, $J=15.1$, 5.5, 3.5 Hz, 1H, C=CHCH_2CH(O)), 1.97–1.92 (m, 1H, C=CHCH_2CH(O)), 1.83–1.79 (m, 1H), 1.60–1.51 (m, 1H), 1.43–1.37 (m, 5H), 1.27 (s, 3H, C(CH_3)$_2$), 1.12 (d, $J=6.6$ Hz, 3H, CH_3CH(O)), 1.01 (s, 3H, C(CH_3)$_2$), 0.95 (d, $J=6.8$ Hz, 3H, CH_3CH); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta=220.3$, 170.7, 166.7, 151.9, 128.3, 125.4, 116.3, 74.9, 72.6, 72.5, 64.0, 63.2, 56.8, 52.8, 43.5, 39.0, 36.6, 32.3, 30.6, 27.5, 22.5, 20.7, 20.1, 19.1, 17.4, 14.4; MALDI HRMS (DHB): m/z: 510.2522 $[M+H]^+$ calcd for $C_{26}H_{39}NO_7S$ 510.2525.

Iodide 44: To a stirred solution of epoxide **43** (82 mg, 0.2 mmol, 1.0 equiv) in CH_2Cl_2 (1.6 mL, 0.1M) at $0\,^{\circ}C$ was added Et_3N (0.07 mL, 0.5 mmol, 3.0 equiv) followed by tosyl chloride (0.04g, 0.24 mmol, 1.5 equiv) and 4-DMAP (0.02 g, 0.2 mmol, 1.0 equiv). The reaction mixture was warmed to $25\,^{\circ}C$ and stirred for 1 h before saturated aqueous NH_4Cl solution (20 mL) was added. The layers were separated and the aqueous phase was extracted with EtOAc (3×10 mL). The combined organic extracts were dried ($MgSO_4$), and concentrated under reduced pressure. The residue was then dissolved in acetone (0.1M) and treated with NaI (72.0 mg, 0.5 mmol, 3.0 equiv). After stirring at $25\,^{\circ}C$ for 24 h, the solvent was removed under reduced pressure and the residue was dissolved in 60% EtOAc in hexanes and filtered through a short plug of silica gel. Purification by flash column chromatography (60% EtOAc in hexanes) provided pure iodide **44** (90.5 mg, 91%). **44**: $R_f=0.60$ (50% EtOAc in hexanes); $[\alpha]_D^{22}=+8.2$ ($c=1.0$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}=3478$, 2961, 1732, 1688, 1506, 1464, 1253, 1153, 1146, 1076, 975, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=6.97$ (s, 1H, SCH=C), 6.64 (d, $J=15.7$ Hz, 1H, C*H*=CH), 6.53 (dd, $J=15.7$, 6.5 Hz, 1H, CH=C*H*), 5.68 (dd, $J=10.0$, 6.5 Hz, 1H, $CH_2CH(O)$), 4.09 (d, $J=9.2$ Hz, 1H, C*H*OH), 3.84 (br s, 1H, OH), 3.74 (br s, 1H, C*H*OH), 3.34–3.27 (m, 1H, $CH_3CHC(O)$), 3.16 (d, $J=10.2$ Hz, 1H, CH_2I), 3.11 (d, $J=10.0$ Hz, 1H, CH_2I), 3.06 (dd, $J=6.2$ Hz, 1H, C*H*-epoxide), 2.71 (s, 3H, N=C(CH_3)S), 2.55–2.49 (m, 2H, $CH_2C(O)$, OH), 2.38 (dd, $J=14.3$, 3.5 Hz, 1H, $CH_2C(O)$), 2.02–1.87 (m, 4H), 1.67–1.61 (m, 2H), 1.28 (s, 3H, C(CH_3)$_2$), 1.90 (d, $J=7.8$ Hz, 3H, CH_3CH(O)), 1.05 (s, 3H, C(CH_3)$_2$), 0.98 (d, $J=6.8$ Hz, 3H, CHCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=220.6$, 170.6, 166.7, 151.9, 127.9, 125.8, 116.6, 74.9, 73.2, 72.4, 63.2, 62.0, 52.5, 43.7, 39.0, 36.5, 33.1, 30.4, 28.8, 22.6, 20.8, 20.6, 19.2, 17.3, 14.3, 11.9; FAB HRMS (NBA/CsI): m/z: 752.0542 $[M+Cs]^+$ calcd for $C_{26}H_{38}INO_6S$ 752.0519.

16-Desmethylepothilone B 14: Iodide **44** (50 mg, 0.1 mmol, 1.0 equiv) and sodium cyanoborohydride (50 mg, 0.8 mmol, 10.0 equiv) were dissolved in anhydrous HMPA (0.4 mL, 0.2M) and the resulting mixture was heated at $45\,^{\circ}C$ for 40 h. After cooling to $25\,^{\circ}C$, water (60 mL) was added and the aqueous phase extracted with EtOAc (4×100 mL). The combined organic fractions were dried (Na_2SO_4) and passed through a short plug of silica gel to remove traces of HMPA (50% EtOAc in hexanes). Following evaporation of solvents, the residue was purified by preparative thin layer chromatography (50% EtOAc in hexanes) to provide pure 16-desmethylepothilone B (**14**) (26 mg, 67%). **14**: $R_f=0.20$ (4% MeOH in CH_2Cl_2); $[\alpha]_D^{22}=-34.0$ ($c=1.0$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}=3418$, 2960, 2936, 1735, 1686, 1465, 1379, 1251, 1144, 1070, 1043, 968, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta=6.96$ (s, 1H, SCH=C), 6.65 (d, $J=15.4$ Hz, 1H, C*H*=CH), 6.54 (dd, $J=15.4$, 5.0 Hz, 1H, CH=C*H*), 5.68 (dd, $J=10.0$, 6.2 Hz, 1H, $CH_2CH(O)$), 4.12–4.06 (m, 1H, C*H*OH), 3.96 (br s, 1H, OH), 3.76 (m, 1H, C*H*OH), 3.32 (dq, $J=7.5$, 1.5 Hz, 1H, $CH_3CHC(O)$), 2.89 (dd, $J=6.3$, 6.3 Hz, 1H, C*H*-epoxide), 2.71 (s, 3H, N=C(CH_3)S), 2.53 (dd, $J=14.3$, 10.0 Hz, 1H, $CH_2C(O)$), 2.46 (br s, 1H, OH), 2.38 (dd, $J=14.2$, 3.6 Hz, 1H, $CH_2C(O)$), 2.07–2.03 (m, 1H), 1.97–1.90 (m, 1H), 1.84–1.59 (m, 4H), 1.50–1.43 (m, 3H), 1.36 (s, 3H, (CH_3)-epoxide), 1.28 (s, 3H, C(CH_3)$_2$), 1.17 (d, $J=6.6$ Hz, 3H, CH_3CHC(O)), 1.08 (s, 3H, C(CH_3)$_2$), 0.99 (d, $J=7.0$ Hz, 3H, CH_3CH); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta=220.9$, 170.7, 166.5, 152.1, 128.3, 125.6, 116.3, 76.7, 74.8, 73.5, 72.7, 60.9, 60.8, 52.4, 43.6, 38.9, 36.7, 32.8, 31.5, 30.6, 23.0, 22.9, 20.5, 19.2, 17.2, 14.3; FAB HRMS (NBA/NaI): m/z: 494.2564 $[M+H]^+$ calcd for $C_{26}H_{39}NO_6S$ 494.2576.

The aldol **51** was converted to epoxide **52** by a previously reported procedure.[5k]

Iodide 53: To a stirred solution of alcohol **52** (1.28 g, 2.3 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL) at $0\,^{\circ}C$ was added Et_3N (0.97 mL, 6.9 mmol, 3.0 equiv) followed by tosyl chloride (0.93 g, 3.5 mmol, 1.5 equiv) and 4-DMAP (0.28 g, 2.3 mmol, 1.0 equiv). The reaction mixture was warmed to $25\,^{\circ}C$ and stirred for 2 h before saturated aqueous NH_4Cl solution (30 mL) was added. The layers were separated and the aqueous phase was extracted with EtOAc (3×120 mL). The combined organic extracts were dried ($MgSO_4$), and concentrated in vacuo. The residue was then dissolved in acetone (40 mL) and treated with NaI (1.65 g, 11.0 mmol, 4.5 equiv). After stirring at $25\,^{\circ}C$ for 12 h, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (25 to 90%, EtOAc in hexanes) to provide iodide **53** (1.2 g, 75%, two steps). **53**: $R_f=0.34$ (50% EtOAc in hexanes); $[\alpha]_D^{22}=+8.2$ ($c=0.4$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}=3474$, 2964, 2936, 1736, 1688, 1465, 1379, 1255, 1146, 1072, 977, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta=6.48$ (s, 1H, C*H*=CCH$_3$), 5.46 (dd, $J=4.4$, 4.4 Hz, 1H, $CH_2CH(O)$), 4.05–4.01 (m, 1H, C*H*OH), 3.77 (dd, $J=8.9$, 4.4 Hz, 1H, C*H*OH), 3.40 (d, $J=7.0$ Hz, 1H, C*H*OH), 3.28 (dq, $J=7.0$, 7.0 Hz, 1H, $CH_3CHC(O)$), 3.17 (d, $J=10.3$ Hz, 1H, CH_2I), 3.12 (d, $J=10.3$ Hz, 1H, CH_2I), 2.90 (dd, $J=6.6$, 6.6 Hz, 1H, CH-epoxide), 2.52 (dd, $J=14.4$, 9.2 Hz, 1H, $CH_2C(O)$), 2.44 (dd, $J=14.3$, 3.3 Hz, 1H, $CH_2C(O)$), 2.39 (br d, $J=5.4$ Hz, 1H, OH), 1.98–1.94 (m, 2H, C=CHCH_2CH(O)), 1.88 (s, 3H, CH=CCH_3), 1.69–1.64 (m, 4H), 1.34 (s, 3H, C(CH_3)$_2$), 1.28–1.24 (m, 2H), 1.16 (d, $J=6.6$ Hz, 3H, CH_3CHC(O)), 1.09 (s, 3H, C(CH_3)$_2$), 1.00 (d, $J=7.0$ Hz, 3H, CH_3CH); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta=220.3$, 170.1, 143.7, 80.8, 75.1, 73.7, 63.0, 62.2, 52.2, 43.9, 38.8, 36.3, 31.6, 30.3, 28.9, 22.5, 21.5, 20.6, 17.3, 14.4, 11.6; FAB HRMS (NBA/CsI): m/z: 794.9672 $[M+Cs]^+$ calcd for $C_{23}H_{36}I_2O_6$ 794.9656.

Vinyl iodide 19: Iodide **53** (0.55 g, 0.8 mmol, 1.0 equiv) and sodiumcyanoborohydride (0.59 g, 8.9 mmol, 11.5 equiv) were dissolved in anhydrous 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (6.0 mL) and the resulting mixture was heated at $45\,^{\circ}C$ for 24 h. After cooling to $25\,^{\circ}C$, water (10 mL) was added and the aqueous phase extracted with EtOAc (4×20 mL). The combined organic fractions were dried (Na_2SO_4) and passed through a short plug of silica gel to remove traces of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (50% EtOAc in hexanes). Following evaporation of solvents, the residue was purified by column chromatography (20 to 50%, EtOAc in hexanes) to provided pure iodide **19** (300 mg, 70%). **19**: $R_f=0.31$ (50% EtOAc in hexanes); $[\alpha]_D^{22}=-24.6$ ($c=0.6$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}=3412$, 2957, 2929, 2875, 1736, 1689, 1464, 1380, 1257, 1147, 1052, 977 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta=6.46$ (s, 1H, C*H*=CCH$_3$), 5.48 (dd, $J=4.8$, 4.8 Hz, 1H, $CH_2CH(O)$), 4.06–4.02 (m, 1H, C*H*OH), 3.78 (dd, $J=5.4$, 3.6 Hz, 1H, C*H*OH), 3.63 (d, $J=7.0$ Hz, 1H, C*H*OH), 3.31 (dq, $J=7.0$, 7.0 Hz, 1H, $CH_3CHC(O)$), 2.73 (dd, $J=6.2$, 6.2 Hz, 1H, CH-epoxide), 2.54 (dd, $J=14.3$, 9.6 Hz, 1H, $CH_2C(O)$), 2.44 (dd, $J=14.4$, 3.3 Hz, 1H, $CH_2C(O)$), 2.36 (br s, 1H, OH), 1.92 (dd, $J=5.6$, 5.6 Hz, 2H, C=CHCH_2CH(O)), 1.88 (s, 3H, CH=CCH_3), 1.35 (s, 3H, (CH_3)-epoxide), 1.28 (s, 3H, C(CH_3)$_2$), 1.16 (d, $J=7.0$ Hz, 3H, CH_3CHC(O)), 1.09 (s, 3H, C(CH_3)$_2$), 0.99 (d, $J=6.9$ Hz, 3H, CH_3CH); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=220.5$, 170.3, 143.9, 80.4, 75.4, 75.0, 73.8, 60.9, 60.6, 52.2, 43.9, 38.7, 36.4, 31.5, 31.2, 30.4, 29.6, 22.9, 21.2, 21.6, 20.4, 17.3, 14.4; FAB HRMS (NBA/CsI): m/z: 669.0669 $[M+Cs]^+$ calcd for $C_{23}H_{37}IO_6$ 669.0689.

Stannanes **54a** and **54b** were prepared by a previously reported procedure.[5k]

Epothilone B_{10} (3): To a solution of vinyl iodide **19** (13.3 mg, 0.025 mmol, 1.0 equiv) in degassed DMF (0.2 mL) were added thiazole stannane **54a** (20.0 mg, 0.05 mmol, 2.0 equiv), Et_3N (3.48 mL, 0.025 mmol, 1.0 equiv), and $[PdCl_2(MeCN)_2]$ (1.30 mg, 0.005 mmol, 0.2 equiv) and the mixture was stirred at 25 °C for 24 h. The reaction mixture was diluted with EtOAc (2 mL) and filtered through Celite eluting with EtOAc. The organic solution was washed with water (0.5 mL), a saturated aqueous NaCl solution (0.5 mL) and concentrated under reduced pressure. The remaining solid was purified by preparative TLC (30% EtOAc in hexanes) to obtain pure epothilone B_{10} (**3**) (6.9 mg, 53%). **3**: $R_f = 0.41$ (60% EtOAc in hexanes); $[\alpha]_D^{22} = -44.6$ ($c = 0.3$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3444, 2931, 2872, 1732, 1688, 1455, 1383, 1250, 1150, 1053, 980, 734\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.98$ (s, 1H, SCH=C), 6.59 (s, 1H, C*H*=CCH$_3$), 5.39 (d, $J = 8.5$ Hz, 1H, CH_2CH(O)), 4.32–4.20 (m, 2H, C*H*OH, OH), 3.76 (m, 1H, C*H*OH), 3.29 (dd, $J = 6.6$, 4.0 Hz, 1H, CH_3CHC(O)), 3.01 (q, $J = 7.7$ Hz, 2H, S(CN)CH_2CH$_3$), 2.80 (dd, $J = 7.4$, 4.4 Hz, 1H, CH-epoxide), 2.69 (m, 1H, OH), 2.53 (dd, $J = 13.6$, 10.3 Hz, 1H, CH_2C(O)), 2.34 (d, $J = 13.2$ Hz, 1H, CH_2C(O)), 2.07–2.06 (m, 1H, C=CHCH_2CH(O)), 2.08 (s, 3H, CH=CCH_3), 1.89 (m, 3H), 1.74–1.61 (m, 5H), 1.49–1.46 (m, 2H), 1.40 (t, $J = 7.4$ Hz, 3H, S(CN)CH$_2$CH_3), 1.37 (s, 3H, (CH_3)-epoxide), 1.27 (s, 3H, C$(CH_3)_2$), 1.16 (d, $J = 7.0$ Hz, 3H, CH_3CHC(O)), 1.07 (s, 3H, C$(CH_3)_2$), 0.99 (d, $J = 7.0$ Hz, 3H, CH_3CH); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 220.7$, 170.6, 119.5, 115.4, 73.9, 72.6, 61.8, 61.4, 53.2, 42.6, 39.2, 36.4, 32.4, 32.1, 30.7, 29.7, 26.7, 22.7, 22.2, 21.6, 19.3, 17.0, 16.0, 14.0, 13.5; FAB HRMS (NBA/NaI): m/z: 522.2899 $[M+H]^+$ calcd for $C_{28}H_{43}NO_6S$ 522.2889.

Epothilone F (5): Epothilone F (**5**) was prepared from vinyl iodide **19** and stannane **54b** according to the same procedure as described for epothilone B_{10} (**3**). **5**: (64%); $R_f = 0.13$ (70% EtOAc in hexanes); $[\alpha]_D^{22} = -21.3$ ($c = 0.8$, EtOH); IR (thin film): $\tilde{\nu}_{max} = 3416, 2962, 2932, 1737, 1688, 1462, 1381, 1263, 1148, 1055, 979, 736\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.13$ (s, 1H, SCH=C), 6.60 (s, 1H, C*H*=CCH$_3$), 5.44 (dd, $J = 7.7$, 3.0 Hz, 1H, CH_2CH(O)), 4.93 (d, $J = 5.9$ Hz, 2H, CH_2OH), 4.19 (ddd, $J = 8.4$, 6.6, 3.3 Hz, 1H, C*H*OH), 4.04 (d, $J = 6.7$ Hz, 1H, OH), 3.77 (dd, $J = 8.0$, 4.0 Hz, 1H, C*H*OH), 3.30 (m, 1H, CH_3CHC(O)), 2.87 (br s, 1H, OH), 2.81 (dd, $J = 6.0$, 4.1 Hz, 1H, CH-epoxide), 2.60 (br s, 1H, OH), 2.55 (dd, $J = 14.3$, 10.3 Hz, 1H, CH_2C(O)), 2.39 (dd, $J = 14.4$, 3.3 Hz, 1H, CH_2C(O)), 2.10 (s, 3H, CH=CCH_3), 2.07 (dd, $J = 8.4$, 5.1 Hz, 1H, C=CHCH_2CH(O)), 1.94 (m, 1H, C=CHCH_2CH(O)), 1.73–1.71 (m, 2H,), 1.45–1.40 (m, 5H), 1.36 (s, 3H, (CH_3)-epoxide), 1.28 (s, 3H, C$(CH_3)_2$), 1.16 (d, $J = 5.6$ Hz, 3H, (CH_3)CHC(O)), 1.08 (s, 3H, C$(CH_3)_2$), 1.00 (d, $J = 7.0$ Hz, 3H, CH_3CH);^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 220.6$, 170.5, 152.1, 137.7, 119.4, 116.9, 74.3, 73.0, 62.0, 61.5, 61.3, 52.9, 43.0, 39.1, 36.4, 32.2, 31.9, 30.7, 29.7, 22.7, 22.5, 21.3, 19.9, 17.1, 15.8, 13.8; FAB HRMS (NBA/NaI): m/z: 524.2662 $[M+H]^+$ calcd for $C_{27}H_{41}NO_7S$ 524.2682.

Pyridine stannanes 56a–g: To a solution of bromopyridine **55a** (2.0 g, 0.01 mmol, 1.0 equiv) in THF (20 mL) at −78 °C was added *n*-BuLi (8.7 mL, 1.6 M in hexanes, 13.9 mmol, 1.1 equiv) and the resulting mixture was stirred at −78 °C for 1 h. Tri-*n*-butyltinchloride (3.25 mL, 0.013 mmol, 1.2 equiv) was added and the solution stirred at −78 °C for 1 h and then warmed to 25 °C. The reaction mixture was diluted with EtOAc and saturated aqueous KF solution (10 mL) was added. The aqueous phase was extracted with EtOAc (3 × 20 mL) and the combined organic fractions were dried (Na_2SO_4) and purified by flash column chromatography (5 to 10% EtOAc in hexanes) to provided the pyridine stannane **56a**[28c] (3.2 g, 86%).

Similar procedures were employed to prepare stannanes **56b–f**. The preparation of stannane **56g** was carried out using a similar procedure, starting from the commercially available hydrochloride salt of **55g** and using 2.2 equiv of *n*-BuLi (1.6 M in hexanes). **56b**: (82%); $R_f = 0.50$ (20% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 3035, 2956, 2926, 2870, 2851, 1569, 1458, 1395, 1072, 866, 785, 688, 667, 595\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.53$ (d, $J = 4.4$ Hz, 1H, ArH), 7.31 (d, $J = 7.9$ Hz, 1H, ArH), 7.00 (dd, $J = 7.5$, 4.4 Hz, 1H, ArH), 2.36 (s, 3H, CH_3), 1.55 (m, 6H, 3CH$_2$), 1.33 (m, 6H, 3CH$_2$), 1.15 (m, 6H, 3CH$_2$), 0.87 (t, $J = 7.3$ Hz, 9H, 3CH$_2$CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 175.2$, 148.1, 141.4, 134.8, 122.3, 30.0, 28.2, 22.6, 14.5, 11.3; MALDI HRMS (DHB): m/z: 384.1718 $[M+H]^+$ calcd for $C_{18}H_{33}NSn$ 384.1713. **56c**: (73%); $R_f = 0.46$ (20% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 3051, 2956, 2925, 2870, 2851, 1585, 1454, 1376, 1073, 984, 871, 818, 688, 667, 595, 516\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.52$ (d, $J = 4.8$ Hz, 1H, ArH), 7.20 (s, 1H, ArH), 6.92 (d, $J = 4.8$ Hz, 1H, ArH), 2.28 (s, 3H, 3CH$_3$), 1.55 (m, 6H, 3CH$_2$), 1.32 (m, 6H, 3CH$_2$), 1.10 (m, 6H, 3CH$_2$), 0.87 (t, $J = 7.3$ Hz, 9H, 3CH$_2$CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 174.0$, 151.0, 144.8, 134.2, 123.9, 29.9, 28.2, 21.8, 14.5, 10.5; MALDI HRMS (DHB): m/z: 384.1725 $[M+H]^+$ calcd for $C_{18}H_{33}NSn$ 384.1713. **56d**:[28e] (88%); $R_f = 0.43$ (20% EtOAc in hexanes). **56e**: (89%); $R_f = 0.42$ (20% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 3047, 2956, 2926, 2870, 2850, 1574, 1558, 1458, 1436, 1375, 1166, 1074, 868, 772, 689, 666, 595, 504\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.44$ (dd, $J = 7.7$, 7.3 Hz, 1H, ArH), 7.28 (d, $J = 7.3$ Hz, 1H, ArH), 7.04 (d, $J = 7.3$ Hz, 1H, ArH), 2.63 (s, 3H, 3CH$_3$), 1.67 (m, 6H, 3CH$_2$), 1.44 (m, 6H, 3CH$_2$), 1.20 (m, 6H, 3CH$_2$), 0.98 (t, $J = 7.3$ Hz, 9H, 3CH$_2$CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 173.5$, 159.0, 133.6, 129.7, 121.9, 29.5, 27.8, 25.3, 14.1, 10.3; MALDI HRMS (DHB): m/z: 384.1720 $[M+H]^+$ calcd for $C_{18}H_{33}NSn$ 384.1713. **56f**: (40%); $R_f = 0.37$ (20% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 2956, 2924, 2870, 2851, 1683, 1560, 1461, 1392, 1074, 869, 786, 714, 691, 664, 598\ cm^{-1}$; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 8.58$ (s, 1H, ArH), 8.48 (d, $J = 4.4$ Hz, 1H, ArH), 7.71 (m, 1H, ArH), 7.19 (m, 1H, ArH), 1.53 (m, 6H, 3CH$_2$), 1.28 (m, 6H, 3CH$_2$), 1.11 (m, 6H, 3CH$_2$), 0.87 (t, $J = 7.3$ Hz, 9H, 3CH$_2$CH_3); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 156.0$, 149.1, 144.0, 136.8, 123.8, 28.9, 27.2, 13.6, 8.3; MALDI HRMS (DHB): m/z: 370.1548 $[M+H]^+$ calcd for $C_{17}H_{31}NSn$ 370.1551. **56g**: (40%); $R_f = 0.51$ (20% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 2957, 2924, 2851, 1571, 1459, 1398, 1094, 870, 790, 691, 663, 591\ cm^{-1}$; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 8.48$ (br s, 2H, ArH), 7.36 (d, $J = 4.8$ Hz, 2H, ArH), 1.53 (m, 6H, 3CH$_2$), 1.32 (m, 6H, 3CH$_2$), 1.09 (m, 6H, 3CH$_2$), 0.87 (t, $J = 7.3$ Hz, 9H, 3CH$_2$CH_3); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 153.1$, 148.3, 131.9, 28.9, 27.3, 13.6, 9.5; MALDI HRMS (DHB): m/z: 370.1555 $[M+H]^+$ calcd for $C_{17}H_{31}NSn$ 370.1551.

Benzenoid stannanes 66b–g and distannane 60b: To a solution of 3-bromoacetophenone **65f** (0.24 g, 1.2 mmol, 1.0 equiv) in degassed toluene (5 mL) was added hexamethylditin (0.47 g, 1.4 mmol, 1.2 equiv) followed by $[Pd(PPh_3)_4]$ (0.14 g, 0.1 mmol, 0.1 equiv). The mixture was heated at reflux for 1 h, then diluted with hexanes (10 mL) and saturated aqueous KF solution (10 mL) and the resulting mixture was stirred at 25 °C for 30 min. After filtration through Celite, the phases were separated and the organic layer was washed with saturated aqueous NaCl solution (20 mL) dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography (5% ether in hexanes) furnished stannane **66f** (0.32 mg, 95%). **66f**: $R_f = 0.50$ (25% ether in hexanes); IR (thin film): $\tilde{\nu}_{max} = 2979, 2914, 1683, 1576, 1400, 1355, 1257, 958, 772, 695, 591, 531\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.27$ (s, 1H, ArH), 7.87 (d, $J = 7.8$ Hz, 1H, ArH), 7.68 (d, $J = 7.3$ Hz, 1H, ArH), 7.42 (dd, $J = 7.6$, 7.3 Hz, 1H, ArH), 2.61 (s, 3H, CH_3C=O), 0.33 (s, 9H, $(CH_3)_3Sn$); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 198.5$, 142.9, 140.7, 140.4, 136.3, 135.4, 128.1, 26.5, −9.6.

Similar procedures were employed to prepare stannanes **66b–e**, **66g** and distannane **60b**. **66b**:[28a] (71%); $R_f = 0.77$ (10% ether in hexanes). **66c**: (67%); $R_f = 0.56$ (25% ether in hexanes); IR (thin film): $\tilde{\nu}_{max} = 2985, 2919, 2846, 2363, 1722, 1584, 1434, 1399, 1276, 1258, 1193, 1114, 1064, 973, 835, 767, 741, 529\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.15$ (s, 1H, ArH), 7.96 (d, $J = 8.0$ Hz, 1H, ArH), 7.67 (d, $J = 6.9$ Hz, 1H, ArH), 7.39 (dd, $J = 7.3$, 7.3 Hz, 1H, ArH), 3.91 (s, 3H, CH_3(CO)), 0.31 (s, 9H, $(CH_3)_3Sn$); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 167.5$, 142.8, 140.3, 136.7, 129.5, 129.4, 127.8, 52.1, −9.5; MALDI-FTMS HRMS (DHB): m/z: 301.0737 $[M+H]^+$ calcd for $C_{11}H_{16}O_2Sn$ 301.0250.

66d:[28a,f] (71%); $R_f = 0.60$ (25% ether in hexanes). **66e**: (50%); $R_f = 0.53$ (10% ether in hexanes); IR (thin film): $\tilde{\nu}_{max} = 3052, 2984, 2923, 2853, 1672, 1638, 1584, 1559, 1543, 1459, 1433, 1358, 1287, 1262, 1182, 1123, 1085, 1023, 958, 761, 703\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.03$ (d, $J = 7.3$ Hz, 1H, ArH), 7.75 (d, $J = 7.0$ Hz, 1H, ArH), 7.54 (dd, $J = 7.3$, 7.3 Hz, 1H, ArH), 7.45 (dd, $J = 7.6$, 7.6 Hz, 1H, ArH), 2.68 (s, 3H, CH_3(CO)), 0.24 (s, 9H, $(CH_3)_3Sn$); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 188.2$, 137.0, 132.2, 130.3, 128.4, 26.3, −7.5. **66g**:[28a] (84%); $R_f = 0.44$ (25% ether in hexanes). **60b**:[28b,d] (83%); $R_f = 0.87$ (10% ether in hexanes).

Pyridine analogues 57a–e: To a solution of vinyl iodide **19** (9.0 mg, 0.02 mmol, 1.0 equiv) and stannane **56a** (15 mg, 0.04 mmol, 2.5 equiv) in degassed DMF (0.2 mL) was added a solution of $[PdCl_2(MeCN)_2]$ (2.5 mg, 0.01 mmol, 0.5 equiv), CuI (7.6 mg, 0.04 mmol, 2.0 equiv), and $AsPh_3$ (6.1 mg, 0.02 mmol, 1.0 equiv) in degassed DMF (0.3 mL) and the reaction mixture was stirred at 25 °C for 1 h. EtOAc (5 mL) was added and the mixture was passed through Celite eluting with EtOAc. The organic solution was washed with water (3 mL) and saturated aqueous NaCl solution (3 mL) and concentrated under reduced pressure. Flash column chromatography (20 to 80%, EtOAc in hexanes) provided pyridine

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analogue **57a** (6.4 mg, 66%). **57a**: $R_f = 0.57$ (100% EtOAc); $[\alpha]_D^{22} = -81.3$ ($c = 1.0$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3421, 2929, 1735, 1684, 1601, 1460, 1260, 1055\ cm^{-1}$; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 8.51$ (d, $J = 4.0$ Hz, 1H, ArH), 7.68 (dd, $J = 7.9, 7.9$ Hz, 1H, ArH), 7.26 (d, $J = 7.9$ Hz, 1H, ArH), 7.14 (dd, $J = 7.5, 4.8$ Hz, 1H, ArH), 6.61 (s, 1H, C*H*=CCH$_3$), 5.37 (dd, $J = 7.5, 0.8$ Hz, 1H, CH$_2$C*H*(O)), 5.12–5.16 (brs, 1H, CHO*H*), 4.34 (bd, $J = 11.7$ Hz, 1H, C*H*OH), 3.75–3.72 (m, 1H, C*H*OH), 3.29–3.24 (m, 1H, CH$_3$C*H*C(O)), 2.86 (brs, 1H, OH), 2.80 (dd, $J = 7.0, 7.0$ Hz, 1H, CH-epoxide), 2.52 (dd, $J = 14.9, 10.9$ Hz, 1H, C*H*$_2$C(O)), 2.40 (dd, $J = 14.9, 2.6$ Hz, 1H, C*H*$_2$C(O)), 2.19–2.04 (m, 1H, C=CHC*H*$_2$CH(O)), 2.05 (s, 3H, CH=CC*H*$_3$), 1.92–1.85 (m, 1H, C=CHC*H*$_2$CH(O)), 1.78–1.70 (m, 1H), 1.64–1.58 (m, 1H), 1.54–1.40 (m, 3H), 1.37 (s, 3H, (CH$_3$)-epoxide), 1.34–1.28 (m, 1H), 1.26–1.22 (m, 1H), 1.27 (s, 3H, C(CH$_3$)$_2$), 1.14 (d, $J = 7.0$ Hz, 3H, C*H*$_3$CHC(O)), 1.06 (s, 3H, C(CH$_3$)$_2$), 0.98 (d, $J = 7.0$ Hz, 3H, C*H*$_3$CH); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 221.5, 171.5, 156.4, 149.9, 141.9, 137.4, 126.21, 124.8, 122.5, 77.3, 72.7, 62.9, 62.7, 61.2, 54.6, 43.7, 40.4, 37.1, 33.2, 32.3, 31.6, 23.4, 22.8, 22.7, 21.9, 17.7, 16.4, 15.0$; MALDI HRMS (DHB): m/z: 510.2830 $[M+Na]^+$ calcd for $C_{28}H_{41}NO_6$ 510.2832.

A similar procedure was employed to prepare the pyridine analogues **57b–g**. **57b**: (66%); $R_f = 0.34$ (100% EtOAc); $[\alpha]_D^{22} = -35.0$ ($c = 0.3$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3442, 2925, 1732, 1688, 1589, 1462, 1435, 1380, 1260, 1075, 739, 692\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.37$ (d, $J = 4.8$ Hz, 1H, ArH), 7.53 (d, $J = 7.4$ Hz, 1H, ArH), 7.13 (dd, $J = 7.7, 4.5$ Hz, 1H, ArH), 6.64 (s, 1H, C*H*=CCH$_3$), 5.49 (dd, $J = 9.6, 2.2$ Hz, 1H, CH$_2$C*H*(O)), 4.28 (dd, $J = 11.0, 2.6$ Hz, 1H, C*H*OH), 3.74 (m, 1H, C*H*OH), 3.23 (dq, $J = 6.6, 3.3$ Hz, 1H, CH$_3$C*H*C(O)), 2.91 (brs, 1H, OH), 2.84 (dd, $J = 8.4, 3.3$ Hz, 1H, CH-epoxide), 2.49 (dd, $J = 13.5, 11.0$, 1H, C*H*$_2$C(O)), 2.28 (d, $J = 3.0$ Hz, 1H, C*H*$_2$C(O)), 2.26 (s, 3H, ArCH$_3$), 2.23–2.16 (m, 2H, C=CHC*H*$_2$CH(O)), 1.84 (s, 3H, CH=CC*H*$_3$), 1.80–1.72 (m, 3H), 1.68–1.58 (m, 3H), 1.34 (s, 3H, (CH$_3$)-epoxide), 1.29 (s, 3H, C(CH$_3$)$_2$), 1.13 (d, $J = 7.0$ Hz, 3H, C*H*$_3$CHC(O)), 1.07 (s, 3H, C(CH$_3$)$_2$), 1.00 (d, $J = 7.0$ Hz, 3H, C*H*$_3$CH); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 220.7, 170.9, 154.6, 146.1, 141.7, 138.3, 132.2, 124.8, 122.2, 71.5, 62.1, 61.8, 54.0, 41.9, 39.8, 36.3, 33.1, 31.9, 30.8, 29.7, 22.5, 22.2, 21.7, 17.7, 17.5, 16.8, 15.2, 14.2$; MALDI HRMS (DHB): m/z: 502.3174 $[M+H]^+$ calcd for $C_{29}H_{43}NO_6$ 502.3169. **57c**: (68%); $R_f = 0.71$ (100% EtOAc); $[\alpha]_D^{22} = -77.5$ ($c = 1.3$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3441, 2930, 1735, 1682, 1600, 1460, 1376, 1260, 1148, 1054\ cm^{-1}$; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 8.35$ (d, $J = 4.8$ Hz, 1H, ArH), 7.08 (s, 1H, ArH), 6.95 (d, $J = 4.8$ Hz, 1H, ArH), 6.56 (s, 1H, C*H*=CCH$_3$), 5.38 (brs, 1H, CHO*H*), 5.35 (dd, $J = 9.6, 1.8$ Hz, 1H, CH$_2$C*H*(O)), 4.38–4.32 (m, 1H, C*H*OH), 3.74–3.70 (m, 1H, C*H*OH), 3.29–3.24 (m, 1H, CH$_3$C*H*C(O)), 2.92 (brs, 1H, OH), 2.78 (dd, $J = 8.8, 3.5$ Hz, 1H, CH-epoxide), 2.49 (dd, $J = 13.2, 11.0$ Hz, 1H, C*H*$_2$C(O)), 2.35 (s, 3H, ArCH$_3$), 2.31 (m, 1H), 2.25 (dd, $J = 13.2$, 2.6 Hz, 1H, C*H*$_2$C(O)), 2.20–2.14 (m, 1H, C=CHC*H*$_2$CH(O)), 2.02 (s, 3H, CH=CC*H*$_3$), 1.88 (s, 3H, (CH$_3$)-epoxide), 1.78–1.70 (m, 2H), 1.64–1.56 (m, 1H), 1.54–1.40 (m, 3H), 1.32–1.28 (m, 1H), 1.26 (s, 3H, C(CH$_3$)$_2$), 1.13 (d, $J = 6.6$ Hz, 3H, CH(C*H*$_3$), 1.05 (s, 3H, C(CH$_3$)$_2$), 0.97 (d, $J = 7.0$ Hz, 3H, C*H*$_3$CH); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 220.7, 170.7, 155.2, 148.7, 147.8, 140.8, 125.1, 124.7, 122.6, 76.3, 71.5, 62.2, 61.7, 60.3, 53.9, 39.6, 36.1, 32.9, 32.3, 30.7, 22.5, 22.1, 21.7, 21.1, 20.9, 17.7, 16.8, 15.8, 14.1$; MALDI HRMS (DHB): m/z: 524.2983 $[M+Na]^+$ calcd for $C_{29}H_{43}NO_6$ 524.2988. **57d**: (71%), $R_f = 0.60$ (100% EtOAc); $[\alpha]_D^{22} = -66.0$ ($c = 1.9$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3412, 2961, 2917, 1732, 1682, 1600, 1456, 1374, 1259, 1154, 1044, 1006, 973, 796, 670\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.34$ (s, 1H, ArH), 7.48 (dd, $J = 6.5, 1.8$ Hz, 1H, ArH), 7.16 (d, $J = 6.5$ Hz, 1H, ArH), 6.58 (s, 1H, C*H*=CCH$_3$), 5.36 (dd, $J = 7.6, 1.5$ Hz, 1H, CH$_2$C*H*(O)), 4.34 (dd, $J = 9.5, 2.2$ Hz, 1H, C*H*OH), 3.72 (dd, $J = 4.4, 4.4$ Hz, 1H, C*H*OH), 3.25 (q, $J = 5.5$ Hz, 1H, CH$_3$C*H*C(O)), 2.79 (dd, $J = 10.2, 2.9$ Hz, 1H, CH-epoxide), 2.50 (dd, $J = 10.9, 9.1$, 1H, C*H*$_2$C(O)), 2.31 (s, 3H, ArCH$_3$), 2.27 (dd, $J = 11.3, 2.2$ Hz, 1H, C*H*$_2$C(O)), 2.16 (dt, $J = 12.8, 7.2$ Hz, 1H, C=CHC*H*$_2$CH(O)), 2.01 (s, 3H, CH=CC*H*$_3$), 1.87 (dt, $J = 12.8, 7.2$ Hz, 1H, C=CHC*H*$_2$CH(O)), 1.73 (m, 2H), 1.59 (m, 2H), 1.45 (s, 3H, (CH$_3$)-epoxide), 1.36 (s, 3H, C(CH$_3$)$_2$), 1.14 (d, $J = 5.5$ Hz, 3H, C*H*$_3$CHC(O)), 1.05 (s, 3H, C(CH$_3$)$_2$), 0.98 (d, $J = 5.8$ Hz, 3H, C*H*$_3$CH); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 220.7, 170.7, 152.6, 149.4, 140.2, 137.1, 131.2, 125.0, 123.4, 76.4, 71.6, 62.1, 61.7, 53.9, 42.0, 39.6, 36.2, 32.9, 32.3, 30.8, 29.6, 22.5, 22.1, 21.7, 18.1, 17.8, 16.8, 15.7, 14.1$; MALDI-FTMS HRMS (DHB): m/z: 502.3171 $[M+H]^+$ calcd for $C_{29}H_{43}NO_6$ 502.3169. **57e**: (72%); $R_f = 0.73$ (100% EtOAc); $[\alpha]_D^{22} = -56.0$ ($c = 1.0$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3441, 2925, 1732, 1692, 1455, 1006, 1380, 1259, 1149, 1071\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.57$ (dd, $J = 7.7, 7.7$ Hz, 1H, ArH), 7.08 (d, $J = 7.7$ Hz, 1H, ArH), 6.99 (d, $J = 7.7$ Hz, 1H, ArH), 6.56 (s, 1H, C*H*=CCH$_3$), 5.84 (brs, 1H, CHO*H*), 5.29 (dd, $J = 10.3, 1.0$ Hz, 1H, CH$_2$C*H*(O)), 4.46 (dd, $J = 11.4, 1.8$ Hz, 1H, C*H*OH), 3.72 (dd, $J = 5.9, 2.6$ Hz, 1H, C*H*OH), 3.25 (dq, $J = 13.6, 2.6$ Hz, 1H, CH$_3$C*H*C(O)), 3.02 (brs, 1H, OH), 2.77 (dd, 9.2, 2.6 Hz, 1H, CH-epoxide), 2.50 (s, 3H, ArCH$_3$), 2.49 (dd, $J = 12.8$, 11.4 Hz, 1H, C*H*$_2$C(O)), 2.24–2.18 (m, 2H, C=CHC*H*$_2$CH(O), CH$_2$C(O)), 1.99 (s, 3H, CH=CC*H*$_3$), 1.40 (s, 3H, (CH$_3$)-epoxide), 1.86–1.66 (m, 2H), 1.61–1.54 (m, 2H), 1.52–1.46 (m, 2H), 1.36–1.30 (m, 1H), 1.27 (s, 3H, C(CH$_3$)$_2$), 1.14 (d, $J = 6.6$ Hz, 3H, C*H*$_3$CHC(O)), 1.07 (s, 3H, C(CH$_3$)$_2$), 0.98 (d, $J = 7.0$ Hz, 3H, C*H*$_3$CH); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 220.8, 170.7, 157.9, 154.5, 141.5, 136.9, 124.8, 121.4, 120.7, 72.8, 71.0, 62.6, 61.9, 54.4, 39.9, 36.1, 33.4, 32.6, 30.9, 29.7, 27.8, 22.9, 22.4, 21.3, 17.5, 16.1, 13.6$; MALDI HRMS (DHB): m/z: 502.3176 $[M+H]^+$ calcd for $C_{29}H_{43}NO_6$ 502.3169. **57f**: (52%); $R_f = 0.23$ (100% EtOAc); $[\alpha]_D^{22} = -11$ ($c = 0.4$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3463, 2927, 1736, 1684, 1451, 1252, 1065, 977, 734\ cm^{-1}$; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 8.51$ (m, 2H, ArH), 7.58 (d, $J = 7.9$ Hz, 1H, ArH), 7.27 (m, 1H, ArH), 6.56 (s, 1H, C*H*=CCH$_3$), 5.49 (dd, $J = 6.6, 3.7$ Hz, 1H, CH$_2$C*H*(O)), 4.10–3.97 (brs, 1H, C*H*OH), 3.81–3.78 (brs, 1H, C*H*OH), 3.60–3.55 (brs, 1H, CHO*H*), 3.34–3.28 (m, 1H, CH$_3$C*H*C(O)), 2.82 (dd, $J = 6.6, 6.6$ Hz, 1H, CH-epoxide), 2.57 (dd, $J = 14.5, 9.6$ Hz, 1H, C*H*$_2$C(O)), 2.49–2.44 (m, 2H, OH, C*H*$_2$C(O)), 2.10–2.05 (m, 1H, C=CHC*H*$_2$CH(O)), 2.02–1.80 (m, 1H, C=CHC*H*$_2$CH(O)), 1.92 (s, 3H, CH=CC*H*$_3$), 1.75–1.66 (m, 2H), 1.65–1.55 (m, 4H), 1.36 (s, 3H, (CH$_3$)-epoxide), 1.30 (s, 3H, C(CH$_3$)$_2$), 1.17 (d, $J = 7.0$ Hz, 3H, C*H*$_3$CHC(O)), 1.10 (s, 3H, C(CH$_3$)$_2$), 1.00 (d, $J = 7.0$ Hz, 3H, C*H*$_3$CH); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 220.6, 170.5, 150.1, 147.9, 136.0, 123.6, 74.5, 73.9, 61.1, 60.4, 52.3, 51.7, 43.7, 39.0, 36.4, 31.8, 31.6, 30.7, 29.7, 22.9, 31.3, 21.0, 20.8, 17.3, 14.2, 14.2$; ESI (DHB): m/z: 510 $[M+Na]^+$ calcd for $C_{28}H_{41}NO_6$ 510. **57g**: (73%); $R_f = 0.20$ (100% EtOAc); $[\alpha]_D^{22} = -27$ ($c = 0.4$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3451, 2950, 2919, 1733, 1687, 1457, 1247, 1063, 987, 797\ cm^{-1}$; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 8.56$ (brs, 2H, ArH), 7.15 (d, $J = 2.4$ Hz, 2H, ArH), 6.53 (s, 1H, C*H*=CCH$_3$), 5.47 (dd, $J = 6.2, 3.7$ Hz, 1H, CH$_2$C*H*(O)), 4.13–3.97 (brs, 1H, C*H*OH), 3.82–3.77 (brs, 1H, C*H*OH), 3.75–3.65 (brs, 1H, CHO*H*), 3.35–3.28 (m, 1H, CH$_3$C*H*C(O)), 2.81 (dd, $J = 6.2, 6.2$ Hz, 1H, CH-epoxide), 2.58 (dd, $J = 14.3, 9.5$ Hz, 1H, C*H*$_2$C(O)), 2.51–2.44 (m, 2H, OH, C*H*$_2$C(O)), 2.10–2.04 (m, 1H, C=CHC*H*$_2$CH(O)), 2.02–1.96 (m, 1H, C=CHC*H*$_2$CH(O)), 1.93 (s, 3H, CH=CC*H*$_3$), 1.74–1.66 (m, 2H), 1.65–1.56 (m, 4H), 1.36 (s, 3H, (CH$_3$)-epoxide), 1.30 (s, 3H, C(CH$_3$)$_2$), 1.17 (d, $J = 7.0$ Hz, 3H, C*H*$_3$CHC(O)), 1.10 (s, 3H, C(CH$_3$)$_2$), 1.01 (d, $J = 7.0$ Hz, 3H, C*H*$_3$CH); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 220.5, 170.5, 149.7, 144.5, 139.1, 124.8, 123.7, 74.8, 73.7, 61.1, 60.4, 53.4, 52.4, 43.7, 39.0, 36.4, 31.8, 31.6, 30.7, 27.8, 26.8, 22.8, 21.2, 21.0, 20.8, 17.3, 14.9, 14.2$; ESI (DHB): m/z: 510 $[M+Na]^+$ calcd for $C_{28}H_{41}NO_6$ 510.

Epothilone stannane 58: To a solution of vinyl iodide **19** (42.5 mg, 0.079 mmol, 1.0 equiv) and diisopropylethylamine (3 μL, 0.016 mmol, 0.2 equiv) in toluene (0.8 mL) was added $[Pd(PPh_3)_4]$ (9 mg, 0.008 mmol, 0.1 equiv) followed by hexamethylditin (107 μL, 0.396 mmol, 5.0 equiv). The reaction mixture was heated at 85 °C for 30 min with monitoring by TLC (50% EtOAc in hexanes) every 5 min, then quickly filtered through silica gel and the filtrate concentrated under reduced pressure. Flash column chromatography (silica gel pre-treated with Et_3N, 17 to 50% EtOAc in hexanes) provided stannane **58** (29.0 mg, 64%). **58**: $R_f = 0.59$ (50% EtOAc in hexanes); $[\alpha]_D^{22} = -2.5$ ($c = 0.3$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3471, 2961, 2922, 2845, 2363, 1734, 1691, 1623, 1459, 1377, 1296, 1257, 1151, 1093, 1031, 978, 881, 800\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.88$ (s, 1H, C*H*=CCH$_3$), 5.33 (dd, $J = 6.1, 3.9$ Hz, 1H, CH$_2$C*H*(O)), 4.05 (ddd, $J = 9.6, 6.3, 3.3$ Hz, 1H, C*H*OH), 3.77 (dd, $J = 8.5, 4.4$ Hz, 1H, C*H*OH), 3.65 (d, $J = 5.9$ Hz, 1H, OH), 3.32 (dq, $J = 6.6, 5.2$ Hz, 1H, CH$_3$C*H*C(O)), 2.75 (dd, $J = 6.3, 6.3$ Hz, 1H, CH-epoxide), 2.53 (dd, $J = 14.7, 9.6$ Hz, 1H, C*H*$_2$C(O)), 2.50 (d, $J = 4.4$ Hz, 1H, OH), 2.42 (dd, $J = 14.7, 3.7$ Hz, 1H, C*H*$_2$C(O)), 1.96 (ddd, $J = 15.1, 5.6, 4.2$ Hz, 1H, C=CHC*H*$_2$CH(O)), 1.87 (ddd, $J = 14.7, 7.0, 6.7$ Hz, 1H), 1.84 (s, 3H, CH$_3$C=CH), 1.67 (m, 2H), 1.51 (m, 1H), 1.43 (m, 2H), 1.35 (m, 2H), 1.34 (s, 3H, C(CH$_3$)$_2$), 1.27 (s, 3H), 1.16 (d, $J = 7.0$ Hz, 3H, C*H*$_3$CHC(O)), 1.08 (s, 3H, C(CH$_3$)$_2$), 0.99 (d, $J = 7.0$ Hz, 3H, C*H*$_3$CH), 0.18 (s, 9H, Sn(CH$_3$)$_3$); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 220.8, 170.7, 149.8, 125.9, 73.7, 61.2, 60.9, 52.2, 43.7, 39.0, 36.4, 31.7, 31.6, 29.7, 22.7, 21.4, 20.9, 17.3, 14.2, 1.0, -8.8$; FAB HRMS (NBA/CsI): m/z: 707.1402 $[M+Cs]^+$ calcd for $C_{26}H_{46}O_6Sn$ 707.1376.

Epothilone dimer 59: In a similar procedure as was employed for the preparation of analogues **57a–e**, vinyl iodide **19** (2.7 mg, 0.005 mmol,

1.0 equiv) and epothilone stannane **58** (4.3 mg, 0.0075 mmol, 1.5 equiv) gave epothilone dimer **59** (1.8 mg, 44%). **59**: $R_f = 0.10$ (60% EtOAc in hexanes; $[\alpha]_D^{22} = -2.5$ ($c = 0.1$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3444, 2958, 2924, 2870, 1732, 1688, 1464, 1381, 1263, 1148, 1050, 981, 739, 668\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.28$ (s, 2H, C*H*=CCH$_3$), 5.38 (dd, $J = 7.4$, 3.7 Hz, 2H, CH$_2$C*H*(O)), 4.06 (ddd, $J = 9.6$, 6.3, 3.3 Hz, 2H, C*H*OH), 3.78 (br s, 2H, C*H*OH), 3.43 (d, $J = 6.3$ Hz, 2H, 2OH), 3.27 (dq, $J = 6.6$, 4.8 Hz, 2H, CH$_3$C*H*C(O)), 2.75 (dd, $J = 7.4$, 4.8 Hz, 2H), 2.53 (s, 2H, OH), 2.51 (dd, $J = 14.7$, 9.6 Hz, 2H, CH_2C(O)), 2.40 (dd, $J = 14.7$, 3.0 Hz, 2H, CH_2C(O)), 2.01 (m, 2H, C=CHCH_2CH(O)), 1.90 (m, 2H, C=CHCH_2CH(O)), 1.81 (s, 6H, CH=CCH_3), 1.69 (m, 4H), 1.50 (m, 2H), 1.41 (m, 2H), 1.38 (m, 4H), 1.34 (m, 2H), 1.33 (s, 6H, (CH$_3$)-epoxide), 1.26 (s, 6H, C(CH$_3$)$_2$), 1.17 (d, $J = 6.6$ Hz, 6H, CH_3CHC(O)), 1.09 (s, 6H, C(CH$_3$)$_2$), 0.99 (d, $J = 7.0$ Hz, 6H, CH_3CH); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 220.5$, 170.6, 135.6, 122.0, 77.1, 74.5, 73.6, 61.4, 61.3, 52.4, 43.4, 39.1, 36.4, 32.2, 31.8, 30.8, 29.7, 22.7, 21.2, 20.8, 17.3, 14.0, 13.5; FAB HRMS (NBA/CsI): m/z: 951.4206 $[M+Cs]^+$ calcd for $C_{46}H_{74}O_{12}$ 951.4235.

Epothilone dimer 61: A solution of vinyl iodide **19** (10.8 mg, 0.020 mmol, 1.0 equiv) in degassed DMF (0.2 mL) was stirred at 25 °C with $[Pd_2(dba)_3]$ (0.9 mg, 0.001 mmol, 0.1 equiv Pd) until the color changed from purple to brown (ca. 2 min), following which a solution of distannane **60b** (4.0 mg, 0.010 mmol, 1.0 equiv) in DMF (0.2 mL) was added and the mixture was heated to 60 °C. After 3 h, the reaction mixture was diluted with EtOAc (2 mL) and filtered through Celite. The filtrate was washed with saturated aqueous NaCl solution (5 mL), concentrated under reduced pressure, and the remaining solid was purified by flash column chromatography (25 to 50% EtOAc in hexanes) to yield dimer **61** as a slightly yellow oil (2.3 mg, 28%). **61**: $R_f = 0.29$ (60% EtOAc in hexanes); $[\alpha]_D^{22} = -2.4$ ($c = 0.2$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3493, 2961, 2927, 2857, 1729, 1659, 1645, 1634, 1555, 1468, 1454, 1388, 1259, 1091, 1009, 794, 755\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.78$ (s, 4H, Ph), 6.66 (s, 2H, C*H*=CCH$_3$), 5.45 (dd, $J = 8.8$, 7.3 Hz, 2H, CH$_2$C*H*(O)), 4.31 (ddd, $J = 16.9$, 9.2, 3.7 Hz, 2H, C*H*OH), 3.68 (br s, 2H, OH), 3.53 (dd, $J = 5.1$, 1.8 Hz, 2H, C*H*OH), 3.29 (dq, $J = 5.1$, 2.2 Hz, 2H, CH$_3$C*H*C(O)), 2.83 (dd, $J = 9.2$, 3.0 Hz, 2H, CH-epoxide), 2.44 (m, 4H, CH_2C(O)), 2.02 (m, 2H, CH_2C(O)), 1.99 (m, 2H, CH_2C(O)), 1.94 (s, 6H, CH=CCH_3), 1.67 (m, 4H), 1.37–1.18 (m, 10H), 1.33 (s, 6H, (CH$_3$)-epoxide), 1.27 (s, 6H, C(CH$_3$)$_2$), 1.15 (d, $J = 7.0$ Hz, 6H, CH_3CHC(O)), 1.02 (s, 6H, C(CH$_3$)$_2$), 0.89 (d, $J = 5.1$ Hz, 6H, CH_3CH); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 220.8$, 160.7, 129.5, 128.5, 127.4, 126.6, 121.3, 115.8, 79.0, 74.6, 74.0, 64.9, 56.8, 51.2, 41.4, 39.8, 37.2, 31.5, 30.9, 29.7, 22.1, 18.3, 17.3, 14.4; MALDI-FTMS HRMS (DHB): m/z: 917.5376 $[M+Na]^+$ calcd for $C_{52}H_{78}O_{12}$ 917.5385.

Vinyl analogue 62: To a solution of vinyl iodide **19** (10.7 mg, 0.02 mmol, 1.0 equiv) and stannane **64** (14.5 mg, 0.045 mmol, 2.25 equiv) in degassed DMF (0.2 mL) was added a solution of $[PdCl_2(MeCN)_2]$ (1.1 mg, 0.004 mmol, 0.2 equiv), CuI (4.6 mg, 0.024 mmol, 1.2 equiv) and $AsPh_3$ (3.7 mg, 0.012 mmol, 0.6 equiv) in degassed DMF (0.2 mL) and the reaction mixture was stirred at 25 °C for 1 h. EtOAc (10 mL) was added and the mixture was passed through silica gel eluting with EtOAc. The organic solution was washed with water (3 mL) and saturated aqueous NaCl solution (3 mL) and concentrated under reduced pressure. Flash column chromatography (20 to 80%, EtOAc in hexane) provided vinyl analogue **62** (4.0 mg, 46%). **62**: $R_f = 0.58$ (60% EtOAc in hexanes); $[\alpha]_D^{22} = -0.6$ ($c = 0.2$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3493, 2969, 2929, 2866, 1735, 1720, 1687, 1460, 1379, 1259, 1157, 1091, 1053, 1009, 978, 909, 805, 667\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.55$ (ddd, $J = 16.9$, 10.6, 10.3 Hz, 1H, C*H*=CH$_2$), 6.13 (d, $J = 10.6$ Hz, 1H, C*H*=CCH$_3$), 5.36 (dd, $J = 6.4$, 3.9 Hz, 1H, CH$_2$C*H*(O)), 5.27 (d, $J = 16.9$ Hz, 1H, CH=CH_2), 5.18 (d, $J = 10.3$ Hz, 1H, CH=CH_2), 4.04 (ddd, $J = 9.5$, 6.2, 3.3 Hz, 1H, C*H*OH), 3.78 (dd, $J = 4.4$, 4.0 Hz, 1H, C*H*OH), 3.53 (d, $J = 5.9$ Hz, 1H, OH), 3.30 (dq, $J = 11.7$, 7.0 Hz, 1H, CH$_3$C*H*C(O)), 2.75 (dd, $J = 6.6$, 5.9 Hz, 1H, CH-epoxide), 2.53 (dd, $J = 14.7$, 9.5 Hz, 1H, CH_2C(O)), 2.42 (dd, $J = 3.3$, 14.7 Hz, 1H, CH_2-C(O)), 2.42 (s, 1H, OH), 1.98 (ddd, $J = 15.0$, 5.1, 4.0 Hz, 1H, C=CHCH_2-CH(O)), 1.85 (ddd, $J = 13.6$, 6.6, 5.5 Hz, 1H, C=CHCH_2CH(O)), 1.81 (s, 3H, CH=CCH_3), 1.68 (m, 2H), 1.51 (m, 1H), 1.45 (m, 2H), 1.39 (m, 1H), 1.38 (s, 3H, (CH$_3$)-epoxide), 1.27 (s, 3H, C(CH$_3$)$_2$), 1.26 (m, 1H), 1.16 (d, $J = 6.6$ Hz, 3H, CH_3CHC(O)), 1.09 (s, 3H, C(CH$_3$)$_2$), 0.99 (d, $J = 7.0$ Hz, 3H, CH_3CH); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 220.6$, 170.6, 134.6, 131.9, 127.5, 126.5, 118.7, 77.5, 76.6, 73.9, 61.2, 39.0, 36.6, 31.9, 31.7, 30.8, 29.7, 23.0, 22.8, 21.5, 20.8, 17.3, 14.2, 13.5; MALDI-FTMS HRMS (DHB): m/z: 459.2714 $[M+Na]^+$ calcd for $C_{25}H_{40}O_6$ 459.2717.

Benzenoid analogues 63a and 63f: To a solution of vinyl iodide **19** (11 mg, 0.02 mmol, 1.0 equiv) and stannane **66a** (15 mg, 0.04 mmol, 2.0 equiv) in degassed DMF (0.2 mL) was added a solution of $[PdCl_2(MeCN)_2]$ (0.1 mg, 0.004 mmol, 0.2 equiv), CuI (5.0 mg, 0.03 mmol, 1.2 equiv), and $AsPh_3$ (4.0 mg, 0.01 mmol, 0.6 equiv) in degassed DMF (0.3 mL) and the reaction mixture was stirred at 25 °C for 1 h. EtOAc was added and the mixture was passed through silica gel eluting with EtOAc. The organic solution was washed with water (3 mL) and saturated aqueous NaCl solution (3 mL) and concentrated under reduced pressure. Flash column chromatography (30% EtOAc in hexanes) provided benzenoid analogue **63a** (8.9 mg, 91%). **63a**: $R_f = 0.53$ (70% EtOAc in hexanes); $[\alpha]_D^{22} = -16.5$ ($c = 6.0$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3494, 2941, 2918, 1736, 1694, 1457, 1379, 1252, 1146, 1050, 976, 748, 696\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.36-7.33$ (m, 2H, Ph), 7.28–7.22 (m, 3H, Ph), 6.60 (s, 1H, C*H*=CCH$_3$), 5.48 (dd, $J = 11.2$, 4.0 Hz, 1H, CH$_2$C*H*(O)), 4.08 (ddd, $J = 9.5$, 6.2, 3.3 Hz, 1H, C*H*OH), 3.82–3.77 (m, 1H, C*H*OH), 3.31 (dq, $J = 6.9$, 2.2 Hz, 1H, CH$_3$C*H*C(O)), 2.84 (dd, $J = 7.3$, 5.5 Hz, 1H, CH-epoxide), 2.54 (dd, $J = 15.1$, 10.0 Hz, 1H, CH_2C(O)), 2.45 (dd, $J = 14.3$, 3.3 Hz, 1H, CH_2C(O)), 2.08 (ddd, $J = 12.5$, 5.2, 3.6 Hz, 1H, C=CHCH_2CH(O)), 1.98 (ddd, $J = 14.7$, 7.3, 7.3 Hz, 1H, C=CHCH_2CH(O)), 1.92 (d, $J = 1.1$ Hz, 3H, CH_3C=CH), 1.88 (d, $J = 1.1$ Hz, 1H), 1.72–1.67 (m, 3H), 1.49–1.37 (m, 5H), 1.35 (s, 3H, C(CH$_3$)$_2$), 1.29 (s, 3H, (CH$_3$)-epoxide), 1.17 (d, $J = 6.6$ Hz, 3H, CH_3CHC(O)), 1.11 (s, 3H, C(CH$_3$)$_2$), 1.01 (d, $J = 7.0$ Hz, 3H, CH_3CH); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 220.5$, 170.6, 136.7, 134.7, 129.0, 127.5, 126.9, 73.9, 61.3, 61.1, 60.9, 60.6, 52.2, 43.6, 39.0, 36.6, 32.0, 31.9, 30.9, 29.7, 22.9, 22.8, 21.4, 21.3, 21.0, 17.3, 14.7, 14.2, 14.1, 14.1; MALDI-FTMS HRMS (DHB): m/z: 509.2867 $[M+Na]^+$ calcd for $C_{29}H_{42}O_6$ 509.2879.

A similar procedure was employed to prepare the benzenoid analogue **63f**. **63f**: (74%); $R_f = 0.41$ (60% EtOAc in hexanes); $[\alpha]_D^{22} = -0.6$ ($c = 0.1$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3483, 2919, 2837, 2335, 1731, 1678, 1454, 1372, 1261, 1078, 1043, 1014, 973, 797, 738, 679\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.83$ (br s, 1H, Ph), 7.81 (d, $J = 6.8$ Hz, 1H, Ph), 7.45 (d, $J = 6.8$ Hz, 1H, Ph), 7.44 (dd, $J = 7.8$, 6.8 Hz, 1H, Ph), 6.63 (s, 1H, C*H*=CCH$_3$), 5.48 (dd, $J = 6.8$, 4.3 Hz, 1H, CH$_2$C*H*(O)), 4.06 (m, 1H, C*H*OH), 3.80 (dd, $J = 4.1$, 4.1 Hz, 1H, C*H*OH), 3.57 (d, $J = 6.5$, 1H, OH), 3.31 (dq, $J = 11.9$, 6.9 Hz, 1H, CH$_3$C*H*C(O)), 2.83 (dd, $J = 6.5$, 6.2 Hz, 1H, CH-epoxide), 2.61 (s, 3H, CH_3CHC(O)), 2.57 (dd, $J = 14.5$, 9.6 Hz, 1H, CH_2C(O)), 2.47 (dd, $J = 14.6$, 3.5 Hz, 1H, CH_2C(O)), 2.08–1.95 (m, 2H, C=CHCH_2CH(O)), 1.89 (s, 3H, CH=CCH_3), 1.70 (m, 2H), 1.57–1.32 (m, 5H), 1.35 (s, 3H, (CH$_3$)-epoxide), 1.30 (s, 3H, C(CH$_3$)$_2$), 1.17 (d, $J = 7.0$ Hz, 3H, CH_3CHC(O)), 1.10 (s, 3H, C(CH$_3$)$_2$), 1.00 (d, $J = 6.8$ Hz, 3H, CH_3CH); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 220.0$, 198.0, 170.6, 137.1, 136.1, 133.5, 128.7, 128.5, 126.9, 126.4, 73.9, 61.2, 61.1, 60.4, 52.3, 39.0, 36.5, 31.9, 31.7, 30.8, 29.7, 26.7, 22.9, 21.4, 21.0, 20.8, 17.3, 15.3, 14.7, 14.2; MALDI HRMS (DHB): m/z: 551.2958 $[M+Na]^+$ calcd for $C_{31}H_{44}O_7$ 551.2985.

Benzenoid analogues 63b–e and 63g: To a solution of vinyl iodide **19** (5.6 mg, 0.010 mmol, 1.0 equiv) in degassed DMF (0.1 mL) was added stannane **66b** (16 mg, 0.052 mmol, 5.0 equiv) followed by $[PdCl_2(MeCN)_2]$ (2.7 mg, 0.010 mmol, 1.0 equiv). The reaction mixture was stirred at 25 °C for 44 h, diluted with EtOAc (2 mL), washed with saturated aqueous NaCl solution (3 mL), and concentrated under reduced pressure. Flash column chromatography (20% EtOAc in hexanes) provided benzenoid analogue **63b** as a colorless syrup (4.1 mg, 72%). **63b**: $R_f = 0.71$ (60% EtOAc in hexanes); $[\alpha]_D^{22} = -9.0$ ($c = 0.2$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3487, 2960, 2925, 2855, 1733, 1717, 1683, 1458, 1380, 1297, 1261, 1130, 1098, 1085, 1017, 979, 795, 748, 673\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.96$ (dd, $J = 7.8$, 1.4 Hz, 1H, Ph), 7.50 (ddd, $J = 7.6$, 7.6, 1.4 Hz, 1H, Ph), 7.32 (ddd, $J = 7.6$, 7.6, 1.0 Hz, 1H, Ph), 7.21 (d, $J = 7.8$ Hz, 1H, Ph), 6.98 (s, 1H, C*H*=CCH$_3$), 5.51 (dd, $J = 9.2$, 2.4 Hz, 1H, CH$_2$C*H*(O)), 4.36 (ddd, $J = 10.8$, 6.0, 2.7 Hz, 1H, C*H*OH), 4.19 (d, $J = 5.9$ Hz, 1H, C*H*OH), 3.86 (s, 3H, OCH$_3$), 3.72 (br s, 1H, OH), 3.27 (dq, $J = 7.0$, 3.2 Hz, 1H, CH$_3$C*H*C(O)), 2.88 (dd, $J = 8.4$, 3.2 Hz, 1H, CH-epoxide), 2.86 (br s, 1H, OH), 2.57 (dd, $J = 14.3$, 10.8 Hz, 1H, CH_2C(O)), 2.34 (dd, $J = 14.3$, 2.7 Hz, 1H, CH_2C(O)), 2.19 (ddd, $J = 15.4$, 3.0, 3.0 Hz, 1H, C=CHCH_2CH(O)), 1.90 (ddd, $J = 15.1$, 8.6, 8.6 Hz, 1H, C=CHCH_2CH(O)), 1.78 (s, 3H, CH=CCH_3), 1.78 (m, 2H), 1.71–1.23 (m, 5H), 1.35 (s, 3H, (CH$_3$)-epoxide), 1.29 (s, 3H, C(CH$_3$)$_2$), 1.13 (d, $J = 7.0$ Hz, 3H, CH_3CHC(O)), 1.08 (s, 3H, C(CH$_3$)$_2$), 0.97 (d, $J = 7.0$ Hz, 3H, CH_3CH); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 220.8$, 170.4, 167.9, 138.9, 135.7, 132.1, 131.1, 130.6, 127.0, 126.1, 76.1, 73.2, 72.0, 61.8, 53.6, 52.3, 39.8, 35.9, 32.8, 31.0, 29.6, 22.5, 22.2, 21.7, 18.2, 16.8, 15.7, 12.8; FAB HRMS (DHB): m/z: 567.2908 $[M+Na]^+$ calcd for $C_{31}H_{44}O_8$ 567.2934.

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A similar procedure was employed to prepare the benzenoid analogues **63c–e** and **63g**. **63c**: (38%); $R_f = 0.52$ (60% EtOAc in hexanes); $[\alpha]_D^{22} = -2.1$ ($c = 0.2$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3493$, 2961, 2923, 2854, 1725, 1690, 1455, 1377, 1292, 1261, 1206, 1148, 1109, 1089, 1018, 980, 794, 750, 735, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.93$ (s, 1H, Ph), 7.90 (dd, $J = 7.3$, 1.9 Hz, 1H, Ph), 7.43 (dd, $J = 7.6$, 1.6 Hz, 1H, Ph), 7.41 (dd, $J = 7.6$, 7.6 Hz, 1H, Ph), 6.62 (s, 1H, C*H*=CCH$_3$), 5.47 (dd, $J = 6.5$, 4.1 Hz, 1H, CH$_2$C*H*(O)), 4.08 (m, 1H, C*H*OH), 3.92 (s, 3H, OCH$_3$), 3.80 (dd, $J = 4.9$, 3.5 Hz, 1H, C*H*OH), 3.58 (d, $J = 3.9$ Hz, 1H, OH), 3.31 (dq, $J = 11.9$, 7.0 Hz, 1H, CH$_3$C*H*C(O)), 2.83 (dd, $J = 6.2$, 6.2 Hz, 1H, CH-epoxide), 2.57 (dd, $J = 14.6$, 9.5 Hz, 1H, C*H*$_2$C(O)), 2.46 (dd, $J = 14.6$, 3.5 Hz, 1H, C*H*$_2$C(O)), 2.06 (ddd, $J = 9.7$, 5.7, 4.1 Hz, 1H, C=CHC*H*$_2$CH(O)), 1.99 (dd, $J = 6.8$, 6.8 Hz, 1H, C=CHC*H*$_2$CH(O)), 1.91 (s, 3H, CH=CC*H*$_3$), 1.69 (m, 2H), 1.61–1.20 (m, 5H), 1.38 (s, 3H, (CH$_3$)-epoxide), 1.29 (s, 3H, C(CH$_3$)$_2$), 1.16 (d, $J = 6.8$ Hz, 3H, C*H*$_3$CHC(O)), 1.10 (s, 3H, C(CH$_3$)$_2$), 0.99 (d, $J = 7.0$ Hz, 3H, C*H*$_3$CH); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 208.4$, 170.6, 162.0, 135.9, 133.4, 130.1, 130.0, 128.3, 128.0, 126.4, 74.7, 73.9, 61.2, 52.2, 43.7, 38.9, 36.5, 31.8, 31.7, 30.7, 29.7, 22.9, 21.5, 20.8, 17.3, 14.7, 14.2; FAB HRMS (NBA/NaI): *m/z*: 567.2940 $[M+Na]^+$ calcd for $C_{31}H_{44}O_8$ 567.2934. **63d**: (63%); $R_f = 0.55$ (60% EtOAc in hexanes); $[\alpha]_D^{22} = -1.1$ ($c = 0.1$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3489$, 2957, 2924, 2856, 1737, 1716, 1606, 1560, 1542, 1509, 1463, 1455, 1436, 1412, 1375, 1282, 1258, 1179, 1152, 1105, 1017, 979, 861, 800, 764, 738, 706 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.00$ (d, $J = 8.4$ Hz, 2H, Ph), 7.32 (d, $J = 8.1$ Hz, 2H, Ph), 6.62 (s, 1H, C*H*=CCH$_3$), 5.47 (dd, $J = 5.4$, 4.6 Hz, 1H, CH$_2$C*H*(O)), 4.07 (m, 1H, C*H*OH), 3.91 (s, 3H, OC*H*$_3$), 3.79 (dd, $J = 5.9$, 4.1 Hz, 1H, C*H*OH), 3.55 (d, $J = 5.7$ Hz, 1H, OH), 3.31 (dq, $J = 7.1$, 5.2 Hz, 1H, CH$_3$C*H*C(O)), 2.82 (dd, $J = 6.2$, 6.2 Hz, 1H, CH-epoxide), 2.56 (dd, $J = 14.7$, 9.6 Hz, 1H, C*H*$_2$C(O)), 2.47 (dd, $J = 14.6$, 3.7 Hz, 1H, C*H*$_2$C(O)), 2.03 (m, 1H), 2.00 (dd, $J = 7.3$, 7.0 Hz, 1H, C=CHC*H*$_2$CH(O)), 1.92 (s, 3H, CH=CC*H*$_3$), 1.70 (m, 2H), 1.59–1.24 (m, 5H), 1.34 (s, 3H, (CH$_3$)-epoxide), 1.29 (s, 3H, C(CH$_3$)$_2$), 1.16 (d, $J = 6.8$ Hz, 3H, C*H*$_3$CHC(O)), 1.09 (s, 3H, C(CH$_3$)$_2$), 1.00 (d, $J = 7.0$ Hz, 3H, C*H*$_3$CH); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 212.5$, 170.6, 165.4, 136.9, 129.5, 128.9, 126.5, 75.1, 74.8, 74.0, 73.9, 61.1, 52.2, 43.8, 38.9, 31.8, 30.7, 29.7, 22.9, 20.8, 18.0, 17.3, 16.7, 14.9, 14.3, 13.5; FAB HRMS (NBA/NaI): *m/z*: 567.2931 $[M+Na]^+$ calcd for $C_{31}H_{44}O_8$ 567.2934. **63e**: (59%); $R_f = 0.50$ (60% EtOAc in hexanes); $[\alpha]_D^{22} = -1.1$ ($c = 0.1$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3491$, 2957, 2925, 2855, 2360, 2338, 1755, 1733, 1681, 1558, 1506, 1456, 1418, 1374, 1287, 1258, 1157, 1072, 1016, 882, 798, 763, 701, 667 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.75$ (dd, $J = 7.8$, 1.1 Hz, 1H, Ph), 7.48 (ddd, $J = 7.6$, 7.6, 1.1 Hz, 1H, Ph), 7.36 (ddd, $J = 1.1$, 7.6, 7.6 Hz, 1H, Ph), 7.22 (d, $J = 8.1$ Hz, 1H, Ph), 6.86 (s, 1H, C*H*=CCH$_3$), 5.50 (dd, $J = 9.7$, 2.4 Hz, 1H, CH$_2$C*H*(O)), 4.40 (br s, 1H, OH), 4.37 (m, 1H, (CH$_3$)$_2$CC*H*OH), 3.72 (dd, $J = 5.8$, 3.1 Hz, 1H, C*H*OH), 3.27 (dq, $J = 6.8$, 3.2 Hz, 1H, CH$_3$C*H*C(O))), 2.89 (br s, 1H, O*H*), 2.86 (dd, $J = 8.5$, 3.4 Hz, 1H, CH-epoxide), 2.56 (s, 3H, CH$_3$C(O)), 2.55 (dd, $J = 14.3$, 9.7 Hz, 1H, C*H*$_2$C(O)), 2.33 (dd, $J = 13.5$, 2.4 Hz, 1H, C*H*$_2$C(O)), 2.18 (ddd, $J = 14.6$, 3.8, 3.0 Hz, 1H, C=CHC*H*$_2$CH(O)), 1.90 (ddd, $J = 15.1$, 8.9, 8.9 Hz, 1H, C=CHC*H*$_2$CH(O)), 1.75 (m, 2H), 1.72 (s, 3H, CH=CC*H*$_3$), 1.65–1.24 (m, 5H), 1.35 (s, 3H, (CH$_3$)-epoxide), 1.29 (s, 3H, C(CH$_3$)$_2$), 1.13 (d, $J = 7.0$ Hz, 3H, C*H*$_3$CHC(O)), 1.09 (s, 3H, C(CH$_3$)$_2$), 0.97 (d, $J = 7.0$ Hz, 3H, C*H*$_3$CH); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 214.4$, 206.4, 172.4, 135.9, 131.7, 131.3, 129.8, 129.4, 127.1, 126.3, 115.3, 79.5, 78.2, 72.0, 61.8, 53.8, 50.4, 39.9, 35.8, 32.8, 31.0, 29.4, 22.5, 22.2, 17.7, 16.7, 15.5, 14.1, 12.7; FAB HRMS (NBA/NaI): *m/z*: 551.2990 $[M+Na]^+$ calcd for $C_{31}H_{44}O_7$ 551.2985. **63g**: (87%); $R_f = 0.53$ (60% EtOAc in hexanes); $[\alpha]_D^{22} = -1.4$ ($c = 0.4$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3491$, 2953, 2924, 2852, 1731, 1715, 1683, 1558, 1539, 1505, 1456, 1377, 1362, 1261, 1091, 1008, 973, 797 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.93$ (d, $J = 8.6$ Hz, 2H, Ph), 7.35 (d, $J = 8.4$ Hz, 2H, Ph), 6.62 (s, 1H, C*H*=CCH$_3$), 5.47 (dd, $J = 6.0$, 4.1 Hz, 1H, CH$_2$C*H*(O)), 4.08 (m, 1H, C*H*OH), 3.79 (dd, $J = 4.3$, 3.8 Hz, 1H, C*H*OH), 3.56 (br s, 1H, OH), 3.31 (dq, $J = 6.8$, 4.9 Hz, 1H, CH$_3$C*H*C(O)), 2.82 (dd, $J = 6.5$, 6.2 Hz, 1H, CH-epoxide), 2.60 (s, 3H, CH$_3$(CO)), 2.55 (dd, $J = 14.6$, 5.1 Hz, 1H, C*H*$_2$C(O)), 2.47 (dd, $J = 14.7$, 3.7 Hz, 1H, C*H*$_2$C(O)), 2.05 (dd, $J = 6.0$, 4.1 Hz, 1H, C=CHC*H*$_2$CH(O)), 2.00 (dd, $J = 6.8$, 6.5 Hz, 1H, C=CHC*H*$_2$CH(O)), 1.93 (s, 3H, CH=CC*H*$_3$), 1.69 (m, 2H), 1.58–1.26 (m, 5H), 1.35 (s, 3H, (CH$_3$)-epoxide), 1.29 (s, 3H, C(CH$_3$)$_2$), 1.16 (d, $J = 7.0$ Hz, 3H, C*H*$_3$CHC(O)), 1.10 (s, 3H, C(CH$_3$)$_2$), 1.00 (d, $J = 7.0$ Hz, 3H, C*H*$_3$CH); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 220.0$, 212.5, 170.6, 161.5, 136.1, 133.5, 128.7, 128.5, 126.9, 126.4, 76.3, 75.8, 73.9, 61.2, 52.9, 52.2, 39.0, 36.5, 31.9, 31.7, 30.7, 26.7, 22.9, 21.5, 20.0, 18.3, 17.3, 14.7, 9.0; FAB HRMS (NBA/NaI): *m/z*: 551.2976 $[M+Na]^+$ calcd for $C_{31}H_{44}O_7$ 567.2985.

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