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Total Syntheses of Epothilones B and D

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A convergent, total synthesis of epothilones B (**2**) and D (**4**) is described. The key steps are Normant coupling to establish the desired (*Z*)-stereochemistry at C12−C13, Wadsworth−Emmons olefination of methyl ketone **28** with the phosphonate ester **8**, diastereoselective aldol condensation of aldehyde **5** with the enolate of keto acid derivatives to form the C6−C7 bond, selective deprotection of acid **52**, and macrolactonization.

Introduction

The naturally occurring macrolactones, epothilones A (**1**) and B (**2**), first isolated and characterized by Höfle et al. from the myxobacterium *Sorangium cellulosum*, have evoked a great deal of interest in recent years due to their novel molecular architecture and taxol-like, antitumor mechanism of action.[1] Both the taxanes and the epothilones exert their therapeutic effects by promoting tubulin polymerization and the formation of stable microtubules, thereby causing cell death through disruption of the normal microtubule dynamics. Since the discovery of the epothilones in 1993, more than 500 reports have been published,[2,3] further indicating the interest in this class of compounds. Taxol (paclitaxel) is currently used in the chemotherapy of a broad range of tumor types including breast, ovarian, lung, head, neck, and AIDS-related cancers (Karposi's sarcoma). Taxol also has activity in malignancies that are refractory to conventional chemotherapy, including previously treated lymphoma and small-cell lung cancers. Unfortunately, the effectiveness of taxol has been hampered by the emergence of multidrug resistance and by side effects[4] (hypersensitivity, neurotoxicity, and hematological toxicity). Furthermore, the development of multidrug resistance in patients treated with Taxol fuels the need for the development of additional chemotherapeutics which possess potency equal to or greater than Taxol without the associated undesirable characteristics. Most significantly, epothilones, unlike paclitaxel (Taxol), are equally active against drug-sensitive and multidrug-resistant cancer cell lines in vitro and epothilone B has shown potent in vivo antitumor activity in Taxol-resistant human tumor models. Epothilone B is currently undergoing phase II clinical trials.[5]

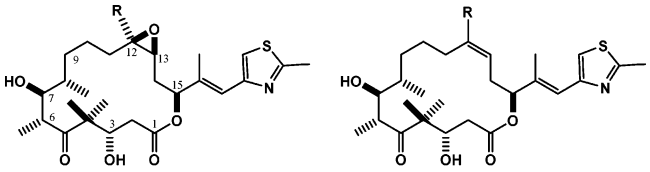

FIGURE 1. Structures of epothilones A−D (**1**−**4**).

Epothilone B is superior to Taxol in the areas of solubility, potency, and effectiveness against Taxol-resistant cancer cell lines. Our interest in the epothilones

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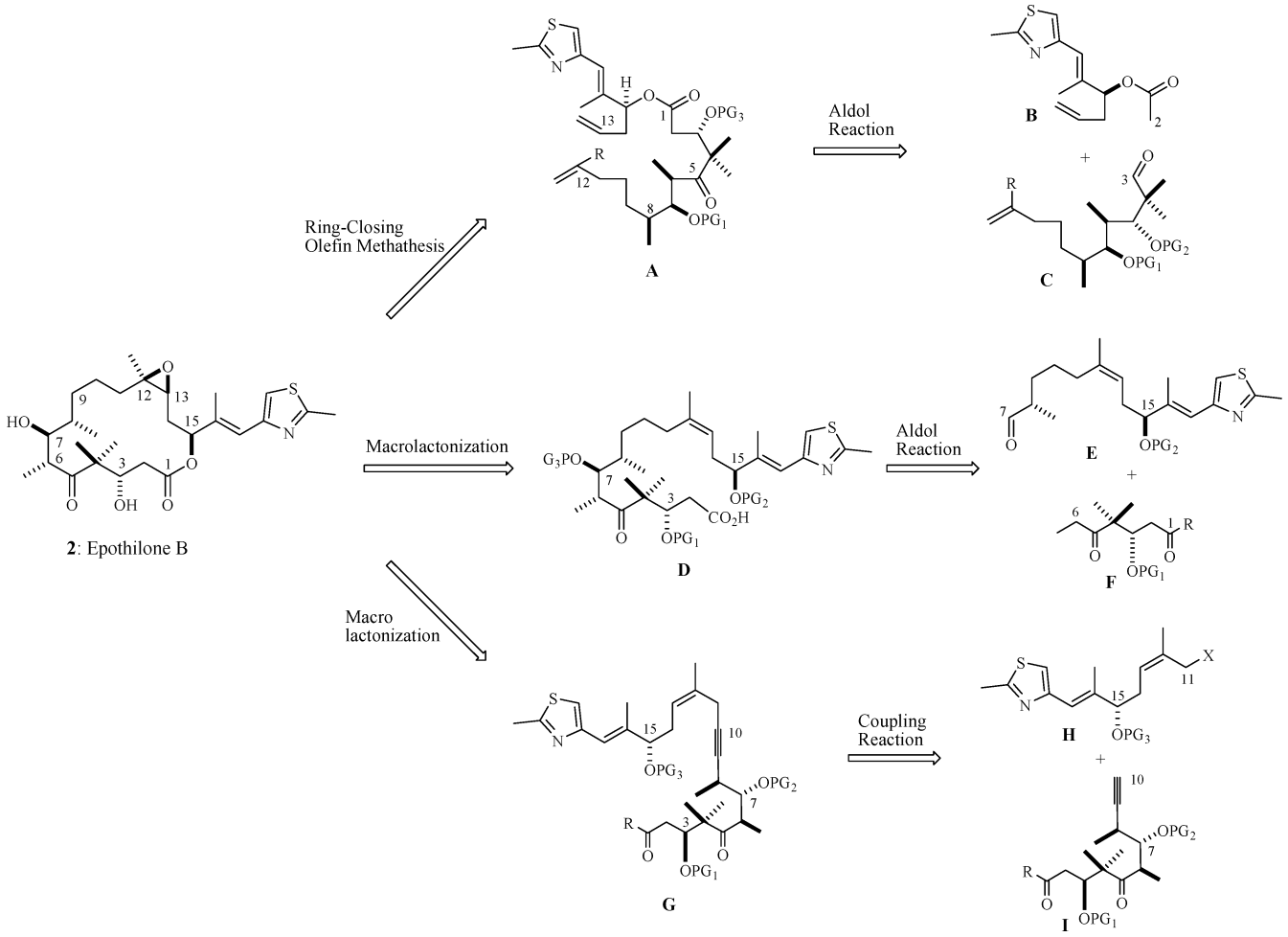

FIGURE 2. General synthetic approaches of epothilone B (**2**).

stems from a desire to perform SAR (structure activity relationship) studies with respect to the C3 and C7 positions. Therefore, a practical synthetic route of epothilones B (**2**) and D (**4**) was needed. The major approaches to the syntheses of epothilones B (**2**) and D (**4**) fall into three categories (Figure 2). Key steps in the first approach include an aldol reaction of acetate **B** and aldehyde **C** to construct the C2−C3 bond of **A** followed by ring-closing olefin metathesis to furnish the C12−C13 olefin of epothilone B (**2**).[3a] Another strategy employed an aldol reaction between aldehyde **E** and keto acid **F** to provide the C6−C7 bond of acid **D**, which could then undergo ring closure via macrolactonization to give epothilone B (**2**).[3b,c,e,j,n] In an alternative approach, Castro−Stephens coupling of allylic halide **H** with terminal alkyne **I** generated the C10−C11 bond of dienyne **G**, which was converted to epothilone B (**2**) via macrolactonization.[3g] In a preliminary communication,[6] we reported the total synthesis of epothilone B (**2**). Key steps include an aldol reaction to establish the C6−C7 bond and macrolactonization to afford epothilone B (**2**) (Scheme 1). Herein, we describe the details of the total synthesis of epothilones B (**2**) and D (**4**) and improvements made to our previous route.

Results and Discussion

Retrosynthetic analysis of epothilones B (**2**) and D (**4**) reveals a convergent, two-step sequence involving a double-diastereoselective aldol condensation of aldehyde **5** and keto acid **9** (derived from acetyl sultam **10** and keto aldehyde **11**), followed by Yamaguchi macrolactonization[7] to give the target framework (Scheme 1). The (*Z*)-olefin, an essential feature of the epothilones, has traditionally been prepared by Wittig olefination methods or ring-closing metathesis approaches. We envisioned utilizing the classic Normant alkyne cupration reaction and electrophile trapping to not only establish the necessary (*Z*)-stereochemistry of olefin **5** but also fix the stereochemistry at C9 (**5**) in a single step. Organocuprate **7**, propyne, and PMB-protected epoxy alcohol **6** could be coupled to accomplish this goal. Furthermore, the resulting Nor-

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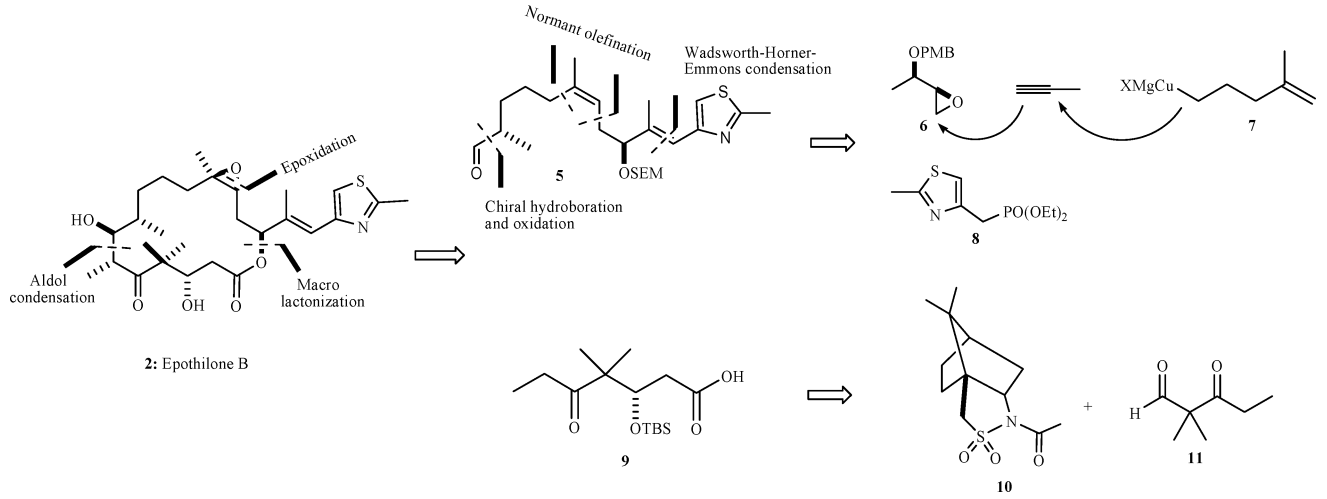
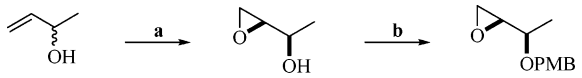
SCHEME 1. Retrosynthetic Analysis of Epothilone B (2)



SCHEME 2. Synthesis of Epoxide 6[a]



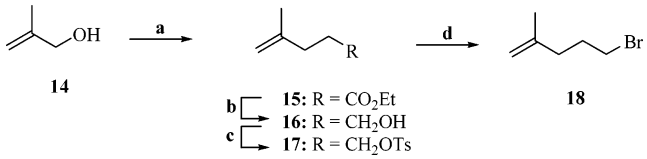
[a] Reagents and conditions: (a) D-(−)-DIPT, molecular sieves (powdered, 4 Å), *tert*-butyl hydroperoxide, $Ti(O\textit{i}\text{-}Pr)_4$, CH_2Cl_2, −23 °C, 2 d, 37%; (b) 4-methoxybenzyl bromide, NaH (60%), Bu_4NI, THF, 0 °C, 6 h, 86%.

mant alkyne cupration product would provide easy access to fragment **5** through a reaction sequence involving deprotection, oxidation, and Wadsworth−Horner−Emmons condensation.

Preparation of Aldehyde 5. Synthesis of fragment **5** first required the development of a suitable method for preparing PMB-protected alcohol **6** (Scheme 2). This was accomplished by subjecting commercially available racemic 3-buten-2-ol (**12**) to Sharpless asymmetric epoxidation.[8] The crude product was purified first by vacuum distillation followed by column chromatography to give pure (2*S*,3*R*)-epoxy alcohol **13**. Compound **13** was protected as the PMB ether with freshly prepared 4-methoxybenzyl bromide [prepared by treating 4-methoxybenzyl alcohol in ether with phosphorus tribromide at 0 °C for 2 h][9] in the presence of sodium hydride to give **6** in 86% yield.

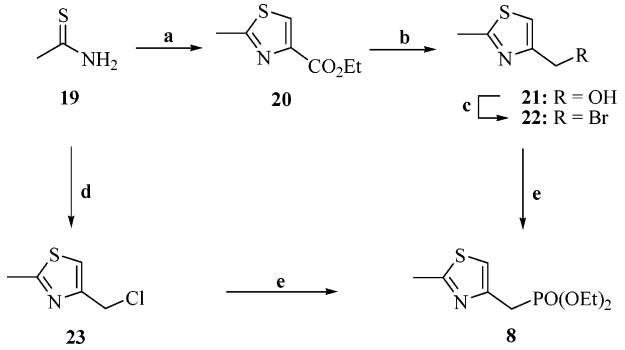
Bromide **18**, also required for the Normant coupling reaction, was easily prepared as shown in Scheme 3. Commercially available alcohol **14** underwent Claisen rearrangement to afford ethyl ester **15**.[10] Without further purification, **15** was reduced with $LiAlH_4$ in ether to yield volatile alcohol **16** in 70% yield. Tosylation of **16** (73%) followed by displacement of the tosylate of **17** gave bromide **18** in 69% yield.[11] The synthesis of phosphonate **8**, the third fragment required for the Normant reaction,

SCHEME 3. Synthesis of Bromide 18[a]



[a] Reagents and conditions: (a) $CH_3C(OEt)_3$/propionic acid, 170 °C, 1 h (quantitative yield); (b) $LiAlH_4$, ether, −5 °C to 0 °C, 2 h, then rt 3 h, 70%; (c) *p*-TsCl, TEA, CH_2Cl_2, 0 °C, 30 min, then rt 3 h, 73%; (d) LiBr, acetone, reflux, 2 h, 69%.

SCHEME 4. Synthesis of Phosphonate 8[a]



[a] Reagents and conditions: (a) ethyl bromopyruvate, EtOH, rt, 20 h, 70%; (b) $LiAlH_4$, ether, −78 °C, 3 h, 84%; (c) Ph_3P, CBr_4, CCl_4, rt, 3 h, 85%; (d) 1,3-dichloroacetone, rt to 50 °C, 20 h, 93%; (e) $P(OEt)_3$, 160 °C, 3 h, 86%.

was accomplished by using two known synthetic methods (Scheme 4). In the original approach, thioacetamide (**19**) was treated with ethyl bromopyruvate to afford thiazole **20** (70%). Reduction of **20** with $LiAlH_4$ afforded alcohol **21** in 84% yield. Bromination of **21** with CBr_4/PPh_3 gave bromide **22** (85%), which was smoothly converted to diethyl (2-methylthiazol-4-yl)methanephosphonate (**8**) in 86% yield following treatment with triethyl phosphite.[12]

In the current approach, phosphonate **8** is formed in a two-step reaction by treating thioacetamide (**19**) with 1,3-dichloroacetone to give thiazole **23**.[13,3j] The crude product was treated with triethyl phosphite to yield **8** (80%, two

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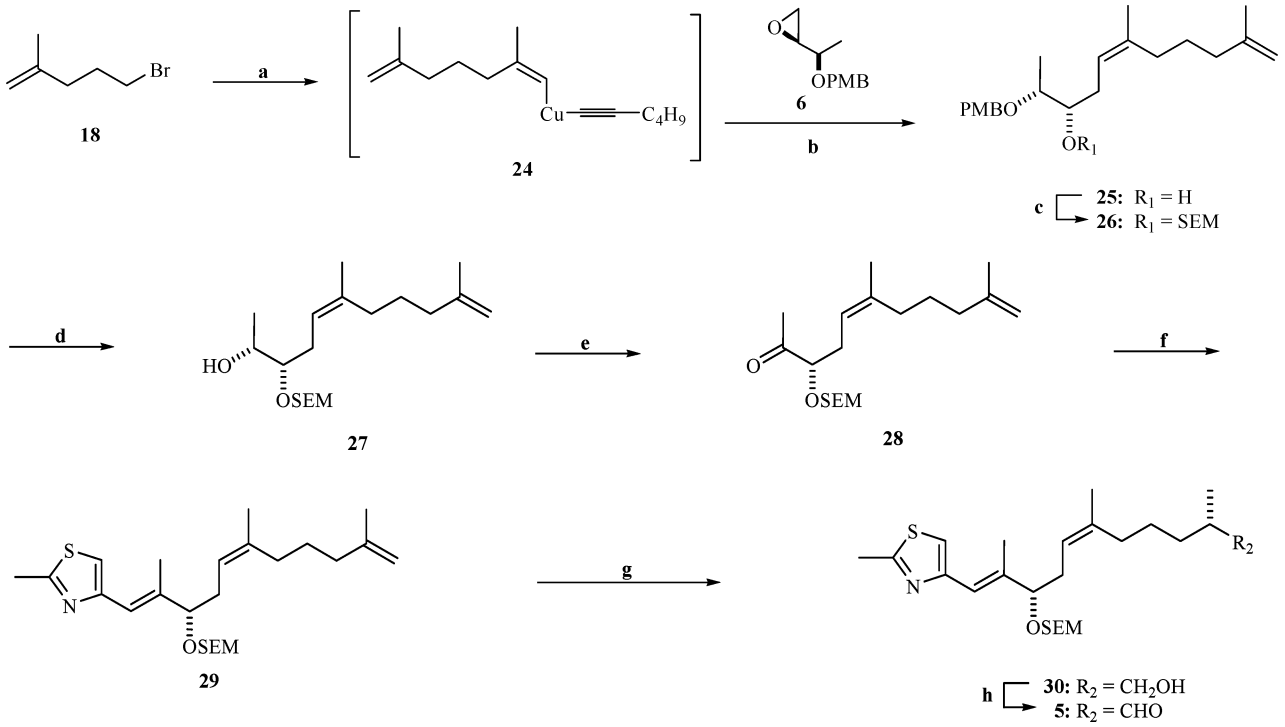
SCHEME 5. Synthesis of Aldehyde 5[a]



[a] Reagents and conditions: (a) (i) Mg, ether, rt to reflux, 1 h; (ii) CuBr-DMS, ether, DMS, −45 °C, 2 h; (iii) propyne, −23 °C, 4 h, then lithiohexyne, −78 °C, 1 h; (b) **6**, −78 °C, 3 h; −25 °C, 14 h, 75%; (c) SEM-Cl, DIPEA, CH_2Cl_2, 0 °C; then rt, 6 h, 92%; (d) DDQ, CH_2Cl_2/H_2O (8:2), rt, 3 h, 91%; (e) DMSO, $(COCl)_2$, TEA, CH_2Cl_2, −78 °C, 2 h, 85%; (f) **8**, *n*-BuLi, THF, −78 °C, 1 h; then rt, 12 h, 86%; (g) $(i\text{-PC})_2$BH, THF, rt, 30 min; then LiOH(aq), $NaBO_3$(aq), rt, 2 h, 78%; (h) DMSO, $(COCl)_2$, TEA, CH_2Cl_2, −78 °C, 1 h, (94%); or TPAP (5 mol %), NMO, molecular sieves (powdered, 4 Å), CH_2Cl_2, 0 °C, 15 min, 72%; or Dess−Martin periodinane, CH_2Cl_2, rt, 30 min, 92%.

steps). The latter method is superior in that it allows access to the desired phosphonate in only two steps and in significantly higher yield.

Having completed the syntheses of fragments **6**, **8**, and **18** we could proceed with the assembly of aldehyde **5** via the Normant olefination reaction[14] (Scheme 5). The Grignard reagent of bromide **18** was transmetalated by using copper(I) bromide−dimethyl sulfide (CuBr-DMS) at −23 °C, followed by chain elongation via the stepwise addition of propyne and freshly prepared lithiohexyne [1-hexyne treated with *n*-butyllithium and hexamethylphosphoramide (HMPA) in ether at −78 °C for 1 h] in ether at −78 °C to form the intermediate **24**, which when treated with **6** led to epoxide opening to provide (*Z*)-alkene **25** in 75% yield.

Protection of the resulting hydroxyl of **25** with SEM-Cl in the presence of DIPEA gave SEM ether **26** (92%). Subsequent removal of the adjacent PMB protecting group with DDQ gave alcohol **27** in 91% yield. Oxidation of alcohol **27** was accomplished by using Swern conditions to generate methyl ketone **28**, which was subjected to Wadsworth−Horner−Emmons olefination[12] with phosphonate ester **8** to afford the (*E*)-olefin **29** in 86% yield. Finally, asymmetric hydroboration of triene **29** with freshly prepared bis(isopinocampheyl)borane [$(i\text{-PC})_2$BH][15] followed by oxidative workup with aqueous lithium hydroxide/sodium perborate furnished **30** (78%).

Swern oxidation of alcohol **30** gave the enantiomerically pure aldehyde **5** in 94% yield. Oxidation of **30** was also accomplished by using Dess−Martin periodinane (DMP)[16] and tetrapropylammonium perruthenate (TPAP)/NMO conditions.[17] Although these latter conditions were more convenient for scale-up due to shorter reaction time and ease of handing, Swern oxidation afforded a superior yield. With the completion of the synthesis of aldehyde **5**, we had assembled the northern hemisphere of epothilones B (**2**) and D (**4**).

Preparation of Enolizable Substrates. The next key step in our synthesis involved the aldol coupling of an enolizable substrate with fragment **5**. Obtaining maximum diastereoselectivity is the primary goal in a reaction of this type. Therefore, we sought to determine the conditions necessary to achieve this goal by varying the enolizable substrate and the reaction conditions for the aldol condensation (Table 1). In our original report,[6b,c] keto acid **9** was used as the enolizable substrate resulting in a 2:1 diastereomeric ratio of **44a**:**44b**. Several derivatives of keto acid **9** including sultam **34**, Weinreb amide **35**, TBS ether **41**, OBO ester **42**, and ABO ester **43** were prepared to investigate the effect of steric bulk on the diastereoselectivity of the aldol reaction.

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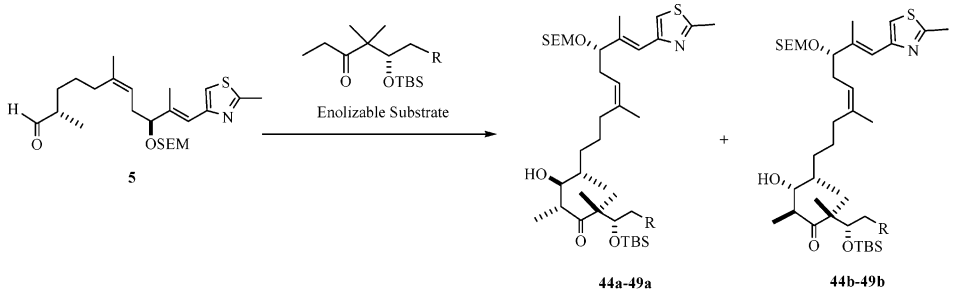
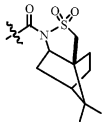
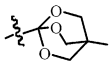
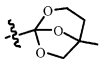
(17) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639−666.

TABLE 1. Effect of Structure of the Enolizable Substrate on Diastereoselectivity



Enolizable Substrate	R	Reaction Conditions	Solvent	Selectivity (dr)[a]	Product	Yield (%)[b]
9	CO_2H	LDA, $ZnCl_2$ –78 °C, 30 min.	THF	2.3:1	**44a/44b**	85
34		$TiCl_4$, DIPEA –78 °C, 30 min.	CH_2Cl_2	10:1	**45a/45b**	60
35	$CON(OMe)CH_3$	LDA, –78 °C, 30 min.	THF	2:1	**46a/46b**	81[c]
41	CH_2OTBS	LDA, –78 °C, 10 min.	THF	3.2:1	**47a/47b**	72[c]
42		LDA, –78 °C, 10 min.	THF	2:1	**48a/48b**	76[c]
43		LDA, –78 °C, 10 min.	THF	1.9:1	**49a/49b**	79[c]

[a] dr = diastereoselective ratio; diastereoselectivity was determined based on isolation (substrates **9**, **42**, and **43**) and HPLC (substrates **34**, **35**, and **41**). [b] Isolated total yield. [c] Based on recovered starting material.

As shown in Scheme 6, sultam **34** was prepared in a six-step reaction sequence. (+)-Camphor-10-sulfonic acid **31** was treated with thionyl chloride to afford the acid chloride, which was subsequently treated with ammonium hydroxide to give imine sultam in quantitative yield. The imine sultam was reduced with sodium borohydride to afford 2-camphorsultam **32** (66%) followed by *N*-acetylation with acetyl chloride in the presence of sodium hydride in toluene to give acetyl sultam **10** (62% yield, four steps). Aldol condensation of acetyl sultam **10** with freshly prepared aldehyde **11** (Scheme 6) [isobutyl aldehyde was treated with morpholine in benzene to afford enamine, which was reacted with propionyl chloride in ether, 34% two steps yield][18] resulted in sultam-3-ol **33** (88%). Compound **33** was protected with TBSOTf/2,6-lutidine in dichloromethane to give **34** in 95% yield.[3n] Enolizable substrate keto acid **9** could be prepared from sultam **34** via hydrolysis with lithium hydroxide and hydrogen peroxide in 76% yield.[19] Weinreb amide **35** was obtained from keto acid **9** in 88% yield with use of *N*,*O*-dimethylhydroxylamine hydrochloride/DMAP/DCC. Generation of TBS ether **41**[20] was accomplished with two routes. In the first method, treatment of sultam **34** with $LiBH_4$ resulted in reduction of both the amide and ketone functionalities to give a diol **36**. Selective silylation of the primary C1 hydroxyl group resulted in TBS ether **37** (57% yield, two steps). Dess–Martin oxidation of the secondary alcohol of **37** yielded **41** (80%). In an alternate method,[3n] keto acid **9** was readily reduced with $B(OMe)_3$/BH_3·DMS to give primary alcohol **40**. The C1 hydroxyl of **40** was silylated with TBSCl/imidazole to afford TBS ether **41** (51% yield, two steps).

The ortho esters **42** and **43** were prepared in two steps.[21] Reaction of keto acid **9** with 3-methoxy-3-oxet-

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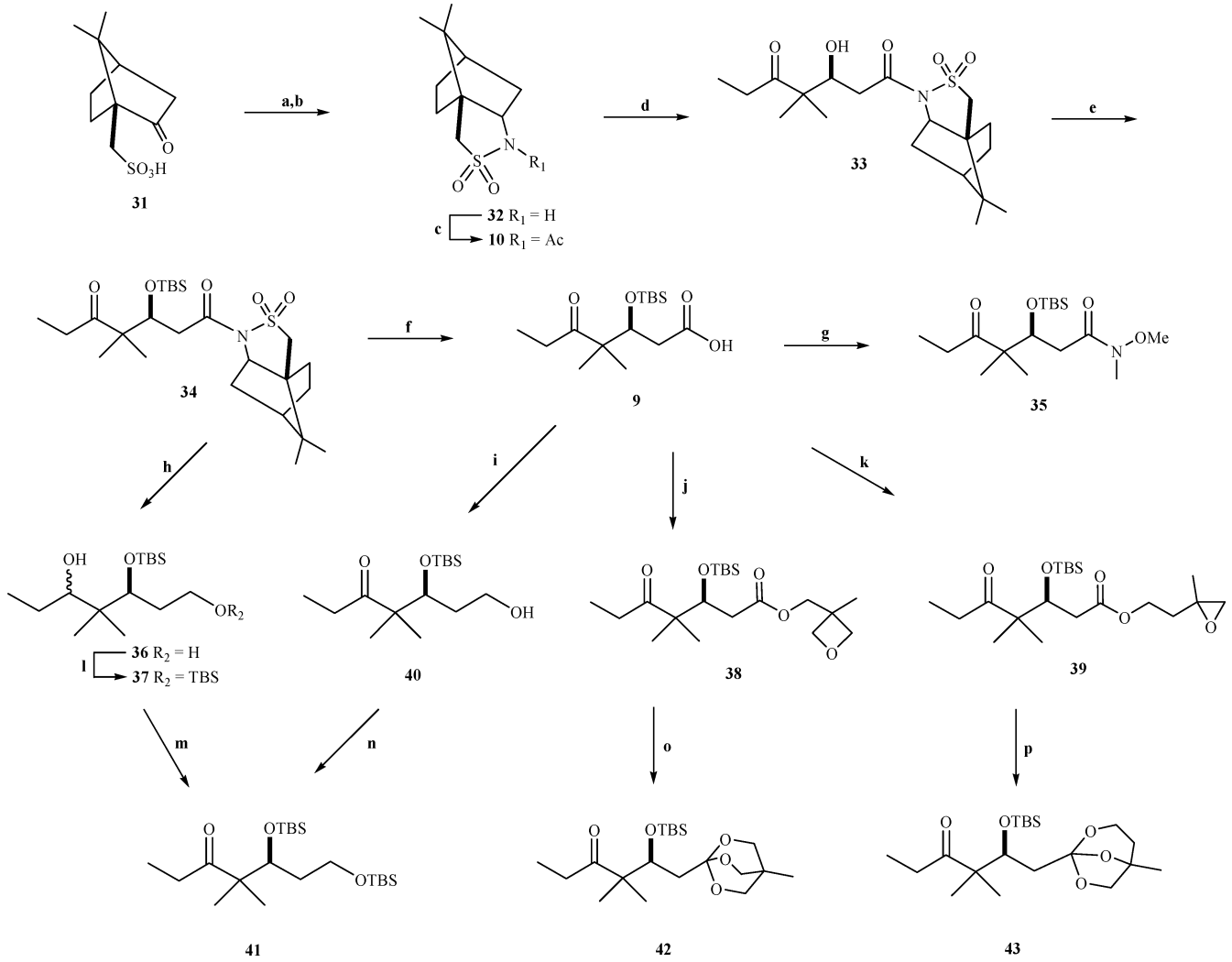
SCHEME 6. Synthesis of Enolizable Substrates[a]



[a] Reagents and conditions: (a) (i) $SOCl_2$, DMF (cat.), rt, 3 h, 99%; (ii) NH_4OH/1,4-dioxane, rt, 2 h, then 95 °C, 4 h, 100%; (b) $NaBH_4$, MeOH/H_2O, 5 °C, 1 h, 66%; (c) CH_3COCl, NaH (60%)/toluene, rt, 16 h, 95%; (d) **11**, Bu_2BOTf, DIPEA/CH_2Cl_2, −78 °C, 1 h, 88%; (e) TBSOTf, 2,6-lutidine/CH_2Cl_2, 0 °C, 1 h, 95%; (f) LiOH, H_2O_2, THF/H_2O, 0 °C to rt, 4 h, 76%; (g) CH_3ONHCH_3·HCl, DMAP, DCC/CH_2Cl_2, rt, 1 h, 88%; (h) $LiBH_4$/THF, rt, 20 h; (i) BH_3·Me_2S, $B(OMe)_3$/THF, 0 °C, 3 h; 15 °C, 6 h, 71%; (j) 3-methoxy-3-oxetanemethanol, DMAP, DCC/CH_2Cl_2, rt, 1 h, 95%; (k) 2-methyloxiraneethanol, DMAP, DCC/CH_2Cl_2, rt, 1 h, 96%; (l) TBSCl, 2,6-lutidine/CH_2Cl_2, 0 °C, 1 h (57%, two steps); (m) Dess−Martin periodinane, pyridine/CH_2Cl_2, 0 °C to rt, 2 h, 80%; (n) TBSCl, imidazole/CH_2Cl_2, 0 °C, 3 h, 72%; (o) BF_3·Et_2O/CH_2Cl_2, 20 °C, 3 h, 73%; (p) BF_3·Et_2O/CH_2Cl_2, 10 °C, 1 h, 75%; or Cp_2ZrCl_2, $AgClO_4$/CH_2Cl_2, 0 °C, 15 min, 93%.

anemethanol or 2-methyloxiraneethanol[22] in the presence of DMAP/DCC gave acyloxetane intermediates **38** and **39** in 95% and 96% yields, respectively. Acyloxetane intermediates **38** and **39** underwent rearrangement when treated with BF_3·Et_2O or Cp_2ZrCl_2 (10 mol %) and $AgClO_4$ (2 mol %) to afford OBO (2,6,7-trioxabicyclo[2.2.2]octyl) ester **42** in 73% yield and ABO (2,7,8-trioxabicyclo[3.2.1]-octyl) ester **43** in 75% yield.[23]

Diastereoselectivity of the Aldol Condensation. The stereocontrolled aldol reaction to generate the C6−C7 bond is one of the important strategic steps in the construction of the epothilone framework. In our previous report,[6c] a diastereomeric ratio of 2:1 was obtained with keto acid **9** as the enolizable substrate. A recent report[24] demonstrated that the diastereomeric ratio may be greatly enhanced by increasing steric bulk on the enolizable substrate six carbons removed from the reaction site. The diastereoselectivity of the aldol condensation is also sensitive to changes in reaction conditions (Table 1). As previously reported, the optimal conditions for the aldol condensation of the parent keto acid **9** required dilithiation [LDA (−78 to −40 °C) in THF] followed by transmetalation with $ZnCl_2$ at −78 °C.[25] The diastereomeric mixture of the aldol products was cleanly separated by flash column chromatography to give (6*R*,7*S*)-**44a** and (6*S*,7*R*)-**44b** (2.3:1 ratio **44a**:**44b**, 85% combined yield). Aldol condensation of TBS ether **41** and aldehyde **5** afforded improved diastereoselectivity (3.2:1 ratio of **47a**:**47b**, 72% combined yield).[3j] Although diastereo-

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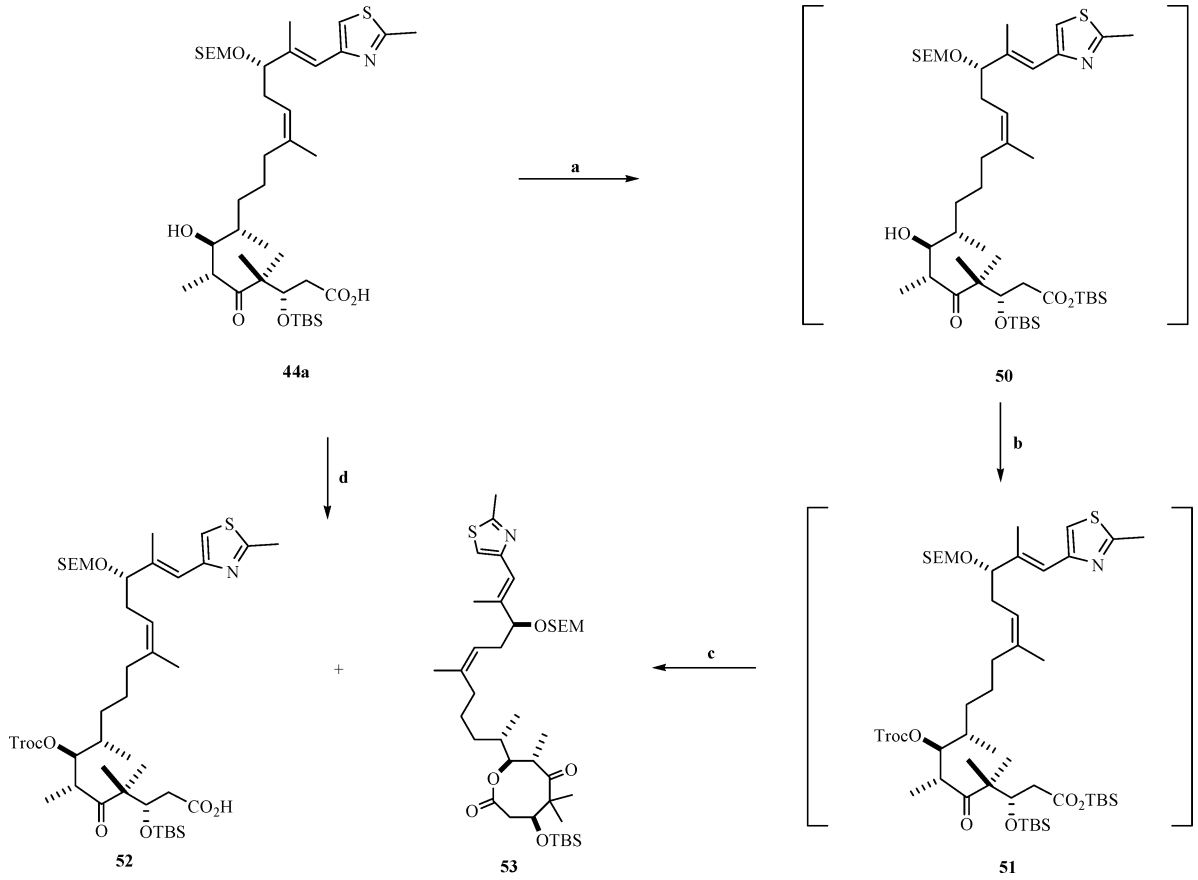
SCHEME 7. Protection of the C7 Hydroxyl of 44a as a Troc Ether[a]



[a] Reagents and conditions: (a) TBSCl (1.2 equiv), pyridine (10.0 equiv), CH_2Cl_2, 0 °C, 1 h; (b) Troc-Cl, CH_2Cl_2, rt, 5 h; (c) AcOH, THF/H_2O (8:2), 0 °C, 3 h, 36% yield for **52**, 12% yield for **53**, three steps; (d) 2,4,6-trichlorobenzoyl chloride (6.0 equiv), Et_3N (10.0 equiv), DMAP (10.0 equiv), CH_2Cl_2, −5 °C, 30 min, 90%.

selectivity was enhanced, the reaction failed to go to completion. Aldol reactions with the Weinreb amide **35** and ortho esters **42** and **43** failed to enhance the diastereoselectivity. The greatest enhancement in diastereoselectivity was achieved with the titanium enolate of sultam **34** (10:1 ratio of **45a**:**45b**, 60% combined yield). The enhancement in diastereoselectivity was not sufficient to compensate for the low yields in both the aldol condensation (60% yield) and the hydrolysis of the resulting sultam **45a** (23% yield). We have found that our original reaction conditions using the dilithio derivative of keto acid **9** followed by transmetalation with $ZnCl_2$ provided acceptable selectivity and yield for preparation of the epothilones B (**2**) and D (**4**).

Protecting Group Strategies. Following the aldol condensation, it was necessary to protect the C1 acid and the resulting C7 hydroxyl of **44a** (Scheme 7). The C1 acid was protected as the TBS ester (**50**) and the C7 hydroxyl as a trichloroethyl (Troc) carbonate (**51**). Surprisingly, attempted acid-catalyzed cleavage of the C1 TBS ester of **51** with acetic acid yielded the desired product **52** (36%) as well as an eight-membered lactone **53** (12%). Obviously, C1 TBS ester hydrolysis was accompanied by cleavage of the C7 Troc group as well. We believe that the C1 acid may have formed an unstable Troc anhydride, which facilitated attack by the nucleophilic unprotected C7 hydroxyl thus accounting for the formation of the undesired eight-membered lactone **53**.

Not surprisingly, attempted Yamaguchi macrolactonization directly from the C7-hydroxyl acid **44a** (2,4,6-trichlorobenzoyl chloride in dichloromethane) resulted exclusively in the formation of the undesired eight-membered lactone **53** (90%). Therefore, selective removal of the C15 SEM protecting group of **52** was required prior to macrolactonization, which proved to be more difficult than expected. Because of these complications, a systematic study was undertaken to optimize the conditions required for selective deprotection of the C15 SEM ether of **52** in the presence of both the C3 TBS and C7 Troc protecting groups (Table 2).

Numerous deprotecting conditions were investigated, including TFA/CH_2Cl_2,[26] TBAF/CH_2Cl_2,[27] BF_3·Et_2O/THF,[28] CBr_4/MeOH,[29] $MgBr_2$/Et_2O,[30] $ZnBr_2$/CH_2Cl_2,[31] InF_3/CH_2-

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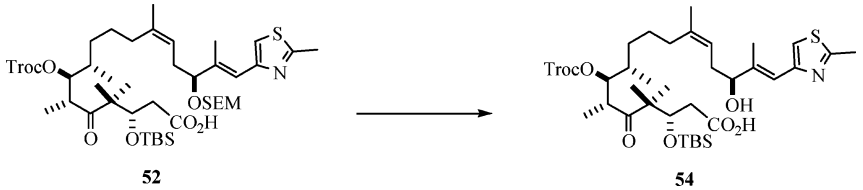
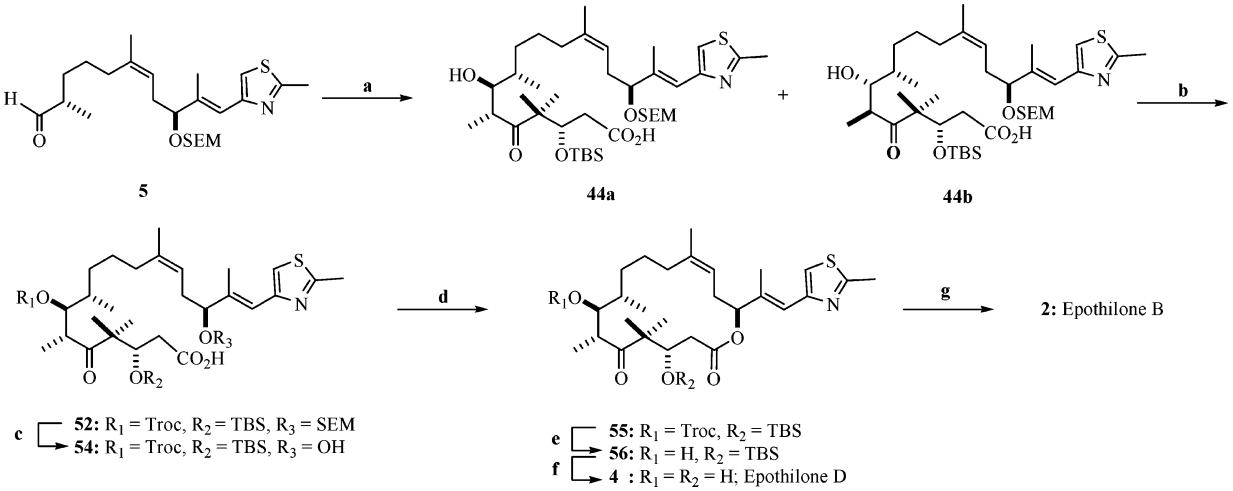
TABLE 2. Selective Cleavage of the SEM Ether of 52 in the Presence of TBS and Troc Groups



entry	reagent	temp (°C)	solvent	time (h)	yield (%)[a]
1	TFA	−30 to rt	CH_2Cl_2	2	42
2	TBAF	−30 to rt	THF	16	*b*
3	$BF_3{\cdot}Et_2O$	−30 to rt	CH_2Cl_2	16	*c*
4	CBr_4	reflux	MeOH	5	33
5	$MgBr_2$	−30 to tr	Et_2O	3	56
6	$MgBr_2$, *n*-BuSH	rt	Et_2O	1	72
7	$ZnBr_2$	−45 to rt	CH_2Cl_2	2	48
8	InF_3	−45 to rt	CH_2Cl_2	2	*d*
9	$LiBF_4$	−20 to rt	CH_3CN	2	*d*
10	1.5% HCl	−10 to rt	MeOH	3	22
11	DAST	−10 to rt	CH_2Cl_2	1	*c*

[a] Isolated yield. [b] Complex mixture. [c] Decomposed product. [d] No reaction.

SCHEME 8. Summary of Assembly of Epothilones B (2) and D (4) from Aldehyde 5[a]



[a] Reagents and conditions: (a) LDA, −5 °C, 20 min; then **9** (1.2 equiv), THF, −78 °C, 15 min; then −40 °C, 1 h; $ZnCl_2$ (2.5 equiv), −78 °C, 30 min; then **5** (1.0 equiv), THF, −78 °C, 15 min, (85%, combined yield); (b) (i) TBSCl (1.2 equiv), pyridine (10.0 equiv), CH_2Cl_2, 0 °C, 1 h; then Troc-Cl, CH_2Cl_2, rt, 5 h; (ii) AcOH, THF/H_2O (8:2), 0 °C, 3 h, 36%; (c) $MgBr_2$ (6.0 equiv), $MeNO_2$ (6.0 equiv), *n*-BuSH (3.0 equiv), Et_2O, rt, 1 h; (d) 2,4,6-trichlorobenzoyl chloride (3.0 equiv), Et_3N (3.6 equiv), THF, 0 °C, 1 h; then toluene, added to DMAP (6.0 equiv) in toluene, rt, 4 h (38%, three steps); (e) Zn, NH_4Cl, MeOH, reflux, 20 min, 92%; (f) HF-Py, THF, rt, 16 h, 95%; (g) *m*-CPBA (2.0 equiv), $CHCl_3$, −10 to 0 °C, 5 h, 30%; or 3,3-dimethyldioxirane, CH_2Cl_2, −78 °C; then −50 °C, 2 h, 53%.

Cl_2, $LiBF_4/CH_3CN$,[32] 1.5% HCl/MeOH,[33] and DAST/CH_2Cl_2. However, these reactions failed to selectively remove the SEM group in the presence of the TBS and Troc protecting groups, giving mixtures of diols and/or the triol in poor yields. Among the various protocols summarized in Table 2, selective removal of the SEM group of **52** was achieved with $MgBr_2$, $MeNO_2$, and *n*-BuSH[34] in ether to give the C15 hydroxy acid **54** in 72% yield. Carboxylic acid **54** was then subjected to macrolactonization under Yamaguchi conditions[7] to give the lactone **55** (38% yield, three steps) (Scheme 8).

To complete our synthesis, selective removal of the Troc group of **55** at the C7 position was effected by using Zn/NH_4Cl in methanol to afford lactone **56** (92%). The C3 TBS protecting group of **56** was removed with HF−pyridine to provide epothilone D (**4**).[35] Epoxidation of the C12−C13 double bond of **4** with Prilezhaev conditions (*m*-CPBA) resulted in a diastereomeric mixture with the desired β-epoxy diastereomer as the major product **2** (2.8:1 ratio of β:α epoxides, 30% combined yield). Dramatic enhancements in both diastereoselectivity and yield were observed with 3,3-dimethyldioxirane[36] (DMDO) (9.5:1 ratio of β:α epoxides, 53% combined yield) (Scheme

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8). The properties of **2** and **4** were identical with the reported spectral and physical data for the these compounds.[3c,36]

Conclusion

We have developed efficient and scalable syntheses of epothilone fragments **5**, **6**, **7**, and **9**, which were subsequently employed in the total syntheses of epothilone B (**2**) and epothilone D (**4**). We have explored the effects of steric bulk in the enolizable substrate on the diastereomeric ratio of the aldol condensation. Through an extensive study of deprotection conditions for the C15 SEM group, the optimal reaction conditions were discovered that would selectively cleave the C15 SEM ether in the presence of C3 TBS and C7 Troc protecting groups in acceptable yields. In addition, the diastereoselectivity of the epoxidation of epothilone D (**4**) to give epothilone B (**2**) was greatly improved resulting in a 3-fold increase in diastereoselectivity. Collectively, these improvements provide a practical route for the syntheses of epothilones B (**2**) and D (**4**).

Experimental Section

(2*S*,3*R*)-3-(4-Methoxybenzyloxy)-1,2-epoxybutane (6). To a suspension of NaH (10.0 g, 248.2 mmol, 60% dispersion in mineral oil) in dry THF (200 mL) was added dropwise (2*S*,3*R*)-1,2-epoxybutanol (**13**,18.20 g, 206.8 mmol) in THF (60 mL) at 0 °C, and the mixture was stirred at 0 °C for 1 h. Tetrabutylammonium iodide (4.60 g, 12.4 mmol) was added, and the mixture was stirred at 0 °C for 15 min. Freshly prepared 4-methoxybenzyl bromide (49.6 g, 248 mmol) [prepared by treating 4-methoxybenzyl alcohol (36.7 g, 260 mmol) in ether (420 mL) with phosphorus tribromide (36.3 g, 130 mmol) at 0 °C][9] in dry THF (50 mL) was added dropwise, and the resulting mixture was stirred at 0 °C for 6 h. The reaction mixture was quenched at 0 °C by slow addition of water (50 mL) and extracted with ethyl acetate (120 mL). The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (2 × 30 mL). The combined organic solution was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 15% ethyl acetate/hexanes) to give **6** (36.8 g, 176.9 mmol, 86%) as a colorless oil. R_f 0.3 (15% ethyl acetate/hexanes); $[\alpha]^{22}_D$ −6.8 (*c* 1.8, $CHCl_3$); IR (neat, NaCl) 2983, 2836, 1737, 1612, 1513, 1247 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.28 (d, J = 5.8 Hz, 2H, aromaticH), 6.90 (d, J = 8.6 Hz, 2H, aromaticH), 4.54 (dd, J = 11.4 Hz, J = 11.4 Hz, 2H, CH_2OCH), 3.83 (s, 3H, OCH_3), 3.42 (dq, J = 5.5 Hz, J = 6.1 Hz, 1H, CH_3C*H*CH), 2.96−2.94 (m, 1H, CH_2-OC*H*CH), 2.81 (dd, J = 4.0 Hz, J = 3.9 Hz, 1H, CH_2OCHCH), 2.71 (dd, J = 2.6 Hz, J = 2.6 Hz, 1H, CH_2OCHCH), 1.31 (d, J = 6.4 Hz, 3H, CH_3CHO); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.6, 131.0, 129.6, 114.2, 74.4, 71.5, 55.7, 54.8, 46.2, 18.0; HRMS calcd for $C_{12}H_{16}O_3Na$ 231.0997 $[M + Na]^+$, found 231.1029.

Diethyl (2-Methylthiazol-4-yl)methanephosphonate (8). A mixture of chloromethyl-2-methylthiazole (**23**, 50.0 g, 340 mmol) and triethyl phosphite (112.5 g, 677.0 mmol) was heated at 160 °C for 6 h. The mixture was cooled, and excess triethyl phosphite was distilled under reduced pressure. The residue was purified by flash silica chromatography (5% methanol/ether) to afford phosphonate **8** (72.80 g, 292.4 mmol, 86%) as a pale yellow oil. R_f 0.3 (60% ethyl acetate/hexanes); IR (neat, NaCl) 3506, 2983, 2903, 1735, 1521, 1442, 1247, 1016, 953 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.03 (d, J = 3.3 Hz, 1H, SC*H*OC), 4.08 (dq, J = 14.7 Hz, J = 7.2 Hz, 4H, 2 × OCH_2-CH_3), 3.32 (d, J = 21.0 Hz, 2H, POCH_2C), 2.66 (s, 3H, CH_3), 1.27 (t, J = 7.0 Hz, 6H, 2 × CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.6, 145.4, 115.2, 61.5, 29.3, 27.9, 18.3, 15.9; HRMS calcd for $C_9H_{17}O_3PNS$ 250.0661 $[M + H]^+$, found 250.0624.

(3*S*)-3-(*tert*-Butyldimethylsilyloxy)-4,4-dimethyl-5-oxoheptanoic Acid (9). To a solution of sultam **34** (35.0 g, 70.0 mmol) in THF:H_2O (350 mL:150 mL) was added lithium hydroxide (5.90 g, 140.6 mmol) followed by H_2O_2 (56 mL, 490.0 mmol, 30% aqueous solution) at 0 °C. The resulting mixture was stirred at room temperature for 4 h. The mixture was diluted with water (200 mL) and washed with ether (100 mL). The aqueous phase was cooled to 0 °C, neutralized (pH 7.0) with aqueous 2 N HCl, and extracted with ethyl acetate (3 × 300 mL). The combined ethyl acetate layers were dried (anhydrous Na_2SO_4), filtered, and concentrated in vacuo. The crude residue was purified by flash silica chromatography (50% ether/hexanes) to afford keto acid **9** (16.2 g, 53.6 mmol, 76%) as a viscous, colorless oil. R_f 0.2 (50% ethyl acetate/hexanes); $[\alpha]^{22}_D$ −17.6 (*c* 1.0, $CHCl_3$); IR (neat, NaCl) 3032, 2956, 2858, 1713, 1471, 1254, 1092 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 9.63 (br s, 1H, COO*H*), 4.50 (q, J = 3.6 Hz, 1H, C*H*OSi), 2,-57−2.50 (m, 3H, CH_2CH_3, CH_2COOH), 2.35 (dd, J = 6.9 Hz, J = 2.3 Hz, 1H, CH_2COOH), 1.15 (s, 3H, C(CH_3)$_2$), 1.10 (s, 3H, C(CH_3)$_2$), 1.02 (t, J = 7.1 Hz, 3H, CH_3CH$_2$), 0.89 (s, 9H, (CH_3)$_3$C), 0.07 (s, 3H, Si(CH_3)$_2$), 0.06 (s, 3H, Si(CH_3)$_2$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 215.4, 178.4, 73.9, 53.00, 39.7, 32.1, 26.3, 21.4, 20.9, 18.5, 8.1, −4.0, −4.5; HRMS calcd for $C_{15}H_{31}O_4Si$ 303.1986 $[M + H]^+$, found 303.1971.

5-Bromo-2-methyl-1-pentene (18). To a stirred solution of tosylate **17** (23.3 g, 91.7 mmol) in acetone (1 L) was added lithium bromide (9.5 g, 109.4 mmol) in portions at ambient temperature. The reaction mixture was heated to reflux for 2 h and cooled to room temperature. After 3 h at room temperature, the reaction mixture was poured over ice (100 g), and the product was extracted with ether (3 × 500 mL). The combined ether layers were then washed with brine (500 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure to give the crude bromide, which was purified by flash column chromatography (silica gel, 1% ethyl acetate/hexanes), followed by vacuum distillation (68−70 °C/30 mmHg) to yield **18** (10.2 g, 69%) as a colorless oil. R_f 0.6 (1% ethyl acetate in hexanes); IR (neat, NaCl) 2967, 1651, 1438, 1244, 892 cm^{-1}; ^1H NMR[10] ($CDCl_3$, 300 MHz) δ 4.74 (d, J = 12.6 Hz, 2H), 3.40 (t, J = 6.6 Hz, 2H), 2.16 (t, J = 6.6 Hz, 2H), 2.04−1.91 (m, 2H), 1.72 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.9, 111.0, 36.1, 33.3, 30.6, 22.3.

(−)-(2*R*,3*S*,5*Z*)-2-(4-Methoxybenzyloxy)-6,10-dimethylundeca-5,10-dien-3-ol (25). To a solution of copper(I) bromide−dimethyl sulfide complex (22.6 g, 110.0 mmol) in dry ether (110 mL) and dimethyl sulfide (100 mL) was added dropwise freshly prepared 4-methyl-4-pentenylmagnesium bromide [4-methyl-4-pentenyl bromide (22.0 g, 134.9 mmol) in ether (100 mL) was treated with magnesium (3.9 g, 162.5 mmol)] at −45 °C, and the mixture was stirred at this temperature for 2 h. A solution of condensed propyne (6.6 g, 165.0 mmol) in ether (20 mL) was added, and the resulting mixture was stirred at −23 °C for 4 h. The dark green solution was cooled to −78 °C, and a freshly prepared solution of lithiohexyne [1-hexyne (9.0, 109.8 mmol) was treated with *n*-butyllithium (7.1 g, 110.0 mmol; 1.6 M solution in hexanes) and HMPA (18.5 g, 109.3 mmol) in ether (200 mL) at −78 °C for 1 h] was added slowly, and the mixture was stirred at −78 °C for 1 h. (2*S*,3*R*)-3-(4-Methoxybenzyloxy)-1,2-epoxybutane (**6**, 23.1 g, 109. 6 mmol) was added dropwise, and the resulting mixture was stirred at −78 °C for 3 h and an additional 14 h at −25 °C. The reaction mixture was quenched with aqueous saturated NH_4Cl solution (adjusted to pH 8 with $NH_3 \cdot H_2O$) and extracted with ether. The organic layer was separated, dried (anhydrous Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash silica chromatography (15% ethyl acetate/hexanes) to give alcohol **25** (27.3 g, 82.2 mmol, 75%) as a colorless oil. R_f 0.6 (silica gel, 25% ethyl acetate/hexanes); $[\alpha]^{24}_D$ −22.8 (*c* 2.3, $CHCl_3$); IR (neat, NaCl) 3462, 2936, 2864, 1613, 1513, 1456, 1249, 1036 cm^{-1}; ^1H NMR

($CDCl_3$, 500 MHz) δ 7.28 (d, J = 8.0 Hz, 2H, aromatic H), 6.90 (d, J = 8.0 Hz, 2H, aromatic H), 5.20 (t, J = 7.0 Hz, 1H, CH_2CH=$C(CH_3)CH_2$), 4.72 (d, J = 15.0 Hz, 2H, CH_2=$C(CH_3)CH_2$), 4.56 (d, J = 11.5 Hz, 1H, OCH_2), 4.47 (d, J = 11.5 Hz, 1H, OCH_2), 3.82 (s, 3H, OCH_3), 3.73 (d, J = 3.5 Hz, 1H, $CH_2CH(OH)CH$), 3.53 (t, J = 3.9 Hz, 1H, CH_2OCHCH), 2.56 (br s, 1H, OH), 2.21 (dd, J = 6.4 Hz, J = 6.4 Hz, 2H, $CHCH_2CHOH$), 2.08−2.00 (m, 4H), 1.74 (s, 6H, CH=$CHCH_3$, $CH_2(CH_3)C$=CH), 1.58−1.51 (m, 2H), 1.20 (d, J = 6.0 Hz, 3H, CH_3CHOCH_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ158.9, 145.6, 138.0, 130.6, 129.1, 120.7, 113.8, 109.9, 73.5, 70.6, 55.5, 37.9, 31.9, 31.3, 26.2, 23.9, 22.8, 14.2; HRMS calcd for $C_{21}H_{33}O_3$ 333.2424 $[M + H]^+$, found 333.2429.

(−)-(2*R*,3*S*,5*Z*)-2-(4-Methoxybenzyloxy)-3-(trimethylsilylethoxymethoxy)-6,10-dimethylundeca-5,10-diene (26). To a stirred solution of alcohol **25** (25.0 g, 75.3 mmol) and DIPEA (14.5 g, 112.2 mmol) in dichloromethane (300 mL) was added SEM-Cl (15.0 g, 90.0 mL) dropwise at 0 °C. The mixture was warmed to room temperature and stirred for 6 h. The reaction was quenched with saturated aqueous NH_4Cl solution (120 mL) and extracted with ethyl acetate (200 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the desired product, which was purified by flash column chromatography (silica gel, 10% ethyl acetate/hexanes) to afford 3-SEM diene **26** (32.0 g, 69.2 mmol, 92%) as a colorless oil. R_f 0.6 (15% ethyl acetate/hexanes); $[\alpha]^{24}_D$ −13.2 (c 2.5, $CHCl_3$); IR (neat, NaCl) 2953, 2893, 1613, 1513, 1457, 1376, 1249, 1171, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.28 (d, J = 8.0 Hz, 2H, aromatic H), 6.90 (d, J = 8.0 Hz, 2H, aromatic H), 5.21 (t, J = 6.5 Hz, 1H, CH_2CH=$C(CH_3)CH_2$), 4.81 (d, J = 8.5 Hz, 1H, CH_2=$C(CH_3)CH_2$), 4.75 (d, J = 7.0 Hz, 1H, CH_2=$C(CH_3)CH_2$), 4.71 (d, J = 15.0 Hz, 2H, OCH_2O), 4.51 (dd, J = 11.5 Hz, J = 11.5 Hz, 2H, OCH_2), 3.81 (s, 3H, OCH_3), 3.76−3.66 (m, 3H), 3.56 (dd, J = 4.0 Hz, J = 3.5 Hz, 1H, $CH_3CH(OCH_2)CH$), 2.32 (q, J = 6.0 Hz, 1H, $CHCH_2CHOH$), 2.24 (d, J = 6.5 Hz, 1H, $CHCH_2CHOH$), 2.05−1.99 (m, 4H), 1.73 (s, 3H, CH=$CHCH_3$), 1.72 (s, 3H, $CH_2(CH_3)C$=CH), 1.53 (dd, J = 6.5 Hz, J = 7.0 Hz, 2H, $CH_2CH_2CH_2$), 1.21 (d, J = 6.0 Hz, 3H, CH_3CHOCH_2), 0.97 (dd, J = 7.0 Hz, J = 8.5 Hz, 2H, $CH_2Si(CH_3)_3$), 0.03 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.0, 145.6, 136.8, 130.8, 129.0, 121.1, 113.6, 109.8, 94.3, 79.2, 76.1, 70.6, 65.3, 55.4, 38.0, 31.9, 29.9, 26.2, 23.9, 22.8, 18.5, 15.5, −0.9; HRMS calcd for $C_{27}H_{47}O_4Si$ 463.3238 $[M + H]^+$, found 463.3258.

(+)-(2*R*,3*S*,5*Z*)-3-(Trimethylsilylethoxymethoxy)-6,10-dimethylundeca-5,10-dien-2-ol (27). To a mixture of **26** (40 g, 86.5 mmol) in dichloromethane (400 mL) and water (80 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (23.6 g, 103.9 mmol) portionwise at room temperature. The resulting mixture was stirred for 3 h and extracted with dichloromethane (200 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the deprotected alcohol, which was purified by flash column chromatography (silica gel, 10% ethyl acetate/hexanes) to afford 3-SEM alcohol **27** (26.9 g, 78.7 mmol, 91%) as a colorless oil. R_f 0.7 (25% ethyl acetate/hexanes); $[\alpha]^{24}_D$ +29.8 (c 1.7, $CHCl_3$); IR (neat, NaCl) 3478, 2953, 2891, 1625, 1454, 1376, 1250, 1102, 1033 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.17 (t, J = 6.0 Hz, 1H, CH_2CH=$C(CH_3)CH_2$), 4.80 (d, J = 7.0 Hz, 1H, CH_2=$C(CH_3)CH_2$), 4.72 (d, J = 7.0 Hz, 1H, CH_2=$C(CH_3)CH_2$), 4.67 (d, J = 7.0 Hz, 2H, OCH_2O), 3.77 (dd, J = 6.5 Hz, J = 6.5 Hz, 2H, OCH_2Si), 3.60 (dd, J = 10.0 Hz, J = 10.0 Hz, 1H, $CH_2CH(OH)CH$), 3.54 (dd, J = 5.5 Hz, J = 5.0 Hz 1H, $CH_2CH(OH)CH$), 3.20 (br s, 1H, OH), 2.34 (q, J = 7.5 Hz, 1H, $CHCH_2CHOH$), 2.14 (dd, J = 8.0 Hz, J = 8.0 Hz, 1H, $CHCH_2CHOH$), 2.04−1.99 (m, 4H), 1.72 (s, 3H, CH=$CHCH_3$), 1.71 (s, 3H, $CH_2(CH_3)C$=CH), 1.53 (dd, J = 6.5 Hz, J = 6.5 Hz, 2H, $CH_2CH_2CH_2$), 1.16 (d, J = 6.5 Hz, 3H, CH_3CHOCH_2), 0.97 (dd, J = 7.0 Hz, J = 8.0 Hz, 2H, $CH_2Si(CH_3)_3$), 0.03 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.5, 137.3, 120.7, 109.8, 95.5, 85.0, 68.9, 65.8, 37.9, 31.9, 30.1, 26.1, 23.8, 22.7, 18.4, 17.5, −1.0; HRMS calcd for $C_{19}H_{39}O_3Si$ 343.2663 $[M + H]^+$, found 343.2668.

(−)-(3*S*,5*Z*)-3-(Trimethylsilylethoxymethoxy)-6,10-dimethylundeca-5,10-dien-2-one (28). To a solution of oxalyl chloride (12.8 g, 100.8 mmol) in dichloromethane (300 mL) was added DMSO (15.8 g, 202.2 mmol) dropwise at −78 °C, and the mixture was stirred at this temperature for 15 min. 3-SEM alcohol **27** (23.0 g, 67.2 mmol) in dichloromethane (30 mL) was added dropwise at −78 °C, and the resulting mixture was stirred for 2 h. The reaction mixture was quenched by slow addition of triethylamine (40.7 g, 402.6 mmol) at −78 °C. The reaction mixture was allowed to warm to 0 °C. After 10 min, ethyl acetate (220 mL) was added followed by saturated aqueous NH_4Cl solution (200 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 10% ethyl acetate/hexanes) to afford ketone **28** (19.4 g, 57.1 mmol, 85%) as a colorless oil. R_f 0.6 (15% ethyl acetate/hexanes); $[\alpha]^{24}_D$ −6.6 (c 2.4, $CHCl_3$); IR (neat, NaCl) 2953, 2892, 1717, 1456, 1376, 1249, 1107, 1029 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.12 (t, J = 6.5 Hz, 1H, CH_2CH=$C(CH_3)CH_2$), 4.68 (d, J = 7.0 Hz, 2H, CH_2=$C(CH_3)CH_2$), 4.64 (d, J = 5.5 Hz, 2H, OCH_2O), 3.98 (t, J = 6.0 Hz, 1H, $CH_2CH(OH)CH$), 3.60 (q, J = 7.5 Hz, 2H, OCH_2Si), 2.38−3.36 (m, 2H), 2.14 (s, 3H, $COCH_3$), 2.00−1.95 (m, 4H), 1.69 (s, 3H, CH=$CHCH_3$), 1.67 (s, 3H, $CH_2(CH_3)C$=CH), 1.48 (dd, J = 7.0 Hz, J = 7.0 Hz, 2H, $CH_2CH_2CH_2$), 0.88 (dd, J = 8.0 Hz, J = 8.0 Hz, 2H, $CH_2Si(CH_3)_3$), −0.01 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 209.2, 145.4, 138.5, 118.8, 109.9, 94.4, 82.5, 65.9, 37.9, 31.8, 30.8, 26.6, 26.1, 23.7, 22.7, 18.3, −1.0; HRMS calcd for $C_{19}H_{36}O_3SiNa$ 363.5710 $[M + Na]^+$, found 363.2321.

(−)-(1*E*,3*S*,5*Z*)-1-(2-Methyl-1,3-thiazol-4-yl)-3-trimethylsilylethoxymethoxy-2,6,10-trimethylundeca-1,5,10-triene (29). To a solution of diethyl (2-methyl-1,3-thiazol-4-yl)methyl phosphonate (**8**, 13.2 g, 52.8 mmol) in THF (150 mL) was added dropwise *n*-butyllithium (3.4 g, 53.1 mmol, 1.6 M solution in hexanes) at −78 °C, and the mixture was stirred for 1 h. Ketone **28** (12.2 g, 35.8 mmol) was added slowly at −78 °C, and the resulting mixture was warmed to room temperature over a period of 12 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (60 mL) and extracted with ethyl acetate (120 mL). The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (2 × 40 mL). The combined organic phases were washed with brine (150 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the diene, which was purified by flash column chromatography (silica gel, 10% ethyl acetate/hexanes) to afford triene **29** (12.6 g, 30.9 mmol, 86%) as a colorless oil. R_f 0.81 (25% ethyl acetate/hexanes); $[\alpha]^{24}_D$ −66.8 (c 2.5, $CHCl_3$); IR (neat, NaCl) 2954, 2892, 1507, 1248, 1102, 1024 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.93 (s, 1H, SCH=C), 6.48 (s, 1H, CH=CCH_3), 5.18 (t, J = 5.5 Hz, 1H, CH_2CH=CCH_3), 4.68 (d, J = 6.5 Hz, 1H, CH_2=$C(CH_3)CH_2$), 4.65 (d, J = 7.0 Hz, 2H, OCH_2O), 4.60 (d, J = 6.5 Hz, 1H, CH_2=$C(CH_3)CH_2$), 4.07 (t, J = 6.5 Hz, 1H, $CCHOCH_2$), 3.76 (dd, J = 8.0 Hz, J = 8.0 Hz, 1H, OCH_2CH_2Si), 3.51 (dd, J = 8.0 Hz, J = 8.0 Hz, 1H, OCH_2CH_2Si), 2.69 (s, 3H, N=C(S)CH_3), 2.37 (dd, J = 7.0 Hz, J = 7.0 Hz, 1H, $CHCH_2CHO$), 2.30 (dd, J = 6.5 Hz, J = 6.5 Hz, 1H, $CHCH_2CHO$), 2.03−1.97 (m, 7H), 1.70 (s, 3H, CH=CCH_3), 1.68 (s, 3H, CH_2CH=CCH_3), 1.53−1.48 (m, 2H), 0.93 (dd, J = 7.0 Hz, J = 8.0 Hz, 2H, $CH_2Si(CH_3)_3$), 0.01 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.1, 152.6, 145.5, 138.7, 136.9, 121.1, 120.9, 115.6, 109.8, 92.0, 81.9, 65.3, 37.9, 32.9, 31.9, 26.2, 23.8, 22.7, 19.5, 18.4, 14.2, −0.9; HRMS calcd for $C_{24}H_{42}NO_2SSi$ 436.2700 $[M + H]^+$, found 436.2685.

(−)-(2*S*,6*Z*,9*S*,10*E*)-11-(2-Methyl-1,3-thiazol-4-yl)-9-trimethylsilylethoxymethoxy-2,6,10-trimethylundeca-6,10-dien-1-ol (30). To a solution of freshly prepared (i-PC)$_2$BH (7.0 g, 24.5 mmol) [(1*R*)-(+)-pinene in THF was treated with BH_3·DMS in THF (100 mL)] was added diene **29** (10.0 g, 24.5

mmol) slowly at 0 °C, and the resulting mixture was stirred at room temperature for 30 min. Aqueous lithium hydroxide (3.1 g, 73.5 mmol, in 25 mL of water) and sodium perborate (11.3 g, 73.5 mmol) were added, and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was extracted with ethyl acetate (100 mL), and the organic layer was separated, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to give the alcohol, which was purified by flash column chromatography (silica gel, 15% ethyl acetate/hexanes) to afford trienol **30** (8.1 g, 19.0 mmol, 78%) as a colorless oil. R_f 0.3 (25% ethyl acetate/hexanes); $[\alpha]^{24}_D$ −64.7 (*c* 1.9, $CHCl_3$); IR (neat, NaCl) 2953, 2893, 1455, 1377, 1249, 1100, 1025 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.94 (s, 1H, SC*H*=C), 6.48 (s, 1H, C*H*=CCH_3), 5.17 (t, J = 6.5 Hz, 1H, CH_2CH=CCH_3), 4.62 (dd, J = 6.5 Hz, J = 6.5 Hz, 2H, OCH_2O), 4.07 (t, J = 6.0 Hz, 1H, CC*H*OCH_2), 3.78−3.69 (m, 1H, CH_2-OH), 3.48 (ddd, J = 7.5, Hz, J = 6.0 Hz, J = 6.0 Hz, 2H, OCH_2-CH_2Si), 3.40 (dd, J = 7.0 Hz, J = 7.5 Hz, 1H, CH_2OH), 2.69 (s, 3H, N=C(S)CH_3), 3.00 (br s, 1H, O*H*), 2.36 (dd, J = 7.0 Hz, J = 7.0 Hz, 1H, CHCH_2CHO), 2.30 (dd, J = 6.5 Hz, J = 6.5 Hz, 1H, CHCH_2CHO), 2.04−2.00 (m, 2H), 1.99 (s, 3H, CH=CCH_3), 1.67 (s, 3H, CH_2CH=CCH_3), 1.61−1.58 (m, 1H), 1.46−1.31 (m, 4H), 0.93 (dd, J = 7.0 Hz, J = 8.0 Hz, 2H, CH_2Si$(CH_3)_3$), 0.89 (d, J = 6.0 Hz, 3H, CH_3C$HOCH_2$), 0.03 (s, 9H, Si(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.4, 152.1, 138.8, 137.1, 121.1, 120.8, 115.5, 92.0, 82.1, 68.1, 65.3, 36.0, 33.3, 33.0, 32.4, 25.5, 23.8, 19.4, 18.4, 17.0, 14.2, −1.0; HRMS calcd for $C_{24}H_{44}NO_3SSi$ 454.2805 $[M + H]^+$, found 454.2781.

(+)-(2*S*,6*Z*,9*S*,10*E*)-2,6,10-Trimethyl-11-(2-methyl-1,3-thiazol-4-yl)-9-(2-trimethylsilylethoxymethoxy)undeca-6,10-dienal (5). Method A: To a solution of oxalyl chloride (0.3 g, 2.6 mmol) in dichloromethane (20 mL) was added DMSO (0.4 g, 5.3 mmol) dropwise at −78 °C, and the mixture was stirred for 15 min. Trienol **30** (1.0 g, 2.2 mmol) in dichloromethane (3 mL) was added dropwise at −78 °C, and the resulting mixture was stirred for 1 h. The reaction mixture was quenched by slow addition of triethylamine (1.1 g, 10.6 mmol) at −78 °C, and the reaction mixture was allowed to warm to 0 °C. After 10 min, ether (30 mL) was added followed by saturated aqueous NH_4Cl solution (30 mL). The organic layer was separated, and the aqueous phase was extracted with ether (20 mL). The combined organic phases were washed with brine (30 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the aldehyde, which was purified by flash column chromatography (silica gel, 10% ethyl acetate/hexanes) to afford aldehyde **5** (0.94 g, 2.1 mmol, 94%) as a colorless oil. R_f 0.6 (20% ethyl acetate/hexanes); $[\alpha]^{26}_D$ −51.2 (*c* 0.5, $CHCl_3$); IR (neat, NaCl) 2955, 2857, 1711, 1470, 1250, 1097, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 9.61 (d, J = 0.8 Hz, 1H, C*H*O), 6.96 (s, 1H, SC*H*=C), 6.50 (s, 1H, C*H*=CCH_3), 5.21 (t, J = 6.9 Hz, 1H, CH_2CH=CCH_3), 4.64 (dd, J = 6.9 Hz, J = 6.9 Hz, 2H, OCH_2O), 4.09 (t, J = 7.0 Hz, 1H, CC*H*O), 3.77 (dd, J = 9.7 Hz, J = 9.3 Hz, 1H, OCH_2CH_2), 3.52 (dd, J = 9.3 Hz, J = 10.0 Hz, 1H, OCH_2CH_2), 2.72 (s, 3H, N=C(S)CH_3), 2.41−2.30 (m, 3H), 2.08−2.05 (m, 2H), 2.02 (s, 3H, CH=CCH_3), 1.72−1.70 (m, 1H), 1.68 (s, 3H, CH_2CH=CCH_3), 1.46−1.31 (m, 3H), 1.09 (d, J = 7.0 Hz, 3H, CH_3CH), 0.96−0.89 (m, 2H), 0.03 (s, 9H, Si(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 205.4, 165.0, 153.2, 139.3, 137.0, 121.8, 121.6, 116.2, 92.5, 82.2, 65.6, 46.6, 33.1, 32.5, 30.7, 25.6, 23.8, 19.6, 18.5, 14.3, 13.7, −1.0; HRMS calcd for $C_{24}H_{42}NO_3SSi$ 452.2649 $[M + H]^+$, found 452.2610.

Method B: To a solution of trienol **30** (1.0 g, 2.2 mmol) in dichloromethane (20 mL) were added molecular sieves (1.0 g, 4 Å, powdered) and 4-methylmorpholine *N*-oxide (0.4 g, 3.3 mmol) followed by addition of tetrapropylammonium perruthenate (38.7 mg, 0.11 mmol) at 0 °C. The resulting mixture was stirred for 15 min. The reaction mixture was filtered through a short pad of silica (10% ethyl acetate/hexanes) to give aldehyde **5** (0.72 g, 1.6 mmol, 72%) as a colorless oil.

Method C: To a stirred solution of trienol **30** (1.0 g, 2.2 mmol) in dichloromethane (20 mL) was added Dess−Martin periodinane (1.4 g, 3.3 mmol) at room temperature, and the resulting mixture was stirred for 30 min. The reaction mixture was quenched by slow addition of saturated aqueous $Na_2S_2O_3$ solution (3 mL) and saturated aqueous $NaHCO_3$ solution (5 mL). The organic layer was separated, and the aqueous phase was extracted with ether (2 × 10 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the aldehyde, which was purified by flash column chromatography (silica gel, 10% ethyl acetate/hexanes) to afford aldehyde **5** (0.92 g, 2.0 mmol, 92%) as a colorless oil.

(−)-(3*S*)-3-(*tert*-Butyldimethylsilyloxy)-4,4-dimethyl-5-oxoheptanoic Acid 3-Methoxymethyl Amide (35). To a stirred suspension of the keto acid **9** (1.0 g, 3.3 mmol), DMAP (0.46 g, 3.6 mmol), and DCC (0.75 g, 3.6 mmol) in dichloromethane (12 mL) at ambient temperature was added *N*,*O*-dimethylhydroxylamine hydrochloride (0.34 g, 3.5 mmol) at 5 °C. The reaction mixture was stirred at room temperature for 1 h and diluted with ethyl acetate (10 mL). The resulting mixture was filtered through a pad of Celite and concentrated under reduced pressure. The residue was purified by column chromatography (20% ethyl acetate/hexanes) to afford pure amide **35** (1.0 g, 88%) as a colorless oil. R_f 0.5 (15% ethyl acetate/hexanes); $[\alpha]^{22}_D$ −12.6 (*c* 1.0, $CHCl_3$); IR (neat, NaCl) 2937, 2857, 1705, 1667, 1471, 1388, 1254, 1089, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.55 (t, J = 6.5 Hz, 1H), 3.66 (s, 3H), 3.13 (s, 3H), 2.65−2.42 (m, 3H), 2.37 (dd, J = 6.0 Hz, J = 6.5 Hz, 1H), 1.10 (s, 6H), 0.97 (t, J = 7.5 Hz, 3H), 0.84 (s, 9H), 0.08 (s, 3H), −0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 215.6, 172.6, 73.5, 61.6, 53.2, 37.0, 33.5, 32.0, 26.3, 22.3, 20.5, 18.5, 8.1, −3.9, −4.5; HRMS calcd for $C_{17}H_{35}NO_4SiNa$ 368.2233 $[M + Na]^+$, found 368.2276.

(−)-(3*S*)-3-(*tert*-Butyldimethylsilyloxy)-4,4-dimethyl-5-oxoheptanoic Acid 3-Methyloxetan-3-ylmethyl Ester (38). To a stirred solution of the keto acid **9** (2.0 g, 6.6 mmol) in dichloromethane (20 mL) at ambient temperature was added oxetanemethanol (0.75 g, 7.3 mmol), DMAP (0.24 g, 2.0 mmol), and DCC (1.50 g, 7.3 mmol). The reaction mixture was stirred at room temperature for 1 h, and diluted with ethyl acetate (18 mL). The resulting mixture was filtered through a pad of Celite, and concentrated under reduced pressure. The residue was purified by column chromatography (20% ethyl acetate/hexanes) to afford methyl ester **38** (2.4 g, 95%) as a colorless oil. R_f 0.5 (20% ethyl acetate/hexanes); $[\alpha]^{22}_D$ −20.0 (*c* 1.0, $CHCl_3$); IR (neat, NaCl) 2957, 2859, 1740, 1705, 1471, 1253, 1177, 1090, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.48 (d, J = 4.0 Hz, 3H), 4.36 (d, J = 6.0 Hz, 2H), 4.13 (q, J = 11.0 Hz, 2H), 2.56−2.44 (m, 3H), 2.32 (dd, J = 6.5 Hz, J = 7.0 Hz, 1H), 1.32 (s, 3H), 1.11 (s, 3H), 1.07 (s, 3H), 0.98 (t, J = 6.5 Hz, 3H), 0.83 (s, 9H), 0.05 (s, 3H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 214.4, 171.8, 79.6, 73.8, 69.2, 52.7, 39.6, 39.2, 32.0, 26.2, 21.5, 20.8, 18.4, 8.1, −4.0, −4.5; HRMS calcd for $C_{20}H_{38}O_5SiNa$ 409.2381 $[M + Na]^+$, found 409.2372.

(−)-(3*S*)-3-(*tert*-Butyldimethylsilyloxy)-4,4-dimethyl-5-oxoheptanoic Acid 2-(2-Methyloxiranyl) Ethyl Ester (39). To a stirred solution of the keto acid **9** (2.0 g, 6.6 mmol) in dichloromethane (20 mL) at ambient temperature was added freshly prepared [3-methyl-3-buten-1-ol (4.4 g, 50.0 mmol) in dichloromethane was treated with *m*-CPBA (13.2 g, 52.7 mmol, 70% purity) at −78 °C for 4 h in 58% yield][22] 2-methyloxiraneethanol (0.68 g, 6.6 mmol), DMAP (0.24 g, 2.0 mmol), and DCC (1.5 g, 7.3 mmol). The reaction mixture was stirred at room temperature for 1 h, and diluted with ethyl acetate (10 mL). The resulting mixture was filtered through a pad of Celite and concentrated under reduced pressure. The residue was purified by column chromatography (15% ethyl acetate/hexanes) to afford ethyl ester **39** (2.5 g, 96%) as a colorless oil. R_f 0.4 (15% ethyl acetate/hexanes); $[\alpha]^{22}_D$ −13.9 (*c* 1.3, $CHCl_3$); IR (neat, NaCl) 2958, 2933, 2857, 1737, 1705, 1472, 1254, 1090, 835 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.42 (d, J = 4.5 Hz, 1H), 4.19−4.01 (m, 2H), 2.61−2.30 (m, 5H), 2.23 (dd, J = 8.0 Hz, J = 9.0 Hz, 1H), 1.89 (tq, J = 8.0 Hz, J = 7.5 Hz 1H), 1.80

(tq, J = 8.5 Hz, J = 9.0 Hz 1H), 1.30 (s, 3H), 1.07 (s, 3H), 1.01 (s, 3H), 0.94 (t, J = 8.5 Hz, 3H), 0.79 (s, 9H), 0.01 (s, 3H), −0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 215.2, 172.2, 74.0, 61.4, 55.1, 53.9, 52.9, 39.8, 35.8, 32.1, 26.2, 21.6, 21.4, 18.4, 8.0, −4.1, −4.6; HRMS calcd for $C_{20}H_{38}O_5SiNa$ 409.2410 [M + Na]$^+$, found 409.2407.

(−)-(5*S*)-5,7-Bis(*tert*-butyldimethylsilyloxy)-4,4-dimethylheptan-3-one (41). Method A: To a stirred solution of sultam **34** (0.1 g, 0.2 mmol) in THF (2 mL) was added $LiBH_4$ (4.3 mg, 0.2 mmol) at 0 °C, and the mixture was stirred at room temperature for 20 h. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl solution (2 mL) and the aqueous phase was extracted with ethyl acetate (5 mL). The combined organic layers were washed with brine (6 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford the diol, which was treated with dry DMF (2 mL), triethylamine (0.024 g, 0.24 mmol), and DMAP (3.0 mg, 0.024 mmol) at 0 °C, followed by TBSCl (0.036 g, 0.24 mmol). The reaction mixture was stirred at room temperature for 1 h and diluted with ethyl acetate (4 mL). The mixture was washed with water (4 mL) and brine (4 mL). The organic phase was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography (20% ethyl acetate/hexanes) to afford (−)-(5*S*)-5,7-bis(*tert*-butyldimethylsilyloxy)-4,4-dimethylheptan-3-ol (**37**, 0.046 g, 57%) as a colorless oil. R_f 0.4 (15% ethyl acetate/hexanes); $[\alpha]^{22}_D$ −13.1 (c 1.2, $CHCl_3$); IR (neat, NaCl) 3721, 2955, 2927, 2851, 1473, 1258, 1087, 837 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.76−3.64 (m, 3H), 3.33 (d, J = 10.4 Hz, 1H), 2.80 (br s, 1H), 2.02−1.98 (m, 1H), 1.53−1.46 (m, 2H), 1.36−1.25 (m, 1H), 0.98 (t, J = 7.2 Hz, 3H), 0.90 (s, 3H), 0.89 (s, 9H), 0.85 (s, 9H), 0.74 (s, 3H), 0.04−0.07 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 78.4, 75.9, 62.3, 43.2, 36.9, 26.5, 26.4, 24.6, 19.1, 19.0, 18.8, 18.7, 12.1, −3.2, −4.0, −5.0; MS (ESI) (m/z) $C_{21}H_{49}O_3Si$, 405 [M + H]$^+$.

To a stirred solution of the alcohol **37** (0.025 g, 0.06 mmol) in dry dichloromethane (2 mL) and pyridine (0.1 mL) at 0 °C was added Dess−Martin periodinane (0.039 g, 0.09 mmol). The reaction mixture was stirred at room temperature for 2 h. The mixture was diluted with cold ether (4 mL), filtered, and washed with saturated aqueous $NaHCO_3$−$Na_2S_2O_3$ (3 mL, 1:1, v/v). The organic solution was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the ketone, which was purified by flash column chromatography (silica gel, 10% ethyl acetate/hexanes) to afford pure ketone **41** (0.02 g, 80%) as a colorless oil. R_f 0.7 (10% ethyl acetate/hexanes); $[\alpha]^{22}_D$ −8.1 (c 1.2, $CHCl_3$); IR (neat, NaCl) 2959, 2927, 2851, 1699, 1469, 1389, 1258, 1099, 944, 835 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.07 (dd, J = 7.5 Hz, J = 3.0 Hz, 1H), 3.65−3.57 (m, 2H), 2.58−2.42 (m, 2H), 1.57−1.45 (m, 2H), 1.11 (s, 3H), 1.04 (s, 3H), 0.99 (t, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.09 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 214.8, 73.5, 60.2, 53.2, 37.5, 31.8, 26.4, 26.2, 22.4, 20.3, 18.7, 18.5, 8.1, −3.6, −4.9; HRMS calcd for $C_{21}H_{47}O_3Si_2$ 403.3053 [M + H]$^+$, found 403.3053.

Method B: To a stirred solution of the keto acid **9** (1.0 g, 3.3 mmol) in THF (5 mL) was added dropwise trimethyl borate (1.4 g, 13.2 mmol) at 10 °C within 5 min, followed by borane−methyl sulfide complex (0.75 g, 9.9 mmol). The reaction mixture was stirred at 0 °C for 3 h, warmed to 15 °C, and stirred for 6 h. The reaction mixture was cooled to −5 °C, ice water (2.6 g) was added portionwise, and the resulting mixture was stirred at room temperature for 30 min. The solvents were removed by evaporation, and ether (10 mL) and hexane (40 mL) were added to the milky residue followed by water (1.0 g) and Na_2SO_4 (1.3 g). The resulting mixture was stirred at room temperature for 1 h and filtered through a pad of Celite. The residue was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography (20% ethyl acetate/hexanes) to afford (−)-(5*S*)-5-(*tert*-butyldimethylsilyloxy)-5-hydroxy-4,4-dimethylheptan-3-one (**40**, 0.68 g, 71%) as a colorless oil. R_f 0.5 (20% ethyl acetate/hexanes); $[\alpha]^{24}_D$ +33.2 (c 0.5, $CHCl_3$); IR (neat, NaCl) 3459, 2956, 2884, 2859, 1706, 1471, 1259, 1077, 835 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.00 (dd, J = 14.0 Hz, J = 14.0 Hz, 1H), 4.18−4.00 (m, 1H), 3.73−3.54 (m, 2H), 2.23−2.04 (m, 1H), 1.72−1.33 (m, 3H), 1.07 (s, 3H), 1.00 (s, 6H), 0.94 (s, 9H), 0.11 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 101.4, 54.8, 39.9, 29.2, 28.0, 25.7, 23.0, 17.8, 5.9, −3.9, −4.4; HRMS calcd for $C_{15}H_{32}O_3SiNa$ 311.2018 [M + Na]$^+$, found 311.2135.

To a stirred solution of the alcohol **40** (1.1 g, 3.8 mmol) and imidazole (0.4 g, 5.8 mmol) in dichloromethane (50 mL) at 0 °C was added TBSCl (0.7 g, 4.6 mmol), and the reaction mixture was stirred at 0 °C for 3 h. The mixture was quenched by addition of saturated aqueous NH_4Cl solution (20 mL), and the aqueous phase was extracted with dichloromethane (25 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the ketone, which was purified by flash column chromatography (silica gel, 10% ethyl acetate/hexanes) to afford pure ketone **41** (1.1 g, 72%) as a colorless oil.

(−)-(5*S*)-5-(*tert*-Butyldimethylsilyloxy)-4,4-dimethyl-6-(4-methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)hexan-3-one (42). To a stirred solution of methyl ester **38** (2.2 g, 5.7 mmol) in dichloromethane (10 mL) at −10 °C was added boron trifluoride etherate (165 μL, 1.3 mmol). The reaction mixture was stirred for 20 min and warmed to 20 °C over 1 h. After being stirred for 3 h, the mixture was quenched by addition of triethylamine (0.8 mL, 5.7 mmol) at 0 °C. The resulting mixture was diluted with ethyl acetate (12 mL), filtered through a pad of Celite, and concentrated under reduced pressure. The residue was purified by column chromatography (10% ethyl acetate/hexanes) to afford OBO ester **42** (1.6 g, 73%) as a colorless oil. R_f 0.6 (15% ethyl acetate/hexanes); $[\alpha]^{22}_D$ −3.2 (c 1.5, $CHCl_3$); IR (neat, NaCl) 2958, 2932, 2879, 1706, 1471, 1251, 1106, 1053, 837 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.33 (s, 1H), 3.86 (s, 6H), 2.51 (q, J = 6.5 Hz, 2H), 1.92 (dd, J = 3.8 Hz, J = 3.8 Hz, 1H), 1.71 (dd, J = 4.5 Hz, J = 4.5 Hz, 1H), 1.33 (s, 3H), 1.00 (s, 3H), 0.99 (s, 3H), 0.83 (s, 9H), 0.80 (s, 3H), 0.10 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 214.5, 108.5, 72.4, 72.3, 53.5, 41.8, 31.4, 30.6, 26.4, 21.2, 20.7, 18.7, 14.9, 8.2, −3.7, −4.4; HRMS calcd for $C_{20}H_{39}O_5Si$ 387.2489 [M + H]$^+$, found 387.2573.

(−)-(5*S*)-5-(*tert*-Butyldimethylsilyloxy)-4,4-dimethyl-6-(5-methyl-2,7,8-trioxabicyclo[3.2.1]oct-1-yl)hexan-3-one (43). A stirred solution of ethyl ester **39** (0.37 g, 0.96 mmol) in dry dichloromethane (5 mL) was treated at 0 °C with bis(cyclopentadienyl)zirconium dichloride (0.03 g, 0.096 mmol) and silver perchlorate (0.01 g, 0.048 mmol), and the reaction mixture was stirred at 0 °C for 15 min. The mixture was warmed to 5 °C over 30 min and quenched by addition of saturated aqueous $NaHCO_3$ solution (3 mL). The mixture was separated, and the aqueous phase was washed with dichloromethane (5 mL). The combined organic solution was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (10% ethyl acetate/hexanes) to afford ABO ester **43** (0.35 g, 93%) as a colorless oil. R_f 0.4 (10% ethyl acetate/hexanes); $[\alpha]^{22}_D$ −13.6 (c 1.6, $CHCl_3$); IR (neat, NaCl) 2936, 2858, 1734, 1706, 1471, 1379, 1254, 1090, 837 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.38 (t, J = 6.5 Hz, 1H), 3.97 (t, J = 11.0 Hz, 1H), 3.83 (t, J = 8.5 Hz, 2H), 3.67 (d, J = 12.5 Hz, 1H), 2.56−2.40 (m, 3H), 2.36−2.28 (m, 1H), 2.21 (dd, J = 5.5 Hz, J = 5.5 Hz, 1H), 1.99−1.90 (m, 1H), 1.56 (s, 3H), 1.06 (s, 3H), 1.02 (s, 3H), 0.94 (t, J = 9.0 Hz, 3H), 0.80 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 215.3, 172.7, 87.3, 73.7, 67.5, 53.0, 40.6, 39.8, 32.2, 26.2, 22.6, 21.2, 21.1, 18.4, 8.1, −3.8, −4.5; HRMS calcd for $C_{20}H_{38}O_5SiNa$ 409.2410 [M + Na]$^+$, found 409.2464.

(3*S*,6*R*,7*S*,8*S*,12*Z*,15*S*,16*E*)-3-(*tert*-Butyldimethylsilyloxy)-7-hydroxy-15-(2-trimethylsilylethoxymethoxy)-

4,4,6,8,12,16-hexamethyl-17-(2-methyl-1,3-thiazol-4-yl)-5-oxoheptadeca-12,16-dienoic Acid/(3*S*,6*S*,7*R*,8*S*,12*Z*,15*S*,-16*E*)-3-(*tert*-Butyldimethylsilyloxy)-7-hydroxy-15-(2-trimethylsilyl ethoxymethoxy)-4,4,6,8,12,16-hexamethyl-17-(2-methyl-1,3-thiazol-4-yl)-5-oxoheptadeca-12,16-dienoic Acid (44a/44b). A solution of keto acid **9** (2.3 g, 7.6 mmol) in THF (10 mL) was added dropwise to a freshly prepared solution of LDA [diisopropylamine (2.6 mL, 18.0 mmol) was added to *n*-BuLi (16.5 mL, 1.6 M solution in hexanes, 18.0 mmol) in 30 mL of THF at −5 °C] at −78 °C. The reaction mixture was stirred at −78 °C for 15 min, warmed to −40 °C, and stirred for 1 h. The temperature was reduced to −78 °C, and $ZnCl_2$ (18 mL, 1.0 M solution in ether, 15.0 mmol) was added dropwise over 30 min. A solution of aldehyde **5** (2.7 g, 6.0 mmol) was added dropwise, and the resulting mixture was stirred for 15 min and quenched by slow addition of saturated aqueous NH_4Cl solution (30 mL). The mixture was warmed to 0 °C, and AcOH (2.1 mL, 36.0 mmol) was added, followed by addition of ethyl acetate (20 mL). The organic phase was separated, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the aldol products as a diastereomeric mixture (2.3:1), which was purified by column chromatography (silica gel; 600 g, ethyl acetate/hexanes/methanol, 15:80:5) to give 7-hydroxy acids **44a** (2.6 g, 3.5 mmol, 59%) and **44b** (1.2 g, 1.6 mmol, 26%) as colorless oils.

For **44a**: R_f 0.42 (ethyl acetate/hexanes/methanol; 15:80:5); $[\alpha]^{22}_D$ −40.7 (*c* 1.8, $CHCl_3$); IR (neat, NaCl) 3484, 3110, 2953, 2895, 1714, 1693, 1470, 1250, 1096 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.97 (s, 1H, SC*H*═C), 6.50 (s, 1H, C*H*═CCH_3), 5.25 (t, J = 7.0 Hz, 1H, CH_2CH═CCH_3), 4.69 (dd, J = 7.0 Hz, J = 7.0 Hz, 1H, OCH_2O), 4.54 (d, J = 7.0 Hz, 1H, CH_2-$COOCHCH_2$), 4.45 (br s, 1H, O*H*), 4.08 (dd, J = 5.5 Hz, J = 5.5 Hz, 1H, C*H*$OCOOCCH_2$), 3.83 (dd, J = 8.0 Hz, J = 7.5 Hz, 1H), 3.76 (t, J = 8.5 Hz, 1H), 3.62−3.57 (m, 1H), 3.46 (dd, J = 8.0 Hz, J = 7.5 Hz, 1H, C*H*OSi), 3.35 (q, J = 7.0 Hz, 1H, $COCHCH_3$), 2.78 (s, 3H, N═CCH_3), 2.72 (d, J = 2.0 Hz, 1H, CH_2COOCH), 2.34−2.22 (m, 5H), 2.16−2.11 (m, 1H), 2.06−2.00 (m, 2H), 1.95 (s, 3H, CH═C(CH_3)), 1.70 (s, 3H, CH_2C-(CH_3)═CH), 1.57−1.53 (m, 3H), 1.40−1.34 (m, 1H), 1.22 (s, 3H, $C(CH_3)_2$), 1.09 (d, J = 4.5 Hz, 3H, $CH(CH_3)$), 1.07 (d, J = 7.0 Hz, 3H, $CH(CH_3)$), 0.93 (s, 3H, $C(CH_3)_2$), 0.91 (s, 9H, $SiC(CH_3)_3$), 0.15 (s, 3H, $Si(CH_3)_2$), 0.08 (s, 3H, $Si(CH_3)_2$), 0.05 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 213.7, 173.9, 165.0, 152.1, 138.6, 137.1, 121.4, 121.0, 115.0, 91.5, 82.5, 73.6, 72.5, 65.4, 60.4, 55.2, 41.4, 40.4, 36.3, 33.3, 33.2, 32.4, 26.4, 25.1, 23.8, 23.3, 19.1, 18.6, 18.4, 15.7, 14.1, 10.4, −1.0, −3.8, −4.3; HRMS calcd for $C_{39}H_{72}NO_7SSi_2$ 754.4562 $[M + H]^+$, found 754.4554.

For **44b**: R_f 0.40 (ethyl acetate/hexanes/methanol; 15:80:5); $[\alpha]^{22}_D$ −35.7 (*c* 1.6, $CHCl_3$); IR (neat, NaCl) 3491, 3106, 2953, 2896, 1730, 1713, 1470, 1251, 1097 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.92 (s, 1H, SC*H*═C), 6.48 (s, 1H, C*H*═CCH_3), 5.16 (t, J = 6.5 Hz, 1H, CH_2CH═CCH_3), 4.61 (dd, J = 7.0 Hz, J = 7.0 Hz, 1H, OCH_2O), 4.40 (q, J = 3.5 Hz, 1H, CH_2-$COOCHCH_2$), 4.07 (dd, J = 6.0 Hz, J = 6.0 Hz, 1H, C*H*$OCOOCCH_2$), 3.74 (dd, J = 8.3 Hz, J = 9.0 Hz, 1H), 3.67 (dd, J = 7.0 Hz, J = 6.5 Hz, 1H), 3.52 (t, J = 8.5 Hz, 1H), 3.46 (dd, J = 7.0 Hz, J = 7.0 Hz, 1H), 3.41 (dd, J = 3.0 Hz, J = 3.0 Hz, 1H), 3.25 (q, J = 3.5 Hz, 1H), 2.69 (s, 3H, N═CCH_3), 2.62 (d, J = 1.0 Hz, 1H, CH_2COOCH), 2.50−2.40 (m, 2H), 2.31−2.25 (m, 3H), 2.03−1.98 (m, 2H), 1.96 (s, 3H, CH═C(CH_3), 1.83 (br s, 1H, O*H*), 1.68 (s, 3H, $CH_2C(CH_3)$═CH), 1.22−1.17 (m, 4H), 1.12 (d, J = 1.5 Hz, 3H, $CH(CH_3)$), 1.06 (d, J = 7.0 Hz, 3H, $CH(CH_3)$), 0.95 (s, 3H, $C(CH_3)_2$), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.82 (s, 3H, $C(CH_3)_2$), 0.11 (s, 3H, $Si(CH_3)_2$), 0.06 (s, 3H, $Si(CH_3)_2$), 0.01 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 214.5, 175.5, 164.7, 152.2, 139.0, 136.9, 122.2, 120.9, 115.4, 92.0, 82.0, 75.0, 73.5, 65.9, 58.1, 54.0, 42.3, 40.2, 35.9, 33.4, 33.0, 32.5, 26.3, 25.4, 23.9, 22.8, 19.2, 18.5, 18.4, 15.5, 14.2, 11.8, −0.9, −3.8, −4.3; HRMS calcd for $C_{39}H_{72}NO_7SSi_2$ 754.4562 $[M + H]^+$, found 754.4640.

(3*S*,6*R*,7*S*,8*S*,12*Z*,15*S*,16*E*)-3-(*tert*-Butyldimethylsilyloxy)-1-[(*S*)-10,10-dimethyl-3,3-dioxothia-4-aza-tricyclo-[5.2.1.0]dec-4-yl]-7-hydroxy-15-(2-trimethylsilylethoxymethoxy)-4,4,6,8,12,16-hexa methyl-17-(2-methyl-1,3-thiazol-4-yl)-5-oxoheptadeca-12,16-dienoic Ester (45a). To a stirred solution of sultam **34** (0.5 g, 1.0 mmol) in dichloromethane (4.0 mL) was added $TiCl_4$ (1.1 g, 1.0 M solution in dichloromethane, 1.1 mmol) dropwise followed by DIPEA (0.14 mg, 1.1 mmol) at −78 °C, and the reaction mixture was stirred for 1 h. A solution of aldehyde **5** (0.45 g, 1.0 mmol) in dichloromethane was added dropwise to the mixture at −78 °C. The reaction mixture was stirred for 30 min and then allowed to warm to −40 °C over a period of 1 h. The resulting mixture was quenched by slow addition of phosphate buffer solution (3.7 mL, pH 7.0) and extracted with dichloromethane (10 mL). The aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic solution was washed with saturated $NaHCO_3$ solution (10 mL) and brine (10 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the aldol products as a diastereomeric mixture (10:1), which was purified by column chromatography (20% ethyl acetate/hexanes) to give aldol product **45a** (0.57 g, 60%) as a colorless oil. R_f 0.4 (20% ethyl acetate/hexanes); $[\alpha]^{24}_D$ −95.0 (*c* 0.2, $CHCl_3$); IR (neat, NaCl) 3509, 2956, 2858, 1696, 1471, 1333, 1218, 1095, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.92 (s, 1H), 6.48 (s, 1H), 5.14 (t, J = 6.6 Hz, 1H), 4.62 (d, J = 6.6 Hz, 1H), 4.56 (dd, J = 7.2 Hz, J = 4.2 Hz, 1H), 4.05 (q, J = 7.2 Hz, 1H), 3.84 (dd, J = 4.2 Hz, J = 4.2 Hz, 1H)), 3.73 (q, J = 8.4 Hz, 1H), 3.50 (q, J = 7.8 Hz, 1H), 3.46 (d, J = 3.0 Hz, 1H), 3.44 (br s, 1H), 3.41−3.36 (m, 1H), 3.27 (d, J = 9.0 Hz, 1H), 3.20 (q, J = 6.6 Hz, 1H), 2.92 (dd, J = 5.4 Hz, J = 4.8 Hz, 1H), 2.69 (s, 3H), 2.61 (dd, J = 3.6 Hz, J = 3.6 Hz, 1H), 2.36−2.16 (m, 3H), 2.07 (dd, J = 8.4 Hz, J = 7.8 Hz, 1H), 2.03−1.91 (m, 2H), 1.98 (s, 3H), 1.91−1.75 (m, 4H), 1.63 (s, 3H), 1.58−1.46 (m, 2H), 1.34 (dd, J = 9.0 Hz, J = 7.8 Hz, 1H), 1.31−1.22 (m, 2H), 1.19 (s, 3H), 1.14 (s, 3H), 1.13 (s, 3H), 1.00 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 7.8 Hz, 3H), 0.95 (s, 3H), 0.86 (s, 9H), 0.81 (dd, J = 7.2 Hz, J = 7.2 Hz, 2H), 0.09 (s, 3H), 0.07 (s, 3H), 0.00 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 222.4, 170.1, 164.7, 153.0, 139.5, 137.7, 121.2, 120.8, 115.8, 92.3, 82.1, 75.1, 72.3, 65.4, 60.6, 54.6, 53.2, 48.7, 47.9, 44.9, 41.7, 41.2, 38.5, 35.6, 33.2, 32.8, 32.7, 26.7, 26.2, 26.1, 25.2, 23.7, 22.7, 21.0, 20.1, 19.3, 18.3, 18.2, 15.6, 14.1, 9.8, −4.0, −4.1, −4.7, −4.8; HRMS calcd for $C_{49}H_{87}N_2O_8S_2Si_2$ 951.5442 $[M + H]^+$, found 951.5413.

General Procedure for the Aldol Condensation of Aldehyde 5 with Various Keto Acid Derivatives (46a−49a). A solution of the appropriate keto acid derivative (**41**−**43**) (0.37 mmol) in THF (1 mL) was added dropwise to a freshly prepared solution of LDA [diisopropylamine (140 μL) was added to *n*-BuLi (0.7 mL, 1.6 M solution in hexanes) in 1 mL of THF at −5 °C] at −78 °C. The reaction mixture was stirred at −78 °C for 15 min and warmed to −40 °C for 30 min. A solution of aldehyde **5** (0.33 mmol) in THF (1 mL) was added dropwise at −78 °C, and the resulting mixture was stirred for 10 min and quenched by slow addition of saturated aqueous NH_4Cl solution (1.5 mL). The mixture was warmed to 0 °C, and ethyl acetate (2 mL) was added to the mixture. The organic phase was separated, and the aqueous layer was extracted with ethyl acetate (3 × 3 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the aldol products, which were purified by flash column chromatography.

(3*S*,6*R*,7*S*,8*S*,12*Z*,15*S*,16*E*)-1,3-Bis(*tert*-butyldimethylsilyloxy)-7-hydroxy-15-(2-trimethyl silylethoxymethoxy)-4,4,6,8,12,16-hexamethyl-17-(2-methyl-1,3-thiazol-4-yl)-heptadeca-12,16-dien-5-one (47a). R_f 0.6 (ethyl acetate/hexanes/methanol; 15:80:5); $[\alpha]^{22}_D$ −56.5 (*c* 0.4, $CHCl_3$); IR (neat, NaCl) 3503, 2884, 2857, 1683, 1471, 1251, 1100, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.96 (s, 1H), 6.50 (s, 1H),

5.18 (t, J = 7.0 Hz, 1H), 4.64 (dd, J = 6.5 Hz, J = 6.5 Hz, 2H), 4.09 (dd, J = 6.5 Hz, J = 6.0 Hz, 1H), 3.90 (d, J = 7.0 Hz, 1H), 3.77 (q, J = 8.0 Hz, 1H), 3.68 (dd, J = 6.0 Hz, J = 6.0 Hz, 1H), 3.62 (dd, J = 7.8 Hz, J = 7.8 Hz, 1H), 3.51 (dd, J = 11.0 Hz, J = 11.0 Hz, 2H), 3.32 (d, J = 8.0 Hz, 1H), 2.72 (s, 3H), 2.42−2.19 (m, 2H), 2.07−2.03 (m, 2H), 2.02 (s, 3H), 1.80−1.73 (m, 2H), 1.69 (s, 3H), 1.66−1.61 (m, 1H), 1.59−1.44 (m, 4H), 1.36−1.28 (m, 2H), 1.22 (s, 3H), 1.11 (s, 3H), 1.04 (d, J = 7.0 Hz, 3H), 0.92 (s, 9H), 0.90 (s, 9H), 0.84 (d, J = 7.0 Hz, 3H), 0.12 (s, 3H), 0.10 (s, 3H), 0.05 (s, 6H), 0.01 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 217.5, 174.9, 166.1, 152.8, 142.8, 137.2, 120.5, 118.6, 115.3, 92.2, 74.3, 65.4, 53.9, 45.1, 39.4, 33.0, 32.9, 31.5, 26.5, 26.4, 26.2, 26.0, 23.9, 21.4, 18.9, 18.6, 18.5, 17.6, 16.2, 14.4, 1.5, −0.9, −3.1, −3.3, −3.4, −3.7, −3.9, −4.1, −4.4; HRMS calcd for $C_{45}H_{88}NO_6SSi_3$ 854.5640 $[M + H]^+$, found 854.5611.

(2*S*,5*R*,6*S*,7*S*,11*Z*,14*S*,15*E*)-2-(*tert*-Butyldimethylsilyloxy)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octyl)-6-hydroxy-14-(2-trimethylsilylethoxymethoxy)-3,3,5,7,11,15-hexamethyl-16-(2-methyl-1,3-thiazol-4-yl)hexadeca-11,15-dien-4-one (48a). R_f 0.6 (20% ethyl acetate in hexanes); $[\alpha]^{22}_D$ −24.5 (*c* 0.4, $CHCl_3$); IR (neat, NaCl) 3500, 2954, 2930, 1685, 1471, 1249, 1102, 1055, 836 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.96 (s, 1H), 6.50 (s, 1H), 5.20 (t, J = 7.0 Hz, 1H), 4.63 (dd, J = 6.5 Hz, J = 6.5 Hz, 2H), 4.19 (s, 1H), 4.08 (t, J = 6.5 Hz 1H), 3.86 (s, 6H), 3.77 (q, J = 8.0 Hz, 1H), 3.64−3.48 (m, 2H), 3.35 (d, J = 9.5 Hz, 1H), 3.27 (q, J = 7.0 Hz, 1H), 2.71 (s, 3H), 2.42−2.28 (m, 2H), 2.08−2.02 (m, 2H), 2.01 (s, 3H), 1.95−1.84 (m, 1H), 1.81−1.73 (m, 2H), 1.68 (s, 3H), 1.58−1.43 (m, 3H), 1.37−1.25 (m, 3H), 1.14 (s, 3H), 1.10 (s, 3H), 1.03 (d, J = 7.0 Hz, 3H), 0.94 (t, J = 8.5 Hz, 3H), 0.88 (s, 9H), 0.79 (s, 3H), 0.13 (s, 3H), 0.09 (s, 3H), 0.02 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 213.7, 173.9, 165.0, 152.1, 138.6, 137.1, 121.4, 121.0, 115.0, 91.5, 82.5, 73.6, 72.5, 65.4, 60.4, 55.2, 41.4, 40.4, 36.3, 33.3, 33.2, 32.4, 26.4, 25.1, 23.8, 23.3, 19.1, 18.6, 18.4, 15.7, 14.1, 10.4, −1.0, −3.8, −4.3; HRMS calcd for $C_{44}H_{80}NO_8SSi_2$ 838.5143 $[M + H]^+$, found 838.5118.

(2*S*,5*R*,6*S*,7*S*,11*Z*,14*S*,15*E*)-2-(*tert*-Butyldimethylsilyloxy)-1-(5-methyl-2,7,8-trioxabicyclo [3.2.1]octyl)-6-hydroxy-14-(2-trimethylsilylethoxymethoxy)-3,3,5,7,11,15-hexamethyl-16-(2-methyl-1,3-thiazol-4-yl)hexadeca-11,-15-dien-4-one (49a). R_f 0.7 (20% ethyl acetate in hexanes); $[\alpha]^{22}_D$ −31.0 (*c* 0.2, $CHCl_3$); IR (neat, NaCl) 3447, 2958, 2924, 1717, 1559, 1458, 1293, 1101, 1028, 836 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 6.97 (s, 1H), 6.50 (s, 1H), 5.19 (t, J = 6.5 Hz, 1H), 4.65 (dd, J = 8.5 Hz, J = 8.5 Hz, 2H), 4.22−4.15 (m, 1H), 4.10−4.04 (m, 2H), 3.95−3.86 (m, 4H), 3.79−3.72 (m, 3H), 3.51 (q, J = 7.0 Hz, 1H), 2.73 (s, 3H), 2.69 (d, J = 8.0 Hz, 1H), 2.44−2.27 (m, 3H), 2.10−2.03 (m, 2H), 2.02 (s, 3H), 1.95−1.79 (m, 3H), 1.70 (s, 3H), 1.60−1.44 (m, 2H), 1.36−1.23 (m, 4H), 1.13 (s, 3H), 1.10 (s, 3H), 1.00 (d, J = 7.5 Hz, 3H), 0.96 (t, J = 8.0 Hz, 3H), 0.89 (s, 9H), 0.81 (s, 3H), 0.12 (s, 3H), 0.10 (s, 3H), 0.01 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 214.3, 170.8, 162.2, 155.0, 140.4, 136.5, 127.5, 124.4, 115.3, 92.7, 83.6, 71.1, 65.5, 61.6, 60.4, 56.6, 55.7, 43.8, 40.7, 36.3, 35.9, 34.1, 33.9, 31.1, 30.0, 26.5, 22.9, 22.4, 21.9, 19.1, 18.7, 18.3, 16.5, 15.6, 14.4, 9.8, −1.2, −3.6, −4.9; HRMS calcd for $C_{44}H_{80}NO_8SSi_2$ 838.5143 $[M + H]^+$, found 838.5112.

(3*S*,6*R*,7*S*,8*S*,12*Z*,15*S*,16*E*)-3-(*tert*-Butyldimethylsilyloxy)-7-[(2,2,2-trichloroethoxycarbonyl)oxy]-15-(2-trimethylsilylethoxymethoxy)-4,4,6,8,12,16-hexamethyl-17-(2-methyl-1,3-thiazol-4-yl)-5-oxoheptadeca-12,16-dienoic Acid (52). To a stirred solution of acid **44a** (1.5 g, 2.0 mmol) in dichloromethane (20 mL) were sequentially added pyridine (1.6 g, 20.0 mmol) and *tert*-butyldimethylsilyl chloride (0.37 g, 2.4 mmol) at 0 °C, and the reaction mixture was stirred for 1 h. To the solution was added 2,2,2-trichloroethyl chloroformate (2.2 g, 10.0 mmol) dropwise at 0 °C, and the resulting mixture was stirred at room temperature for 5 h. After completion of the reaction, water (20 mL) was slowly added followed by addition of dichloromethane (20 mL). The organic layer was separated, and the aqueous phase was extracted with dichloromethane (2 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Acetic acid (2.2 mL) was added to a solution of the protected acid **51** in THF:H_2O (20 mL, 8:2) at 0 °C and the mixture was stirred for 3 h. The reaction mixture was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate (30 mL). The organic phase was washed with water (20 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, ethyl acetate/hexanes/methanol, 15:80:5) to give acid **52** (0.67 g, 0.72 mmol, 36%) as a colorless oil. R_f 0.3 (ethyl acetate/hexanes/methanol; 15:80:5); $[\alpha]^{22}_D$ −35.8 (*c* 1.0, $CHCl_3$); IR (neat, NaCl) 2954, 2859, 1732, 1715, 1472, 1383, 1251, 1100, 837 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.92 (s, 1H, SC*H*=C), 6.48 (s, 1H, C*H*=CCH_3), 5.16 (t, J = 7.50 Hz, 1H, CH_2CH=CCH_3), 4.83 (d, J = 11.0 Hz, 1H), 4.75 (d, J = 8.7 Hz, 2H, OCH_2CCl_3), 4.67 (d, J = 7.1 Hz, 1H), 4.62 (dd, J = 7.5 Hz, J = 7.5 Hz, 2H, OCH_2O), 4.35 (q, J = 3.0 Hz, 1H, CH_2-$COOCHCH_2$), 4.00 (d, J = 6.2 Hz, 1H, $CHOCOOCCH_2$), 3.76 (dd, J = 8.1 Hz, J = 8.1 Hz, 1H), 3.52 (dd, J = 8.1 Hz, J = 8.1 Hz, 1H), 3.42 (q, J = 3.0 Hz, 1H), 2.70 (s, 3H, N=CCH_3), 2.59 (d, J = 1.2 Hz, 1H, CH_2COOCH), 2.33−2.23 (m, 3H), 2.04−1.93 (m, 5H), 1.75−1.68 (m, 1H), 1.64 (s, 3H, $CH_2C(CH_3)$=CH), 1.46−1.1.38 (m, 2H), 1.21 (s, 3H), 1.10 (d, J = 2.8 Hz, 3H, CH-(CH_3)), 1.07 (d, J = 3.7 Hz, 3H, $CH(CH_3)$), 0.93 (s, 3H, $C(CH_3)_2$), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.84 (s, 3H, $C(CH_3)_2$), 0.12 (s, 3H, Si-$(CH_3)_2$), 0.05 (s, 3H, $Si(CH_3)_2$), 0.00 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 214.5, 175.8, 164.5, 153.9, 152.5, 139.3, 136.6, 121.6, 115.8, 94.8, 92.2, 82.6, 82.0, 74.3, 73.9, 65.7, 60.5, 54.7, 41.6, 40.3, 39.5, 35.2, 33.0, 32.5, 32.2, 26.3, 26.2, 23.8, 23.3, 19.4, 18.6, 14.1, −0.9, −1.0, −3.8, −4.2; HRMS calcd for $C_{42}H_{73}Cl_3NO_9SSi_2$ 928.3605 $[M + H]^+$, found 928.3620.

(4*S*,7*S*,8*S*,5*Z*,9*E*)-4-(*tert*-Butyldimethylsilyloxy)-5,5,7-trimethyl-8-[1,5,9-trimethyl-10-(2-methylthiazol-4-yl)-8-(2-trimethylsilanylethoxymethoxy)-deca-5,9-dienyl]oxocane-2,6-dione (53). To a stirred solution of acid **44a** (0.3 g, 0.4 mmol) in dichloromethane (10 mL) was added triethylamine (0.4 g, 4.0 mmol) and DMAP (0.5 g, 4.0 mmol) followed by 2,4,6-trichlorobenzoyl chloride (0.6 g, 2.4 mmol) at −5 °C. The mixture was stirred at 0 °C for 30 min. The mixture was quenched by addition of saturated aqueous NH_4Cl solution (2 mL) and diluted with dichloromethane (5 mL). The mixture was separated, and the aqueous phase was washed with dichloromethane (5 mL). The combined organic solution was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (10% ethyl acetate/hexanes) to afford eight-membered lactone **53** (0.26 g, 90%) as a colorless oil. R_f 0.3 (5% ethyl acetate/hexanes); $[\alpha]^{22}_D$ −37.7 (*c* 1.2, $CHCl_3$); IR (neat, NaCl) 2954, 2929, 2859, 1735, 1704, 1472, 1384, 1251, 1021, 838 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.95 (s, 1H), 6.45 (s, 1H), 5.16 (t, J = 6.5 Hz, 1H), 4.81 (d, J = 12.0 Hz, 1H), 4.70 (d, J = 8.5 Hz, 1H), 4.60 (dd, J = 6.5 Hz, J = 7.0 Hz, 2H), 4.01 (d, J = 7.0 Hz, 1H), 3.70 (tq, J = 7.0 Hz, J = 8.5 Hz, 4H), 3.52−3.43 (m, 3H), 2.70 (s, 3H), 2.45−2.22 (m, 4H), 2.10−2.02 (m, 2H), 1.99 (s, 3H), 1.65 (s, 3H), 1.48−1.39 (m, 1H), 1.33 (s, 3H), 1.25 (s, 3H), 1.20 (s, 3H), 1.17 (s, 3H), 1.22−1.07 (m, 2H), 0.90 (s, 9H), 1.13 (s, 3H), 0.07 (s, 3H), 0.00 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 210.2, 170.0, 164.2, 152.6, 138.7, 136.7, 121.0, 115.7, 94.7, 92.0, 81.9, 74.2, 65.3, 53.5, 51.9, 41.22, 39.0, 34.9, 32.9, 32.5, 31.9, 26.0, 25.0, 23.8, 19.5, 18.5, 15.8, 14.3, 12.4, 11.4, −1.2, −3.6, −4.6; MS (ESI) (*m*/*z*) 736 $[M + H]^+$; HRMS calcd for $C_{39}H_{70}NO_6SSi_2$ 736.4462 $[M + H]^+$, found 736.4434.

(4*S*,7*R*,8*S*,9*S*,13*Z*,16*S*)-4-(*tert*-Butyldimethylsilyloxy)-8-[(2,2,2-trichloroethoxycarbonyl)oxy]-5,5,7,9,13-pentamethyl-16-[(*E*)-1-methyl-(2-methyl-1,3-thiazol-4-yl)ethenyl]oxacyclohexadec-13-ene-2,6-dione (55). To a stirred suspension of magnesium bromide (0.56 g, 3.0 mmol) in ether (10 mL) were added nitromethane (0.19 g, 3.0 mmol) and 1-butanethiol (0.14 g, 1.5 mmol) at room temperature, and the

mixture was stirred for 20 min. The resulting solution was added to a stirred solution of acid **52** (0.46 g, 0.5 mmol) in ether (10 mL) at room temperature, and the mixture was stirred for 1 h. The reaction mixture was diluted with ether (30 mL) and dichloromethane (10 mL) and washed with water (25 mL). The organic layer was separated, and the aqueous phase was extracted with ether (30 mL) and dichloromethane (10 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the acid **54**, which was used in the next reaction without further purification.

To a stirred solution of **54** (0.27 g, 0.3 mmol) in THF (12 mL) was added triethylamine (0.18 g, 1.8 mmol) followed by 2,4,6-trichlorobenzoyl chloride (0.36 g, 1.5 mmol) at −5 °C. The mixture was stirred at 0 °C for 1 h. The solution was added dropwise to a solution of DMAP (0.37 g, 3.0 mmol) in toluene (120 mL) at room temperature, and the resulting mixture was stirred for 4 h. The mixture was concentrated under reduced pressure to a small volume and filtered through silica gel. The residue was washed with 40% ether in *n*-hexanes. The resulting solution was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, 15% ethyl acetate/hexanes) to give lactone **55** (0.14 g, 0.36 mmol, 38%) as a colorless oil. R_f 0.5 (20% ethyl acetate/hexanes); $[\alpha]^{22}_D$ −16.9 (*c* 1.4, $CHCl_3$); IR (neat, NaCl) 2957, 2858, 1759, 1740, 1698, 1385, 1249, 1097 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.99 (s, 1H, SC*H*=C), 6.56 (s, 1H, C*H*=CCH_3), 5.22 (d, J = 10.3 Hz, 1H, CH_2CH=CCH_3), 5.21 (d, J = 15.9 Hz, 1H, $CH_2COOCHCH_2$), 5.00 (d, J = 10.4 Hz, 1H, $CHOCOOCCH_2$), 4.90 (d, J = 11.9 Hz, 1H, CH_2CCl_3), 4.80 (d, J = 11.9 Hz, 1H, CH_2CCl_3), 4.06 (d, J = 10.3 Hz, 1H, CHOSi), 3.34 (q, J = 6.7 Hz, 1H, $COCHCH_3$), 2.84 (d, J = 16.1 Hz, 1H, CH_2COOCH), 2.73 (s, 3H, N=CCH_3), 2.71−2.66 (m, 1H, CH_2COOCH), 2.56−2.52 (m, 1H), 2.14 (s, 3H, CH=C(CH_3)), 2.09−2.03 (m, 2H), 1.80−1.74 (m, 3H), 1.70 (s, 3H, $CH_2C(CH_3)$=CH), 1.38 (d, J = 9.3 Hz, 1H), 1.29 (d, J = 8.4 Hz, 2H), 1.24 (s, 3H, $C(CH_3)_2$), 1.20 (s, 3H, $C(CH_3)_2$), 1.15 (d, J = 6.7 Hz, 3H, CH(CH_3)), 1.05 (d, J = 6.9 Hz, 3H, CH(CH_3)), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.14 (s, 3H, $Si(CH_3)_2$), 0.09 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 212.9, 172.3, 165.0, 155.0, 152.9, 140.8, 138.9, 120.2, 119.7, 116.7, 95.3, 86.9, 80.8, 76.7, 53.9, 46.2, 39.4, 35.8, 32.8, 32.1, 31.7, 28.0, 26.6, 25.1, 24.3, 23.4, 19.6, 19.3, 19.1, 16.7, 15.2, −3.2, −5.3; HRMS calcd for $C_{36}H_{57}Cl_3NO_7SSi$ 780.2691 $[M + H]^+$, found 780.2668.

(4*S*,7*R*,8*S*,9*S*,13*Z*,16*S*)-4-(*tert*-Butyldimethylsilyloxy)-8-hydroxy-5,5,7,9,13-pentamethyl-16-[(*E*)-1-methyl-(2-methyl-1,3-thiazol-4-yl)ethenyl]oxacyclohexadec-13-ene-2,6-dione (56). To a solution of lactone **55** (0.25 g, 0.32 mmol) in methanol (18 mL) was added ammonium chloride (0.42 g, 6.4 mmol) and zinc dust (0.43 g, 8.0 mmol). The mixture was heated to reflux for 20 min. The reaction mixture was diluted with ethyl acetate (16 mL) and filtered through Celite. The filtrate was concentrated under reduced pressure, and the residue was dissolved in ethyl acetate (40 mL) and washed with water (15 mL) and brine (15 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the lactone, which was purified by column chromatography (silica gel, 25% ethyl acetate/hexanes) to yield lactone **56** (0.18 g, 0.30 mmol, 92%) as a colorless oil. R_f 0.3 (20% ethyl acetate/hexanes); $[\alpha]^{22}_D$ −52.6 (*c* 0.3, $CHCl_3$); IR (neat, NaCl) 3487, 2958, 1736, 1684, 1468, 1245, 1113, 842 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.98 (s, 1H, SC*H*=C), 6.57 (s, 1H, C*H*=CCH_3), 5.17 (dd, J = 6.1 Hz, J = 5.9 Hz, 1H, CH_2CH=CCH_3), 5.00 (d, J = 10.4 Hz, 1H, $CH_2COOCHCH_2$), 4.08 (dd, J = 3.7 Hz, J = 3.9 Hz, 1H, $CHOCOOCCH_2$), 3.95 (t, J = 3.1 Hz, 1H, CHOSi), 3.08 (dd, J = 3.6 Hz, J = 3.6 Hz, 1H, $COCHCH_3$), 2.93 (br s, 1H, O*H*), 2.80−2.79 (m, 2H), 2.73 (s, 3H, N=CCH_3), 2.71−2.68 (m, 2H), 2.52−2.49 (m, 1H), 2.12 (s, 3H, CH=C(CH_3)), 1.86−1.78 (m, 3H), 1.73−1.71 (m, 1H), 1.68 (s, 3H, $CH_2C(CH_3)$=CH), 1.47−1.42 (m, 1H), 1.25−1.22 (m, 1H), 1.20 (s, 3H, $C(CH_3)_2$), 1.18 (s, 3H, $C(CH_3)_2$), 1.17 (d, J = 6.7 Hz, 3H, CH(CH_3)), 1.05 (d, J = 7.0 Hz, 3H, CH(CH_3)), 0.85 (s, 9H, $SiC(CH_3)_3$), 0.14 (s, 3H, $Si(CH_3)_2$), −0.04 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 218.2, 171.3, 165.0, 153.0, 139.8, 138.9, 120.7, 119.9, 116.4, 79.9, 73.9, 60.8, 53.9, 43.8, 39.7, 39.4, 33.4, 32.9, 31.7, 26.9, 26.5, 24.9, 23.4, 23.1, 21.4, 19.6, 19.0, 17.3, 15.7, 14.6, −3.5, −5.1; HRMS calcd for $C_{33}H_{56}NO_5SSi$ 606.3643 $[M + H]^+$, found 606.3632.

(4*S*,7*R*,8*S*,9*S*,13*Z*,16*S*)-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16[(*E*)-1-methyl(2-methyl-1,3-thiazol-4-yl)ethenyl]oxacyclohexadec-13-ene-2,6-dione (Epothilone D, 4). To a solution of 7-OH lactone **56** (0.12 g, 0.2 mmol) in THF (10 mL) was added dropwise hydrogen fluoride−pyridine (2.2 mL) at 0 °C. After being stirred at room temperature for 16 h, the mixture was diluted with ether (10 mL) and quenched at 0 °C by slow addition of saturated aqueous $NaHCO_3$ solution until CO_2 evolution ceased. The organic layer was separated, and the aqueous phase was extracted with ether (8 mL). The combined organic phases were washed with saturated aqueous $CuSO_4$ solution (10 mL), water (10 mL), and brine (10 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, ethyl acetate/hexanes/methanol, 20:70:10) to afford epothilone D (**4**, 0.093 g, 0.19 mmol, 95%) as a colorless oil. R_f 0.5 (ethyl acetate/hexanes/methanol; 20:70:10, v/v); $[\alpha]^{22}_D$ −56.2 (*c* 0.3, $CHCl_3$); IR (neat, NaCl) 3506, 2960, 2930, 2874, 1730, 1688, 1464, 1377, 1272, 1146, 977 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.97 (s, 1H, SC*H*=C), 6.61 (s, 1H, C*H*=CCH_3), 5.24 (d, J = 10.0 Hz, 1H, CH_2COOH), 5.16(d, J = 4.5 Hz, 1H, CH_3C=$CHCH_2$), 4.31 (d, J = 11.0 Hz, 1H, $(CH_3)_2CCHOH$), 3.74 (s, 1H, CHOH), 3.50 (q, J = 7.0 Hz, 1H, $COCHCH_3$), 3.18 (d, J = 6.5 Hz, 1H, $COCHCH_3$), 3.05 (br s, 1H, O*H*), 2.71 (s, 3H, N=CCH_3), 2.65 (ddd, J = 5.0 Hz, J = 5.5 Hz, J = 11.0 Hz, 1H, CH_2CH=CCH_3), 2.48 (dd, J = 11.5 Hz, J = 11.0 Hz, 1H, CH_2COOCH), 2.39−2.24 (m, 3H), 2.09 (s, 3H, CH=CCH_3), 1.96−1.87 (m, 1H), 1.77−1.72 (m, 1H), 1.68 (s, 3H, $CH_2C(CH_3)$=CH), 1.36 (s, 3H, $C(CH_3)_2$), 1.34−1.28 (m, 4H), 1.21 (d, J = 7.0 Hz, 3H, CH(CH_3)), 1.09 (s, 3H, $C(CH_3)_2$), 1.04 (d, J = 7.0 Hz, 3H, CH(CH_3)); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 221.4, 170.6, 168.0, 149.2, 143.7, 138.6, 121.0, 115.4, 115.2, 78.3, 74.5, 71.3, 60.6, 54.2, 41.3, 39.6, 39.2, 32.1, 31.7, 25.4, 23.0, 22.9, 17.7, 17.0, 15.4, 14.4, 13.6; HRMS calcd for $C_{27}H_{42}NO_5S$ 492.2784 $[M + H]^+$, found 492.2777.

(1*S*,3*S*,7*S*,10*R*,11*S*,12*S*,16*R*)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[(*E*)-1-methyl-(2-methyl-1,3-thiazol-4-yl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (Epothilone B, 2). Method A: To a stirred solution of epothilone D (**4**, 30.0 mg, 0.061 mmol) in dry chloroform (3 mL) was added *m*-CPBA (30.0 mg, 0.12 mmol, 70% purity) at −12 °C, and the reaction mixture was stirred at −10 to 0 °C for 5 h. The mixture was diluted with dichloromethane (12 mL) and quenched by slow addition of saturated aqueous $NaHCO_3$ solution (10 mL). The organic layer was separated, and the aqueous phase was extracted with dichloromethane (10 mL). The combined organic phases were washed with 5% NaOH solution (10 mL), and the aqueous phase was back-extracted with dichloromethane (10 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 5% methanol/dichloromethane) to provide a mixture of epothilone B (**2**) and its epoxy diastereoisomer (28 mg, 0.11 mmol, ca. 2.8:1 ratio by HPLC), which was purified by preparative HPLC (grad. 50% AcCN/H_2O, v/v) to give pure epothilone B (**2**, 9 mg, 30%) as colorless crystals. R_f 0.3 (ethyl acetate/hexanes/methanol; 20:70:10); mp 117−118 °C (124−125 °C);[37] $[\alpha]^{22}_D$ −74.4 (*c* 0.5, $CHCl_3$); IR (film, NaCl) 3481, 2963, 2931, 1734, 1686, 1457, 1378, 1293, 1259, 1187, 1148, 1054, 1008, 978, 752 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 6.96 (s, 1H, SC*H*=C), 6.58 (s, 1H, C*H*=CCH_3), 5.40 (dd, J = 7.8 Hz, J = 2.4 Hz 1H, CH_2COOH),

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4.22 (br s, 1H), 4.21 (br s, 1H), 3.75 (t, J = 3.0 Hz, 1H, C*H*OH), 3.28 (dq, J = 6.9 Hz, J = 4.8 Hz 1H, (CO)C*H*CH_3), 2.79 (dd, J = 7.2 Hz, J = 4.8 Hz 1H, C*H*OCCH_3), 2.68 (s, 3H, N=CCH_3), 2.52 (dd, J = 10.2 Hz, J = 10.2 Hz, 1H, CH_2COOH), 2.34 (dd, J = 3.0 Hz, J = 3.0 Hz, 1H, CH_2COOCH), 2.10 (td, J = 3.6 Hz, J = 3.6 Hz, 1H, CH_3COCHCH_2CHO), 2.07 (s, 3H, CH=CCH_3), 1.90 (ddd, J = 15.0, J = 7.8 Hz, J = 7.2 Hz, 1H, (CH_3)COCHCH_2CHO), 1.76−1.67 (m, 3H), 1.52−1.42 (m, 2H), 1.41−1.37 (m, 2H), 1.36 (s, 3H, C(CH_3)OCHCH_2), 1.26 (s, 3H, C(CH_3)$_2$), 1.15 (d, J = 6.6 Hz, 3H, CH(CH_3)), 1.06 (s, 3H, C(CH_3)$_2$), 0.99 (d, J = 7.2 Hz, 3H, CH(CH_3)); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 220.8, 170.8, 165.4, 151.9, 137.9, 119.8, 116.3, 76.9, 74.3, 73.0, 61.9, 61.6, 53.3, 43.1, 39.4, 36.6, 32.6, 32.3, 31.0, 23.0, 22.6, 21.7, 19.8, 19.3, 17.3, 16.1, 13.8; HRMS calcd for $C_{27}H_{42}NO_6S$ 508.2733 $[M + H]^+$, found 508.2757.

Method B: To a stirred solution of epothilone D (**4**, 30.0 mg, 0.061 mmol) in dichloromethane (3 mL) was added dropwise DMDO (0.1 M in acetone, 1.4 mL, 1.4 mmol; precooled to −78 °C) at −78 °C, and the reaction mixture was warmed to −50 °C and stirred for 2 h. The excess DMDO was quenched by the addition of dimethyl sulfide (0.3 mL). The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, acetate/hexanes/methanol; 20:70:10) to provide a mixture that was crystallized by the addition of ether (1 mL). The solid was filtered and washed with ether (1 mL) to give a mixture of epothilone B (**2**) and its epoxy diastereoisomer (20 mg, 67%; ca. 9.5:1 ratio by HPLC), which was purified by preparative HPLC (grad. 50% AcCN/H_2O, v/v) to give pure epothilone B (**2**, 16 mg, 53%) as colorless crystals.

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Supporting Information Available: NMR spectra (^{1}H, ^{13}C, DEPT-135, 2D) and HPLC chromatograms of selected intermediates and Epothilones B and D. This material is available free of charge via the Internet at http://pubs.acs.org.

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