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Chemical synthesis and biological evaluation of novel epothilone B and *trans*-12,13-cyclopropyl epothilone B analogues

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Abstract—In addition to the total synthesis of the thiomethyl thiazole side chain analogue of epothilone B (**3**), a series of related *trans*-12,13-cyclopropyl epothilone B analogues (**6**, **8**, **10**, **12**–**14**) was accomplished. While the synthesis of the epothilone B analogue (**3**) proceeded through a Stille coupling of a vinyl iodide substrate containing the epothilone macrocycle with the appropriate side chain stannane, that of the cyclopropyl analogues (**6**, **8**, **10**, **12**–**14**) involved a convergent strategy in which a Nozaki–Hiyama–Kishi coupling as a means of introducing the side chains prior to Yamaguchi macrolactonization and final elaboration to the target molecules. The synthesized analogues were subjected to biological evaluation involving in vitro tubulin polymerization, affinity for the microtubule Taxol® binding site and cell cytotoxicity assays. The results identified the methylthio thiazole side chain as a potency enhancing moiety for the epothilones and shed further light on the structure–activity relationships within this important class of chemotherapeutic agents.

1. Introduction

The excitement generated by the structural elucidation and biological activity of epothilones (e.g. **1** and **2**, Fig. 1) continues to drive multifaceted studies in chemistry, biology and medicine.[1] Advancing clinical trials with a number of drug candidates as anticancer agents add further urgency to continuing research programs in the field. We have recently reported the design, chemical synthesis, and biological evaluation of a number of 12,13-cyclopropyl epothilone analogues.[2,3] Particularly interesting was the potency of the *trans*-12,13-cyclopropyl set of epothilones A carrying the methylthiazole or pyridine side chains (structures **5** and **7**, Fig. 1).[3] This striking observation coupled with our earlier finding of the enhanced potency of thiomethyl thiazole analogues[4] of epothilones C and D prompted us to embark on the synthesis and biological investigation of a new epothilone B series in anticipation of improved biological profiles. In this article we report our most recent studies in the epothilone field culminating in a number of highly potent analogues (i.e. compounds **3**, **6**, **8**–**14**, Fig. 1) active against a variety of cell lines, including Taxol®-resistant tumor cells. It is worth noting at the outset that these biological studies were made possible only through the power of chemical synthesis which served well to deliver them expeditiously, as will now be described.

2. Results and discussion

2.1. Design and chemical synthesis of epothilone analogues

As an initial foray, we decided to confirm the potency enhancement bestowed on the epothilone scaffold by the methylthio group 4 as compared to the methyl substituent in the epothilone B series. The methylthiothiazole epothilone B (**3**) was thus synthesized by Stille coupling of stannane **16**[5] with vinyl iodide **15**[6] (72% yield) as shown in Scheme 1. The observed high potency of analogue **3** against a series of tumor cell lines (see Table 1) encouraged us to proceed with the design and synthesis of an entire family of methylthio analogues as well as a number of new pyridine-containing epothilones.

Keywords: epothilones; antitumor agents; chemical synthesis; structure–activity relationships.

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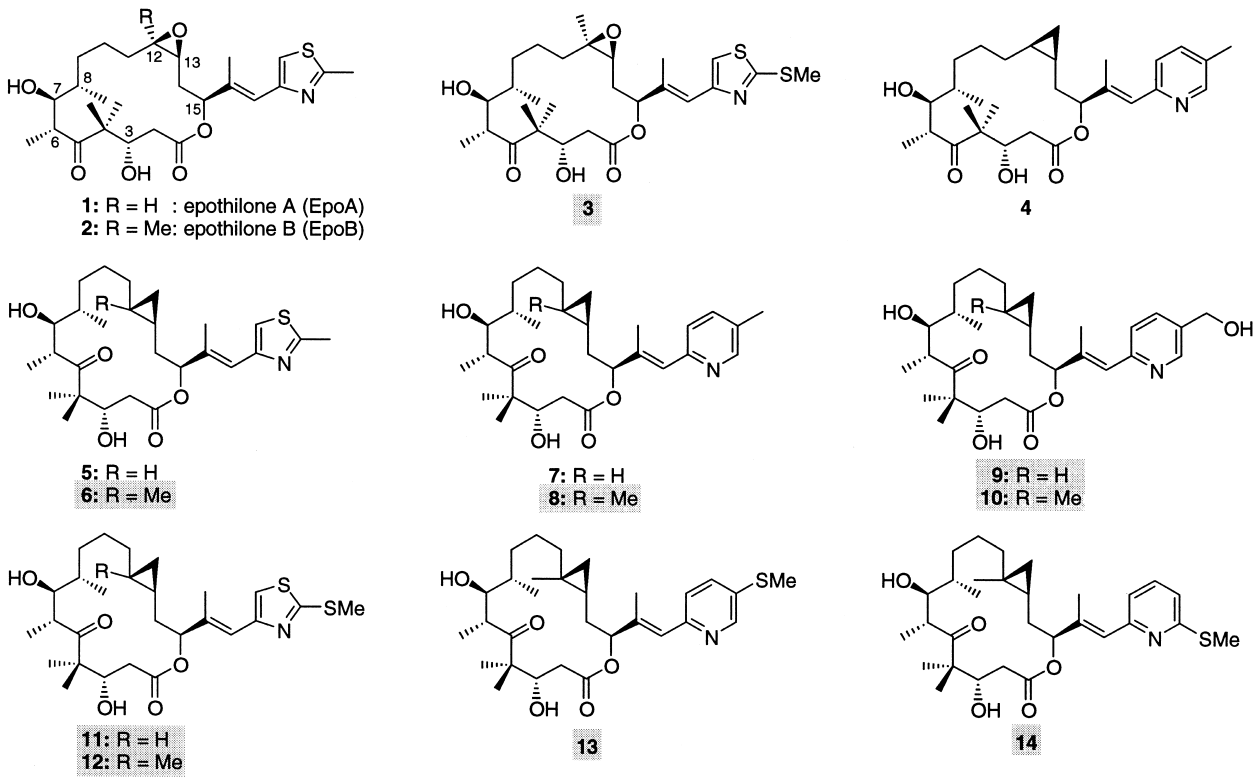
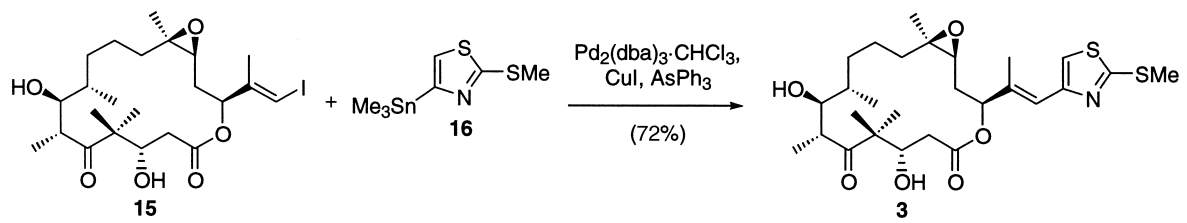


Figure 1. Structures of selected natural and designed epothilones. Grey boxes indicate compounds synthesized in this study.

Scheme 2 outlines, in retrosynthetic format, the pathway that was followed for the construction of the designed epothilone B analogues. Based on our previously reported strategy, the adopted sequence required a Charette cyclopropanation reaction[3,7] to establish early on in the synthesis the 12,13-cyclopropyl site, an aldol reaction according to our optimized procedure[6] to construct the C6–C7 bond with its two stereocenters, a Nozaki–Hiyama–Kishi coupling[3,8] to introduce the side chain, and a Yamaguchi macrolactonizaion[9] to complete the macrocyclic structure. Key building blocks **18**–**20** were thus defined as the starting points for these constructions. Construction of the corresponding epothilone A analogues was envisaged to be carried out in the same manner as previously reported by us.[3]

Scheme 3 outlines the synthesis of the required aldehyde **32** from the readily available geraniol (**18**). Thus, Charette cyclopropanation of **18** (Et_2Zn–CH_2I_2, in the presence of chiral ligand **21**)[7] furnished cyclopropyl alcohol **22** in 87% yield and 93% ee. Protection of the hydroxy group in **22** (NaH–BnBr) (for abbreviations of reagents and protecting groups, see legends in schemes) followed by ozonolysis (O_3; $NaBH_4$) of the remaining double bond led to compound **23** in 89% overall yield. Conversion of alcohol **23** to the corresponding iodide (**24**, 95% yield) was accomplished upon mesylation and subsequent reaction with NaI. Alkylation of (−)-propionaldehyde SAMP hydrazone (**25**)[9c,10] with iodide **24** under the influence of LDA gave compound **26** (84% yield), whose cleavage (MeI; HCl_{aq}) led to aldehyde **17** in 86% yield. The ratio of the resulting C-8 epimers was determined to be ca. 97:3 by ^1H NMR analysis of the MTPA esters derived from aldehyde **17**.[11] The aldol condensation between ketone **19** and aldehyde **17** under the previously defined conditions (LDA (2.4 equiv.), ketone **19** (2.3 equiv.), −78 to −40°C, 30 min; then aldehyde **17**, −78°C, 5 min)[6] afforded aldol product **27** which was isolated in a diastereomerically pure form (81% yield). Subsequent protection of the secondary alcohol in **27** as a TBS ether (TBSOTf, 2,6-lutidine) followed by selective cleavage of the primary TBS group (HF·py) afforded, in 88% overall yield, alcohol **28**. The latter compound was stepwise oxidized to the carboxylic acid (DMP; then $NaClO_2$) which was then protected as the TMSE ester **29** (TMSE-OH, EDC, 4-DMAP) in 74% overall yield. Hydrogenolysis of the benzyl ether in **29** followed by oxidation



Scheme 1. Synthesis of 2-(thiomethyl)thiazole epothilone B (**3**) via Stille coupling. *Reagents and conditions*: **16** (2.0 equiv.), $Pd_2(dba)_3$·$CHCl_3$ (0.2 equiv.), CuI (2.0 equiv.), $AsPh_3$ (0.8 equiv.), DMF, 25°C, 72%. dba, dibenzylideneacetone.

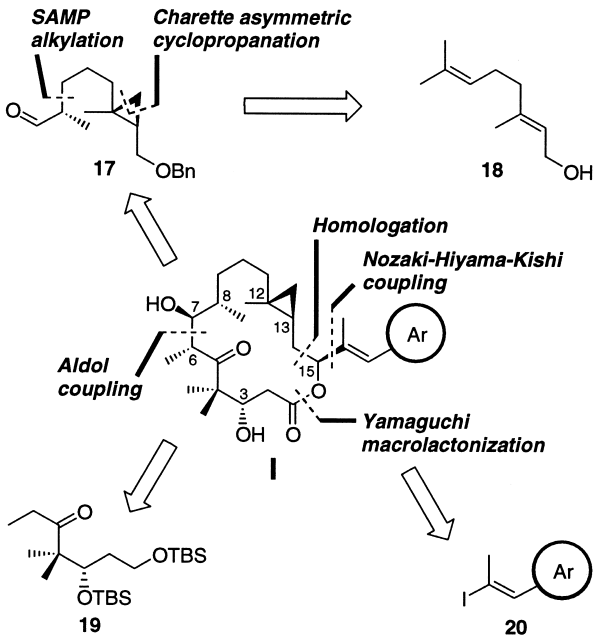
Table 1. Cytotoxicity of epothilones **1**–**14** and paclitaxel against 1A9 human ovarian carcinoma cells and β-tubulin mutant cell lines selected with paclitaxel or epothilone A

Compound	Cell line						
	1A9 IC_{50}	A8 (β274)		PTX10 (β270)		PTX22 (β364)	
		IC_{50}	RR	IC_{50}	RR	IC_{50}	RR
Epothilone A (EpoA) **1**	3.1 ± 0.72	77.3 ± 9.25	24.9	29.1 ± 7.24	9.4	10.1 ± 2.10	3.3
Epothilone B (EpoB) **2**	0.3 ± 0.05	6.5 ± 1.70	21.7	3.7 ± 1.83	12.3	2.1 ± 1.45	7
Paclitaxel (Taxol®)	1.3 ± 0.22	11.3 ± 0.83	8.7	47.7 ± 5.01	36.7	29.4 ± 3.69	22.6
tmt-EpoB **3**	0.17 ± 0.08	1.3 ± 0.65	7.6	0.26 ± 0.11	1.5	0.25 ± 0.17	1.5
cis-CP-py-EpoA **4**	2.4 ± 0.99	41.6 ± 8.58	17.3	19.2 ± 9.39	8	4.2 ± 2.18	1.8
trans-CP-EpoA **5**	10.1 ± 6.59	33.9 ± 5.56	3.4	17.2 ± 5.97	1.7	4.7 ± 1.68	0.5
trans-CP-EpoB **6**	15	> 150	> 10	52	3.5	5	0.3
trans-CP-py-EpoA **7**	0.6 ± 0.22	10.1 ± 2.07	16.8	5.9 ± 1.96	9.8	1.4 ± 0.51	2.3
trans-CP-py-EpoB **8**	1.7 ± 0.76	27.9 ± 6.73	16.4	10.9 ± 3.52	6.4	5.6 ± 3.24	3.3
trans-CP-pyOH-EpoA **9**	0.7 ± 0.16	13.0 ± 2.17	18.6	6.1 ± 1.90	8.7	1.1 ± 0.38	1.6
trans-CP-pyOH-EpoB **10**	1.7 ± 1.12	13.2 ± 5.02	7.8	10.2 ± 3.75	6	2.5 ± 1.41	1.5
trans-CP-tmt-EpoA **11**	1.2 ± 0.67	11.2 ± 2.30	9.3	3.2 ± 1.13	2.7	0.8 ± 0.38	0.7
trans-CP-tmt-EpoB **12**	3.5 ± 1.64	28.9 ± 8.01	8.3	5.7 ± 1.96	1.6	11.5 ± 3.86	3.3
trans-CP-5tmpy-EpoB **13**	14.2 ± 5.73	94 ± 5	6.6	72.0 ± 10.41	5.1	20.6 ± 9.06	1.5
trans-CP-6tmpy-EpoB **14**	114	> 150	> 1.3	> 150	> 1.3	104	0.9

The anti-proliferative effects of the tested compounds against the parental 1A9 and the paclitaxel- and epothilone-selected drug-resistant clones (PTX10, PTX22 and A8, respectively) were assessed in a 72 h growth inhibition assay using the SRB (sulforhodamine-B) assay.[17] IC_{50} values for each compound are given in nM and represent the mean of 3–9 independent experiments ± standard error of the mean. Relative resistance (RR) is calculated as an IC_{50} value for each resistant sub-line divided by that for the parental cell line (1A9). CP, cyclopropyl; py, 5-methylpyridine side chain; pyOH, 5-hydroxymethylpyridine side chain; 5tmpy, 5-thiomethylpyridine side chain; 6tmpy, 6-thiomethylpyridine side chain; tmt, 2-thiomethyl thiazole side chain.

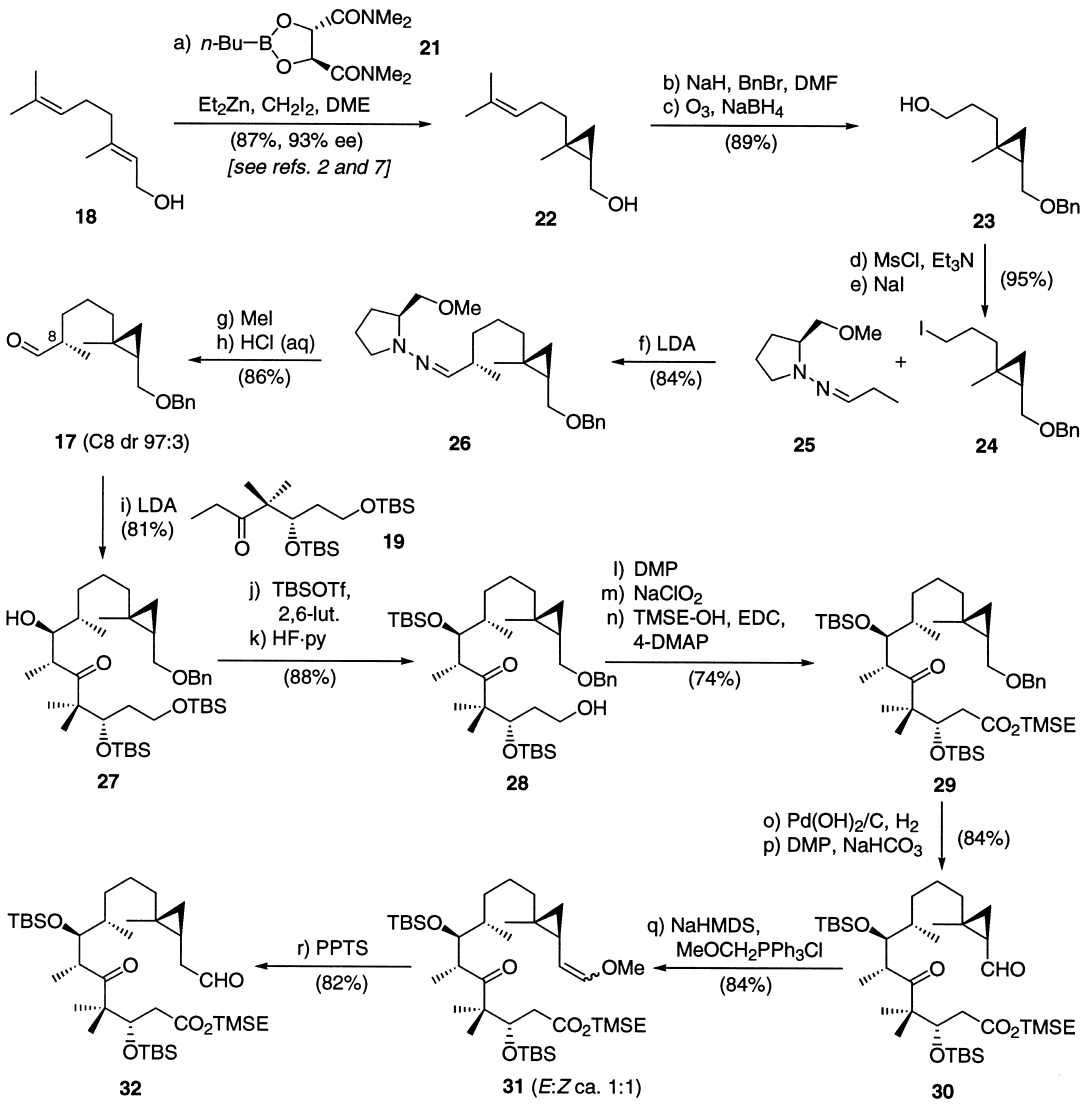
with DMP led to aldehyde **30** (84% yield) whose homologation (NaHMDS–$MeOCH_2PPh_3Cl$; then PPTS) to the coveted higher aldehyde **32** proceeded smoothly, and via vinyl ether **31** (ca. 1:1 *E*:*Z* ratio), with 68% overall yield.

The side chains (**20a**–**g**, Scheme 4) were synthesized either as previously reported (**20a** and **b**)[3] or from the corresponding aryl halides (**33**,[12] **37**–**39**) as shown in Scheme 4. Protection of 4-hydroxymethyl-2-pyridyl bromide **33** as a trityl ether (TrCl, 4-DMAP, 100%) followed by Sonogashira coupling[13] of the resulting aryl bromide **34** with propyne ($Pd(PPh_3)_2Cl_2$–CuI, 96%) led to acetylenic compound **35** which served as a precursor to vinyl iodide **20c** (*n*-BuLi; then $(n\text{-}Bu_3Sn)_2$, CuCN, MeOH; then I_2, 80% yield). Exchange of the trityl for a MOM group within **35** (HCl(g), $CHCl_3$; then NaH, MOM-Cl, 34% overall yield)[14] allowed access to vinyl iodide **20d** (67% yield) by exposure of the resulting intermediate **36** to the same conditions described above for the **35** to **20c** conversion. Similar chemistry was employed to construct vinyl iodides **20e**–**g** from **37** to **39**, respectively, as shown in Scheme 4.



Scheme 2. Retrosynthetic analysis of *trans*-cyclopropyl epothilone B analogues (**I**=**6**, **8**, **10**, **12**–**14**).

Two crucial bond formations and two accompanying deprotections separated key building blocks **32** (prepared in this study for epothilone B analogues), **40** (prepared as previously described for epothilone A analogues),[3] and **20a**–**g** (for side chains) from the targeted epothilone analogues. The first operation was the Nozaki–Hiyama–Kishi coupling[8] of aldehydes **32** and **40** with vinyl iodides **20a**–**g**. This carbon–carbon bond forming reaction worked admirably in this instance ($CrCl_2$, $NiCl_2$, 4-*t*-BuPy, DMSO), furnishing, after TBAF-induced carboxylic acid generation, coupling products (**41a**,**b**,**d**–**g**, **42c** and **e**) in yields indicated in Scheme 5 (as ca. 1:1 mixtures of C-15 diastereomers). Each mixture of hydroxy acid diastereomers (**41a**,**b**,**d**–**g**, **42c** and **e**) was then subjected to Yamaguchi macrocyclization (2,4,6-trichlorobenzoyl chloride, 4-DMAP) to afford the desired 15(*S*) lactone in the indicated (unoptimized) yields together with its 15(*R*) epimer. The separation of the two epimers at this juncture was facilitated by their rather drastically different R_f values on silica gel. Final deprotection of protected derivatives either with 20% TFA in CH_2Cl_2 (**43a**,**b**,**e**–**g**, **44c** and **e**) or with TMSBr–4 Å MS in CH_2Cl_2, followed by 20% TFA in CH_2Cl_2 (**43d**), led to epothilones **6**, **8**–**14** in the indicated (unoptimized) yields (Scheme 5). Chromatographically and spectroscopically pure compounds were subjected to biological evaluations as described below.

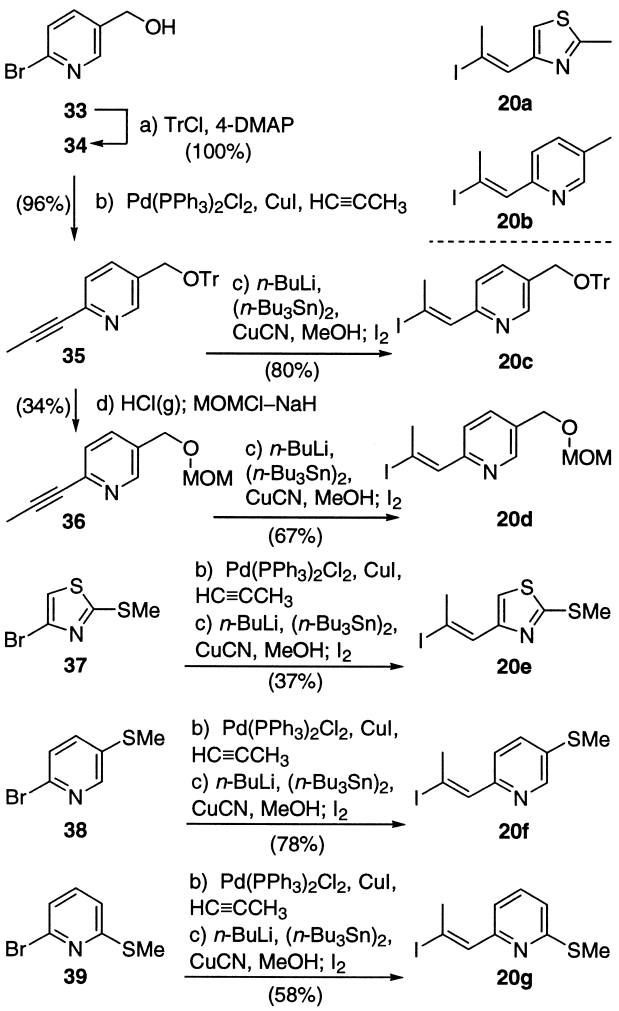


Scheme 3. Construction of aldehyde **32**. *Reagents and conditions*: (a) See Refs. 2 and 7; (b) NaH (1.5 equiv.), BnBr (1.5 equiv.), DMF, 0→ 25°C, 12 h; (c) O_3, CH_2Cl_2/MeOH 4:1, −78°C, 21 min; then $NaBH_4$ (3.0 equiv.), −78→25°C, 1 h, 89% for two steps; (d) MsCl (1.3 equiv.), Et_3N (1.5 equiv.), CH_2Cl_2, 25°C, 1 h; (e) NaI (3.0 equiv.), acetone, reflux, 40 min, 95% for two steps; (f) LDA (1.4 equiv.), **25** (1.3 equiv.), THF, 0°C, 6 h; then **24**, −98→ −10°C, 14 h, 84%; (g) MeI, 60°C, 3 h; (h) 3N HCl:pentane 1:1, 25°C, 3 h, 88% for two steps; (i) LDA (2.4 equiv.), **19** (2.3 equiv.), THF, −78°C, 1 h; then −40°C, 0.5 h; then **17** at −78°C, 5 min, 81%; (j) TBSOTf (2.0 equiv.), 2,6-lutidine (3.0 equiv.), CH_2Cl_2, −20°C, 1 h; (k) HF·py, pyridine, THF, 25°C, 4 h, 88% for two steps; (l) DMP (2.5 equiv.), $NaHCO_3$ (2.5 equiv.), H_2O, CH_2Cl_2, 25°C, 1 h; (m) $NaClO_2$ (3.1 equiv.), NaH_2PO_4 (2.1 equiv.), 2-methyl-2-butene (74 equiv.), *t*-BuOH, THF, H_2O, 25°C, 1 h; (n) 2-(trimethylsilyl)ethanol (4.0 equiv.), EDC (1.5 equiv.), 4-DMAP (0.1 equiv.), DMF, 25°C, 14 h, 74% for three steps; (o) 20% $Pd(OH)_2$/C, H_2 (1 atm), EtOH/EtOAc 1:1, 25°C, 1 h; (p) DMP (2.5 equiv.), $NaHCO_3$ (2.5 equiv.), H_2O, CH_2Cl_2, 25°C, 1 h, 84% for two steps; (q) $MeOCH_2PPh_3Cl$ (3.0 equiv.), NaHMDS (2.8 equiv.), THF, −40→ −10°C, 2 h, 84%; (r) PPTS (8.0 equiv.), dioxane:H_2O 9:1, 70°C, 6 h, 82%. 4-DMAP, 4-(dimethylamino)pyridine; DME, 1,2-dimethoxyethane; DMP, Dess–Martin periodinane; EDC, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; HF·py, hydrogen fluoride–pyridine complex; NaHMDS, sodium hexamethyldisilazide; PPTS, pyridinium para-toluenesulfonate; TMSE, 2-trimethylsilylethyl.

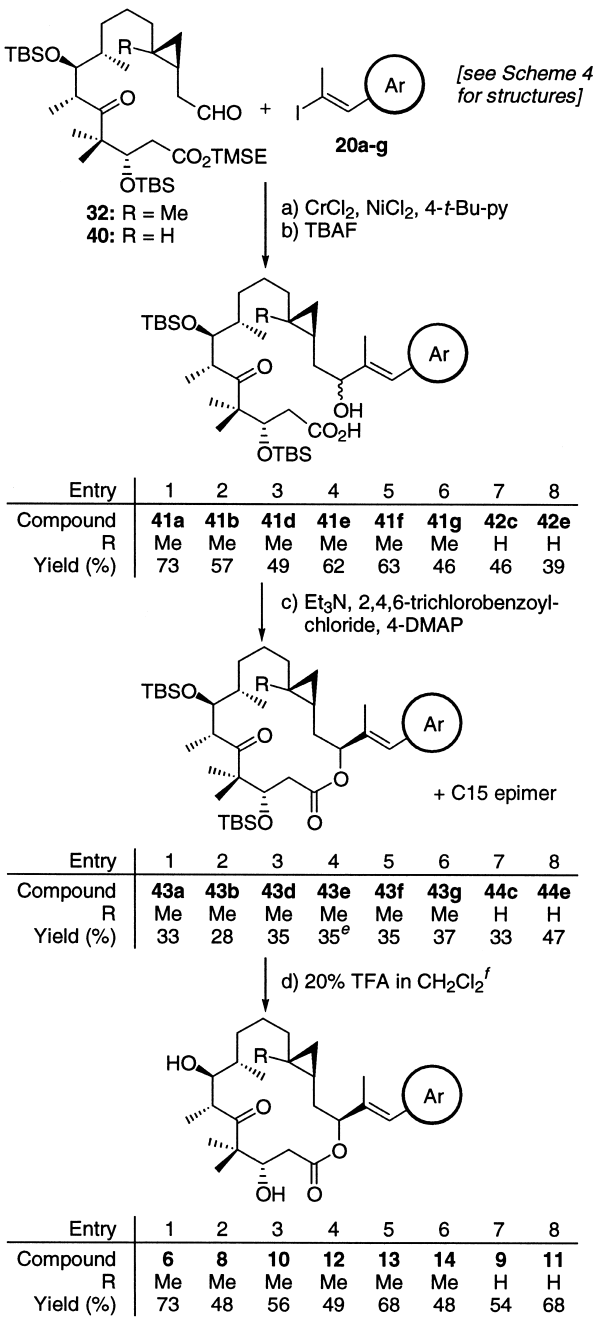
2.2. Chemical biology

The biological activities of the synthesized epothilones were evaluated through cytotoxicity, in vitro tubulin polymerization, and tubulin binding assays. Cytotoxicity was first evaluated in a set of ovarian carcinoma cell lines, including a parental cell line (lA9) and three drug-resistant cell lines, namely the paclitaxel-resistant strains[15] lA9/PTX10 and lA9/PTX22 and the epothilone-resistant strain[16] 1A9/A8. These resistant cell lines harbor distinct acquired β-tubulin mutations which affect drug–tubulin interaction and result in impaired taxane and epothilone-driven tubulin polymerization. The results of these biological investigations are summarized in Table 1.[17] Further cytotoxicity and in vitro tubulin polymerization assays were carried out using a set of human epidermoid cancer cell lines, including a parent cell line (KB-31) and a paclitaxel-resistant (due to Pgp overexpression) cell line (KB-8511). The results of these studies are summarized in Table 2.[18,19]

In general, there is good agreement between the in vitro tubulin polymerization potency and the cytotoxicity profile of the tested compounds against both the 1A9 human ovarian carcinoma cells and the KB-31 human epidermoid carcinoma cells. In agreement with original observations with the naturally occuring epothilones A and B, none of the epothilone A or B analogues tested herein appears to be a good substrate for the drug-efflux pump P-glycoprotein



Scheme 4. Construction of vinyl iodides **20c–g**. *Reagents and conditions*: (a) TrCl (1.4 equiv.), 4-DMAP (1.7 equiv.), DMF, 80°C, 48 h, 100%; (b) $Pd(PPh_3)_2Cl_2$ (0.01 equiv.), CuI (0.02 equiv.), $HC{\equiv}CCH_3$ (1 atm), DMF, i-Pr_2NEt, 25°C, 3 h, **35**: 96%; (c) (i) n-BuLi (4.0 equiv.), $(n\text{-}Bu_3Sn)_2$ (4.0 equiv.), CuCN (2.0 equiv.), MeOH, THF, −10°C, 12 h; (ii) I_2 (1.05 equiv.), CH_2Cl_2, 0°C, 5 min, **20c**: 80% from **35**; **20d**: 67% from **36**; **20e**: 37% from **37**; **20f**: 97% from **38**; **20g**: 58% from **39**; (d) (i) HCl(g), $CHCl_3$, 0°C, 1 h, 69%; (ii) MOMCl (1.2 equiv.), NaH (1.2 equiv.), THF, 0°C, 1 h, 50%. TrCl, triphenylmethyl chloride; 4-DMAP, 4-(dimethylamino)pyridine; MOMCl, chloromethyl methyl ether.



Scheme 5. Synthesis of epothilone analogues **8–14**. *Reagents and conditions*: (a) $CrCl_2$ (10 equiv.), $NiCl_2$ (0.2 equiv.), 4-t-butylpyridine (30 equiv.), **20** (3.0 equiv.), DMSO, 25°C, overnight; (b) TBAF (4.0 equiv.), THF, 0°C, 1 h; then 25°C, 1 h; (c) Et_3N (6.0 equiv.), 2,4,6-trichlorobenzoylchloride (2.4 equiv.), **41** or **42**, THF, 0°C, 1 h; then 4-DMAP (2.2 equiv.), toluene, 75°C, 3 h; (d) 20% v/v TFA in CH_2Cl_2, 25°C, 3 h (except **43d**); (e) Estimated by ^1H NMR; (f) Deprotection of **43d**: TMSBr (10 equiv.), 4 Å MS, CH_2Cl_2, −30°C, 1 h; then 20% v/v TFA in CH_2Cl_2, 25°C, 3 h. TBAF, tetrabutylammonium fluoride; 4-DMAP, 4-(dimethylamino)pyridine; TFA, trifluoroacetic acid; TMSBr, trimethylsilyl bromide; MS, molecular sieves.

(Pgp). This is evident by the lack of cross-resistance of each of these analogues to the Pgp expressing cell line KB-8511, in contrast to paclitaxel—a known Pgp substrate—which is 214-fold less active against KB-8511 cells (see Table 2). It is noteworthy that all the epothilone analogues appear more active against the β-tubulin mutants compared to epothilone A (**1**) and epothilone B (**2**) (see Table 1, RR values). This is more pronounced with compounds **10–14** for which the relative resistance values (RR) range from 1.6 to 7.8 against PTX10 (β270) and A8 (β274) cells compared with 9.4–24.9 RR values for EpoA (**1**) and EpoB (**2**). Furthermore, in the current study, and in agreement with previous reports,[2,15,16] we found that the paclitaxel-selected mutant PTX22 (β364) retains almost full sensitivity to the epothilones, and to all epothilone analogues tested in this report (RR values ≤3.3).

In addition to the above biological assays, the relative potency of each epothilone analogue was measured by the fluorescent taxoid displacement assay.[20] The purpose of these experiments was to compare the equilibrium constants with which microtubules bind at their taxane site the epothilone analogues investigated. The inhibition of the binding of the well-characterized fluorescent taxoid Flutax-2[21–23] to microtubules by each of the epothilone analogues was measured at 37°C (Fig. 2). The resulting

Table 2. Tubulin polymerization potency and cytotoxicity of epothilones **1**–**8**, **10**–**14**, and paclitaxel against human epidermoid cancer cell lines

Compound	%TP[a]	KB-31[b]	KB-8511[b]	RR
Epothilone A (EpoA) **1**	78	2.15[c]	1.91[c]	0.88[c]
Epothilone B (EpoB) **2**	93	0.19[c]	0.18[c]	0.95[c]
Paclitaxel (Taxol®)	52	2.92[c]	626[c]	214[c]
tmt-EpoB **3**	99	0.11	0.07	0.61
Cis-CP-py-EpoA **4**	100[c]	0.62[c]	0.45[c]	0.72[c]
trans-CP-EpoA **5**	100[c]	0.97[c]	0.64	0.66[c]
trans-CP-EpoB **6**	82	1.84	1.09	0.59
trans-CP-py-EpoA **7**	94[c]	0.84[c]	0.68[c]	0.81[c]
trans-CP-py-EpoB **8**	89	0.90	0.61	0.68
trans-CP-pyOH-EpoB **10**	87	0.44	0.55	1.25
trans-CP-tmt-EpoA **11**	93	0.66	0.32	0.48
trans-CP-tmt-EpoB **12**	91	0.67	0.45	0.67
trans-CP-5tmpy-EpoB **13**	88	6.88	5.28	0.77
trans-CP-6tmpy-EpoB **14**	58	109	74	0.68

[a] The extent of porcine tubulin polymerization (TP) by 4 μM compound was quantified relative to the effect of 25 μM epothilone B (which was defined as 100%) as described.[18]

[b] Drug concentration required for maximal inhibition of cell growth (IC_{50} values given in nM) was assessed after a 96 h drug exposure by quantification of cell mass using a protein dye method as described.[19] KB-31: epidermoid Taxol®-sensitive cells, KB-8511: epidermoid Taxol®-resistant cells (due to Pgp overexpression). Relative resistance (RR) was calculated by dividing the IC_{50} value for the resistant cell line by that of the sensitive cell line.

[c] Data from Ref. 3 (%TP values for Taxol®, EpoA and EpoB were 49, 69 and 90, respectively). CP, cyclopropyl; py, 5-methylpyridine side chain; pyOH, 5-hydroxymethylpyridine side chain; 5tmpy, 5-thiomethylpyridine side chain; 6tmpy, 6-thiomethylpyridine side chain; tmt, 2-thiomethyl thiazole side chain.

Table 3. Binding affinities of epothilone analogues to the taxoid binding site of microtubules

Compound	Kd (37°C)[a]	ΔG^0_{app} (37°C)[b]
Epothilone A (EpoA) **1**	34 ± 4	−44.5 ± 0.3
Epothilone B (EpoB) **2**	1.6 ± 0.1	−52.6 ± 0.5
Paclitaxel (Taxol®)	93 ± 26	−42.2 ± 0.2
tmt-EpoB **3**	0.64 ± 0.24	−54.5 ± 1.2
cis-CP-py-EpoA **4**	5.2 ± 0.8	−49.4 ± 0.3
trans-CP-EpoA **5**	6.5 ± 0.1	−48.6 ± 0.1
trans-CP-EpoB **6**	8.0 ± 1.8	−48.0 ± 0.1
trans-CP-py-EpoA **7**	2.1 ± 0.4	−51.5 ± 0.2
trans-CP-py-EpoB **8**	1.9 ± 0.6	−51.8 ± 0.8
trans-CP-pyOH-EpoB **10**	6.0 ± 0.6	−48.9 ± 0.3
trans-CP-tmt-EpoA **11**	1.6 ± 0.5	−52.2 ± 0.9
trans-CP-tmt-EpoB **12**	1.8 ± 0.2	−51.8 ± 0.3
trans-CP-5tmpy-EpoB **13**	1.9 ± 0.3	−51.6 ± 0.5
trans-CP-6tmpy-EpoB **14**	53 ± 8	−43.1 ± 0.5

The binding of the different ligands to the taxoid site of microtubules was measured by the displacement of a fluorescent Taxol® derivative (Flutax-2)[22] from its binding site (Fig. 2). The Flutax-2 displacement isotherm of each ligand was measured at least twice with a fluorescence polarization microplate reader in a modified procedure from the previous report.[20] Cross-linked stabilized microtubules which had been stored under liquid nitrogen were employed. The binding constant of the reference ligand Flutax-2 was measured by centrifugation and fluorescence anisotropy,[22] at each temperature. The resulting reference value was 2.2×10^7 M^{-1} at 37°C.

[a] The equilibrium dissociation constants (Kd) are given in nM.

[b] The standard binding free energy changes (ΔG^0_{app}) are given in kJ mol^{-1}.

equilibrium dissociation constants shown in Table 3 indicate that epothilone A (**1**) has the lowest binding affinity among the epothilone analogues tested (Kd = 34 ± 4). The most powerful ligand among those measured in this assay is compound **3**, with a Kd value of 0.64 ± 0.24 nM, followed by compounds **8**, **11**–**13**, with similar Kd values comprised between 1.6 and 1.9 nM. With the possible exception of compound **13**, the binding affinities of the analogues tested mirror their respective activities in both cell growth inhibition and in vitro tubulin polymerization assays.

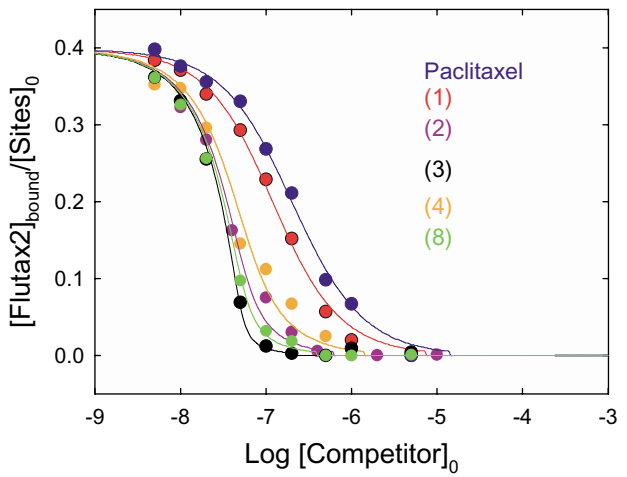


Figure 2. Displacement of the fluorescent taxoid Flutax-2 (50 nM) from microtubule binding sites (50 nM) by competing ligands at 37°C. The dots indicate acquired data points and the lines were generated so that they give the best fit value of the binding equilibrium constant of each competitor, assuming one-to-one binding to the same site. Ligands assayed are paclitaxel (Taxol®) (dark blue), epothilone A (**1**) (red), epothilone B (**2**) (violet), compound **3** (black), compound **4** (light brown), and compound **8** (green). Representative curves for selected epothilone analogues (**3**, **4**, and **8**) are presented in this figure to exemplify how the binding affinities were measured for each compound in Table 3.

Collectively from all three biological assays employed herein, a number of conclusions can be drawn in terms of structure–activity relationships within the epothilone family. First, the addition of the C12 methyl group does not enhance the activity in the *trans*-cyclopropyl series (compound **5** vs **6**, **7** vs **8**, **9** vs **10**), contrary to the result in the *cis* epoxide series, where epothilone B (**2**) is at least 10-fold more active than epothilone A (**1**). This could be due to the different orientation of the C12 methyl group in the *cis* and *trans* compounds or to overall differences in conformation between the *cis* and *trans* compounds, although the details remain to be elucidated. Second, the introduction of the 2-thiomethylthiazole side chain enhances the activity compared with the natural 2-methylthiazole side chain (compounds **2** vs **3**, **5** vs **11**, and **6** vs **12**). This effect was previously observed for epothilone C and D analogues.[4] Third, the replacement of a methyl group with a thiomethyl group in the pyridine side chain series (compounds **8** vs **13**) reduces potency, contrary to the results obtained for the thiazole side chains above. This conclusion was based on the cell cytotoxicity and in vitro tubulin polymerization data, while in the fluorescent taxoid displacement assay the replacement of the methyl group with a thiomethyl moiety in the pyridine side chain is indifferent in terms of binding affinity. This discrepancy may simply reflect differences in cell uptake and permeability of the compounds tested or differences in the sensitivity of the two tubulin assays. Despite this discrepancy, it is clear from these data that the introduction of a thiomethyl group at the thiazole side chain is a more favorable modification than the introduction of a thiomethyl group at the pyridine side chain, which may be

due to differing steric requirements by the two side chain scaffolds. In agreement with previous data obtained with *cis* pyridine epothilone analogues,[18] relocation of the thiomethyl group of the pyridine side chain from the position 5 (compound **13**) to position 6 (compound **14**) resulted in significant loss of activity. Fourth, mixed results are obtained with compounds **7** vs **9** and **8** vs **10** in which the 5-methylpyridine side chain (compounds **7** and **8**) is substituted by the 5-hydroxymethylpyridine side chain (compounds **9** and **10**). This substitution appears indifferent in cytotoxicity assays against the 1A9 human ovarian carcinoma cells (Table 1) where very similar IC_{50} values are obtained for each pair (e.g. 0.6 and 0.7 nM for compounds **7** and **9**, respectively; 1.7 nM for compounds **8** and **10**). On the other hand, in the human epidermoid carcinoma cells KB-31, compound **10** is 2-fold more active than its counterpart compound **8** with IC_{50}s at 0.44 vs 0.9 nM, respectively. Given the small differences in the growth rate of the two human cancer cell lines that could account for the differential results, we could conclude that the introduction of the 5-hydroxymethylpyridine side chain is not likely to enhance activity in, at least, *trans*-12,13-cyclopropyl analogues of the epothilone family.

3. Conclusions

A series of epoxide and cyclopropane epothilones with varying side chains were constructed by chemical synthesis and biologically evaluated. These investigations led to the identification of the thiomethylthiazole side chain as a desirable pharmacophoric group improving the biological activity of the epothilones with regard to cytotoxicity and tubulin polymerizing properties. The enhanced activity was confirmed by three distinct biological assays where the effects of the compounds tested were determined both in cells and in vitro. Further studies to expand this family of potent epothilones in search of new drug candidates and biological tools are in progress.

4. Experimental

4.1. General

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Anhydrous solvents were obtained by passing them through commercially available activated alumina columns. All reagents were purchased at highest commercial quality and used without further purification. Reactions were generally monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254). 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). Optical rotations were recorded on a Perkin–Elmer 241 polarimeter. NMR spectra were recorded on Bruker DRX-600, DRX-500, AMX-400 or Varian Mercury-300 instruments and calibrated using residual undeuterated solvents as an internal reference. All labeling of carbon atoms, e.g. C15, refers to epothilone A (1) numbering (see Fig. 1). IR spectra were recorded on a Perkin–Elmer 1600 series FT-IR spectrometer. High resolution mass spectra were recorded on a PerSeptive Biosystems Voyager™ IonSpec mass spectrometer (MALDI-FTMS) or on an API 100 Perkin–Elmer mass spectrometer (ESI).

4.2. Synthesis of epothilone 3

4.2.1. Stille coupling of vinyl iodide 15 with stannane 16. A solution of $Pd_2(dba)_3{\cdot}CHCl_3$ (3.9 mg, 3.8 μmol), $AsPh_3$ (4.6 mg, 15 μmol), and CuI (7.2 mg, 38 μmol) in DMF (degassed, 0.5 mL) was added at 25°C to a solution of iodide **15**[6] (10 mg, 19 μmol) and stannane **16**[5] (11 mg, 38 μmol) in DMF (degassed, 0.5 mL), and the resulting solution was stirred for 2 h. Water (10 mL) was added, and the mixture was extracted with EtOAc (3×10 mL). The combined organic phase was washed with water (30 mL), brine (30 mL), and dried (Na_2SO_4). After evaporation of the volatiles, the residue was purified by flash column chromatography (silica, hexanes/EtOAc 2:1→1:1) to yield epothilone **3** as a white solid (7.2 mg, 72%); TLC R_f=0.29 (silica, hexanes/EtOAc 1:1); $[\alpha]_D^{22}=-53$ (*c* 0.51, CH_2Cl_2); IR (film) ν_{max} 3472 (br), 2967, 2920, 1731, 1684, 1461, 1420, 1378, 1249, 1143, 1032, 973, 879, 732, 667 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.00 (d, J= 7.0 Hz, 3H, C(8)CH_3), 1.08 (s, 3H, C(4)$C_aH_3C_bH_3$), 1.17 (d, J=6.5 Hz, 3H, C(6)CH_3), 1.28 (s, 3H, C(4)$C_aH_3C_bH_3$), 1.36 (s, 3H, C(12)CH_3), 1.36–1.56 (m, 6H, C(9)H_2, C(10)H_2, C(11)H_2), 1.67–1.75 (m, 1H, C(8)H), 1.91–1.97 (m, 1H, C(14)H_aH_b), 2.00–2.11 (m, 1H, C(14)H_aH_b), 2.13 (s, 3H, vinyl CH_3), 2.39 (dd, J=3.1, 14.0 Hz, 1H, C(2)H_aH_b), 2.55 (dd, J=10.1, 14.0 Hz, 1H, C(2)H_aH_b), 2.60 (br s, 1H, OH), 2.70 (s, 3H, thiazole CH_3), 2.81 (dd, J=5.3, 7.0 Hz, 1H, C(13)H), 3.28–3.34 (m, 1H, C(6)H), 3.76–3.79 (m, 1H, C(7)H), 3.92 (br d, J=6.1 Hz, 1H, OH), 4.15–4.20 (m, 1H, C(3)H), 5.43 (dd, J=3.1, 7.5 Hz, 1H, C(15)H), 6.52 (s, 1H, vinyl H), 7.00 (s, 1H, thiazole H); ^{13}C NMR (150 MHz, $CDCl_3$, C(15) signal is obscured by the chloroform peak.) δ 13.8, 15.7, 16.7, 17.1, 20.2, 21.2, 22.5, 22.8, 30.7, 31.8, 32.1, 36.4, 39.1, 43.2, 52.8, 61.3, 61.5, 73.2, 74.3, 116.2, 119.2, 137.3, 152.5, 165.8, 170.6, 220.6; MALDI-FTMS *m/z* 562.2267 (MNa^+), calcd for $C_{27}H_{41}NO_6S_2Na$ 562.2267.

4.3. Construction of aldehyde 32

4.3.1. Alcohol 23. To a solution of cyclopropyl alcohol **22**[7] (4.08 g, 24 mmol) in DMF (40 mL) was added sodium hydride (1.45 g, 36 mmol, 60% in mineral oil) portionwise with stirring at 0°C. After stirring for 0.5 h at 25°C, the mixture was cooled to 0°C, benzyl bromide (4.3 mL, 36 mmol) was added over 2 min, and stirring was continued for 12 h at 25°C. The reaction was quenched with NH_4Cl (sat., 50 mL), the mixture was extracted with EtOAc (3×50 mL) and the combined extract was washed with brine (2×100 mL), dried (Na_2SO_4) and evaporated. The residue was dissolved in CH_2Cl_2/MeOH 4:1 (60 mL), and the solution was ozonized (100 L/h, ca. 5 g O_3/h) at −78°C for 21 min. (*Note*: Longer reaction times must be avoided to prevent oxidation of the benzyl ether to the corresponding benzoate.) Excess ozone was removed by flushing with N_2 for 1 min, and then $NaBH_4$ (2.75 g, 73 mmol) was added in

small portions (*Caution*! Exothermic!) followed by methanol (20 mL). The mixture was warmed to 25°C over 1 h, and the reaction was quenched by the addition of NH_4Cl (sat., 20 mL). The mixture was extracted with CH_2Cl_2 (2×50 mL), and the combined extract was washed with brine (100 mL), dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (silica, hexanes/EtOAc 5:2) to yield **23** as a yellow oil (5.07 g, 89%). TLC R_f=0.20 (silica, hexanes/EtOAc 3:1); $[\alpha]_D^{22}$=−7.5 (*c* 1.76, $CHCl_3$); IR (film) ν_{max} 3390 (br), 2933, 2859, 1452, 1070, 739, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.12 (m, 1H, *c*-propyl CH_2), 0.51 (dd, *J*=4.4, 8.8 Hz, 1H, *c*-propyl CH_2), 0.92–1.00 (m, 1H, *c*-propyl CH), 1.07 (s, 3H, CH_3), 1.15–1.24 (m, 1H, CH_2), 1.39–1.48 (m, 1H, CH_2), 1.60–1.75 (m, 2H, CH_2), 1.82 (br s, 1H, OH), 3.31 (dd, *J*=8.8, 10.3 Hz, 1H, C*H*$_2$OBn), 3.60 (dd, *J*=6.0, 10.3 Hz, 1H, C*H*$_2$OBn), 3.65 (t, *J*=6.3 Hz, 2H, C*H*$_2$OH), 4.50 (d, *J*=12.0 Hz, 1H, OC*H*$_2$Ph), 4.57 (d, *J*=12.0 Hz, 1H, OC*H*$_2$Ph), 7.28–7.36 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.3, 17.8, 19.6, 23.5, 30.1, 37.8, 63.2, 71.1, 72.8, 127.7, 127.9, 128.5, 138.7; MALDI-FTMS *m*/*z* 257.1519 (MNa^+), calcd for $C_{15}H_{22}O_2Na$ 257.1512.

4.3.2. Iodide 24. To a solution of cyclopropyl alcohol **23** (10.08 g, 43.0 mmol) in dry CH_2Cl_2 (100 mL) at 0°C was added methanesulfonyl chloride (4.2 mL, 54 mmol) followed by triethylamine (9.0 mL, 65 mmol) dropwise. A white precipitate started to form immediately. The mixture was stirred at 25°C for 1 h, then NH_4Cl (sat., 50 mL) and water (50 mL) were added and the phases were separated. The aqueous phase was extracted with EtOAc (100 mL), and the combined organic phase was washed with brine, dried (Na_2SO_4) and evaporated. The residue was dissolved in dry acetone (200 mL), and sodium iodide (19.3 g, 129 mmol) was added. The initially almost clear solution was refluxed for 40 min, during which time a white precipitate formed. Water (100 mL) was added and the mixture was extracted with ether (500+250 mL). The combined extract was dried and evaporated, and the residue was purified by flash chromatography (silica, hexanes/EtOAc 5:1) to yield **24** as a colorless oil (14.16 g, 95%). TLC R_f=0.66 (silica, hexanes/EtOAc 5:1); $[\alpha]_D^{22}$=−16 (*c* 2.05, $CHCl_3$); IR (film) ν_{max} 2916, 2848, 1453, 1217, 1098, 1073, 735, 697 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.13 (m, 1H, *c*-propyl CH_2), 0.55 (dd, *J*=4.4, 8.8 Hz, 1H, *c*-propyl CH_2), 0.94–1.02 (m, 1H, *c*-propyl CH), 1.05 (s, 3H, CH_3), 1.25–1.31 (m, 1H, CH_2), 1.37–1.42 (m, 1H, CH_2), 1.90–2.00 (m, 2H, CH_2), 3.23 (t, *J*=7.0 Hz, 1H, CH_2I), 3.33 (dd, *J*=8.8, 10.3 Hz, 1H, C*H*$_2$OBn), 3.59 (dd, *J*=6.2, 10.3 Hz, 1H, C*H*$_2$OBn), 4.50 (d, *J*=11.8 Hz, 1H, OC*H*$_2$Ph), 4.56 (d, *J*=11.8 Hz, 1H, OC*H*$_2$Ph), 7.28–7.36 (m, 5H, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 7.3, 17.2, 17.5, 18.9, 23.2, 31.1, 41.5, 70.9, 72.5, 127.5, 127.6, 128.3, 138.6; ESI-MS *m*/*z* 367 (MNa^+), calcd for $C_{15}H_{21}IONa$ 367.

4.3.3. Hydrazone 26. A solution of LDA was prepared by adding *n*-BuLi (13.1 mL, 21.0 mmol, 1.6 M in hexanes) to diisopropylamine (2.94 mL, 21.0 mmol) in THF (10 mL) at −78°C, then warming the solution to 0°C, and stirring for 10 min. To this LDA solution was added propionaldehyde SAMP hydrazone **25**[9c,10] (3.32 g, 19.5 mmol), and the mixture was stirred for 6 h at 0°C, during which time a white precipitate formed. The mixture was cooled to −98°C ($MeOH/N_2$(l) bath) and a solution of iodide **24** (5.16 g, 15.0 mmol) in THF (20 mL) was added over 0.5 h. The reaction mixture was then allowed to warm to −10°C over 14 h, and then the reaction was quenched with NH_4Cl (sat., 10 mL). The mixture was extracted with EtOAc (100 mL+2×50 mL), the combined extract was dried (Na_2SO_4) and evaporated, and the residue was purified by flash chromatography (silica, hexanes/EtOAc 6:1→4:1) to yield hydrazone **26** as a yellow oil (4.88 g, 84%). TLC R_f=0.38 (silica, hexanes/EtOAc 5:1); $[\alpha]_D^{22}$=−61 (*c* 1.45, $CHCl_3$); IR (film) ν_{max} 2926, 1454, 1097, 736, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.09 (t, *J*=5.0 Hz, 1H, *c*-propyl CH_2), 0.50 (dd, *J*=4.4, 8.5 Hz, 1H, *c*-propyl CH_2), 0.86–0.93 (m, 1H, *c*-propyl CH), 1.03 (s, 3H, CH_3), 1.04 (d, *J*=5.9 Hz, 3H, CHC*H*$_3$), 1.20–1.24 (m, 2H, CH_2), 1.30–1.44 (m, 4H, CH_2), 1.75–1.81 (m, 1H, CH_2), 1.84–1.98 (m, 3H, CH_2), 2.27–2.33 (m, 1H, C*H*CH_3), 265–2.70 (m, 1H, NC*H*CH_2OMe), 3.34–3.45 (m, 7H, C*H*$_2$OC*H*$_3$, C*H*$_2$OBn, CH_2N), 3.51–3.60 (m, 2H, C*H*$_2$OCH$_3$, C*H*$_2$OBn), 4.50 (d, *J*=12.1 Hz, 1H, OC*H*$_2$Ph), 4.55 (d, *J*=11.8 Hz, 1H, OC*H*$_2$Ph), 6.50 (d, *J*=6.3 Hz, 1H, N=CH), 7.28–7.36 (m, 5H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.3, 17.7, 19.0, 19.8, 22.1, 23.1, 24.2, 26.5, 35.5, 37.1, 41.0, 50.5, 59.2, 63.5, 71.0, 72.4, 74.8, 127.4, 127.6, 128.3, 138.7, 144.6; MALDI-FTMS *m*/*z* 387.3008 (MH^+), calcd for $C_{24}H_{39}N_2O_2$ 387.3006.

4.3.4. Aldehyde 17. A solution of hydrazone **26** (3.82 g, 9.9 mmol) in iodomethane (10 mL) was heated at 60°C (reflux condenser) for 3 h, and was then cooled to 25°C. Excess iodomethane was evaporated and traces removed under oil pump vacuum. The residual yellow syrup was vigorously stirred with 3N HCl (190 mL) and pentane (190 mL) for 3 h at 25°C, the phases were separated, and the aqueous phase was extracted with pentane (100 mL). The combined organic phase was dried (Na_2SO_4, $NaHCO_3$) and evaporated to yield aldehyde **17** as a yellow oil (2.38 g, 88%). $[\alpha]_D^{22}$=+2 (*c* 1.3, $CHCl_3$); IR (film) ν_{max} 2931, 2856, 1724, 1454, 1095, 1074, 736, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.12 (m, 1H, *c*-propyl CH_2), 0.51 (dd, *J*=4.6, 8.6 Hz, 1H, *c*-propyl CH_2), 0.89–0.96 (m, 1H, *c*-propyl CH), 1.04 (s, 3H, CH_3), 1.08 (d, *J*=7.0 Hz, 3H, CHC*H*$_3$), 1.16–1.24 (m, 1H, CH_2), 1.26–1.33 (m, 1H, CH_2), 1.36–1.50 (m, 3H, CH_2), 1.63–1.72 (m, 1H, CH_2), 2.30–2.38 (m, 1H, C*H*CH_3), 3.37 (dd, *J*=8.3, 10.5 Hz, 1H, C*H*$_2$OBn), 3.57 (dd, *J*=6.3, 10.3 Hz, 1H, C*H*$_2$OBn), 4.51 (d, *J*=11.9 Hz, 1H, OC*H*$_2$Ph), 4.56 (d, *J*=11.9 Hz, 1H, OC*H*$_2$Ph), 7.28–7.36 (m, 5H, ArH), 9.62 (d, *J*=1.9 Hz, 1H, CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.3, 17.2, 17.6, 19.6, 23.2, 24.0, 30.5, 41.0, 46.4, 71.0, 72.5, 127.4, 127.6, 128.3, 138.7, 205.3; MALDI-FTMS *m*/*z* 297.1830 (MNa^+), calcd for $C_{18}H_{26}O_2Na$ 297.1825.

Due to the configurational lability at C8 (epothilone numbering), the aldehyde should be used immediately in the next step. The dr at C8 was estimated as follows: A sample of **17** was treated with excess $NaBH_4$ in methanol for 10 min. The reaction was quenched with NH_4Cl (sat.), the mixture was extracted with EtOAc, and the extract was dried (Na_2SO_4) and evaporated. The residue was treated with (*R*)-(−)-MTPACl (2–3 equiv.), excess triethylamine

and 4-DMAP in CH_2Cl_2 for 3 h. Purification by preparative TLC yielded a sample of the (*S*)-MTPA ester, which by ^1H NMR analysis showed a dr=97:3, with the correct absolute stereochemistry at C8 as the major isomer.[11] Analogous results were obtained by using (*S*)-(+)-MTPACl.

4.3.5. Aldol product 27. A solution of LDA was prepared by adding *n*-BuLi (7.5 mL, 12 mmol, 1.6 M in hexanes) to diisopropylamine (1.68 mL, 12 mmol) in THF (12 mL) at −78°C, then warming the solution briefly to 0°C, and finally cooling back to −78°C. A solution of ketone **19**[9c] (4.63 g, 11.5 mmol) in THF (12 mL) was added dropwise over 2 min, and the mixture was stirred for 1 h at −78°C and then for 0.5 h at −40°C. It was again cooled to −78°C, and a solution of aldehyde **17** (1.37 g, 5.0 mmol) in THF (25 mL), pre-cooled to −78°C, was added via cannula over 1 min, taking care to ensure minimal warming during transfer. The mixture was stirred for 5 min, and the reaction was then quenched by rapid injection of a solution of AcOH (1.4 mL) in THF (4.2 mL). After 5 min at −78°C, the mixture was warmed to 25°C and partitioned between NH_4Cl (sat., 50 mL) and ether (50 mL). The aqueous phase was extracted with ether (2×50 mL), the combined extract was dried (Na_2SO_4) and evaporated, and the residue was purified by flash chromatography (silica, hexanes/ether 20:1→6:1) to yield recovered ketone **19** (1.71 g, 4.25 mmol) followed by the aldol product **27** in diastereomerically pure form (2.73 g, 81%). TLC R_f=0.34 (silica, hexanes/EtOAc 5:1); $[\alpha]_D^{22}=-40$ (*c* 1.0, $CHCl_3$); IR (film) ν_{max} 3502 (br), 2954, 2928, 2856, 1681, 1472, 1255, 1098, 836, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 6H, CH_3Si), 0.08–0.10 (m, 4H, CH_3Si, *c*-propyl CH_2), 0.11 (s, 3H, CH_3Si), 0.51 (dd, *J*=4.4, 8.8 Hz, 1H, *c*-propyl CH_2), 0.84 (d, *J*=7.0 Hz, 3H, CH_2CHCH_3), 0.87–0.92 (m, 1H, *c*-propyl CH), 0.90 (s, 9H, $(CH_3)_3CSi$), 0.91 (s, 9H, $(CH_3)_3CSi$), 1.02–1.08 (m, 1H, CH_2), 1.03 (d, *J*=5.9 Hz, 3H, $C(O)CHCH_3$), 1.04 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.12–1.18 (m, 1H, CH_2) 1.21 (s, 3H, CH_3), 1.25–1.33 (m, 2H, CH_2), 1.45–1.56 (m, 3H, CH_2CHCH_3, CH_2), 1.61–1.68 (m, 1H, CH_2CH_2OTBS), 1.70–1.79 (m, 1H, CH_2), 3.28–3.33 (m, 2H, $C(O)CH(CH_3)CHOH$), 3.40 (dd, *J*=8.1, 10.3 Hz, 1H, CH_2OBn), 3.52 (s, 1H, OH), 3.54 (dd, *J*=6.6, 10.3 Hz, 1H, CH_2OBn), 3.59–3.64 (m, 1H, CH_2OTBS), 3.66–3.71 (m, 1H, CH_2OTBS), 3.99 (dd, *J*=2.6, 7.3 Hz, 1H, CHOTBS), 4.51 (d, *J*=12.1 Hz, 1H, OCH_2Ph), 4.56 (d, *J*=12.1 Hz, 1H, OCH_2Ph), 7.26–7.36 (m, 5H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.3, −4.1, −3.8, 9.6, 15.3, 17.3, 17.7, 18.2, 18.3, 19.8, 20.4, 22.8, 23.1, 23.9, 25.9, 26.1, 32.9, 35.6, 37.8, 41.2, 41.5, 53.9, 60.4, 71.0, 72.3, 74.0, 74.9, 127.4, 127.6, 128.2, 138.8, 222.3; MALDI-FTMS *m/z* 699.4796 (MNa^+), calcd for $C_{39}H_{72}O_5Si_2Na$ 699.4816.

4.3.6. Alcohol 28. A solution of aldol product **27** (2.71 g, 4.0 mmol) and 2,6-lutidine (1.40 mL, 12 mmol) in CH_2Cl_2 (25 mL) was cooled to −20°C and then TBSOTf (1.84 mL, 8.0 mmol) was added dropwise. The mixture was stirred for 1 h at −20°C and the reaction was then quenched by the addition of NH_4Cl (sat., 25 mL). The mixture was warmed to 25°C, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (25 mL) and ether (25 mL). The combined organic phase was dried (Na_2SO_4) and evaporated, and the residue was filtered through a plug of silica eluting with hexane/ether 10:1. The filtrate was evaporated and the resulting crude silyl ether (3.14 g, 4.0 mmol, 99%) was dissolved in THF (40 mL). To this was added a cold (0°C) solution of HF·pyridine complex (6.4 mL) and pyridine (18 mL) in THF (32 mL) at 0°C (this solution was prepared by slowly adding the HF·pyridine complex to a solution of pyridine in THF at 0°C; *Caution*! HF·pyridine is highly corrosive. The addition of HF·pyridine to the pyridine–THF solution is highly exothermic, and must be done with stirring and cooling in ice bath to prevent splashing), and the resulting solution was stirred at 25°C for 4 h. The mixture was diluted with EtOAc (100 mL), placed in an ice bath, and quenched by careful addition of $NaHCO_3$ (sat., 100 mL) and as much solid $NaHCO_3$ as needed to ensure complete neutralization (*Caution*! Foaming!). The mixture was extracted with EtOAc (3×100 mL), and the combined extract was dried (Na_2SO_4) and evaporated, and the residue was purified by flash chromatography (silica, hexanes/EtOAc 5:1) to yield **28** as a colorless oil (2.40 g, 89%). TLC R_f=0.39 (silica, hexanes/EtOAc 5:1); $[\alpha]_D^{22}=-26$ (*c* 1.1, $CHCl_3$); IR (film) ν_{max} 3458 (br), 2929, 2856, 1693, 1472, 1462, 1255, 1093, 986, 836, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.08 (s, 9H, CH_3Si), 0.08–0.13 (m, 4H, CH_3Si, *c*-propyl CH_2), 0.49 (dd, *J*=4.4, 8.8 Hz, 1H, *c*-propyl CH_2), 0.88–0.92 (m, 19H, $(CH_3)_3CSi$, *c*-propyl CH), 0.93 (d, *J*=6.6 Hz, 3H, CH_2CHCH_3), 1.01–1.25 (m, 4H, CH_2), 1.03 (s, 3H, CH_3), 1.06 (d, *J*=5.9 Hz, 3H, $C(O)CHCH_3$), 1.07 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.29–1.38 (m, 2H, CH_2CHCH_3, CH_2), 1.42–1.52 (m, 1H, CH_2), 1.56–1.63 (m, 2H, CH_2CH_2OH), 2.01 (s, 1H, OH), 3.10–3.17 (m, 1H, $C(O)CHCH_3$), 3.40 (dd, *J*=8.1, 10.3 Hz, 1H, CH_2OBn), 3.53 (dd, *J*=6.6, 10.3 Hz, 1H, CH_2OBn), 3.62–3.67 (m, 2H, CH_2OH), 3.79–3.83 (m, 1H, $C(O)CH(CH_3)CHOTBS$), 4.07 (dd, *J*=4.2, 6.1 Hz, 1H, $CH(OTBS)CH_2CH_2OH$), 4.51 (d, *J*=12.1 Hz, 1H, OCH_2Ph), 4.55 (d, *J*=12.1 Hz, 1H, OCH_2Ph), 7.27–7.36 (m, 5H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.0, −3.9, −3.8, −3.7, 15.6, 17.3, 17.6, 17.7, 18.2, 18.5, 19.8, 23.1, 24.7, 24.8, 26.0, 26.2, 31.0, 38.3, 38.9, 41.7, 45.0, 53.7, 60.2, 71.0, 72.4, 73.0, 127.4, 127.6, 128.3, 138.7, 219.5; MALDI-FTMS *m/z* 699.4807 (MNa^+), calcd for $C_{39}H_{72}O_5Si_2Na$ 699.4816.

4.3.7. Ester 29. The alcohol **28** (2.40 g, 3.5 mmol), Dess–Martin periodinane (3.75 g, 8.8 mmol), $NaHCO_3$ (0.74 g, 8.8 mmol) and water (76 μL, 4.2 mmol) were mixed in CH_2Cl_2 (80 mL), and the resulting suspension was stirred for 1 h. The mixture was diluted with ether (200 mL), water (100 mL) and $NaHCO_3$ (sat., 100 mL), and was then filtered. The phases were separated and the aqueous phase was extracted with ether (2×100 mL). The combined extract was dried (Na_2SO_4) and evaporated, and the residue was filtered through a plug of silica eluting with hexanes/EtOAc 6:1. The filtrate was evaporated and the resulting crude aldehyde (2.15 g, 3.2 mmol, 90%) was dissolved in a mixture of THF (80 mL), *t*-BuOH (145 mL) and 2-methyl-2-butene (25 mL). To this solution was added a solution of NaH_2PO_4 (0.95 g, 6.7 mmol) and $NaClO_2$ (1.14 g, 10 mmol) in water (31 mL), and the resulting mixture was stirred vigorously for 1 h. The volatiles were removed by evaporation, and the residue was partitioned between EtOAc (100 mL) and brine (100 mL). The phases

were separated and the aqueous phase was extracted with EtOAc (3×100 mL). The combined extract was dried (Na_2SO_4) and evaporated, and the residue was dissolved in DMF (5 mL) and evaporated again to remove traces of *t*-BuOH. The so obtained crude acid (2.4 g, ca. 3.2 mmol >100%,) was again dissolved in DMF (10 mL), to which 2-(trimethylsilyl)ethanol (1.83 mL, 12.7 mmol), EDC (0.92 g, 4.8 mmol), and 4-DMAP (40 mg, 0.33 mmol) were added. The resulting suspension was stirred for 14 h, after which time a clear solution was obtained. Water (10 mL) was added and the mixture was extracted with ether (3×50 mL). The combined extract was washed with water–brine mixture (100+100 mL), dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (silica, hexanes/EtOAc 10:1) to yield ester **29** as a viscous, pale yellow oil (2.08 g, 74%). TLC R_f=0.57 (silica, hexanes/EtOAc 10:1); $[\alpha]_D^{22}=-33$ (*c* 1.2, $CHCl_3$); IR (film) ν_{max} 2954, 2930, 2856, 1735, 1695, 1472, 1385, 1252, 1090, 988, 836, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.04–0.06 (m, 18H, CH_3Si), 0.10–0.12 (m, 4H, CH_3Si, *c*-propyl CH_2), 0.50 (dd, *J*=4.4, 8.4 Hz, 1H, *c*-propyl CH_2), 0.85–0.93 (m, 22H, $(CH_3)_3CSi$, *c*-propyl CH, CH_2CHCH_3), 0.99 (t, *J*=8.6 Hz, 2H, CH_2CH_2TMS), 1.03 (s, 3H, CH_3), 1.05 (d, *J*=7.0 Hz, 3H, $C(O)CHCH_3$), 1.05–1.10 (m, 1H, CH_2), 1.07 (s, 3H, CH_3), 1.16–1.22 (m, 3H, CH_2), 1.24 (s, 3H, CH_3), 1.31–1.38 (m, 2H, CH_2CHCH_3, CH_2), 1.44–1.50 (m, 1H, CH_2), 2.25 (dd, *J*=6.6, 16.5 Hz, 1H, CH_2CO_2TMSE), 2.43 (dd, *J*=3.3, 16.5 Hz, 1H, CH_2CO_2TMSE), 3.12–3.18 (m, 1H, $C(O)CHCH_3$), 3.40 (dd, *J*=8.1, 10.3 Hz, 1H, CH_2OBn), 3.53 (dd, *J*=6.6, 10.3 Hz, 1H, CH_2OBn), 3.77 (dd, *J*=1.6, 6.8 Hz, 1H, $C(O)CH(CH_3)CHOTBS$), 4.10–4.21 (m, 2H, CH_2CH_2TMS), 4.39 (dd, *J*=3.3, 6.6 Hz, 1H, $CH(OTBS)CH_2CO_2TMSE$), 4.51 (d, *J*=12.1 Hz, 1H, OCH_2Ph), 4.55 (d, *J*=12.1 Hz, 1H, OCH_2Ph), 7.27–7.36 (m, 5H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.7, −4.4, −3.8, −3.7, −1.5, 15.4, 17.2, 17.3, 17.7, 17.8, 18.2, 18.5, 19.6, 19.8, 23.2, 23.5, 24.8, 26.0, 26.2, 31.0, 39.0, 40.4, 41.8, 45.1, 53.4, 62.7, 71.0, 72.4, 73.9, 77.5, 127.4, 127.6, 128.3, 138.7, 172.2, 217.9; MALDI-FTMS *m/z* 813.5315 (MNa^+), calcd for $C_{44}H_{82}O_6Si_3Na$ 813.5311.

4.3.8. Aldehyde 30. To a solution of benzyl ether **29** (2.08 g, 2.63 mmol) in EtOH/EtOAc 1:1 (50 mL) was added 20% $Pd(OH)_2$ on carbon (2.1 g, 60% moisture), and the mixture was hydrogenated for 1 h H_2, 1 atm. It was then filtered through celite to remove the catalyst, the filtrate was evaporated, and the residue was co-evaporated with benzene to remove traces of EtOH. The resulting crude alcohol (1.89 g, ca. 2.6 mmol, >100%) was dissolved in CH_2Cl_2 (60 mL), Dess–Martin periodinane (2.76 g, 6.5 mmol), $NaHCO_3$ (0.55 g, 6.5 mmol) and water (56 μL, 3.1 mmol) were added, and the resulting suspension was stirred for 1 h. The mixture was diluted with ether (150 mL), water (75 mL) and $NaHCO_3$ (sat., 75 mL), and was then filtered. The phases were separated and the aqueous phase was extracted with ether (2×75 mL). The combined extract was dried (Na_2SO_4) and evaporated, and the residue was purified by flash chromatography (silica, hexanes/EtOAc 15:1) to yield aldehyde **30** as a viscous oil (1.55 g, 84%). TLC R_f=0.24 (silica, hexanes/EtOAc 15:1); $[\alpha]_D^{22}=-47$ (*c* 1.3, $CHCl_3$); IR (film) ν_{max} 2954, 2856, 1734, 1703, 1251, 1173, 1084, 988, 837, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.03–0.06 (m, 18H, CH_3Si), 0.10 (s, 3H, CH_3Si), 0.87 (s, 9H, $(CH_3)_3CSi$), 0.90 (s, 9H, $(CH_3)_3CSi$), 0.91 (d, *J*=6.6 Hz, 3H, CH_2CHCH_3), 0.98 (t, *J*=8.6 Hz, 2H, CH_2CH_2TMS), 1.04 (d, *J*=7.0 Hz, 3H, $C(O)CHCH_3$), 1.05–1.11 (m, 2H, CH_2, *c*-propyl CH_2), 1.06 (s, 3H, CH_3), 1.19–1.29 (m, 2H, CH_2), 1.23 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.31–1.39 (m, 4H, *c*-propyl CH_2, CH_2CHCH_3, CH_2), 1.43–1.52 (m, 1H, CH_2), 1.67–1.71 (m, 1H, *c*-propyl CH), 2.23 (dd, *J*=6.6, 16.5 Hz, 1H, CH_2CO_2TMSE), 2.42 (dd, *J*=3.3, 16.3 Hz, 1H, CH_2CO_2TMSE), 3.11–3.16 (m, 1H, $C(O)CHCH_3$), 3.76 (dd, *J*=1.9, 7.2 Hz, 1H, $C(O)CH(CH_3)CHOTBS$), 4.09–4.20 (m, 2H, CH_2CH_2TMS), 4.38 (dd, *J*=3.3, 6.6 Hz, 1H, $CH(OTBS)CH_2CO_2TMSE$), 9.36 (d, *J*=5.5 Hz, 1H, CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.7, −4.5, −3.8, −3.7, −1.6, 15.5, 17.2, 17.3, 17.7, 18.2, 18.5, 19.6, 22.6, 22.8, 23.4, 24.6, 26.0, 26.2, 30.1, 30.8, 31.6, 35.8, 38.8, 40.4, 41.3, 45.3, 53.4, 62.7, 73.8, 77.6, 172.1, 201.5, 217.7; MALDI-FTMS *m/z* 721.4671 (MNa^+), calcd for $C_{37}H_{74}O_6Si_3Na$ 721.4685.

4.3.9. Enol ether 31. To a suspension of $MeOCH_2PPh_3Cl$ (3.09 g, 9.0 mmol) in THF (20 mL) at 0°C was added NaHMDS (8.5 mL, 8.5 mmol, 1 M in THF) dropwise. A red color developed. The mixture was stirred at 0°C for 0.5 h and it was then cooled to −40°C. A solution of aldehyde **30** (2.12 g, 3.0 mmol) in THF (7 mL) was added, and the mixture was allowed to warm to −10°C over 2 h. The reaction was quenched with NH_4Cl (sat., 15 mL), the phases were separated, and the aqueous phase was extracted with EtOAc (2×75 mL). The combined extract was dried (Na_2SO_4) and evaporated, and the residue was purified by flash chromatography (silica, hexanes/EtOAc 30:1) to yield enol ether **31** as a colorless, viscous oil (1.85 g, 84%, olefin *cis*:*trans* ca. 1:1 by ^1H NMR). TLC R_f=0.23 (silica, hexanes/EtOAc 30:1); $[\alpha]_D^{22}=-36$ (*c* 1.2, $CHCl_3$); IR (film) ν_{max} 2954, 2930, 2856, 1735, 1695, 1251, 1171, 1105, 988, 836, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, total integral normalized to 78H) δ 0.03–0.06 (m, 18H, CH_3Si), 0.11 (s, 3H, CH_3Si), 0.14–0.20 (m, 1H, *c*-propyl CH_2), 0.53 (dd, *J*=4.4, 8.5 Hz, 0.5H, *c*-propyl CH_2), 0.66 (dd, *J*=4.2, 8.6 Hz, 0.5H, *c*-propyl CH_2), 0.85–0.92 (m, 21H, $(CH_3)_3CSi$, CH_2CHCH_3), 0.96–1.01 (m, 5H, CH_3, CH_2CH_2TMS), 1.03–1.07 (m, 6H, CH_3, $C(O)CHCH_3$), 1.07–1.12 (m, 2.5H, CH_2, *c*-propyl CH), 1.19–1.37 (m, 4H, CH_2, CH_2CHCH_3), 1.23 (s, 3H, CH_3), 1.40–1.51 (m, 1.5H, CH_2, *c*-propyl CH), 2.21–2.26 (m, 1H, CH_2CO_2TMSE), 2.43 (dd, *J*=3.3, 16.5 Hz, 1H, CH_2CO_2TMSE), 3.10–3.18 (m, 1H, $C(O)CHCH_3$), 3.50 (s, 1.5H, OCH_3), 3.61 (s, 1.5H, OCH_3), 3.75–3.78 (m, 1H, $C(O)CH(CH_3)CHOTBS$), 4.09 (dd, *J*=6.3, 9.4 Hz, 0.5H, *cis*-HC=C(H)OCH_3), 4.10–4.20 (m, 2H, CH_2CH_2TMS), 4.37–4.40 (m, 1H, $CH(OTBS)CH_2CO_2TMSE$), 4.61 (dd, *J*=7.5, 12.5 Hz, 0.5H, *trans*-HC=C(H)OCH_3), 5.96 (dd, *J*=1.1, 6.3 Hz, 0.5H, *cis*-HC=C(H)OCH_3), 6.33 (d, *J*=12.5 Hz, 0.5H, *trans*-HC=C(H)OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$, more than one set of peaks counted due to the presence of *E*- and *Z*-isomers) δ −4.7, −4.5, −3.8, −3.7, −1.5, 14.1, 15.4, 15.5, 17.2, 17.6, 17.7, 18.1, 18.2, 18.5, 19.6, 19.7, 20.8, 21.5, 21.6, 22.3, 22.6, 22.8, 23.4, 23.5, 24.7, 24.8, 26.0, 26.2, 31.0, 31.6, 38.9, 40.4, 41.5, 45.1, 45.2 53.4, 56.1, 59.6, 62.7, 73.8, 73.9, 77.5, 77.6, 103.0, 106.9, 146.7, 147.7, 172.1, 217.8, 217.9; MALDI-FTMS *m/z* 749.4996 (MNa^+), calcd for $C_{39}H_{78}O_6Si_3Na$ 749.4998.

4.3.10. Aldehyde 32. To a solution of enol ether **31** (847 mg, 1.16 mmol) in dioxane:water 9:1 (12mL) was added pyridinium *para*-toluenesulfonate (2.34 g, 9.31 mmol) and the mixture was stirred at 70°C until TLC indicated the completion of the reaction (6–10 h). The reaction was then quenched with $NaHCO_3$ (sat., 15 mL), and the mixture was extracted with EtOAc (3×50 mL). The combined extract was dried (Na_2SO_4) and evaporated, and the residue was purified by flash chromatography (silica, hexanes/EtOAc 15:1) to yield **32** as a colorless, viscous oil (681 mg, 82%). TLC R_f=0.29 (silica, hexanes/EtOAc 15:1); $[\alpha]_D^{22}=-34$ (*c* 1.0, $CHCl_3$); IR (film) ν_{max} 2954, 2856, 1731, 1695, 1251, 1086, 988, 836, 776 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.03–0.07 (m, 19H, CH_3Si, *c*-propyl CH_2), 0.11 (s, 3H, CH_3Si), 0.57 (dd, *J*=4.6, 8.6 Hz, 1H, *c*-propyl CH_2), 0.77–0.84 (m, 1H, *c*-propyl CH), 0.88 (s, 9H, $(CH_3)_3CSi$), 0.90 (s, 9H, $(CH_3)_3CSi$), 0.92 (d, *J*=7.0 Hz, 3H, CH_2CHCH_3), 0.95–0.99 (m, 2H, CH_2CH_2TMS), 1.00 (s, 3H, CH_3), 1.04 (d, *J*=7.0 Hz, 3H, $C(O)CHCH_3$), 1.07 (s, 3H, CH_3), 1.09–1.22 (m, 2H, CH_2), 1.23 (s, 3H, CH_3), 1.26–1.36 (m, 4H, CH_2CHCH_3, CH_2), 1.42–1.50 (m, 1H, CH_2), 2.24 (dd, *J*=6.8, 16.5 Hz, 1H, CH_2CO_2TMSE), 2.36 (ddd, *J*=2.2, 7.4, 17.2 Hz, 1H, CH_2CHO), 2.42 (m, 2H, CH_2CHO, CH_2CO_2TMSE), 3.12–3.17 (m, 1H, $C(O)CHCH_3$), 3.77 (dd, *J*=1.7, 7.0 Hz, 1H, $C(O)CH(CH_3)CHOTBS$), 4.10–4.20 (m, 2H, CH_2CH_2TMS), 4.39 (dd, *J*=3.3, 6.8 Hz, 1H, $CH(OTBS)CH_2CO_2TMSE$), 9.81 (t, *J*=2.2 Hz, 1H, CHO); ^{13}C NMR (150 MHz, $CDCl_3$) δ −4.7, −4.4, −3.7, −3.6, −1.5, 15.5, 16.8, 17.2, 17.6, 17.7, 18.2, 18.5, 19.0, 19.6, 23.5, 24.8, 26.0, 26.2, 31.0, 38.9, 40.4, 41.7, 44.1, 45.2, 53.4, 62.7, 73.9, 77.6, 172.2, 202.6, 217.9; MALDI-FTMS *m/z* 735.4823 (MNa^+), calcd for $C_{38}H_{76}O_6Si_3Na$ 735.4842.

4.4. Construction of vinyl iodides 20c–g

4.4.1. 2-Bromo-5-[(trityloxy)methyl]pyridine 34. Trityl chloride (3.90 g, 14 mmol), 4-DMAP (2.08 g, 17 mmol) and 2-bromo-5-hydroxymethylpyridine **33**[12] (1.88 g, 10 mmol) were dissolved in DMF (15 mL) and the solution was stirred at 80°C for 48 h. A white precipitate formed during this time. After cooling, the mixture was diluted with $NaHCO_3$ (sat., 25 mL) and extracted with EtOAc (3×50 mL). The combined extract was washed with brine, with a few drops of NaOH (1 M) added (2×100 mL). After drying and evaporation, the solid residue was purified by flash chromatography (silica, hexanes/EtOAc 15:1) to yield **34** as a white solid (4.46 g, 100%). TLC R_f=0.30 (silica, hexanes/EtOAc 15:1); IR (film) ν_{max} 3057, 1448, 1086, 764, 700, 632 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.18 (s, 2H, CH_2), 7.24–7.36 (m, 10H, ArH), 7.44–7.49 (m, 6H, ArH), 7.57 (dd, *J*=2.1, 8.2 Hz, 1H, ArH), 8.32 (d, *J*=2.6 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.8, 87.5, 127.2, 127.3, 128.0, 128.5, 133.9, 137.4, 140.7, 143.5, 148.8; MALDI-FTMS *m/z* 430.0792 (MH^+), calcd for $C_{25}H_{21}BrNO$ 430.0801.

4.4.2. Sonogashira coupling of aryl bromides (34, 37–39) with propyne (general procedure). To a briefly deoxygenated (Ar bubbling) solution of the aryl bromide **34**, **37**, **38**, or **39** (3.5 mmol) in DMF (3 mL) and diisopropyl amine (2.5 mL) were added $Pd(PPh_3)_2Cl_2$ (25 mg, 36 μmol) and CuI (13 mg, 70 μmol) under Ar(g), and then the inert atmosphere was replaced by propyne (1 atm, balloon). The mixture was stirred at 25°C for 3 h. During this time, a precipitate formed, and the reaction mixture turned dark brown. Water (15 mL) was added, the mixture was extracted with EtOAc, and the combined extract was dried (Na_2SO_4) and evaporated. The pure 1-arylpropyne was obtained by flash chromatography (silica, hexane:EtOAc mixtures).

4.4.3. Propynylpyridine 35. Brown foam (96%); TLC R_f=0.23 (silica, hexanes/EtOAc 5:1); IR (film) ν_{max} 3057, 2229, 1594, 1560, 1478, 1448, 1075, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.09 (s, 3H, CH_3), 4.21 (s, 2H, CH_2), 7.26–7.35 (m, 10H, ArH), 7.48–7.51 (m, 6H, ArH), 7.67 (m, 1H, ArH), 8.47 (d, *J*=1.5 Hz, 1H, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 4.3, 63.3, 79.5, 86.3, 87.3, 126.1, 127.2, 127.9, 128.5, 133.2, 134.8, 142.6, 143.6, 148.6; MALDI-FTMS *m/z* 390.1851 (MH^+), calcd for $C_{28}H_{24}NO$ 390.1852.

4.4.4. Pyridine 36. A solution of trityl ether **35** (1.38 g, 3.54 mmol) in $CHCl_3$ (15 mL) was cooled to 0°C and then saturated with HCl (g). After 1 h at 0°C, the reaction was quenched by the addition of $NaHCO_3$ (sat., 50 mL), and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (50 mL) and the combined organic phase was dried (Na_2SO_4) and evaporated. Flash chromatography (silica, hexanes/EtOAc 1:2+5% MeOH) afforded 5-hydroxymethyl-2-prop-1-ynylpyridine as a yellow, viscous oil (0.36 g, 69%). TLC R_f=0.29 (silica, hexanes/EtOAc 1:2+5% MeOH); IR (film) ν_{max} 3262, 2916, 2230, 1596, 1561, 1023, 838 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.02 (s, 3H, CH_3), 4.23 (br s, 1H, OH), 4.67 (s, 2H, CH_2), 7.30 (d, *J*=8.1 Hz, 1H, ArH), 7.62 (dd, *J*=2.2, 8.1 Hz, 1H, ArH), 8.37 (d, *J*=2.2 Hz, 1H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.2, 61.8, 79.1, 86.9, 126.4, 135.0, 135.7, 142.3, 148.0; MALDI-FTMS *m/z* 148.0754 (MH^+), calcd for $C_9H_{10}NO$ 148.0757. To a solution of this alcohol (0.40 g, 2.7 mmol) in THF (10 mL) at 0°C was added NaH (0.13 g, 3.3 mmol, 60% in oil). After stirring for 5 min, chloromethyl methyl ether (0.25 mL, 3.3 mmol) was added, and the mixture was stirred at 0°C for 1 h. The reaction was then quenched with NaCl (sat.), and a few drops of NaOH (1 M) were added. The mixture was extracted with EtOAc (3×50 mL), the combined extract was dried (Na_2SO_4) and evaporated, and the residue was purified by flash chromatography (silica, hexanes/EtOAc 1:1) to yield **36** as a pale yellow oil (0.26 g, 50%). TLC R_f=0.41 (silica, hexanes/EtOAc 1:1); IR (film) ν_{max} 2947, 2230, 1595, 1560, 1478, 1149, 1104, 1047, 919, 830 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.09 (s, 3H, $CH_3C{\equiv}C$), 3.40 (s, 3H, CH_3O), 4.60 (s, 2H, OCH_2O), 4.71 (s, 2H, $ArCH_2O$), 7.36 (d, *J*=7.7 Hz, 1H, ArH), 7.63 (dd, *J*=1.8, 7.7 Hz, 1H, ArH), 8.52 (d, *J*=7.8 Hz, 1H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.77, 55.9, 66.9, 79.9, 96.4, 126.7, 132.6, 136.0, 143.6, 149.7; MALDI-FTMS *m/z* 192.1014 (MH^+), calcd for $C_{11}H_{14}NO_2$ 192.1019.

4.4.5. Sonogashira coupling product from 37. The reaction was very slow, probably due to Pd coordination to the thioether moiety; therefore, 10 mol% $Pd(PPh_3)_2Cl_2$ and 20 mol% CuI were used. The product was obtained as a brown oil (42%). TLC R_f=0.37 (silica, hexanes/EtOAc

15:1); IR (film) ν_{max} 3110, 2914, 2240, 1493, 1417, 1278, 1037, 966, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.06 (s, 3H, C≡CCH$_3$), 2.71 (s, 3H, SCH$_3$), 7.19 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.3, 16.4, 73.7, 86.4, 120.3, 137.7, 165.9; MALDI-FTMS *m/z* 170.0092 (MH^+), calcd for $C_7H_8NS_2$ 170.0093.

4.4.6. Sonogashira coupling product from 38. Brown oil (97%); TLC R_f=0.21 (silica, hexanes/EtOAc 5:1); IR (film) ν_{max} 2908, 2226, 1567, 1531, 1461, 1431, 1361, 1108, 1008, 832 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.05 (s, 3H, C≡CCH$_3$), 2.48 (s, 3H, SCH$_3$), 7.24 (d, *J*=8.2 Hz, 1H, ArH), 7.44 (d, *J*=8.2 Hz, 1H, ArH), 8.38 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.3, 15.5, 79.2, 86.7, 126.2, 133.8, 134.4, 140.1, 147.4; MALDI-FTMS *m/z* 164.0527 (MH^+), calcd for $C_9H_{10}NS$ 164.0528.

4.4.7. Sonogashira coupling product from 39. Yellow oil (70%); TLC R_f=0.36 (silica, hexanes/EtOAc 20:1); IR (film) ν_{max} 2924, 2231, 1566, 1554, 1431, 1156, 1140, 790 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.11 (s, 3H, C≡CCH$_3$), 2.58 (s, 3H, SCH$_3$), 7.06 (d, *J*=7.8 Hz, 1H, ArH), 7.08 (d, *J*=7.8 Hz, 1H, ArH), 7.41 (t, *J*=7.8 Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 4.6, 13.4, 79.6, 86.7, 120.1, 122.3, 135.6, 143.3, 160.0; MALDI-FTMS *m/z* 164.0526 (MH^+), calcd for $C_9H_{10}NS$ 164.0528.

4.4.8. Hydrostannylation–iodination (general procedure). This is an adaption of the previously reported procedure.[14] To a solution of hexabutylditin (10.1 mL, 20 mmol) in dry THF (40 mL) at −78°C was added *n*-BuLi (12.9 mL, 20 mmol, 1.55 M in hexanes), and the resulting clear solution was stirred at −40°C for 30 min. It was then transferred via cannula to a suspension of CuCN (0.90 g, 10 mmol) in THF (2 mL) at −78°C. A clear yellow solution formed, and it was stirred for 5 min at −40°C before being re-cooled to −78°C. Then dry methanol (23 mL, 0.57 mol) was added to yield a red solution, which was stirred at −40°C for 15 min, after which a solution of the arylpropyne (5.0 mmol) in THF (5 mL) was added. The orange–red solution was stirred at −10°C overnight (some Cu and/or Cu^{2+} salts precipitate), then cooled to −20°C, followed by the addition of methanol (10 mL). After 15 min at −20°C, water (10 mL) was added, and stirring was continued for another 15 min, while warming to 25°C. The mixture was extracted with ether, and the organic phase was washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography (silica, hexanes/EtOAc mixtures) yielded the intermediate vinylstannane, which was dissolved in CH_2Cl_2 (5 mL). A solution of iodine (1.05 equiv.) in CH_2Cl_2 (40 mL per g I_2) was then added dropwise to this solution at 0°C. After the last few drops, the color of I_2 persisted, and the reaction was allowed to continue for another 5 min at 0°C. Then the solvent was evaporated and the residue was dissolved in ether. KF (1 M solution in water, 3 equiv.) and $Na_2S_2O_3$ (sat., 10 mL per mmol substrate) were added, and the mixture was stirred for 15 min at 25°C during which time a white precipitate formed. The mixture was filtered through celite, and the organic phase was dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (silica, hexanes/EtOAc mixtures) to yield the desired vinyl iodide.

4.4.9. Vinyl iodide 20c. White cloudy film (80%). TLC R_f=0.25 (silica, hexanes/EtOAc 20:1); IR (film) ν_{max} 3060, 2919, 1619, 1596, 1484, 1443, 1373, 1214, 1061, 985, 873, 761, 703, 632 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.99 (d, *J*=1.5 Hz, 3H, CH$_3$C(I)=C), 4.18 (s, 2H, CH$_2$O), 7.10 (d, *J*=8.2 Hz, 1H, pyridine ArH), 7.23–7.35 (m, 10H, trityl ArH, CH=C), 7.47–7.51 (m, 6H, trityl ArH), 7.66 (dd, *J*=1.8, 8.2 Hz, 1H, pyridine ArH), 8.56 (d, *J*=1.8 Hz, 1H, pyridine ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.5, 63.5, 87.3, 105.0, 123.5, 127.2, 127.9, 128.6, 132.6, 135.2, 139.3, 143.7, 148.0, 154.8; MALDI-FTMS *m/z* 518.0990 (MH^+), calcd for $C_{28}H_{25}INO$ 518.0975.

4.4.10. Vinyl iodide 20d. Yellow oil (67%). TLC R_f=0.51 (silica, hexanes/EtOAc 4:1); IR (film) ν_{max} 2924, 1716, 1619, 1596, 1481, 1372, 1211, 1149, 1102, 1045, 918, 873, 609, 517 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.97 (d, *J*=1.7 Hz, 3H, CH$_3$C(I)=C), 3.40 (s, 3H, OCH$_3$), 4.57 (s, 2H, CH$_2$O), 4.70 (s, 2H, CH$_2$O), 7.10 (d, *J*=7.9 Hz, 1H, ArH), 7.24 (d, *J*=1.7 Hz, 1H, HC=C), 7.65 (d, *J*=7.9 Hz, 1H, ArH), 8.55 (s, 1H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.5, 55.5, 66.5, 95.9, 105.4, 123.5, 131.3, 135.9, 139.2, 148.8, 155.4; MALDI-FTMS *m/z* 320.0142 (MH^+), calcd for $C_{11}H_{15}INO_2$ 320.0142.

4.4.11. Vinyl iodide 20e. The intermediate vinyl stannane is readily protodestannylated; therefore, flash chromatography of this intermediate must be performed using hexanes/EtOAc/Et_3N 50:1:1 as eluent, and the so obtained vinylstannane contained other butyl tin compunds. Following the general procedure, the mixture was treated with enough I_2 that the brown color persisted at the end of the addition (ca. 2 equiv. of I_2). After flash chromatography (hexanes/EtOAc 50:1), vinyl iodide **20e** was obtained as a yellow oil (74%). TLC R_f=0.41 (silica, hexanes/EtOAc 50:1); IR (film) ν_{max} 3102, 2923, 1620, 1423, 1300, 1065, 1035, 964, 863, 723, 562 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.70 (s, 3H, CH$_3$S), 2.99 (d, *J*=1.5 Hz, 3H, CH$_3$C(I)=C), 6.93 (s, 1H, ArH), 7.08 (q, *J*=1.5 Hz, 1H, HC=C); ^{13}C NMR (150 MHz, $CDCl_3$) δ 16.5, 30.7, 101.6, 116.6, 132.6, 152.9, 165.9; MALDI-FTMS *m/z* 297.9215 (MH^+), calcd for $C_7H_9INS_2$ 297.9216.

4.4.12. Vinyl iodide 20f. Yellow solid (80%). TLC R_f= 0.19 (silica, hexanes/EtOAc 40:1); IR (film) ν_{max} 2919, 1619, 1567, 1467, 1431, 1373, 1108, 1067, 1014, 961, 867, 820, 521 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.50 (s, 3H, SCH$_3$), 2.97 (d, *J*=1.5 Hz, 3H, CH$_3$C(I)=C), 7.00 (d, *J*=8.2 Hz, 1H, ArH), 7.18 (q, *J*=1.5 Hz, 1H, HC=C), 7.49 (dd, *J*=2.6, 8.2 Hz, 1H, ArH), 8.45 (d, *J*=2.6 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.6, 30.5, 104.8, 123.6, 133.4, 134.2, 138.8, 147.0, 152.6; MALDI-FTMS *m/z* 291.9655 (MH^+), calcd for $C_9H_{11}INS$ 291.9651.

4.4.13. Vinyl iodide 20g. Yellow oil (83%). TLC R_f=0.28 (silica, hexanes/EtOAc 40:1); IR (film) ν_{max} 2919, 1620, 1549, 1425, 1155, 1138, 1061, 991, 961, 861, 785, 732, 550 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.54 (s, 3H, SCH$_3$), 3.08 (d, *J*=1.5 Hz, 3H, CH$_3$C(I)=C), 6.75 (d, *J*= 7.6 Hz, 1H, ArH), 7.04 (d, *J*=8.2 Hz, 1H, ArH), (q, *J*= 1.5 Hz, 1H, HC=C), 7.43 (dd, *J*=7.6, 8.2 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 31.2, 105.6, 119.6,

119.7, 136.0, 139.1, 155.6, 159.4; MALDI-FTMS *m/z* 291.9653 (MH^+), calcd for $C_9H_{11}INS$ 291.9651.

4.5. Synthesis of epothilone analogues 8–14

4.5.1. Nozaki–Hiyama–Kishi coupling of aldehydes (32, 40) with vinyl stannanes (20a–g) (general procedure). To a briefly vacuum-degassed solution of aldehyde **32** (107 mg, 0.15 mmol), the requisite vinyl iodide **20** (0.45 mmol), and 4-*tert*-butylpyridine (665 μL, 4.5 mmol) in DMSO (3 mL) were added anhydrous $CrCl_2$ (184 mg, 1.5 mmol) and anhydrous $NiCl_2$ (4 mg, 0.03 mmol). The mixture was stirred at 25°C for 3 h, after which another portion of vinyl iodide (0.45 mmol) was added, and stirring was continued for a further 3 h. This was repeated one more time, after which stirring was continued overnight. The reaction was then quenched with water (5 mL), pyridine (1 mL) was added to prevent Cr-product complexes from being extracted into the water phase, and the mixture was extracted with EtOAc (3×25 mL). The combined extract was washed with brine (2×100 mL), dried (Na_2SO_4) and evaporated. Flash chromatography (silica, hexanes/EtOAc mixtures) yielded the coupling product, in most cases inseparable from excess 4-*tert*-butylpyridine.

4.5.2. Product from 20a and 32. Yellow oil (85% as a ca. 1:1 mixture of C15 epimers). TLC R_f=0.26 (silica, hexanes/EtOAc 4:1); $[\alpha]_D^{22}=-25$ (*c* 0.36, CH_2Cl_2); IR (film) ν_{max} 2943, 2860, 1731, 1696, 1467, 1384, 1290, 1249, 1173, 1079, 985, 832, 773 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, total integral normalized to 83H) δ −0.11 to −0.01 (m, 1H, *c*-propyl CH), −0.01 to 0.06, (m, 18H, CH_3Si), 0.09 (s, 3H, CH_3Si), 0.37–0.41 (dd, *J*=4.1, 8.5 Hz, 0.5H, *c*-propyl CH_2), 0.42–0.46 (dd, *J*=4.1, 8.5 Hz, 0.5H, *c*-propyl CH_2), 0.51–0.59 (m, 1H, *c*-propyl CH_2), 0.83–0.93 (m, 21H, $(CH_3)_3CSi$, CH_2CHCH_3), 0.96 (t, *J*=8.5 Hz, 2H, CH_2CH_2TMS), 0.96–1.07 (m, 9H, CH_3, C(O)CHCH_3), 1.16–1.44 (m, 6H, C(8)H, C(9)H_aH_b, and C(10)H_2C(11)H_2), 1.21 (s, 3H, C(12)CH_3), 1.45–1.53 (m, 1H, C(14)H_aH_b), 1.56–1.67 (m, 1H, C(9)H_aH_b), 1.72–1.80 (m, 1H, C(14)H_aH_b), 2.02 (s, 3H, CH_3), 2.22 (dd, *J*=6.6, 16.3 Hz, 1H, C(2)H_aH_b), 2.41 (dd, *J*=3.1, 16.3 Hz, 1H, C(2)H_aH_b), 2.69 (s, 3H, CH_3), 3.08–3.16 (m, 1H, C(6)H), 3.71–3.77 (m, 1H, C(7)H), 4.08–4.16 (m, 2H, CH_2CH_2TMS), 4.18–4.24 (m, 1H, C(15)H), 4.36 (dd, *J*=3.1, 6.6 Hz, C(3)H), 6.55 (s, 0.5H, vinyl H), 6.56 (s, 0.5H, vinyl H), 6.92 (s, 1H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$, more than 44 peaks counted due to the presence of two C15 epimers.) δ −4.7, −4.5, −3.8, −3.7, −1.6, 13.6, 14.2, 15.4, 17.2, 17.4, 17.5, 17.6, 18.2, 18.5, 18.9, 19.0, 19.1, 19.2, 19.4, 19.6, 20.3, 20.5, 22.6, 23.4, 23.5, 24.8, 26.0, 26.2, 26.8, 27.8, 31.0, 31.1, 31.5, 35.1, 35.4, 38.9, 40.4, 42.0, 42.1, 45.1, 62.7, 73.9, 77.5, 77.6, 78.3, 78.5, 115.3, 115.4, 118.9, 119.2, 142.1, 142.2, 152.8, 152.9, 164.6, 172.2, 217.8; MALDI-FTMS *m/z* 860.5128 (MNa^+), calcd for $C_{44}H_{83}NO_6SSi_3Na$ 860.5141.

4.5.3. Product from 20b and 32. This coupling product was inseparable from 4-*tert*-butyl pyridine, and was subjected to the TBAF deprotection conditions (vide infra) as a crude mixture.

4.5.4. Product from 20d and 32. This coupling product was inseparable from 4-*tert*-butyl pyridine, and was subjected to the TBAF deprotection conditions (vide infra) as a crude mixture.

4.5.5. Product from 20e and 32. Yellow glass (78%, ca. 1:1 mixture of C15 epimers). TLC R_f=0.40 (silica, hexanes/EtOAc 5:1); $[\alpha]_D^{22}=-28$ (*c* 2.0, $CHCl_3$); IR (film) ν_{max} 3416 (br), 2929, 2856, 1732, 1694, 1472, 1251, 1037, 988, 836, 776 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, total integral normalized to 85H) δ −0.09 to −0.06 (m, 0.5H, *c*-propyl CH_2), −0.03 to 0.00 (m, 0.5H, *c*-propyl CH_2), 0.01–0.06 (m, 18H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.40 (dd, *J*=4.0, 8.3 Hz, 0.5H, *c*-propyl CH_2), 0.45 (dd, *J*=3.9, 8.3 Hz, 0.5H, *c*-propyl CH_2), 0.53–0.59 (m, 1H, *c*-propyl CH), 0.86–0.91 (m, 21H, $SiC(CH_3)_3$, CH_2CHCH_3), 0.95–0.99 (m, 2H, CH_2TMS), 1.01–1.10 (m, 12H, 2×CH_3, C(O)CHCH_3, CH_2), 1.15–1.21 (m, 1H, CH_2), 1.22 (s, 3H, CH_3), 1.28–1.35 (m, 2H, CH_2CHCH_3, CH_2), 1.39–1.44 (m, 1H, CH_2), 1.44–1.54 (m, 1H, CH_2CHOH), 1.72–1.81 (m, 1H, CH_2-CHOH), 1.87 (br s, 0.5H, OH), 1.97 (br s, 0.5H, OH), 2.08 (s, 3H, HC≡CCH_3), 2.23 (dd, *J*=6.6, 16.2 Hz, 1H, CH_2CO_2), 2.42 (dd, *J*=3.1, 16.2 Hz, 1H, CH_2CO_2), 2.70 (s, 3H, SCH_3), 3.11–3.16 (m, 1H, C(O)CHCH$_3$), 3.73–3.77 (m, 1H, C(O)CH(CH$_3$)CHOTBS), 4.11–4.20 (m, 2H, OCH_2CH_2TMS), 4.20–4.23 (m, 1H, CHOH), 4.37 (dd, *J*=3.1, 6.6 Hz, 1H, CH(OTBS)CH_2CO_2), 6.49 (s, 0.5H, C═CH), 6.50 (s, 0.5H, C═CH), 6.94 (s, 0.5H, ArH), 6.95 (s, 0.5H, ArH); ^{13}C NMR (150 MHz, $CDCl_3$, more than one set of peaks counted due to the presence of C15 epimers) δ −4.7, −4.5, −3.8, −3.7, −1.6, 14.2, 14.3, 15.4, 16.5, 17.2, 17.4, 17.5, 17.7, 18.1, 18.5, 18.8, 18.9, 19.1, 19.4, 19.6, 20.3, 20.4, 23.5, 24.8, 26.0, 26.2, 31.0, 35.1, 35.4, 38.9, 40.4, 42.0, 45.1, 53.3, 62.6, 73.8, 77.5, 77.6, 78.3, 78.5, 115.2, 118.1, 118.5, 142.3, 142.4, 153.4, 153.5, 164.9, 172.1, 217.8; MALDI-FTMS *m/z* 906.5021 (MNa^+), calcd for $C_{45}H_{85}NO_6S_2Si_3Na$ 906.5018.

4.5.6. Product from 20f and 32. This coupling product was inseparable from 4-*tert*-butyl pyridine, and was subjected to the TBAF deprotection conditions (vide infra) as a crude mixture.

4.5.7. Product from 20g and 32. This coupling product was inseparable from 4-*tert*-butyl pyridine, and was subjected to the TBAF deprotection conditions (vide infra) as a crude mixture.

4.5.8. Product from 20c and 40. Yellow glass (87%, ca. 1:1 mixture of C15 epimers). TLC R_f=0.15 (silica, hexanes/EtOAc 4:1); $[\alpha]_D^{22}=-23$ (*c* 0.19, CH_2Cl_2); IR (film) ν_{max} 2931, 2861, 1731, 1690, 1467, 1384, 1355, 1249, 1167, 1061, 985, 832, 773, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.02–0.08 (m, 18H, CH_3Si), 0.11 (s, 3H, CH_3Si), 0.22–0.34 (m, 2H, *c*-propyl CH_2), 0.44–0.60 (m, 2H, C(12)H, C(13)H), 0.83–0.93 (m, 21H, $(CH_3)_3CSi$, C(8)CH_3), 0.98 (t, *J*= 8.6 Hz, 2H, CH_2CH_2TMS), 1.04 (d, *J*=6.6 Hz, 3H, C(6)CH_3), 1.07 (s, 3H, C(4)$C_aH_3C_bH_3$), 1.10–1.42 (m, 7H, C(8)H, C(9)H_2, C(10)H_2, C(11)H_2), 1.23 (s, 3H, C(4)$C_aH_3C_bH_3$), 1.44–1.54 (m, 1H, C(14)H_aH_b), 1.62–1.73 (m, 1H, C(14)H_aH_b), 2.0 (s, 3H, vinyl CH_3), 2.24 (dd, *J*=6.6, 16.2 Hz, 1H, C(2)H_aH_b), 2.43 (dd, *J*=3.3, 16.2 Hz, 1H, C(2)H_aH_b), 3.10–3.18 (m, 1H, C(6)H), 3.75–3.79 (m, 1H, C(7)H), 4.09–4.17 (m, 2H, CH_2CH_2TMS),

4.19 (s, 2H, $ArCH_2O$), 4.26–4.31 (m, 1H, C(15)H), 4.39 (dd, J=3.3, 6.6 Hz, C(3)H), 6.60 (s, br 1H, vinyl H), 7.20–7.28 (m, 4H, ArH), 7.32 (t, J=7.4 Hz, 6H, ArH), 7.50 (d, J=7.4 Hz, 6H, ArH), 7.65 (d, J=8.1 Hz, 1H, ArH), 8.58 (s, 1H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$, more than one set of peaks counted due to the presence of two C15 epimers.) δ −4.7, −4.5, −3.8, −3.7, −1.6, 11.3, 11.9, 13.9, 14.0, 15.3, 15.5, 17.2, 17.7, 18.2, 18.3, 18.5, 18.9, 19.5, 23.5, 26.0, 26.2, 27.7, 29.7, 30.5, 30.7, 34.8, 38.9, 39.9, 40.4, 45.1, 53.4, 62.7, 63.5, 73.8, 77.6, 78.1, 78.3, 87.2, 123.7, 124.5, 124.6, 127.1, 127.9, 128.6, 131.7, 134.9, 143.8, 144.7, 144.9, 148.0, 155.7, 172.2, 217.9; MALDI-FTMS m/z 1112.6634 (MNa^+), calcd for $C_{65}H_{99}NO_7Si_3Na$ 1112.6621.

4.5.9. Product from 20e and 40. Colorless glass (59%, ca. 1:1 mixture of C15 epimers). TLC R_f=0.27 (silica, hexanes/EtOAc 5:1); $[\alpha]_D^{22}$=−28 (c 2.0, $CHCl_3$); IR (film) ν_{max} 3396 (br), 2928, 2855, 1734, 1693, 1472, 1251, 1037, 988, 836, 775 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, total integral normalized to 83H) δ −0.06 to −0.02 (m, 18H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.20–0.31 (m, 2H, c-propyl CH_2), 0.42–0.54 (m, 2H, c-propyl CH), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.88–0.91 (m, 12H, $SiC(CH_3)_3$, CH_2CHCH_3), 0.96–0.99 (t, J=8.6 Hz, 2H, CH_2TMS), 1.04 (d, J=6.8 Hz, 3H, $C(O)CHCH_3$), 1.06 (s, 3H, CH_3), 1.09–1.22 (m, 3H, CH_2), 1.23 (s, 3H, CH_3), 1.28–1.41 (m, 3H, CH_2CHCH_3, CH_2), 1.43–1.51 (m, 2H, CH_2, CH_2CHOH), 1.57–1.62 (m, 1H, CH_2CHOH), 1.69 (br s, 0.5H, OH), 1.85 (br s, 0.5H, OH), 2.07 (s, 3H, HC≡CCH_3), 2.24 (dd, J=6.8, 16.4 Hz, 1H, CH_2CO_2), 2.42 (dd, J=3.1, 16.4 Hz, 1H, CH_2CO_2), 2.71 (s, 3H, SCH_3), 3.10–3.17 (m, 1H, $C(O)CHCH_3$), 3.75–3.78 (m, 1H, $C(O)CH(CH_3)CHOTBS$), 4.10–4.19 (m, 2H, OCH_2CH_2TMS), 4.20–4.23 (t, J=6.4 Hz, 1H, CHOH), 4.37 (m, 1H, $CH(OTBS)CH_2CO_2$), 6.50 (s, 0.5H, C=CH), 6.51 (s, 0.5H, C=CH), 6.95 (s, 0.5H, ArH), 6.96 (s, 0.5H, ArH); ^{13}C NMR (150 MHz, $CDCl_3$, more than one set of peaks counted due to the presence of C15 epimers) δ −4.7, −4.4, −3.7, −3.6, −1.6, 11.3, 11.8, 14.2, 14.3, 15.2, 15.3, 15.5, 16.6, 17.2, 17.6, 17.7, 18.2, 18.3, 18.5, 18.9, 19.5, 23.5, 26.0, 26.2, 27.7, 30.7, 34.7, 34.8, 38.8, 39.8, 39.9, 40.4, 45.1, 53.4, 62.7, 73.8, 77.6, 78.1, 78.3, 115.3, 118.2, 118.3, 142.2, 142.4, 153.5, 165.0, 172.2, 217.9; MALDI-FTMS m/z 892.4861 (MNa^+), calcd for $C_{44}H_{83}NO_6S_2Si_3Na$ 892.4862.

4.5.10. TBAF deprotection (general procedure). The product mixture from the Nozaki–Hiyama–Kishi coupling was dissolved in THF (1.5 mL), and TBAF (1 M in THF, 0.30 mL, 0.30 mmol) was added at 0°C. After 1 h at 0°C, another portion of TBAF (0.30 mL, 0.30 mmol) was added, and the mixture was stirred at 25°C for 1 h. The reaction was quenched with NH_4Cl (sat., 5 mL), and the mixture was extracted with EtOAc (4×20 mL). The combined extract was dried (Na_2SO_4) and evaporated, and the residue was purified by flash chromatography (silica, hexanes/EtOAc mixtures) to yield the desired hydroxy acid as a ca. 1:1 mixture of C15 epimers (inseparable at this stage).

4.5.11. Hydroxy acid 41a. The reaction mixture from the deprotection was quickly filtered through a plug of silica gel, and this crude product (73% yield from aldehyde **32**) was subjected to the Yamaguchi macrolactonization (vide infra) without further purification.

4.5.12. Hydroxy acid 41b. Yellow solid (57%, ca. 1:1 mixture of C15 epimers). TLC R_f=0.19 (silica, hexanes/EtOAc 2:1); $[\alpha]_D^{22}$=−6 (c 1.0, $CHCl_3$); IR (film) ν_{max} 3369 (br), 2930, 2857, 1783, 1694, 1471, 1251, 1085, 1084, 988, 836, 775 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, total integral normalized to 75H) δ −0.07 (0.5H, c-propyl CH_2), −0.03 (0.5H, c-propyl CH_2), 0.02–0.11 (m, 12H, $SiCH_3$), 0.43 (dd, J=4.0, 8.4 Hz, 0.5H, c-propyl CH_2), 0.48 (dd, J=4.1, 8.5 Hz, 0.5H, c-propyl CH_2), 0.54–0.63 (m, 1H, c-propyl CH), 0.83–0.91 (m, 21H, $SiC(CH_3)_3$, CH_2CHCH_3), 1.00–1.06 (m, 6H, CH_3, $C(O)CHCH_3$), 1.10 (s, 3H, CH_3), 1.17–1.22 (m, 5H, CH_2, CH_3), 1.25–1.46 (m, 5H, CH_2CHCH_3, CH_2), 1.52–1.60 (m, 1H, CH_2CHOH), 1.73–1.81 (m, 1H, CH_2CHOH), 1.97 (s, 1.5H, HC≡CCH_3), 1.98 (s, 1.5H, HC≡CCH_3), 2.23–2.30 (m, 1H, CH_2CO_2H), 2.32 (s, 3H, $ArCH_3$), 2.41–2.52 (m, 1H, CH_2CO_2H), 3.10–3.17 (m, 1H, $C(O)CHCH_3$), 3.76–3.81 (m, 1H, $C(O)CH(CH_3)$-$CHOTBS$), 4.23–4.28 (m, 1H, CHOH), 4.37–4.41 (m, 1H, $CH(OTBS)CH_2CO_2H$), 6.61 (s, 1H, C=CH), 7.20 (d, J=8.0 Hz, 1H, ArH), 7.48 (d, J=8.0 Hz, 1H, ArH), 8.44 (s, 1H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$, more than one set of peaks counted due to the presence of C15 epimers) δ −4.8, −4.7, −4.1, −3.9, −3.8, −3.7, 13.6, 13.7, 14.2, 15.8, 17.4, 17.5, 17.6, 17.7, 18.2, 18.4, 18.9, 19.0, 19.3, 20.0, 20.2, 20.3, 20.4, 20.5, 21.0, 23.3, 23.4, 24.8, 25.3, 26.0, 26.2, 31.1, 34.9, 35.0, 38.9, 39.0, 40.8, 40.9, 41.8, 41.9, 15.0, 45.1, 51.0, 53.5, 60.4, 74.1, 74.2, 74.3, 77.3, 77.4, 78.3, 78.4, 123.6, 123.7, 124.2, 124.7, 130.8, 130.9, 137.1, 144.3, 144.4, 148.7, 148.8, 153.3, 153.4, 175.5, 175.6, 217.8, 218.0; MALDI-FTMS m/z 768.5028 (MNa^+), calcd for $C_{42}H_{75}NO_6Si_2Na$ 768.5025.

4.5.13. Hydroxy acid 41d. Yellow glass (49% for two steps from aldehyde **32** as a ca. 1:1 mixture of C15 epimers). TLC R_f=0.20 (silica, hexanes/EtOAc 1:1); $[\alpha]_D^{22}$=+1 (c 0.19, CH_2Cl_2); IR (film) ν_{max} 2933, 2858, 1694, 1600, 1563, 1463, 1382, 1357, 1251, 1145, 1096, 1046, 989, 834, 772, 666 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, normalized to 79H) δ −0.08 to −0.05 (m, 0.5H, c-propyl CH_2), −0.05 to −0.02 (m, 0.5H, c-propyl CH_2), 0.02–0.14 (m, 12H, CH_3Si), 0.45–0.49 (m, 0.5H, c-propyl CH_2), 0.49–0.53 (m, 0.5H, c-propyl CH_2), 0.55–0.59 (m, 0.5H, C(13)H), 0.59–0.66 (m, 0.5H, C(13)H), 0.80–0.95 (m, 21H, $(CH_3)_3CSi$, $C(8)CH_3$), 1.00–1.09 (m, 8H, CH_2, $C(6)CH_3$, $C(4)C_aH_3C_bH_3$), 1.14–1.34 (m, 9H, $C(4)C_aH_3C_bH_3$, C(12)H, CH_2), 1.35–1.46 (m, 2H, CH_2), 1.52–1.66 (m, 1H, $C(14)H_aH_b$), 1.73–1.81 (m, 1H, $C(14)H_aH_b$), 1.97 (s, 1.5H, vinyl CH_3), 1.99 (s, 1.5H, vinyl CH_3), 2.29–2.32 (m, 0.5H, $C(2)H_aH_b$), 2.33–2.36 (m, 0.5H, $C(2)H_aH_b$), 2.48–2.58 (m, 1H, $C(2)H_aH_b$), 3.07–3.14 (m, 1H, C(6)H), 3.41 (s, 3H, OCH_3), 3.80–3.88 (m, 1H, C(7)H), 4.26–4.32 (m, 1H, C(15)H), 4.37–4.42 (m, 1H, C(3)H), 4.61 (s, 2H, $PyCH_2O$), 4.72 (s, 2H, OCH_2O), 6.69 (s, 1H, vinyl H), 7.31–7.35 (m, 2H, ArH), 7.72 (d, J=7.7 Hz, 1H, ArH), 8.60 (s, 1.5H, ArH), 8.62 (s, 1.5H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$, more than one set of peaks counted due to the presence of two C15 epimers. C(7) obscure under the chloroform peaks.) δ −4.7, −4.8, −4.1, −4.0, −3.9, −3.8, 13.7, 13.8, 13.9, 16.3, 17.0, 17.1, 17.7, 18.2, 18.4, 18.8, 18.9, 19.0, 19.1, 19.7, 20.0, 20.2, 20.5, 23.9, 24.7, 26.0, 26.2, 29.7, 31.3, 33.0, 34.7, 34.8, 38.9, 39.1, 40.6, 40.7, 41.4, 41.7, 44.9, 45.0, 47.2, 53.6, 53.7, 66.0, 66.4, 73.6, 73.9, 78.2, 95.9, 123.8, 123.9, 124.1, 124.6,

131.2, 136.4, 145.2, 145.3, 147.7, 147.9, 155.6, 217.9, 218.1; MALDI-FTMS *m/z* 806.5437 (MH^+), calcd for $C_{44}H_{80}NO_8Si_2$ 806.5417.

4.5.14. Hydroxy acid 41e. Yellow solid (79%, ca. 1:1 mixture of C15 epimers). TLC R_f=0.37 (silica, hexanes/ EtOAc 2:1); $[\alpha]_D^{22}=-23$ (*c* 2.3, $CHCl_3$); IR (film) ν_{max} 3356 (br), 2929, 2856, 1712, 1472, 1253, 1085, 1038, 988, 836, 776 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, total integral normalized to 73H) δ −0.09 to −0.06 (m, 0.5H, *c*-propyl CH_2), −0.03–0.00 (m, 0.5H, *c*-propyl CH_2), 0.05 (s, 9H, $SiCH_3$), 0.09 (s, 3H, $SiCH_3$), 0.40 (dd, *J*=4.0, 8.3 Hz, 0.5H, *c*-propyl CH_2), 0.45 (dd, *J*=4.2, 8.6 Hz, 0.5H, *c*-propyl CH_2), 0.53–0.59 (m, 1H, *c*-propyl CH), 0.85–0.92 (m, 21H, $SiC(CH_3)_3$, CH_2CHCH_3), 1.00–1.10 (m, 12H, 2×CH_3, $C(O)CHCH_3$, CH_2), 1.15–1.20 (m, 1H, CH_2), 1.21 (s, 3H, CH_3), 1.27–1.34 (m, 2H, CH_2CHCH_3, CH_2), 1.37–1.44 (m, 1H, CH_2), 1.44–1.54 (m, 1H, CH_2CHOH), 1.72–1.79 (m, 1H, CH_2CHOH), 2.07 (s, 3H, HC═CCH_3), 2.30 (dd, *J*= 6.8, 16.4 Hz, 1H, CH_2CO_2H), 2.46–2.51 (m, 1H, CH_2CO_2H), 2.69 (s, 3H, SCH_3), 3.10–3.15 (m, 1H, C(O)C$H$$CH_3$), 3.75–3.79 (m, 1H, C(O)CH(CH_3)-CHOTBS), 4.20–4.24 (m, 1H, CHOH), 4.36–4.39 (m, 1H, CH(OTBS)CH_2CO_2H), 6.50 (s, 0.5H, C═CH), 6.51 (s, 0.5H, C═CH), 6.94 (s, 0.5H, ArH), 6.95 (s, 0.5H, ArH); ^{13}C NMR (150 MHz, $CDCl_3$, more than one set of peaks counted due to the presence of C15 epimers) δ −4.6, −4.3, −3.8, −3.7, 14.2, 14.3, 15.6, 15.7, 16.6, 17.5, 17.6, 17.7, 18.1, 18.5, 18.8, 18.9, 19.1, 19.4, 20.2, 20.4, 23.6, 24.8, 26.0, 26.2, 30.9, 31.0, 35.1, 35.3, 38.8, 38.9, 40.0, 41.9, 42.0, 45.1, 53.4, 73.4, 77.5, 78.3, 78.5, 115.2, 118.2, 118.6, 142.3, 153.4, 153.5, 165.1, 177.2, 218.1; MALDI-FTMS *m/z* 806.4282 (MNa^+), calcd for $C_{40}H_{73}NO_6S_2Si_2Na$ 806.4315.

4.5.15. Hydroxy acid 41f. Colorless glass (63% from **32**, ca. 1:1 mixture of C15 epimers). TLC R_f=0.21 (silica, hexanes/ EtOAc 2:1); $[\alpha]_D^{22}=-3$ (*c* 0.44, CH_2Cl_2); IR (film) ν_{max} 2933, 2858, 1693, 1467, 1253, 1086, 984, 833, 774 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, total integral normalized to 75H) δ −0.08 (m, 0.5H, *c*-propyl CH_2), −0.03 (m, 0.5H, *c*-propyl CH_2), 0.02–0.09 (m, 12H, $SiCH_3$), 0.42 (dd, *J*=4.0, 8.4 Hz, 0.5H, *c*-propyl CH_2), 0.47 (dd, *J*=4.0, 8.4 Hz, 0.5H, *c*-propyl CH_2), 0.53–0.60 (m, 1H, *c*-propyl CH), 0.81–0.90 (m, 21H, $SiC(CH_3)_3$, CH_2-$CHCH_3$), 1.00–1.11 (m, 12H, 2 × CH_3, $C(O)CHCH_3$, CH_2), 1.19 (s, 1.5H, CH_3), 1.20 (s, 1.5H, CH_3), 1.27–1.45 (m, 5H, CH_2CHCH_3, CH_2), 1.47–1.61 (m, 2H, CH_2, CH_2CHOH), 1.74–1.81 (m, 1H, CH_2CHOH), 2.00 (s, 3H, HC═CCH_3), 2.24–2.32 (m, 1H, CH_2CO_2H), 2.44–2.49 (m, 1H, CH_2CO_2H), 2.50 (s, 3H, SCH_3), 3.09–3.15 (m, 1H, C(O)C$H$$CH_3$), 3.75–3.81 (m, 1H, C(O)CH(CH_3)-CHOTBS), 4.21–4.28 (m, 1H, CHOH), 4.35–4.41 (m, 1H, CH(OTBS)CH_2CO_2H), 6.57 (s, 0.5H, C═CH), 6.58 (s, 0.5H, C═CH), 7.19 (d, *J*=8.5 Hz, 1H, ArH), 7.53 (d, *J*=8.5 Hz, 1H, ArH), 8.49 (s, 1H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$, more than one set of peaks counted due to the presence of C15 epimers) δ −4.7, −4.2, −3.8, −3.7, 13.7, 13.9, 14.0, 15.8, 15.9, 17.5, 17.6, 17.7, 18.2, 18.5, 18.9, 19.0, 19.3, 19.6, 19.8, 20.2, 20.4, 23.5, 23.6, 24.8, 25.1, 26.0, 26.2, 29.7, 30.4, 31.1, 31.5, 35.0, 35.2, 38.9, 39.0, 40.4, 41.8, 41.9, 45.1, 51.0, 53.5, 73.8, 73.9, 78.3, 78.4, 123.7, 124.0, 124.2, 132.7, 132.8, 134.8, 145.0, 146.6, 153.0, 153.1, 175.8, 218.0, 218.1; MALDI-FTMS *m/z* 800.4754 (MNa^+), calcd for $C_{42}H_{75}NO_6SSi_2Na$ 800.4746.

4.5.16. Hydroxy acid 41g. Yellow glass (46% for two steps from aldehyde **32** as a ca. 1:1 mixture of C15 epimers). TLC R_f=0.46 (silica, hexanes/EtOAc 2:1); $[\alpha]_D^{22}=-11$ (*c* 0.19, CH_2Cl_2); IR (film) ν_{max} 2933, 2858, 1706, 1557, 1463, 1426, 1364, 1251, 1083, 989, 834, 772, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, total integral normalized to 75H) δ −0.06 (m, 0.5H, *c*-propyl CH_2), 0.00 (m, 0.5H, *c*-propyl CH_2), 0.03–0.10 (m, 12H, $SiCH_3$), 0.42 (dd, *J*=4.0, 8.4 Hz, 0.5H, *c*-propyl CH_2), 0.46 (dd, *J*=4.3, 8.3 Hz, 0.5H, *c*-propyl CH_2), 0.55–0.63 (m, 1H, *c*-propyl CH), 0.85–0.91 (m, 21H, $SiC(CH_3)_3$, CH_2CHCH_3), 1.01–1.10 (m, 12H, 2×CH_3, $C(O)CHCH_3$, CH_2), 1.21 (s, 1.5H, CH_3), 1.22 (s, 1.5H, CH_3), 1.25–1.45 (m, 5H, CH_2CHCH_3, CH_2), 1.46–1.61 (m, 2H, CH_2, CH_2CHOH), 1.72–1.83 (m, 1H, CH_2CHOH), 2.17 (s, 3H, HC═CCH_3), 2.27 (dd, *J*=6.3, 16.6 Hz, 1H, CH_2CO_2H), 2.43–2.50 (m, 1H, CH_2CO_2H), 2.57 (s, 3H, SCH_3), 3.10–3.17 (m, 1H, C(O)C$H$$CH_3$), 3.73–3.78 (m, 1H, C(O)CH(CH_3)CHOTBS), 4.20–4.26 (m, 1H, CHOH), 4.35–4.40 (m, 1H, CH(OTBS)CH_2CO_2H), 6.48 (s, 0.5H, C═CH), 6.50 (s, 0.5H, C═CH), 6.85–6.89 (m, 1H, ArH), 6.98 (d, *J*=7.9 Hz, 1H, ArH), 7.41 (t, *J*=7.9 Hz, 1H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$, more than one set of peaks counted due to the presence of C15 epimers) δ −4.7, −4.3, −3.8, −3.7, 13.3, 13.7, 14.6, 14.8, 15.6, 15.7, 17.5, 17.6, 17.7, 18.2, 18.5, 18.6, 19.1, 19.5, 20.2, 20.3, 20.4, 23.4, 24.8, 25.2, 26.0, 26.2, 29.7, 30.4, 30.9, 35.1, 35.4, 38.9, 40.3, 41.9, 42.0, 45.2, 51.0, 53.5, 73.7, 77.6, 78.5, 78.6, 118.7, 118.8, 119.9, 120.0, 123.9, 124.4, 135.8, 145.4, 156.5, 156.6, 158.9, 176.4, 218.1; MALDI-FTMS *m/z* 800.4746 (MNa^+), calcd for $C_{42}H_{75}NO_6SSi_2Na$ 800.4746.

4.5.17. Hydroxy acid 42c. The reaction mixture from the deprotection was quickly filtered through a plug of silica gel, and this crude product (46% yield from aldehyde **40**) was subjected to the Yamaguchi macrolactonization (vide infra) without further purification.

4.5.18. Hydroxy acid 42e. Pale yellow glass (66%, ca. 1:1 mixture of C15 epimers). TLC R_f=0.39 (silica, hexanes/ EtOAc 2:1); $[\alpha]_D^{22}=-20$ (*c* 1.0, $CHCl_3$); IR (film) ν_{max} 3354 (br), 2928, 2856, 1713, 1471, 1253, 1087, 988, 836, 775 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$, total integral normalized to 71H) δ 0.06–0.08 (m, 9H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.20–0.31 (m, 2H, *c*-propyl CH_2), 0.44–0.55 (m, 2H, *c*-propyl CH), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.90–0.93 (m, 12H, $SiC(CH_3)_3$, CH_2CHCH_3), 1.06 (d, *J*=6.8 Hz, 3H, $C(O)CHCH_3$), 1.11 (s, 3H, CH_3), 1.16–1.22 (m, 3H, CH_2), 1.23 (s, 3H, CH_3), 1.30–1.41 (m, 3H, CH_2CHCH_3, CH_2), 1.42–1.63 (m, 3H, CH_2CHOH, CH_2), 2.06 (s, 3H, HC═CCH_3), 2.32 (dd, *J*=6.5, 16.4 Hz, 1H, CH_2CO_2H), 2.48–2.53 (m, 1H, CH_2CO_2H), 2.71 (s, 3H, SCH_3), 3.12–3.17 (m, 1H, C(O)C$H$$CH_3$), 3.77–3.80 (m, 1H, C(O)CH(CH_3)CHOTBS), 4.23–4.27 (m, 1H, CHOH), 4.37–4.41 (m, 1H, CH(OTBS)CH_2CO_2H), 6.53 (s, 0.5H, C═CH), 6.54 (s, 0.5H, C═CH), 6.95 (s, 0.5H, ArH), 6.96 (s, 0.5H, ArH); ^{13}C NMR (150 MHz, $CDCl_3$, more than one set of peaks counted due to the presence of C15 epimers) δ −3.8, −3.4, −3.3, −2.9, −2.8, 12.1, 12.7, 15.1, 15.2, 16.1, 16.5, 16.6, 17.5, 18.4, 19.0, 19.2, 19.4, 19.7, 19.8,

19.9, 24.6, 26.9, 27.1, 28.5, 31.5, 31.6, 35.5, 35.6, 39.7, 39.8, 40.7, 40.8, 40.9, 45.9, 54.4, 54.5, 74.2, 74.3, 78.3, 78.4, 79.0, 79.1, 116.1, 116.2, 119.2, 119.3, 143.2, 143.3, 154.3, 166.0, 177.4, 177.5, 219.1; MALDI-FTMS *m/z* 792.4161 (MNa^+), calcd for $C_{39}H_{71}NO_6S_2Si_2Na$ 792.4153.

4.5.19. Yamaguchi macrolactonization (general procedure). To a solution of the hydroxy acid (95 μmol) in dry THF (8 mL) at 0°C was added triethylamine (79 μl, 0.57 mmol) and 2,4,6-trichlorobenzoyl chloride (40 μl, 0.23 mmol). After stirring at 0°C for 1 h, the resulting solution was added over 2 h to a solution of 4-DMAP (26 mg, 0.21 mmol) in toluene (20 mL) at 75°C using a syringe pump. Stirring was continued at 75°C for another 1 h after which the toluene was evaporated under reduced pressure. The residue was directly subjected to flash chromatography (silica, hexanes/EtOAc mixtures) to yield the macrolactone and its (15*R*)-epimer, readily separable. In all cases the desired (15*S*)-epimer eluted after the less polar (15*R*)-epimer.

4.5.20. Macrolactone 43a. Colorless glass (28% for two steps from the Nozaki–Hiyama–Kishi coupling product of aldehyde **32** and vinyl iodide **20a**); TLC R_f=0.21 (silica, hexanes/EtOAc 20:1); $[\alpha]_D^{22}=-33$ (*c* 0.56, CH_2Cl_2); IR (film) ν_{max} 2932, 2855, 1739, 1689, 1465, 1383, 1252, 1181, 1153, 1099, 1066, 1017, 984, 869, 836, 776 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ −0.10 to −0.08 (m, 1H, *c*-propyl CH_2), 0.03–0.09 (m, 9H, CH_3Si), 0.12 (s, 3H, CH_3Si), 0.42 (dd, *J*=4.4, 8.3 Hz, 1H, *c*-propyl CH_2), 0.59–0.65 (m, 1H, C(13)H), 0.73–0.80 (m, 1H, C(11)H_aH_b), 0.84 (s, 9H, $(CH_3)_3CSi$), 0.92 (m, 12H, $(CH_3)_3CSi$, C(8)CH_3), 1.06 (s, 3H, C(12)CH_3), 1.12–1.19 (m, 10H, C(6)CH_3, C(4)$(CH_3)_2$, C(9)H_aH_b), 1.26–1.32 (m, 1H, C(10)H_aH_b), 1.46–1.54 (m, 2H, C(10)H_aH_b, C(14)H_aH_b), 1.55–1.64 (m, 2H, C(8)H, C(9)H_aH_b), 1.78–1.84 (m, 1H, C(11)H_aH_b), 1.97–2.04 (m, 1H, C(14)H_aH_b), 2.09 (s, 3H, vinyl CH_3), 2.63–2.75 (m, 2H, C(2)H_2), 2.70 (s, 3H, thiazole CH_3), 3.10–3.15 (m, 1H, C(6)H), 3.80 (dd, *J*=2.2, 4.8 Hz, 1H, C(7)H), 4.48 (br s, 1H, C(3)H), 5.30–5.35 (m, 1H, C(15)H), 6.53 (s, 1H, vinyl H), 6.94 (s, 1H, ArH); ^{13}C NMR (150 MHz, $CDCl_3$, C(7) is obscure under chloroform peaks) δ −4.8, −4.2, −3.4, 14.9, 15.9, 17.3, 18.4, 18.6, 19.2, 19.8, 21.0, 21.6, 22.0, 24.6, 26.1, 32.8, 34.9, 39.4, 40.2, 40.8, 45.1, 54.1, 73.8, 80.6, 116.2, 119.7, 138.8, 152.5, 164.6, 170.6, 215.3; MALDI-FTMS *m/z* 734.4639 (MH^+), calcd for $C_{40}H_{72}NO_5SSi_2$ 734.4664.

4.5.21. Macrolactone 43b. Colorless glass (28%); TLC R_f=0.27 (silica, hexanes/EtOAc 10:1); $[\alpha]_D^{22}=-28$ (*c* 1.0, $CHCl_3$); IR (film) ν_{max} 2929, 2856, 1740, 1695, 1472, 1384, 1253, 1100, 1020, 986, 836, 775 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ −0.06 (1H, *c*-propyl CH_2), 0.05 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$), 0.12 (s, 3H, $SiCH_3$), 0.43 (dd, *J*=4.2, 8.6 Hz, 1H, *c*-propyl CH_2), 0.61–0.67 (m, 1H, *c*-propyl CH), 0.74–0.82 (m, 1H, CH_2), 0.85 (s, 9H, $SiC(CH_3)_3$), 0.93 (s, 9H, $SiC(CH_3)_3$), 0.95 (d, *J*=6.6 Hz, 3H, CH_2CHCH_3), 1.07 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 1.14 (d, *J*=7.0 Hz, 3H, C(O)$CHCH_3$), 1.16 (s, 3H, CH_3), 1.17–1.34 (m, 3H, CH_2), 1.48–1.55 (m, 2H, CO_2CHCH_2, CH_2) 1.59–1.63 (m, 1H, CH_2CHCH_3), 1.79–1.85 (m, 1H, CH_2), 2.03–2.09 (m, 1H, CO_2CHCH_2), 2.11 (s, 3H, HC≡CCH_3), 2.32 (s, 3H, $ArCH_3$), 2.66 (dd, *J*=5.3, 16.2 Hz, 1H, CH_2CO_2), 2.73 (dd, *J*=5.3, 16.2 Hz, 1H, CH_2CO_2), 3.11–3.17 (m, 1H, C(O)CHCH_3), 3.79–3.82 (m, 1H, C(O)CH(CH_3)CHOTBS), 4.42 (br s, 1H, CH(OTBS)CH_2CO_2), 5.36 (d, *J*=10.5 Hz, 1H, CH_2CO_2CH), 6.53 (s, 1H, C=CH), 7.12 (d, *J*=7.9 Hz, 1H, ArH), 7.44 (d, *J*=7.9 Hz, 1H, ArH), 8.42 (s, 1H, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ −4.8, −4.2, −4.1, −3.4, 14.5, 15.8, 17.2, 18.2, 18.3, 18.4, 18.6, 19.1, 19.7, 21.0, 21.5, 21.9, 24.6, 26.0, 26.1, 32.8, 34.9, 39.5, 40.3, 40.8, 44.8, 54.2, 73.7, 76.6, 80.7, 123.9, 125.4, 130.6, 136.5, 140.8, 149.5, 153.5, 170.6, 215.3; MALDI-FTMS *m/z* 728.5109 (MH^+), calcd for $C_{42}H_{74}NO_5Si_2$ 728.5106.

4.5.22. Macrolactone 43d. Yellow glass (35%); TLC R_f=0.14 (silica, hexanes/EtOAc 6:1); $[\alpha]_D^{22}=-28$ (*c* 0.12, CH_2Cl_2); IR (film) ν_{max} 2931, 2861, 1737, 1690, 1596, 1467, 1378, 1249, 1149, 1102, 1049, 985, 832, 773 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ −0.08 to −0.05 (m, 1H, *c*-propyl CH_2), 0.03–0.10 (m, 9H, CH_3Si), 0.11 (s, 3H, CH_3Si), 0.43 (dd, *J*=4.4, 8.3 Hz, 1H, *c*-propyl CH_2), 0.61–0.67 (m, 1H, C(13)H), 0.76–0.82 (m, 1H, C(11)H_aH_b), 0.84 (s, 9H, $(CH_3)_3CSi$), 0.87–0.96 (m, 12H, $(CH_3)_3CSi$, C(8)CH_3), 1.07 (s, 3H, C(4)$C_aH_3C_bH_3$), 1.12–1.17 (m, 9H, C(4)$C_aH_3C_bH_3$, C(6)CH_3, C(12)CH_3), 1.17–1.21 (m, 1H, C(9)H_aH_b), 1.23–1.32 (m, 1H, C(10)H_aH_b), 1.38–1.45 (m, 1H, C(9)H_aH_b), 1.46–1.56 (m, 2H, C(10)H_aH_b, C(14)H_aH_b), 1.57–1.63 (m, 1H, C(8)H), 1.78–1.83 (m, 1H, C(11)H_aH_b), 2.00–2.08 (m, 1H, C(14)H_aH_b), 2.11 (s, 3H, vinyl CH_3), 2.69 (dd, *J*=5.6, 16.2 Hz, 2H, C(2)H_2), 3.10–3.15 (m, 1H, C(6)H), 3.40 (s, 3H, OCH_3), 3.78–3.81 (m, 1H, C(7)H), 4.45–4.53 (m, 1H, C(3)H), 4.59 (s, 2H, CH_2O), 4.70 (s, 2H, CH_2O), 5.35 (br d, *J*=10.1 Hz, 1H, C(15)H), 6.55 (s, 1H, vinyl H), 7.21 (d, *J*=7.9 Hz, 1H, PyH), 7.64 (d, *J*=7.9 Hz, 1H, PyH), 8.56 (s, 1H, PyH); ^{13}C NMR (150 MHz, $CDCl_3$, C(7) is obscure under the chloroform peaks) δ −4.7, −4.2, −4.1, −3.4, 14.6, 15.9, 17.2, 18.3, 18.4, 18.6, 19.1, 19.7, 21.0, 21.6, 21.9, 24.6, 26.0, 26.1, 32.8, 34.8, 39.5, 40.3, 40.8, 44.9 (br), 54.2, 55.4, 66.6, 73.7, 80.6, 95.8, 124.1, 125.1, 130.7, 135.7, 142.1, 148.7, 155.8, 170.6, 215.3; MALDI-FTMS *m/z* 810.5116 (MNa^+), calcd for $C_{44}H_{77}NO_7Si_2Na$ 810.5130.

4.5.23. Macrolactone 43e. This product was isolated as a crude mixture which was directly subjected to the global desilylation conditions (vide infra) without further purification.

4.5.24. Macrolactone 43f. Colorless glass (45%); TLC R_f=0.20 (silica, hexanes/EtOAc 10:1); $[\alpha]_D^{22}=-30$ (*c* 0.10, CH_2Cl_2); IR (film) ν_{max} 2933, 285, 1737, 1668, 1463, 1382, 1357, 1251, 1102, 1015, 983, 871, 834, 772 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ −0.09 to −0.06 (m, 1H, *c*-propyl CH_2), 0.03–0.09 (m, 9H, CH_3Si), 0.11 (s, 3H, CH_3Si), 0.43 (dd, *J*=4.4, 8.3 Hz, 1H, *c*-propyl CH_2), 0.60–0.66 (m, 1H, C(13)H), 0.75–0.82 (m, 1H, C(11)H_aH_b), 0.84 (s, 9H, $(CH_3)_3CSi$), 0.92 (s, 9H, $(CH_3)_3CSi$), 0.94 (d, *J*=7.0 Hz, 3H, C(8)CH_3), 1.06 (s, 3H, C(12)CH_3), 1.12–1.19 (m, 10H, C(6)CH_3, C(4)$(CH_3)_2$, C(9)H_aH_b), 1.26–1.32 (m, 1H, C(10)H_aH_b), 1.39–1.46 (m, 1H, C(9)H_aH_b), 1.46–1.55 (m, 2H, C(10)H_aH_b, C(14)H_aH_b), 1.56–1.63 (m, 1H, C(8)H), 1.77–1.83 (m, 1H, C(11)H_aH_b), 1.98–2.06 (m, 1H, C(14)H_aH_b), 2.11 (s, 3H, vinyl CH_3), 2.45 (s, 3H, SCH_3),

2.65 (dd, J=4.8, 16.2 Hz, 1H, C(2)H_aH$_b$), 2.72 (dd, J=5.7, 16.2 Hz, 1H, C(2)H$_a$$H_b$), 3.09–3.15 (m, 1H, C(6)H), 3.78–3.81 (m, 1H, C(7)H), 4.48 (br s, 1H, C(3)H), 5.33 (br d, J=10.1 Hz, 1H, C(15)H), 6.49 (s, 1H, vinyl H), 7.13 (d, J=8.3 Hz, 1H, PyH), 7.51 (d, J=8.3 Hz, 1H, PyH), 8.48 (s, 1H, PyH); ^{13}C NMR (150 MHz, $CDCl_3$, C(7) is obscure under chloroform peaks.) δ −4.8, −4.2, −4.1, −3.4, 14.7, 15.8, 15.9, 17.2, 18.3, 18.4, 18.6, 19.1, 19.7, 21.0, 21.6, 21.9, 24.6, 26.0, 26.1, 32.8, 34.6, 39.5, 40.3, 40.7, 45.1, 54.1, 73.7, 80.7, 124.2, 124.8, 132.6, 134.3, 141.7, 147.2, 153.1, 170.6, 215.2; MALDI-FTMS m/z 760.4799 (MH^+), calcd for $C_{42}H_{74}NO_5SSi_2$ 760.4820.

4.5.25. Macrolactone 43g. Yellow glass (37%); TLC R_f=0.47 (silica, hexanes/EtOAc 10:1); $[\alpha]_D^{22}$=−14 (c 0.31, $CHCl_3$); IR (film) ν_{max} 2929, 2856, 1740, 1696, 1557, 1461, 1431, 1379, 1250, 1099, 107, 979, 836, 774 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.08 to −0.04 (m, 1H, c-propyl CH_2), 0.02–0.10 (m, 9H, CH_3Si), 0.02–0.10 (m, 9H, CH_3Si), 0.12 (s, 3H, CH_3Si), 0.44 (dd, J=4.4, 8.4 Hz, 1H, c-propyl CH_2), 0.61–0.68 (m, 1H, C(13)H), 0.76–0.82 (m, 1H, C(11)H_aH$_b$), 0.85 (s, 9H, $(CH_3)_3$CSi), 0.92 (s, 9H, $(CH_3)_3$CSi), 0.95 (d, J=7.0 Hz, 3H, C(8)CH_3), 1.07 (s, 3H, C(12)CH_3), 1.12–1.18 (m, 9H, C(6)CH_3, C(4)$(CH_3)_2$), 1.18–1.23 (m, 1H, C(9)H_aH$_b$), 1.24–1.32 (m, 1H, C(10)H_aH$_b$), 1.39–1.46 (m, 1H, C(9)H$_a$$H_b$), 1.46–1.55 (m, 2H, C(10)H$_a$$H_b$, C(14)$H_aH_b$), 1.56–1.63 (m, 1H, C(8)H), 1.78–1.84 (m, 1H, C(11)H$_a$$H_b$), 2.00–2.09 (m, 1H, C(14)H$_a$$H_b$), 2.24 (s, 3H, vinyl CH_3), 2.57 (s, 3H, SCH_3), 2.65 (dd, J=5.2, 16.2 Hz, 1H, C(2)H_aH$_b$), 2.72 (dd, J=5.5, 16.2 Hz, 1H, C(2)H$_a$$H_b$), 3.10–3.16 (m, 1H, C(6)H), 3.79–3.82 (m, 1H, C(7)H), 4.51 (br s, 1H, C(3)H), 5.36 (br d, J=10.3 Hz, 1H, C(15)H), 6.45 (s, 1H, vinyl H), 6.86 (d, J=8.1 Hz, 1H, PyH), 6.99 (d, J=8.1 Hz, 1H, PyH), 7.41 (t, J=8.1 Hz, 1H, PyH); ^{13}C NMR (125 MHz, $CDCl_3$, C(7) is obscure under chloroform peaks.) δ −4.7, −4.2, −3.4, 13.3, 15.3, 15.8, 17.1, 18.3, 18.4, 18.6, 19.1, 19.7, 20.6, 21.6, 24.6, 26.0, 26.1, 32.8, 34.8, 39.6, 40.5, 40.6, 44.7, 54.2, 73.6, 80.8, 119.0, 120.3, 124.8, 135.8, 142.2, 156.1, 158.9, 170.6, 215.2; MALDI-FTMS m/z 760.4802 (MH^+), calcd for $C_{42}H_{74}NO_5SSi_2$ 760.4820.

4.5.26. Macrolactone 44c. Colorless glass (33% for two steps from the Nozaki–Hiyama–Kishi coupling product of aldehyde **40** and vinyl iodide **20c**); TLC R_f=0.46 (silica, hexanes/EtOAc 10:1); $[\alpha]_D^{22}$=−17 (c 0.56, CH_2Cl_2); IR (film) ν_{max} 2931, 2861, 1743, 1696, 1467, 1378, 1249, 1161, 1073, 1020, 985, 873, 833, 773, 703, 579 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.02 (s, 3H, CH_3Si), 0.09 (m, 6H, CH_3Si), 0.14 (m, 3H, CH_3Si), 0.18–0.22 (m, 2H, c-propyl CH_2), 0.45–0.51 (m, 1H, C(13)H), 0.67–0.74 (m, 1H, C(12)H), 0.78–0.84 (m, 1H, C(11)H_aH$_b$), 0.86 (s, 9H, $(CH_3)_3$CSi), 0.91–0.97 (m, 12H, $(CH_3)_3$CSi, C(8)CH_3), 1.10–1.15 (m, 1H, C(9)H_aH$_b$), 1.13 (d, J=7.0 Hz, C(6)CH_3), 1.16 (s, 3H, C(4)C$_a$$H_3C_bH_3$), 1.20 (s, 3H, C(4)C$_aH_3C_b$$H_3$), 1.30–1.39 (m, 1H, C(9)H$_a$$H_b$), 1.42–1.53 (m, 2H, C(10)H_aH$_b$, C(14)H_aH$_b$), 1.58–1.66 (m, 1H, C(8)H), 1.67–1.77 (m, 2H, C(10)H$_a$$H_b$, C(11)H$_a$$H_b$), 1.83–1.90 (m, 1H, C(14)H$_a$$H_b$), 2.12 (s, 3H, CH_3), 2.74 (dd, J=7.7, 16.9 Hz, 1H, C(2)H_aH$_b$), 2.86 (dd, J=3.7, 16.9 Hz, 1H, C(2)H$_a$$H_b$), 3.11–3.17 (m, 1H, C(6)H), 3.86–3.89 (m, 1H, C(7)H), 4.18 (s, 2H, ArCH_2O), 4.23–4.28 (m, 1H, C(3)H), 5.22 (br d, J=11.0 Hz, 1H, C(15)H), 6.53 (s, 1H, vinyl H), 7.20 (d, J=7.7 Hz, 1H, PyH), 7.23–7.28 (m, 3H, ArH), 7.29–7.35 (m, 6H, ArH), 7.47–7.52 (m, 6H, ArH), 7.63 (d, J=7.7 Hz, 1H, PyH), 8.58 (s, 1H, PyH); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.7, −4.5, −3.8, −3.7, −1.6, 13.6, 14.2, 15.4, 17.2, 17.4, 17.5, 17.6, 18.2, 18.5, 18.9, 19.0, 19.1, 19.2, 19.4, 19.6, 20.3, 20.5, 22.6, 23.4, 23.5, 24.8, 26.0, 26.2, 26.8, 27.8, 31.0, 31.1, 31.5, 35.1, 35.4, 38.9, 40.4, 42.0, 42.1, 45.1, 62.7, 73.9, 77.5, 77.6, 78.3, 78.5, 115.3, 115.4, 118.9, 119.2, 142.1, 142.2, 152.8, 152.9, 164.6, 172.2, 217.8; MALDI-FTMS m/z 972.5969 (MH^+), calcd for $C_{60}H_{86}NO_6Si_2$ 972.5988.

4.5.27. Macrolactone 44e. Colorless glass (47%); TLC R_f=0.31 (silica, hexanes/EtOAc 15:1); $[\alpha]_D^{22}$=−19 (c 0.50, $CHCl_3$); IR (film) ν_{max} 2929, 2855, 1741, 1697, 1472, 1254, 1102, 1036, 986, 836, 775 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.02 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$), 0.09 (s, 3H, $SiCH_3$), 0.15 (s, 3H, $SiCH_3$), 0.17–0.22 (m, 2H, c-propyl CH_2), 0.43–0.49 (m, 1H, c-propyl CH), 0.66–0.73 (m, 1H, c-propyl CH), 0.78–0.84 (m, 1H, CH_2), 0.86 (s, 9H, $SiC(CH_3)_3$), 0.91–0.95 (m, 12H, $SiC(CH_3)_3$, CH_2CHCH_3), 1.13 (d, J=6.6 Hz, 3H, C(O)CHCH_3), 1.16 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.23–1.36 (m, 2H, CH_2), 1.41–1.50 (m, 2H, CO_2CHCH_2, CH_2), 1.57–1.66 (m, 1H, CH_2CHCH_3), 1.67–1.78 (m, 2H, CH_2), 1.80–1.86 (m, 1H, CH_2), 2.11 (s, 3H, HC═CCH_3), 2.70 (s, 3H, SCH_3), 2.73 (dd, J=7.7, 16.9 Hz, 1H, CH_2CO_2), 2.85 (dd, J=3.7, 16.9 Hz, 1H, CH_2CO_2), 3.10–3.17 (m, 1H, C(O)CHCH$_3$), 3.88 (d, J=7.4 Hz, 1H, C(O)CH(CH$_3$)CHOTBS), 4.22–4.27 (m, 1H, CH(OTBS)CH_2CO_2), 5.19 (d, J=10.7 Hz, 1H, CH_2CO_2CH), 6.45 (s, 1H, C═CH), 6.96 (s, 1H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.3, −3.9, −3.7, −3.3, 10.8, 14.9, 16.6, 16.9, 17.2, 18.5, 18.57, 18.6, 22.9, 23.2, 26.2, 26.3, 29.7, 31.0, 34.9, 37.6, 39.4, 39.6, 47.0, 53.8, 74.8, 78.5, 80.9, 115.9, 118.7, 139.1, 153.1, 165.0, 170.9, 215.3; MALDI-FTMS m/z 774.4056 (MNa^+), calcd for $C_{39}H_{69}NO_5S_2Si_2Na$ 774.4048.

4.5.28. Global desilylation (general procedure). The macrolactone was dissolved in 20% v/v TFA in CH_2Cl_2, and the solution was kept at 25°C for 3 h, after which the volatiles were evaporated without heating. The residue was dissolved in EtOAc, and the solution was washed with $NaHCO_3$ (sat.), dried (Na_2SO_4) and evaporated. Flash chromatography (silica, hexanes/EtOAc mixtures) afforded the pure epothilone.

4.5.29. Epothilone 6. Colorless glass (73%); TLC R_f=0.25 (silica, hexanes/EtOAc 2:1); $[\alpha]_D^{22}$=−34 (c 0.11, CH_2Cl_2); IR (film) ν_{max} 3472 (br), 2931, 1732, 1684, 1456, 1378, 1258, 1179, 1149, 1067, 1043, 1012, 973, 873, 732 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, δ −0.06 to −0.04 (m, 1H, c-propyl CH), 0.46–0.50 (m, 1H, c-propyl CH), 0.57–0.63 (m, 1H, C(13)H), 0.67–0.73 (m, 1H, C(9)H_aH$_b$), 0.94 (d, J=7.0 Hz, 3H, C(8)HCH_3), 0.98 (s, 3H, C(4)C$_a$H$_3$), 1.07 (s, 3H, C(4)C$_b$H$_3$), 1.12 (d, J=7.0 Hz, 3H, C(6)HCH_3), 1.25–1.45 (m, 5H, C(9)H$_a$$H_b$, C(10)$H_2$, C(11)$H_2$), 1.36 (s, 3H, C(12)$CH_3$), 1.61–1.69 (m, 1H, C(14)H_aH$_b$), 1.72–1.80 (m, 1H, C(8)H), 1.87–1.94 (m, 1H, C(14)H$_a$$H_b$), 2.04 (s, 3H, vinyl CH_3), 2.44 (dd, J=2.6, 15.6 Hz, 1H, C(2)H_aH$_b$), 2.54 (dd, J=10.6, 15.6 Hz, 1H, C(2)H$_a$$H_b$), 2.69 (s, 3H, thiazole CH_3), 3.12 (br s, 1H, OH), 3.22 (br s, 1H, OH), 3.32 (dq,

J=2.4, 7.0 Hz, 1H, C(6)H), 3.63–3.67 (m, 1H, C(7)H), 4.35 (br d, J=10.6 Hz, 1H, C(3)H), 5.28–5.33 (m, 1H, C(15)H), 6.54 (s, 1H, vinyl H), 6.93 (s, 1H, thiazole H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.8, 15.3, 15.9, 18.3, 18.5, 19.1, 19.3, 19.8, 20.8, 21.1, 22.5, 32.0, 33.9, 36.3, 39.0, 40.9, 41.5, 53.5, 71.3, 72.6, 79.5, 115.8, 119.0, 138.2, 152.2, 164.7, 170.6, 220.8; MALDI-FTMS m/z 506.2931 (MH^+), calcd for $C_{28}H_{44}NO_5S$ 506.2935.

4.5.30. Epothilone 8. Colorless glass (48%); TLC R_f=0.52 (silica, hexanes/EtOAc 1:1); $[\alpha]_D^{22}=-54$ (c 0.30, $CHCl_3$); IR (film) ν_{max} 3445 (br), 2936, 1732, 1682, 1454, 1383, 1259, 756 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.03 (m, 1H, c-propyl CH_2), 0.49 (dd, J=4.2, 8.6 Hz, 1H, c-propyl CH_2), 0.60–0.67 (m, 1H, c-propyl CH), 0.68–0.75 (m, 1H, CH_2), 0.90 (d, J=7.4 Hz, 3H, CH_2CHCH_3), 1.01 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.12 (d, J=7.0 Hz, 3H, $C(O)CHCH_3$), 1.37 (s, 3H, CH_3), 1.38–1.46 (m, 3H, CH_2), 1.71–1.80 (m, 3H, CH_2CHCH_3, CH_2), 1.86–1.95 (m, 2H, CH_2), 2.02 (s, 3H, HC═CCH_3), 2.33 (s, 3H, $ArCH_3$), 2.42 (dd, J=2.4, 15.4 Hz, 1H, CH_2CO_2), 2.55 (dd, J=10.6, 15.4 Hz, 1H, CH_2CO_2), 3.24 (br s, 1H, OH), 3.30–3.34 (m, 1H, $C(O)CHCH_3$), 3.66 (d, J=6.3 Hz, 1H, $C(O)CH(CH_3)CHOH$), 3.80 (br s, 1H, OH), 4.42 (m, 1H, $CH(OH)CH_2CO_2$), 5.32 (dd, J=3.3, 8.4 Hz, 1H, CH_2CO_2CH), 6.57 (s, 1H, C═CH), 7.17 (d, J=8.1 Hz, 1H, ArH), 7.47 (dd, J=1.9, 7.7 Hz, 1H, ArH), 8.39 (d, J=1.9 Hz, 1H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.7, 15.1, 15.6, 18.0, 18.2, 18.4, 19.2, 19.7, 20.7, 21.4, 22.4, 32.0, 33.7, 36.3, 39.1, 40.8, 41.3, 53.7, 71.1, 72.5, 79.1, 123.5, 124.6, 130.9, 136.8, 140.1, 149.4, 153.1, 170.5, 221.0; MALDI-FTMS m/z 500.3369 (MH^+), calcd for $C_{30}H_{46}NO_5$ 500.3370.

4.5.31. Epothilone 10. The general procedure failed to cleave the MOM protecting group cleanly. Therefore, this group was first removed using bromotrimethylsilane as follows: To a solution of protected epothilone **43d** (11 mg, 14 μmol) in dry CH_2Cl_2 (0.4 mL) was added powdered 4 Å MS (5 mg), and the resulting mixture was cooled to −30°C. Bromotrimethylsilane (18.4 μL, 140 μmol) was added dropwise, and the mixture was stirred at −30°C for 1 h, after which the reaction was quenched with $NaHCO_3$ (sat.) and extracted five times with EtOAc. The combined extract was dried and evaporated, and the residue subjected to the general desilylation procedure to yield **10** as a colorless glass (56%); TLC R_f=0.42 (silica, hexanes/EtOAc 1:4); $[\alpha]_D^{22}=-52$ (c 0.12, CH_2Cl_2); IR (film) ν_{max} 3401 (br), 2931, 1731, 1684, 1596, 1561, 1461, 1378, 1331, 1290, 1255, 1173, 1149, 1044, 1008, 979, 879, 732 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ −0.03 (m, 1H, c-propyl CH_2), 0.49 (dd, J=4.2, 8.6 Hz, 1H, c-propyl CH_2), 0.60–0.64 (m, 1H, c-propyl CH), 0.64–0.71 (m, 1H, CH_2), 0.87 (d, J=7.0 Hz, 3H, CH_2CHCH_3), 1.00 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.11 (d, J=6.5 Hz, 3H, $C(O)CHCH_3$), 1.38 (s, 3H, CH_3), 1.38–1.44 (m, 3H, CH_2), 1.72–1.80 (m, 3H, CH_2CHCH_3, CH_2), 1.81–1.89 (m, 2H, CH_2), 1.99 (s, 3H, HC═CCH_3), 2.40 (dd, J=2.2, 15.3 Hz, 1H, CH_2CO_2), 2.55 (dd, J=11.0, 15.3 Hz, 1H, CH_2CO_2), 3.08 (br s, 1H, OH), 3.29–3.33 (m, 1H, $C(O)CHCH_3$), 3.63 (d, J=6.5 Hz, 1H, $C(O)CH(CH_3)CHOH$), 4.23 (br s, 1H, OH), 4.45 (m, 1H, $CH(OH)CH_2CO_2$), 4.67 (s, 2H, CH_2OH), 5.30 (dd, J=3.1, 7.9 Hz, 1H, CH_2CO_2CH), 6.60 (s, 1H, C═CH), 7.25 (d, J=8.3 Hz, 1H, ArH), 7.66 (1H, ArH), 8.36 (s, 1H, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.6, 14.9, 16.0, 17.4, 18.4, 19.1, 19.8, 20.8, 21.7, 22.2, 31.9, 33.5, 36.1, 39.3, 40.8, 41.1, 54.0, 62.4, 70.8, 72.3, 78.6, 123.7, 124.0, 133.9, 135.4, 141.2, 147.7, 155.1, 170.5, 221.1; MALDI-FTMS m/z 516.3330 (MH^+), calcd for $C_{30}H_{46}NO_6$ 516.3319.

4.5.32. Epothilone 12. Viscous oil (17% from **41e**); TLC R_f=0.38 (silica, hexanes/EtOAc 2:1); $[\alpha]_D^{22}=-52$ (c 0.50, $CHCl_3$); IR (film) ν_{max} 3490 (br), 2933, 1732, 1686, 1255, 1038, 756 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ −0.04 (m, 1H, c-propyl CH_2), 0.49 (dd, J=4.2, 8.6 Hz, 1H, c-propyl CH_2), 0.59–0.64 (m, 1H, c-propyl CH), 0.67–0.73 (m, 1H, CH_2), 0.94 (d, J=7.0 Hz, 3H, CH_2CHCH_3), 0.99 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.12 (d, J=6.6 Hz, 3H, $C(O)CHCH_3$), 1.37 (s, 3H, CH_3), 1.38–1.46 (m, 3H, CH_2), 1.65–1.71 (m, 1H, CH_2), 1.72–1.81 (m, 3H, CH_2CHCH_3, CH_2), 1.87–1.93 (m, 1H, CH_2), 2.08 (s, 3H, HC═CCH_3), 2.45 (dd, J=2.6, 15.4 Hz, 1H, CH_2CO_2), 2.54 (dd, J=10.5, 15.4 Hz, 1H, CH_2CO_2), 2.70 (s, 3H, SCH_3), 3.15 (br s, 1H, OH), 3.30–3.33 (m, 1H, $C(O)CHCH_3$), 3.66 (dd, J=2.2, 6.6 Hz, 1H, $C(O)CH(CH_3)CHOH$), 4.34 (dd, J=2.6, 10.5 Hz, 1H, $CH(OH)CH_2CO_2$), 5.31 (dd, J=2.9, 8.6 Hz, 1H, CH_2CO_2CH), 6.47 (s, 1H, C═CH), 6.96 (s, 1H, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 12.6, 16.2, 16.7, 17.5, 19.2, 19.3, 20.0, 20.8, 21.7, 22.0, 23.3, 32.8, 34.5, 37.0, 39.8, 41.8, 42.4, 54.4, 72.3, 73.3, 80.5, 116.6, 119.4, 127.7, 139.2, 153.7, 166.1, 171.5, 221.6; MALDI-FTMS m/z 538.2666 (MH^+), calcd for $C_{28}H_{44}NO_5S_2$ 538.2655.

4.5.33. Epothilone 13. Colorless glass (68%); TLC R_f=0.57 (silica, hexanes/EtOAc 1:1); $[\alpha]_D^{22}=-46$ (c 0.34, CH_2Cl_2); IR (film) ν_{max} 3484 (br), 2932, 1731, 1684, 1469, 1367, 1255, 1150, 1044, 1009, 973, 879, 826, 732 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, δ 0.03–0.06 (m, 1H, c-propyl CH), 0.55–0.59 (m, 1H, c-propyl CH), 0.67–0.73 (m, 1H, C(13)H), 0.73–0.81 (m, 1H, $C(9)H_aH_b$), 0.98 (d, J=7.0 Hz, 3H, $C(8)HCH_3$), 1.08 (s, 3H, $C(4)C_aH_3$), 1.15 (s, 3H, $C(4)C_bH_3$), 1.19 (d, J=7.0 Hz, 3H, $C(6)HCH_3$), 1.32–1.52 (m, 5H, $C(9)H_aH_b$, $C(10)H_2$, $C(11)H_2$), 1.45 (s, 3H, $C(12)CH_3$), 1.76–1.88 (m, 2H, C(8)H, $C(14)H_aH_b$), 1.92–2.02 (m, 1H, $C(14)H_aH_b$), 2.12 (s, 3H, vinyl CH_3), 2.51 (dd, J=2.6, 15.4 Hz, 1H, $C(2)H_aH_b$), 2.59 (s, 3H, SCH_3), 2.62 (dd, J=10.7, 15.4 Hz, 1H, $C(2)H_aH_b$), 3.28 (s, 1H, OH), 3.39 (dq, J=2.2, 7.0 Hz, 1H, C(6)H), 3.62 (br s, 1H, OH), 3.69–3.76 (m, 1H, C(7)H), 4.47 (dd, J=2.6, 10.7 Hz, 1H, C(3)H), 5.33–5.43 (m, 1H, C(15)H), 6.61 (s, 1H, vinyl H), 7.26 (d, J=8.3 Hz, 1H, PyH), 7.61 (d, J=8.3 Hz, 1H, PyH), 8.52 (s, 1H, PyH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.7, 15.1, 15.7, 15.9, 18.0, 18.4, 19.2, 19.8, 20.8, 21.4, 22.4, 31.9, 33.7, 36.2, 39.1, 40.8, 41.3, 53.7, 71.2, 72.5, 79.3, 123.9, 124.1, 132.9, 134.5, 140.8, 147.1, 152.7, 170.6, 220.9; MALDI-FTMS m/z 554.2915 (MNa^+), calcd for $C_{30}H_{45}NO_5SNa$ 554.2910.

4.5.34. Epothilone 14. Colorless glass (48%); TLC R_f=0.42 (silica, hexanes/EtOAc 2:1); $[\alpha]_D^{22}=-38$ (c 0.20, CH_2Cl_2); IR (film) ν_{max} 3478 (br), 2930, 1732, 1682, 1556, 1434, 1378, 1257, 1149, 1137, 1067, 1044, 1012, 979, 785, 732 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, δ −0.05 to −0.02 (m, 1H, c-propyl CH), 0.48–0.51 (m, 1H, c-propyl CH), 0.60–0.66 (m, 1H, C(13)H), 0.66–0.72 (m, 1H, $C(9)H_aH_b$), 0.89 (d, J=7.0 Hz, 3H, $C(8)HCH_3$), 1.01 (s,

3H, C(4)C_aH_3), 1.08 (s, 3H, C(4)C_bH_3), 1.11 (d, J=7.0 Hz, 3H, C(6)HCH_3), 1.27–1.46 (m, 5H, C(9)H_aH_b, C(10)H_2, C(11)H_2), 1.38 (s, 3H, C(12)CH_3), 1.71–1.80 (m, 2H, C(8)H, C(14)H_aH_b), 1.85–1.93 (m, 1H, C(14)H_aH_b), 2.15 (s, 3H, vinyl CH_3), 2.45 (dd, J=2.6, 15.4 Hz, 1H, C(2)H_aH_b), 2.51–2.58 (dd, J=10.7, 15.4 Hz, 1H, C(2)H_aH_b), 2.56 (s, 3H, SCH_3), 3.08 (br d, J=4.0 Hz, 1H, OH), 3.16 (s, 1H, OH), 3.28–3.34 (m, 1H, C(6)H), 3.61–3.69 (m, 1H, C(7)H), 4.32–4.39 (m, 1H, C(3)H), 5.30–5.33 (m, 1H, C(15)H), 6.42 (s, 1H, vinyl H), 6.88 (d, J=7.4 Hz, 1H, PyH), 6.99 (d, J=7.9 Hz, 1H, PyH), 7.40–7.47 (m, 1H, PyH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.7, 13.4, 15.2, 16.0, 18.2, 18.4, 19.1, 20.0, 20.9, 21.2, 22.3, 31.8, 33.5, 36.1, 38.9, 41.0, 41.4, 53.6, 71.4, 72.3, 79.7, 119.0, 120.0, 124.5, 135.9, 140.9, 155.8, 159.1, 170.8, 220.7; MALDI-FTMS m/z 532.3078 (MH^+), calcd for $C_{30}H_{45}NO_5S$ 532.3091.

4.5.35. Epothilone 9. Colorless glass (54%); TLC R_f=0.13 (silica, hexanes/EtOAc 1:2); $[\alpha]_D^{22}=-24$ (c 0.14, CH_2Cl_2); IR (film) ν_{max} 3379, 2920, 2857, 1725, 1688, 1600, 1459, 1370, 1255, 1151, 1047, 1010, 979, 880, 734 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.18–0.26 (m, 2H, c-propyl CH_2), 0.47–0.54 (m, 1H, C(13)H), 0.60–0.67 (m, 1H, C(12)H), 0.70–0.78 (m, 1H, C(11)H_aH_b), 0.90 (d, J=7.0 Hz, 3H, C(8)CH_3), 1.10 (s, 3H, C(4)$C_aH_3C_bH_3$), 1.17 (d, J=7.0 Hz, 3H, C(6)CH_3), 1.19–1.32 (m, 2H, C(9)H_aH_b, C(10)H_aH_b), 1.34–1.41 (m, 1H, C(14)H_aH_b), 1.38 (s, 3H, C(4)$C_aH_3C_bH_3$), 1.44–1.58 (m, 2H, C(9)H_aH_b, C(10)H_aH_b), 1.62–1.72 (m, 2H, C(8)H, C(11)H_aH_b), 2.00 (s, 3H, vinyl CH_3), 2.08–2.14 (m, 1H, C(14)H_aH_b), 2.46 (dd, J=2.2, 15.4 Hz, 1H, C(2)H_aH_b), 2.58 (dd, J=10.7, 15.4 Hz, 1H, C(2)H_aH_b), 2.66 (br s, 1H, OH), 3.23–3.29 (m, 1H, C(6)H), 3.72–3.76 (m, 1H, C(7)H), 3.88 (br s, 1H, OH), 4.32 (br d, J=10. 7 Hz, 1H, C(3)H), 4.71 (s, 2H, $PyCH_2O$), 5.36–5.40 (m, 1H, C(15)H), 6.58 (s, 1H, vinyl H), 7.24 (d, J=8.1 Hz, 1H, PyH), 7.69 (d, J=8.1 Hz, 1H, PyH), 8.49 (s, 1H, PyH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.5, 13.7, 15.6, 15.7, 16.3, 18.4, 18.5, 22.1, 24.9, 30.7, 34.3, 35.6, 37.4, 39.1, 42.8, 53.6, 62.6, 71.4, 74.5, 79.5, 123.9, 124.7, 133.7, 135.2, 141.0, 147.8, 155.3, 170.8, 219.3; MALDI-FTMS m/z 524.3004 (MNa^+), calcd for $C_{29}H_{43}NO_6Na$ 524.2982.

4.5.36. Epothilone 11. Colorless glass (68%); TLC R_f=0.28 (silica, hexanes/EtOAc 2:1); $[\alpha]_D^{22}=-26$ (c 0.30, $CHCl_3$); IR (film) ν_{max} 3444 (br), 2925, 1731, 1693, 1454, 1258, 1037, 756 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.18–0.22 (m, 1H, c-propyl CH_2), 0.23–0.26 (m, 1H, c-propyl CH_2), 0.48–0.52 (m, 1H, c-propyl CH), 0.62–0.68 (m, 1H, c-propyl CH), 0.76–0.83 (m, 1H, CH_2), 0.97 (d, J=7.0 Hz, CH_2CHCH_3), 1.12 (s, 3H, CH_3), 1.19 (d, J=6.6 Hz, 3H, C(O)CHCH_3), 1.23–1.31 (m, 2H, CH_2), 1.37–1.42 (m, 4H, CH_3, CO_2CHCH_2), 1.45–1.52 (m, 1H, CH_2), 1.53–1.59 (m, 1H, CH_2), 1.62–1.70 (m, 2H, CH_2, CH_2CHCH_3), 2.02–2.07 (m, 1H, CO_2CHCH_2), 2.08 (s, 3H, HC=CCH_3), 2.51 (dd, J=2.4, 15.8 Hz, 1H, CH_2CO_2), 2.59 (dd, J=10.6, 15.8 Hz, 1H, CH_2CO_2), 2.70 (s, 3H, SCH_3), 3.24–3.28 (m, 1H, C(O)CHCH$_3$), 3.77 (m, 1H, C(O)CH(CH_3)CHOH), 4.21 (m, 1H, CH(OH)CH_2-CO_2), 5.38 (d, J=8.8 Hz, 1H, CH_2CO_2CH), 6.45 (s, 1H, C=CH), 6.97 (s, 1H, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.4, 14.2, 15.3, 16.3, 16.6, 16.8, 18.3, 19.4, 21.9, 25.1, 30.5, 34.5, 35.6, 37.8, 38.8, 43.5, 53.1, 71.8, 75.0, 80.5, 116.0, 119.1, 138.1, 152.7, 165.4, 171.0, 219.1; MALDI-FTMS m/z 546.2330 (MNa^+), calcd for $C_{27}H_{41}NO_5S_2Na$ 546.2318.

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