Total Syntheses of Epothilones A and B via a Macrolactonization-Based Strategy

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Abstract: The total syntheses of epothilones A (**1**) and B (**2**) and several analogues thereof are described. The reported strategy relies on a macrolactonization approach and features selective epoxidation of the macrocycle double bond in precursors **3** and **4** (Scheme 1), respectively, as well as high convergency and flexibility. Building blocks **9**−**12** and **15** were constructed by asymmetric processes and coupled via Wittig, aldol, and macrolactonization reactions to afford the basic skeleton of epothilones and that of several of their analogues by a relatively short route. The utilization of intermediate **14**, obtained via a stereoselective Wittig reaction and its Enders coupling to SAMP hydrazone **13** (Scheme 8), in combination with a stereoselective aldol reaction with the modified substrate **69** (Scheme 10) improved the stereoselectivity and efficiency of the total synthesis of these new and highly potent microtubule binding antitumor agents.

1. Introduction

Epothilones A (**1**) and B (**2**) are two architecturally novel natural products recently isolated from the myxobacteria *Sorangium cellulosum* strain 90[1,2] and possess impressive microtubule binding affinities and antitumor properties.[1−4] Their molecular structures have been secured by a combination of spectroscopic and X-ray crystallographic techniques.[1,2] Interestingly, and despite their structural difference from Taxol, the epothilones were found to bind to the same region on microtubules[4] and to displace Taxol from its binding site.[5,6] The higher potency of these new compounds, and their effectiveness against certain drug-resistant tumor cell lines,[3,4] generated a great deal of excitement among chemists,[7] biologists, and clinicians. At least five total syntheses[8−11] of epothilone A (**1**) have already been achieved. The two from these laboratories were based on an olefin metathesis approach[9] and a macrolactonization approach.[10] The total synthesis of epothilone B (**2**) and its analogues has also been reported first by Danishefsky[12] and then by us[13] in preliminary communications. Here, we report the details of the total synthesis of both epothilones A (**1**) and B (**2**) and of a number of analogues of these compounds by our macrolactonization strategy.[10]

2. Retrosynthetic Analysis

Scheme 1 outlines the macrolactonization-based retrosynthetic analysis of epothilones A (**1**) and B (**2**). Thus, retrosynthetic removal of the epoxide oxygen from **1** and **2** reveals the corresponding *Z*-olefins, **3** and **4**, as potential precursors, respectively. The second major retrosynthetic step along this route is the disconnection of the macrocyclic ring at the lactone site, leading to hydroxy acids **5** and **6** as possible key intermediates. Moving further along the retrosynthetic path, an aldol-type disconnection allows the generation of keto acid **9** as a common intermediate and aldehydes **7** and **8** as reasonable building blocks for **5** and **6**, respectively. Keto acid **9** can be envisioned to arise from an asymmetric allylboration[14] of the corresponding aldehyde, followed by appropriate elaboration of the terminal olefin. The larger intermediates, **7** and **8**, can be disconnected by two slightly different ways. The first

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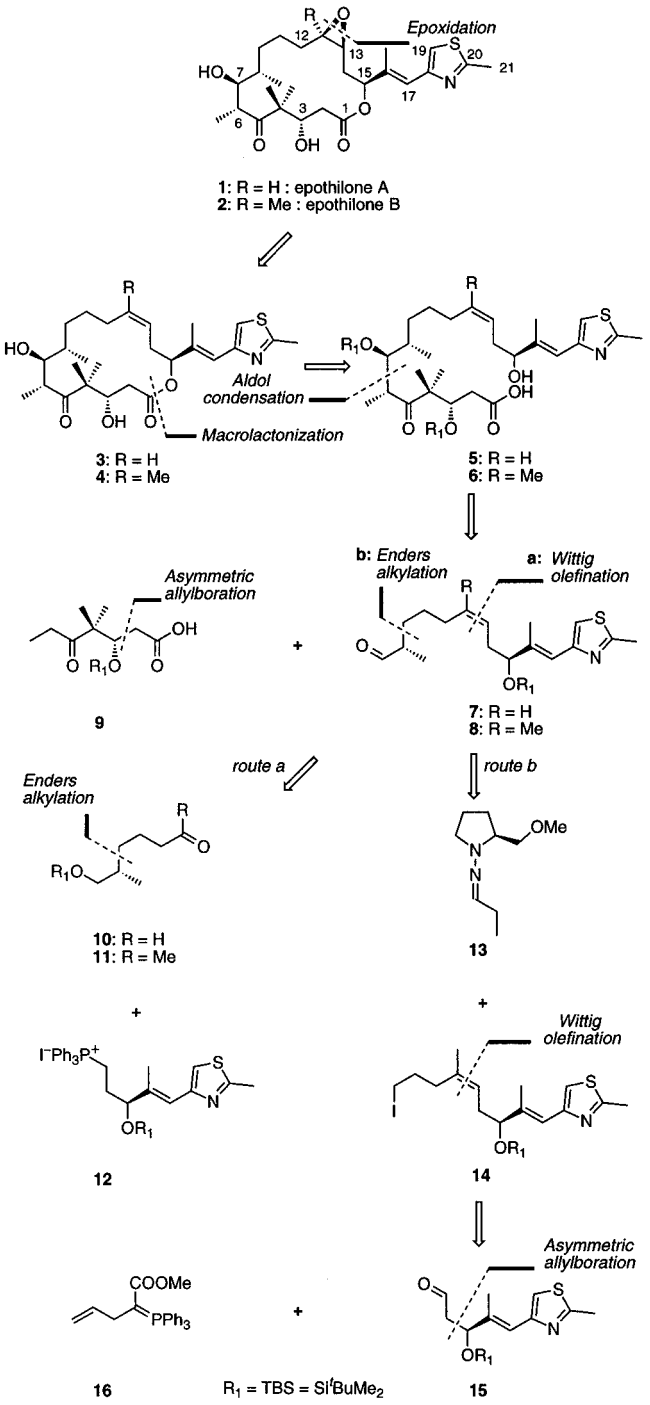
Scheme 1. Molecular Structures and Retrosynthetic Analysis of Epothilones A (**1**) and B (**2**)



disconnection (route a) involves a retro-Wittig type reaction accompanied by a number of functional group interchanges, leading to compounds **10**−**12**. The second disconnection, specifically sought for its potential to address the geometry issue of the trisubstituted double bond of epothilone B (**2**) (route b), involves (i) a retro-Enders alkylation,[15] leading to hydrazone **13** and iodide **14**, and (ii) a retro-Wittig type disconnection of the latter intermediate (**14**) to reveal aldehyde **15** and stabilized ylide **16** as potential building segments. An asymmetric allylboration of **15** then points to Brown's chiral allylborane[14] and an aldehyde carrying the required thiazole moiety as potential starting points.

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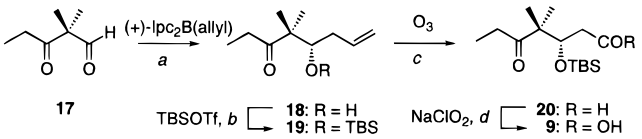
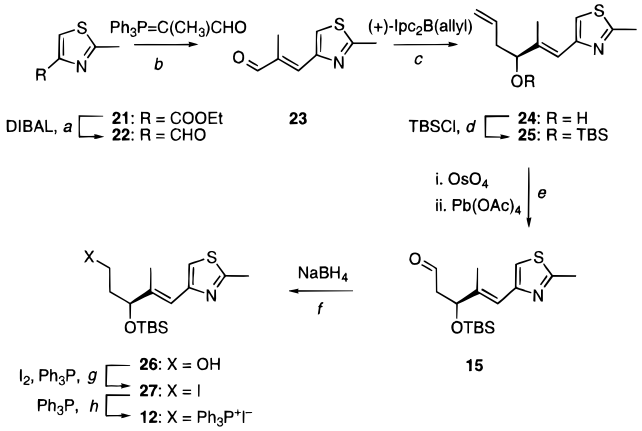
Scheme 2. Synthesis of Keto Acid **9**[a]



[a] Reagents and conditions: (a) 1.2 equiv of (+)-Ipc$_2$B(allyl), Et$_2$O, −100 °C, 0.5 h, 74% (ee >98% by Mosher ester analysis); (b) 1.1 equiv of TBSOTf, 1.2 equiv of 2,6 lutidine, CH_2Cl_2, 25 °C, 98%; (c) O_3, CH_2Cl_2, −78 °C, 0.5 h; then 1.2 equiv Ph_3P, −78 → 25 °C, 1 h, 90%; (d) 3.0 equiv of $NaClO_2$, 4.0 equiv of 2-methyl-2-butene, 1.5 equiv of NaH_2PO_4, ^{t}BuOH:H_2O (5:1), 25 °C, 2 h, 93%.

Scheme 3. Synthesis of Phosphonium Salt **12** and Aldehyde **15**[a]



[a] Reagents and conditions: (a) 1.6 equiv of DIBAL, CH_2Cl_2, −78 °C, 2 h, 90%; (b) $Ph_3P{=}C(CH_3)CHO$, benzene, reflux, 98%; (c) 1.5 equiv of (+)-Ipc$_2$B(allyl), Et$_2$O, −100 °C, 0.5 h, 96% (ee >97% by Mosher ester analysis); (d) 1.2 equiv TBSCl, 1.5 equiv of imidazole, DMF, 0 → 25 °C, 2 h, 99%; (e) i. 1.0 mol % OsO_4, 1.1 equiv of 4-methylmorpholine *N*-oxide (NMO), THF:^{t}BuOH:H_2O (1:1:0.1), 0 → 25 °C, 12 h, 95%; ii. 1.3 equiv of Pb(OAc)$_4$, EtOAc, 0 °C, 0.5 h, 98%, (f) 2.5 equiv of $NaBH_4$, MeOH, 0 °C, 15 min, 96%; (g) 1.5 equiv of I_2, 3.0 equiv of imidazole, 1.5 equiv of Ph_3P, Et$_2$O:MeCN (3:1), 0 °C, 0.5 h, 89%; (h) 1.1 equiv Ph_3P, neat, 100 °C, 2 h, 98%.

3. Total Synthesis

a. Construction of Building Blocks. The strategy derived from the retrosynthetic analysis discussed above (Scheme 1) required building blocks **9**−**12**, **15**, and related compounds. Their construction in optically active form proceeded as follows. Scheme 2 summarizes the synthesis of keto acid **9** starting with the known keto aldehyde **17**.[16] Thus, addition of (+)-Ipc$_2$B-(allyl)[14] to **17** in ether at −100 °C resulted in the formation of enantiomerically enriched alcohol **18** (74% yield, ee > 98% by Mosher ester determination).[17] Silylation of **18** with *tert*-butyldimethylsilyl triflate (TBSOTf) furnished, in 98% yield, silyl ether **19**. The conversion of terminal olefin **19** to carboxylic acid **9** was carried out in two steps: (i) ozonolysis in CH_2Cl_2 at −78 °C followed by exposure to Ph_3P to give aldehyde **20** (90% yield) and (ii) oxidation of **20** with $NaClO_2$ in the presence of 2-methyl-2-butene and NaH_2PO_4 in ^{t}BuOH−H_2O (5:1) (93% yield).

The synthesis of the thiazole-containing fragments **15** and **12** was accomplished as shown in Scheme 3. Thus, the known thiazole derivative **21**[18] was reduced with DIBAL (1.6 equiv, CH_2Cl_2, −78 °C) to aldehyde **22** (90% yield), which reacted

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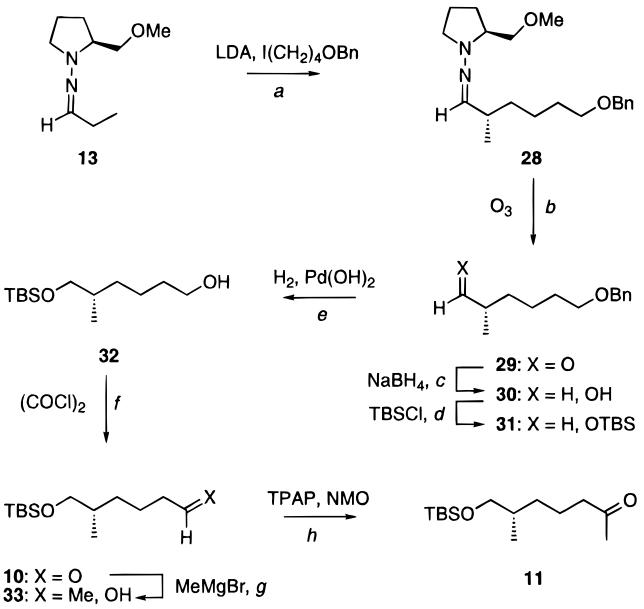
Scheme 4 Synthesis of Aldehyde **10** and Ketone **11**[a]



[a] Reagents and conditions: (a) 1.1 equiv of LDA, THF, 0 °C, 8 h; then 1.5 equiv of 4-iodo-1-(benzyloxy)butane in THF, at −100 → 0 °C, 6 h, 92% (de > 98% by ^{1}H NMR); (b) O_3, CH_2Cl_2, −78 °C, 77% or MeI, 60 °C, 5 h; then 3 N aqueous HCl, *n*-pentane, 25 °C, 1 h, 86%; (c) 3.0 equiv of $NaBH_4$, MeOH, 0 °C, 15 min, 98%; (d) 1.5 equiv of TBSCl, 2.0 equiv of Et_3N, CH_2Cl_2, 0 → 25 °C, 12 h, 95%; (e) H_2, $Pd(OH)_2$ cat., THF, 50 psi, 25 °C, 15 min, 95%; (f) 2.0 equiv of $(COCl)_2$, 4.0 equiv of DMSO, 6.0 equiv of Et_3N, CH_2Cl_2, −78 → 0 °C, 1.5 h, 98%; (g) 1.5 equiv of MeMgBr, THF, 0 °C, 15 min, 84%; (h) 1.5 equiv of NMO, 0.05 equiv of tetrapropylammonium perruthenate (TPAP), 4 Å MS, CH_2Cl_2, 25 °C, 45 min, 96%.

with the appropriate stabilized ylide [Ph_3P═C(Me)CHO] in benzene at 80 °C to afford the required (*E*)-α,β-unsaturated-aldehyde **23**[7a,b,h,9] in 98% yield. Addition of (+)-Ipc_2B(allyl)[14] to **23** in ether/pentane at −100 °C gave allylic alcohol **24** in 96% yield (>97% ee by Mosher ester analysis).[17] Protection of the hydroxyl group in **24** as a TBS ether (TBSCl, imidazole, DMF, 99% yield), followed by chemoselective dihydroxylation (OsO_4 cat., NMO)[19] of the terminal olefin (95% yield) and Pb-$(OAc)_4$ cleavage of the resulting diol (98% yield), furnished aldehyde **15** via intermediate **25**. Finally, $NaBH_4$ reduction of **15** (96% yield), followed by iodination (I_2, imidazole, Ph_3P, 89% yield) and phosphonium salt formation (Ph_3P, neat, 100 °C, 98% yield) gave the requisite fragment **12** via the intermediacy of alcohol **26** and iodide **27**.

The construction of aldehyde **10** and ketone **11** proceeded from SAMP hydrazone **13** as shown in Scheme 4. Thus, reaction of propionaldehyde with SAMP[20] furnished **13**, which upon sequential treatment with LDA (THF, 0 °C) and 4-iodo-1-(benzyloxy)butane (THF, −100 → 0 °C) led to compound **28** in 92% yield and >98% de (^{1}H NMR). Cleavage of the hydrazone moiety by exposure to ozone (CH_2Cl_2, −78 °C, 77% yield) or by treatment with MeI at 60 °C followed by acidic workup (aqueous HCl, 86% yield),[21] followed by $NaBH_4$ reduction of the resulting aldehyde (**29**), furnished alcohol **30** in 98% yield. The latter compound (**30**) was then silylated with TBSCl in CH_2Cl_2 in the presence of Et_3N and 4-DMAP to afford silyl ether **31** in 95% yield. Cleavage of the benzyl ether in **31** by hydrogenolysis [H_2, $Pd(OH)_2$ cat., THF, 50 psi] gave primary alcohol **32** (95% yield), which was smoothly oxidized to the desired aldehyde **10** under Swern conditions[22] [$(COCl)_2$, DMSO, Et_3N, 98% yield]. Addition of MeMgBr to **10** proceeded in 84% yield and was followed by TPAP−NMO oxidation[23] of the resulting secondary alcohol (**33**) to give the other required building block, ketone **11**, in 96% yield.

With the appropriate building blocks at hand, the convergent approach to epothilones A (**1**) and B (**2**) could now enter its second phase.

b. Total Synthesis of Epothilone A. The couplings of building blocks **9**, **10**, and **12** and the total synthesis of epothilone A (**1**) and its 6*S*,7*R*-diastereoisomers (**44** and **45**) are shown in Scheme 5. Thus, generation of the ylide from phosphonium salt **12** with sodium bis(trimethylsilyl)amide (NaHMDS), followed by reaction with aldehyde **10** resulted in the formation of the desired *Z*-olefin **34** ($J_{12,13}$ = 10.8 Hz, obtained from decoupling experiments) as the predominant product in 77% yield [*Z*:*E* ca. 9:1; the minor isomer (*E*) was removed chromatographically in subsequent steps]. Parenthetically, key intermediate **34** was also prepared by Wittig coupling of phosphonium salt **47** and aldehyde **15** in a reversal of the reacting functionalities of the two fragments as shown in Scheme 6. Thus, alcohol **32** was directly converted to iodide **46** by the action of I_2, imidazole, and Ph_3P (91% yield) and then to phosphonium salt **47** by heating with Ph_3P (91% yield). Generation of the ylide from **47** with equimolar amounts of NaHMDS in THF, followed by reaction with aldehyde **15** yielded *Z*-olefin **34** in 69% and in ca. 9:1 ratio with its *E*-isomer.

Returning to Scheme 5, selective desilylation of the primary hydroxyl group from **34** was achieved by the action of camphorsulfonic acid (CSA) in MeOH:CH_2Cl_2 (1:1),[24] leading to hydroxy compound **35** in 86% yield. Oxidation of **35** to aldehyde **7** was then carried out using SO_3·pyr., DMSO, and Et_3N (94% yield).[25] With the availability of **7**, we were then in a position to investigate its aldol condensation with keto acid **9**. It was found that the optimum conditions for this coupling reaction required generation of the dilithio derivative of **9** (1.2 equiv) with 3.0 equiv of lithium diisopropylamide (LDA) in THF (−78 → −40 °C), followed by addition of aldehyde **7** (1.0 equiv), resulting in the formation of a mixture of the desired product **36a** and its 6*S*,7*R*-diastereoisomer **36b** in ca. 1:1 ratio and in high yield. Despite the lack of stereoselectivity in this reaction, the result was welcome at least with regard to the prospect it provided for the construction of the 6*S*,7*R*-diastereoisomer of epothilones A and B. This mixture was then carried through to the stage of carboxylic acids **38** and **39** (Scheme 5), where it was chromatographically separated to its components. Thus, exposure of **36a,b** to excess of TBSOTf and 2,6-lutidine furnished a mixture of tetra-silylated products **37a,b**, which was then briefly treated with K_2CO_3 in MeOH[26] to afford, after silica gel flash or preparative layer chromatography, carboxylic acids **38** (31% overall yield from **7**) and **39** (30% overall yield from **7**) (**38**: R_f = 0.61; **39**: R_f = 0.70, silica gel, 5% MeOH in CH_2Cl_2). The indicated stereochemistry at C7 and C6 in compounds **38** and **39** was assigned later and was based on the successful conversion of **38** to epothilone A (**1**) as described below.

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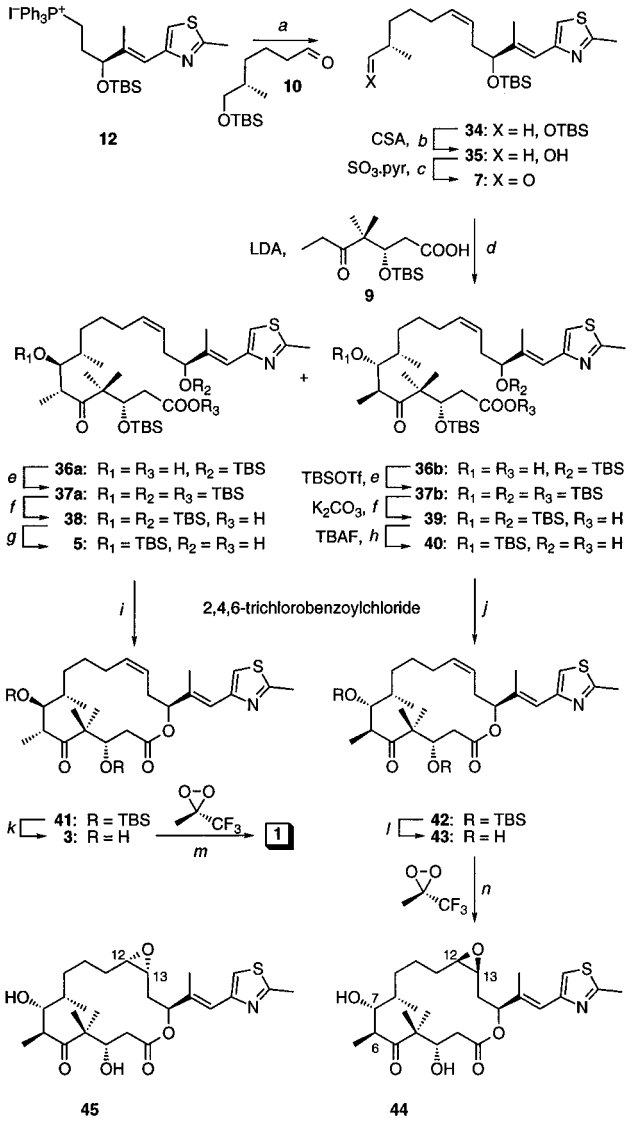
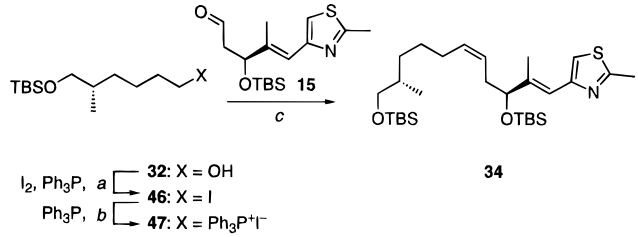
Scheme 5. Total Synthesis of Epothilone A (**1**) and Its 6*S*,7*R*-Diastereoisomers (**44** and **45**)[a]



[a] Reagents and conditions: (a) 1.2 equiv of **12**, 1.2 equiv of NaHMDS, THF, 0 °C, 15 min, then add 1.0 equiv of aldehyde **10**, 0 °C, 15 min, 77% (*Z*:*E* ca. 9:1); (b) 1.0 equiv of CSA portionwise over 1 h, CH_2Cl_2:MeOH (1:1), 0 → 25 °C, 0.5 h, 86%; (c) 2.0 equiv of SO_3·pyr., 10.0 equiv of DMSO, 5.0 equiv of Et_3N, CH_2Cl_2, 25 °C, 0.5 h, 94%; (d) 3.0 equiv of LDA, THF, 0 °C, 15 min; then 1.2 equiv of **9** in THF, −78 → −40 °C, 0.5 h; then 1.0 equiv of **7** in THF at −78 °C, high yield of **36a** and its 6*S*,7*R*-diastereoisomer **36b** (ca. 1:1 ratio); (e) 3.0 equiv of TBSOTf, 5.0 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 2 h; (f) 2.0 equiv of K_2CO_3, MeOH, 25 °C, 15 min, 31% of **38** and 30% of 6*S*,7*R*-diastereoisomer **39** from **7**; (g) 6.0 equiv of TBAF, THF, 25 °C, 8 h, 78%; (h) same as g, 82%; (i) 5.0 equiv of 2,4,6-trichlorobenzoylchloride, 6.0 equiv of Et_3N, THF, 25 °C, 15 min; then add to a solution of 10.0 equiv of 4-DMAP in toluene (0.002 M based on **5**), 25 °C, 0.5 h, 90%; (j) same as i, 85%; (k) 20% CF_3COOH (by volume) in CH_2Cl_2, 0 °C, 1 h, 92%; (l) same as k, 95%; (m) methyl(trifluoromethyl)dioxirane, MeCN, 0 °C, 75% (ca. 5:1 ratio of diastereoisomers), see ref 27); (n) same as m, 87% (**44**:**45** ca. 2:1 ratio of diastereoisomers, tentative stereochemistry).

At this stage, it was necessary to selectively remove the TBS group from the allylic hydroxyl group of **38**, so as to allow macrolactonization of the *seco*-acid substrate (**5**). This goal was achieved by treatment of **38** with tetra-*n*-butylammonium fluoride (TBAF) in THF at 25 °C, generating the desired hydroxy acid **5** in 78% yield. The key macrolactonization reaction of **5** was carried out using the Yamaguchi method[27] (2,4,6-trichlorobenzoyl chloride, Et_3N, 4-DMAP) at 25 °C, affording compound **41** in 90% yield. Removal of both TBS groups from **41** (CF_3COOH, CH_2Cl_2, 0 °C) furnished diol **3** in 92% yield. Finally, treatment of **3** with methyl(trifluoromethyl)-dioxirane[28] led cleanly to epothilone A (**1**) (62% yield) and its α-epoxide epimer (13% yield). The reaction of macrocyclic olefin **3** with *m*CPBA gave a number of other products as described in detailed in the preceding article.[29] Synthetic epothilone A (**1**) was chromatographically purified (preparative thin-layer chromatography, silica gel) and exhibited properties identical to those of an authentic sample (TLC, HPLC, $[\alpha]_D$, IR, ^1H and ^{13}C NMR, and HRMS).[30]

Scheme 6. Synthesis of Compound **34**[a]



[a] Reagents and conditions: (a) 1.5 equiv of I_2, 3.0 equiv of imidazole, 1.5 equiv of Ph_3P, Et_2O:MeCN (3:1), 0 °C, 0.5 h, 91%; (b) 1.1 equiv of Ph_3P, neat, 100 °C, 2 h, 91%; (c) 1.2 equiv of **47**, 1.2 equiv of NaHMDS, THF, 0 °C, 15 min; then add 1.0 equiv of aldehyde **15**, 0 °C, 15 min, 69% (*Z*:*E* ca. 9:1).

A similar sequence was followed for the synthesis of the 6*S*,7*R*-diastereoisomers **44** and **45** of epothilone A (**1**) from compound **39** (Scheme 5) via intermediates **40** (82% yield from **39**), **42** (85% yield from **40**), and **43** (95% yield from **42**). Epothilone **44** was obtained as the major product, together with its α-epoxide epimer **45** (87% total yield, ca. 2:1 ratio), from olefinic precursor **43** by methyl(trifluoromethyl)dioxirane epoxidation.[28] The epoxide stereochemistry assignments in **44** and **45** are tentative.

c. Total Synthesis of Epothilone B. The first approach to epothilone B (**2**) was designed with the aim of delivering not only the natural substance but also its 12*S*-diastereoisomer **58** (Scheme 7), which in turn required the generation of both 12*Z*- and 12*E*-olefins. To this end, the ylide generated from phosphonium salt **12** with equimolar amounts of NaHMDS in THF was reacted with ketone **11** to afford a mixture of *Z*- and *E*-olefins **48** (ca. 1:1 ratio) in 73% total yield. This mixture was carried through the sequence to the stage of carboxylic acids **52′** and **53′** (see Scheme 7 for details), which were chromatographically separable. Carboxylic acid **53′** (mixture of geometrical isomers) with the wrong stereochemistry at C6 and C7 (6*S*,7*R*) was abandoned at this stage, whereas the mixture of *Z*- and *E*-isomers **52′** with the correct stereochemistry at C6 and C7 (6*R*,7*S*) was taken to the macrolactone stage (compounds **54** and **55**) via hydroxy acid **6′**, by (i) selective desilylation of the C15 hydroxyl group (TBAF, THF, 75% yield) and (ii) Yamaguchi cyclization (37% yield of **54**, plus 40% of **55**).[27] Deprotection of bis(silyl ether) **54** by treatment with CF_3COOH in CH_2Cl_2 afforded diol **4** in 91% yield. Finally, epoxidation of **4** with *m*CPBA in benzene at 3 °C gave epothilone B (**2**) together with its α-epoxide epimer **57** in 66% total yield and

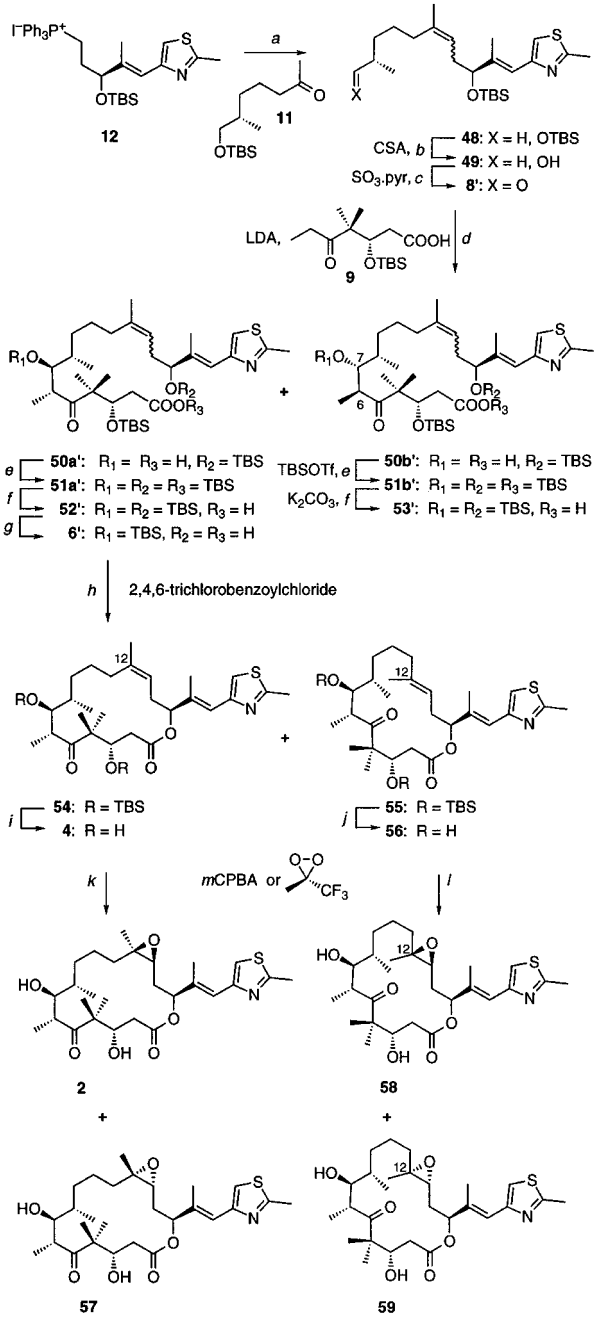
(27) (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989. (b) Mulzer, J.; Mareski, P. A.; Buschmann, J.; Luger, P. *Synthesis* **1992**, 215−228. (c) Nicolaou, K. C.; Patron, A. P.; Ajito, K.; Richter, P. K.; Khatuya, H.; Bertinato, P.; Miller, R. A.; Tomaszewski, M. J. *Chem. Eur. J.* **1996**, *2*, 847−868.

(28) Yang, D.; Wong, M.-K.; Yip, Y.-C. *J. Org. Chem.* **1995**, *60*, 3887−3889.

(29) Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.; Roschangar, F.; Sarabia, F.; Ninkovic, S.; Yang, Z.; Trujillo, J. I. *J. Am. Chem. Soc.* **1997**, *119*, 7960−7973 (preceding paper).

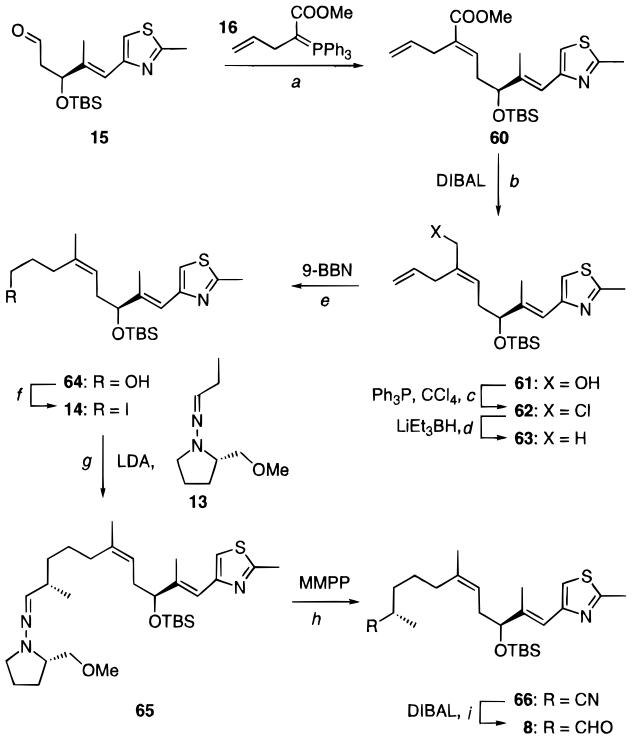
(30) We thank Dr. G. Höfle for samples of natural epothilones A (**1**) and B (**2**).

Scheme 7. Total Synthesis of Epothilone B (**2**) and Analogues[a]



[a] Reagents and conditions: (a) 1.5 equiv of **12**, 1.5 equiv of NaHMDS, THF, 0 °C, 15 min, then add 1.0 equiv of ketone **11**, −20 °C, 12 h, 73% (*Z*:*E* ca. 1:1); (b) 1.0 equiv of CSA portionwise over 1 h, CH_2Cl_2:MeOH (1:1), 0 °C; then 25 °C, 0.5 h, 97%; (c) 2.0 equiv of SO_3·pyr., 10.0 equiv of DMSO, 5.0 equiv of Et_3N, CH_2Cl_2, 25 °C, 0.5 h, 95%; (d) 3.0 equiv of LDA, THF, 0 °C, 15 min; then 1.2 equiv of **9** in THF, −78 → −40 °C, 0.5 h; then 1.0 equiv of **8'** in THF at −78 °C, high yield of **50a'** and its 6*S*,7*R*-diastereoisomer **50b'** (ca. 1:1 ratio); (e) 3.0 equiv of TBSOTf, 5.0 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 2 h; (f) 2.0 equiv of K_2CO_3, MeOH, 25 °C, 15 min, 31% of **52'** and 30% of 6*S*,7*R*-diastereoisomer **53'** from **8'**; (g) 6.0 equiv of TBAF, THF, 25 °C, 8 h, 75%; (h) 1.3 equiv of 2,4,6-trichlorobenzoylchloride, 2.2 equiv of Et_3N, THF, 0 °C, 1 h; then add to a solution of 10.0 equiv of 4-DMAP in toluene (0.002 M based on **6'**), 25 °C, 12 h, 37% of **54**; and 40% of **55**; (i) 20% CF_3COOH (by volume) in CH_2Cl_2 −10 → 0 °C, 1 h, 91%; (j) same as i, 89%; (k) dimethyldioxirane, CH_2Cl_2, −50 °C, 75% (**2**:**57** ca. 5:1 ratio of diastereoisomers) or 1.5 equiv of *m*CPBA, benzene, 3 °C, 2 h, 66% (**2**:**57** ca. 5:1 ratio of diastereoisomers) or methyltrifluoromethyl)dioxirane, MeCN, 0 °C, 85% (**2**:**57** ca. 5:1 ratio of diastereoisomers); (l) 1.5 equiv of *m*CPBA, benzene, 3 °C, 2 h, 73% (**58**:**59** ca. 1:4 ratio of stereoisomers) or methyl(trifluoromethyl)dioxirane, MeCN, 0 °C, 86% (**58**:**59** ca. 1:1 ratio of diastereoisomers).

Scheme 8. Stereoselective Synthesis of Aldehyde **8** for Epothilone B (**2**)[a]



[a] Reagents and conditions: (a) 1.5 equiv of **16**, benzene, reflux 5 h, 95%; (b) 3.0 equiv of DIBAL, THF, −78 °C, 2 h, 98%; (c) 2.0 equiv of Ph_3P, CCl_4, reflux, 24 h, 83%. (d) 2.0 equiv of $LiEt_3BH$, THF, 0 °C, 1 h, 99%; (e) 1.2 equiv of 9-BBN, THF, 0 °C, 2 h, 91%; (f) 1.5 equiv of I_2, 3.0 equiv of imidazole, 1.5 equiv of Ph_3P, Et_2O:MeCN (3:1) 0 °C, 0.5 h, 92%; (g) 1.5 equiv of **13**, 1.5 equiv of LDA, THF, 0 °C, 8 h; then 1.0 equiv of **14** in THF, −100 → −20 °C, 10 h, 70%; (h) 2.5 equiv of monoperoxyphthalic acid, magnesium salt (MMPP), MeOH:phosphate buffer pH7 (1:1), 0 °C, 1 h, 80%; (i) 2.0 equiv of DIBAL, toluene, −78 °C, 1 h, 82%.

ca. 5:1 ratio (^{1}H NMR), while the use of dimethyldioxirane,[31] first reported by Danishefsky,[8a,12] gave **2** and **27** in 75% total yield in the same ratio (ca. 5:1 in favor of **2**). Epoxidation of **4** with methyl(trifluoromethyl)dioxirane[28] in CH_3CN at 0 °C improved the yield of epothilone B (**2**) and its α-epimer **57** to 85% but did not significantly change the diastereoselectivity of the reaction. Epothilone B (**2**) was purified by silica gel preparative layer chromatography and exhibited identical properties (TLC, HPLC, $[\alpha]_D$, IR, ^{1}H and ^{13}C NMR, and HRMS) with those of an authentic sample.[30]

By the same sequence, and in similar yields, the macrocycle **55** containing the *E*-endocyclic double bond (Scheme 7) was converted to the 12*S*-epimeric epothilone B **58** and its α-epoxy epimer **59** via dihydroxy macrocyclic compound **56** [epoxidation with methyl(trifluoromethyl)dioxirane].[28] The stereochemistry of epoxides **58** and **59** was tentatively assigned by comparisons with the corresponding epothilone A epoxides whose stereochemistry was determined by NMR spectroscopy and molecular dynamics computations and molecular modeling as described in the preceding article[29] (see also Supporting Information for ^{1}H−^{1}H NOESY and ^{1}H−^{1}H COSY).

To improve the efficiency of the route to epothilone B (**2**), a more stereoselective total synthesis was devised and executed as follows. Scheme 8 addresses the stereoselective construction of intermediate **8** with the 12*Z*-geometry. Thus, condensation of the stabilized ylide **16** [obtained from 4-bromo-1-butene by (i) phosphonium salt formation, (ii) anion formation with

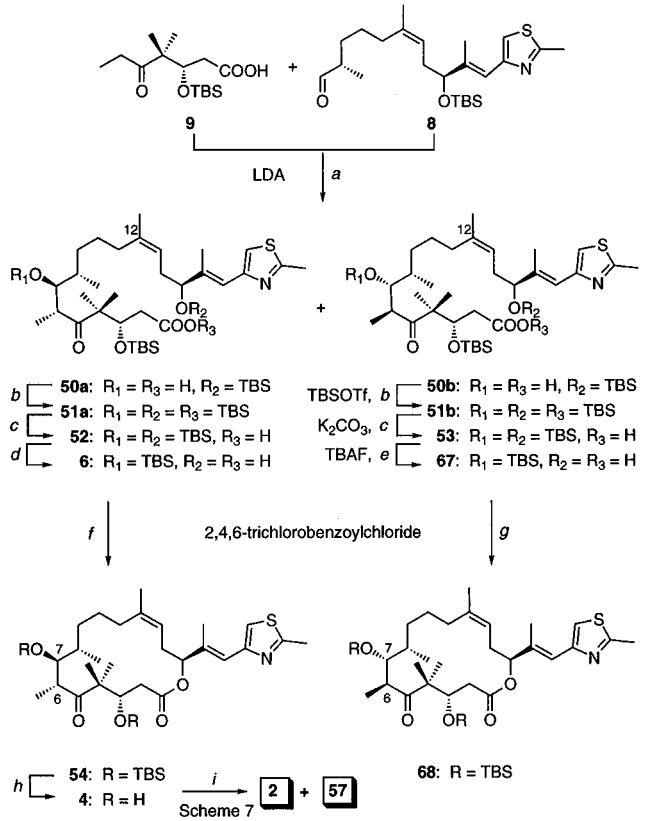
(31) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847−2853.

NaHMDS, and (iii) quenching with MeOC(O)Cl][32] with aldehyde **15** proceeded smoothly to afford olefinic compound **60** in 95% yield and as a single isomer. Reduction of the methyl ester in **60** with DIBAL resulted in the formation of allylic alcohol **61** (98% yield), which was deoxygenated by first reacting it with Ph_3P-CCl_4 and then with $LiEt_3BH$,[33] to afford the desired trisubstituted 12*Z*-olefin **63**, via chloride **62**, in 82% overall yield. The latter compound **63** was regioselectively hydroborated with 9-BBN and converted to the primary alcohol **64** (91%), which was then treated with I_2-imidazole$-Ph_3P$ to afford iodide **14** (92% yield). This iodide was then used in an Enders alkylation reaction with SAMP hydrazone **13** to give compound **65** as a single isomer (^{1}H NMR) and in 70% yield. Treatment of hydrazone **65** with monoperoxyphthalic acid magnesium salt (MMPP) in MeOH:phosphate pH 7 buffer (1:1)[20c,34] resulted in clean conversion to nitrile **66** (80% yield), which formed aldehyde **8** (82% yield) upon exposure to DIBAL at −78 °C in toluene solution.

The homogeneous aldehyde **8** was converted to epothilone B (**2**) by the sequence depicted in Scheme 9. Thus, condensation of the dianion of **9** with **8** as before (Scheme 7), produced two diastereoisomers, **50a** (6*R*,7*S* stereoisomer) and **50b** (6*S*,7*R* stereoisomer), in high yield and in ca. 1.3:1.0 ratio (**50a**:**50b**). This mixture was carried through the indicated sequence to carboxylic acids **52** (32% overall yield from **8**) and **53** (28% overall yield from **8**), which were separated by silica gel preparative layer or flash column chromatography and taken individually further along the sequence as described for the corresponding stereoisomeric mixtures shown in Scheme 7. Thus, **52** was selectively deprotected with TBAF to afford hydroxy acid **6** (73% yield), which was then cyclized to macrolactone **54** in 77% yield by the Yamaguchi method.[27] The conversion of **54** to epothilone B (**2**) and its α-epoxide epimer **57** has already been described above (Scheme 7).

In an effort to improve the diastereoselectivity of the aldol condensation between C1−C6 and C7−C15 fragments, the following chemistry was explored (Scheme 10). Thus, ketone **69** [prepared from ketone **20** (Scheme 2) by selective reduction, followed by silylation] was converted to its enolate with stoichiometric amounts of LDA and reacted with aldehyde **8** (*Z*-isomer), affording coupling products **70** and **71** in 85% total yield and ca. 3:1 ratio, with the desired compound **70** predominating as proven by its conversion to **52** and epothilone B (**2**). Thus, chromatographic purification (silica gel, 20% ether in hexanes) led to **70**, which was efficiently transformed to the previously synthesized intermediate **52** (Scheme 9) as follows. The newly generated hydroxyl group in **70** was silylated with TBSOTf-2,6-lutidine to furnish **72** (96% yield), which was then selectively desilylated at the primary position by the mild action of camphorsulfonic acid (CSA) in $MeOH-CH_2Cl_2$, leading to **73** (85%). Finally, sequential oxidation of the primary alcohol with $(COCl)_2-$DMSO$-Et_3N$ (95% yield) and $NaClO_2-NaH_2PO_4$ (90% yield) led to hydroxy acid **52** via aldehyde **74**. The conversion of **52** to **2** has already been described above (Scheme 9). This sequence represents a stereoselective and highly efficient synthesis of epothilone B (**2**) and opens the way for the construction of further analogues within this important family of microtubule binding agents.

Scheme 9. First Stereoselective Total Synthesis of Epothilone B (**2**)[a]



[a] Reagents and conditions: (a) 3.0 equiv of LDA, THF, 0 °C, 15 min; then 1.2 equiv of **9** in THF, −78 → −40 °C, 0.5 h, then 1.0 equiv of **8** in THF at −78 °C, high yield of **50a** and 6*S*,7*R*-diastereoisomer **50b** (ca. 1.3:1.0 ratio of diastereoisomers); (b) 3.0 equiv of TBSOTf, 5.0 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 2 h; (c) 2.0 equiv of K_2CO_3, MeOH, 25 °C, 15 min, 32% of **52** and 28% of 6*S*,7*R*-diastereoisomer **53** from **8**; (d) 6.0 equiv of TBAF, THF, 25 °C, 8 h, 73%; (e) same as d, 71%; (f) 5.0 equiv of 2,4,6-trichlorobenzoyl chloride, 6.0 equiv of Et_3N, THF, 25 °C, 15 min, then add to a solution of 10.0 equiv of 4-DMAP in toluene (0.002 M based on **6**), 25 °C, 12 h, 77%; (g) same as f, 76%; (h) 20% CF_3COOH (by volume) in CH_2Cl_2, 0 °C, 1 h, 91%; (i) see Scheme 7.

4. Conclusion

The chemistry described in this article defines a concise strategy for the construction of epothilones A (**1**) and B (**2**) based on a macrolactonization strategy, and which enjoys convergency and flexibility for structural diversity. It is expected that the numerous intermediates and structural analogues included herein, as well as several new ones currently under construction, will play a crucial role in elucidating structure−activity relationships of these new substances and in determining their relevance to cancer chemotherapy. Indeed, independent reports from the Danishefsky[8b,12] and from these laboratories[13] demonstrated impressive tubulin binding affinities and cytotoxicities for some of these compounds. Further details on the biological actions of these and other compounds will be published elsewhere.

Experimental Section

General Techniques. See preceding paper.[29]

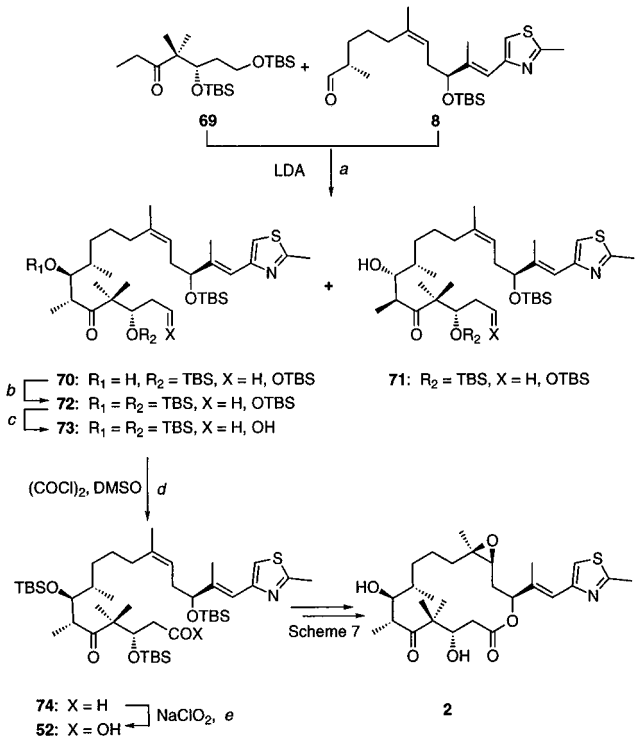
Alcohol 18. Allylboration of Keto Aldehyde 17. Aldehyde **17**[16] (16.0 g, 0.125 mol) was dissolved in ether (400 mL) and cooled to −100 °C. To this solution was added (+)-diisopinocampheylallylborane (800 mL, 0.15 M in pentane, 0.125 mol, 1.0 equiv) by cannulation during 45 min. [(+)-Diisopinocampheylallylborane in pentane was typically prepared by the adaptation of the original method reported by Brown.[14] Allyllmagnesium bromide (66.0 mL, 1 M solution in ether,

(32) (a) Marshall, J. A.; DeHoff, B. S.; Cleary, D. G. *J. Org. Chem.* **1986**, *51*, 1735−1741. (b) Bestmann, H. J. *Angew. Chem., Int. Ed. Engl.* **1965**, 645−660.

(33) Heissler, D.; Jenn, T.; Nagano, H. *Tetrahedron Lett.* **1991**, *32*, 7587−7590.

(34) Enders, D.; Backhaus, D.; Runsink, J. *Tetrahedron* **1996**, *52*, 1503−1528.

Scheme 10. Second Stereoselective Synthesis of Epothilone B (**2**)[a]



[a] Reagents and conditions: (a) 1.2 equiv of LDA, THF, 0 °C, 15 min; then 1.2 equiv of **69** in THF, −78 → −40 °C, 1 h; then 1.0 equiv of **8** in THF at −78 °C, 85% of **70** and 6*S*,7*R*-diastereoisomer **71** (ca. 3:1 ratio); (b) 1.2 equiv of TBSOTf, 2.0 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 2 h, 96%; (c) 1.0 equiv of CSA portionwise over 1 h, CH_2Cl_2:MeOH (1:1), 0 → 25 °C, 0.5 h, 85%; (d) 2.0 equiv of $(COCl)_2$, 4.0 equiv of DMSO, 6.0 equiv of Et_3N, CH_2Cl_2, −78 → 0 °C, 1.5 h, 95%; (e) 3.0 equiv of $NaClO_2$, 4.0 equiv of 2-methyl-2-butene, 1.5 equiv of NaH_2PO_4, ^{t}BuOH:H_2O (5:1), 25 °C, 2 h, 90%.

0.066 mol) was added dropwise to a well-stirred solution of (−)-*B*-methoxydiisopinocampheylborane (20.9 g, 0.066 mol) in ether (400 mL) at 0 °C. After the completion of the addition, the reaction mixture was stirred at room temperature for 1 h and the solvent was removed under reduced pressure. The residue was extracted with pentane (3 × 400 mL) under argon, and stirring was discontinued to allow precipitation of the magnesium salts. The clear pentane solution was cannulated into another flask using a double-ended needle through a Kramer filter and used without further purification. After the addition was complete, the mixture was stirred at the same temperature for 30 min. Methanol (20 mL) was added at −100 °C, and the reaction mixture was allowed to reach room temperature. To this solution was added saturated aqueous $NaHCO_3$ solution (200 mL), followed by H_2O_2 (80 mL of 50% solution in H_2O), and the reaction mixture was allowed to stir at room temperature for 12 h. The reaction mixture was extracted with EtOAc (3 × 200 mL), and the organic extracts were combined, washed with saturated aqueous NH_4Cl solution (100 mL), and dried (Na_2SO_4). Evaporation of the solvents followed by flash column chromatography (silica gel, 3% acetone in CH_2Cl_2) resulted in pure alcohol **18** (14.6 g, 74%). **18**: colorless oil; R_f = 0.20 (silica gel, 3% acetone in CH_2Cl_2); $[\alpha]^{22}_D$ −4.0 (*c* 1.5, $CHCl_3$); IR (thin film) ν_{max} 3492, 2976, 2939, 1699, 1641, 1469, 1379, 1087, 1020, 990, 973, 914 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.85−5.80 (m, 1 H, C*H*═CH_2), 5.11−5.07 (m, 2 H, CH═CH_2), 3.73 (dd, J = 10.5, 2.0 Hz, 1 H, C*H*OH), 2.54−2.40 (m, 3 H), 2.25−2.18 (m, 1 H), 2.03−1.96 (m, 1 H), 1.14 (s, 3 H, $C(CH_3)_2$), 1.10 (s, 3 H, $C(CH_3)_2$), 0.99 (t, J = 7.0 Hz, 3 H, C$H_3$$CH_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 217.2, 135.6, 117.7, 75.5, 51.2, 36.4, 31.3, 21.8, 19.5, 7.8; FAB HRMS (NBA/NaI) *m/e* 193.1200, M + Na^+ calcd for $C_{10}H_{18}O_2$ 193.1204.

Ketone 19. Silylation of Alcohol 18. Alcohol **18** (11.0 g, 0.0647 mol) was dissolved in CH_2Cl_2 (200 mL), the solution was cooled at −78 °C, and 2,6-lutidine (10.5 mL, 0.0906 mol, 1.4 equiv) was added. After being stirred for 5 min at that temperature, *tert*-butyldimethylsilyl triflate (19.3 mL, 0.0841 mol, 1.3 equiv) was added dropwise and the reaction mixture was allowed to stir at −78 °C for 45 min, after which time no starting material was detected by TLC. Saturated aqueous NH_4Cl solution (30 mL) was added, and the reaction mixture was allowed to warm to room temperature. The organic phase was separated, and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and filtered through Celite, and the solvents were removed under reduced pressure. Purification by flash column chromatography (silica gel, 2 → 10% ether in hexanes) gave pure **19** (18.0 g, 98%): R_f = 0.75 (silica gel, 20% ether in hexanes); $[\alpha]^{22}_D$ +2.6 (*c* 0.8, $CHCl_3$); IR (thin film) ν_{max} 2935, 1705, 1467, 1362, 1254, 1089, 911, 836, 775 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.78−5.71 (m, 1 H, C*H*═CH_2), 5.01−4.94 (m, 2 H, CH═CH_2), 3.97 (dd, J = 6.2, 5.2 Hz, 1 H, CHOSi), 2.54 (dq, J = 14.3, 7.2 Hz, 1 H, C$H_2$$CH_3$), 2.44 (dq, J = 14.2, 7.1 Hz, 1 H, CH_2-CH_3), 2.21−2.16 (m, 1 H, CH_2CH═CH_2), 2.14−2.08 (m, 1 H, CH_2-CH═CH_2), 1.10 (s, 3 H, $C(CH_3)_2$), 1.07 (s, 3 H, $C(CH_3)_2$), 0.98 (t, J = 7.1 Hz, 3 H, C$H_3$$CH_2$), 0.87 (s, 9 H, $SiC(CH_3)_3$), 0.05 (s, 3 H, Si-$(CH_3)_2$), 0.01 (s, 3 H, $Si(CH_3)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 215.9, 136.2, 116.5, 76.7, 52.9, 39.0, 31.9, 26.0, 22.4, 20.1, 18.2, 7.7, −3.6, −4.4.

Keto Aldehyde 20. Ozonolysis of Ketone 19. Alkene **19** (2.84 g, 10 mmol) was dissolved in CH_2Cl_2 (25 mL, 0.4 M), and the solution was cooled to −78 °C. Oxygen was bubbled through for 2 min, after which time ozone was passed through until the reaction mixture adopted a blue color (ca. 30 min). The solution was then purged with oxygen for 2 min at −78 °C (disappearance of blue color) and Ph_3P (3.16 g, 12.0 mmol, 1.2 equiv) was added. The cooling bath was removed, and the reaction mixture was allowed to reach room temperature and stirred for an additional 1 h. The solvent was removed under reduced pressure, and the mixture was purified by flash column chromatography (silica gel, 25% ether in hexanes) to provide pure keto aldehyde **20** (2.57 g, 90%): R_f = 0.45 (silica gel, 20% ether in hexanes); $[\alpha]^{22}_D$ −1.9 (*c* 4.0, $CHCl_3$); IR (thin film) ν_{max} 2935, 2858, 1707, 1467, 1388, 1255, 1093, 1004, 837, 777 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.78 (dd, J = 2.1, 2.0 Hz, CHO), 4.55 (dd, J = 6.0, 4.5 Hz, 1 H, CHOSi), 2.59−2.44 (m, 4 H, C$H_2$$CH_3$, C$H_2$CH═O), 1.13 (s, 3 H, $C(CH_3)_2$), 1.09 (s, 3 H, $C(CH_3)_2$), 1.00 (t, J = 7.0 Hz, 3 H, C$H_3$$CH_2$), 0.85 (s, 9 H, $(CH_3)_3$C), 0.06 (s, 3 H, $Si(CH_3)_2$), 0.03 (s, 3 H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 215.3, 200.9, 71.3, 52.3, 48.5, 31.9, 25.8, 21.3, 20.4, 18.0, 7.5, −4.4, −4.9; FAB HRMS (NBA/NaI) *m/e* 309.1854, M + Na^+ calcd for $C_{15}H_{30}O_3Si$ 309.1862.

Keto Acid 9. Oxidation of Keto Aldehyde 20. Aldehyde **20** (2.86 g, 10 mmol), ^{t}BuOH (50 mL, 0.2 M), isobutylene (20 mL, 2 M solution in THF, 40 mmol, 4.0 equiv), H_2O (10 mL), $NaClO_2$ (2.71 g, 30.0 mmol, 3.0 equiv), and NaH_2PO_4 (1.80 g, 15.0 mmol, 1.5 equiv) were combined and stirred at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure, and the residue was subjected to flash column chromatography (silica gel, 50% ether in hexanes) to produce pure keto acid **9** (2.81 g, 93%): R_f = 0.12 (silica gel, 20% ether in hexanes); $[\alpha]^{22}_D$ +16.1 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 2934, 2858, 1710, 1467, 1254, 1093, 834 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.46 (dd, J = 7.0, 3.6 Hz, 1 H, CHOSi), 2.64−2.34 (m, 3 H, CH_2-CH_3, CH_2COOH), 2.32 (q, J = 7.0 Hz, 1 H, C$H_2$$CH_3$), 1.13 (s, 3 H, $C(CH_3)_2$), 1.11 (s, 3 H, $C(CH_3)_2$), 0.99 (t, J = 7.0 Hz, 3 H, C$H_3$$CH_2$), 0.83 (s, 9 H, $(CH_3)_3$C), 0.04 (s, 3 H, $Si(CH_3)_2$), 0.03 (s, 3 H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 215.1, 178.2, 73.4, 52.4, 39.2, 31.6, 25.8, 20.8, 20.5, 18.0, 7.6, −4.5, −5.0; FAB HRMS (NBA) *m/e* 303.1996, M + H^+ calcd for $C_{15}H_{30}O_3Si$ 303.1992.

Aldehyde 22. Reduction of Ester 21. Ethyl ester **21**[18] (52.5 g, 0.306 mol) was dissolved in CH_2Cl_2 (1 L) and cooled to −78 °C. DIBAL (490.0 mL, 1 M solution in CH_2Cl_2, 0.4896 mol, 1.6 equiv) was added dropwise via a cannula while the temperature of the reaction mixture was maintained at −78 °C. After the addition was complete, the reaction mixture was stirred at the same temperature until its completion was verified by TLC (ca. 1 h). Methanol (100 mL) was added at −78 °C and was followed by addition of EtOAc (1 L) and saturated aqueous NH_4Cl solution (300 mL). The quenched reaction mixture was allowed to warm to room temperature and stirred for 12 h. The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 200 mL). The combined organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash column chromatography (silica gel, 10 → 90% ether in hexanes) furnished the desired aldehyde **22** (33.6 g, 90%): R_f =

0.68 (silica gel, ether); IR (thin film) ν_{max} 3095, 2828, 1695, 1485, 1437, 1378, 1334, 1178, 1129, 1011 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.96 (s, 1 H, CHO), 8.0 (s, 1 H, SCH═C), 2.77 (s, 3 H, N═C(S)-CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 184.2, 167.5, 154.8, 128.0, 19.1; FAB HRMS (NBA/NaI) *m/e* 149.9992, M + Na$^+$ calcd for C_5H_5-NOS 149.9990.

Aldehyde 23. Aromatic aldehyde **22** (31.1 g, 0.245 mol) was dissolved in benzene (500 mL), and 2-(triphenylphosphoranilidenyl)-propionaldehyde (90.0 g, 0.282 mol, 1.15 equiv) was added. The reaction mixture was heated at reflux until the reaction was complete as judged by TLC (ca. 2 h). Evaporation of the solvent under reduced pressure followed by flash column chromatography (10 → 90% ether in hexanes) produced the desired aldehyde **23** (40.08 g, 98%): R_f = 0.78 (silica gel, ether); IR (thin film) ν_{max} 3089, 1675, 1624, 1190, 1141, 1029, 947.6, 881 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.57 (s, 1 H, CHO), 7.46 (s, 1 H), 7.26 (s, 1 H), 2.77 (s, 3 H, N═C(S)CH_3), 2.20 (s, 3 H, CH═C(CHO)C*H*$_3$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 195.3, 165.7, 151.9, 140.9, 138.2, 122.6, 19.2, 10.9; FAB HRMS (NBA) *m/e* 168.0481, M + H$^+$ calcd for C_8H_9NOS 168.0483.

Alcohol 24. Allylboration of Aldehyde 23. Aldehyde **23** (20.0 g, 0.120 mol) was dissolved in anhydrous ether (400 mL), and the solution was cooled to −100 °C. (+)-Diisopinocampheylallylborane (1.5 equiv in pentane, prepared from 60.0 g of (−)-Ipc$_2$BOMe and 1.0 equiv of allylmagnesium bromide according to the method described for the synthesis of alcohol **18**),[14] was added dropwise under vigorous stirring, and the reaction mixture was allowed to stir for 1 h at the same temperature. Methanol (40 mL) was added at −100 °C, and the reaction mixture was allowed to warm to room temperature. Aminoethanol (72.43 mL, 1.2 mol, 10.0 equiv) was added, and stirring was continued for 15 h. The workup procedure was completed by the addition of saturated aqueous NH_4Cl solution (200 mL), extraction with EtOAc (4 × 100 mL), and drying of the combined organic layers with $MgSO_4$. Filtration followed by evaporation of the solvents under reduced pressure and flash column chromatography (silica gel, 35% ether in hexanes for several fractions until all the boron complexes were removed; then 70% ether in hexanes) provided alcohol **24** (24.09 g, 96%): R_f = 0.37 (60% ether in hexanes); $[\alpha]^{22}_D$ −20.2 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 3357, 2923, 1642, 1505, 1437, 1322, 1186, 1018, 914, 878 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.81 (s, 1 H, SCH═C), 6.46 (s, 1 H, C*H*═CCH_3), 5.87−5.79 (m, 1 H, C*H*═CH_2), 5.02 (d, *J* = 17.1 Hz, 1 H, CH═C*H*$_2$), 4.97 (d, *J* = 10.3 Hz, 1 H, CH═C*H*$_2$), 4.12 (dd, *J* = 7.8, 5.0 Hz, 1 H, C*H*OH), 3.8 (bs, 1 H, OH), 2.59 (s, 3 H, N═C(S)CH_3), 2.31 (dd, *J* = 7.0, 6.5 Hz, 2 H, CH_2═CHC*H*$_2$), 1.91 (s, 3 H, CH═CC*H*$_3$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 164.5, 152.5, 141.8, 134.8, 118.7, 117.1, 115.1, 76.3, 39.8, 18.8, 14.1; FAB HRMS (NBA) *m/e* 210.0956, M + H$^+$ calcd for $C_{11}H_{15}NOS$ 210.0953.

Compound 25. Silylation of Alcohol 24. Alcohol **24** (7.0 g, 0.033 mol) was dissolved in DMF (35 mL, 1.0 M), the solution was cooled to 0 °C, and imidazole (3.5 g, 0.050 mol, 1.5 equiv) was added. After stirring for 5 min, *tert*-butyldimethylsilyl chloride (6.02 g, 0.040 mol, 1.2 equiv) was added portionwise and the reaction mixture was allowed to stir at 0 °C for 45 min, and then at 25 °C for 2.5 h, after which time no starting alcohol was detected by TLC. Methanol (2 mL) was added at 0 °C, and the solvent was removed under reduced pressure. Ether (100 mL) was added followed by saturated aqueous NH_4Cl solution (20 mL), the organic phase was separated, and the aqueous phase was extracted with ether (2 × 20 mL). The combined organic solution was dried ($MgSO_4$) and filtered over Celite, and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, 10 → 20% ether in hexanes) provided pure **25** (10.8 g, 99%): R_f = 0.70 (40% ether in hexanes); $[\alpha]^{22}_D$ +1.39 (*c* 3.0, $CHCl_3$); IR (thin film) ν_{max} 2931, 2060, 1496, 1460, 1249, 1173, 1073, 908, 837, 779 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.91 (s, 1 H, SCH═C), 6.45 (s, 1 H, C*H*═CCH_3), 5.80−5.75 (m, 1 H, C*H*═CH_2), 5.03 (ddd, *J* = 17.1, 3.5, 1.5 Hz, 1 H, CH═C*H*$_2$), 4.99 (ddd, *J* = 10.2, 2.1, 0.9 Hz, 1 H, CH═C*H*$_2$), 4.14 (dd, *J* = 6.6, 6.1 Hz, 1 H, C*H*OH), 2.69 (s, 3 H, N═C-(S)CH_3), 2.37−2.32 (m, 1 H, CH_2═CHC*H*$_2$), 2.31−2.25 (m, 1 H, CH_2═CHC*H*$_2$), 1.99 (s, 3 H, CH═CC*H*$_3$), 0.88 (s, 9 H, SiC$(CH_3)_3$), 0.05 (s, 3 H, Si$(CH_3)_2$), 0.00 (s, 3 H, Si$(CH_3)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 165.2, 153.9, 142.9, 136.2, 119.7, 117.4, 115.9, 79.3, 42.1, 26.7, 20.1, 19.0, 14.8, −3.8, −4.1; FAB HRMS (NBA) *m/e* 324.1804, M + H$^+$ calcd for $C_{17}H_{29}NOSSi$ 324.1817.

Aldehyde 15. Dihydroxylation of Olefin 25 and 1,2 Glycol Cleavage. Olefin **25** (16.7 g, 51.6 mmol) was dissolved in THF/^{t}-BuOH (1:1, 500 mL) and H_2O (50 mL). 4-Methylmorpholine *N*-oxide (NMO) (7.3 g, 61.9 mmol, 1.2 equiv) was added at 0 °C, followed by OsO_4 (5.2 mL, solution in ^{t}BuOH 1.0 mol %, 2.5% by weight). The mixture was vigorously stirred for 2.5 h at 0 °C and then for 12 h at 25 °C. After completion of the reaction, Na_2SO_3 (5.0 g) was added at 0 °C, followed by H_2O (100 mL). Stirring was continued for another 30 min, and then ether (1 L) was added, followed by saturated aqueous NaCl solution (2 × 100 mL). The organic phase was separated, and the aqueous phase was extracted with ether (2 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and filtered, and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, ether → EtOAc) provided 17.54 g (95%) of the expected 1,2-diol as a 1:1 mixture of diastereoisomers: R_f = 0.55 (silica gel, EtOAc); IR (thin film) ν_{max} 3380, 2931, 2856, 1656, 1505, 1465, 1460, 1254, 1187, 1073, 908, 837, 777 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.90 and 6.88 (singlets, 1 H total, SCH═C), 6.52 and 6.47 (singlets, 1 H total, C*H*═CCH_3), 4.44−4.39 (m, 1 H), 3.95−3.84 (m, 1 H), 3.81−3.72 and 3.63−3.34 (m, 4 H total), 2.66 and 2.65 (singlets, 3 H total, N═C(S)CH_3), 1.96 and 1.95 (singlets, 3 H total), 1.82−1.75 and 1.69−1.56 (m, 2 H total), 0.87 and 0.86 (singlets, 9 H total, SiC$(CH_3)_3$), 0.08 and −0.01 (singlets, 3 H total, Si$(CH_3)_2$), 0.07 and 0.10 (singlets, 3 H total, Si$(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 164.6, 164.5, 152.8, 152.4, 141.6, 141.5, 119.4, 118.4, 115.3, 115.2, 78.0, 75.4, 70.4, 68.8, 66.8, 66.5, 38.9, 38.7, 25.7, 19.0, 18.9, 18.0, 17.9, 14.6, 13.5, −4.6, −4.8, −5.2, −5.4; FAB HRMS (NBA/NaI) *m/e* 380.1699, M + Na$^+$ calcd for $C_{17}H_{31}NO_3SSi$ 380.1692.

The diol obtained from **25** as described above (5.2 g, 14.5 mmol) was dissolved in EtOAc (150 mL) and cooled to 0 °C. $Pb(OAc)_4$ (8.1 g, 95% purity, 18.3 mmol, 1.2 equiv) was then added portionwise over 10 min, and the mixture was vigorously stirred for 15 min at 0 °C. After completion of the reaction, the mixture was filtered through silica gel and washed with 60% ether in hexanes. The solvents were then removed under reduced pressure providing pure aldehyde **15** (4.7 g, 98%): R_f = 0.76 (silica gel, 60% ether in hexanes); $[\alpha]^{22}_D$ −20.3 (*c* 1.4, $CHCl_3$); IR (thin film) ν_{max} 2931, 2856, 1726, 1504, 1466, 1389, 1254, 1182, 1087, 999, 839, 784 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.69 (dd, *J* = 2.7, 2.2 Hz, 1 H, CHO), 6.86 (s, 1 H, SCH═C), 6.48 (s, 1 H, C*H*═CCH_3), 4.60 (dd, *J* = 8.2, 3.9 Hz, 1 H, CHOSi), 2.64 (ddd, *J* = 15.5, 8.3, 2.9 Hz, 1 H, CHOC*H*$_2$), 2.59 (s, 3 H, N═C(S)CH_3), 2.41 (ddd, *J* = 15.5, 4.0, 2.0 Hz, 1 H, CHOC*H*$_2$), 1.95 (s, 3 H, CH═CC*H*$_3$), 0.79 (s, 9 H, SiC$(CH_3)_3$), 0.00 (s, 3 H, Si$(CH_3)_2$), −0.06 (s, 3 H, Si$(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 201.0, 164.5, 152.4, 140.3, 119.0, 115.8, 73.7, 49.9, 25.6, 18.9, 17.9, 13.9, −4.8, −5.4; FAB HRMS (NBA) *m/e* 326.1615, M + H$^+$ calcd for $C_{16}H_{27}NO_2SSi$ 326.1610.

Alcohol 26. Reduction of Aldehyde 15. A solution of aldehyde **15** (440 mg, 1.35 mmol) in MeOH (13 mL) was treated with $NaBH_4$ (74 mg, 2.0 mmol, 1.5 equiv) at 0 °C for 15 min. The solution was diluted with ether (100 mL), and then saturated aqueous NH_4Cl solution (5 mL) was carefully added. The organic phase was washed with brine (10 mL), dried ($MgSO_4$), and concentrated. Flash column chromatography (silica gel, 60% ether in hexanes) gave alcohol **26** (425 mg, 96%) as a colorless oil. **26**: R_f = 0.52 (silica gel, 60% ether in hexanes); $[\alpha]^{22}_D$ −29.4 (*c* 0.8, $CHCl_3$); IR (thin film) ν_{max} 3362, 2950, 2856, 1656, 1505, 1466, 1362, 1254, 1186, 1075, 839, 777 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.86 (s, 1 H, SCH═C), 6.40 (s, 1 H, C*H*═CCH_3), 4.30 (dd, *J* = 7.6, 5.3 Hz, 1 H, CHOSi), 3.69−3.59 (m, 2 H, C*H*$_2$OH), 3.15 (s, 1 H, OH), 2.61 (s, 3 H, N═C(S)CH_3), 1.92 (s, 3 H, CH═CC*H*$_3$), 1.82−1.76 (m, 1 H, C*H*$_2$CH$_2$OH), 1.73−1.67 (m, 1 H, C*H*$_2$CH$_2$OH), 0.82 (s, 9 H, SiC$(CH_3)_3$), 0.02 (s, 3 H, Si$(CH_3)_2$), −0.05 (s, 3 H, Si-$(CH_3)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 164.3, 152.7, 141.6, 118.5, 115.1, 76.6, 59.6, 38.3, 25.8, 18.9, 18.0, 14.0, −4.8, −5.4; FAB HRMS (NBA/CsI) *m/e* 460.0727, M + Cs$^+$ calcd for $C_{16}H_{29}NO_2SSi$ 460.0743.

Iodide 27. Iodination of Alcohol 26. A solution of alcohol **26** (14.0 g, 42.7 mmol) in ether: MeCN (3:1, 250 mL) was cooled to 0 °C. Imidazole (8.7 g, 128.1 mmol, 3.0 equiv), Ph_3P (16.8 g, 64.1 mmol, 1.5 equiv), and iodine (16.3 g, 64.1 mmol, 1.5 equiv) were sequentially added, and the mixture was stirred for 0.5 h at 0 °C. A saturated aqueous solution of $Na_2S_2O_3$ (50 mL) was added, followed by the addition of ether (600 mL). The organic phase was washed with brine (50 mL) and dried ($MgSO_4$), and the solvents were removed under

vacuum. Flash column chromatography (silica gel, 15% ether in hexanes) gave pure iodide **27** (16.6 g, 89%) as a colorless oil: R_f = 0.40 (silica gel, 10% ether in hexanes); $[\alpha]^{22}_D$ +11.0 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 2951, 2856, 1503, 1466, 1253, 1179, 1081, 936, 884, 836, 777 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.90 (s, 1 H, SCH=C), 6.53 (s, 1 H, C*H*=CCH_3), 4.19 (dd, *J* = 7.7, 4.5 Hz, 1 H, CHOSi), 3.18 (t, *J* = 7.3 Hz, 2 H, CH_2I), 2.67 (s, 3 H, N=C(S)CH_3), 2.10−2.05 (m, 1 H, C*H*$_2$$CH_2I$), 2.01−1.95 (m, 1 H, C*H*$_2$$CH_2I$), 1.99 (s, 3 H, CH=CC*H*$_3$), 0.87 (s, 9 H, SiC$(CH_3)_3$), 0.09 (s, 3 H, Si$(CH_3)_2$), 0.00 (s, 3 H, Si$(CH_3)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 164.4, 152.7, 140.9, 119.3, 115.4, 78.0, 40.2, 25.8, 19.2, 18.1, 13.9, 3.1, −4.6, −5.0; FAB HRMS (NBA) *m*/*e* 438.0768, M + H^+ calcd for $C_{16}H_{28}INOSSi$ 438.0784.

Phosphonium Salt 12. A mixture of iodide **27** (16.5 g, 37.7 mmol) and Ph_3P (10.9 g, 41.5 mmol, 1.1 equiv) was heated neat at 100 °C for 2 h. Purification by flash column chromatography (silica gel, CH_2Cl_2; then 7% MeOH in CH_2Cl_2) provided phosphonium salt **12** (25.9 g, 98%) as a white solid: R_f = 0.50 (silica gel, 7% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ +3.7 (*c* 0.7, $CHCl_3$); IR (thin film) ν_{max} 2951, 2856, 1503, 1466, 1253, 1179, 1081, 936, 884, 836, 777 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.78−7.28 (m, 15 H, aromatic), 6.97 (s, 1 H, SCH=C), 6.57 (s, 1 H, C*H*=CCH_3), 4.48 (dd, *J* = 6.3, 4.8 Hz, 1 H, CHOSi), 3.72−3.65 (m, 1 H, CH_2P), 3.31−3.25 (m, 1 H, CH_2P), 2.61 (s, 3 H, N=C(S)CH_3), 1.91 (s, 3 H, CH=CC*H*$_3$), 1.95−1.86 (m, 1 H, C*H*$_2$$CH_2P$), 1.82−1.74 (m, 1 H, C*H*$_2$$CH_2$ P), 0.83 (s, 9 H, SiC$(CH_3)_3$), 0.07 (s, 3 H, Si$(CH_3)_2$), −0.02 (s, 3 H, Si$(CH_3)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 164.4, 152.3, 139.4, 135.1, 133.3, 133.2, 130.5, 130.4, 128.1, 119.8, 117.9, 117.3, 116.5, 76.0, 28.9, 25.7, 19.1, 18.4, 17.9, 14.5, −4.8.

Hydrazone 28. Alkylation of Hydrazone 13. Hydrazone **13**[15] (20.0 g, 117.0 mmol, 1.0 equiv), dissolved in THF (80 mL), was added to a freshly prepared solution of LDA [19.75 mL of diisopropylamine (141.0 mmol, 1.2 equiv) was added to a solution of 88.1 mL of 1.6 M solution of *n*-BuLi in hexanes (141 mmol, 1.2 equiv) in 160 mL of THF at 0 °C] at 0 °C. After the mixture was stirred at this temperature for 8 h, the resulting yellow solution was cooled to −100 °C and a solution of 4-iodo-1-(benzyloxy)butane (36.0 g, 124.0 mmol, 1.2 equiv) in THF (40 mL) was added dropwise over a period of 30 min. The mixture was allowed to warm to room temperature over 8 h and was then poured into saturated aqueous NH_4Cl solution (40 mL) and extracted with ether (3 × 200 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated. Purification by flash column chromatography on silica gel (20% ether in hexanes) provided hydrazone **28** as a yellow oil (35.8 g, 92%, de > 98% by ^1H NMR): R_f = 0.45 (silica gel, 50% ether in hexanes); $[\alpha]^{22}_D$ −55.0 (*c* 1.2, $CHCl_3$); IR (thin film) ν_{max} 2929, 2862, 1603, 1455, 1362, 1198, 1108, 737, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (s, 5 H, Ph), 6.48 (d, *J* = 6.5 Hz, 1 H, CH=NN), 4.46 (s, 2 H, CH_2Ph), 3.54 (dd, *J* = 9.0, 3.8 Hz, 1 H, C*H*$_2$$OCH_3$), 3.44 (t, *J* = 6.5 Hz, 2 H, CH_2OBn), 3.40 (dd, *J* = 9.0, 6.8 Hz, 1 H, C*H*$_2$$OCH_3$), 3.33 (s, 3 H, OCH_3), 2.65 (m, 1 H, C*H*CH_2OCH_3), 2.29 (m, 1 H, C*H*(CH_3)C=N), 1.94−1.76 (m, 4 H), 1.61 (m, 2 H), 1.45−1.36 (m, 6 H), 1.01 (d, *J* = 6.8 Hz, 3 H, CHC*H*$_3$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 144.6, 138.6, 128.2, 127.5, 127.3, 74.7, 72.7, 70.2, 63.4, 59.1, 50.4, 37.0, 35.2, 29.7, 26.4, 23.7, 22.0, 18.9; FAB HRMS (NBA) *m*/*e* 333.2552, M + H^+ calcd for $C_{20}H_{32}N_2O_2$ 333.2542.

Aldehyde 29. Cleavage of Hydrazone 28. Procedure A: A solution of hydrazone **28** (13.0 g, 39.1 mmol) in CH_2Cl_2 (50 mL) was treated with ozone at −78 °C until the solution turned blue-green. The solution was purged with oxygen for 2 min at −78 °C, allowed to warm to room temperature, and then concentrated. The crude mixture so obtained was purified by flash column chromatography (silica gel, 10% ether in hexanes) to give aldehyde **29** (6.6 g, 77%) as a colorless oil. **Procedure B:** A solution of hydrazone **28** (30 g, 90.3 mmol) in MeI (100 mL) was heated at 60 °C. After 5 h, the reaction was complete (TLC) and the mixture was concentrated. The resulting crude product was suspended in *n*-pentane (360 mL) and was treated with 3 N aqueous HCl (360 mL). The two-phase system was vigorously stirred for 1 h, and the aqueous phase was extracted with *n*-pentane (3 × 200 mL). The combined organic solution was dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, 10% ether in hexanes) to give **29** (17.1 g, 86%): R_f = 0.49 (silica gel, 50% ether in hexanes); $[\alpha]^{22}_D$ +11.6 (*c* 1.7, $CHCl_3$); IR (thin film) ν_{max} 2932, 2856, 1715, 1450, 1361, 1272, 1202, 1102, 920, 732, 697 cm^{-1}; ^{1} H NMR (500 MHz, $CDCl_3$) δ 9.60 (d, *J* = 2.0 Hz, 1 H, CHO), 7.34 (s, 5 H, Ph), 4.50 (s, 2 H, CH_2Ph), 3.47 (t, *J* = 6.5 Hz, 2 H, CH_2OBn), 2.33 (m, 1 H, C*H*(CH_3)CO), 1.75−1.69 (m, 1 H), 1.65−1.61 (m, 2 H), 1.49−1.34 (m, 3 H), 1.08 (d, *J* = 7.0 Hz, 3 H, CHC*H*$_3$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 205.0, 138.4, 128.2, 127.5, 127.4, 72.8, 69.9, 46.1, 30.1, 29.6, 23.6, 13.2; FAB HRMS (NBA) *m*/*e* 221.1538, M + H^+ calcd for $C_{14}H_{20}O_2$ 221.1542.

Alcohol 30. Reduction of Aldehyde 29. A solution of aldehyde **29** (17.0 g, 77.0 mmol) in MeOH (200 mL) was treated with $NaBH_4$ (8.6 g, 228 mmol, 3.0 equiv) at 0 °C for 15 min. The solution was then diluted with ether (400 mL), and saturated aqueous NH_4Cl solution (50 mL) was carefully added. The organic phase was washed with brine (50 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by flash column chromatography (silica gel, 40% ether in hexanes) to give alcohol **30** (16.8 g, 98%) as a colorless oil: R_f = 0.23 (silica gel, 50% ether in hexanes); $[\alpha]^{22}_D$ −5.1 (*c* 1.9, $CHCl_3$); IR (thin film) ν_{max} 3401, 2931, 2860, 1455, 1361, 1267, 1202, 1102, 1037, 937, 732, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (s, 5 H, Ph), 4.51 (s, 2 H, CH_2Ph), 3.50 (dd, *J* = 11.0, 6.0 Hz, 1 H, C*H*$_2$OH), 3.48 (t, *J* = 6.5 Hz, 2 H, CH_2OBn), 3.42 (dd, *J* = 11.0, 6.5 Hz, 1 H, C*H*$_2$-OH), 1.65−1.59 (m, 2 H), 1.47−1.34 (m, 4 H), 1.15−1.12 (m, 1 H), 0.91 (d, *J* = 6.7 Hz, 3 H, CHC*H*$_3$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 138.6, 128.2, 127.6, 127.3, 72.9, 70.3, 68.1, 35.7, 32.9, 30.1, 23.6, 14.1; FAB HRMS (NBA) *m*/*e* 223.1705, M + H^+ calcd for $C_{14}H_{22}O_2$ 223.1698.

Silyl Ether 31. Silylation of Alcohol 30. Alcohol **30** (17.0 g, 76.0 mmol) was dissolved in CH_2Cl_2 (350 mL), the solution was cooled to 0 °C and Et_3N (21.2 mL, 152.0 mmol, 2.0 equiv) and 4-DMAP (185 mg, 1.52 mmol, 0.05 equiv) were added. After the mixture was stirred for 5 min, *tert*-butyldimethylsilyl chloride (17.3 g, 115 mmol, 1.5 equiv) was added portionwise and the reaction mixture was allowed to stir at 0 °C for 2 h and then at 25 °C for 10 h. Methanol (20 mL) was added at 0 °C, and the solvents were removed under reduced pressure. Ether (200 mL) and saturated aqueous NH_4Cl solution (30 mL) were sequentially added, and the organic phase was separated. The aqueous phase was extracted with ether (2 × 100 mL), and the combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 5% ether in hexanes) provided pure silyl ether **31** (24.4 g, 95%): R_f = 0.54 (silica gel, 10% ether in hexanes); $[\alpha]^{22}_D$ −2.3 (*c* 1.1, $CHCl_3$); IR (thin film) ν_{max} 2931, 2860, 1461, 1361, 1249, 1091, 839, 773, 738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (s, 5 H, Ph), 4.51 (s, 2 H, CH_2Ph), 3.48 (t, *J* = 6.5 Hz, 2 H, CH_2OBn), 3.43 (dd, *J* = 10.5, 6.0 Hz, 1 H, CH_2OSi), 3.36 (dd, *J* = 10.5, 6.5 Hz, 1 H, CH_2OSi), 1.64−1.60 (m, 3 H), 1.47−1.29 (m, 3 H), 1.15−1.05 (m, 1 H), 0.90 (s, 9 H, SiC$(CH_3)_3$), 0.87 (d, *J* = 6.8 Hz, 3 H, CHC*H*$_3$), 0.043 (s, 3 H, Si$(CH_3)_2$), 0.041 (s, 3 H, Si$(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 138.6, 128.2, 127.5, 127.3, 72.7, 70.3, 68.3, 35.6, 32.9, 30.0, 25.8, 23.5, 18.1, 16.6, −5.5; FAB HRMS (NBA) *m*/*e* 337.2553, M + H^+ calcd for $C_{20}H_{36}O_2Si$ 337.2563.

Alcohol 32. Hydrogenolysis of Benzyl Ether 31. To a solution of benzyl ether **31** (21.0 g, 62.5 mmol) in THF (200 mL) was added 10% $Pd(OH)_2$/C (1.0 g). The reaction was allowed to proceed under an atmosphere of H_2 at a pressure of 50 psi and at 25 °C (Parr hydrogenetor apparatus). After 15 min, no starting benzyl ether was detected by TLC and the mixture was filtered through Celite. The clear solution was concentrated under reduced pressure, and the resulting crude product was purified by flash column chromatography (silica gel, 40% ether in hexanes) to give alcohol **32** (14.7 g, 95%) as a colorless oil: R_f = 0.32 (silica gel, 50% ether in hexanes); $[\alpha]^{22}_D$ −3.6 (*c* 3.6, $CHCl_3$); IR (thin film) ν_{max} 3342, 2931, 2860, 1467, 1384, 1249, 1085, 838, 773, 667 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.63 (t, *J* = 7.0 Hz, 2 H, C*H*$_2$OH), 3.42 (dd, *J* = 11.0, 6.0 Hz, 1 H, CH_2OSi), 3.35 (dd, *J* = 11.0, 7.0 Hz, 1 H, CH_2OSi), 1.57−1.53 (m, 3 H), 1.42−1.39 (m, 3 H), 1.16−1.06 (m, 1 H), 0.88 (s, 9 H, SiC$(CH_3)_3$), 0.85 (d, *J* = 6.5 Hz, 3 H, CHC*H*$_3$), 0.03 (s, 3 H, Si$(CH_3)_2$), 0.02 (s, 3 H, Si$(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 68.2, 62.7, 35.6, 32.9, 32.8, 25.7, 23.0, 18.2, 16.5, −5.5; FAB HRMS (NBA) *m*/*e* 247.2097, M + H^+ calcd for $C_{13}H_{30}O_2Si$ 247.2093.

Aldehyde 10. Oxidation of Alcohol 32. To a solution of oxalyl chloride (5.6 mL, 65.0 mmol, 2.0 equiv) in CH_2Cl_2 (250 mL) was added dropwise DMSO (9.2 mL, 130 mmol, 4.0 equiv) at −78 °C. After the mixture was stirred for 15 min, a solution of alcohol **32** (8.0 g, 32.0

mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) was added dropwise at −78 °C over a 15 min period. The solution was stirred for a further 30 min at −78 °C, and Et_3N (27.1 mL, 194 mmol, 6.0 equiv) was added at the same temperature. The reaction mixture was allowed to warm to 0 °C over 30 min, and then ether (400 mL) was added, followed by saturated aqueous NH_4Cl solution (100 mL). The organic phase was separated, and the aqueous phase was extracted with ether (2 × 300 mL). The combined organic solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 20% ether in hexanes) provided aldehyde **10** (7.9 g, 98%) as a colorless oil: $R_f = 0.64$ (silica gel, 50% ether in hexanes); $[\alpha]^{22}_D$ −5.1 (*c* 0.7, $CHCl_3$); IR (thin film) ν_{max} 2952, 2858, 1728, 1466, 1389, 1254, 1095, 841, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.74 (t, $J = 1.5$ Hz, 1 H, CHO), 3.39 (dd, $J = 9.8$, 6.1 Hz, 1 H, CH_2OSi), 3.36 (dd, $J = 9.8$, 6.3 Hz, 1 H, CH_2OSi), 2.39 (m, 2 H, CH_2CHO), 171−1.64 (m, 1 H), 1.61−1.53 (m, 2 H), 1.44−1.38 (m, 1 H), 1.11−1.05 (m, 1 H), 0.87 (s, 9 H, $SiC(CH_3)_3$), 0.85 (d, $J = 6.5$ Hz, 3 H, CHCH_3), 0.019 (s, 3 H, $Si(CH_3)_2$), 0.004 (s, 3 H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 202.7, 68.9, 44.1, 35.5, 32.6, 25.8, 23.0, 18.2, 16.5, −5.5; FAB HRMS (NBA) *m/e* 245.1932, M + H^+ calcd for $C_{13}H_{28}O_2Si$ 245.1937.

Alcohol 33. To a cold (0 °C) solution of aldehyde **10** (7.8 g, 32.0 mmol) in THF (300 mL) was slowly added MeMgBr (1.0 M solution in THF, 48.0 mL, 48.0 mmol, 1.5 equiv). The reaction mixture was stirred for 15 min at 0 °C, and then it was diluted with ether (500 mL) and quenched by carefull addition of saturated aqueous NH_4Cl solution (100 mL). The organic phase was washed with brine (100 mL), dried ($MgSO_4$), and concentrated. The crude product so obtained was purified by flash column chromatography (silica gel, 30% ether in hexanes) to give alcohol **33** (7.0 g, 84%) as a colorless oil: $R_f = 0.38$ (silica gel, 50% ether in hexanes); IR (thin film) ν_{max} 3352, 2931, 2858, 1465, 1384, 1253, 1096, 839, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.79 (m, 1 H, CH(CH_3)OH), 3.43 (dd, $J = 9.8$, 6.0 Hz, 1 H, CH_2OSi), 3.36 (dd, $J = 9.8$, 6.8 Hz, 1 H, CH_2OSi), 1.61−1.57 (m, 1 H), 1.47−1.35 (m, 4 H), 1.30−1.26 (m, 1 H), 1.19 (d, $J = 6.1$ Hz, 3 H, CH(OH)-CH_3), 1.09−1.05 (m, 1 H), 0.89 (s, 9 H, $SiC(CH_3)_3$), 0.86 (d, $J = 6.7$ Hz, 3 H, CHCH_3), 0.04 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 68.2, 67.9, 39.5, 35.6, 33.0, 25.9, 23.4, 23.1, 18.2, 16.6, −5.4; FAB HRMS (NBA) *m/e* 261.2256, M + H^+ calcd for $C_{14}H_{32}O_2Si$ 261.2250.

Ketone 11. Oxidation of Alcohol 33. To a solution of alcohol **33** (7.0 g, 27.0 mmol) in CH_2Cl_2 (250 mL) were added molecular sieves (4 Å, 6.0 g), 4-methylmorpholine *N*-oxide (NMO) (4.73 g, 40.0 mmol, 1.5 equiv), and tetrapropylammonium perruthenate (TPAP) (189 mg, 0.54 mmol, 0.02 equiv) at room temperature. After being stirred for 45 min (depletion of starting material, TLC), the reaction mixture was filtered through Celite and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 20% ether in hexanes) to give ketone **11** (6.6 g, 96%) as a colorless oil: $R_f = 0.67$ (silica gel, 50% ether in hexanes); $[\alpha]^{22}_D$ −4.5 (*c* 1.1, $CHCl_3$); IR (thin film) ν_{max} 2931, 2849, 1713, 1461, 1355, 1249, 1161, 1091, 838, 773, 667 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.41 (dd, $J = 9.8$, 6.0 Hz, 1 H, CH_2OSi), 3.36 (dd, $J = 9.8$, 6.3 Hz, 1 H, CH_2OSi), 2.41 (m, 2 H, CH_2COCH_3), 2.13 (s, 3 H, $COCH_3$), 168−1.48 (m, 3 H), 1.42−1.35 (m, 1 H), 1.09−1.00 (m, 1 H), 0.88 (s, 9 H, $SiC(CH_3)_3$), 0.86 (d, $J = 6.7$ Hz, 3 H, CHCH_3), 0.03 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 209.8, 68.0, 43.9, 35.5, 32.6, 29.7, 25.8, 21.2, 18.2, 16.4, −5.5; FAB HRMS (NBA) *m/e* 259.2097, M + H^+ calcd for $C_{14}H_{30}O_2Si$ 259.2093.

Iodide 46. Iodination of Alcohol 32. A solution of alcohol **32** (3.8 g, 15.0 mmol) in ether:MeCN, 3:1 (150 mL), was cooled to 0 °C. Imidazole (3.1 g, 45.0 mmol, 3.0 equiv), Ph_3P (5.9 g, 22.5 mmol, 1.5 equiv), and iodine (5.7 g, 22.5 mmol, 1.5 equiv) were sequentially added, and the reaction mixture was stirred at 0 °C for 0.5 h. A saturated aqueous solution of $Na_2S_2O_3$ (200 mL) was added followed with ether (200 mL). The organic phase was washed with brine (200 mL) and dried ($MgSO_4$), and the solvents were removed under vacuum. The crude product was purified by flash column chromatography (silica gel, 10% ether in hexanes) to give pure iodide **46** (4.9 g, 91%) as a colorless oil: $R_f = 0.68$ (silica gel, 10% ether in hexanes); $[\alpha]^{22}_D$ −4.3 (*c* 1.2, $CHCl_3$); IR (thin film) ν_{max} 2929, 2860, 1461, 1386, 1248, 1090, 836, 774, 664 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.42 (dd, $J =$ 10.0, 6.5 Hz, 1 H, CH_2OSi), 3.38 (dd, $J = 10.0$, 6.0 Hz, 1 H, CH_2-OSi), 3.19 (t, $J = 7.0$ Hz, 2 H, CH_2I), 1.85−1.78 (m, 2 H), 1.61−1.55 (m, 1 H), 1.47−1.33 (m, 3 H), 1.10−1.02 (m, 1 H, CH_2), 0.89 (s, 9 H, $SiC(CH_3)_3$), 0.87 (d, $J = 6.7$ Hz, 3 H, CHCH_3), 0.04 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 68.1, 35.4, 33.7, 31.8, 27.8, 25.8, 18.2, 16.5, 7.1, −5.5; FAB HRMS (NBA) *m/e* 229.1983, M − I^- calcd for $C_{13}H_{39}IOSi$ 229.1988.

Phosphonium Salt 47. A mixture of iodide **46** (4.7 g, 13.1 mmol) and Ph_3P (3.8 g, 14.4 mmol, 1.1 equiv) was heated neat at 100 °C for 2 h. Purification by flash column chromatography (silica gel, CH_2Cl_2 → 7% MeOH in CH_2Cl_2) provided phosphonium salt **47** (7.4 g, 91%) as a white solid: $R_f = 0.42$ (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −7.3 (*c* 1.5, $CHCl_3$); IR (thin film) ν_{max} 2931, 2849, 1578, 1461, 1431, 1243, 1184, 1102, 997, 914, 838, 720, 685, 532, 503 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.82−7.77 (m, 9 H, Ph), 7.74−7.68 (m, 6 H, Ph), 3.62 (dt, $J = 12.5$, 8.0 Hz, 2 H, CH_2P), 3.34 (dd, $J = 9.5$, 6.5 Hz, 1 H, CH_2OSi), 3.30 (dd, $J = 9.5$, 6.5 Hz, 1 H, CH_2OSi), 1.69−1.55 (m, 4 H), 1.50−1.46 (m, 1 H), 1.39−1.32 (m, 1 H), 1.10−1.01 (m, 1 H), 0.83 (s, 9 H, $SiC(CH_3)_3$), 0.79 (d, $J = 6.6$ Hz, 3 H, CHCH_3), −0.04 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 135.0, 133.6, 133.5, 133.2, 130.5, 130.4, 68.0, 35.2, 32.4, 27.8, 25.8, 23.2, 22.7, 18.2, 16.4, −5.5.

Olefin 34. Method A. From Phosphonium Salt 12 and Aldehyde 10: Phosphonium salt **12** (13.60 g, 19.4 mmol, 1.2 equiv) was dissolved in THF (80 mL, 0.2 M), and the solution was cooled to 0 °C. Sodium hexamethyldisilylamide (NaHMDS, 19.4 mL, 19.4 mmol, 1.0 M solution in THF, 1.2 equiv) was slowly added, and the resulting mixture was stirred for 15 min before aldehyde **10** (3.96 g, 16.2 mmol, 1.0 equiv, in 10 mL of THF) was added at the same temperature. Stirring was continued for another 15 min at 0 °C, and then, the reaction mixture was quenched with saturated aqueous NH_4Cl solution (25 mL). Ether (250 mL) was added, and the organic phase was separated and washed with brine (2 × 40 mL), dried ($MgSO_4$), and concentrated under *vacuo*. The crude product was purified by flash column chromatography (silica gel, 10% ether in hexane) to afford olefin **34** (6.70 g, 77%) as a mixture of *Z*- and *E*-isomers (ca. 9:1 by ^1H NMR). **Method B. From Phosphonium Salt 47 and Aldehyde 15:** Phosphonium salt **47** (7.40 g, 11.96 mmol, 1.2 equiv) was dissolved in THF (120 mL, 0.1 M), and the solution was cooled to 0 °C. Sodium hexamethyldisilylamide (NaHMDS, 11.96 mL, 11.96 mmol, 1.0 M solution in THF, 1.2 equiv) was slowly added at the same temperature, and the resulting mixture was stirred for 15 min, before aldehyde **15** (3.20 g, 9.83 mmol, 1.0 equiv, in 20 mL of THF) was slowly added. Stirring was continued for another 15 min at 0 °C, and then the mixture was quenched with saturated aqueous NH_4Cl solution (150 mL). Ether (200 mL) was added, and the organic phase was separated and washed with brine (2 × 150 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford the crude product. Flash column chromatography (silica gel, 10% ether in hexane) furnished olefin **34** (3.65 g, 69% yield) as a mixture of *Z*- and *E*-isomers (ca. 9:1 by ^1H NMR): $R_f = 0.75$ (silica gel, 50% ether in hexane); $[\alpha]^{22}_D$ +4.0 (*c* 0.5, $CHCl_3$); IR (thin film) ν_{max} 2930, 2856, 1465, 1388, 1253, 1089, 939, 838 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (signals for the *Z*-isomer (**34**) only reported) δ 6.92 (s, 1 H, SCH═C), 6.46 (s, 1 H, CH═CCH_3), 5.49−5.31 (m, 2 H, CH═CH), 4.12 (dd, $J = 6.5$, 6.4 Hz, 1 H, CHOSi), 3.44 (dd, $J = 9.8$, 5.8 Hz, 1 H, CH_2OSi), 3.34 (dd, $J = 9.8$, 6.8 Hz, 1 H, CH_2OSi), 2.71 (s, 3 H, N═C(S)CH_3), 2.39−2.24 (m, 2 H, CH_2CHOSi), 2.00 (s, 3 H, CH═CCH_3), 2.05−1.96 (m, 2 H), 1.59−1.51 (m, 1 H), 1.42−1.23 (m, 3 H), 1.10−0.98 (m, 1 H), 0.89 (s, 18 H, $SiC(CH_3)_3$), 0.85 (d, $J = 6.8$ Hz, 3 H, CH_3CH), 0.06 (s, 3 H, $Si(CH_3)_2$), 0.04 (s, 6 H, $Si(CH_3)_2$), 0.01 (s, 3 H, $Si(CH_3)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 164.3, 153.1, 142.2, 131.4, 125.7, 118.8, 114.9, 78.7, 68.3, 35.7, 34.6, 32.9, 27.8, 27.1, 25.9, 25.8, 19.2, 18.3, 18.2, 16.7, 13.9, −4.7, −4.9, −5.4; FAB HRMS (NBA) *m/e* 538.3582, M + H^+ calcd for $C_{29}H_{55}NO_2SSi_2$ 538.3570.

Alcohol 35. Compound **34** (1.77 g, 3.29 mmol) was dissolved in CH_2Cl_2:MeOH (1:1, 66 mL), the solution was cooled to 0 °C, and CSA (764 mg, 3.29 mmol, 1.0 equiv) was added over a 5 min period. The mixture was stirred for 30 min at 0 °C and then for 1 h at 25 °C. Et_3N (2.0 mL) was added, and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, 50% ether in hexanes) furnished the desired alcohol **35** (1.2 g, 86%): $R_f = 0.72$ (silica gel, 80% ether in hexanes); $[\alpha]^{22}_D$ +1.1 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 3370, 2923, 2857, 1464, 1384, 1253, 1185, 1074, 836, 776

cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 (s, 1 H, SCH═C), 6.44 (s, 1 H, C*H*═CCH_3), 5.45−5.32 (m, 2 H, CH═CH), 4.12 (dd, J = 6.5, 6.4 Hz, 1 H, CHOSi), 3.46 (dd, J = 10.5, 5.9 Hz, 1 H, CH_2OH), 3.37 (dd, J = 10.5, 6.5 Hz, 1 H, CH_2OH), 2.68 (s, 3 H, N═C(S)CH_3), 2.39−2.21 (m, 2 H, CH_2CHOSi), 2.21 (s, 1 H, OH), 1.98 (s, 3 H, CH═CCH_3), 2.05−1.95 (m, 2 H), 1.59−1.51 (m, 1 H), 1.42−1.23 (m, 3 H), 1.10−0.98 (m, 1 H), 0.88 (d, J = 6.5 Hz, 3 H, CH_3CH), 0.87 (s, 9 H, SiC-$(CH_3)_3$), 0.05 (s, 3 H, Si$(CH_3)_2$), −0.01 (s, 3 H, Si$(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 164.4, 152.9, 142.2, 131.2, 125.8, 118.7, 114.8, 78.6, 67.9, 35.5, 34.6, 32.7, 27.5, 26.9, 25.8, 25.7, 18.9, 16.5, 13.7, −4.8, −5.1; FAB HRMS (NBA/NaI) *m*/*e* 446.2534, M + Na^+ calcd for $C_{23}H_{41}NO_2SSi$ 446.2525.

Aldehyde 7. Oxidation of Alcohol 35. Alcohol **35** (1.9 g, 4.5 mmol) was dissolved in CH_2Cl_2 (45 mL, 0.1 M). DMSO (13.5 mL), Et_3N (3.0 mL, 22.4 mmol, 5.0 equiv), and SO_3·pyr (1.43 g, 8.98 mmol, 2.0 equiv) were added at 25 °C, and the resulting mixture was stirred for 30 min. Saturated aqueous NH_4Cl solution (100 mL) and ether (200 mL) were added sequentially. The organic phase was washed with brine (2 × 30 mL) and dried ($MgSO_4$), and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, 30% ether in hexanes) furnished aldehyde **7** (1.79 g, 94%): R_f = 0.55 (silica gel, 40% ether in hexanes); $[\alpha]^{22}_D$ +13.3 (*c* 0.7, $CHCl_3$); IR (thin film) ν_{max} 2930, 2856, 1725, 1504, 1462, 1385, 1253, 1182, 1076, 938, 836, 776 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.57, (d, J = 1.8 Hz, 1 H, CHO), 6.91 (s, 1 H, SCH═C), 6.44 (s, 1 H, C*H*═CCH_3), 5.45−5.35 (m, 2 H, CH═CH), 4.11 (dd, J = 6.6, 6.3 Hz, 1 H, CHOSi), 2.69 (s, 3 H, N═C(S)CH_3), 2.34−2.24 (m, 3 H), 2.05−2.01 (m, 2 H), 1.98 (s, 3 H, CH═CCH_3), 1.71−1.64 (m, 1 H), 1.41−1.29 (m, 3 H), 1.05 (d, J = 7.0 Hz, 3 H, CH_3CH), 0.87 (s, 9 H, SiC$(CH_3)_3$), 0.04 (s, 3 H, Si$(CH_3)_2$), −0.01 (s, 3 H, Si$(CH_3)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 205.2, 164.4, 153.0, 142.0, 130.6, 126.4, 118.8, 115.0, 78.7, 46.2, 34.7, 30.0, 27.3, 26.9, 25.8, 19.2, 18.2, 13.9, 13.2, −4.7, −5.0; FAB HRMS (NBA) *m*/*e* 422.2559, M + H^+ calcd for $C_{23}H_{39}NO_2SSi$ 422.2549.

Aldol Reaction of Keto Acid 9 with Aldehyde 7. A solution of keto acid **9** (1.52 g, 5.10 mmol, 1.2 equiv) in THF (10 mL) was added dropwise to a freshly prepared solution of LDA [diisopropylamine (1.78 mL, 12.78 mmol) was added to *n*-BuLi (7.95 mL, 1.6 M solution in hexanes, 12.78 mmol) in 20 mL of THF at 0 °C] at −78 °C. After being stirred for 15 min, the solution was allowed to warm to −40 °C, and after 0.5 h at that temperature, it was recooled to −78 °C. A solution of aldehyde **7** (1.79 g, 4.24 mmol, 1.0 equiv) was added dropwise, and the resulting mixture was stirred for 15 min and then quenched at −78 °C by slow addition of saturated aqueous NH_4Cl solution (20 mL). The reaction mixture was warmed to 0 °C, and AcOH (2.03 mL, 26.84 mmol, 6.3 equiv) was added, followed by addition of EtOAc (50 mL). The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 25 mL). The combined organic solution was dried over $MgSO_4$ and concentrated under vacuum to afford a mixture of aldol products **36a**:**36b** in a ca. 1:1 ratio (^{1}H NMR) and unreacted keto acid **9**. The mixture was dissolved in CH_2Cl_2 (50 mL) and treated, at 0 °C, with 2,6-lutidine (3.2 mL, 27.36 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (4.2 mL, 18.24 mmol). After stirring for 2 h (complete reaction by TLC), aqueous HCl (20 mL, 10% solution) was added and the resulting biphasic mixture was separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic solution was washed with brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a mixture of the tetra-*tert*-butyldimethylsilyl ethers **37a,b**. The crude product was dissolved in MeOH (50 mL), and K_2CO_3 (1.40 g, 10.20 mmol) was added at 25 °C. The reaction mixture was vigorously stirred for 15 min and then filtered. The residue was washed with MeOH (20 mL), and the solution was acidified with ion-exchange resin (DOWEX 50WX8−200) to pH 4−5 and filtered again. The solvent was removed under reduced pressure, and the resulting residue was dissolved in EtOAc (50 mL) and washed with saturated aqueous NH_4Cl solution (50 mL). The aqueous phase was extracted with EtOAc (4 × 25 mL), and the combined organic solution was dried ($MgSO_4$), filtered, and concentrated to furnish a mixture of carboxylic acids **38, 39,** and **9**. Purification by preparative thin-layer chromatography (silica gel, 5% MeOH in CH_2Cl_2) gave pure acids **38** (1.1 g, 31% from **7**) and **39** (1.0 g, 30% from **7**) as colorless oils. **38:** R_f = 0.61 (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −8.8 (*c* 0.8, $CHCl_3$); IR (thin film) ν_{max} 2931, 2856, 1712, 1466, 1254, 1083, 836 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.94 (s, 1 H, SCH═C), 6.61 (s, 1 H, C*H*═CCH_3), 5.44−5.41 (m, 2 H, CH═CH), 4.40 (dd, J = 6.5, 3.2 Hz, 1 H, $(CH_3)_2$-CC*H*OSi), 4.11 (dd, J = 6.5, 5.9 Hz, 1 H, CH_2C*H*OSi), 3.75 (dd, J = 6.5, 3.0 Hz, 1 H, CH(CH_3)C*H*OSi), 3.12 (dq, J = 7.0, 6.5 Hz, 1 H, C(O)C*H*(CH_3)), 2.69 (s, 3 H, N═C(CH_3)S), 2.48 (dd, J = 16.0, 3.2 Hz, 1 H, CH_2COOH), 2.35 (dd, J = 16.0, 6.7 Hz, 1 H, CH_2COOH), 2.39−2.28 (m, 2 H, CH_2CH═CH), 2.10−1.92 (m, 2 H, CH═CHCH_2), 1.95 (s, 3 H, CH═C(CH_3)), 1.42−1.30 (m, 5 H, C*H*(CH_3), 2 x CH_2), 1.18 (s, 3 H, C$(CH_3)_2$), 1.10 (s, 3 H, C$(CH_3)_2$), 1.06 (d, J = 7.0 Hz, 3 H, CH(CH_3)), 0.90−0.85 (m, 30 H, CH(CH_3), 3 x SiC$(CH_3)_3$), 0.12 (s, 3 H, Si$(CH_3)_2$), 0.09 (s, 3 H, Si$(CH_3)_2$), 0.07 (s, 3 H, Si$(CH_3)_2$), 0.05 (s, 3 H, Si$(CH_3)_2$), 0.04 (s, 3 H, Si$(CH_3)_2$), 0.03 (s, 3 H, Si$(CH_3)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 218.1, 176.7, 164.8, 152.8, 142.6, 131.3, 125.9, 118.6, 114.7, 78.6, 77.4, 73.4, 53.5, 44.9, 40.1, 38.8, 34.6, 30.7, 28.0, 27.8, 26.2, 26.0, 25.8, 23.6, 19.1, 18.8, 18.5, 18.2, 17.4, 15.7, 13.8, −3.7, −3.8, −4.2, −4.6, −4.7, −4.9; FAB HRMS (NBA/CsI) *m*/*e* 970.4318, M + Cs^+ calcd for $C_{44}H_{83}NO_6SSi_3$ 970.4303. **39:** R_f = 0.70 (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ +2.2 (*c* 3.5, $CHCl_3$); IR (thin film) ν_{max} 2929, 2856, 1713, 1470, 1386, 1254, 1082, 988, 836, 776 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.91 (s, 1 H, SCH═C), 6.45 (s, 1 H, C*H*═CCH_3), 5.44−5.38 (m, 1 H, CH═C*H*), 5.37−5.32 (m, 1 H, C*H*═CH), 4.55 (dd, J = 6.7, 3.7 Hz, 1 H, $(CH_3)_2$CC*H*OSi), 4.11 (dd, J = 6.7, 6.2 Hz, 1 H, CH_2C*H*OSi), 3.83 (d, J = 8.4, 1 H, CH(CH_3)C*H*OSi), 3.09 (dq, J = 7.0, 6.9 Hz, 1 H, C(O)C*H*(CH_3)), 2.73 (s, 3 H, N═C(CH_3)S), 2.40 (dd, J = 16.3, 3.8 Hz, 1 H, CH_2COOH), 2.35−2.22 (m, 3 H, CH_2COOH, CH_2CH═CH), 1.98−1.94 (m, 2 H, CH═CHCH_2), 1.92 (s, 3 H, CH═C(CH_3)), 1.34−1.21 (m, 5 H, C*H*(CH_3), 2 x CH_2), 1.18 (s, 3 H, C$(CH_3)_2$), 1.07 (s, 3 H, C$(CH_3)_2$), 1.05 (d, J = 7.0 Hz, 3 H, CH(CH_3)), 0.89 (s, 9 H, SiC$(CH_3)_3$), 0.88 (s, 9 H, SiC$(CH_3)_3$), 0.85 (s, 9 H, SiC$(CH_3)_3$), 0.82 (d, J = 6.9 Hz, 3 H, CH(CH_3)), 0.07 (s, 6 H, 2 x Si$(CH_3)_2$), 0.06 (s, 3 H, Si$(CH_3)_2$), 0.05 (s, 3 H, Si$(CH_3)_2$), 0.04 (s, 3 H, Si$(CH_3)_2$), 0.01 (s, 3 H, Si$(CH_3)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 217.7, 175.3, 165.4, 152.4, 143.1, 131.3, 125.9, 118.3, 114.6, 78.6, 76.7, 72.3, 53.8, 45.7, 40.1, 37.9, 34.9, 34.6, 27.7, 27.3, 26.3, 26.2, 26.0, 25.8, 22.4, 19.0, 18.6, 18.2, 18.1, 16.8, 13.9, 13.5, −3.4, −3.6, −4.3, −4.6, −4.7, −4.9; FAB HRMS (NBA/CsI) *m*/*e* 970.4331, M + Cs^+ calcd for $C_{44}H_{83}NO_6SSi_3$ 970.4303.

Hydroxy Acid 5. Selective Desilylation of Tris(silyl ether) 38. A solution of tris(silyl ether) **38** (300 mg, 0.36 mmol) in THF (7.0 mL) at 25 °C was treated with TBAF (2.2 mL, 1 M solution in THF, 2.2 mmol, 6.0 equiv). After being stirred for 8 h, the reaction mixture was diluted with EtOAc (10 mL) and washed with aqueous HCl (10 mL, 1 N solution). The aqueous solution was extracted with EtOAc (4 × 10 mL), and the combined organic phase was washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The crude mixture was purified by flash column chromatography (silica gel, 5% MeOH in CH_2Cl_2) to provide hydroxy acid **5** (203 mg, 78%) as a yellow oil: R_f = 0.40 (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −19.2 (*c* 0.1, $CHCl_3$); IR (thin film) ν_{max} 3358, 2932, 2857, 1701, 1466, 1254, 1088, 988, 835 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.95 (s, 1 H SCH═C), 6.67 (s, 1 H, C*H*═CCH_3), 5.58−5.54 (m, 1 H, CH═C*H*), 5.43−5.39 (m, 1 H, C*H*═CH), 4.39 (dd, J = 6.7, 3.9 Hz, 1 H, $(CH_3)_2$CC*H*OSi), 4.18 (dd, J = 7.5, 5.0 Hz, 1 H, CH_2C*H*OH), 3.78 (dd, J = 6.9, 1.0 Hz, 1 H, CH(CH_3)C*H*OSi), 3.11 (dq, J = 6.9, 6.7 Hz, 1 H, C(O)C*H*CH_3), 2.70 (s, 3 H, N═C(CH_3)S), 2.43 (dd, J = 16.2, 3.9 Hz, 1 H, CH_2COOH), 2.40−2.35 (m, 2 H, CH_2CH═CH), 2.35 (dd, J = 16.2, 6.7 Hz, 1 H, CH_2COOH), 2.15−2.10 (m, 1 H, CH═CHCH_2), 2.00 (s, 3 H, CH═C-(CH_3)), 1.99−1.95 (m, 1 H, CH═CHCH_2), 1.48−1.30 (m, 5 H, C*H*(CH_3), 2 x CH_2), 1.18 (s, 3 H, C$(CH_3)_2$), 1.08 (s, 3 H, C$(CH_3)_2$), 1.05 (d, J = 6.7 Hz, 3 H, CH(CH_3)), 0.89−0.84 (m, 21 H, CH(CH_3), SiC(CH_3)$_3$), 0.09 (s, 3 H, Si$(CH_3)_2$), 0.05 (s, 3 H, Si$(CH_3)_2$), 0.04 (s, 3 H, Si$(CH_3)_2$), 0.03 (s, 3 H, Si$(CH_3)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 218.9, 175.4, 166.3, 152.8, 143.5, 134.4, 125.7, 119.5, 115.9, 74.4, 54.7, 45.5, 40.9, 40.0, 34.3, 31.9, 30.6, 28.9, 28.8, 27.0, 26.8, 26.7, 24.4, 20.0, 19.6, 19.3, 19.1, 17.9, 17.1, 15.5, −2.9, −3.1, −3.3, −3.8; FAB HRMS (NBA/CsI) *m*/*e* 856.3459, M + Cs^+ calcd for $C_{38}H_{69}NO_6SSi_2$ 856.3439.

Hydroxy Acid 40. **Selective Desilylation of Tris(silyl ether) 39.** Carboxylic acid **39** (150 mg, 0.18 mmol) was converted to hydroxy acid **40** (107 mg, 82%) according to the procedure described above for **5**. **40**: yellow oil; R_f = 0.45 (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −8.0 (*c* 0.2, $CHCl_3$); IR (thin film) ν_{max} 3225, 2943, 2860, 1719,

1690, 1461, 1384, 1296, 1250, 1190, 1085, 985, 832, 761, 667 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.93 (s, 1 H SCH=C), 6.60 (s, 1 H, C*H*=CCH$_3$), 5.54−5.50 (m, 1 H, CH=C*H*), 5.40−5.34 (m, 1 H, C*H*=CH), 4.54 (dd, J = 6.4, 3.7 Hz, 1 H, (CH$_3$)$_2$CC*H*OSi), 4.15 (dd, J = 6.5, 6.3 Hz, 1 H, CH$_2$C*H*OH), 3.82 (d, J = 7.6 Hz, 1 H, CH(CH$_3$)C*H*OSi), 3.09 (dq, J = 6.9, 6.5 Hz, 1 H, C(O)C*H*CH$_3$), 2.71 (s, 3 H, N=C(CH$_3$)S), 2.37−2.32 (m, 3 H, C*H*$_2$CH=CH, C*H*$_2$COOH), 2.30 (dd, J = 16.3, 6.4 Hz, 1 H, C*H*$_2$COOH), 2.15−2.10 (m, 2 H, CH=CHC*H*$_2$), 1.97 (s, 3 H, CH=C(C*H*$_3$)), 1.36−1.18 (m, 5 H, C*H*(CH$_3$), 2 x CH$_2$), 1.17 (s, 3 H, C(CH$_3$)$_2$), 1.07 (s, 3 H, C(CH$_3$)$_2$), 1.05 (d, J = 6.8 Hz, 3 H, CH(C*H*$_3$)), 0.88 (s, 9 H, SiC(CH$_3$)$_3$), 0.85−0.82 (m, 12 H, CH(C*H*$_3$), SiC(CH$_3$)$_3$), 0.07 (s, 3 H, Si(CH$_3$)$_2$), 0.06 (s, 3 H, Si(CH$_3$)$_2$), 0.05 (s, 6 H, Si(CH$_3$)$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 218.2, 175.4, 165.4, 152.2, 142.0, 133.1, 124.9, 118.6, 115.1, 74.4, 53.8, 45.8, 40.2, 38.9, 37.7, 34.8, 33.2, 27.9, 27.5, 27.1, 26.2, 26.1, 26.0, 22.6, 21.4, 18.8, 18.6, 16.9, 14.5, 13.3, −3.4, −3.6, −4.3, −4.6; FAB HRMS (NBA/CsI) *m/e* 856.3402, M + Cs^+ calcd for $C_{38}H_{69}NO_6SSi_2$ 856.3439.

Lactone 41. Macrolactonization of Hydroxy Acid 5. A solution of hydroxy acid **5** (200 mg, 0.28 mmol) in THF (4 mL) was treated at 0 °C with Et_3N (0.23 mL, 1.68 mmol, 6.0 equiv) and 2,4,6-trichlorobenzoyl chloride (0.22 mL, 1.40 mmol, 5.0 equiv). The reaction mixture was stirred at 0 °C for 15 min and then added to a solution of 4-DMAP (342 mg, 2.80 mmol, 10.0 equiv) in toluene (140 mL) at 25 °C and stirred at that temperature for 0.5 h. The reaction mixture was concentrated under reduced pressure to a small volume and filtered through silica gel. The residue was washed with 40% ether in hexanes, and the resulting solution was concentrated. Purification by flash column chromatography (silica gel, 2% MeOH in CH_2Cl_2) furnished lactone **41** (178 mg, 90%) as a colorless oil: R_f = 0.37 (silica gel, 30% ether in hexanes); $[\alpha]^{22}_D$ −22.9 (*c* 0.3, $CHCl_3$); IR (thin film) ν_{max} 2925, 2854, 1734, 1693, 1464, 1381, 1252, 1187, 1158, 1099, 988, 829, 758 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.98 (s, 1 H, SCH=C), 6.58 (s, 1 H, C*H*=CCH$_3$), 5.53 (m, 1 H, CH=C*H*), 5.43−5.34 (m, 1 H, C*H*=CH), 5.00 (d, J = 10.2 Hz, 1 H, O=COCH), 4.03 (d, J = 10.5 Hz, 1 H, CHOSi), 3.89 (d, J = 9.0 Hz, 1 H, CHOSi), 2.98 (dq, J = 6.9, 6.7 Hz, 1 H, C(O)C*H*CH$_3$), 2.85 (d, J = 16.7 Hz, 1 H, CH$_2$COO), 2.72 (s, 3 H, N=C(CH$_3$)S), 2.66 (dd, J = 16.7, 10.7 Hz, 1 H, CH$_2$COO), 2.40−2.30 (m, 1 H, CH=CHC*H*$_2$), 2.11 (s, 3 H, CH=C(C*H*$_3$)), 2.10−2.04 (m, 2 H, C*H*$_2$CH=CH), 1.92−1.83 (m, 1 H, CH=CHC*H*$_2$), 1.66−1.38 (m, 5 H, C*H*(CH$_3$), 2 x CH$_2$), 1.17 (s, 3 H, C(CH$_3$)$_2$), 1.13 (s, 3 H, C(CH$_3$)$_2$), 1.06 (d, J = 7.0 Hz, 3 H, CH(C*H*$_3$)), 0.94 (d, J = 7.0 Hz, 3 H, CH(C*H*$_3$)), 0.92 (s, 9 H, SiC(CH$_3$)$_3$), 0.83 (s, 9 H, SiC(CH$_3$)$_3$), 0.09 (s, 3 H, Si(CH$_3$)$_2$), 0.07 (s, 3 H, Si(CH$_3$)$_2$), 0.05 (s, 3 H, Si(CH$_3$)$_2$), −0.12 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 215.0, 171.3, 165.4, 135.7, 135.1, 125.8, 122.7, 119.9, 115.9, 79.5, 76.4, 53.3, 48.0, 38.8, 31.7, 31.3, 29.7, 29.2, 28.4, 26.4, 26.2, 26.1, 25.9, 24.2, 19.1, 18.7, 18.6, 17.7, 15.3, −3.1, −3.2, −3.7, −5.8; FAB HRMS (NBA) *m/e* 706.4382, M + H^+ calcd for $C_{38}H_{67}NO_5SSi_2$ 706.4357.

Lactone 42. Macrolactonization of Hydroxy Acid 40. The cyclization of hydroxy acid **40** (100 mg, 0.14 mmol) was carried out exactly as described for **41** above and yielded lactone **42** (84 mg, 85%) as a colorless oil: R_f = 0.40 (silica gel, 30% ether in hexanes); $[\alpha]^{22}_D$ −40.5 (*c* 0.2, $CHCl_3$); IR (thin film) ν_{max} 2929, 2855, 1739, 1690, 1469, 1384, 1253, 1180, 1089, 1053, 985, 835, 775 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.94 (s, 1 H, SCH=C), 6.53 (s, 1 H, C*H*=CCH$_3$), 5.55−5.46 (m, 1 H, CH=C*H*), 5.39−5.30 (m, 1 H, C*H*=CH), 5.32 (dd, J = 7.0, 3.0 Hz, 1 H, O=COCH), 4.43 (dd, J = 7.5, 2.9 Hz, 1 H, CHOSi), 3.99 (d, J = 7.1 Hz, 1 H, CHOSi), 3.20 (dq, J = 7.3, 7.1 Hz, 1 H, C(O)C*H*CH$_3$), 2.71 (s, 3 H, N=C(CH$_3$)S), 2.59 (m, 1 H, CH=CHC*H*$_2$), 2.21 (dd, J = 14.6, 3.2 Hz, 1 H, CH$_2$COO), 2.20 (dd, J = 14.6, 7.6 Hz, 1 H, CH$_2$COO), 2.16 (s, 3 H, CH=C(C*H*$_3$)), 2.15−1.95 (m, 3 H, CH=CHC*H*$_2$, C*H*$_2$CH=CH), 1.60−1.50 (m, 3 H, C*H*(CH$_3$), 2 x CH$_2$), 1.47−1.35 (m, 2 H, C*H*(CH$_3$), 2 x CH$_2$), 1.24 (s, 3 H, C(CH$_3$)$_2$), 1.11 (d, J = 7.2 Hz, 3 H, CH(C*H*$_3$)), 1.09 (s, 3 H, C(CH$_3$)$_2$), 0.90 (s, 9 H, SiC(CH$_3$)$_3$), 0.86 (s, 9 H, SiC(CH$_3$)$_3$), 0.83 (d, J = 6.7 Hz, 3 H, CH(C*H*$_3$)), 0.09 (s, 6 H, 2 x Si(CH$_3$)$_2$), 0.01 (s, 3 H, Si(CH$_3$)$_2$), −0.05 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 221.2, 171.6, 165.8, 134.9, 134.1, 125.7, 125.2, 120.7, 117.1, 78.8, 75.2, 74.5, 54.3, 48.1, 42.5, 37.9, 33.7, 32.4, 26.8, 26.7, 26.5, 26.2, 25.8, 19.7, 19.2, 19.0, 18.8, 17.7, 15.9, 14.1, −3.0, −3.3, −3.7, −4.3; FAB HRMS (NBA) *m/e* 706.4333, M + H^+ calcd for $C_{38}H_{67}NO_5SSi_2$ 706.4357.

Dihydroxy Lactone 3. To lactone **41** (50 mg, 0.071 mmol), cooled to −20 °C, was added a freshly prepared 20% (v/v) CF_3COOH solution in CH_2Cl_2 (400 μL). The reaction mixture was allowed to reach 0 °C and was stirred for 1 h at that temperature. The solvents were evaporated under reduced pressure, and the crude product was purified by preparative thin-layer chromatography (silica gel, 6% MeOH in CH_2Cl_2) to afford pure dihydroxy lactone **3** (31 mg, 92%): R_f = 0.38 (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −80.2 (*c* 1.7, $CHCl_3$); IR (thin film) ν_{max} 3470, 2929, 1733, 1686, 1464, 1380, 1250, 1182, 1045, 978, 732 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.83 (s, 1 H, SCH=C), 6.56 (s, 1 H, C*H*=CCH$_3$), 5.48 (dd, J = 7.0, 3.0 Hz, 1 H, O=COCH), 5.43−5.41 (m, 2 H, CH=CH), 4.21 (d, J = 11.5 Hz, 1 H, C*H*OH), 3.77 (bs, 1 H, C*H*OH), 3.13 (bs, 1 H, OH), 3.01 (bs, 1 H, OH), 2.95 (m, 1 H, C(O)C*H*CH$_3$), 2.70−2.62 (m, 1 H, CH$_2$COO), 2.47 (ddd, J = 14.6, 11.5 Hz, 1 H, CH$_2$COO), 2.27 (s, 3 H, N=C(CH$_3$)S), 2.18−2.12 (m, 2 H, CH=CHC*H*$_2$), 2.15 (s, 3 H, CH=C(C*H*$_3$)), 1.97−1.83 (m, 2H, C*H*$_2$CH=CH), 1.56−1.50 (m, 1 H, C*H*(CH$_3$)), 1.41−1.22 (m, 4 H, 2 x CH$_2$), 1.15 (d, J = 7.0 Hz, 3 H, CH(C*H*$_3$)), 1.07 (d, J = 6.0 Hz, 3 H, CH(C*H*$_3$)), 1.07 (s, 3 H, C(CH$_3$)$_2$), 1.06 (s, 3 H, C(CH$_3$)$_2$); ^{13}C NMR (150.9 MHz, C_6D_6) δ 220.2, 170.6, 165.4, 153.8, 139.2, 134.1, 126.1, 120.4, 116.9, 79.2, 74.9, 73.2, 54.2, 42.5, 40.3, 39.5, 32.9, 32.6, 28.6, 28.4, 23.3, 19.3, 19.1, 16.4, 16.3, 14.4; FAB HRMS (NBA/CsI) *m/e* 610.1580, M + Cs^+ calcd for $C_{26}H_{39}NO_5S$ 610.1603.

Dihydroxy Lactone 43. Lactone **42** (38.0 mg, 0.054 mmol) was treated with CF_3COOH in exactly the same way as described above for **3**, yielding dihydroxy lactone **43** (24.5 mg, 95%): R_f = 0.30 (silica gel, 6% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −93.1 (*c* 0.1, $CHCl_3$); IR (thin film) ν_{max} 3450, 2929, 1735, 1685, 1464, 1380, 1250, 1182, 1045, 978, 732 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.96 (s, 1 H, SCH=C), 6.51 (s, 1 H, C*H*=CCH$_3$), 5.60−5.50 (m, 2 H, CH=CH), 5.40−5.32 (m, 1 H, O=COCH), 4.25 (d, J = 9.5 Hz, 1 H, C*H*OH), 3.55 (d, J = 9.6 Hz, 1 H, C*H*OH), 3.39 (bs, 1 H, OH), 3.31 (dq, J = 6.9, 6.7 Hz, 1 H, C(O)C*H*CH$_3$), 2.99 (bs, 1 H, OH), 2.71 (s, 3 H, N=C(CH$_3$)S), 2.69−2.61 (m, 1 H, CH=CHC*H*$_2$), 2.59 (d, J = 16.3 Hz, 1 H, CH$_2$COO), 2.45−2.35 (m, 2 H, CH$_2$COO, CH=CHC*H*$_2$), 2.20−2.10 (m, 1 H, C*H*$_2$CH=CH), 2.08 (s, 3 H, CH=C(C*H*$_3$)), 1.98−1.90 (m, 1 H, C*H*$_2$CH=CH), 1.59−1.50 (m, 1 H, C*H*(CH$_3$)), 1.49−1.30 (m, 4 H, 2 x CH$_2$), 1.17 (s, 3 H, C(CH$_3$)$_2$), 1.11 (d, J = 6.9 Hz, 3 H, CH(C*H*$_3$)), 1.03 (s, 3 H, C(CH$_3$)$_2$), 1.01 (d, J = 7.0 Hz, 3 H, CH(C*H*$_3$)); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 222.2, 171.1, 165.2, 153.5, 139.5, 133.2, 125.1, 120.0, 116.7, 78.4, 74.1, 72.9, 52.5, 40.7, 39.5, 37.9, 34.5, 32.7, 31.3, 27.6, 24.7, 22.2, 18.9, 17.5, 15.5, 15.3; FAB HRMS (NBA) *m/e* 478.2610, M + H^+ calcd for $C_{26}H_{39}NO_5S$ 478.2627.

Epothilone A (1). Epoxidation of Lactone 3 with Methyl(trifluoromethyl)dioxirane. To a solution of **3** (10 mg, 21.0 μmol) in MeCN (200 μL) was added 4 × 10^{-4} M aqueous solution of disodium ethylenediaminetetraacetate (Na_2EDTA, 120 μL), and the reaction mixture was cooled to 0 °C. 1,1,1-Trifluoroacetone (200 μL) was added followed by a mixture of Oxone (61 mg, 0.10 mmol, 5.0 equiv) and $NaHCO_3$ (14.0 mg, 0.17 mmol, 8.0 equiv) with stirring until completion of the reaction was revealed by TLC. The reaction mixture was treated with excess Me_2S (100 μL) and water (500 μL) and was then extracted with EtOAc (4 × 2 mL). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated. Purification by preparative thin-layer chromatography (silica gel, 5% MeOH in CH_2Cl_2) gave a mixture of epothilones A (**1**) and its α-epoxide epimer (8.6 mg, 78% total yield). A second preparative thin-layer chromatography (silica gel, 70% EtOAc in hexanes) furnished pure epothilone A (**1**) (6.4 mg, 65%) as a white solid. For a more extensive study of the epoxidation of **3** and isolation of a number of epothilone A analogues, see ref 29. **1**: R_f = 0.23 (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −45.0 (*c* 0.02, MeOH); IR (thin film) ν_{max} 3476, 2974, 1738, 1692 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 6.71 (s, 1 H, C*H*=CCH$_3$), 6.45 (s, 1 H, SCH=C), 5.45 (dd, J = 8.2, 2.3 Hz, 1 H, O=COCH), 4.15 (dd, J = 10.8, 2.9 Hz, 1 H, C*H*OH), 3.81−3.78 (m, 1 H, C*H*OH), 3.65 (bs, 1 H, OH), 3.03 (dq, J = 6.9, 6.5 Hz, 1 H, C(O)C*H*CH$_3$), 2.77 (ddd, J = 7.9, 4.0, 4.0 Hz, 1 H, CH$_2$C*H*O), 2.62−2.58 (m, 1 H, CH$_2$C*H*O), 2.40 (dd, J = 14.4, 10.8 Hz, 1 H, CH$_2$COO), 2.26 (bs, 1 H, OH), 2.21 (s, 3 H, N=C(CH$_3$)S), 2.19 (dd, J = 14.4, 2.9 Hz, 1 H, CH$_2$COO), 2.05 (s, 3 H, CH=C(C*H*$_3$)), 1.86 (ddd, J = 15.2, 2.5, 2.5 Hz, 1 H, C*H*$_2$CHO), 1.81−1.74

(m, 1 H, CH_2CHO), 1.68 (ddd, J = 15.2, 7.6, 7.6 Hz, 1 H, CH_2CHO), 1.53−1.49 (m, 1 H, CH_2CHO), 1.40−1.15 (m, 5 H, CH(CH_3), 2 x CH_2), 1.06 (d, J = 7.0 Hz, 3 H, CH(CH_3)), 1.03 (s, 3 H, C(CH_3)$_2$), 0.97 (s, 3 H, C(CH_3)$_2$), 0.95 (d, J = 6.9 Hz, 3 H, CH(CH_3)); ^{13}C NMR (150.9 MHz, C_6D_6) δ 219.0, 170.2, 164.7, 153.0, 137.5, 119.9, 116.6, 76.6, 75.2, 73.5, 57.2, 54.2, 52.9, 43.8, 39.1, 36.3, 31.7, 30.3, 27.3, 23.9, 21.1, 20.6, 18.7, 17.4, 15.7, 14.6; HRMS (FAB), calcd for $C_{26}H_{39}CsNO_6S$ (M + Cs^+) 626.1552, found 626.1531.

6*S*,7*R*-Epothilones 44 and 45. Epoxidation of Lactone 43. To a solution of lactone **43** (9.0 mg, 18.8 μmol) in MeCN (0.5 mL) were added disodium ethylenediaminetetraacetate (Na_2EDTA, 4 × 10^{-4} M aqueous solution, 200 μL) and 1,1,1-trifluoroacetone (200 μL) at 0 °C. The resulting solution was stirred at 0 °C, while a mixture of solid Oxone (58 mg, 94.0 mmol, 5.0 equiv) and $NaHCO_3$ (14.0 mg, 0.17 mmol, 8.8 equiv) was added portionwise until completion of the reaction was established by TLC). The reaction mixture was treated with excess Me_2S (100 μL) and water (500 μL) and was extracted with EtOAc (4 × 2 mL). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated. Purification by preparative thin-layer chromatography (silica gel, 5% MeOH in CH_2Cl_2) gave a mixture of epothilones **44** and **45** (8.1 mg, 87% total yield, ca. 2:1 ratio by ^{1}H NMR). The major diastereoisomer (**44**, stereochemistry unassigned) was isolated by preparative thin-layer chromatography (silica gel, 70% EtOAc in hexanes) (5.4 mg, 58%) and exhibited the following properties: R_f = 0.23 (silica gel, 6% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −20.0 (*c* 0.2, $CHCl_3$); IR (thin film) ν_{max} 3448, 2919, 1725, 1684, 1455, 1378, 1284, 1149, 1061, 1020, 973, 750 cm^{-1}; ^{1}H NMR (500 MHz, $CHCl_3$) δ 6.99 (s, 1 H, SCH═C), 6.68 (s, 1 H, CH═CCH_3), 5.64−5.61 (m, 1 H, O═COCH), 4.43 (d, J = 2.1 Hz, 1 H, OH), 4.29 (ddd, J = 7.6, 2.5, 2.5 Hz, 1 H, CHOH), 3.82 (d, J = 8.2 Hz, 1 H, CHOH), 3.35 (bs, 1 H, OH), 3.22 (q, J = 7.0 Hz, 1 H, C(O)C$H$$CH_3$), 3.14 (ddd, J = 10.3, 4.1, 3.2 Hz, 1 H, CH_2CHO), 2.90 (ddd, J = 10.3, 4.3, 2.3 Hz, 1 H, CH_2CHO), 2.71 (s, 3 H, N═C(CH_3)S), 2.54 (dd, J = 13.7, 7.6 Hz, 1 H, CH_2COO), 2.51 (dd, J = 13.7, 2.5 Hz, 1 H, CH_2COO), 2.21−2.19 (m, 1 H, CH_2-CHO), 2.18 (s, 3 H, CH═C(CH_3)), 1.94 (ddd, J = 15.3, 10.3, 3.7 Hz, 1 H, CH_2CHO), 1.77−1.69 (m, 2 H, CH_2CHO), 1.60−1.00 (m, 5 H, CH(CH_3), 2 x CH_2), 1.15 (s, 3 H, C(CH_3)$_2$), 1.14 (d, J = 6.9 Hz, 3 H, CH(CH_3)), 1.06 (s, 3 H, C(CH_3)$_2$), 1.02 (d, J = 7.0 Hz, 3 H, CH-(CH_3)); ^{13}C NMR (150.9 MHz, $CHCl_3$) δ 221.8, 172.1, 165.1, 152.6, 134.7, 119.8, 116.8, 76.0, 74.4, 72.8, 56.4, 53.8, 53.0, 40.2, 39.1, 34.1, 32.7, 29.4, 27.8, 22.7, 20.9, 19.0, 16.1, 15.9, 15.0, 11.8; FAB HRMS (NBA) *m/e* 494.2587, M + H^+ calcd for $C_{26}H_{39}NO_6S$ 494.2576.

Olefinic Compound 48. Phosphonium salt **12** (9.0 g, 12.93 mmol, 1.5 equiv) was dissolved in THF (90 mL), and the solution was cooled to 0 °C. Sodium bis(trimethylsilyl)amide (NaHMDS, 1.0 M solution in THF, 12.84 mL, 12.84 mmol, 1.48 equiv) was slowly added, and the resulting mixture was stirred at 0 °C for 15 min. The reaction mixture was then cooled to −20 °C before ketone **11** (2.23 g, 8.62 mmol, 1.0 equiv) in THF (10 mL) was added, and the reaction mixture was stirred at the same temperature for 12 h. Saturated aqueous NH_4-Cl solution (50 mL) was added, and the mixture was extracted with ether (200 mL). The organic phase was washed with brine (2 × 100 mL), dried ($MgSO_4$), and concentrated to afford, after flash column chromatography (silica gel, 2% ether in hexanes), olefins **48** (3.8 g, 73%, *Z*:*E* ca. 1:1 by ^{1}H NMR).

Hydroxy Olefins 49. Desilylation of Silyl Ether 48. Silyl ether **48** (3.80 g, 6.88 mmol) was dissolved in CH_2Cl_2:MeOH (1:1, 70 mL), and the solution was cooled to 0 °C prior to addition of CSA (1.68 g, 7.23 mmol, 1.05 equiv) during a 5 min period. The resulting mixture was stirred for 30 min at 0 °C and then for 1 h at 25 °C. Et_3N (1.57 mL, 7.23 mmol, 1.05 equiv) was added, and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, 50% ether in hexanes) furnished pure hydroxy compound **49** (2.9 g, 97%).

Aldehyde 8′. **Oxidation of Alcohol 49.** Alcohol **49** (mixtures of *Z* and *E* geometrical isomers, 4.60 g, 10.64 mmol) was dissolved in CH_2Cl_2 (105 mL, 0.1 M). DMSO (35 mL), Et_3N (7.4 mL, 53.20 mmol, 5.0 equiv), and SO_3·pyr (3.4 g, 21.28 mmol, 2.0 equiv) were added at 25 °C, and the resulting mixture was stirred for 30 min. Saturated aqueous NH_4Cl solution (50 mL) and ether (300 mL) were added, and the organic phase was separated and washed with brine (2 × 30 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Flash column chromatography (silica gel, 20% ether in hexanes) furnished aldehyde **8′** (4.40 g, mixture of *Z*:*E* isomers, ca. 1:1, 95%).

Tris(silyl ethers) 52′ and 53′. Aldol Reaction of Keto Acid 9 with Aldehyde 8′. A solution of keto acid **9** (773 mg, 2.56 mmol, 1.2 equiv) in THF (7.0 mL) was reacted with aldehyde **8′** (930 mg, mixture of *Z*:*E* olefins, ca. 1:1, 2.13 mmol, 1.0 equiv) according to the same procedure as described above for the condensation of **9** and **7**, to afford, after similar processing, pure carboxylic acids **52′** (564 mg, mixture of *Z* and *E* isomers, ca. 1:1, 31% from **8′**) and **53′** (545 mg, mixture of *Z* and *E* isomers, ca. 1:1, 30% from **8′**) as colorless oils and recovered keto acid **9** (125 mg).

Hydroxy Acid 6′. Selective Desilylation of 52′. Carboxylic acid **52′** (300 mg, mixture of *Z* and *E* isomers, ca. 1:1, 0.35 mmol) was converted to hydroxy acid **6′** (194 mg, mixture of *Z* and *E* isomers, ca. 1:1, 75%) according to the same procedure described above for hydroxy acid **5**.

Lactones 54 and 55. Macrolactonization of Hydroxy Acid 6′. A solution of hydroxy acid **6′** (140 mg, mixture of *Z* and *E* isomers, ca. 1:1, 0.189 mmol) in THF (2.6 mL) was treated at 0 °C with Et_3N (58 μL, 0.416 mmol, 2.2 equiv) and 2,4,6-trichlorobenzoyl chloride (29.4 μL, 0.246 mmol, 1.3 equiv). The reaction mixture was stirred at 0 °C for 1 h and then added to a solution of 4-DMAP (233 mg, 1.896 mmol, 10.0 equiv) in toluene (90 mL, 0.002 M) at 25 °C and stirred at that temperature for 10 h. The solvents were removed in vacuo, and the crude product obtained was suspended in 40% ether in hexanes and filtered through silica gel. Concentration followed by preparative thin-layer chromatography (silica gel, 5% MeOH in CH_2Cl_2) gave pure lactones **54** (50 mg, 37%) and **55** (54 mg, 40%) as colorless oils. **54**: R_f = 0.40 (silica gel, 1% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −11.8 (*c* 0.8, $CHCl_3$); IR (thin film) ν_{max} 2931, 2848, 1737, 1690, 1461, 1378, 1249, 1184, 1158, 1097, 1020, 984, 835, 775 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.95 (s, 1 H, SCH═C), 6.56 (s, 1 H, CH═CCH_3), 5.16 (dd, J = 8.4, 7.5 Hz, 1 H, CH_3C═C$H$$CH_2$), 4.96 (d, J = 10.1 Hz, 1 H, CH_2COOCH), 4.02 (d, J = 9.9 Hz, 1 H, CHOSi), 3.88 (d, J = 8.9 Hz, 1 H, CHOSi), 3.02 (dq, J = 6.9, 6.7 Hz, 1 H, C(O)C$H$$CH_3$), 2.79 (d, J = 15.6 Hz, 1 H, CH_2COOCH), 2.70 (s, 3 H, N═C(CH_3)S), 2.70−2.65 (m, 2 H), 2.48−2.40 (m, 1 H), 2.10 (s, 3 H, CH═C(CH_3)), 2.10−2.04 (m, 2 H), 1.75−1.69 (m, 2 H), 1.67 (s, 3 H, CH_2C(CH_3)═CH), 1.66−1.45 (m, 3 H), 1.18 (s, 3 H, C(CH_3)$_2$), 1.13 (s, 3 H, C(CH_3)$_2$), 1.09 (d, J = 6.8 Hz, 3 H, CH(CH_3)), 0.97 (d, J = 6.8 Hz, 3 H, CH-(CH_3)), 0.94 (s, 9 H, SiC(CH_3)$_3$), 0.84 (s, 9 H, SiC(CH_3)$_3$), 0.10 (s, 3 H, Si(CH_3)$_2$), 0.09 (s, 3 H, Si(CH_3)$_2$), 0.07 (s, 3 H, Si(CH_3)$_2$), −0.12 (s, 3 H, Si(CH_3)$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 215.1, 171.2, 164.6, 152.5, 140.6, 138.8, 119.3, 119.1, 115.9, 79.9, 76.3, 53.4, 39.1, 32.4, 31.9, 31.4, 29.7, 27.4, 26.4, 26.1, 26.0, 24.5, 24.3, 23.1, 19.2, 18.7, 18.6, 17.8, 15.3, −3.3, −3.7, −5.7; FAB HRMS (NBA) *m/e* 720.4534, M + H^+ calcd for $C_{39}H_{69}NO_5SSi_2$ 720.4513. **55:** R_f = 0.50 (silica gel, 1% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −22.7 (*c* 0.6, $CHCl_3$); IR (thin film) ν_{max} 2931, 2860, 1731, 1696, 1461, 1378, 1249, 1179, 1079, 985, 832, 773 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.92 (s, 1 H, SCH═C), 6.53 (s, 1 H, CH═CCH_3), 5.27 (dd, J = 8.0, 2.7 Hz, 1 H, CH_2COOCH), 5.16 (dd, J = 6.9, 6.6 Hz, 1 H, CH_3C═C$H$$CH_2$), 4.47 (t, J = 5.1 Hz, 1 H, CHOSi), 3.89 (dd, J = 4.5, 1.0 Hz, 1 H, CHOSi), 3.05 (dq, J = 6.7, 6.2 Hz, 1 H, C(O)C$H$$CH_3$), 2.70 (s, 3 H, N═C($CH_3$)S), 2.60 (dd, J = 15.8, 5.8 Hz, 1 H, CH_2COOCH), 2.55 (m, 1 H, CH_3C═CHCH_2), 2.51−2.47 (m, 2 H, CH_2COOCH, CH_3C═CHCH_2), 2.13 (s, 3 H, CH═C(CH_3)), 2.10−2.05 (m, 1 H, CH_2C(CH_3)═CH), 1.91 (m, 1 H, CH_2C(CH_3)═CH), 1.68−1.45 (m, 4 H), 1.57 (s, 3 H, CH_2C(CH_3)═CH), 1.27−1.23 (m, 1 H), 1.17 (s, 3 H, C(CH_3)$_2$), 1.04 (d, J = 6.8 Hz, 3 H, CH(CH_3)), 1.07 (s, 3 H, C(CH_3)$_2$), 0.93 (d, J = 6.9 Hz, 3 H, CH-(CH_3)), 0.88 (s, 9 H, SiC(CH_3)$_3$), 0.86 (s, 9 H, SiC(CH_3)$_3$), 0.07 (s, 6 H, Si(CH_3)$_2$), 0.06 (s, 3 H, Si(CH_3)$_2$), 0.05 (s, 3 H, Si(CH_3)$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 217.2, 171.3, 165.5, 153.6, 139.0, 138.3, 120.9, 120.2, 117.0, 80.1, 77.2, 73.9, 54.8, 44.9, 42.7, 41.1, 40.2, 32.8, 26.9, 26.8, 25.6, 23.5, 21.1, 20.1, 19.2, 19.1, 17.7, 16.8, 16.6, 16.3, −2.7, −3.1, −3.4, −3.6; FAB HRMS (NBA) *m/e* 720.4533, M + H^+ calcd for $C_{39}H_{69}NO_5SSi_2$ 720.4513.

Dihydroxy Lactone 4. Dihydroxy lactone **4** was prepared from bis(silyl ether) lactone **54** (13.3 mg, 0.018 mmol) by treatment with CF_3COOH according to the same procedure described above for the preparation of **3**, to obtain pure lactone **4** (8.4 mg, 91%) as a colorless oil. **4**: R_f = 0.21 (silica gel, 4% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −91.5 (c 0.3, $CHCl_3$); IR (thin film) ν_{max} 3460, 2954, 2919, 1725, 1684, 1455, 1379, 1290, 1249, 1184, 1143, 1043, 1008, 973, 750 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.94 (s, 1 H, SCH═C), 6.57 (s, 1 H, CH═CCH_3),

5.20 (d, J = 9.7 Hz, 1 H, CH_2COOCH), 5.13 (dd, J = 9.6, 4.6 Hz, 1 H, $CH_3C{=}CHCH_2$), 4.28 (d, J = 9.7 Hz, 1 H, $(CH_3)_2CCHOH$), 3.71 (s, 1 H, $CHOH$), 3.47 (bs, 1 H, OH), 3.15 (q, J = 6.8 Hz, 1 H, C(O)-$CHCH_3$), 3.04 (bs, 1 H, OH), 2.68 (s, 3 H, $N{=}C(CH_3)S$), 2.62 (ddd, J = 15.0, 10.2, 10.1 Hz, 1 H, $CH_2CH{=}CCH_3$), 2.45 (dd, J = 14.7, 11.1 Hz, 1 H, CH_2COOCH), 2.38−2.24 (m, 1 H), 2.28 (dd, J = 14.8, 2.2 Hz, CH_2COOCH), 2.22 (d, J = 14.9 Hz, 1 H, $CH_2C(CH_3){=}CHCH_2$), 2.06 (s, 3 H, $CH{=}CCH_3$), 1.90−1.84 (m, 1 H), 1.76−1.69 (m, 1 H), 1.65 (s, 3 H, $CH_2C(CH_3){=}CH$), 1.33 (s, 3 H, $C(CH_3)_2$), 1.32−1.22 (m, 4 H), 1.19 (d, J = 6.8 Hz, 3 H, $CH(CH_3)$), 1.06 (s, 3 H, $C(CH_3)_2$), 1.00 (d, J = 7.0 Hz, 3 H, $CH(CH_3)$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 220.4, 170.2, 164.9, 151.8, 139.1, 138.3, 120.8, 119.1, 115.5, 78.9, 74.1, 72.3, 53.6, 41.7, 39.7, 32.6, 31.8, 31.7, 25.4, 23.0, 19.1, 18.1, 16.0, 15.8, 13.5; FAB HRMS (NBA) m/e 492.2795, M + H^+ calcd for $C_{27}H_{41}NO_5S$ 492.2784.

Dihydroxy Lactone 56. Dihydroxy lactone **56** was prepared from bis(silyl ether) lactone **55** (40.0 mg, 0.055 mmol) by treatment with CF_3COOH according to the same procedure described above for the preparation of **3**. Obtained pure **56** (24.3 mg, 89%): R_f = 0.19 (silica gel, 4% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −61.0 (c 0.2, $CHCl_3$); IR (thin film) ν_{max} 3418, 2932, 1731, 1691, 1466, 1381, 1252, 1159, 1067, 1044, 1012, 978, 755 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.99 (s, 1 H, SCH═C), 6.54 (s, 1 H, $CH{=}CCH_3$), 5.38 (dd, J = 6.7, 3.8 Hz, 1 H, CH_2COOCH), 5.08 (t, J = 6.9 Hz, 1 H, $CH_3C{=}CHCH_2$), 4.32 (dd, J = 10.0, 2.4 Hz, 1 H, $(CH_3)_2CCHOH$), 3.65 (t, J = 3.4 Hz, 1 H, $CHOH$), 3.25 (dq, J = 6.7, 3.9 Hz, 1 H, $C(O)CHCH_3$), 2.68 (s, 3 H, $N{=}C(CH_3)S$), 2.55−2.43 (m, 3 H, CH_2COOCH, $C(CH_3){=}CHCH_2$), 2.40 (dd, J = 15.3, 2.5 Hz, 1 H, CH_2COOCH), 2.17−2.10 (m, 1 H, $CH_2C(CH_3){=}CH$), 2.05 (s, 3 H, $CH{=}CCH_3$), 1.95 (ddd, J = 13.4, 10.0, 3.3 Hz, 1 H, $CH_2C(CH_3){=}CH$), 1.70−1.57 (m, 3 H), 1.57 (s, 3 H, $CH_2C(CH_3){=}CH$), 1.50−1.35 (m, 2 H), 1.33 (s, 3 H, $C(CH_3)_2$), 1.15 (d, J = 6.8 Hz, 3 H, $CH(CH_3)$), 1.03 (s, 3 H, $C(CH_3)_2$), 0.97 (d, J = 7.0 Hz, 3 H, $CH(CH_3)$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 220.7, 170.7, 165.3, 152.3, 138.5, 137.4, 119.6, 119.4, 115.7, 77.7, 76.2, 71.6, 52.7, 42.7, 39.4, 39.0, 37.3, 30.7, 24.5, 20.5, 19.7, 18.7, 15.9, 15.8, 15.5, 14.3; FAB HRMS (NBA) m/e 492.2772, M + H^+ calcd for $C_{27}H_{41}NO_5S$ 492.2784.

Epothilone B (2) and Its α-Epoxide Epimer 57. **Epoxidation of Lactone 4**. **Procedure A:** To a solution of lactone **4** (3.0 mg, 6.1 μmol) in benzene (0.2 mL) at −10 °C was added *m*-chloroperbenzoic acid (2.9 mg, 50−60% purity, 8.4−10.1 μmol, 1.4−1.6 equiv), and the reaction mixture was stirred at that temperature for 2 h, at which time TLC indicated completion of the reaction. The reaction mixture was diluted with EtOAc (5 mL) and washed with saturated aqueous $NaHCO_3$ solution (2 mL), and the aqueous phase was extracted with EtOAc (3 × 2 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification by preparative thin-layer chromatography (silica gel, 5% MeOH in CH_2Cl_2) provided a mixture of epothilone B (**2**) and its α-epoxy diastereoisomer **57** (2.0 mg, 66%, ca. 5:1 ratio by ^{1}H NMR), which was separated to its components by a second preparative thin-layer chromatography (silica gel, 70% EtOAc in hexanes) furnishing pure epothilone B (**2**) (1.6 mg, 52%) as a white solid. **Procedure B:** To a solution of lactone **4** (5.0 mg, 10.2 μmol) in CH_2Cl_2 (0.5 mL) at −50 °C was added dropwise a solution of dimethyldioxirane in acetone untill the starting material disappeared (TLC). The resulting solution was concentrated, and the crude product was subjected to preparative thin-layer chromatography (silica gel, 5% MeOH in CH_2Cl_2) to give epothilone B (**2**) and its α-epoxy diastereoisomer **57** in ca. 5:1 ratio (3.9 mg, 75%). Pure epothilone B (**2**) was obtained (3.1 mg, 60%) by preparative thin-layer chromatography as described above. **Procedure C:** Lactone **4** (3.0 mg, 6.1 μmol) was epoxidized with methyl(trifluoromethyl)dioxirane according to the procedure described above for the epoxidation of **3**, to yield a mixture of **2** and its α-epoxy diastereoisomer **57** in ca. 5:1 ratio by ^{1}H NMR (2.6 mg, 85% yield). The major diastereoisomer, epothilone B (**2**), was isolated as described above (2.1 mg, 69%). **2**: colorless crystals; mp 93 °C (crystallized in CH_2Cl_2/petroleum ether); R_f = 0.24 (silica gel, 4% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −34.3 (c 0.2, MeOH); IR (thin film) ν_{max} 3436, 2954, 2931, 1731, 1684, 1455, 1373, 1290, 1249, 1184, 1143, 1043, 1049, 973, 750 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.97 (s, 1 H, SCH═C), 6.59 (s, 1 H, $CH{=}CCH_3$), 5.41 (dd, J = 7.8, 2.8 Hz, 1 H, CH_2COOCH), 4.22 (bs, 2 H, $(CH_3)_2CCHOH$, OH), 3.77 (dd, J = 4.3, 4.2 Hz, 1 H, $CHOH$), 3.30 (dq, J = 6.8, 4.1 Hz, 1 H, $C(O)CHCH_3$), 2.80 (dd, J = 7.6, 4.7 Hz, 1 H, $CHOCCH_3$), 2.70 (s, 3 H, $N{=}C(CH_3)S$), 2.64 (bs, 1 H, OH), 2.54 (dd, J = 14.0, 10.2 Hz, 1 H, CH_2COOCH), 2.36 (d, J = 14.0, 2.9 Hz, 1 H, CH_2COOCH), 2.12 (dd, J = 4.7, 2.8 Hz, 1 H, $(CH_3)COCHCH_2CHO$), 2.08 (s, 3 H, $CH{=}CCH_3$), 1.91 (ddd, J = 15.4, 7.8, 7.6 Hz, 1 H, $(CH_3)COCHCH_2CHO$), 1.77−1.68 (m, 3 H), 1.53−1.46 (m, 2 H), 1.43−1.37 (m, 2 H), 1.36 (s, 3 H, $C(CH_3)OCHCH_2$), 1.27 (s, 3 H, $C(CH_3)_2$), 1.16 (d, J = 6.9 Hz, 3 H, $CH(CH_3)$), 1.08 (s, 3 H, $C(CH_3)_2$), 1.00 (d, J = 7.0 Hz, 3 H, $CH(CH_3)$); ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.34 (s, 1 H, SCH═C), 6.49 (s, 1 H, $CH{=}CCH_3$), 5.27 (dd, J = 9.0, 2.0 Hz, 1 H, CH_2COOCH), 5.07 (d, J = 6.9 Hz, 1 H, OH), 4.45 (bs, 1 H, OH), 4.08 (m, 1 H, $(CH_3)_2CCHOH$), 3.47 (d, J = 7.4 Hz, 1 H, $CHOH$), 3.10 (dq, J = 6.8, 6.5 Hz, 1 H, $C(O)CHCH_3$), 2.81 (dd, J = 9.5, 3.3 Hz, 1 H, $CHOCCH_3$), 2.64 (s, 3 H, $N{=}C(CH_3)S$), 2.40−2.30 (m, 2 H, CH_2COOCH), 2.08 (s, 3 H, $CH{=}CCH_3$), 2.05 (ddd, J = 15.0, 2.6, 1.0 Hz, 1 H, $(CH_3)COCHCH_2CHO$), 1.83 (ddd, J = 15.0, 9.3, 9.1 Hz, 1 H, $(CH_3)COCHCH_2CHO$), 1.61 (m, 1 H), 1.45−1.35 (m, 3 H), 1.35−1.25 (m, 3 H), 1.17 (s, 6 H, $C(CH_3)OCHCH_2$, $C(CH_3)_2$), 1.05 (d, J = 6.6 Hz, 3 H, $CH(CH_3)$), 0.87 (d, J = 7.0 Hz, 3 H, $CH(CH_3)$), 0.86 (s, 3 H, $C(CH_3)_2$); ^{13}C NMR (150.9 MHz, DMSO-d_6) δ 218.1, 170.7, 164.8, 152.5, 137.6, 119.5, 118.0, 76.7, 75.7, 70.7, 61.6, 61.1, 53.3, 44.9, 35.6, 33.0, 32.1, 29.6, 23.0, 22.4, 22.0, 19.7, 18.8, 18.4, 16.4, 14.1; FAB HRMS (NBA/CsI) m/e 640.1725, M + Cs^+ calcd for $C_{27}H_{41}NO_6S$ 640.1709. A natural sample[30] of epothilone B (**2**) exhibited properties identical to those reported above.

Epothilone 58 and 59. Epoxidation of Lactone 56. **Procedure A:** Compound **56** (5.0 mg, 10.2 μmol) was epoxidized with *m*CPBA according to procedure A described above for **2** to yield a mixture of 12*S-epi*-epothilone B (**58**) and its α-epoxy diastereoisomer **59** (3.7 mg, 73% total yield, ca. 1:4 by ^{1}H NMR). Purification by preparative thin-layer chromatography (silica gel, 5% MeOH in CH_2Cl_2) gave pure 12*R*-epothilone **59** (2.5 mg, 49%) as a white solid. **Procedure B:** The epoxidation of **56** (3.0 mg, 6.1 μmol) according to the procedure described above for **1** led to epothilones **58** and its α-epoxy diastereoisomer **59** (2.6 mg, 86% total yield, ca. 1:1 ratio by ^{1}H NMR). Preparative thin-layer chromatography (silica gel, 5% MeOH in CH_2Cl_2) furnished pure epothilone **58** (1.3 mg, 43%) and its α-epoxy diastereoisomer **59** (1.3 mg, 43%). **58**: R_f = 0.52 (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −33.1 (c 0.1, $CHCl_3$); ^{1}H NMR (600 MHz, C_6D_6) δ 6.62 (s, 1 H, $CH{=}CCH_3$), 6.44 (s, 1 H, SCH═C), 5.46 (dd, J = 7.2, 5.1 Hz, 1 H, CH_2COOCH), 4.22 (dd, J = 8.3, 3.0 Hz, 1 H, $(CH_3)_2CCHOH$), 3.71 (dd, J = 4.2, 3.6 Hz, 1 H, $CHOH$), 3.10 (dq, J = 8.6, 3.7 Hz, 1 H, $C(O)CHCH_3$), 2.95 (bs, 1 H, OH), 2.86 (dd, J = 5.8, 5.7 Hz, 1 H, $CHOCCH_3$), 2.82 (bs, 1 H, OH), 2.30 (dd, J = 14.8, 10.1 Hz, 1 H, CH_2COOCH), 2.24 (dd, J = 14.8, 3.5 Hz, 1 H, CH_2COOCH), 2.19 (s, 3 H, $N{=}C(CH_3)S$), 1.99 (s, 3 H, $CH{=}CCH_3$), 1.79−1.75 (m, 2 H), 1.74−1.70 (m, 1 H, $(CH_3)COCHCH_2CHO$), 1.60−1.55 (m, 1 H), 1.37−1.20 (m, 3 H), 1.18−1.11 (m, 1 H), 1.05 (d, J = 6.9 Hz, 3 H, $CH(CH_3)$), 1.04 (s, 6 H, $C(CH_3)OCHCH_2$), $C(CH_3)_2$), 0.92 (s, 3 H, $C(CH_3)_2$), 0.85 (d, J = 7.1 Hz, 3 H, $CH(CH_3)$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 220.3, 170.8, 134.0, 133.8, 132.3, 128.7, 116.3, 73.7, 72.2, 61.5, 59.7, 53.0, 42.5, 38.7, 38.4, 36.7, 32.4, 32.1, 22.5, 21.4, 19.5, 17.8, 15.7, 15.4, 13.9, 12.5. **59**: R_f = 0.55 (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −34.5 (c 0.1, $CHCl_3$); IR (thin film) ν_{max} 3440, 2929, 1731, 1693, 1467, 1384, 1294, 1257, 1151, 1050, 977, 755 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.97 (s, 1 H, SCH═C), 6.60 (s, 1 H, $CH{=}CCH_3$), 5.50 (dd, J = 8.0, 4.0 Hz, 1 H, CH_2COOCH), 4.25 (dd, J = 10.1, 3.2 Hz, 1 H, $(CH_3)_2CCHOH$), 3.80 (bs, 1 H, OH), 3.75 (dd, J = 5.5, 3.6 Hz, 1 H, $CHOH$), 3.31 (dq, J = 6.7, 6.3 Hz, 1 H, $C(O)CHCH_3$), 2.88 (dd, J = 6.3, 4.5 Hz, 1 H, $CHOCCH_3$), 2.69 (s, 3 H, $N{=}C(CH_3)S$), 2.59 (bs, 1 H, OH), 2.55 (dd, J = 13.5, 10.4 Hz, 1 H, CH_2COOCH), 2.45 (dd, J = 13.5, 3.7 Hz, 1 H, CH_2COOCH), 2.08 (s, 3 H, $CH{=}CCH_3$), 2.05−1.97 (m, 3 H), 1.95−1.90 (m, 1 H, $(CH_3)COCHCH_2CHO$), 1.75−1.70 (m, 2 H), 1.51−1.45 (m, 3 H), 1.37 (s, 3 H, $C(CH_3)OCHCH_2$), 1.27 (s, 3 H, $C(CH_3)_2$), 1.14 (d, J = 6.9 Hz, 3 H, $CH(CH_3)$), 1.04 (s, 3 H, $C(CH_3)_2$), 0.95 (d, J = 6.9 Hz, 3 H, $CH(CH_3)$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 219.6, 170.7, 164.9, 152.1, 136.6, 119.8, 116.4, 77.6, 75.9, 73.3, 61.3, 59.9, 52.9, 44.2, 38.8, 37.2, 36.4, 32.9, 31.3, 21.9, 21.3, 19.8, 19.4, 17.9, 17.4, 14.8; FAB HRMS (NBA/CsI) m/e 640.1686, M + Cs^+ calcd for $C_{27}H_{41}NO_6S$ 640.1709.

α,β-Unsaturated Ester 60. A mixture of aldehyde **15** (5.17 g, 15.9 mmol) and stabilized ylide **16** (8.92 g, 24.0 mmol, 1.5 equiv, prepared from 4-bromo-1-butene by (i) phosphonium salt formation, (ii) anion

formation with NaHMDS, and (iii) quenching with $MeOC(O)Cl$[32]) in benzene (300 mL, 0.05 M) was heated at reflux for 3 h. After being cooled to 25 °C, the solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (silica gel, 30% ether in hexanes) to afford α,β-unsaturated ester **60** (7.15 g, 95%): R_f = 0.65 (silica gel, 40% ether in hexanes); $[\alpha]^{22}_D$ +10.4 (*c* 1.4, $CHCl_3$); IR (thin film) ν_{max} 2939, 2856, 1715, 1644, 1504, 1464, 1437, 1365, 1284, 1252, 1209, 1076, 955, 836, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.91 (s, 1 H, SCH═C), 6.87 (d, *J* = 7.4 Hz, 1 H, C*H*═CCOOCH$_3$), 6.47 (s, 1 H, C*H*═CCH$_3$), 5.83−5.71 (m, 1 H, C*H*═CH$_2$), 5.01−4.92 (m, 2 H, CH═C*H*$_2$), 4.19 (dd, *J* = 7.7, 4.9 Hz, 1 H, CHOSi), 3.69 (s, 3 H, COOCH$_3$), 3.05 (d, *J* = 6.0 Hz, 2 H, C*H*$_2$-CH═CH$_2$), 2.67 (s, 3 H, N═C(S)CH$_3$), 2.46 (ddd, *J* = 15.1, 7.7, 7.4 Hz, 1 H, C*H*$_2$CHOSi), 2.39 (ddd, *J* = 15.0, 7.5, 5.0 Hz, 1 H, C*H*$_2$-CHOSi), 1.99 (s, 3 H, CH═CC*H*$_3$), 0.86 (s, 9 H, SiC(CH$_3$)$_3$), 0.03 (s, 3 H, Si(CH$_3$)$_2$), −0.02 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 167.8, 164.4, 152.8, 141.5, 140.6, 135.3, 130.7, 119.1, 115.5, 115.1, 77.6, 51.7, 36.1, 30.9, 25.7, 19.2, 18.1, 13.9, −4.7, −5.1; FAB HRMS (NBA/CsI) *m/e* 554.1168, M + Cs^+ calcd for $C_{22}H_{35}NO_3SSi$ 554.1161.

Allylic Alcohol 61. Methyl ester **60** (6.1 g, 14.4 mmol) was dissolved in THF (80 mL) and cooled to −78 °C. DIBAL (44.0 mL, 1 M solution in CH_2Cl_2, 44.0 mmol, 3.0 equiv) was added dropwise at −78 °C, and the reaction mixture was stirred for 3 h. The reaction mixture was quenched with MeOH (1.0 mL) at −78 °C, and then ether (100 mL) was added, followed by saturated aqueous sodium−potasium tartrate solution (10 mL). The resulting mixture was allowed to warm to room temperature, where it was stirred for 3 h. The organic layer was separated, and the aqueous phase was extracted with ether (2 × 50 mL). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash column chromatography (silica gel, 40 → 80% ether in hexanes) furnished alcohol **61** (5.58 g, 98%): R_f = 0.18 (silica gel, 40% ether in hexanes); $[\alpha]^{22}_D$ +6.6 (*c* 1.1, $CHCl_3$); IR (thin film) ν_{max} 3380, 2928, 2855, 1637, 1505, 1464, 1386, 1253, 1185, 1074, 836, 776 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.88 (s, 1 H, SCH═C), 6.41 (s, 1 H, C*H*═CCH$_3$), 5.77−5.69 (m, 1 H, C*H*═CH$_2$), 5.48 (dd, *J* = 7.3, 7.2 Hz, 1 H, C*H*═CCH$_2$-OH), 5.00 (dd, *J* = 15.5, 3.3 Hz, 1 H, CH═C*H*$_2$), 4.93 (dd, *J* = 10.0, 3.3 Hz, 1 H, CH═C*H*$_2$), 4.12 (dd, *J* = 6.5, 6.4 Hz, 1 H, CHOSi), 3.97 (s, 2 H, C*H*$_2$OH), 2.86−2.76 (m, 2 H, C*H*$_2$CH═CH$_2$), 2.65 (s, 3 H, N═C(S)CH$_3$), 2.53 (bs, 1 H, OH), 2.36−2.24 (m, 2 H, C*H*$_2$CHOSi), 1.94 (s, 3 H, CH═CC*H*$_3$), 0.86 (s, 9 H, SiC(CH$_3$)$_3$), 0.02 (s, 3 H, Si-(CH$_3$)$_2$), −0.02 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 164.5, 152.8, 142.0, 138.1, 123.7, 118.7, 115.2, 114.9, 78.3, 66.6, 34.7, 32.4, 25.7, 19.0, 18.1, 13.7, −4.8, −5.0; FAB HRMS (NBA) *m/e* 394.2232, M + H^+ calcd for $C_{21}H_{35}NO_2SSi$ 394.2236.

Compound 62. Chlorination of Alcohol 61. Alcohol **61** (3.00 g, 7.60 mmol) was dissolved in CCl_4 (75 mL, 0.1 M), and Ph_3P (4.00 g, 15.2 mmol, 2.0 equiv) was added. The reaction mixture was stirred at 100 °C for 24 h and cooled to room temperature, and the solvent was removed under reduced pressure. Flash column chromatography (silica gel, 10% ether in hexanes) furnished pure **62** (2.6 g, 83%): R_f = 0.50 (silica gel, 15% ether in hexanes); $[\alpha]^{22}_D$ +13.7 (*c* 1.0, $CHCl_3$); IR (thin film) ν_{max} 2953, 2928, 2855, 1637, 1504, 1470, 1439, 1387, 1254, 1182, 1075, 953, 917, 836, 776 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.93 (s, 1 H, SCH═C), 6.47 (s, 1 H, C*H*═CCH$_3$), 5.77−5.69 (m, 1 H, C*H*═CH$_2$), 5.66 (dd, *J* = 7.5, 7.2 Hz, 1 H, CH$_2$C*H*═CCH$_2$Cl), 5.07 (dd, *J* = 17.1, 1.6 Hz, 1 H, CH═C*H*$_2$), 5.02 (dd, *J* = 10.1, 1.4 Hz, 1 H, CH═C*H*$_2$), 4.14 (dd, *J* = 7.2, 5.5 Hz, 1 H, CHOSi), 4.02 (s, 2 H, CH$_2$Cl), 2.99−2.89 (m, 2 H, C*H*$_2$CH═CH$_2$), 2.71 (s, 3 H, N═C(S)CH$_3$), 2.52−2.27 (m, 2 H, C*H*$_2$CHOSi), 1.99 (s, 3 H, CH═CC*H*$_3$), 0.88 (s, 9 H, SiC(CH$_3$)$_3$), 0.05 (s, 3 H, Si(CH$_3$)$_2$), 0.00 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 164.3, 152.9, 141.8, 134.9, 134.7, 128.9, 119.0, 116.2, 115.2, 78.1, 49.9, 35.3, 32.3, 25.8, 19.2, 18.2, 13.9, −4.7, −5.0; FAB HRMS (NBA) *m/e* 412.1884, M + H^+ calcd for $C_{21}H_{34}$-ClNOSSi 412.1897.

Compound 63. Reduction of 62. Compound **62** (2.60 g, 6.30 mmol) was dissolved in THF (60 mL, 0.1 M) and cooled to 0 °C. $LiEt_3$-BH (12.6 mL, 1.0 M solution in THF, 12.6 mmol, 2.0 equiv) was added dropwise, and the reaction mixture was stirred at 0 °C for 1 h. Aqueous NaOH (1.0 mL, 3.0 N) solution was added followed by addition of Et_20 (150 mL). The organic phase was washed with brine (2 × 20 mL), dried ($MgSO_4$) and concentrated. Flash column chromatography (silica gel, 20% ether in hexanes) furnished pure **63** (2.38 g, 99%): R_f = 0.60 (silica gel, 15% ether in hexanes); $[\alpha]^{22}_D$ +17.1 (*c* 0.7, $CHCl_3$); IR (thin film) ν_{max} 2928, 2856, 1637, 1505, 1464, 1253, 1181, 1075, 946, 836, 776 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.91 (s, 1 H, SCH═C), 6.45 (s, 1 H, C*H*═CCH$_3$), 5.77−5.68 (m, 1 H, C*H*═CH$_2$), 5.22 (dd, *J* = 7.3, 7.0 Hz, 1 H, CH$_2$C*H*═CCH$_3$), 5.01 (dd, *J* = 17.1, 3.2 Hz, 1 H, CH═C*H*$_2$), 4.96 (dd, *J* = 10.1, 3.3 Hz, 1 H, CH═C*H*$_2$), 4.09 (dd, *J* = 7.2, 5.9 Hz, 1 H, CHOSi), 2.80 (dd, *J* = 14.5, 6.5 Hz, 1 H, C*H*$_2$CH═CH$_2$), 2.73−2.68 (m, 1 H, C*H*$_2$CH═CH$_2$), 2.70 (s, 3 H, N═C(S)CH$_3$), 2.32−2.19 (m, 2 H, C*H*$_2$CHOSi), 1.99 (s, 3 H, CH═CC*H*$_3$), 1.66 (s, 3 H, CH$_2$CH═CC*H*$_3$), 0.88 (s, 9 H, SiC(CH$_3$)$_3$), 0.04 (s, 3 H, Si(CH$_3$)$_2$), −0.01 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 164.3, 153.2, 142.5, 136.0, 134.4, 122.5, 118.7, 115.1, 114.9, 78.9, 36.6, 35.3, 25.8, 23.5, 19.2, 18.2, 13.9, −4.8, −5.0; FAB HRMS (NBA) *m/e* 378.2279, M + H^+ calcd for $C_{21}H_{35}NOSSi$ 378.2287.

Primary Alcohol 64. Selective Hydroboration of Olefinic Compound 63. Compound **63** (1.1 g, 2.91 mmol) was dissolved in THF (3.0 mL, 1.0 M), and the solution was cooled to 0 °C. 9-BBN (7.0 mL, 0.5 M solution in THF, 3.5 mmol, 1.2 equiv) was added, and the reaction mixture was stirred for 2 h at 0 °C. Aqueous NaOH (7.0 mL, 3 N solution, 21.0 mmol, 7.2 equiv) was added with stirring, followed by H_2O_2 (2.4 mL, 30%, aqueous solution). Stirring was continued for 0.5 h at 0 °C, after which time the reaction mixture was diluted with ether (30 mL). The organic solution was separated, and the aqueous phase was extracted with ether (2 × 15 mL). The combined organic layer was washed with brine (2 × 5 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash column chromatography (silica gel, 50 → 80% ether in hexanes) furnished primary alcohol **64** (1.0 g, 91%): R_f = 0.17 (silica gel, 50% ether in hexanes); $[\alpha]^{22}_D$ +3.6 (*c* 0.2, $CHCl_3$); IR (thin film) ν_{max} 3381, 2953, 2929, 2856, 1723, 1660, 1469, 1444, 1376, 1253, 1185, 1073, 941, 837, 776 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.91 (s, 1 H, SCH═C), 6.44 (s, 1 H, C*H*═CCH$_3$), 5.17 (dd, *J* = 7.0, 6.9 Hz, 1 H, CH$_2$C*H*═CCH$_3$), 4.11 (dd, *J* = 7.1, 5.7 Hz, 1 H, CHOSi), 3.59 (dd, *J* = 6.5, 6.4 Hz, 2 H, C*H*$_2$OH), 2.70 (s, 3 H, N═C-(S)CH$_3$), 2.35−2.28 (m, 1 H, C*H*$_2$CHOSi), 2.27−2.20 (m, 1 H, C*H*$_2$-CHOSi), 2.10 (dd, *J* = 7.6, 7.5 Hz, 2 H C*H*$_2$CH$_2$CH$_2$OH), 1.98 (s, 3 H, CH═CC*H*$_3$), 1.67 (s, 3 H, CH$_2$CH═CC*H*$_3$), 1.67−1.58 (m, 2 H, C*H*$_2$CH$_2$OH), 0.88 (s, 9 H, SiC(CH$_3$)$_3$), 0.04 (s, 3 H, Si(CH$_3$)$_2$), −0.01 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 164.5, 153.0, 142.7, 136.2, 122.2, 118.5, 115.0, 78.9, 62.4, 35.4, 30.7, 28.0, 25.8, 23.3, 19.2, 18.3, 14.0, −4.7, −5.0; FAB HRMS (NBA) *m/e* 396.2382, M + H^+ calcd for $C_{21}H_{37}NO_2SSi$ 396.2393.

Iodide 14. Iodide **14** (1.18 g, 92%) was prepared from alcohol **64** (1.0 g, 2.53 mmol) according to the procedure described above for **27**. **14**: Colorless oil; R_f = 0.65 (silica gel, 20% ether in hexanes); $[\alpha]^{22}_D$ +7.5 (*c* 0.8, $CHCl_3$); IR (thin film) ν_{max} 2955, 2930, 2855, 1504, 1462, 1444, 1376, 1360, 1253, 1183, 1074, 942, 837, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.91 (s, 1 H, SCH═C), 6.46 (s, 1 H, C*H*═CCH$_3$), 5.20 (dd, *J* = 7.3, 7.1 Hz, 1 H, CH$_2$C*H*═CCH$_3$), 4.09 (dd, *J* = 7.4, 5.5 Hz, 1 H, CHOSi), 3.14 (dd, *J* = 7.1, 7.0 Hz, 2 H, CH$_2$I), 2.69 (s, 3 H, N═C(S)CH$_3$), 2.34−2.27 (m, 1 H, C*H*$_2$CHOSi), 2.26−2.19 (m, 1 H, C*H*$_2$CHOSi), 2.17−2.03 (m, 2 H), 2.00 (s, 3 H, CH═CC*H*$_3$), 1.93−1.86 (m, 2 H), 1.67 (s, 3 H, CH$_2$CH═CC*H*$_3$) 0.88 (s, 9 H, SiC(CH$_3$)$_3$), 0.04 (s, 3 H, Si(CH$_3$)$_2$), −0.01 (s, 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 164.2, 153.1, 142.3, 134.6, 123.1, 118.6, 115.0, 78.8, 35.4, 32.6, 31.9, 25.8, 23.4, 19.2, 18.2, 14.0, 6.5, −4.7, −5.0; FAB HRMS (NBA) *m/e* 506.1422, M + H^+ calcd for $C_{21}H_{36}INOSSi$ 506.1410.

Hydrazone 65. Alkylation of SAMP Hydrazone 13 with Iodide 14. SAMP hydrazone **13**[15] (337 mg, 0.2 mmol, 2.0 equiv) in THF (2.5 mL) was added to a freshly prepared solution of LDA at 0 °C [diisopropylamine (277 μL, 0.20 mmol, 2.0 equiv) was added to *n*-BuLi (1.39 mL, 1.42 M solution in hexanes, 0.20 mmol. 2.0 equiv) in 2.5 mL of THF at 0 °C] at 0 °C. After being stirred at that temperature for 8 h, the resulting yellow solution was cooled to −100 °C and a solution of iodide **14** (0.5 g, 0.99 mmol, 1.0 equiv) in THF (3 mL) was added dropwise over a period of 5 min. The mixture was allowed to warm to −20 °C over 10 h and then poured into saturated aqueous NH_4Cl solution (5 mL) and extracted with ether (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated. Purification by flash column chromatography on silica gel (20 → 40% ether in hexanes) provided hydrazone **65** (380 mg, 70%, de > 98% by

^{1}H NMR) as a yellow oil: $R_f = 0.17$ (silica gel, 20% ether in hexanes); $[\alpha]^{22}_D$ −27.8 (*c* 2.6, $CHCl_3$); IR (thin film) ν_{max} 2931, 2861, 1724, 1653, 1599, 1499, 1451, 1374, 1249, 1178, 1077, 940, 834, 774, 727, 673 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 (s, 1 H, SCH═C), 6.48 (d, J = 6.6 Hz, 1 H, CNH), 6.44 (s, 1 H, C*H*═CCH_3), 5.12 (dd, J = 7.1, 6.9 Hz, 1 H, CH_2CH═CCH_3), 4.07 (dd, J = 6.8, 6.2 Hz, 1 H, CHOSi), 3.55 (dd, J = 9.1, 3.7 Hz, 1 H, C*H*$_2$$OCH_3$), 3.41 (dd, J = 9.1, 6.9 Hz, 1 H, C*H*$_2$$OCH_3$), 3.36 (s, 3 H, CH_2OCH_3), 3.35−3.32 (m, 2 H, CH_2N), 2.70 (s, 3 H, N═C(S)CH_3), 2.69−2.62 (m, 1 H), 2.31−2.17 (m, 3 H), 2.04−1.84 (m, 5 H), 1.99 (s, 3 H, CH═CCH_3), 1.79−1.72 (m, 1 H), 1.64 (s, 3 H, CH_2CH═CCH_3) 1.41−1.22 (m, 4 H), 1.01 (d, J = 6.9 Hz, $CHCH_3$), 0.88 (s, 9 H, $SiC(CH_3)_3$), 0.04 (s, 3 H, Si-$(CH_3)_2$), −0.01 (s, 3 H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 164.2, 153.1, 144.3, 142.4, 136.6, 121.5, 118.5, 114.8, 78.9, 74.7, 63.4, 59.1, 50.4, 37.0, 35.3, 35.2, 31.8, 26.4, 25.7, 25.4, 23.3, 22.0, 19.1, 18.9, 18.1, 13.8, −4.8, −5.0; FAB HRMS (NBA) *m*/*e* 548.3728, M + H^+ calcd for $C_{30}H_{53}N_3O_2SSi$ 548.3706.

Nitrile 66. Monoperoxyphthalic acid magnesium salt (MMPP·$6H_2O$, 233 mg, 0.38 mmol, 2.5 equiv) was suspended in a rapidly stirred mixture of MeOH and pH 7 phosphate buffer (1:1, 3.0 mL) at 0 °C. Hydrazone **65** (83 mg, 0.15 mmol, 1.0 equiv) in MeOH (1.0 mL) was added dropwise, and the mixture was stirred at 0 °C until the reaction was complete by TLC (ca. 1 h). The resulting suspension was placed in a separating funnel along with ether (15 mL) and saturated aqueous $NaHCO_3$ solution (5 mL). The organic layer was separated, and the aqueous phase was extracted with ether (10 mL). The combined organic solution was washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated. Flash column chromatography (silica gel, 50% ether in hexanes) afforded nitrile **66** (53 mg, 80%) as a colorless oil: $R_f = 0.44$ (silica gel, 50% ether in hexanes); $[\alpha]^{22}_D$ +10.3 (*c* 3.2, $CHCl_3$); IR (thin film) ν_{max} 2926, 2855, 1503, 1457, 1381, 1250, 1179, 1072, 935, 833, 773, cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (s, 1 H, SCH═C), 6.45 (s, 1 H, C*H*═CCH_3), 5.18 (dd, J = 7.0, 6.5 Hz, 1 H, CH_2CH═CCH_3), 4.08 (dd, J = 6.5, 6.0 Hz, 1 H, CHOSi), 2.70 (s, 3 H, N═C(S)CH_3), 2.60−2.53 (m, 1 H), 2.30−2.18 (m, 2 H), 2.11−1.97 (m, 2 H), 1.99 (s, 3 H, CH═CCH_3), 1.67 (s, 3 H, CH_2CH═CCH_3) 1.67−1.45 (m, 4 H), 1.29 (d, J = 6.9 Hz, $CHCH_3$), 0.88 (s, 9 H, $SiC(CH_3)_3$), 0.04 (s, 3 H, $Si(CH_3)_2$), −0.01 (s, 3 H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 164.3, 153.0, 142.3, 135.5, 122.8, 122.4, 118.6, 114.9, 78.4, 35.3, 33.6, 31.1, 25.7, 25.4, 25.1, 23.2, 19.1, 18.1, 17.9, 13.9, −4.8, −5.1; FAB HRMS (NBA) *m*/*e* 433.2720, M + H^+ calcd for $C_{24}H_{40}N_2OSSi$ 433.2709.

Aldehyde 8. Nitrile **66** (53 mg, 0.12 mmol) was dissolved in toluene (2.0 mL) and cooled to −78 °C. DIBAL (245 μL, 1 M solution in toluene, 0.22 mmol, 2.0 equiv) was added dropwise at −78 °C, and the reaction mixture was stirred at that temperature until its completion was verified by TLC (ca. 1 h). Methanol (150 μL) and aqueous HCl (150 μL, 1 N solution) were sequentially added, and the resulting mixture was brought up to 0 °C and stirred at that temperature for 30 min. Ether (5 mL) and water (2 mL) were added, and the organic layer was separated. The aqueous phase was extracted with ether (2 × 5 mL), and the combined organic solution was washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash column chromatography (silica gel, 15% ether in hexanes) furnished pure aldehyde **8** (44 mg, 82%): $R_f = 0.48$ (silica gel, 50% ether in hexanes); $[\alpha]^{22}_D$ +14.7 (*c* 1.7, $CHCl_3$); IR (thin film) ν_{max} 2915, 2859, 1721, 1500, 1455, 1381, 1251, 1183, 1070, 940, 832, 770 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.60 (d, J = 1.9 Hz, 1 H, CHO), 6.92 (s, 1 H, SCH═C), 6.45 (s, 1 H, C*H*═CCH_3), 5.16 (dd, J = 7.1, 7.0 Hz, 1 H, CH_2CH═CCH_3), 4.08 (dd, J = 7.0, 5.5 Hz, 1 H, CHOSi), 2.70 (s, 3 H, N═C(S)CH_3), 2.36−2.18 (m, 3 H), 2.07−2.01 (m, 2H), 1.99 (s, 3 H, CH═CCH_3), 1.71−1.64 (m, 1 H), 1.66 (d, J = 1.0 Hz, 3 H, CH_2CH═CCH_3), 1.43−1.29 (m, 3 H), 1.08 (d, J = 7.0 Hz, 3 H, CH_3CH), 0.88 (s, 9 H, $SiC(CH_3)_3$), 0.04 (s, 3 H, $Si(CH_3)_2$), −0.01 (s, 3 H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 205.0, 164.4, 153.1, 142.3, 135.9, 122.0, 118.6, 114.9, 78.8, 46.1, 35.3, 31.7, 30.2, 25.7, 25.1, 23.3, 19.1, 18.2, 13.8, 13.2, −4.8, −5.1; FAB HRMS (NBA) *m*/*e* 436.2717, M + H^+ calcd for $C_{24}H_{41}NO_2SSi$ 436.2706.

12*Z*-Carboxylic Acids 52 and 53. Aldol Reaction of Keto Acid 9 with 12*Z*-Aldehyde 8. A solution of keto acid **9** (365 mg, 1.21 mmol, 1.6 equiv) in THF (5.0 mL) was reacted with 12*Z*-aldehyde **8** (330 mg, 0.76 mmol, 1.0 equiv) according to the same procedure as described above for the condensation of **9** and **8** to afford, after similar processing, geometrically pure 12*Z*-carboxylic acids **52** (207 mg, 32%) and **53** (181 mg, 28%) and recovered **9**. **12*Z*-Carboxylic acid 52**: R_f = 0.56 (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −2.9 (*c* 0.8, $CHCl_3$); IR (thin film) ν_{max} 2933, 2854, 1708, 1464, 1385, 1249, 1187, 1079, 983, 830, 773 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (s, 1 H, SCH═C), 6.58 (s, 1 H, C*H*═CCH_3), 5.15 (dd, J = 7.4, 7.1 Hz, 1 H, $(CH_3)C$═C*H*CH_2), 4.39 (dd, J = 6.7, 3.0 Hz, 1 H, $(CH_3)_2CC$*H*OSi), 4.11 (dd, J = 7.3, 5.7 Hz, 1 H, CH_2CHOSi), 3.74 (dd, J = 6.1, 1.8 Hz, 1 H, $CH(CH_3)CH$OSi), 3.13 (dq, J = 7.0, 6.5 Hz, 1 H, C(O)C*H*(CH_3)), 2.70 (s, 3 H, N═$C(CH_3)$S), 2.44 (dd, J = 16.4, 3.1 Hz, 1 H, C*H*$_2$-COOH), 2.31 (dd, J = 16.4, 6.8 Hz, 1 H, C*H*$_2$COOH), 2.28−2.04 (m, 3 H, C*H*$_2C(CH_3)$═CH, $CH_2C(CH_3)$═CH*CH*$_2$), 1.94 (s, 3 H, CH═C-(C*H*$_3$)), 1.96−1.86 (m, 1 H), 1.66 (s, 3 H, $CH_2C(CH_3)$═CH), 1.47−1.31 (m, 4 H), 1.17 (s, 3 H, $C(CH_3)_2$), 1.12 (s, 3 H, $C(CH_3)_2$), 1.21−1.09 (m, 1 H), 1.08 (d, J = 6.8 Hz, 3 H, $CH(CH_3)$), 0.90−0.85 (m, 30 H, $CH(CH_3)$, 3 x $SiC(CH_3)_3$), 0.10 (s, 3 H, $Si(CH_3)_2$), 0.06 (s, 3 H, $Si(CH_3)_2$), 0.05 (s, 3 H, $Si(CH_3)_2$), 0.03 (s, 3 H, $Si(CH_3)_2$), 0.02 (s, 3 H, $Si(CH_3)_2$), −0.02 (s, 3 H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 218.2, 175.5, 165.0, 152.8, 143.4, 137.0, 121.6, 118.2, 114.5, 79.1, 73.1, 53.8, 44.4, 40.0, 39.2, 35.3, 32.4, 31.4, 26.2, 26.0, 25.8, 25.7, 23.5, 23.4, 18.8, 18.7, 18.4, 18.2, 16.8, 15.8, 13.9, −3.9, −4.0, −4.1, −4.6, −4.7, −5.0; FAB HRMS (NBA/CsI) *m*/*e* 984.4427, M + Cs^+ calcd for $C_{45}H_{85}NO_6SSi_3$ 984.4460. **12*Z*-Carboxylic acid 53:** R_f = 0.65 (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ +6.2 (*c* 0.6, $CHCl_3$); IR (thin film) ν_{max} 2933, 2854, 1708, 1459, 1386, 1249, 1074, 988, 830, 773 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 (s, 1 H, SCH═C), 6.45 (s, 1 H, C*H*═CCH_3), 5.12 (dd, J = 7.4, 6.9 Hz, 1 H, $(CH_3)C$═C*H*CH_2), 4.56 (dd, J = 6.1, 5.6 Hz, 1 H, $(CH_3)_2CC$*H*OSi), 4.07 (dd, J = 7.6, 5.6 Hz, 1 H, CH_2CHOSi), 3.85 (d, J = 8.4 Hz, 1 H, $CH(CH_3)CH$OSi), 3.10 (dq, J = 7.1, 7.0 Hz, 1 H, C(O)C*H*(CH_3)), 2.75 (s, 3 H, N═C-(CH_3)S), 2.43−2.10 (m, 4 H), 1.96−1.88 (m, 2 H), 1.91 (s, 3 H, CH═C-(C*H*$_3$)), 1.66 (s, 3 H, $CH_2C(CH_3)$═CH), 1.35−1.02 (m, 14 H, C*H*(CH_3), 2 x CH_2, $C(CH_3)_2$, $C(CH_3)_2$, $CH(CH_3)$), 0.92−0.80 (m, 30 H, 3 x SiC-$(CH_3)_3$, $CH(CH_3)$), 0.09−0.01 (m, 18 H, 3 x $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 218.1, 174.2, 165.4, 152.3, 143.7, 137.1, 121.6, 117.9, 114.4, 78.9, 72.4, 53.8, 45.8, 40.4, 38.3, 35.6, 35.3, 32.3, 26.7, 26.3, 26.2, 26.0, 25.8, 25.7, 23.9, 23.3, 18.6, 18.5, 18.4, 17.1, 13.9, 13.4, −3.4, −3.6, −4.3, −4.6, −4.7, −4.9; FAB HRMS (NBA/CsI) *m*/*e* 984.4430, M + Cs^+ calcd for $C_{45}H_{85}NO_6SSi_3$ 984.4460.

12*Z*-Hydroxy Acid 6. 12*Z*-Carboxylic acid **52** (400 mg, 0.47 mmol) was converted to 12*Z*-hydroxy acid **6** (253 mg, 73% yield) according to the same procedure described above for **5**. **6**: yellow oil; $R_f = 0.41$ (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −10.4 (*c* 0.4, $CHCl_3$); IR (thin film) ν_{max} 3227, 2933, 2852, 1711, 1696, 1468, 1387, 1245, 1189, 1087, 986, 834, 773 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (s, 1 H SCH═C), 6.67 (s, 1 H, C*H*═CCH_3), 5.19 (dd, 1 H, J = 7.5, 7.0 Hz, CH_3C═C*H*CH_2), 4.41 (dd, J = 6.0, 3.5 Hz, 1 H, $(CH_3)_2CC$*H*OSi), 4.16 (dd, J = 6.6, 6.5 Hz, 1 H, CH_2CHOH), 3.78 (d, J = 6.9 Hz, 1 H, $CH(CH_3)CH$OSi), 3.13 (dq, J = 6.9, 6.6 Hz, 1 H, C(O)C*H*CH_3), 2.72 (s, 3 H, N═$C(CH_3)$S), 2.47 (dd, J = 16.2, 3.9 Hz, 1 H, C*H*$_2$COOH), 2.40−2.35 (m, 3 H, C*H*$_2C(CH_3)$═CH, C*H*$_2$COOH), 2.17−2.10 (m, 1 H, $C(CH_3)$═CH*CH*$_2$), 2.00 (s, 3 H, CH═C(C*H*$_3$)), 1.99−1.93 (m, 1 H, $C(CH_3)$═CH*CH*$_2$), 1.72 (s, 3 H, $CH_2C(CH_3)$═CH), 1.53−1.35 (m, 5 H), 1.19 (s, 3 H, $C(CH_3)_2$), 1.14 (s, 3 H, $C(CH_3)_2$), 1.07 (d, J = 6.7 Hz, 3 H, $CH(CH_3)$), 0.94−0.84 (m, 21 H, $CH(CH_3)$, $SiC(CH_3)_3$), 0.11 (s, 3 H, $Si(CH_3)_2$), 0.07 (s, 6 H, $Si(CH_3)_2$), 0.05 (s, 3 H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 217.9, 174.8, 165.1, 152.3, 142.1, 139.4, 120.2, 118.5, 115.0, 73.2, 53.8, 44.5, 40.0, 39.1, 34.1, 32.4, 31.2, 26.2, 26.1, 25.9, 23.5, 23.3, 18.9, 18.6, 18.3, 18.1, 16.8, 16.0, 14.6, −3.9, −4.1, −4.2, −4.7; FAB HRMS (NBA/CsI) *m*/*e* 870.3632, M + Cs^+ calcd for $C_{39}H_{71}NO_6SSi_2$ 870.3595.

Hydroxy Acid 67. 12*Z*-Carboxylic acid **53** (200 mg, 0.24 mmol) was converted to 12*Z*-hydroxy acid **67** (123 mg, 71% yield) according to the procedure described above for **5**. **67**: yellow oil; $R_f = 0.45$ (silica gel, 5% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −8.1 (*c* 0.3, $CHCl_3$); IR (thin film) ν_{max} 3227, 2933, 2862, 1711, 1691, 1463, 1382, 1250, 1189, 1082, 986, 834, 773 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (s, 1 H SCH═C), 6.61 (s, 1 H, C*H*═CCH_3), 5.15 (dd, 1 H, J = 7.5, 7.0 Hz, CH_3C═C*H*CH_2), 4.55 (dd, J = 6.1, 3.5 Hz, 1 H, $(CH_3)_2CC$*H*OSi), 4.12 (dd, J = 8.0, 4.5 Hz, 1 H, CH_2CHOH), 3.86 (d, J = 8.2 Hz, 1 H, $CH(CH_3)CH$OSi), 3.12 (dq, J = 7.2, 7.0 Hz, 1 H, C(O)C*H*CH_3), 2.75 (s, 3 H, N═$C(CH_3)$S), 2.37−2.30 (m, 5 H, C*H*$_2C(CH_3)$═CH, C*H*$_2$-COOH, $C(CH_3)$═CH*CH*$_2$), 1.98 (s, 3 H, CH═C(C*H*$_3$)), 1.94−1.89 (m,

1 H), 1.72 (s, 3 H, $CH_2C(CH_3)$═CH), 1.39−1.04 (m, 14 H, C*H*(CH_3), CH(CH_3), 2 x CH_2, $C(CH_3)_2$), 0.95−0.84 (m, 21 H, $SiC(CH_3)_3$, CH(CH_3)), 0.09 (s, 3 H, $Si(CH_3)_2$), 0.08 (s, 3 H, $Si(CH_3)_2$), 0.07 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 218.6, 174.0, 165.6, 152.0, 142.4, 139.4, 120.1, 118.0, 114.7, 72.4, 53.8, 45.8, 40.4, 38.4, 35.5, 34.0, 32.1, 26.4, 26.2, 26.0, 25.9, 23.8, 23.6, 18.5, 18.4, 18.2, 17.2, 14.9, 13.2, −3.5, −3.7, −4.4, −4.8; FAB HRMS (NBA/CsI) *m*/*e* 870.3574, M + Cs^+ calcd for $C_{39}H_{71}NO_6SSi_2$ 870.3595.

Lactone 54. Macrolactonization of 12*Z*-Hydroxy Acid 6. 12*Z*-Hydroxy acid **6** (8.1 mg, 0.011 mmol) was cyclized according to the procedure described above for **6′** to afford lactone **54** (6.1 mg, 77%).

Lactone 68. Macrolactonization of 12*Z*-Hydroxy Acid 67. The macrolactonization of 12*Z*-hydroxy acid **67** (5.0 mg, 0.007 mmol) to lactone **68** (3.7 mg, 76%) was carried out according to the procedure described above for **6′**. **68**: colorless oil; R_f = 0.83 (silica gel, 2% MeOH in CH_2Cl_2); $[\alpha]^{22}_D$ −31.8 (*c* 0.1, $CHCl_3$); IR (thin film) ν_{max} 2931, 2860, 1736, 1690, 1461, 1384, 1360, 1296, 1249, 1084, 985, 832, 773 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.98 (s, 1 H, SCH═C), 6.45 (s, 1 H, C*H*═CCH_3), 5.07−5.21 (m, 2 H, CH_3C═C*H*CH_2, CH_2-COOC*H*), 4.32 (dd, *J* = 6.8, 5.0 Hz, 1 H, CHOSi), 4.05 (d, *J* = 5.7 Hz, 1 H, CHOSi), 3.17 (dq, *J* = 7.0, 6.8 Hz, 1 H, C(O)C*H*CH_3), 2.70 (s, 3 H, N═$C(CH_3)$S), 2.57−2.52 (m, 1 H), 2.29 (dd, *J* = 14.4, 4.6 Hz, 1 H, C*H*$_2$COOCH), 2.27−2.13 (m, 1 H), 2.25 (dd, *J* = 14.5, 7.0 Hz, 1 H, CH_2COO), 2.20−2.15 (m, 1 H), 2.14 (s, 3 H, CH═C(C*H*$_3$)), 1.88−1.82 (m, 1 H), 1.57−1.52 (m, 2 H), 1.47−1.38 (m, 3 H), 1.30 (s, 3 H, $C(CH_3)_2$), 1.11 (d, *J* = 7.2 Hz, 3 H, CH(C*H*$_3$)), 1.08 (s, 3 H, $C(CH_3)_2$), 0.91 (s, 9 H, $SiC(CH_3)_3$), 0.89−0.82 (bs, 12 H, $SiC(CH_3)_3$, CH(C*H*$_3$)), 0.11 (s, 3 H, $Si(CH_3)_2$), 0.09 (s, 3 H, $Si(CH_3)_2$), 0.06 (s, 3 H, $Si(CH_3)_2$), −0.03 (s, 3 H, $Si(CH_3)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 220.2, 170.9, 164.8, 153.1, 140.0, 137.6, 120.2, 118.9, 116.3, 79.3, 74.0, 53.3, 48.0, 41.2, 39.7, 34.9, 31.4, 31.3, 26.6, 26.1, 25.9, 25.3, 23.9, 19.0, 18.5, 18.4, 18.1, 16.2, 14.9, 13.8, −3.9, −4.4, −4.6, −4.9; FAB HRMS (NBA/CsI) *m*/*e* 852.3451, M + Cs^+ calcd for $C_{39}H_{69}$-NO_5SSi_2 852.3489.

Ketone 69. To a solution of aldehyde **20** (1.3 g, 4.53 mol) in THF (20 mL) at −78 °C was added dropwise lithium tri-*tert*-butoxyaluminohydride (4.98 mL, 1.0 M solution in THF, 4.98 mmol, 1.1 equiv). After 5 min, the reaction mixture was brought up to 0 °C and stirred at that temperature for 15 min, before quenching with saturated aqueous solution of sodium−potasium tartrate (25 mL). The aqueous phase was extracted with ether (3 × 20 mL), and the combined organic layer was dried ($MgSO_4$), filtered, and concentrated. The crude primary alcohol so obtained was dissolved in CH_2Cl_2 (25 mL) and cooled to 0 °C. Et_3N (2.5 mL, 15.85 mmol, 3.5 equiv), 4-DMAP (60 mg, 0.09 mmol, 0.02 equiv), and *tert*-butyldimethylsilyl chloride (2.0 g, 13.59 mmol, 3.0 equiv) were added. The reaction mixture was allowed to stir at 0 °C for 2 h, then at 25 °C for 10 h. MeOH (5 mL) was added, and the solvents were removed under reduced pressure. Ether (100 mL) was added followed by saturated aqueous NH_4Cl solution (25 mL), and the organic phase was separated. The aqueous phase was extracted with ether (2 × 50 mL), and the combined organic solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 5% ether in hexanes) provided pure bis(silyl ether) **69** (1.26 g, 70% yield from **20**): R_f = 0.67 (silica gel, 20% ether in hexanes); $[\alpha]^{22}_D$ −7.3 (*c* 1.8, $CHCl_3$); IR (thin film) ν_{max} 2941, 2856, 1701, 1466, 1388, 1252, 1095, 1024, 946, 832, 775 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.06 (dd, *J* = 8.0, 3.0 Hz, 1 H, CHOSi), 3.65−3.56 (m, 2 H, CH_2OSi), 2.56 (dq, *J* = 18.5, 7.0 Hz, 1 H, C*H*$_2CH_3$), 2.46 (dq, *J* = 18.5, 7.0 Hz, 1 H, C*H*$_2CH_3$), 1.56−1.43 (m, 2 H, C*H*$_2CH_2$OSi), 1.11 (s, 3 H, $C(CH_3)_2$), 1.04 (s, 3 H, $C(CH_3)_2$), 0.98 (t, *J* = 7.0 Hz, 3 H, C*H*$_3CH_2$), 0.88 (s, 9 H, SiC-$(CH_3)_3$), 0.87 (s, 9 H, $SiC(CH_3)_3$), 0.09 (s, 3 H, $Si(CH_3)_2$), 0.04 (s, 3 H, $Si(CH_3)_2$), 0.03 (s, 3 H, $Si(CH_3)_2$), 0.02 (s, 3 H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 215.5, 73.2, 59.9, 52.9, 37.1, 31.4, 25.9, 25.7, 22.0, 19.8, 18.2, 18.1, 7.6, −4.1, −4.2, −5.4, −5.5; FAB HRMS (NBA) *m*/*e* 403.3075, M + H^+ calcd for $C_{21}H_{46}O_3Si_2$ 403.3064.

Tris(silyl ethers) 70 and 71. Aldol Reaction of Ketone 69 with Aldehyde 8. A solution of ketone **68** (270 mg, 0.67 mmol, 1.2 equiv) in THF (1.5 mL) was added dropwise to a freshly prepared solution of LDA [diisopropylamine (94 μL, 0.67 mmol) was added to *n*-BuLi (0.43 mL, 1.6 M solution in hexanes, 0.67 mmol) in 2.5 mL of THF at 0 °C] in THF (2.5 mL) at −78 °C. After being stirred for 15 min at −78 °C, the solution was allowed to warm to −40 °C over a period of 1 h. The reaction mixture was cooled to −78 °C, and a solution of aldehyde **8** (244 mg, 0.56 mmol, 1.0 equiv) in THF (1.0 mL) was added dropwise. The resulting mixture was stirred for 15 min at −78 °C and then quenched by dropwise addition of saturated aqueous NH_4Cl solution (2 mL). The aqueous phase was extracted with ether (3 × 5 mL), and the combined organic layer was dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (silica gel, 20% ether in hexanes) provided a mixture of aldol products **70**:**71** (354 mg (85%) of ca. 3:1 by ^{1}H NMR). Separation of these diastereoisomers was carried out by preparative thin-layer chromatography (silica gel, 20% ether in hexanes), leading to pure **70** (270 mg, 64%) and **71** (84 mg, 20%). **70**: colorless oil; R_f = 0.40 (silica gel, 20% ether in hexanes); $[\alpha]^{22}_D$ −17.5 (*c* 0.5, $CHCl_3$); IR (thin film) ν_{max} 3490, 2932, 2873, 1683, 1463, 1385, 1249, 1089, 840, 775 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.89 (s, 1 H, SCH═C), 6.44 (s, 1 H, C*H*═CCH_3), 5.12 (dd, *J* = 7.1, 7.0 Hz , 1 H, $C(CH_3)$═C*H*CH_2), 4.08 (dd, *J* = 6.8, 6.5 Hz, 1 H, $(CH_3)_2$CC*H*OSi), 3.89 (dd, *J* = 7.6, 2.7 Hz, 1 H, CH_2C*H*OSi), 3.69−3.65 (m, 1 H, CH(CH_3)C*H*OH), 3.59 (t, *J* = 7.5 Hz, 2 H, CH_2OSi), 3.32−3.27 (m, 1 H, C(O)C*H*(CH_3)), 2.68 (s, 3 H, N═$C(CH_3)$S), 2.30−2.19 (m, 2 H, $C(CH_3)$═CHC*H*$_2$), 2.10−1.90 (m, 2 H, C*H*$_2C(CH_3)$═CH), 1.98 (s, 3 H, CH═C(C*H*$_3$)), 1.65 (s, 3 H, C(C*H*$_3$)═$CHCH_2$), 1.80−1.46 (m, 5 H), 1.34−1.25 (m, 2 H), 1.19 (s, 3 H, $C(CH_3)_2$), 1.07 (s, 3 H, $C(CH_3)_2$), 1.01 (d, *J* = 6.8 Hz, 3 H, CH(C*H*$_3$)), 0.89 (s, 18 H, 2 x $SiC(CH_3)_3$), 0.87 (s, 9 H, $SiC(CH_3)_3$), 0.81 (d, *J* = 6.8 Hz, 3 H, CH-(C*H*$_3$)), 0.10 (s, 3 H, $Si(CH_3)_2$), 0.08 (s, 3 H, $Si(CH_3)_2$), 0.03 (s, 3 H, $Si(CH_3)_2$), 0.02 (s, 6 H, $Si(CH_3)_2$), −0.01 (s, 3 H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 222.0, 164.1, 153.1, 142.4, 136.7, 121.3, 118.5, 114.7, 78.9, 74.7, 74.0, 60.3, 53.8, 41.2, 37.7, 35.9, 32.8, 32.5, 32.2, 26.0, 25.9, 25.8, 25.0, 24.9, 23.5, 22.8, 20.4, 19.0, 18.2, 18.1, 18.0, 15.2, 13.8, 9.5, −3.8, −4.2, −4.8, −5.1, −5.4; FAB HRMS (NBA/CsI) *m*/*e* 970.4620, M + Cs^+ calcd for $C_{45}H_{87}NO_5SSi_3$ 970.4667. **71**: colorless oil; R_f = 0.33 (silica gel, 20% ether in hexanes); IR (thin film) ν_{max} 3490, 2932, 2873, 1683, 1463, 1385, 1249, 1089, 840, 775 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.90 (s, 1 H, SCH═C), 6.44 (s, 1 H, C*H*═CCH_3), 5.16−5.12 (m, 1 H, $C(CH_3)$═C*H*CH_2), 4.09−4.05 (m, 1 H, $(CH_3)_2$CC*H*OSi), 3.65−3.58 (m, 3 H, CH_2C*H*OSi, CH_2OSi), 3.42−3.38 (m, 1 H, CH(CH_3)C*H*OH), 3.24−3.19 (m, 1 H, C(O)-C*H*(CH_3)), 2.69 (s, 3 H, N═$C(CH_3)$S), 2.31−2.18 (m, 2 H, $C(CH_3)$═CHC*H*$_2$), 1.98 (s, 3 H, CH═C(C*H*$_3$)), 1.99−1.88 (m, 2 H, C*H*$_2C(CH_3)$═CH), 1.67 (s, 3 H, C(C*H*$_3$)═$CHCH_2$), 1.55−1.40 (m, 5 H), 1.35−1.25 (m, 2 H), 1.20 (s, 3 H, $C(CH_3)_2$), 1.13 (s, 3 H, $C(CH_3)_2$), 1.09 (d, *J* = 7.0 Hz, 3 H, CH(C*H*$_3$)), 0.95 (d, *J* = 7.0 Hz, 3 H, CH-(C*H*$_3$)), 0.88 (s, 18 H, 2 x $SiC(CH_3)_3$), 0.87 (s, 9 H, $SiC(CH_3)_3$), 0.10 (s, 3 H, $Si(CH_3)_2$), 0.05 (s, 3 H, $Si(CH_3)_2$), 0.04 (s, 3 H, $Si(CH_3)_2$), 0.03 (s, 6 H, $Si(CH_3)_2$), −0.01 (s, 3 H, $Si(CH_3)_2$); FAB HRMS (NBA) *m*/*e* 838.5653, M + Cs^+ calcd for $C_{45}H_{87}NO_5SSi_3$ 838.5691.

Tetrakis(silyl ether) 72. Compound **70** (275 mg, 0.33 mmol) was dissolved in CH_2Cl_2 (5.0 mL), cooled to 0 °C, and treated with 2,6-lutidine (76 μL, 0.66 mmol, 2.0 equiv) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (88 μL, 0.39 mmol, 1.2 equiv). After being stirred for 2 h at 0 °C, the reaction mixture was quenched with aqueous HCl (5 mL, 1.0 N solution) and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic solution was washed with brine (5 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 3% ether in hexanes) provided tetrakis(silyl ether) **72** (300 mg, 96%) as a colorless oil. **72**: R_f = 0.56 (silica gel, 10% ether in hexanes); $[\alpha]^{22}_D$ −10.8 (*c* 0.5, $CHCl_3$); IR (thin film) ν_{max} 2919, 2872, 1690, 1461, 1384, 1361, 1249, 1085, 985, 838, 773, 732, 667 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.88 (s, 1 H, SCH═C), 6.43 (s, 1 H, C*H*═CCH_3), 5.13 (dd, *J* = 7.1, 7.0 Hz, 1 H, $C(CH_3)$═C*H*CH_2), 4.08 (dd, *J* = 6.8, 6.7 Hz, 1 H, $(CH_3)_2$-CC*H*OSi), 3.89 (dd, *J* = 7.6, 2.7 Hz, 1 H, CH_2C*H*OSi), 3.77 (dd, *J* = 6.7, 1.0 Hz, 1 H, CH(CH_3)C*H*OSi), 3.67−3.62 (m, 1 H, CH_2OSi), 3.58−3.53 (m, 1 H, CH_2OSi), 3.14 (dd, *J* = 6.8, 6.7 Hz, 1 H, C(O)-C*H*(CH_3)), 2.68 (s, 3 H, N═$C(CH_3)$S), 2.29−2.17 (m, 2 H, $C(CH_3)$═CHC*H*$_2$), 1.98 (s, 3 H, CH═C(C*H*$_3$)), 1.97−1.89 (m, 2 H, C*H*$_2C(CH_3)$═CH), 1.64 (s, 3 H, C(C*H*$_3$)═$CHCH_2$) 1.50−1.45 (m, 5 H), 1.34−1.23 (m, 2 H), 1.20 (s, 3 H, $C(CH_3)_2$), 1.02 (d, *J* = 6.8 Hz, 3 H, CH(C*H*$_3$)), 1.00 (s, 3 H, $C(CH_3)_2$), 0.88−0.86 (m, 39 H, CH-(C*H*$_3$), 4 x $SiC(CH_3)_3$), 0.08 (s, 3 H, $Si(CH_3)_2$), 0.07 (s, 3 H, $Si(CH_3)_2$), 0.04 (s, 3 H, $Si(CH_3)_2$), 0.03 (s, 3 H, $Si(CH_3)_2$), 0.02 (s, 6 H, $Si(CH_3)_2$), 0.01 (s, 3 H, $Si(CH_3)_2$), −0.02 (s, 3 H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 218.2, 164.2, 153.2, 142.4, 136.6, 121.5, 118.5, 114.9,

78.8, 77.3, 73.9, 60.9, 53.6, 44.9, 38.8, 37.9, 35.2, 32.4, 30.9, 26.2, 26.1, 25.9, 24.4, 23.4, 19.2, 19.1, 18.5, 18.3, 18.2, 18.1, 17.5, 13.9, −3.7, −3.8, −4.0, −4.7, −4.9, −5.2, −5.3; FAB HRMS (NBA) *m*/*e* 952.6515, M + H^+ calcd for $C_{51}H_{101}NO_5SSi_4$ 952.6556.

Alcohol 73. Alcohol **73** (200 mg, 85%) was obtained from compound **72** (264 mg, 0.28 mmol) according to the procedure described above for **35**. **73**: colorless oil; R_f = 0.25 (silica gel, 20% ether in hexanes); $[\alpha]^{22}_D$ −9.3 (*c* 0.2, $CHCl_3$); IR (thin film) ν_{max} 3392, 2939, 2865, 1689, 1463, 1378, 1357, 1252, 1083, 988, 867, 835, 772, 730 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.90 (s, 1 H, SCH═C), 6.44 (s, 1 H, C*H*═CCH_3), 5.14 (dd, *J* = 7.0, 6.9 Hz , 1 H, $C(CH_3)$═C*H*CH_2), 4.10−4.05 (m, 2 H, $(CH_3)_2$CC*H*OSi, CH_2C*H*OSi), 3.78 (dd, *J* = 7.0, 1.0 Hz, 1 H, CH(CH_3)C*H*OSi), 3.63 (t, *J* = 7.0 Hz , 2 H, C*H*$_2$OH), 3.11 (dd, *J* = 7.0, 6.8 Hz, 1 H, C(O)C*H*(CH_3)), 2.70 (s, 3 H, N═C-(CH_3)S), 2.27−2.19 (m, 2 H, $C(CH_3)$═CHC*H*$_2$), 1.99 (d, *J* = 1.0 Hz, 3 H, CH═C(C*H*$_3$)), 2.10−1.90 (m, 2 H, C*H*$_2$$C(CH_3)$═CH), 1.65 (s, 3 H, C(C*H*$_3$)═$CHCH_2$), 1.50−1.39 (m, 2 H), 1.36−1.29 (m, 3 H), 1.21 (s, 3 H, $C(CH_3)_2$), 1.20−1.10 (m, 2 H), 1.05 (s, 3 H, $C(CH_3)_2$), 1.04 (d, *J* = 6.8 Hz, 3 H, CH(C*H*$_3$)), 0.91−0.87 (m, 30 H, CH(C*H*$_3$), 3 x $SiC(CH_3)_3$), 0.11 (s, 3 H, $Si(CH_3)_2$), 0.07 (s, 3 H, $Si(CH_3)_2$), 0.06 (s, 6 H, $Si(CH_3)_2$), 0.04 (s, 3 H , $Si(CH_3)_2$), −0.01 (s, 3 H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 219.5, 164.2, 153.1, 142.4, 136.6, 121.5, 118.5, 114.8, 78.8, 77.4, 72.9, 60.1, 53.6, 45.8, 44.9, 38.6, 38.2, 35.2, 32.4, 30.6, 26.1, 25.9, 24.7, 23.4, 19.1, 18.4, 18.1, 18.0, 17.6, 15.5, 13.8, −3.7, −3.8, −4.0, −4.7, −5.1; FAB HRMS (NBA/CsI) *m*/*e* 970.4694, M + Cs^+ calcd for $C_{45}H_{87}NO_5SSi_3$ 970.4667.

Aldehyde 74. Oxidation of Alcohol 73. To a solution of oxalyl chloride (54 μL, 0.61 mmol, 2.0 equiv) in CH_2Cl_2 (5.0 mL) was added dropwise DMSO (86 μL, 1.21 mmol, 4.0 equiv) at −78 °C. After the mixture was stirred for 15 min at −78 °C, a solution of alcohol **73** (255 mg, 0.305 mmol, 1.0 equiv) in CH_2Cl_2 (2.0 mL) was added dropwise at −78 °C over a period of 5 min. The solution was stirred at −78 °C for 30 min, and then Et_3N (250 μL, 1.82 mmol, 6.0 equiv) was added. The reaction mixture was allowed to warm to 0 °C over a period of 30 min, and then ether (20 mL) was added, followed by saturated aqueous NH_4Cl solution (10 mL). The organic phase was separated, and the aqueous phase was extracted with ether (2 × 10 mL). The combined organic solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 20% ether in hexanes) provided aldehyde **74** (241 mg, 95%) as a colorless oil. **74**: R_f = 0.47 (silica gel, 20% ether in hexanes); $[\alpha]^{22}_D$ −12.0 (*c* 0.1, $CHCl_3$); IR (thin film) ν_{max} 2943, 2849, 1725, 1690, 1461, 1384, 1249, 1079, 985, 832, 773 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.74 (m, 1 H, CHO), 6.89 (s, 1 H, SCH═C), 6.43 (s, 1 H, C*H*═CCH_3), 5.14 (dd, *J* = 7.1, 7.0 Hz, 1 H, $C(CH_3)$═C*H*CH_2), 4.48−4.44 (m, 1 H, $(CH_3)_2$CC*H*OSi), 4.07 (dd, *J* = 6.1, 5.3 Hz, 1 H, CH_2C*H*OSi), 3.75 (dd, *J* = 7.4, 1.0 Hz, 1 H, CH-(CH_3)C*H*OSi), 3.11 (dd, *J* = 7.0, 6.7 Hz, 1 H, C(O)C*H*(CH_3)), 2.69 (s, 3 H, N═$C(CH_3)$S), 2.50 (ddd, *J* = 16.6, 4.5, 1.0 Hz, 1 H, C*H*$_2$CHO), 2.37 (ddd, *J* = 16.6, 3.2, 1.0 Hz, 1 H, C*H*$_2$CHO), 2.28−2.16 (m, 2 H, $C(CH_3)$═CHC*H*$_2$), 1.97 (s, 3 H, CH═C(C*H*$_3$)), 1.97−1.89 (m, 2 H, C*H*$_2$$C(CH_3)$═CH), 1.64 (s, 3 H, C(C*H*$_3$)═$CHCH_2$), 1.50−1.25 (m, 5 H), 1.22 (s, 3 H, $C(CH_3)_2$), 1.05 (s, 3 H, $C(CH_3)_2$), 1.01 (d, *J* = 6.9 Hz, 3 H, CH(C*H*$_3$)), 0.89−0.84 (m, 30 H, CH(C*H*$_3$), 3 x $SiC(CH_3)_3$), 0.08 (s, 3 H, $Si(CH_3)_2$), 0.04 (s, 6 H, $Si(CH_3)_2$), 0.03 (s, 3 H, $Si(CH_3)_2$), 0.02 (s, 3 H, $Si(CH_3)_2$), −0.02 (s, 3 H, $Si(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 218.5, 201.0, 164.3, 153.2, 142.7, 136.7, 121.5, 118.5, 114.8, 78.9, 77.7, 71.3, 53.4, 45.1, 38.7, 35.3, 32.5, 30.7, 26.2, 25.9, 25.8, 24.1, 23.5, 19.1, 18.7, 18.6, 18.5, 17.7, 15.6, 13.9, −3.6, −3.7, −4.1, −4.5, −4.7, −5.0; FAB HRMS (NBA) *m*/*e* 836.5500, M + H^+ calcd for $C_{45}H_{85}NO_5SSi_3$ 836.5535.

Carboxylic Acid 52. Oxidation of Aldehyde 74. Aldehyde **74** (224 mg, 0.29 mmol), ^{t}BuOH (5.0 mL), isobutylene (5.0 mL, 2 M solution in THF, 10.0 mmol), H_2O (1.0 mL), $NaClO_2$ (90 mg, 0.86 mmol, 3.0 equiv), and NaH_2PO_4 (60 mg, 0.43 mmol, 1.5 equiv) were combined and stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was subjected to flash column chromatography (silica gel, 6% MeOH in CH_2Cl_2) to afford carboxylic acid **52** (220 mg, 90%) whose spectroscopic data were identical with those exhibited by **52** obtained above.

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Supporting Information Available: Selected physical data for compounds **48**, **49**, **8′**, **52′**, **53′**, and **6′** and $^1H-^1H$ NOESY and $^1H-^1H$ COSY spectra for epoxides **58** and **59** (8 pages). See any current masthead page for ordering and Internet access instructions.

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