Methodology Based on Chiral Silanes in the Synthesis of Polypropionate-Derived Natural Products − Total Synthesis of Epothilone A

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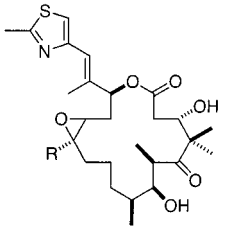
Epothilones A and B (**1** and **2**) are natural products with potent antitumor activity. These compounds have a Taxol™-like mechanism of action against tumor cells. A total synthesis of epothilone A (**1**) is reported, which is based on the synthesis and union of two advanced fragments: C3-C11 fragment **4** and C12-C21 fragment **5**. Bond construction methodology based on chiral silanes was utilized to introduce the key C6 and C7 stereocenters of fragment **4**. A lipase-mediated kinetic resolution established the C15 stereocenter of fragment **5**. The 16-membered lactone was constructed using a three-step sequence: an intermolecular *B*-alkyl Suzuki coupling of **4** and **5**, an aldol condensation, and a Yamaguchi-type macrolactonization reaction.

Introduction

Epothilones A and B (**1** and **2**) (Figure 1) are potent cytotoxic natural products isolated from the myxobacterium *Sorangium cellulosum* by Höfle and co-workers.[1] These compounds exhibit potent antitumor activity, and more importantly, posses a similar antitumor mechanism as that of paclitaxel (Taxol™). Both epothilones and paclitaxel kill tumor cells through induction of tubulin polymerization and microtubule stabilization.[2] Moreover, epothilones have also demonstrated their effectiveness against a number of paclitaxel-resistant tumor cell lines.[3] Intrigued by the remarkable biological activities and unique structures of the epothilones, extensive research efforts have been devoted to these compounds with the aim to develop new and effective anticancer agents. Consequently, there has been intense synthetic research activity directed toward the chemical synthesis of epothilones and analogs. Shortly after the disclosure of the absolute stereostructure of epothilones, several total syntheses of epothilone A and B (**1** and **2**), and numerous synthetic studies were reported.[4]



1: R =H, epothilone A
2: R = Me, epothilone B

Figure 1. Epothilones A and B (**1** and **2**)

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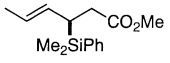
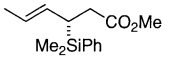
Our interest in these natural products is derived from the notion that the development of a highly convergent and stereoselective synthetic route toward these biologically important compounds would constitute a useful contribution to the epothilone field. It also offered us an opportunity to expand the utility of bond construction methodology based on chiral silanes in synthesizing complex molecules.[5] We report herein a highly convergent synthesis of epothilone A (**1**), utilizing methodology based on chiral silanes to construct the key C6 and C7 stereocenters.

The chiral silane reagents (Figure 2) developed in our laboratory have demonstrated their usefulness in a number of syntheses of complicated natural products.[6] In addition to their wide application range and capability of providing excellent levels of diastereo- and enantioselectivity in condensations with various electrophiles, a unique feature of these reagents is that the chirality of these silicon-bearing reagents is derived from a *Pseudomonas* AK lipase[7] mediated kinetic resolution.[8] Demonstrated in the following discussion, this biocatalytic process is the ultimate source of all enantioenriched materials used in our total synthesis of epothilone A (**1**).



R-**3**



S-**3**

Figure 2. Chiral silane reagents

Results and Discussion

Retrosynthetic Analysis

Scheme 1 outlines the retrosynthetic analysis of epothilone A (**1**). Literature precedent has demonstrated that the installation of the C12-C13 *cis*-epoxide could be delayed until the end of the synthesis and could be derived from a C12-C13 *cis*-olefin. The illustrated bond disconnection at the C1 ester linkage, the C2−C3 bond and the C11−C12 bond afforded three intermediates: the C3-C11 fragment **4**,

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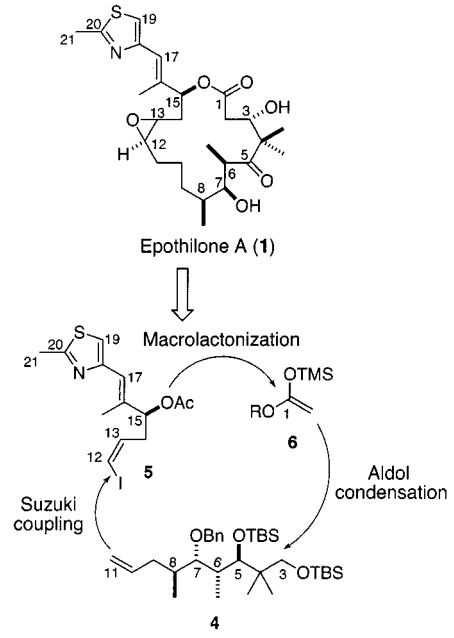
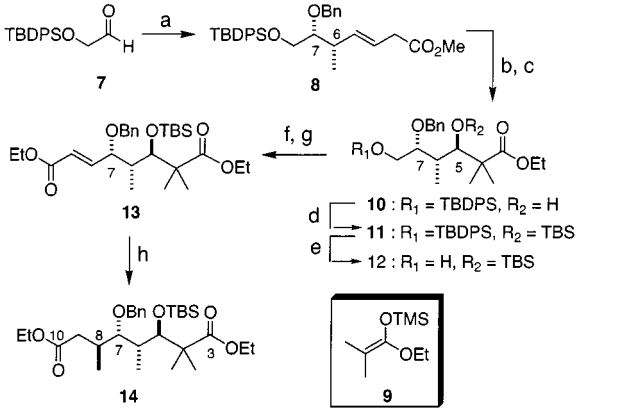
the C12-C21 fragment **5** and silyl ketene acetal **6**. The fragments **4** and **5** were to be united using an intermolecular Suzuki cross-coupling reaction.[9] Danishefsky and co-workers have reported a similar coupling strategy in their total syntheses of epothilones A and B (**1** and **2**), in which a Suzuki coupling reaction gave *cis*-C12−C13 olefin as the only double-bond isomer.[10] The 16-membered lactone was to be constructed by a substrate-directed aldol condensation reaction with silyl ketene acetal **6** to establish the C3 stereocenter followed by macrolactonization. In order to achieve the desired directing effect in the aldol condensation to establish the C3 stereocenter, a substituent was required at the C5 position in fragment **4**. Accordingly, methodology based on chiral crotylsilanes would be used to generate the C6 and C7 stereocenters in **4**, which would then direct the establishment of the C8 and C5 stereocenters in this polypropionate-like fragment.



Scheme 1. Retrosynthetic analysis of epothilone A (**1**)

Synthesis of C3-C11 Fragment 4

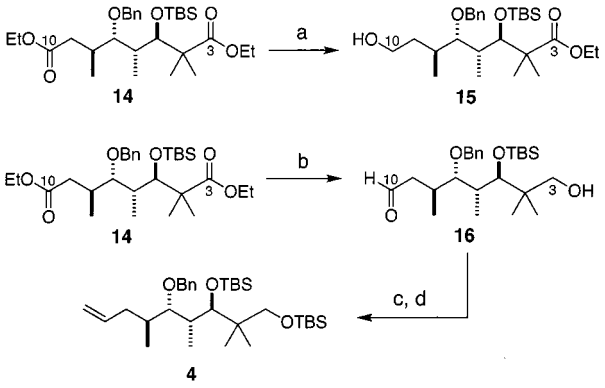
The synthesis of fragment **4** began with the known aldehyde **7** (Scheme 2). This material was first converted into a dibenzyl acetal by the treatment with TMSOBn/TMSOTf. This acetal was then treated with chiral silane reagent *S*-**3** in the presence of $BF_3{\cdot}OEt_2$ to give the desired homoallylic ether **8** in 83% yield and good diastereoselectivity (C6−C7 *syn*/*anti* = 15:1).[11] It is noteworthy to point out that the above acetal formation and crotylation could be carried out in one pot. The double bond of homoallylic ether **8** was oxidatively cleaved under standard ozonolysis conditions, and the resulting aldehyde was subjected to a chelation-controlled aldol condensation with silyl ketene acetal **9** using $TiCl_4$ as the catalyst.[12] The aldol product was obtained in 83% yield as a 6:1 mixture favoring the desired C5−C7 *anti* diastereomer **10**. The secondary hydroxy group of **10** was then protected by a *tert*-butyldimethylsilyl (TBS) group and gave bis(silyl ether) **11**. Selective deprotection of the primary *tert*-butyldiphenylsilyl (TBDPS) group in the presence of the secondary TBS ether was initially examined under the previously reported conditions.[13] Unfortunately, when bis(silyl ether) **11** was treated with 1 equiv. of tetrabutylammonium fluoride (TBAF) in THF, the two silyl groups (the primary TBDPS group and the secondary TBS group) of **11** could not be differentiated under these conditions. After considerable experimentation, the selective deprotection was eventually achieved by treating **11** with acetic acid buffered TBAF solution, which cleanly removed the primary TBDPS group without affecting the secondary TBS ether. The resulting primary alcohol **12** was oxidized using Swern oxidation conditions to afford the corresponding aldehyde, which was then converted into the α,β-unsaturated ester **13** by a phosphorus-based olefination reaction with the stabilized ylide $Ph_3P{=}CHCO_2Et$. This α,β-unsaturated ester was subjected to a diastereoselevtive conjugate addition under similar conditions described by Hanessian and co-workers,[14] which involved the treatment with freshly generated lithium dimethylcuprate (Me_2CuLi) in the presence of trimethylsilyl chloride (TMSCl) at low temperature (−78 °C). The reaction proceeded smoothly to give the 1,4-adduct **14** in 94% yield with a high diastereoselectivity (C8−C7 *anti*/*syn* ratio > 10:1) (Scheme 2). The stereochemical outcome of this cuprate addition reaction is consistent with the results reported by Hanessian and co-workers.



Scheme 2. Establishment of the C5, C6, C7 and C8 stereocenters: reagents and conditions: a) TMSOBn, cat. TMSOTf, CH_2Cl_2, −78 to −50 °C, 16 h; *S*-**3**, $BF_3{\cdot}Et_2O$, −30 °C, 24 h, 83%, *syn*/*anti* = 15:1; b) O_3, MeOH/CH_2Cl_2 (2:1), pyridine, Me_2S, −78 °C to room temp., 88%; c) $TiCl_4$, **9**, CH_2Cl_2, −78 °C, 30 min, 83%, *anti*/*syn* = 6:1; d) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 2 h, 95%; e) Bu_4NF/AcOH (1:1), THF, room temp., 24 h, 92%; f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to room temp., 95%; g) $Ph_3P{=}CHCO_2Et$, benzene, reflux, 4 h, 91%; h) Me_2CuLi, TMSCl, THF, −78 °C, 4 h, 94%, *anti*/*syn* > 10:1

Having successfully established the C5, C6, C7 and C8 stereocenters, our attention was turned to the conversion of bis(ethyl ester) **14** into the required C3-C11 fragment **4**. The different steric environments of the C3 and C10 ester moieties suggested the possibility of different reactivity in reductive transformations. Fortunately, a DIBAL-H reduction easily differentiated these two ester groups. More interestingly, different products were obtained by conducting the

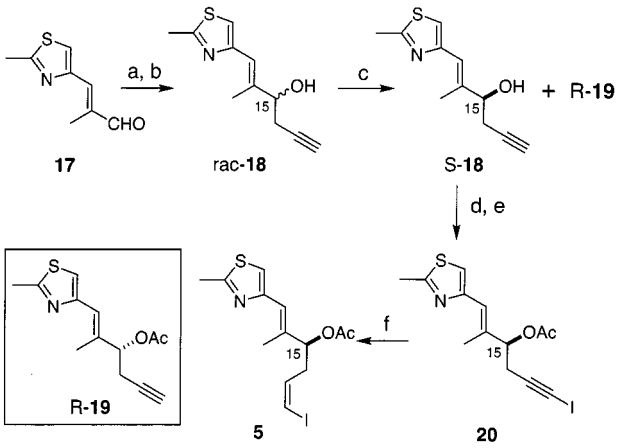
DIBAL-H reduction reaction in THF and in CH_2Cl_2 (Scheme 3). The treatment of bis(ester) **14** with DIBAL-H in THF cleanly transformed the C10 ester to a primary hydroxy group without reducing the C3 ester group, and afforded the hydroxy ester **15**. However, when the reduction was conducted in CH_2Cl_2, the C10 and C3 ester groups were converted into an aldehyde and a primary hydroxy group, respectively, to give the hydroxy aldehyde **16**. This hydroxy aldehyde **16** was first protected as a silyl ether by TBSCl/imidazole, and the aldehyde group was then subjected to a Wittig olefination to install the terminal olefin and complete the synthesis of C3-C11 fragment **4**.



Scheme 3. DIBAL-H reduction of bis(ester) **14** and synthesis of C3-C11 fragment **4**; reagents and conditions: a) DIBAL-H (4 equiv.), THF, −78 °C, 4 h, 91%; b) DIBAL-H (4 equiv.), CH_2Cl_2, −78 °C, 15 min; c) TBSCl, imidazole, DMF, 68% for two steps; d) CH_3PPh_3Br, $NaN(TMS)_2$, THF, 0 °C, 90%

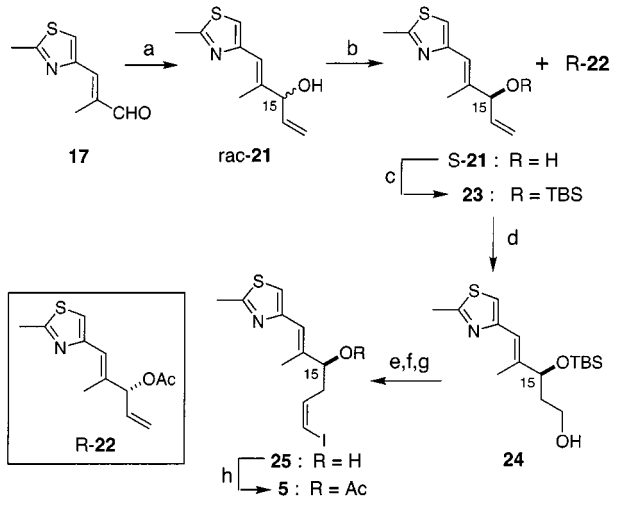
Synthesis of C12-C21 Fragment 5

In considering practical and efficient routes toward the synthesis of the thiazole-bearing fragment **5**, we decided to adopt an enzymatic approach to establish the C15 stereocenter.[15] Importantly, lipase-mediated kinetic resolution generally requires mild reaction conditions and simple operation procedures. Our initial synthesis of C12-C21 fragment **5** started with a Reformatsky-type addition to the known thiazole-containing aldehyde **17**.[16] Aldehyde **17** was treated with zinc dust and 3-bromo-1-(trimethylsilyl)-1-propyne in the presence of $HgCl_2$ in refluxing THF. The resulting material was desilylated by treatment with TBAF to give racemic secondary alcohol *rac*-**18**. An enzymatic kinetic resolution of *rac*-**18** using *Pseudomanas* AK lipase provided the enantiomerically enriched alcohol *S*-**18** in 40% yield (80% yield based on 50% conversion) and 94% *ee* (E = 115.1),[17] along with the enantiomerically enriched acetate *R*-**19**. The alcohol *S*-**18** and acetate *R*-**19** were easily separated by column chromatography purification. The alcohol *S*-**18** was converted into an acetate under standard conditions (Ac_2O, Et_3N, DMAP) and was further transformed to alkynyl iodide **20** by the treatment with *n*BuLi followed by I_2. The alkynyl iodide moiety of **20** was then reduced to the (*Z*)-vinyl iodide using Corey's protocol[18] to finish the synthesis of C12-C21 fragment **5** (Scheme 4).



Scheme 4. Synthesis of C12-C21 fragment **5**; reagents and conditions: a) 3-bromo-1-(trimethylsilyl)-1-propyne, Zn, $HgCl_2$, THF, reflux, 16 h, 91%; b) TBAF, THF, room temp., 30 min, 94%; c) *Pseudomonas* AK Lipase (100% wt), vinyl acetate, hexane, room temp., 7−14 d, 40% (80% based on 50% conversion), 94% *ee*; (d) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 95%; (e) *n*BuLi, I_2, THF, −78 °C to room temp., 80%; f) $BH_3{\cdot}Me_2S$, cyclohexene, Et_2O, AcOH, 60%

While the lipase resolution of *rac*-**18** provided the desired (*S*)-secondary alcohol with good yield, high *ee* and eventually led to the C12-C21 fragment **5**, the length of resolution time of this particular substrate (7−14 d) indicated that further improvement was necessary. We then turned our attention to the divinyl carbinol *rac*-**21**, which was easily obtained from a vinylmagnesium bromide addition to the thiazole-containing aldehyde **17**.[19] The *Pseudomonas* AK lipase mediated kinetic resolution of *rac*-**21** proceeded much faster than that of *rac*-**18**. The resolution process reached 50% completion in 48−72 h, and provided enantiomerically enriched alcohol *S*-**21** in 48% yield (96% based on 50% conversion) and 90% *ee* (E = 58.4). The resolved alco-

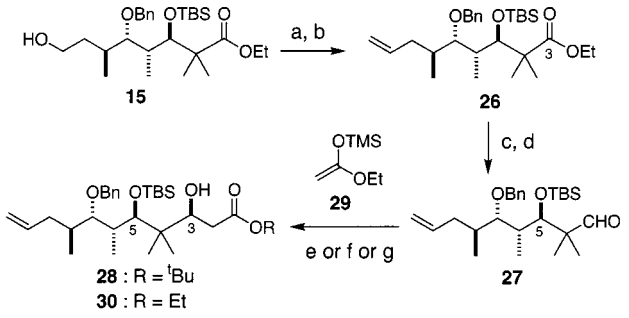


Scheme 5. New version of C12-C21 fragment **5** synthesis; reagents and conditions: a) vinylmagnesium bromide, THF, −78 °C, 90%; b) *Pseudomonas* AK Lipase (50% wt), vinyl acetate, hexane, room temp., 48−72 h, 48%, 90% *ee*; c) TBSCl, imidazole, DMF, 95%; d) $BH_3{\cdot}THF$, cyclohexene, THF, NaOH, H_2O_2, 90%; e) Dess−Martin periodinane, CH_2Cl_2; f) CH_2IPPh_3I, $NaN(TMS)_2$, THF; g) HF (48% aqueous), CH_3CN, 65% for 3 steps; h) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 95%

hol was then protected as its TBS ether **23** by the treatment with TBSCl/imidazole. It is worthy to point out that the treatment of *S*-**21** with more powerful silylation reagents (TBSOTf/2,6-lutidine) led to high percentages of decomposition. Selective hydroboration of the terminal olefin of **23** was achieved with dicyclohexylborane, and oxidation of the resulting borane species afforded alcohol **24**. This intermediate was converted into the *cis*-vinyl iodide **25** by a four-step sequence, which included a Dess−Martin oxidation,[20] a Wittig olefination to install the *cis*-vinyl iodide, and an HF-promoted desilylation of the protected secondary hydroxy group. Acetylation of **25** completed the improved synthesis of C12-C21 fragment **5** (Scheme 5).

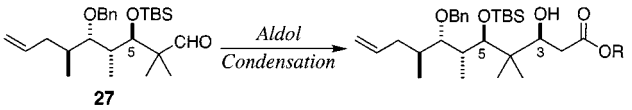
Establishment of the C3 Stereocenter

Before proceeding to the planned coupling of C3-C11 fragment **4** and C12-C21 fragment **5**, we examined the installation of the C3 stereocenter on a model aldehyde substrate **27** (Scheme 6). This aldehyde was easily prepared from the previously described hydroxy ester **15** through a four-step protocol. Swern oxidation of the primary hydroxy group of **15** followed by a Wittig olefination provided terminal olefin **26**. The ester group of **26** was reduced with DIBAL-H in CH_2Cl_2 to afford the corresponding primary alcohol, which was oxidized using Dess−Martin periodinane to give aldehyde **27**. The initial aldol condensation experiments using metal enolates gave poor diastereoselectivity. Treatment of aldehyde **27** with *tert*-butyl lithioacetate at low temperature gave the aldol product **28** in 79% yield as a ca. 2:1 mixture of the C3 diastereomers, presumably favoring the desired C3-C5 *syn* diastereomer, which is consistent with earlier studies.[21] To achieve a useful level of diastereoselectivity, aldehyde **27** was then subjected to a Mukaiyama-type aldol reaction[22] with silyl ketene acetal **29** under the catalysis of different Lewis acids. The condensation promoted by $BF_3{\cdot}Et_2O$ provided the aldol product in 89% yield, however as an inseparable ca. 1.5:1 mixture of the desired C3-C5 *syn* diastereomer **30** and its C3 diastereomer. Gratifyingly, the use of $TiCl_4$ as the Lewis acid led to much higher diastereoselectivity (C3-C5 *syn*/*anti* > 5:1) in this aldol condensation reaction (Table 1).



Scheme 6. Establishment of the C3 stereocenter; reagents and conditions: a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; b) CH_3PPh_3Br, $NaN(TMS)_2$, THF, 92% for two steps; c) DIBAL-H, CH_2Cl_2, −78 °C; d) Dess−Martin periodinane, CH_2Cl_2, 86% for two steps; e) LDA, *tert*-butyl acetate, THF. −78 °C, 30 min, 79%, C3-C5 *syn*/*anti* ≈ 2:1; f) **29**, $BF_3{\cdot}Et_2O$, −78 °C, 1 h, CH_2Cl_2, 89%, C3-C5 *syn*/*anti* ≈ 1.5:1; g) **29**, $TiCl_4$, −78 °C, 15 min, 90%, C3-C5 *syn*/*anti* > 5:1

Table 1. Model studies concerning the introduction of the C3 stereocenter



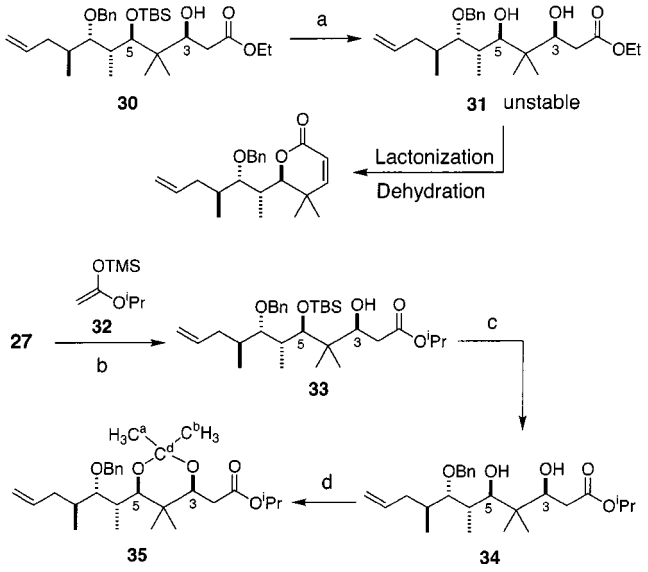
Nucleophile	*Lewis Acid*	*Product*	*Yield*	C3-C5 dr (*syn*/*anti*)[a]
OLi, O^{t}Bu		**28** : R = ^{t}Bu	79%	ca. 2 : 1
OTMS, OEt (**29**)	$BF_3{\cdot}Et_2O$	**30** : R = Et	89%	ca. 1.5 : 1
	$TiCl_4$	**30** : R = Et	90%	> 5 : 1
OTMS, O^{i}Pr (**32**)	$TiCl_4$	**33** : R = ^{i}Pr	81%	8 : 1

[a] The C5-C3 *syn*/*anti* ratios were determined by ^{1}H NMR analysis of the crude aldol products.

Unfortunately, further use of the resulting hydroxy ester **30** in the synthesis was prevented by the difficulties encountered in the removal of its C5 TBS group. The only successful method found was to treat **30** briefly with TBAF at 0 °C, which afforded low yield of the desired diol **31**. The low yield of this deprotection was obviously derived from the instability of this diol **31**, which showed a strong propensity to lactonize (Scheme 7). To avoid the undesired lactonization, a hydrolytically-resistant group had to be used as the C1 ester group. However, the synthetic plan also required this ester group be removable by base-promoted hydrolysis. Accordingly, an isopropyl group was thus employed and installed using silyl ketene acetal **32**. Aldol condensation of aldehyde **27** with **32** in the presence of $TiCl_4$ provided the desired hydroxy ester **33** in 81% yield and good diastereoselectivity (C3-C5 *syn*/*anti* = 8:1). Brief treatment of **33** with TBAF (0 °C, 10 min) afforded the diol **34** in 89% yield. The diol **34** was then converted into the corresponding C3-C5 acetonide **35** and ^{13}C NMR analysis of **35** confirmed the stereochemical outcome of the Mukaiyama-type aldol condensation (Scheme 7).

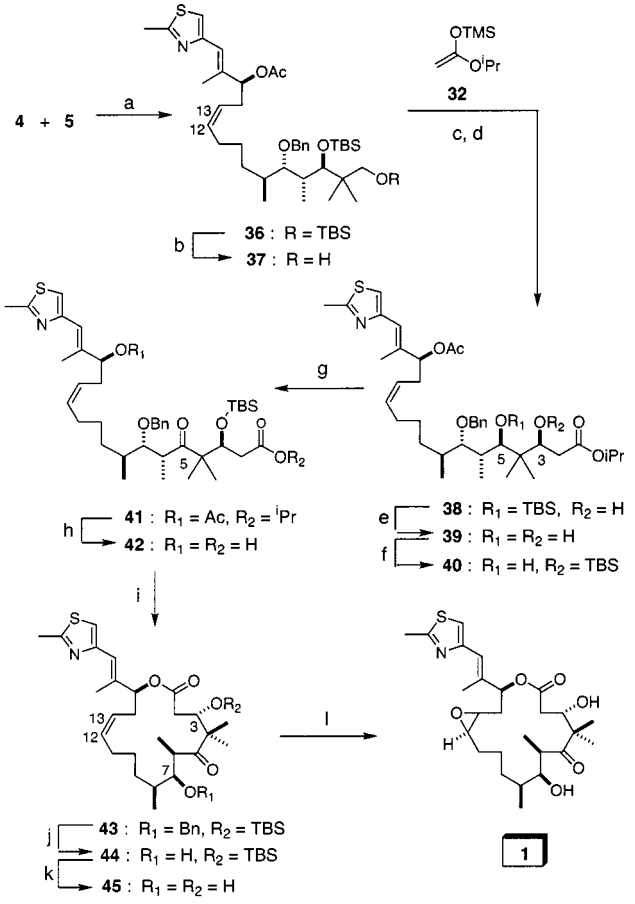
B-Alkyl Suzuki Coupling of Fragments 4 and 5 and Completion of Synthesis

In a similar manner as Danishefsky's synthesis of epothilone A (**1**),[10] an intermolecular *B*-alkyl Suzuki coupling of C3-C11 fragment **4** and C12-C21 fragment **5** was planned to unite these two fragments with the retention of the C12−C13 *cis* double bond. Hydroboration of the terminal olefin of **4** with 9-BBN was achieved using relatively vigorous conditions (room temp., ca. 4−5 h, 0.5 M).[23] The resulting borane species was then successfully coupled to vinyl iodide **5** under the catalysis of $PdCl_2$(dppf) to give the coupling product **36** with the desired C12−C13 *cis*-olefin as a single double-bond isomer (Scheme 8). Compound **36** was selectively deprotected at the primary position using



Scheme 7. Reagents and conditions: a) TBAF, THF, 0 °C, 5 min, low yield; b) $TiCl_4$, CH_2Cl_2, −78 °C, 15 min, 81%, C3-C5 *syn/anti* dr = 8:1; c) TBAF, THF, 0 °C, 10 min, 89%; d) $(CH_3)_2C(OMe)_2$, TsOH (cat.), 90%, ^{13}C NMR: C^a and C^b δ = 19.2 and 30.0, C^d δ =98.4

pyridine-buffered HF to give alcohol **37**. Dess−Martin oxidation of alcohol **37** provided the corresponding aldehyde, which was then subjected to a $TiCl_4$-catalyzed aldol condensation reaction with silyl ketene acetal **32**. A macrocyclization strategy using intramolecular aldol condensation with this aldehyde was initially examined. In Danishefsky's total synthesis of epothilone A (**1**) an intramolecular aldol reaction with a similar aldehyde was employed to form the 16-membered lactone (see ref.[10b]). However, with our aldehyde, the intramolecular aldol approach was unsuccessful. The enhanced selectivity in the Danishefsky route may be attributed to a subtle conformational difference between our aldehyde and the Danishefsky substrate, which have different hydroxy protecting groups at C5 and C7. The resulting condensation product was obtained in 87% yield as a 9:1 mixture of two C3 diastereomers, favoring the desired β-hydroxy ester **38** with the correct stereochemistry at the C3 position. Deprotection of the C5 TBS group of **38** was carried out under similar conditions as described in the desilylation of **33**, and the resulting diol **39** was obtained in 89% yield. Selective silylation at the C3 position of **39** was initially examined using TBSOTf/2,6-lutidine at low temperature, which showed no selectivity between the C3 and C5 hydroxy groups. It was later discovered that treatment of diol **39** with an excess amount of TBSCl/imidazole in DMF selectively silylated the C3 hydroxy group. The free hydroxy group at C5 of the resulting compound **40** was oxidized using Dess−Martin periodinane to give ketone **41**. A base-promoted hydrolysis using aqueous NaOH in refluxing MeOH successfully removed the C1 isopropyl ester group and the C15 acetyl group to furnish the hydroxy acid **42**. This hydrolysis process required close monitoring, since prolonged reaction time led to formation of elimination products. Hydroxy acid **42** was then subjected to a macrolactonization protocol utilizing the Yamaguchi conditions (2,4,6-trichlorobenzoyl chloride, Et_3N, THF, DMAP, toluene) to give the l6-membered lactone **43** in 73% yield.[24] The benzyl protecting group of the C7 hydroxy group was removed by the action of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in CH_2Cl_2/H_2O. Subsequent desilylation at the C3 position with 20% trifluoroacetic acid in CH_2Cl_2 afforded dihydroxy lactone **45.** The final stages of the synthesis require the installation of the C12-C13 epoxide.[10b] Recent literature precedent has documented the stereoselective epoxidation of the C12-C13 *cis*-olefin using dimethyldioxirane. In that regard, epoxidation of the C12-C13 *cis*-olefin using in situ generated methyl peroxycarboximidic acid (30% aq. H_2O_2, CH_3CN, $KHCO_3$, MeOH) installed the C12-C13 *cis*-epoxide and completed the total synthesis of epothilone A (**1**).[25]



Scheme 8. Suzuki coupling of fragments **4** and **5**, and completion of the total synthesis of epothilone A (**1**); reagents and conditions: a) **4**, 9-BBN, THF; then **5**, $Pd(dppf)Cl_2$, Cs_2CO_3, DMF, H_2O, room temp., 60%; b) HF/pyridine, THF, room temp., 93%; c) Dess−Martin periodinane, CH_2Cl_2, 91%; d) **32**, $TiCl_4$, CH_2Cl_2, −78 °C, 15 min, 87%, *syn/anti* = 9:1; e) Bu_4NF, THF, 0 °C, 10 min, 89%; f) TBSCl, imidazole, DMF, room temp., 36 h, 91%; g) Dess−Martin periodinane, CH_2Cl_2, 93%; h) NaOH (aq.), MeOH, reflux, 1.5 h, 62%; i) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 0 °C, 15 min; DMAP, toluene, room temp., 30 min, 73%; j) DDQ, CH_2Cl_2/H_2O (4:1), 82%; k) 20% CF_3CO_2H in CH_2Cl_2, room temp., 2.5 h, 90%; l) CH_3CN, H_2O_2 (30% aq. solution), $KHCO_3$, MeOH, room temp., 24 h, ca. 60% (based on recovered starting material)

Conclusion

We have successfully carried out a highly convergent synthesis of epothilone A (**1**). The approach is based on the preparation and palladium-catalyzed cross-coupling of two advanced intermediates: the polypropionate-like C3-C11 fragment **4** and the thiazole-containing C12-C21 fragment **5**. Bond construction methodology based on chiral silanes was utilized to construct the key stereocenters C6 and C7 which directed the installation of other stereocenters in fragment **4**. A *Pseudomonas* AK lipase mediated kinetic resolution provided the enantiomerically enriched thiazole-containing divinylcarbinol *S*-**21**, which led to the C12-C21 fragment **5**. A *B*-alkyl Suzuki coupling of **4** and **5**, followed by a substrate-directed aldol condensation, introduced the C3 stereocenter and established the C1-C21 carbon skeleton. A Yamaguchi-type macrolactonization formed the 16-membered lactone, and the total synthesis of epothilone A (**1**) was completed by a regio- and stereoselective epoxidation at the C12-C13 *cis*-olefin. The accomplishment of epothilone A (**1**) synthesis once again demonstrated the utility of bond construction methodology based on allylsilanes bearing C-centered chirality. Synthetic studies toward a variety of natural products utilizing this methodology are currently under investigation in our laboratory and will be reported in due course.

Experimental Section

General Information: ^{1}H and ^{13}C NMR spectra were taken in $CDCl_3$ at 400 MHz and 75.0 MHz respectively unless specified otherwise. Chemical shifts are reported in parts per million using the solvent resonance internal standard (chloroform, δ = 7.24 and δ = 77.0, unless specified otherwise). Data are reported as follows: chemical shift, multiplicity (app = apparent, par obsc = partially obscured, ovrlp = overlapping, s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, br = broad, AB-quat. = AB quadruplet), integration, and coupling constant. Ratios of diastereomers were determined by ^{1}H NMR (400 MHz) operating at a signal/noise ratio of > 200:1. − Infrared resonance spectra were recorded with a Perkin−Elmer 7700 series FTIR spectrophotometer. − Optical rotations were recorded with an AUTOPOL III digital polarimeter at 589 nm, and are reported as $[\alpha]_D$ (concentration in grams/100 mL solvent). − High resolution mass spectra were obtained with a Finnigan MAT-90 spectrometer in the Boston University Mass Spectrometry Laboratory. Dichloromethane (CH_2Cl_2), benzene, toluene and dimethyl sulfoxide (DMSO) were distilled from calcium hydride; and tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium and benzophenone prior to use. Titanium tetrachloride ($TiCl_4$) and tin tetrachloride ($SnCl_4$) were freshly distilled from copper powder before each use. $BF_3{\cdot}OEt_2$ and TMSOTf were distilled under argon before use. All other reagents were used as supplied. All reactions were carried out in oven-dried glassware under argon unless otherwise noted. Analytical thin layer chromatography was performed on Whatman Reagent 0.25 mm silica gel 60-Å plates. Flash chromatography was performed on E. Merck silica gel 230−400 mesh.

Homoallylic Ether 8: To a stirred solution of aldehyde **7** (10.0 g, 33.6 mmol) and benzyloxytrimethylsilane (TMSOBn) (14.0 mL, 71.2 mmol) in CH_2Cl_2 (110 mL) at −78 °C was added trimethylsilyl trifluoromethanesulfonate (TMSOTf) (0.6 mL, 3.3 mmol). The reaction mixture was slowly warmed up to −50 °C for 16 h before crotylsilane reagent[8] *S*-**3** (8.80 g, 33.6 mmol) was added followed by $BF_3{\cdot}Et_2O$ (9.0 mL, 73.1 mmol). The resulting solution was allowed to further warm up to −30 °C for 24 h. The reaction was then quenched with saturated aqueous $NaHCO_3$ (50 mL) and the mixture was extracted with CH_2Cl_2 (300 mL × 2). The organic layer was washed with saturated aqueous NaCl (50 mL) and was dried with $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography (silica gel, 5% EtOAc in hexane) afforded crotylation product **8** (14.4 g, 83%) as colorless oil. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, 2 H, *J* = 8 Hz), 7.65 (d, 2 H, *J* = 8 Hz), 7.43−7.25 (m, 11 H), 5.49 (m, 2 H), 4.68 and 4.47 (AB-quat., 2 H, *J* = 11.6 Hz), 3.71 (d, 2 H, *J* = 4.8 Hz), 3.61 (s, 3 H), 3.32 (dt, 1 H, *J* = 5.2 Hz, 6 Hz), 2.95 (d, 2 H, *J* = 5.6 Hz), 2.51 (ddq, 1 H, *J* = 6.4 Hz, 6.4 Hz, 6.8 Hz), 1.03 (s, 9 H), 0.99 (d, 3 H, *J* = 6.8 Hz). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.3, 139.0, 137.1, 135.6, 133.6, 129.6, 128.2, 127.6, 127.4, 121.5, 83.6, 72.8, 64.6, 51.7, 38.4, 38.3, 38.0, 26.9, 19.2, 15.4. − IR (neat): $\tilde{\nu}_{max}$ = 2956, 2931, 2858, 1741, 1472, 1429, 1255, 1166, 1113. − $[\alpha]_D^{23}$ = +14.1 (*c* = 1.35, CH_2Cl_2).

Aldol Adduct 10: Into a solution of homoallylic ether **8** (8.3 g, 16.1 mmol) and pyridine (1.3 mL, 16.1 mmol) in MeOH (120 mL)/CH_2Cl_2 (60 mL) at −78 °C was bubbled ozone gas for 30 min. Dimethylsulfide (11.8 mL, 161 mmol) was added to the resulting blue solution to quench the reaction. The dry ice bath was removed and the reaction mixture was stirred at room temperature for 16 h before the solvent was removed in vacuo. The residue was diluted with CH_2Cl_2 (300 mL), and the solution was washed with H_2O (50 mL × 2) and saturated aqueous NaCl (50 mL) and was dried with $MgSO_4$. The CH_2Cl_2 was removed in vacuo to afford the crude aldehyde as colorless oil (6.3 g, 88%). This aldehyde (6.3 g, 14.1 mmol) was dissolved in CH_2Cl_2 (45 mL) and the resulting solution was cooled to −78 °C. To this stirred solution was added freshly distilled $TiCl_4$ (1.70 mL, 15.5 mmol) followed by silyl ketene acetal **9** (3.9 mL, 18.7 mmol) after 20 min. The reaction mixture was stirred at −78 °C for 45 min before being quenched with EtOAc (10 mL) and H_2O (50 mL). The mixture was extracted with CH_2Cl_2 (150 mL × 2). The organic layer was washed with saturated aqueous NaCl, and was dried with $MgSO_4$ and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel, 5% EtOAc in hexane) to give alcohol **10** as colorless oil (6.6 g, 83%, *anti*/*syn* = 6:1). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (m, 4 H), 7.43−7.35 (m, 6 H), 7.34−7.25 (m, 5 H), 4.69 and 4.54 (AB-quat., 2 H, *J* = 11.2 Hz), 4.06 (dq, 2 H, *J* = 2 Hz, 7.2 Hz), 3.92 (dd, 1 H, *J* = 6.4 Hz, 10.8 Hz), 3.86−3.80 (m, 2 H), 3.70 (dd, 1 H, *J* = 5 Hz, 6.2 Hz), 3.35 (d, 1 H, *J* = 4.4 Hz), 1.97 (ddq, 1 H, *J* = 2.4 Hz, 7.2 Hz, 7.2 Hz), 1.19 (s, 3 H), 1.18 (t, 3 H, *J* = 7.2 Hz), 1.12 (s, 3 H), 1.04 (s, 9 H), 0.77 (d, 3 H, *J* = 7.2 Hz). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.4, 138.4, 135.6, 133.3, 129.8, 128.4, 127.7, 127.6, 82.4, 78.1, 77.2, 72.4, 64.1, 60.3, 47.0, 36.9, 26.8, 23.7, 19.2, 18.9, 14.1, 13.1. − IR (neat): $\tilde{\nu}_{max}$ = 3472, 2943, 2866, 1717, 1464, 1388, 1258, 1113. − CIHRMS $[M + H]^+$ calculated for $C_{34}H_{47}O_5Si$: 563.3193, found 563.3228. − $[\alpha]_D^{23}$ = +8.0 (*c* = 0.5, CH_2Cl_2).

Bis(silyl ether) 11: To a solution of alcohol **10** (0.80 g, 1.42 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added successively 2,6-lutidine (0.50 mL, 4.3 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) (0.50 mL, 2.18 mmol). The reaction mixture was diluted with CH_2Cl_2 (50 mL) after 2 h. The solution was washed with 0.1 N HCl (5 mL) and saturated aqueous NaCl

(10 mL), and was dried with $MgSO_4$. Purification by flash chromatography (silica, 2% EtOAc in hexane) afforded TBS ether **11** as a colorless oil (914 mg, 95%). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66–7.63 (m, 4 H), 7.41–7.21 (m, 11 H), 4.74 and 4.57 (AB-quat., 2 H, *J* = 12 Hz), 4.09 (d, 1 H, *J* = 5.6 Hz), 4.04 (dq, 2 H, *J* = 1.6 Hz, 7 Hz), 3.86 (m, 1 H), 3.73 (dd, 1 H, *J* = 6 Hz, 10.4 Hz), 3.64 (dd, 1 H, *J* = 4.8 Hz, 10.4 Hz), 1.86 (m, 1 H), 1.19 (t, 3 H, *J* = 7 Hz), 1.16 (s, 3 H), 1.08 (s, 3 H), 1.03 (s, 9 H), 0.89 (d, 3 H, *J* = 7.2 Hz), 0.89 (s, 9 H), 0.07 (s, 3 H), 0.04 (s, 3 H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.3, 139.7, 135.7, 135.6, 133.5, 133.4, 129.6, 129.5, 128.1, 127.6, 126.9, 79.1, 78.9, 71.8, 65.9, 60.2, 48.2, 39.6, 26.9, 28.5, 25.9, 19.1, 18.6, 18.5, 14.0, 13.1, −2.9, −3.6. – IR (neat): $\tilde{\nu}_{max}$ = 2931, 2858, 1731, 1473, 1389, 1257, 1113. – CIHRMS $[M]^+$ calculated for $C_{40}H_{60}O_5Si$: 676.3979, found 676.3968. – $[\alpha]_D^{23}$ = −4.9 (*c* = 0.55, CH_2Cl_2).

Pirmary Alcohol 12: To a solution of bis(silyl ether) **11** (914 mg, 1.35 mmol) in THF (10 mL) was added a 1:1 mixture of tetrabutylammonium fluoride (TBAF) (1.0 M in THF, 2.70 mL, 2.70 mmol) and acetic acid (AcOH) (0.155 mL, 2.70 mmol). The reaction mixture was stirred at room temperature for 24 h before being quenched with saturated aqueous $NaHCO_3$ (5 mL). The mixture was extracted with EtOAc (20 mL × 2). The organic layer was washed with saturated aqueous NaCl (5 mL), dried with $MgSO_4$ and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel, 10% EtOAc in hexane) to give the alcohol **12** (545 mg, 92%). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (m, 5 H), 4.59 (s, 2 H), 4.08 (dq, 2 H, *J* = 2.8 Hz, 4 Hz), 3.94 (d, 1 H, *J* = 4.4 Hz), 3.77 (m, 1 H), 3.61 (m, 1 H), 3.50 (dt, 1 H, *J* = 4 Hz, 7.2 Hz), 1.92 (ddq, 1 H, *J* = 4 Hz, 4 Hz, 7.2 Hz), 1.88 (t, 1 H, *J* = 6.2 Hz), 1.23 (t, 3 H, *J* = 7 Hz), 1.18 (s, 3 H), 1.14 (s, 3 H), 1.06 (d, 3 H, *J* = 7.2 Hz), 0.88 (s, 9 H), 0.05 (s, 6 H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.0, 138.6, 128.4, 127.6, 127.5, 79.9, 79.8, 72.3, 63.3, 60.5, 48.5, 38.3, 26.2, 24.3, 19.6, 18.4, 16.1, 14.0, −3.0, −4.2. – IR (neat): $\tilde{\nu}_{max}$ = 3496, 2930, 2858, 1727, 1473, 1388, 1256, 1065. – CIHRMS $[M + H]^+$ calculated for $C_{24}H_{43}O_5Si$: 439.2880, found 439.2885. – $[\alpha]_D^{23}$ = −4.8 (*c* = 0.42, CH_2Cl_2).

α,β-Unsaturated Ester 13: To a solution of $(COCl)_2$ (0.73 mL, 8.36 mmol) in dry CH_2Cl_2 (60 mL) at −78 °C was added dropwise DMSO (1.37 mL, 19.34 mmol). The solution was stirred at −78 °C for 30 min before a solution of alcohol **12** (2.83 g, 6.46 mmol) in 5 mL dry CH_2Cl_2 was added. The reaction mixture was kept at −78 °C for another 45 min, and Et_3N (4.5 mL, 32.3 mmol) was then added. The dry ice bath was removed and the reaction mixture was stirred at room temperature for 1.5 h before being quenched with H_2O (50 mL). The resulting mixture was poured into hexane (300 mL). The organic layer was separated and washed with H_2O (50 mL × 2) and saturated aqueous NaCl. The aqueous layers were combined and re-extracted with hexane (50 mL). The combined organic extracts were dried with $MgSO_4$ and concentrated in vacuo to give the crude aldehyde as light yellow oil. To a solution of this crude aldehyde in dry benzene (50 mL) was added ylide $PPh_3{=}CHCO_2Et$ (95%, 2.8 g, 7.63 mmol). The resulting solution was heated under reflux condition for 4 h before being cooled to room temperature and concentrated under reduced pressure. Purification by flash chromatography (silica gel, 5% EtOAc in hexane) afforded the α,β-unsaturated ester **13** as colorless oil (2.98 g, 91% for 2 steps). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (m, 5 H), 6.98 (dd, 1 H, *J* = 5.6 Hz, 15.6 Hz), 5.98 (dd, 1 H, *J* = 1.2 Hz, 16 Hz), 4.53 and 4.34 (AB-quat., 2 H, *J* = 11.6 Hz), 4.20 (m, 1 H), 4.18 (q, 2 H, *J* = 7.2 Hz), 4.11 (d, 1 H, *J* = 5.6 Hz), 4.05 (dq, 2 H, *J* = 2 Hz, 7.2 Hz), 1.70 (m, 1 H), 1.28 (t, 3 H, *J* = 7.2 Hz), 1.19 (t, 3 H, *J* = 7.2 Hz), 1.16 (s, 3 H), 1.09 (s, 3 H), 0.96 (d, 3 H, *J* = 7.2 Hz), 0.89 (s, 9 H), 0.05 (s, 3 H), 0.006 (s, 3 H) . – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.1, 166.3, 148.8, 138.6, 128.2, 127.3, 127.1, 121.6, 78.2, 77.8, 70.6, 60.4, 48.0, 43.8, 26.3, 26.2, 18.6, 18.4, 14.2, 14.1, 14.0, 12.8, −3.1, −3.6. – IR (neat): $\tilde{\nu}_{max}$ = 2930, 2857, 1722, 1473, 1367, 1174, 1077. – CIHRMS $[M + H]^+$ calculated for $C_{28}H_{47}O_6Si$: 507.3142, found 507.3141. – $[\alpha]_D^{23}$ = −11.5 (*c* = 1.5, CH_2Cl_2).

Bis(ethyl ester) 14: To a stirred suspension of CuI (3 g, 15.4 mmol) in THF (80 mL) at 0 °C was added slowly MeLi·LiBr (1.5 M in diethyl ether, 20.5 mL, 30.8 mmol). The resulting clear solution was stirred at 0 °C for 10 min before being cooled to −78 °C. To this cooled solution of Me_2CuLi was added successively TMSCl (8 mL, 63 mmol) and a solution of α,β-unsaturated ester **13** in 5 mL THF. The reaction mixture was stirred at −78 °C for 4 h before being quenched with a 1:1 mixed solution of 30% aqueous ammonium hydroxide and saturated aqueous NH_4Cl (60 mL). The mixture was poured into EtOAc (150 mL). The organic layer was washed with H_2O (50 mL) and saturated aqueous NaCl (30 mL) and was dried with $MgSO_4$. Purification by flash chromatography (silica gel, 5% EtOAc in hexane) afforded ester **14** as colorless oil (1.26 g, 94%). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (m, 5 H), 4.68 and 4.53 (AB-quat., 2 H, *J* = 11.2 Hz), 4.12 (d, 1 H, *J* = 6 Hz), 4.14–4.00 (m, 4 H), 3.49 (dd, 1 H, *J* = 4 Hz, 6 Hz), 2.56 (dd, 1 H, *J* = 4 Hz, 14.8 Hz), 2.26 (m, 1 H), 2.15 (dd, 1 H, *J* = 9.6 Hz, 14.8 Hz), 1.83 (m, 1 H), 1.21 (t, 3 H, *J* = 7 Hz), 1.20 (s, 3 H), 1.19 (t, 3 H, *J* = 6.8 Hz), 1.15 (s, 3 H), 0.97 (d, 3 H, *J* = 6.4 Hz), 0.95 (d, 3 H, *J* = 6.8 Hz), 0.90 (s, 9 H), 0.11 (s, 3 H), 0.09 (s, 3 H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.2, 173.4, 139.1, 128.2, 127.2, 127.1, 82.0, 79.0, 73.7, 60.4, 60.1, 48.0, 41.6, 37.3, 34.5, 26.7, 26.4, 18.7, 18.4, 17.8, 14.2, 14.0, 12.6, −1.7, −3.9. – IR (neat): $\tilde{\nu}_{max}$ = 2958, 2858, 1733, 1473, 1464, 1388, 1256, 1176, 1070. – CIHRMS $[M + H]^+$ calculated for $C_{29}H_{51}O_6Si$: 523.3454, found 523.3495. – $[\alpha]_D^{23}$ = −18.6 (*c* = 0.7, CH_2Cl_2).

Primary Alcohol 15: To a solution of bis(ethyl ester) **14** (660 mg, 1.26 mmol) in THF (20 mL) at −78 °C was added DIBAL-H (1.0 M solution in hexane, 3.8 mL, 3.8 mmol). The reaction mixture was stirred at −78 °C for 3 h before being quenched with MeOH (2 mL) and 1 N HCl aqueous solution (20 mL). The aqueous layer was extracted with CH_2Cl_2 (50 mL × 2), and the organic layers were combined and washed with saturated aqueous NaCl (20 mL) and dried with $MgSO_4$. Removal of solvent under reduced pressure followed by flash chromatography (silica gel, 10% EtOAc in hexane) gave alcohol **15** as colorless oil (550 mg, 91%). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (m, 5 H), 4.69 and 4.53 (AB-quat., 2 H, *J* = 11.4 Hz), 4.20–4.00 (m, 2 H), 4.08 (d, 1 H, *J* = 5.2 Hz), 3.71 (dt, 1 H, *J* = 12.8 Hz, 6.4 Hz), 3.57 (dt, 1 H, *J* = 10.4 Hz, 6.8 Hz), 3.50 (dd, 1 H, *J* = 4.6 Hz), 1.90 (m, 2 H), 1.76 (m, 1 H), 1.56 (m, 1 H), 1.22 (t, 3 H, *J* = 7.2 Hz), 1.20 (s, 3 H), 1.16 (s, 3 H), 1.00 (d, 3 H, *J* = 7.2 Hz), 0.96 (d, 3 H, *J* = 6.8 Hz), 0.91 (s, 9 H), 0.12 (s, 3 H), 0.09 (s, 3 H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.3, 138.9, 128.3, 127.4, 127.2, 82.8, 79.2, 74.1, 60.6, 60.5, 48.2, 41.7, 34.4, 34.2, 26.4, 18.7, 17.2, 14.0, 13.4, −1.8, −4.0. – IR (neat): $\tilde{\nu}_{max}$ = 3423, 2958, 2858, 1718, 1653, 1473, 1388, 1256, 1068. – CIHRMS $[M + H]^+$ calculated for $C_{27}H_{49}O_5Si$: 481.3350, found 481.3331. – $[\alpha]_D^{23}$ = −18.6 (*c* = 1.15, CH_2Cl_2).

C3-C11 Fragment 4: To a solution of ester **14** (270 mg, 0.52 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added DIBAL-H (1.0 M in hexane, 2.6 mL, 2.6 mmol). The resulting solution was stirred at −78 °C for 15 min before being quench with MeOH (1 mL) followed by 1 N HCl (5 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (20 mL × 2). The organic extracts were combined

and washed with saturated aqueous NaCl (5 mL). The solution was dried with $MgSO_4$ and concentrated in vacuo to give the crude hydroxy aldehyde **16** which was dissolved in dry DMF (1 mL). To the solution at 0 °C was added imidazole (141 mg, 2.08 mmol) and TBSCl (157 mg, 1.04 mmol) successively. The reaction mixture was kept at 0 °C for 2 h before being quenched with saturated aqueous $NaHCO_3$ (5 mL). The mixture was extracted with CH_2Cl_2 (15 mL × 2). The organic layer was washed with H_2O (5 mL) and saturated aqueous NaCl (5 mL) and was dried with $MgSO_4$. Purification by flash chromatography (silica gel, 5% EtOAc in hexane) afforded the silyl ether aldehyde as colorless oil (193 mg, 68% for two steps). To a suspension of CH_3PPh_3Br (320 mg, 0.90 mmol) in THF (5 mL) was added NaHMDS (1.0 M in THF, 0.78 mL). The resulting yellow mixture was stirred for 30 min before being cooled to 0 °C. To this mixture was added a solution of above described silyl ether aldehyde (193 mg, 0.35 mmol) in 1 mL THF. The reaction mixture was stirred at 0 °C for 15 min before being quenched with saturated aqueous NH_4Cl. The mixture was extracted with hexane (30 mL) and the organic layer was washed with saturated aqueous NaCl. The solution was dried with $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (silica, 2% EtOAc in hexane) afforded olefin **4** as colorless oil (173 mg, 90%). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (m, 5 H), 5.77 (m, 1 H), 5.01 (d, 1 H, *J* = 18 Hz), 4.97 (d, 1 H, *J* = 11.6 Hz), 4.63 and 4.54 (AB-quat., 2 H, *J* = 11.6 Hz), 3.77 (d, 1 H, *J* = 3.2 Hz), 3.45 (d, 1 H, *J* = 7.2 Hz), 3.38 and 3.08 (AB-quat., 2 H, *J* = 9.2 Hz), 2.29 (m, 1 H), 2.08 (m, 1 H), 1.96 (m, 2 H), 1.12 (d, 3 H, *J* = 7.2 Hz), 0.97 (d, 3 H, *J* = 6 Hz), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.07 (s, 3 H), 0.05 (s, 3 H), 0.004 (s, 3 H), 0.002 (s, 3 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.5, 138.1, 128.2, 127.1, 115.6, 84.7, 76.4, 74.5, 70.7, 42.0, 41.5, 36.1, 34.9, 26.3, 26.0, 21.9, 21.5, 18.6, 18.3, 17.3, 14.9, −2.7, −4.7, −5.3, −5.5. − IR (neat): $\tilde{\nu}_{max}$ = 2957, 2858, 1641, 1472, 1361, 1256, 1088. − CIHRMS $[M + H]^+$ calculated for $C_{32}H_{60}O_3Si_2$: 548.4081, found 548.4035. − $[\alpha]_D^{23}$ = −5.3 (*c* = 0.6, CH_2Cl_2).

Chiral Alcohol *S*-18: A mixture of aldehyde **17** (1.2 g, 7.2 mmol), 3-bromo-1-(trimethylsilyl)-1-propyne (2.04 mL, 14.4 mmol), zinc dust (1.87 g, 28.8 mmol) and $HgCl_2$ (30 mg, 0.064 mmol) in dry THF (70 mL) was heated under reflux condition for 16 h. The resulting mixture was diluted with EtOAc (200 mL) and filtered. The organic layer was washed with H_2O (30 mL × 2) and saturated aqueous NaCl (30 mL), and was dried with $MgSO_4$. Concentration in vacuo and purification by flash chromatography (silica gel, 20% EtOAc in hexane) afforded racemic alcohol as light yellow solid (1.82 g, 91%). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00 (s, 1 H), 6.84 (s, 1 H), 4.36 (t, 1 H, *J* = 6 Hz), 3.03 (s, 3 H), 2.59 (d, 1 H, *J* = 6.4 Hz), 1.83 (s, 3 H), 0.11 (s, 9 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.5, 152.6, 140.4, 119.3, 115.5, 103.3, 87.3, 75.2, 27.6, 18.9, 14.1, −0.1. − IR (neat): $\tilde{\nu}_{max}$ = 3360, 2959, 2177, 1658, 1509, 1442, 1325, 1249, 1188, 1033. − CIHRMS $[M + H]^+$ calculated for $C_{14}H_{22}NOSSi$: 280.1191, found 280.1193. − To a solution of this racemic alcohol (1.7 g, 6.09 mmol) in THF (60 mL) at room temperature was added TBAF (1.0 M solution in THF). The reaction mixture was stirred for 30 min before being quenched with saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (100 mL × 2). The organic layer was washed with saturated aqueous NaCl (20 mL) and was dried with $MgSO_4$. Removal of solvent and purification by flash chromatography (silica gel, 33% EtOAc in hexane) afforded the racemic alcohol *rac*-**18** as light yellow solid (1.2 g, 94%). The racemic alcohol *rac*-**18** (560 mg, 2.71 mmol) was dissolved in hexane/diethyl ether (3:1) (80 mL). To the resulting solution was added vinyl acetate (5 mL, 54.3 mmol) and lipase AK powder (560 mg). The mixture was stirred at room temperature, and the progress of resolution was monitored by ^{1}H NMR measuring the signal integration of the methine protons adjacent to hydroxy and acetate groups, respectively. When the ratio of alcohol and acetate in the reaction mixture reached 1:1 (14 d), the insoluble enzyme was filtered off and washed with diethyl ether (100 mL). The filtrate was concentrated in vacuo and purified by flash chromatography (silica gel) to give *R*-**19** (15% EtOAc in hexane) and *S*-**18** [33% EtOAc in hexane, light yellow solid, 225 mg, 40% (80% yield based on 50% conversion), 94% *ee*]. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95 (s, 1 H), 6.59 (s, 1 H), 4.34 (m, 1 H), 2.69 (s, 3 H), 2.56−2.52 (m, 2 H), 2.16 (d, 1 H, *J* = 3.6 Hz), 2.05 (s, 3 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.7, 152.4, 140.2, 119.5, 115.7, 80.8, 75.2, 70.5, 25.9, 18.9, 14.0. − IR (neat): $\tilde{\nu}_{max}$ = 3296, 2917, 2118, 1655, 1508, 1441, 1377, 1270, 1191, 1036. − CIHRMS $[M]^+$ calculated for $C_{11}H_{13}NOS$: 207.0718, found 207.0719. − $[\alpha]_D^{23}$ = −2.6 (*c* = 0.58, CH_2Cl_2).

Chiral Acetate *R*-19: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.96 (s, 1 H), 6.56 (s, 1 H), 5.39 (t, 1 H, *J* = 6.8 Hz), 2.68 (s, 3 H), 2.62−2.59 (m, 2 H), 2.08 (s, 3 H), 2.07 (d, 3 H, *J* = 1.6 Hz), 1.97 (t, 1 H, *J* = 2.6 Hz). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.9, 164.7, 152.3, 135.9, 121.4, 116.7, 79.5, 76.6, 70.5, 23.6, 21.0, 19.2, 14.6. − IR (neat): $\tilde{\nu}_{max}$ = 3295, 2924, 2120, 1738, 1503, 1433, 1371, 1236, 1184, 1021. − CIHRMS $[M + H]^+$ calculated for $C_{13}H_{16}NO_2S$: 250.0902, found 250.0891. − $[\alpha]_D^{23}$ = +20.8 (*c* = 1.39, CH_2Cl_2).

Alkynyl Iodide 20: To a solution of alcohol *S*-**18** (210 mg, 1.01 mmol) and DMAP (37 mg, 0.3 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added Et_3N (0.28 mL, 2.01 mmol) and Ac_2O (0.14 mL, 1.4 mmol). The resulting mixture was allowed to warm up to room temperature and was stirred for 16 h before being quenched with saturated aqueous $NaHCO_3$ (5 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL × 2). The organic layers were combined and washed with saturated aqueous NaCl (5 mL) and dried with $MgSO_4$. Removal of the solvent under reduced pressure followed by flash chromatography (silica gel, 15% ethyl acetate in hexane) afforded acetate *S*-**19** as light yellow oil (240 mg, 95%). To a solution of acetate *S*-**19** (100 mg, 0.4 mmol) in THF (4 mL) at −78 °C was added *n*BuLi (2.5 M solution in hexane, 0.19 mL, 0.48 mmol). The resulting yellow solution was stirred at −78 °C for 15 min before a solution of I_2 (0.15 g, 0.59 mmol) in THF (1 mL) was added. The reaction mixture was kept at −78 °C for 1.5 h and was then warmed up to room temperature and stirred for 30 min. The reaction was quenched with saturated aqueous NaS_2O_3 (5 mL) and the mixture was extracted with CH_2Cl_2 (20 mL × 2). The organic layer was washed with H_2O (10 mL) and saturated aqueous NaCl (5 mL) and was dried with $MgSO_4$. Removal of solvent in vacuo and purification by flash chromatography (silica gel, 15% ethyl acetate in hexane) provided alkynyl iodide **20** as yellow oil (120 mg, 80%). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.96 (s, 1 H), 6.53 (s, 1 H), 5.35 (t, 1 H, *J* = 6.6 Hz), 2.78−2.69 (m, 2 H), 2.68 (s, 3 H), 2.08 (s, 3 H), 2.06 (d, 3 H, *J* = 0.8 Hz). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.8, 164.7, 152.3, 135.9, 121.3, 116.7, 89.6, 76.6, 25.9, 21.1, 19.2, 14.7. − IR (neat): $\tilde{\nu}_{max}$ = 2925, 1738, 1505, 1433, 1371, 1235, 1187, 1022. − CIHRMS $[M]^+$ calculated for $C_{13}H_{14}INO_2S$: 374.9788, found 374.9754. − $[\alpha]_D^{23}$ = +3.0 (*c* = 1.0, CH_2Cl_2).

C12-C21 Fragment 5: To a solution of cyclohexene (0.10 mL, 1.0 mmol) in diethyl ether (4 mL) at 0 °C was added $BH_3{\cdot}Me_2S$ (10 mmol/mL, 0.05 mL, 0.5 mmol). The mixture was then warmed up to room temperature and stirred for 1 h. The resulting white cloudy mixture was cooled again to 0 °C, and to which a solution of alkynyl iodide **20** (0.12 g, 0.32 mmol) in ether (1 mL) was added. The reaction mixture was warmed up to room temperature and

stirred for 1.5 h before acetic acid (0.4 mL) was added. After being stirred at room temperature for another 30 min, the reaction mixture was poured into saturated aqueous $NaHCO_3$ (10 mL) and was extracted with CH_2Cl_2 (20 mL × 2). The organic layer was washed with saturated aqueous NaCl and dried with $MgSO_4$. Removal of solvent and purification by flash chromatography (silica gel, 10% EtOAc in hexane) afforded vinyl iodide **5** as light yellow oil (72 mg, 60%). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95 (s, 1 H), 6.52 (s, 1 H), 6.33 (dt, 1 H, *J* = 1.2 Hz, 7.6 Hz), 6.16 (dt, 1 H, *J* = 7.2 Hz, 7.2 Hz), 5.38 (t, 1 H, *J* = 6.4 Hz), 2.69 (s, 3 H), 2.64−2.51 (m, 2 H), 2.08 (d, 3 H, *J* = 1.6 Hz), 2.07 (s, 3 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.9, 164.6, 152.3, 136.6, 136.2, 120.8, 116.4, 85.1, 76.8, 38.4, 21.1, 19.2, 14.9. − IR (neat): $\tilde{\nu}_{max}$ = 2923, 1736, 1611, 1505, 1435, 1370, 1235, 1183, 1020. − CIHRMS [M + H]$^+$ calculated for $C_{13}H_{17}INO_2S$: 378.0023, found 378.0060. − $[\alpha]_D^{23}$ = −28.3 (*c* = 0.90, $CHCl_3$).

Chiral Divinyl Carbinol *S*-21: To a solution of aldehyde **17** (3.4 g, 20.1 mmol) in THF (70 mL) at −78 °C was added vinylmagnesium bromide (1.0 M in THF, 24 mL, 24 mmol). The reaction mixture was stirred at −78 °C for 30 min before being quenched with saturated aqueous NH_4Cl (50 mL). The aqueous layer was extracted with EtOAc (100 mL × 3). The organic extracts were combined, dried with $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (silica gel, 20 to 33% EtOAc in hexane) afforded racemic alcohol *rac*-**21** as light yellow oil (3.6 g, 90%). To a stirred solution of *rac*-**21** (3.6 g, 18.3 mmol) in hexane (170 mL) and vinyl acetate (17 mL) at room temperature was added lipase AK powder (1.80 g, 50 wt-%, Amano International Enzyme Co.). The progress of the resolution was monitored by ^{1}H NMR, measuring the signal integration of the methine proton adjacent to the hydroxy group and the methine proton adjacent to the acetate group. When the ratio of acetate and remaining alcohol in the reaction mixture reached 1:1 (ca. 72 h), the insoluble enzyme was removed by filtration and was washed with diethyl ether (200 mL). Concentration of the filtrate in vacuo and purification by flash chromatography (silica gel) afforded the acetate *R*-**22** as light yellow oil (15% EtOAc in hexane, 2.1 g, 48%) and the unchanged alcohol *S*-**21** as light yellow oil (35% EtOAc in hexane, 1.73 g, 48%, 90% *ee* by mandelate ester formation). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.94 (s, 1 H), 6.60 (s, 1 H), 5.89 (ddd, 1 H, *J* = 5.6 Hz, 10 Hz, 16.8 Hz), 5.34 (d, 1 H, *J* = 17.6 Hz), 5.19 (d, 1 H, *J* = 10.4 Hz), 4.66 (br. s, 1 H), 2.69 (s, 3 H), 1.56 (s, 3 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.6, 152.7, 140.8, 136.7, 119.1, 115.4, 78.1, 19.0, 14.5. − IR (neat): $\tilde{\nu}_{max}$ = 3346, 2979, 2855, 1639, 1508, 1440, 1379, 1269, 1189. − CIHRMS [M + H]$^+$ calculated for $C_{10}H_{14}NOS$: 196.0796, found 196.0808. − $[\alpha]_D^{23}$ = +6.9 (*c* = 0.8, CH_2Cl_2).

Chiral Acetate *R*-22: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.96 (s, 1 H), 6.57 (s, 1 H), 5.84 (ddd, 1 H, *J* = 6.4 Hz, 10.8 Hz, 17.2 Hz), 5.71 (d, 1 H, *J* = 6 Hz), 5.31 (d, 1 H, *J* = 16.8 Hz), 5.23 (d, 1 H, *J* = 10.4 Hz), 2.69 (s, 3 H), 2.10 (s, 3 H), 2.03 (s, 3 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.5, 164.4, 152.3, 136.4, 134.7, 120.7, 117.1, 116.2, 79.0, 21.0, 19.0, 14.8. − IR (neat): $\tilde{\nu}_{max}$ = 1739, 1370, 1235, 1183, 1019. − CIHRMS [M + H]$^+$ calculated for $C_{12}H_{16}NO_2S$: 238.0902, found 238.0930. − $[\alpha]_D^{23}$ = +35 (*c* = 0.7, CH_2Cl_2).

TBS Ether 23: To a solution of *S*-**21** (0.79 g, 4.0 mmol) in dry DMF (8 mL) at 0 °C was added successively imidazole (0.82 g, 12.0 mmol) and TBSCl (0.9 g, 6.0 mmol), and the reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was poured into H_2O (20 mL) and the mixture was extracted with CH_2Cl_2 (30 mL × 2). The organic layer was washed with H_2O (20 mL) and saturated aqueous NaCl (20 mL) and was dried with $MgSO_4$. Concentration in vacuo and purification by flash chromatography (silica gel, 5% EtOAc in hexane) afforded the TBS ether **23** as colorless oil (1.2 g, 96%). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.92 (s, 1 H), 6.54 (s, 1 H), 5.78 (ddd, 1 H, *J* = 4.8 Hz, 10.4 Hz, 17.2 Hz), 5.29 (dt, 1 H, *J* = 17.2 Hz, 1.6 Hz), 5.08 (dt, 1 H, *J* = 1.6 Hz, 10 Hz), 4.59 (d, 1 H, *J* = 4.8 Hz), 2.69 (s, 3 H), 1.93 (d, 3 H, *J* = 1.2 Hz), 0.89 (s, 9 H), 0.06 (s, 3 H), 0.04 (s, 3 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.3, 153.2, 144.3, 139.8, 118.6, 115.2, 114.2, 79.1, 25.8, 19.1, 18.3, 14.0, −4.8. − IR (neat): $\tilde{\nu}_{max}$ = 2956, 2857, 1639, 1504, 1472, 1360, 1252, 1182, 1031. − CIHRMS [M + H]$^+$ calculated for $C_{16}H_{28}NOSSi$: 310.1661, found 310.1666. − $[\alpha]_D^{23}$ = −28.6 (*c* = 1.8, CH_2Cl_2).

Primary Alcohol 24: To BH_3·THF (1.0 M in THF, 5.8 mL) at 0 °C was added cyclohexene (1.17 mL, 11.6 mmol), and the reaction mixture was stirred at 0 °C for 1 h. To the resulting mixture at 0 °C was added a solution of silyl ether **23** in THF (2 mL). The reaction mixture was allowed to slowly warm up to room temperature for 3 h before 2.5 M aqueous NaOH (4.6 mL) and 30% aqueous H_2O_2 (1.8 mL) were added. Stirring was continued for 45 min and the reaction mixture was then extracted with EtOAc (30 mL × 3). The organic layer was washed with H_2O (20 mL) and saturated aqueous NaCl (10 mL) and was dried with $MgSO_4$. Concentration in vacuo and purification by flash chromatography (silica gel, 20−33% EtOAc in hexane) afforded alcohol **24** as colorless oil (1.14 g, 90%). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.91 (s, 1 H), 6.50 (s, 1 H), 4.37 (dd, 1 H, *J* = 4.4 Hz, 7.2 Hz), 3.73 (m, 2 H), 2.69 (s, 3 H), 2.00 (s, 3 H), 3.79−3.68 (m, 2 H), 0.89 (s, 9 H), 0.09 (s, 3 H), 0.02 (s, 3 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.5, 153.0, 141.6, 118.8, 115.4, 77.2, 60.5, 38.2, 25.8, 19.2, 18.2, 14.4, −4.6, −5.2. − IR (neat): $\tilde{\nu}_{max}$ = 3363, 2954, 2929, 2885, 2856, 1658, 1507, 1472, 1361, 1255, 1072. − CIHRMS [M + H]$^+$ calculated for $C_{16}H_{30}NO_2SSi$: 328.1767, found 328.1742. − $[\alpha]_D^{23}$ = −27.7 (*c* = 0.7, CH_2Cl_2).

Hydroxyvinyl Iodide 25: To a solution of alcohol **24** (0.64 g, 1.95 mmol) in CH_2Cl_2 (40 mL) was added Dess−Martin periodinane (1.2 g, 2.83 mmol). The resulting mixture was stirred at room temperature for 15 min before being quenched with H_2O (30 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (20 mL × 2). The organic layer was washed with saturated aqueous NaCl (20 mL) and was dried with $MgSO_4$. The solvent was removed under reduced pressure and the resulting residue was diluted with hexane (100 mL) and filtered through a pad of Celite. Removal of solvent in vacuo gave the crude aldehyde as light yellow oil. To a suspension of CH_2IPPh_3I (2.6 g, 4.9 mmol) in THF (20 mL) was added $NaN(TMS)_2$ (1.0 M solution in THF, 4.4 mL, 4.4 mmol). The resulting red solution was stirred at room temperature for 15 min before being cooled to −78 °C. To this cooled solution was added a solution of above described aldehyde in THF (2 mL), and the reaction mixture was warmed to 0 °C for 20 min. The reaction was then quenched with saturated aqueous NH_4Cl (20 mL) and the mixture was extracted with hexane (100 mL). The organic layer was washed with H_2O (20 mL) and saturated aqueous NaCl (10 mL), and was dried with $MgSO_4$. Removal of solvent afforded the crude vinyl iodide as light yellow oil. This crude vinyl iodide was dissolved in CH_3CN (15 mL) in a plastic vial, and 48% aqueous HF was added slowly to the resulting solution. The reaction mixture was stirred for 16 h before being poured into saturated aqueous Na_2CO_3 (30 mL). The aqueous layer was extracted with EtOAc (30 mL × 3). The organic layers were combined and washed with saturated aqueous NaCl and dried with $MgSO_4$. Concentration under reduced pressure and purification by flash chromato-

graphy (silica, 30% EtOAc in hexane) afforded vinyl iodide **25** as light yellow oil (0.42 g, 65%). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.94 (s, 1 H), 6.55 (s, 1 H), 6.33–6.25 (m, 2 H), 4.30 (t, 1 H, *J* = 6.4 Hz), 2.69 (s, 3 H), 2.49 (m, 2 H), 2.05 (s, 3 H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.7, 152.5, 141.3, 137.5, 119.2, 115.7, 84.4, 75.9, 40.6, 19.1, 14.4. – IR (neat): $\tilde{\nu}_{max}$ = 3347, 2920, 1734, 1654, 1608, 1437, 1375, 1292, 1190, 1045. – CIHRMS $[M + H]^+$ calculated for $C_{11}H_{15}INOS$: 335.9917, found 335.9921. – $[\alpha]_D^{23}$ = −19.4 (*c* = 0.35, CH_2Cl_2).

C12-C21 Fragment 5: To a solution of vinyl iodide **25** (310 mg, 0.93 mmol) and DMAP (34 mg, 0.28 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added Et_3N (0.26 mL, 1.87 mmol) and Ac_2O (0.13 mL, 1.38 mmol). The reaction was stirred for 2 h at 0 °C before being quenched with saturated aqueous $NaHCO_3$ (5 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL × 2). The organic layer was washed with H_2O (5 mL) and saturated aqueous NaCl (5 mL) and was dried with $MgSO_4$. Removal of solvent under reduced pressure and purification by flash chromatography (silica gel, 10% EtOAc in hexane) afforded vinyl iodide **5** as light yellow oil (330 mg, 95%). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95 (s, 1 H), 6.52 (s, 1 H), 6.33 (dt, 1 H, *J* = 1.2 Hz, 7.6 Hz), 6.16 (dt, 1 H, *J* = 7.2 Hz, 7.2 Hz), 5.38 (t, 1 H, *J* = 6.4 Hz), 2.69 (s, 3 H), 2.64–2.51 (m, 2 H), 2.08 (d, 3 H, *J* = 1.6 Hz), 2.07 (s, 3 H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.9, 164.6, 152.3, 136.6, 136.2, 120.8, 116.4, 85.1, 76.8, 38.4, 21.1, 19.2, 14.9. – IR (neat): $\tilde{\nu}_{max}$ = 2923, 1736, 1611, 1505, 1435, 1370, 1235, 1183, 1020. – CIHRMS $[M + H]^+$ calculated for $C_{13}H_{17}INO_2S$: 378.0023, found 378.0060. – $[\alpha]_D^{23}$ = −28.3 (*c* = 0.90, $CHCl_3$).

Olefin 26: To a solution of $(COCl)_2$ (0.14 mL, 1.60 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added DMSO (0.27 mL, 3.80 mmol). The resulting mixture was stirred at −78 °C for 30 min before a solution of alcohol **15** (600 mg, 1.25 mmol) in CH_2Cl_2 (2 mL) was added. The reaction mixture was kept at −78 °C for another 30 min and Et_3N (0.87 mL, 6.25 mmol) was then added. The reaction mixture was allowed to warm up to room temperature and stirred for 1 h before being quenched with H_2O (10 mL). The aqueous layer was extracted with hexane (50 mL × 2). The organic layers were combined and washed with saturated aqueous NaCl (20 mL) and dried with $MgSO_4$. Removal of solvent under reduced pressure afforded the crude aldehyde as light yellow oil (600 mg). To a suspension of CH_3PPh_3Br (1.0 g, 2.8 mmol) in THF (20 mL) was added NaHMDS (1.0 M in THF, 2.5 mL, 2.5 mmol). The resulting yellow mixture was stirred at room temperature for 15 min before being cooled to 0 °C, and to which a solution of above described aldehyde (600 mg, crude) in THF (5 mL) was added. The reaction mixture was kept at 0 °C for 15 min and was then quenched with saturated aqueous NH_4Cl (20 mL). The mixture was extracted with hexane (50 mL × 2), and the organic layers were combined and washed with saturated aqueous NaCl (20 mL) and dried with $MgSO_4$. Removal of solvent under reduced pressure followed by flash chromatography (silica gel, 5% EtOAc in hexane) afforded olefin **26** as colorless oil (550 mg, 92%). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.24 (m, 5 H), 5.80 (m, 1 H), 5.01 (d, 1 H, *J* = 16 Hz), 4.98 (d, 1 H, *J* = 9.6 Hz), 4.66 and 4.55 (AB-quat., 2 H, *J* = 11.4 Hz), 4.13 (d, 1 H, *J* = 6.0 Hz), 4.08 (m, 2 H), 3.49 (dd, 1 H, *J* = 3.6 Hz, 5.2 Hz), 2.40–2.36 (m, 1 H), 1.96–1.78 (m, 3 H), 1.21 (t, 3 H, *J* = 7.2 Hz), 1.20 (s, 3 H), 1.16 (s, 3 H), 0.95 (d, 3 H, *J* = 7.2 Hz), 0.90 (s, 9 H), 0.89 (d, 3 H, *J* = 4.0 Hz), 0.12 (s, 3 H), 0.08 (s, 3 H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.4, 139.4, 137.9, 128.2, 127.1, 115.7, 82.5, 79.0, 73.7, 60.4, 48.1, 41.6, 36.7, 36.4, 26.6, 26.5, 18.8, 18.5, 16.7, 14.0, 12.6, −1.7, −3.8. – IR (neat): $\tilde{\nu}_{max}$ = 2959, 2932, 2858, 1731, 1641, 1473, 1388, 1257, 1070. – CIHRMS $[M + H]^+$ calculated for $C_{28}H_{49}O_4Si$: 477.3400, found 477.3443. – $[\alpha]_D^{23}$ = −23.3 (*c* = 0.6, CH_2Cl_2).

β-Hydroxy Ester 28: To a solution of olefin **26** (130 mg, 0.27 mmol) in CH_2Cl_2 (3 mL) at − 78 °C was added DIBAL-H (1.0 M in hexane, 1.1 mL, 1.1 mmol). The reaction mixture was kept at −78 °C for 30 min before being quenched with MeOH (1 mL) and 1 N HCl aqueous solution (10 mL). The mixture was extracted with CH_2Cl_2 (30 mL × 2), and the organic layer was washed with saturated aqueous NaCl (10 mL) and was dried with $MgSO_4$. Removal of the solvent under reduced pressure afforded the crude alcohol as light yellow oil. This alcohol was then dissolved in CH_2Cl_2 (2 mL), and to the resulting solution was added Dess–Martin periodinane (250 mg, 0.59 mmol). The reaction mixture was stirred at room temperature for 15 min before being transferred to a short silica gel column and washed with 5% EtOAc in hexane. Removal of the solvent under reduced pressure afforded aldehyde **27** as colorless oil (102 mg, 86% for two steps). To a solution of aldehyde **27** (100 mg, 0.23 mmol) and *tert*-butyl acetate (0.13 mL, 0.97 mmol) in THF (4 mL) at −78 °C was added freshly prepared LDA solution (0.35 M in THF, 2 mL, 0.70 mmol). The reaction mixture was kept at −78 °C for 30 min before being quenched with saturated aqueous NH_4Cl (10 mL). The mixture was extracted with CH_2Cl_2 (30 mL × 2), and the organic layer was washed with saturated aqueous NaCl (10 mL) and was dried with $MgSO_4$. Removal of solvent under reduced pressure followed by flash chromatograph (silica gel, 5% EtOAc in hexane) afforded a ca. 2:1 mixture of β-hydroxy ester **28** and its C3 diastereomer as colorless oil (100 mg, 79%). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (m, 5 H), 5.76 (m, 1 H), 5.00 (d, 1 H, *J* = 18 Hz), 4.97 (d, 1 H, *J* = 10.0 Hz), 4.65 and 4.53 (AB-quat., 2 H, *J* = 11.6 Hz), 3.98 (d, 1 H, *J* = 10.8 Hz), 3.72 (d, 1 H, *J* = 3.2 Hz), 3.57 (d, 1 H, *J* = 6.0 Hz), 3.24 (d, 1 H, *J* = 2.8 Hz), 2.44 (dd, 1 H, *J* = 2.0 Hz, 16.4 Hz), 2.33–2.24 (m, 2 H), 2.16 (m, 1 H), 1.93 (m, 2 H), 1.43 (s, 9 H), 1.14 (d, 3 H, *J* = 7.6 Hz), 0.96 (d, 3 H, *J* = 6.0 Hz), 0.93 (s, 3 H), 0.91 (s, 9 H), 0.84 (s, 3 H), 0.10 (s, 3 H), 0.07 (s, 3 H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.5, 139.6, 138.2, 128.1, 126.9, 115.5, 83.2, 81.3, 79.7, 73.6, 71.4, 43.6, 39.6, 37.7, 36.7, 35.4, 28.1, 26.5, 20.8, 19.3, 18.7, 17.0, 15.5, −2.2, −4.6. – $[\alpha]_D^{23}$ = −11.0 (*c* = 0.36, CH_2Cl_2).

β-Hydroxy Ester 30: To a solution of aldehyde **27** (120 mg, 0.28 mmol) and silyl ketene acetal **29** (0.1 mL, 0.56 mmol) in CH_2Cl_2 (1.5 mL) at −78 °C was added $TiCl_4$ (0.037 mL, 0.34 mmol). The reaction mixture was kept at −78 °C for 15 min before being quenched with EtOAc (4 mL) and H_2O (5 mL). The mixture was extracted with CH_2Cl_2 (30 mL × 2), and the organic layer was washed with saturated aqueous NaCl (10 mL) and was dried with $MgSO_4$. Removal of solvent under reduced pressure followed by flash chromatography (silica gel, 5% EtOAc in hexane) afforded β-hydroxy ester **30** as colorless oil (130 mg, 90%). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (m, 5 H), 5.77 (m, 1 H), 5.00 (d, 1 H, *J* = 17.2 Hz), 4.97 (d, 1 H, *J* = 9.6 Hz), 4.64 and 4.54 (AB-quat., 2 H, *J* = 11.6 Hz), 4.11 (m, 2 H), 4.04 (d, 1 H, *J* = 10.4 Hz), 3.73 (d, 1 H, *J* = 2.8 Hz), 3.58 (dd, 1 H, *J* = 2.0 Hz, 6.2 Hz), 3.11 (d, 1 H, *J* = 2.8 Hz), 2.52 (dd, 1 H, *J* = 2.0 Hz, 16.4 Hz), 2.37 (dd, 1 H, *J* = 10.8 Hz, 16.4 Hz), 2.29 (m, 1 H), 2.17 (m, 1 H), 1.93 (m, 2 H), 1.23 (t, 3 H, *J* = 7.0 Hz), 1.14 (t, 3 H, *J* = 7.2 Hz), 0.96 (d, 3 H, *J* = 6.0 Hz), 0.94 (s, 3 H), 0.92 (s, 9 H), 0.86 (s, 3 H), 0.10 (s, 3 H), 0.08 (s, 3 H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.0, 139.7, 138.1, 128.1, 127.0, 126.9, 115.6, 83.1, 80.0, 73.5, 71.6, 60.8, 43.6, 39.9, 36.9, 36.7, 35.5, 26.5, 26.4, 20.9, 19.5, 18.7, 16.9, 15.3, 14.1, −2.2, −4.6. – $[\alpha]_D^{23}$ = −10.5 (*c* = 1.25, CH_2Cl_2).

β-Hydroxy Ester 33: To a solution of aldehyde **27** (140 mg, 0.32 mmol) and silyl ketene acetal **32** (0.125 mL, 0.64 mmol) in CH_2Cl_2 (2 mL) at −78 °C was added $TiCl_4$ (0.046 mL, 0.42 mmol). The reaction mixture was kept at −78 °C for 20 min before being quenched with EtOAc (4 mL) and H_2O (5 mL). The mixture was extracted with CH_2Cl_2 (30 mL × 2), and the organic layer was washed with saturated aqueous NaCl (10 mL) and was dried with $MgSO_4$. Removal of solvent under reduced pressure followed by flash chromatography (silica gel, 5% EtOAc in hexane) afforded β-hydroxy ester **33** as colorless oil (140 mg, 81%). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (m, 5 H), 5.76 (m, 1 H), 5.00−4.96(m, 3 H), 4.65 and 4.53 (AB-quat., 2 H, *J* = 11.6 Hz), 4.02 (d, 1 H, *J* = 10.4 Hz), 3.72 (d, 1 H, *J* = 3.6 Hz), 3.56 (d, 1 H, *J* = 6.4 Hz), 3.15 (d, 1 H, *J* = 2.8 Hz), 2.49 (dd, 1 H, *J* = 2.0 Hz, 16.4 Hz), 2.35 (dd, 1 H, *J* = 10.4 Hz, 16.4 Hz), 2.29 (m, 1 H), 2.16 (m, 1 H), 1.93 (m, 2 H), 1.22 (d, 3 H, *J* = 6.0 Hz), 1.21 (d, 3 H, *J* = 6.4 Hz), 1.14 (t, 3 H, *J* = 7.2 Hz), 0.96 (d, 3 H, *J* = 6.0 Hz), 0.94 (s, 3 H), 0.91 (s, 9 H), 0.85 (s, 3 H), 0.10 (s, 3 H), 0.07 (s, 3 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.5, 139.6, 138.1, 128.1, 126.9, 115.5, 83.1, 79.9, 73.5, 71.5, 68.3, 43.6, 39.8, 37.1, 36.7, 35.5, 26.5, 21.8, 20.8, 19.4, 18.7, 17.0, 15.3, −2.2, −4.6. − IR (neat): $\tilde{\nu}_{max}$ = 3513, 2959, 2931, 2858, 1715, 1641, 1472, 1375, 1256, 1108, 1063. − CIHRMS $[M + H]^+$ calculated for $C_{31}H_{55}O_5Si$: 535.3819, found 535.3850. − $[\alpha]_D^{23}$ = −11.9 (*c* = 0.43, CH_2Cl_2).

Diol 34: To a solution of β-hydroxy ester **33** (80 mg, 0.15 mmol) in THF (3 mL) at 0 °C was added TBAF (1.0 M in THF, 0.3 mL, 0.3 mmol). The reaction mixture was kept at 0 °C for 10 min before being quenched with saturated aqueous NH_4Cl (5 mL). The mixture was extracted with EtOAc (30 mL × 2), and the organic layer was washed with saturated aqueous NaCl (10 mL) and was dried with $MgSO_4$. Removal of the solvent under reduced pressure followed by flash chromatography (silica gel, 15% EtOAc in hexane) afforded diol **34** as colorless oil (56 mg, 89%). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (m, 5 H), 5.78 (m, 1 H), 5.06−5.01(m, 3 H), 4.62 and 4.54 (AB-quat., 2 H, *J* = 11.2 Hz), 4.07−4.00 (m, 2 H), 3.74 (d, 1 H, *J* = 6.4 Hz), 3.53 (br. s, 1 H), 2.52−2.33 (m, 3 H), 2.09−1.90 (m, 4 H), 1.23 (d, 6 H, *J* = 6.0 Hz), 1.10 (d, 3 H, *J* = 6.8 Hz), 0.97 (s, 3 H), 0.94 (d, 3 H, *J* = 6.8 Hz), 0.81 (s, 3 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.1, 138.5, 137.4, 128.4, 127.6, 127.4, 116.1, 83.7, 83.1, 75.7, 72.0, 68.0, 41.7, 37.7, 37.2, 35.8, 35.4, 21.8, 21.2, 16.5, 15.9. − IR (neat): $\tilde{\nu}_{max}$ = 3454, 2976, 2931, 1717, 1640, 1455, 1375, 1180, 1109, 910.

Suzuki Coupling Product 36: To olefin **4** (200 mg, 0.365 mmol) was added 9-BBN (0.5 M solution in THF, 1.5 mL, 0.75 mmol) and the reaction was stirred for 4 h at room temperature. In a separate flask, vinyl iodide **5** (170 mg, 0.451 mmol) was dissolved in DMF (5 mL). Cs_2CO_3 powder (240 mg, 0.736 mmol) was added to the resulting solution under vigorous stirring, followed by $AsPh_3$ (17 mg, 0.056 mmol), $PdCl_2$(dppf) (30 mg, 0.037 mmol) and H_2O (0.24 mL, 13.3 mmol) successively. The mixture was stirred for 5 min before the borane solution was added. The reaction mixture was then stirred for 1.5 h, and the color of the mixture turned from dark brown to yellow. The reaction was quenched with saturated aqueous NH_4Cl, and the mixture was extracted with CH_2Cl_2 (30 mL × 3). The organic layer was washed with H_2O (20 mL) and saturated aqueous NaCl (10 mL), and was dried with $MgSO_4$. Purification by flash chromatography (silica gel, 5−10% EtOAc in hexane) afforded coupling product **36** as light yellow oil (175 mg, 60%). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (m, 5 H), 6.91 (s, 1 H), 6.50 (s, 1 H), 5.48 (m, 1 H), 5.28 (m, 1 H), 5.25 (t, 1 H, *J* = 6.8 Hz), 4.56 (AB-quat., 2 H, *J* = 11.2 Hz), 3.75 (d, 1 H, *J* = 3.2 Hz), 3.40 (dd, 1 H, *J* = 2 Hz, 8.8 Hz), 3.38 and 3.05 (AB-quat., 2 H, *J* = 9.4 Hz), 2.68 (s, 3 H), 2.44 (m, 2 H), 2.04 (s, 3 H), 2.03 (s, 3 H), 2.01 (m, 2 H), 1.80−1.65 (m, 2 H), 1.50−1.38 (m, 2 H), 1.30−1.19 (m, 2 H), 1.11 (d, 3 H, *J* = 6.8 Hz), 0.96 (d, 3 H, *J* = 6.8 Hz), 0.89 (s, 3 H), 0.88 (s, 9 H), 0.87 (s, 9 H), 0.86 (s, 3 H), 0.06 (s, 3 H), 0.04 (s, 3 H), 0.00 (s, 6 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1, 164.8, 152.3, 139.6, 137.8, 132.8, 128.2, 127.2, 127.1, 123.9, 120.2, 116.1, 85.1, 78.5, 76.2, 74.3, 70.8, 42.0, 41.7, 36.3, 31.1, 30.2, 29.7, 28.1, 26.3, 26.0, 25.7, 21.9, 21.4, 21.2, 19.1, 18.5, 18.2, 17.3, 14.9, 14.6, −2.8, −4.7, −5.3, −5.5. − IR (neat): $\tilde{\nu}_{max}$ = 2928, 1741, 1653, 1507, 1472, 1371, 1240, 1064. − CIHRMS $[M + H]^+$ calculated for $C_{45}H_{78}NO_5SSi_2$: 800.5140, found 800.5071. − $[\alpha]_D^{23}$ = −11.3 (*c* = 0.80, CH_2Cl_2).

Primary Alcohol 37: To a solution of silyl ether **36** (140 mg, 0.175 mmol) in THF (8 mL) in a plastic vial was added pyridine-buffered HF·pyridine solution (8 mL, prepared from 5 mL of THF, 2 mL of pyridine and 1 mL of HF·pyridine). The reaction mixture was stirred at room temperature for 36 h before being quenched with saturated aqueous Na_2CO_3 (15 mL). The mixture was extracted with EtOAc (20 mL × 3) and the organic layer was washed with saturated aqueous NaCl. The solution was dried with $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (silica gel, 10 to 20% EtOAc in hexane) afforded alcohol **37** as white solid (112 mg, 93%). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (m, 5 H), 6.93 (s, 1 H), 6.52 (s, 1 H), 5.48 (m, 1 H), 5.29 (m, 1 H), 5.24 (t, 1 H, *J* = 6.6 Hz), 4.55 (s, 2 H), 3.68 and 3.21 (AB-quat., 2 H, *J* = 10.6 Hz), 3.61 (d, 1 H, *J* = 2.8 Hz), 3.45 (dd, 1 H, *J* = 2 Hz, 6.8 Hz), 2.70 (s, 3 H), 2.45 (m, 2 H), 2.34−1.98 (m, 2 H), 2.04 (s, 3 H), 2.03 (s, 3 H), 1.83 (m, 1 H), 1.47 (m, 2 H), 1.30−1.20 (m, 3 H), 1.16 (d, 3 H, *J* = 7.2 Hz), 1.04 (s, 3 H), 0.97 (d, 3 H, *J* = 6.8 Hz), 0.90 (s, 9 H), 0.88 (s, 3 H), 0.06 (s, 6 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.2, 164.8, 152.2, 139.4, 137.8, 132.8, 128.2, 127.1, 124.0, 120.3, 116.1, 84.2, 81.4, 78.5, 73.6, 70.9, 41.1, 40.8, 36.4, 31.1, 29.7, 28.0, 26.3, 24.0, 22.1, 21.2, 19.1, 18.5, 16.9, 14.7, 14.1, −2.8, −4.8. − IR (neat): $\tilde{\nu}_{max}$ = 3447, 2928, 2856, 1736, 1463, 1370, 1238, 1060. − CIHRMS $[M]^+$ calculated for $C_{39}H_{63}NO_5SSi$: 685.4196, found 685.4227. − $[\alpha]_D^{23}$ = −9.7 (*c* = 0.70, CH_2Cl_2).

β-Hydroxy Ester 38: To a solution of alcohol **37** (152 mg, 0.222 mmol) in CH_2Cl_2 (4 mL) was added Dess−Martin periodinane (190 mg, 0.448 mmol). The resulting mixture was stirred at room temperature for 1 h before being transferred to a column of silica gel and eluted with 20% EtOAc in hexane. Removal of the solvent afforded the corresponding aldehyde as light yellow oil (140 mg, 92%). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.66 (s, 1 H), 7.30 (m, 5 H), 6.92 (s, 1 H), 6.50 (s, 1 H), 5.47 (m, 1 H), 5.30 (m, 1 H), 5.25 (t, 1 H, *J* = 6.6 Hz), 4.55 and 4.46 (AB-quat., 2 H, *J* = 7.4 Hz), 3.81 (d, 1 H, *J* = 3.6 Hz), 3.33 (dd, 1 H, *J* = 3.6 Hz, 5.2 Hz), 2.68 (s, 3 H), 2.45 (m, 2 H), 2.05 (s, 3 H), 2.05 (d, 3 H, *J* = 1.2 Hz), 2.04 (s, 3 H), 2.10−1.90 (m, 3 H), 1.76 (m, 1 H), 1.45 (m, 2 H), 1.23 (m, 2 H), 1.09 (s, 3 H), 1.07 (s, 3 H), 1.01 (d, 3 H, *J* = 7.6 Hz), 0.91 (d, 3 H, *J* = 6.8 Hz), 0.88 (s, 9 H), 0.88 (s, 3 H), 0.09 (s, 3 H), 0.06 (s, 3 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.0, 170.1, 164.6, 152.5, 139.1, 137.3, 132.5, 128.2, 127.2, 127.1, 124.1, 120.6, 116.1, 83.4, 79.8, 78.5, 73.5, 51.6, 41.9, 36.0, 31.2, 31.1, 27.9, 26.1, 21.2, 20.7, 20.4, 19.1, 18.5, 16.4, 14.8, 13.0, −2.9, −4.5. − To a solution of above prepared aldehyde (140 mg, 0.205 mmol) in CH_2Cl_2 (1 mL) at −78 °C was added silyl ketene acetal **32** (0.08 mL, 0.41 mmol) and $TiCl_4$ (0.03 mL, 0.274 mmol). The reaction was quenched after 15 min with EtOAc (3 mL) and H_2O (3 mL), and the mixture was extracted with EtOAc (15 mL × 3). The organic layer was washed with saturated aqueous NaCl and dried with $MgSO_4$. Purification by flash chromatography (silica gel,

20% EtOAc in hexane) afforded β-hydroxy ester **38** as light yellow oil (140 mg, 87%). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (m, 5 H), 6.92 (s, 1 H), 6.50 (s, 1 H), 5.48 (m, 1 H), 5.29 (m, 1 H), 5.25 (t, 1 H, *J* = 7 Hz), 4.98 (qq, 1 H, *J* = 6.2 Hz, 6.2 Hz), 4.60 and 4.52 (AB-quat., 2 H, *J* = 11.6 Hz), 3.70 (d, 1 H, *J* = 2.8 Hz), 3.56 (dd, 1 H, *J* = 2.8 Hz, 6 Hz), 3.21 (br. s, 1 H), 2.68 (s, 3 H), 2.54−2.30 (m, 4 H), 2.13 (m,1 H), 2.08−1.96 (m,2 H), 2.04 (s, 3 H), 2.03 (s, 3 H), 1.83 (m,1 H), 1.46 (m, 2 H), 1.23 (m, 2 H), 1.21 (d, 3 H, *J* = 6.4 Hz), 1.18 (d, 3 H, *J* = 6.4 Hz), 1.12 (d, 3 H, *J* = 7.2 Hz), 0.94 (d, 3 H, *J* = 8.8 Hz), 0.93 (s, 3 H), 0.91 (s, 9 H), 0.85 (s, 3 H), 0.08 (s, 3 H), 0.06 (s, 3 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.6, 170.1, 164.5, 152.6, 139.8, 137.4, 132.8, 128.1, 126.9, 124.0, 120.6, 116.2, 83.3, 79.8, 78.6, 73.1, 71.5, 68.2, 43.7, 40.2, 37.1, 36.7, 31.1, 31.0, 28.0, 27.9, 26.5, 26.4, 21.8, 21.2, 20.9, 19.5, 19.2, 18.7, 16.8, 14.8, −2.4, −4.6. − IR (neat): $\tilde{\nu}_{max}$ = 3516, 2930, 1737, 1464, 1373, 1237, 1109, 1062. − CIHRMS [M + H]$^+$ calculated for $C_{44}H_{72}NO_7SSi$: 786.4799, found 786.4771. − $[\alpha]_D^{23}$ = −13.2 (*c* = 1.05, CH_2Cl_2).

Diol 39: To a solution of silyl ether **38** (130 mg, 0.166 mmol) in THF (5 mL) at 0 °C was added tetrabutylammonium fluoride (TBAF) (1.0 M solution in THF, 0.5 mL, 0.5 mmol). The reaction mixture was kept at 0 °C for 10 min before being quenched with saturated aqueous NH_4Cl (3 mL). The resulting mixture was extracted with EtOAc (20 mL × 3). The organic layer was washed with saturated aqueous NaCl and was dried with $MgSO_4$. Purification by flash chromatography (silica, 30% EtOAc in hexane) afforded diol **39** as light yellow oil (99 mg, 89%). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (m, 5 H), 6.92 (s, 1 H), 6.50 (s, 1 H), 5.47 (m, 1 H), 5.30 (m, 1 H), 5.25 (t, 1 H, *J* = 6.8 Hz), 5.02 (qq, 1 H, *J* = 6.4 Hz, 6.4 Hz), 4.61 and 4.47 (AB-quat., 2 H, *J* = 11.2 Hz), 4.05 (br. s, 1 H), 4.00 (dd, 1 H, *J* = 2.8 Hz, 10 Hz), 3.73 (d, 1 H, *J* = 6.4 Hz)], 3.50 (d, 1 H, *J* = 3.6 Hz), 2.68 (s, 3 H), 2.52−2.32 (m, 4 H), 2.10−1.88 (m, 3 H), 2.04 (s, 6 H), 1.66−1.42 (m, 2 H), 1.34−1.12 (m, 3 H), 1.22 (d, 3 H, *J* = 6.4 Hz), 1.22 (d, 3 H, *J* = 7.2 Hz), 1.08 (d, 3 H, *J* = 6.8 Hz), 0.97 (s, 3 H), 0.94 (d, 3 H, *J* = 6.8 Hz), 0.80 (s, 3 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.1, 170.1, 164.6, 152.5, 138.4, 137.3, 132.5, 128.4, 127.6, 127.5, 124.2, 120.6, 116.2, 83.7, 83.5, 78.5, 75.8, 71.7, 68.0, 41.7, 37.3, 35.7, 35.2, 32.8, 31.1, 27.7, 27.6, 27.5, 21.8, 21.2, 19.2, 16.5, 16.1, 14.8. − IR (neat): $\tilde{\nu}_{max}$ = 3461, 2975, 2933, 1736, 1498, 1454, 1373, 1238, 1181, 1109. − CIHRMS [M]$^+$ calculated for $C_{38}H_{57}NO_7S$: 671.3855, found 671.3882. − $[\alpha]_D^{23}$ = −7.2° (*c* = 0.25, CH_2Cl_2).

Silyl Ether 40: To a solution of diol **39** (99 mg, 0.148 mmol) in DMF (1 mL) was added sequentially imidazole (0.30 g, 4.41 mmol) and TBSCl (0.33 g, 2.19 mmol). The resulting solution was stirred at room temperature for 36 h before being quenched with H_2O (5 mL). The mixture was extracted with EtOAc (20 mL × 3), and the organic layer was washed with H_2O (5 mL) and saturated aqueous NaCl (5 mL) and was dried with $MgSO_4$. Purification by flash chromatography (silica gel, 20% EtOAc in hexane) afforded silyl ether **40** as light yellow oil (105 mg, 91%). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (m, 5 H), 6.92 (s, 1 H), 6.50 (s, 1 H), 5.47 (m, 1 H), 5.28 (m, 1 H), 5.25 (t, 1 H, *J* = 6.8 Hz), 4.95 (qq, 1 H, *J* = 6.4 Hz, 6.4 Hz), 4.59 and 4.53 (AB-quat., 2 H, *J* = 11.2 Hz), 4.14 (t, 1 H, *J* = 4.8 Hz), 3.70 (d, 1 H, *J* = 6.8 Hz), 3.42 (s, 1 H), 2.75 (dd, 1 H, *J* = 4.8 Hz, 17.2 Hz), 2.68 (s, 3 H), 2.53−2.35 (m, 2 H), 2.26 (dd, 1 H, *J* = 5.2 Hz, 16.8 Hz), 2.04 (s, 6 H), 2.10−1.90 (m, 3 H), 1.84 (m, 1 H), 1.65−1.40 (m, 2 H), 1.35−1.20 (m, 2 H), 1.20 (d, 3 H, *J* = 6.4 Hz), 1.17 (d, 3 H, *J* = 6 Hz), 1.04 (d, 3 H, *J* = 6.8 Hz), 0.93 (s, 3 H), 0.90 (d, 3 H, *J* = 6.4 Hz), 0.85 (s, 9 H), 0.84 (s, 3 H), 0.06 (s, 3 H), 0.00 (s, 3 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0, 170.1, 164.5, 152.6, 139.1, 137.4, 132.7, 128.3, 127.3, 124.0, 120.6, 116.1, 83.8, 78.9, 78.6, 75.1, 72.4, 67.9, 43.6, 39.9, 36.2, 36.1, 32.8, 31.1, 27.8, 27.5, 26.0, 21.8, 21.7, 21.2, 20.2, 19.6, 19.2, 18.2, 16.5, 15.0, 14.8, −4.2, −4.9. − IR (neat): $\tilde{\nu}_{max}$ = 3410, 2929, 2857, 1738, 1463, 1370, 1237, 1182, 1067. − CIHRMS [M + H]$^+$ calculated for $C_{44}H_{72}NO_7SSi$: 786.4799, found 786.4770. − $[\alpha]_D^{23}$ = −9.0 (*c* = 0.67, CH_2Cl_2).

Ketone 41: To a solution of the alcohol **40** (100 mg, 0.127 mmol) in CH_2Cl_2 (3 mL) was added Dess−Martin periodinane (162 mg, 0.382 mmol). After 2 h at room temperature, the reaction mixture was transferred to a silica gel column and eluted with 10−20% EtOAc in hexane. The solvent was removed in vacuo to give ketone **41** as light yellow oil (95 mg, 95%). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35−7.25 (m, 5 H), 6.91 (s, 1 H), 6.49 (s, 1 H), 5.44 (m, 1 H), 5.29 (m, 1 H), 5.25 (t, 1 H, *J* = 7.2 Hz), 4.98 (qq, 1 H, *J* = 6 Hz, 6 Hz), 4.56 and 4.48 (AB-quat., 2 H, *J* = 10.6 Hz), 4.36 (dd, 1 H, *J* = 3.2 Hz, 6.4 Hz), 3.44 (dd, 1 H, *J* = 4 Hz, 6.4 Hz)], 3.29 (dq, 1 H, *J* = 6.6 Hz, 6.6 Hz), 2.68 (s, 3 H), 2.52−2.34 (m, 3 H), 2.21 (dd, 1 H, *J* = 6 Hz, 12.8 Hz), 2.04 (s, 3 H), 2.03 (s, 3 H), 2.01 (m, 2 H), 1.54−1.34 (m, 3 H), 1.30−1.16 (m, 2 H), 1.24 (s, 3 H), 1.22 (d, 3 H, *J* = 6.4 Hz), 1.21 (d, 3 H, *J* = 6.4 Hz), 1.12 (d, 3 H, *J* = 6.8 Hz), 1.06 (s, 3 H), 0.93 (s, 3 H), 0.95 (d, 3 H, *J* = 6.8 Hz), 0.85 (s, 9 H), 0.09 (s, 3 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 217.7, 171.5, 170.1, 164.6, 152.6, 138.9, 137.4, 132.7, 128.3, 127.8, 127.4, 124.1, 120.6, 116.2, 85.0, 78.5, 75.3, 74.21, 67.9, 53.5, 44.8, 40.6, 37.5, 31.1, 30.9, 29.7, 27.9, 27.6, 26.0, 23.3, 21.9, 21.8, 21.2, 20.0, 19.2, 18.2, 17.8, 14.8, 14.0, −4.4, −4.6. − IR (neat): $\tilde{\nu}_{max}$ = 2933, 1735, 1695, 1471, 1373, 1237, 1090. − CIHRMS [M + H]$^+$ calculated for $C_{44}H_{70}NO_7SSi$: 784.4628, found 784.4635. − $[\alpha]_D^{23}$ = −29.8 (*c* = 0.33, CH_2Cl_2).

Hydroxy Acid: To a solution of ketone **41** (90 mg, 0.115 mmol) in MeOH (10 mL) was added 2 N NaOH aqueous solution (5 mL). The resulting mixture was stirred at room temperature for 10 min before being heated under reflux condition for 1.5 h. MeOH was then partially removed under reduced pressure, and the solution was acidified with 1 N HCl aqueous solution to pH = 3−4. The mixture was extracted with EtOAc (15 mL × 4), and the organic layer was washed with saturated aqueous NaCl (5 mL) and dried with $MgSO_4$. Purification by flash chromatography (silica, 2% MeOH in CH_2Cl_2) afforded hydroxy acid **42** as light yellow oil (50 mg, 62%). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39−7.22 (m, 5 H), 6.93 (s, 1 H), 6.63 (s, 1 H), 5.53 (m, 1 H), 5.38 (m, 1 H), 5.25 (t, 1 H, *J* = 7.2 Hz), 4.58 and 4.50 (AB-quat., 2 H, *J* = 10.8 Hz), 4.41 (dd, 1 H, *J* = 3.6 Hz, 6.4 Hz), 4.16 (t, 1 H, *J* = 6.2 Hz), 3.47 (dd, 1 H, *J* = 4 Hz, 7.2 Hz)], 3.29 (dq, 1 H, *J* = 6.8 Hz, 6.8 Hz), 2.69 (s, 3 H), 2.54−2.26 (m, 4 H), 2.16−1.95 (m, 2 H), 1.99 (s, 3 H), 1.75−1.40 (m, 3 H), 1.26−1.10 (m, 2 H), 1.19 (s, 3 H), 1.15 (d, 3 H, *J* = 6.8 Hz), 1.13 (s, 3 H), 0.86 (s, 9 H), 0.09 (s, 3 H), 0.05 (s, 3 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 217.8, 175.0, 165.0, 152.6, 141.8, 138.9, 133.4, 128.2, 127.7, 127.4, 124.9, 118.8, 115.2, 84.8, 77.2, 75.1, 73.5, 54.0, 44.3, 40.0, 37.3, 33.5, 30.9, 27.9, 27.6, 26.0, 23.4, 19.1, 18.8, 18.2, 17.6, 14.7, 14.6, −4.1, −4.6. − IR (neat): $\tilde{\nu}_{max}$ = 3400, 2930, 2857, 1696, 1472, 1255, 1191, 1091. − CIHRMS [M + H]$^+$ calculated for $C_{39}H_{62}NO_6SSi$: 700.4067, found 700.4012. − $[\alpha]_D^{23}$ = −38.2 (*c* = 0.55, CH_2Cl_2).

Lactone 43: To a solution of hydroxy acid **42** (10 mg, 0.014 mmol) in THF (0.5 mL) was added Et_3N (0.02 mL, 0.144 mmol) followed by 2,4,6-trichlorobenzoyl chloride (0.015 mL, 0.096 mmol). The reaction mixture was stirred at 0 °C for 15 min before being diluted with toluene (2 mL). The resulting solution was added dropwise to a solution of DMAP (26 mg, 0.21 mmol) in toluene (8 mL) at room temperature. The mixture was stirred at room temperature for 30 min and was filtered and concentrated in vacuo. Purification by

flash chromatography (silica, 20% EtOAc in hexane) afforded lactone **43** as light yellow oil (7.1 mg, 73%). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (m, 5 H), 6.93 (s, 1 H), 6.51 (s, 1 H), 5.52 (dt, 1 H, *J* = 3.2 Hz, 11.2 Hz), 5.36 (dt, 1 H, *J* = 6.8 Hz, 10 Hz), 4.98 (d, 1 H, *J* = 10.4 Hz), 4.69 and 4.60 (AB-quat., 2 H, *J* = 10.8 Hz), 4.00 (d, 1 H, *J* = 10 Hz), 3.69 (d, 1 H, *J* = 9.6 Hz), 3.14 (dq, 1 H, *J* = 7.2 Hz, 9.6 Hz), 2.82−2.60 (m, 2 H), 2.69 (s, 3 H), 2.36 (m, 1 H), 2.08 (s, 3 H), 2.05−1.97 (m, 1 H), 1.85 (m, 1 H), 1.68−1.52 (m, 3 H), 1.32−0.98 (m, 3 H), 1.19 (d, 3 H, *J* = 6.4 Hz), 1.18 (s, 3 H), 1.14 (s, 3 H), 1.06 (d, 3 H, *J* = 7.2 Hz), 0.84 (s, 9 H), 0.11 (s, 3 H), −0.12 (s, 3 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 214.6, 171.1, 164.7, 152.5, 139.1, 138.4, 135.0, 128.3, 127.6, 127.4, 122.7, 119.8, 116.3, 87.1, 79.8, 77.2, 76.1, 53.4, 47.8, 38.9, 37.0, 31.8, 31.5, 29.3, 28.3, 26.2, 24.9, 24.0, 20.1, 19.2, 18.7, 17.1, 14.8, −3.1, −5.7. − IR (neat): $\tilde{\nu}_{max}$ = 2929, 1740, 1696, 1464, 1379, 1256, 1160, 1097. − CIHRMS $[M]^+$ calculated for $C_{39}H_{59}NO_5SSi$: 681.3883, found 681.3825. − $[\alpha]_D^{23}$ = −10.4 (*c* = 0.45, CH_2Cl_2).

Hydroxy Lactone 44: To a solution of lactone **43** (28 mg, 0.041 mmol) in CH_2Cl_2 (4 mL) was added H_2O (1 mL) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (100 mg, 0.44 mmol). The reaction mixture was under vigorous stirring for 2.5 h before being quenched with saturated aqueous $NaHCO_3$ (5 mL). The mixture was extracted with CH_2Cl_2 (15 mL × 2) and diethyl ether (10 mL), and the organic layers were combined and dried with $MgSO_4$. Purification by flash chromatography (silica gel, 30% EtOAc in hexane) afforded hydroxy lactone **44** as white solid (20 mg, 82%). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95 (s, 1 H), 6.55 (s, 1 H), 5.44 (dt, 1 H, *J* = 3.2 Hz, 11.2 Hz), 5.33 (m, 1 H), 5.01 (d, 1 H, *J* = 9.6 Hz), 4.04 (dd, 1 H, *J* = 5.6 Hz, 6.8 Hz), 3.92 (br. s, 1 H), 3.04 (dq, 1 H, *J* = 2.8 Hz, 6.8 Hz), 2.98 (br. s, 1 H), 2.79 (d, 2 H, *J* = 7.2 Hz), 2.76−2.67 (m, 1 H), 2.70 (s, 3 H), 2.34 (m, 1 H), 2.16−2.05 (m, 1 H), 2.09 (s, 3 H), 1.95 (m, 1 H), 1.76 (m, 1 H), 1.62 (m, 1 H), 1.45 (m, 1 H), 1.30−1.10 (m, 2 H), 1.15 (s, 6 H), 1.12 (d, 3 H, *J* = 6.4 Hz), 1.00 (d, 3 H, *J* = 6.8 Hz), 0.81 (s, 9 H), 0.10 (s, 3 H), −0.07 (s, 3 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 217.9, 170.8, 164.6, 152.5, 138.3, 134.6, 124.1, 119.6, 116.1, 79.1, 76.3, 73.3, 53.6, 43.1, 39.2, 38.8, 33.6, 32.0, 28.4, 27.9, 26.2, 24.7, 23.0, 19.2, 18.6, 16.5, 15.3, 14.1, −3.6, −5.4. − IR (neat): $\tilde{\nu}_{max}$ = 3462, 2927, 2855, 1740, 1695, 1507, 1464, 1389, 1261, 1182, 1098. − CIHRMS $[M]^+$ calculated for $C_{32}H_{53}NSSiO_5$: 591.3413, found 591.3412. − $[\alpha]_D^{23}$ = −44.3 (*c* = 0.30, CH_2Cl_2).

Dihydroxy Lactone 45: To a solution of lactone **44** (18 mg, 0.030 mmol) in CH_2Cl_2 (2 mL) was added trifluoroacetic acid (TFA) (0.5 mL). The reaction mixture was stirred at room temperature for 2.5 h before being concentrated under reduced pressure. The residue was diluted with EtOAc (20 mL) and the solution was washed with saturated aqueous $NaHCO_3$ (1 mL). The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (silica gel, 33% EtOAc in hexane) afforded dihydroxy lactone **44** as white foam (13 mg, 90%). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.94 (s, 1 H), 6.58 (s, 1 H), 5.41 (ddt, 1 H, *J* = 4.4 Hz, 10 Hz, 10 Hz), 5.34 (ddt, 1 H, *J* = 4.8 Hz, 10 Hz, 10 Hz), 5.27 (dd, 1 H, *J* = 1.2 Hz, 9.6 Hz), 4.22 (d, 1 H, *J* = 10.8 Hz), 3.71 (br. s, 1 H), 3.32 (br. s, 1 H), 3.12 (dq, 1 H, *J* = 2 Hz, 6.8 Hz), 3.03 (br. s, 1 H), 2.71−2.62 (m, 1 H), 2.68 (s, 3 H), 2.48 (dd, 1 H, *J* = 11.6 Hz, 15.2 Hz), 2.33 (dd, 1 H, *J* = 2.8 Hz, 15.2 Hz), 2.28−2.12 (m, 2 H), 2.06 (d, 3 H, *J* = 0.8 Hz), 2.04−1.96 (m, 1 H), 1.74 (m, 1 H), 1.67 (m, 1 H), 1.38−1.28 (m, 1 H), 1.31 (s, 3 H), 1.26−1.14 (m, 2 H), 1.16 (d, 3 H, *J* = 6.8 Hz), 1.06 (s, 3 H), 0.98 (d, 3 H, *J* = 7.2 Hz). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 220.4, 170.3, 165.0, 152.1, 138.6, 133.5, 125.0, 119.5, 115.9, 78.5, 74.1, 72.5, 53.3, 41.9, 39.3, 38.5, 32.4, 31.8, 27.6, 27.5, 22.6, 19.1, 18.8, 15.8, 15.6, 13.5. − IR (neat): $\tilde{\nu}_{max}$ = 3409, 2923, 1734, 1686, 1464, 1260, 1152, 1092. − CIHRMS $[M + H]^+$ calculated for $C_{26}H_{40}NO_5S$: 478.2627, found 478.2640. − $[\alpha]_D^{23}$ = −82.1 (*c* = 0.28, CH_2Cl_2).

Epothilone A (1): To a solution of dihydroxy lactone **45** (7 mg, 0.0147 mmol) in MeOH (0.3 mL) was added CH_3CN (0.03 mL, 0.575 mmol), $KHCO_3$ (5 mg, 0.05 mmol) and 30% aqueous H_2O_2 (0.03 mL, 0.265 mmol). The reaction mixture was stirred at room temperature for 4 h before additional CH_3CN (0.03 mL, 0.575 mmol), $KHCO_3$ (5 mg, 0.05 mmol) and 30% aqueous H_2O_2 (0.03 mL, 0.265 mmol) was added. Another portion of above reagents was added after 12 h, and the reaction mixture was stirred for another 8 h. The reaction mixture was then passed through a short column of silica gel and eluted with 80% EtOAc in hexane. Concentration and purification by flash chromatography (silica gel, 40% EtOAc in hexane) afforded recovered dihydroxy lactone **82** (2 mg) and epothilone A (**1**) (3 mg, 60% based on recovered starting material). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00 (s, 1 H), 6.56 (s, 1 H), 5.39 (dd, 1 H, *J* = 2 Hz, 9.2 Hz), 4.17 (ddd, 1 H, *J* = 3.2 Hz, 6.4 Hz, 9.6 Hz), 3.74 (ddd, 1 H, *J* = 4 Hz, 4 Hz, 4.8 Hz), 3.67 (d, 1 H, *J* = 6.8 Hz), 3.20 (dq, 1 H, *J* = 4.8 Hz, 6.8 Hz), 3.00 (dt, 1 H, *J* = 8.8 Hz, 4 Hz), 2.88 (dt, 1 H, *J* = 8 Hz, 4 Hz), 2.68 (s, 3 H), 2.51−2.45 (m, 2 H), 2.39 (dd, 1 H, *J* = 3.2 Hz, 14.4 Hz), 2.14−2.06 (m, 1 H), 2.09 (d, 3 H, *J* = 0.8 Hz), 1.86 (dt, 1 H, *J* = 14.8 Hz, 8.8 Hz), 1.76−1.66 (m, 2 H), 1.58−1.35 (m, 1 H), 1.38−1.28 (m, 4 H), 1.35 (s, 3 H), 1.15 (d, 3 H, *J* = 6.8 Hz), 1.07 (s, 3 H), 0.99 (d, 3 H, *J* = 7.2 Hz). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 220.4, 171.1, 165.8, 152.7, 138.3, 120.4, 116.9, 77.4, 75.1, 73.7, 58.0, 55.3, 53.9, 44.0, 39.8, 37.0, 32.3, 31.1, 30.3, 28.0, 24.1, 22.2, 20.5, 19.5, 17.5, 15.8, 14.5. − IR (neat): $\tilde{\nu}_{max}$ = 3464, 2926, 1737, 1689, 978. − CIHRMS $[M + H]^+$ calculated for $C_{26}H_{40}NO_6S$: 494.2576, found 494.2553. − $[\alpha]_D^{23}$ = −42.05 (*c* = 0.20, MeOH).

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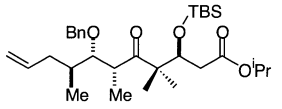

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