Total Synthesis of Epothilone A through Stereospecific Epoxidation of the *p*-Methoxybenzyl Ether of Epothilone C

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Abstract: The total synthesis of epothilone A is described by the coupling four segments **4**–**7a**. Three of the segments, **4**, **5** and **7a**, have only one chiral center; all other chiral centers were introduced by simple asymmetric catalytic reactions. The key steps are the ring opening of epoxide **5** with acetylide **8** for the construction of the C12–C13 *cis* double bond and a practical hydrolytic kinetic resolution (HKR) developed by Jacobsen group for the introduction the chiral center at C3. Especially, the stereospecific epoxidation of 3-*O*-PMB epothilone C **3b** through long-range effect of 3-*O*-PMB protecting group gave high yields of the C12–C13 α-epoxide for the synthesis of target molecule.

Keywords: epothilone · natural products · stereospecific epoxidation · total synthesis

Introduction

Epothilone A (**1**) and B (**2**), first isolated by the Höfle group,[1] represent a new class of macrolides, which has attracted much attention due to their high antitumor activity with the same mechanism of action as Taxol but new chemical structure. Contrary to Taxol, epothilones retain a much greater toxicity against P-glycoprotein overexpressing multiple drug resistant (MDR) cells. Due to the important antitumor activity combined with their relative structural simplicity and better water solubility compared with Taxol, epothilones generated a lot of excitement among synthetic chemists, biologists, and clinicians as a potential development of new powerful anticancer drugs. Many elegant total synthesis of epothilones have been achieved so far.[2] However, the ideal synthetic route for the complex natural product as a promising drug candidate should be of high efficiency, low cost with minimal pollution. It is also essential to avoid low-yield reaction(s) performed at the last step(s) from economical point of view.

Six different groups have synthesized epothilone A so far, where the direct epoxidation of epothilone C **3a** was performed in the last step of the reaction in 46–62.5% yield along with the β-epoxide isomer in 2.9–12.5% yield and other by-products.[3] Recently, the Carriera group[4] synthesized the C12–C13 epoxide in a chain intermediate and finally removed the 3-*O*-TBS protecting group to give epothilone A in 38% yield at the last step. Herein, we report the details of a total synthesis of epothilone A based on simple asymmetric catalytic reactions[5] and through a stereospecific α-epoxidation of the 3-*O*-PMB epothilone C **3b** in high yields within the last two steps in a total of 25 steps and 4.4% overall yield. Retrosynthetic analysis reveals, as shown in Scheme 1, that **3b** can be disconnected into four segments **4**–**7a**; three of the segments, **4**, **5** and **7a**, have only one chiral center, which were easily introduced by asymmetric catalytic Sharpless epoxidation and Jacobsen's *h*ydrolytic *k*inetic *r*esolution (HKR) method.

Results and Discussion

The investigation of the conformation of epothilone A (**1**) in the solid state[1b] and in solution[6] revealed that the 3β-hydroxy group is opposite to the C12–C13 α-epoxide with respect to the macrolide ring plane. Thus, protection of the 3β-hydroxy group of epothilone C **3a** would hamper β-epoxidation at C12–C13 through the long-range interaction. This derivatization should increase the yield of α-epoxidation product. Therefore, we first synthesized 3-*O*-PMB epothilone C

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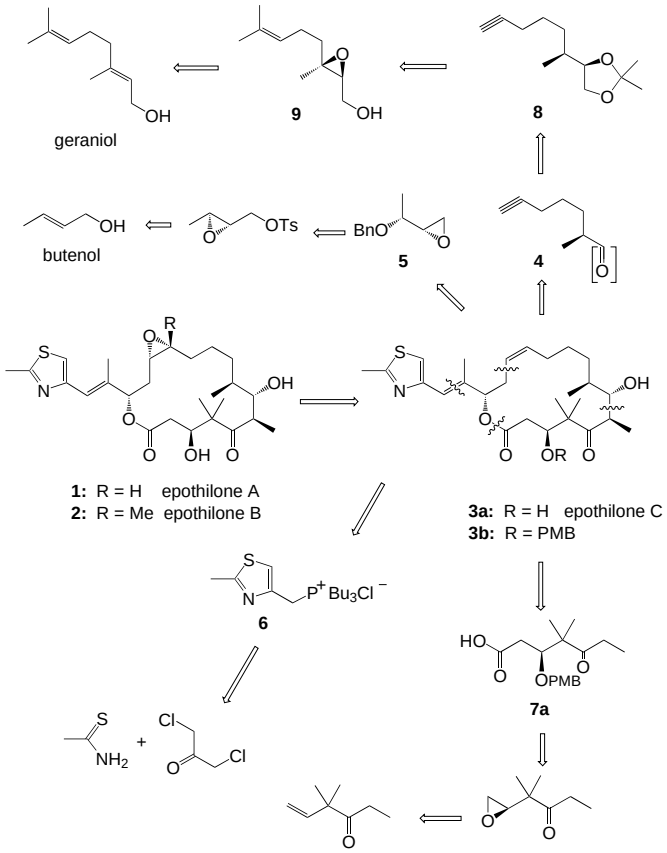
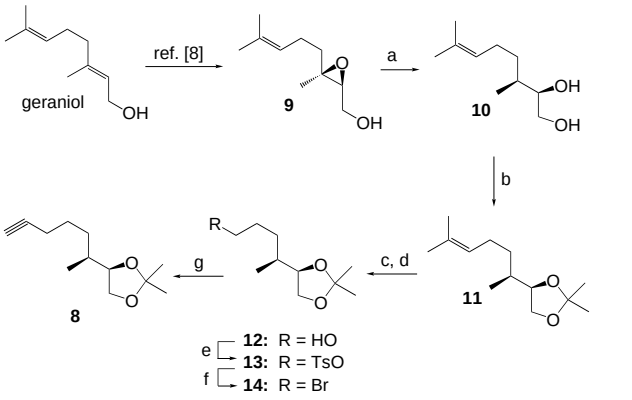


Scheme 1. Retrosynthetic analysis of epothilone A.

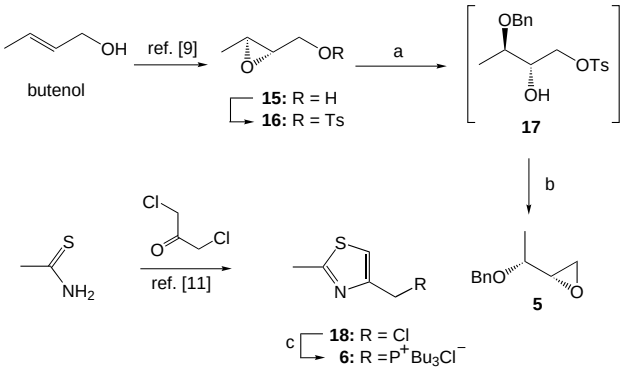
3b and then further epothilone A by stereospecific epoxidation.

The synthesis of acetylide segment **8** was accomplished as depicted in Scheme 2 according to a modified previously reported synthesis.[7] Olefinic epoxide **9**, prepared by catalytic Sharpless epoxidation similar to a known procedure[8] from inexpensive geraniol in 94.1% yield, was converted into olefinic acetonide **11** by stereospecific reduction and acetonization. With this simple functional group interconversion, the olefinic acetonide **11** was converted into acetylide **8** in 46.1% overall yield and eight steps from geraniol.



Scheme 2. Synthesis of acetylide **8**. a) $NaBH_3CN/BF_3 \cdot Et_2O$, THF, RT, 6 h; b) $Me_2C(OMe)_2$, conc. H_2SO_4 (cat.), acetone, 0 °C, 30 min, 62.2% from **9**; c) O_3, CH_2Cl_2, −78 °C, 2 h; d) $LiAlH_4$, Et_2O, 0 °C, 1 h, 90% from **11**; e) TsCl/Py, −10 °C → RT, 6 h; f) LiBr (2 equiv), K_2CO_3 (0.2 equiv), acetone, reflux, 45 min, 91.7% from **12**; g) Na/acetylene, liq. NH_3, −40 °C, 2 h, 95.4%.

Epoxide segment **5** was obtained by employing a Sharpless epoxidation strategy starting from crotyl alcohol (Scheme 3). Tosylate **16**, prepared under literature conditions[9] (99.5% *ee*, 66% yield for two steps in a one-pot reaction), was treated with benzyl alcohol in the presence of Lewis acid[10] to afford alcohol **17**, which was then converted without purification to epoxide fragment **5** by treatment with base in 87% yield (97.8% *ee*) for two steps in a one-pot reaction. Modified Wittig reagent **6** was easily synthesized by heating chloride **18** (synthesized from 1,3-dichloroacetone)[11] and tri-*n*-butylphosphine in 84% yield (over two steps).



Scheme 3. Synthesis of fragments **5** and **6**. a) Benzyl alcohol (1.5 equiv), $BF_3 \cdot Et_2O$ (0.1 equiv), CH_2Cl_2, RT, 1.5 h; b) K_2CO_3 (2.0 equiv), MeOH, RT, 2 h, 87.4% for two steps; c) 70 °C, 4 h, without solvent, 87%.

We wish to report a practical preparation of the important C1 – C6 segment **7a**. The segments **7b**,**c** and the corresponding acetonide of **7c** (from the free diol) have been synthesized (see Scheme 4) using stoichiometric asymmetric reactions,[3c, 12] chiral auxiliary methods,[3d, 13–15] asymmetric Aldol condensation,[16, 17] Sharpless epoxidation,[18, 19] and enzyme-catalyzed kinetic resolution.[20] Our strategy for the synthesis of **7a** is based on the Jacobsen's HKR[21] and methoxycarbonylation of the chiral terminal epoxide[22] as the key steps. This method features high optical purity and easy large-scale preparation. Thus, vinyl ketone **19**[23] was epoxidized with Oxone in mixture solution of acetone and water to give racemic epoxide **20**. The racemic terminal epoxide was then treated under the general procedure of Jacobson's HKR to afford the desired chiral epoxide ketone **21** (>99% *ee*, 48.3% yield) and chiral diol **22** (90% *ee*, 40.5% yield), which can be easily converted into the required epoxide ketone **21** with additional three steps in 66.9% overall yield. Regioselective carbomethoxylation of the chiral terminal epoxide ketone **21** in the presence of $Co_2(CO)_8$ as catalyst and 3-hydroxylpyridine as co-catalyst afforded β-hydroxyester **23** in 65% yield.

At this stage, we first had to consider the selection of a suitable orthogonal protecting group for the hydroxy group in **23** that should also be easily removable at the last steps of the synthesis after introducing C12 – C13 α-epoxide group. 4-Methoxybenzyl (PMB) was preferred since it is stable under acidic conditions necessary for cleavage of the TBS group at

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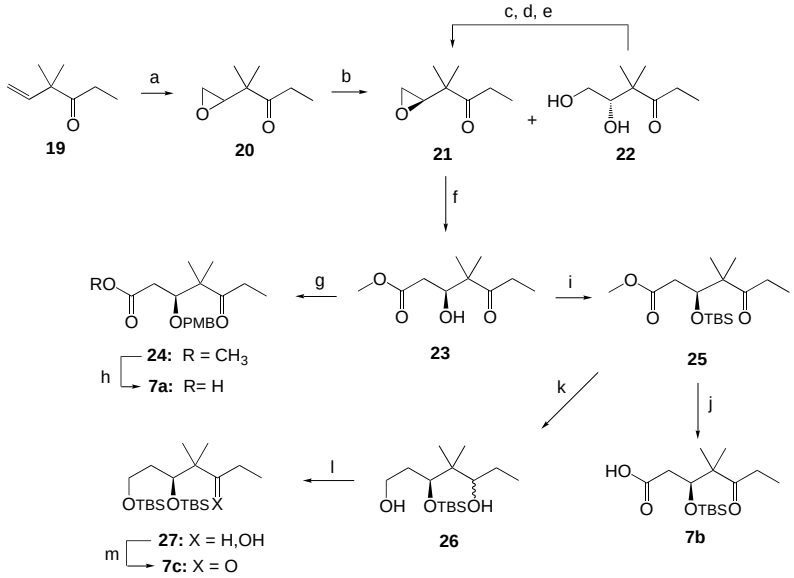
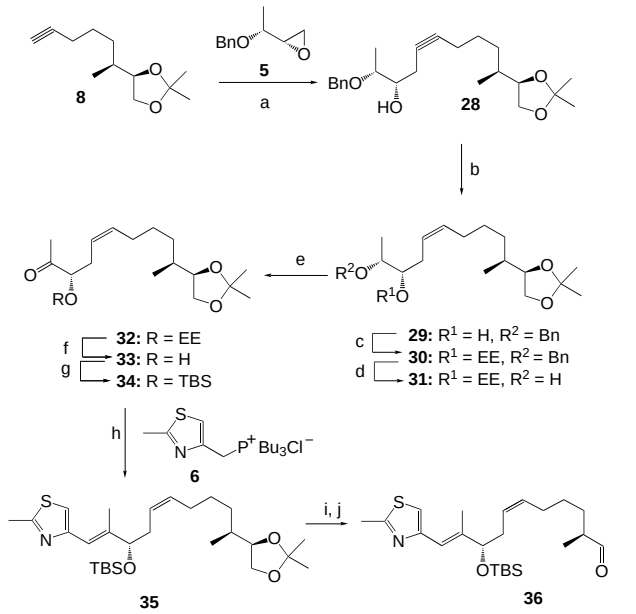


Scheme 4. Synthesis of the C1–C6 fragments **7a**,**b** and **7c**. a) Oxone (1.0 equiv), $NaHCO_3$, acetone/H_2O (1:1), RT, 3 h, 85.6%; b) salen-Co^{III}OAc (2.0 mol%), H_2O (0.6 equiv), RT, 36 h, 48.3% for epoxide **21** (> 99% *ee*) and 40.5% for diol **22** (90% *ee*); c) PhCOCl (1.2 equiv), pyridine, 0 °C, 2 h, then RT, 12 h, 92.1%; d) MsCl/Et_3N, CH_2Cl_2, RT, 12 h; e) K_2CO_3, MeOH, RT, 30 min, 72.6% for two steps; f) 5 mol% $Co_2(CO)_8$, 10 mol% 3-hydroxypyridine, THF/MeOH (1:1), 750 psi CO, 65 °C, 24 h, 65%; g) PMBOC(=NH)CCl_3 (2.0 equiv), CF_3SO_3H (cat.), cyclohexane/CH_2Cl_2 (2:1), RT, 30 min, 95.1%; h) LiOH (1.2 equiv), THF/H_2O (1:1), RT, 5 h, 88.6%; i) TBSOTf (1.3 equiv), 2,6-lutidine (2.1 equiv), CH_2Cl_2, RT, 30 min, 96.4%; j) NaOH (4.9 equiv), *i*PrOH, RT, 6 h, 95%; k) $NaBH_4$ (4.0 equiv), $CaCl_2$ (2.0 equiv), THF/EtOH (4:6), RT, 18 h, 98%; l) TBSCl (1.5 equiv), imidazole (2.5 equiv), DMF, RT, 3 h, 85%; m) Dess–Martin periodinane (1.5 equiv), CH_2Cl_2, RT, 30 min, 96.5%.

C15 and C7 position and can be easily removed by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) under neutral conditions necessary to avoid epoxide opening in the last step. Protection of the 3-hydroxy group of the β-hydroxyester **23** gave **24** in excellent yields, which then was hydrolyzed to keto acid **7a** by saponification with LiOH. The β-hydroxyester **23** is also a key intermediate for the synthesis of the other C1–C6 fragments **7b** and **7c**. Silylation of **23** with *tert*-butyldimethylsilyl triflate (TBSOTf) furnished silyl ether **25**, which was converted to keto acid **7b**[24] by saponification with NaOH. Reduction of **25** with $NaBH_4/CaCl_2$ in a solution of THF/EtOH (2:1) provided diol **26** in excellent yields, which was then converted to ketone **7c**[3b] by selective silylation of the primary hydroxy group and subsequent oxidation of the remaining free secondary hydroxy group in 82% yield over two steps..

After the successful syntheses of the segments **5**, **6**, **7a**, and **8** by simple and practical catalytic asymmetric reactions in order to introduce the necessary chiral centers at C3, C8 and C15, we next focussed on the connection of the four segments to obtain the macrolactone of epothilone A.

The synthesis of the C7–C21 segment by coupling the building blocks **5**, **6** and **8** was accomplished as depicted in Scheme 5. Acetylide anion, prepared by reaction of **8** with *n*BuLi, was treated with the epoxide segment **5** in the presence of $BF_3 \cdot Et_2O$ to give acetylide alcohol **28**, which underwent partial hydrogenation in the presence of Lindlar catalyst. The reaction provided the desired *cis* double bond product **29**[25] in excellent yields. At this stage, it is very important to choose a suitable protecting group for the resulting C15-hydroxy group. Not only should this protecting group be stable, and non-migratable from C16-O to C15-O position in the next reductive cleavage of C16-OBn under strongly basic conditions (Na/liq. NH_3), but it also should be stable in the acidic hydrolysis of the acetonide group and sensitive enough to be removed selectively in the presence of the C3-OH and C7-OH protecting groups for further macrolactonization. In fact, it is rather impossible to select such a protecting group, which meets all above-mentioned requirements. Thus, two different protecting groups were chosen for the C15-OH group. Firstly, the C15-OH group of **29** was protected with the ethoxy ethyl (EE) group to give **30** in excellent yields. Reductive cleavage of the benzyl ether of **30** with Na/liq. NH_3 gave secondary alcohol **31**, which was smoothly oxidized to ketone **32** under Swern conditions. Next, replacement of the EE group of **32** with TBS was accomplished by a two-step procedure.



Scheme 5. Synthesis of C7–C21 fragment **36**. a) *n*BuLi (1.0 equiv), THF, −78 °C, 15 min, then to −40 °C for 40 min, then $BF_3 \cdot Et_2O$ (0.6 equiv) at −78 °C, 10 min; then epoxide **6** (0.5 equiv), −78 °C, 30 min, 89.6%; b) Lindlar catalyst (10 wt %), MeOH, H_2, RT, 1.5 h, 93%; c) vinyl ethyl ether (10 equiv), PPTS (cat.), CH_2Cl_2, RT, 2 h, 96%; d) Na (10 equiv), NH_3 (liq), THF, −78 °C, 30 min, 97.9%; e) Swern oxidation; f) *n*PrOH, PPTS, RT, 2 h; g) TBSCl (2.6 equiv), imidazole (8.7 equiv), DMF, RT, 5 h, 85.3% for 3 steps; h) **7** (3.0 equiv), *t*BuOK (2.5 equiv), THF, 0 °C, 30 min; then **30**, RT, 2 h, 92%; i) $CuCl_2$ (3.0 equiv), CH_3CN, RT, 2 h; j) $NaIO_4$/silica gel, CH_2Cl_2, RT, 15 min, 79.6% over two steps.

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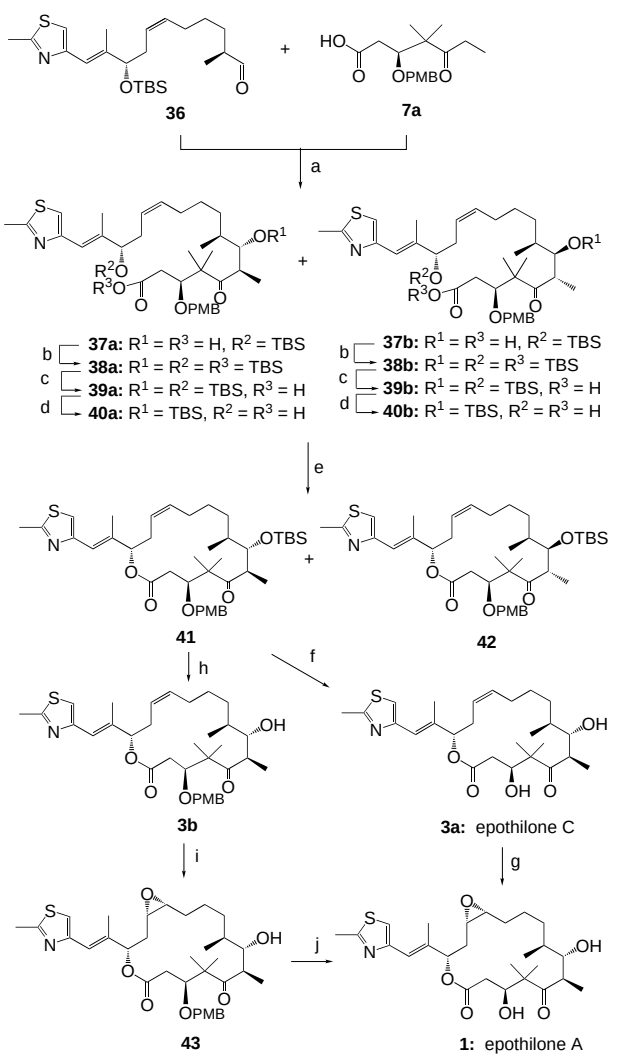
In order to introduce the thiazole side chain stereospecifically with an *E* double bond, Armstrong's method was applied.[26] A modified Wittig reaction of the tributylphosphonium salt **6**[7b, 27] and the silyl ketone **34** with a long chain stereoselectively produces **35** without any *Z* isomer detectable by NMR. Selective hydrolysis of the acetonide of **35** followed by oxidative cleavage of the resulting diol gave the aldehyde **36** in 18 steps and 22.4% overall yield starting from geraniol.

With the synthesis of the C7–C21 segment **36** achieved with a highly stereospecific formation of the *cis* double bond at C12–C13 and the C1–C6 segments **7a** as described above, our next objective was the synthesis of the macrolactone to finish the synthesis of epothilone A.

The convergent approach to epothilone A is shown in Scheme 6. Keto acid **7a** was treated with lithium diisopropylamide (LDA) in THF to generate the dilithio derivative, followed by addition of aldehyde **36** to give a mixture of the desired aldol product **37a** and its (6*S*,7*R*)-diastereoisomer **37b** in ≈1:1 ratio. Since the stereocontrolled Aldol condensation for the synthesis of epothilones had been achieved,[3d, 16, 28] we focussed on the following stereospecific α-epoxidation despite the lack of stereoselectivity in this reaction. Thus, exposure of **37a**,**b** to excess of TBSOTf and 2,6-lutidine gave a mixture of trisilylated products **38a**,**b**, which were then treated with K_2CO_3 in MeOH to afford carboxylic acids **39a**,**b** (72.7%, four steps). Selective removal of TBS group at the C15-OH position was achieved by treatment of **39a**,**b** with tetra-*n*-butylammonium fluoride (TBAF) in THF to generate hydroxy acids **40a**,**b** in 85.3% yield. The macrolactonization reaction was carried out using Yamaguchi method (2,4,6-trichlorobenzoyl chloride, Et_3N, 4-DMAP). Interestingly it turned out that the yields of lactone products did depend on the reaction temperature: The combined yields of **41** and **42** were 35, 44, 60, 81 and 74% under reaction temperatures at 20, 25, 50, 80 and 90 °C, respectively, so that the optimum reaction temperature was 80 °C. At this stage, lactone **41** and **42** can be easily separated by flash chromatography. Exposure of **41** to trifluoroacetic acid (TFA) produced epothilone C **3a** in 88% yield. All spectra data of the synthesized epothilone C are identical to those of an authentic sample.[29] Similarly, (6*S*,7*R*)-isomer of epothilone C was obtained from **42**. Direct epoxidation of epothilone C **3a** with 3,3-dimethyldioxirane (DMDO) provided epothilone A **1** (52% yield) and its β-epoxide isomer (10%). The results for the non-stereospecific epoxidation are similar to those achieved by other groups for the direct epoxidation of epothilone C.[3, 30]

Therefore, we were interested in opening a new access to the C12–C13 epoxide by a stereospecific α-epoxidation. Still crucial for this goal was an adequate protection of the 3β-hydroxy group in epothilone C which would direct stereoselective α attack at C12–C13 double bond by long-range interactions. Thus, selective desilylation of 7-OTBS with HF·py led to 3-*O*-PMB epothilone C **3b** in 91% yield. Then, exposure of **3b** to DMDO in CH_2Cl_2 at −35 °C provided the desired α-epoxide product **43** in 88% yield without β-epoxide isomer detectable by ^1H NMR spectroscopy. Finally, smooth removal of the 3-*O*-PMB protecting group in **43** with DDQ under neutral conditions furnished epothilone A **1** in 93% yield.[31] All spectral data of the synthesized epothilone A **1** are identical to those of an authentic sample.[29]



Scheme 6. Total synthesis of epothilone A. a) LDA (6.0 equiv), THF, 0 °C, 15 min; then **7a** (3.0 equiv), THF, −78 °C, 15 min, then −40 °C for 30 min; then **36** (1.0 equiv), THF, −78 °C, 10 min; b) TBSOTf (6.0 equiv), 2,6-lutidine (10.0 equiv), CH_2Cl_2, 0 °C, 2 h; c) K_2CO_3 (6.0 equiv), MeOH, 25 °C, 15 min, 72.2% for a mixture of **39a**/**39b** (ca. 1:1); d) TBAF (6.4 equiv), THF, RT, 8 h, 85.3%; e) 2,4,6-trichlorobenzoylchloride (7.5 equiv), Et_3N (8.3 equiv), THF, RT, 15 min; then toluene, add to 4-DMAP (10 equiv) in toluene, 80 °C, 3 h, 40.5% for **41** and 40.5% for **42;** f) 20% CF_3COOH, CH_2Cl_2, 0 °C, 1 h, 88%; g) 3,3-dimethyldioxirane, CH_2Cl_2, −30 °C, 1 h, epothilone A (**1**) (52%) and its β-epoxide diastereoisomer (10%) (5:1); h) HF·pyridine, THF, RT, 2 h, 91%; i) same as g), 88%; j) DDQ (2.6 equiv), CH_2Cl_2/H_2O (20:1), RT, 1 h, 93%.

Conclusion

We have presented an efficient synthesis of epothilone A based on utilizing simple catalytic asymmetric reactions for the formation of crucial chiral centers using the acetylide opening epoxide strategy for the highly stereoselective construction of *cis* double bond at C12–C13 and Jacobsen's HKR as key step for the practical synthesis of C1–C6 fragment. We would like to emphasize that the methodologies

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used, especially the directed α-epoxidation and the usage of the 3-*O*-PMB protecting group would be useful for the future syntheses of epothilones and their analogues.

Experimental Section

General: Solvents were dried by standard procedures and redistilled under N_2 atmosphere prior to use. All reactions were routinely performed under N_2 atmosphere unless otherwise indicated. Flash chromatography was accomplished using silica gel H (10–40 μm). Analytical thin-layer chromatography (TLC) was performed on precoated glass-backed plates (F_{254}) and visualized by using either a UV lamp, phosphomolybdic acid (PMA), sulfuric acidic/vanilline, or potassium permanganate solution. Melting points are uncorrected. ^{1}H NMR spectra were recorded on Bruker AM 300 spectrometer. IR spectra were recorded on Perkin–Elmer 983 spectrometer. Mass Spectra were recorded on HP-5989 spectrometer; high-resolution mass spectra were obtained on Finnigan MAT 8430 spectrometer (reference PFK, peak matching method, accuracy ± 2 ppm). Optical rotations were measured on a Perkin–Elmer 241 polarimeter.

(1*R*)-1-[(2*S*)-Oxiran-2-yl]-1-(benzyloxy)ethane (5): A solution of **16** (4.085 g, 16.86 mmol) in CH_2Cl_2 (30 mL) was cooled to 0 °C, benzyl alcohol (2.6 mL, 25.3 mmol, 1.5 equiv) and $BF_3 \cdot Et_2O$ (0.2 mL, 1.58 mmol, 0.1 equiv) were added. The mixture was stirred for 1.5 h at RT, then concentrated under reduced pressure. The residue was dissolved in MeOH (30 mL), and K_2CO_3 (4.66 g, 33.7 mmol, 2 equiv) was added. After the solution was vigorously stirred for 2 h at RT, the mixture was concentrated under reduced pressure to remove most of the MeOH. The residue was diluted with Et_2O (60 mL), washed with water and brine, dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography to give **6** (2.626 g, 87.4 %) as a colorless oil. $[\alpha]_D^{20} = -8.4$ ($c = 1.5$, $CHCl_3$); MS: *m*/*z* (%): 178 (0.76) [M^+], 107 (38.18), 108 (11.93), 91 (100), 65 (13.53); IR (film): $\tilde{\nu}_{max} = 3064$, 3032, 2982, 2870, 1497, 1454, 1372, 1105, 1072, 923, 738, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.38-7.26$ (m, 5H, Ph-H), 4.63, 4.57 (AB, $J_{AB} = 11.8$ Hz, 2H, OCH_2Ph), 3.43 (td, $J = 6.4$, 11.9 Hz, 1H), 2.96 (ddd, $J = 2.7$, 3.8, 5.5 Hz, 1H), 2.80 (dd, $J = 3.9$, 5.0 Hz, 1H), 2.71 (dd, $J = 2.7$, 5.2 Hz, 1H), 1.31 (d, $J = 6.4$ Hz, 3H, CH_3CH); elemental analysis calcd for $C_{11}H_{14}O_2$ (178.23): C 74.13, H 7.92; found: C 73.89, H 8.01.

[(2-Methylthiazol-4-yl)-methyl]-tri-*n*-butylphosphonium chloride (6): A mixture of 4-chloromethyl-2-methyl-thiazole (**18**; 21.17 g, 158.6 mmol) and tri-*n*-butylphosphine (33.6 g, 166 mmol) was heated under stirring at 70 °C for 4 h and the mixture was cooled to RT, followed by the addition of anhydride Et_2O (200 mL), led to the precipitation of **6** as hygroscopic crystals (46.3 g, 87 %). IR (KBr): $\tilde{\nu}_{max} = 3057$, 2959, 2931, 2872, 1517, 1465, 1187, 1098, 954, 918, 806, 718cm^{-1}; MS: *m*/*z* (%): 314 (15.65) [$M^+ - Cl$], 313 (100) [$M^+ - HCl$], 284 (22.21), 257 (18.22), 200 (11.48), 172 (16.68), 113 (47.17), 41 (11.59); ^{1}H NMR (300 Mz, $CDCl_3$): $\delta = 7.75$ (d, $J = 3.2$ Hz, 1H), 4.38 (d, $J = 14.5$ Hz, 2H), 2.67 (s, 3H), 2.47–2.37 (m, 6H), 1.51–1.46 (m, 12H), 0.95 (t, $J = 6.9$ Hz, 9H); HRMS: calcd for $C_{17}H_{33}NSP$ [$M^+ - Cl$]: 314.2073; found: 314.2068.

(3*S*)-3-(4-Methoxybenzyloxy)-4,4-dimethyl-5-oxo-heptanoic acid (7a): H_2O (25 mL) and $LiOH \cdot H_2O$ (203 mg, 4.85 mmol) were added to solution of ester **24** (1.315 g, 4.08 mmol) in THF (25 mL). The mixture was stirred for 5 h at RT. The solution was concentrated under reduced pressure to remove THF. The resulting aqueous phase was washed with CH_2Cl_2 (5 × 10 mL) and acidified with a 1M $KHSO_4$ solution to pH 4–5. The aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo to give acid **7a** (1.114 g, 88.6 %) as a yellowish oil. $[\alpha]_D^{20} = -17.7$ ($c = 2.2$, $CHCl_3$); MS: *m*/*z* (%): 307 (0.52) [$M^+ - H$], 172 (1.42), 137 (14.06), 122 (11.14), 121 (100), 57 (10.64); IR (film): $\tilde{\nu}_{max} = 2976$, 2936, 1709, 1614, 1515, 1468, 1249, 1088, 822 cm^{-1}; ^{1}H MNR (300 MHz, $CDCl_3$): $\delta = 9.18$ (br s, 1H, CO_2H), 7.18 (d, $J = 8.2$ Hz, 2H, Ar-H), 6.84 (d, $J = 8.2$ Hz, 2H, Ar-H), 4.57, 4.39 (AB, $J_{AB} = 10.8$ Hz, 2H, $ArCH_2O$), 4.24 (dd, $J = 4.5$, 6.7 Hz, 1H, CH-OPMB), 3.77 (s, 3H, Ar-OCH_3), 2.65–2.38 (m, 4H, $COCH_2CH_3$, CH_2CO_2H), 1.19 [s, 3H, $C(CH_3)_2$], 1.10 [s, 3H, $C(CH_3)_2$], 0.99 (t, $J =$ 7.1 Hz, 3H, CH_3CH_2); elemental analysis calcd for $C_{17}H_{24}O_5$ (308.37): C 66.21, H 7.84; found: C 65.99, H 8.05.

(3*S*)-3-(*tert*-Butyldimethylsilyloxy)-4,4-dimethyl-5-oxo-heptanoic acid (7b): NaOH (63 mg, 1.58 mmol, 4.9 equiv) was added to a solution of **25** (100 mg, 0.32 mmol) in isopropanol (8 mL). After being stirred for 6 h at RT, the reaction mixture was quenched by addition of 1M $KHSO_4$ to adjust the pH to 4–5. The mixture was extracted with EtOAc (3 × 20 mL), and the combined organic phases were washed with saturated aqueous NH_4Cl and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography to obtain acid **15** (91 mg, 95 %) as a viscous, colorless oil. $[\alpha]_D^{20} = -17.7$ ($c = 0.8$, $CHCl_3$); $[\alpha]_D^{22} = +16.1$ ($c = 1.0$, $CHCl_3$)[3b]; MS: *m*/*z* (%): 303 (93.43) [M^++H], 302 (100), 285 (48.32), 245 (32.14), 203 (88.75), 153 (57.1), 75 (82.28), 57 (78.25); IR (film): $\tilde{\nu}_{max} = 2957$, 2933, 1713, 1473, 1255, 1093, 837 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.48$ (dd, $J = 3.7$, 6.9 Hz, 1H, CHOSi), 2.59–2.47 (m, 3H, CH_2CH_3, CH_2COOH), 2.33 (q, $J = 7.0$ Hz, 1H, CH_2CH_3), 1.14 [s, 3H, $C(CH_3)_2$], 1.09[s,3H, $C(CH_3)_2$], 1.01 (t, $J = 7.0$ Hz, 3H, CH_3CH_2), 0.85 [s, 9H, $(CH_3)_3C$], 0.06 [s, 3H, $Si(CH_3)_2$], 0.04 [s, 3H, $Si(CH_3)_2$]; HRMS(EI): calcd for $C_{11}H_{21}O_4Si$: 245.1210; found: 245.1222 [$M^+ - t$Bu].

(5*S*)-5,7-Di-(*tert*-Butyldimethylsilyloxy)-4,4-dimethylheptan-3-one (7c): Imidazole (37 mg, 0.55 mmol, 2.5 equiv) and TBSCl (50 mg, 0.33 mmol, 1.5 equiv) were added to a solution of diol **26** (64 mg, 0.22 mmol) in dry DMF (2 mL). The reaction mixture was stirred at RT for 3 h and quenched with slowly addition of MeOH (1 mL). The mixture was diluted with Et_2O (30 mL) and washed with water and brine, dried over Na_2SO_4. Removal of the solvent afforded **27** (76 mg, 85 %) as a colorless oil, which was used for preparation of **18** without further purification.

Dess–Martin periodinane (119 mg, 0.28 mmol, 1.5 equiv) was added to a solution of **27** (76 mg, 0.19 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred for 30 min at RT and quenched with addition of saturated aqueous $Na_2S_2O_3$ (2 mL) and saturated aqueous $NaHCO_3$ (2 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography of the residue afforded **7c** (73 mg, 96.5 %) as a colorless oil. $[\alpha]_D^{20} = -8.4$ ($c = 1.20$, $CHCl_3$); [lit:[3b] $[\alpha]_D^{22} = -7.3$ ($c = 1.8$, $CHCl_3$)]; MS: *m*/*z* (%): 387 (9.24), 345 (7.93), 303 (100), 187 (88.47), 171 (49.37), 89 (37.96), 57 (52.09); IR (film): $\tilde{\nu}_{max} = 2938$, 2859, 1708, 1473, 1388, 1257, 1098, 940, 837, 776 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.06$ (dd, $J = 3.2$, 7.3 Hz, 1H, CHOSi), 3.63–3.58 (m, 2H, CH_2OSi), 2.51 (q, $J = 7.2$ Hz, 2H, CH_2CH_3), 1.51–1.47 (m, 2H, CH_2CH_2OSi), 1.10 [s, 3H, $C(CH_3)_2$], 1.04 [s, 3H, $C(CH_3)_2$], 0.99 (t, $J =$ 7.2 Hz, 3H, CH_3CH_2), 0.88 [s, 18H, $SiC(CH_3)_3$], 0.088 [s, 6H, $Si(CH_3)_2$], 0.032[s, 6H, $Si(CH_3)_2$].

4-Chloromethyl-2-methyl-thiazole (18): The title compound (27.5 g, 92.9 %) was prepared from thioacetamide (15 g) and 1,3-dichloro-propan-2-one (25 g) by the method of Hooper.[11]

(±)-2-Methyl-2-oxiranylpentan-3-one (20): 4,4-Dimethyl-5-hexen-3-one (**8**; 10.0 g, 80 mmol), acetone (100 mL), H_2O (100 mL) and EDTA (30 mg) were combined under stirring in a 500 mL three-necked flask. The solution was cooled to 0–5 °C, then a mixture of Oxone (48.5 g, 80 mmol, 1.5 equiv) and $NaHCO_3$ (48.5 g) were added in several portions. The mixture was stirred for 3 h at RT and was subsequently filtered under reduced pressure. The filtrate was extracted with CH_2Cl_2 (2 × 50 mL). The organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was distilled in vacuo to give pure **20** (9.644 g, 85.6 %) as a colorless oil. B.p. 90–92 °C at 20 mm Hg; IR (film): $\tilde{\nu}_{max} = 2980$, 1711, 1378, 1365, 1101, 974, 834 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.05$ (dd, $J = 4.3$, 2.8 Hz, 1H), 2.75 (dd, $J = 8.7$, 4.3 Hz,1H), 2.64 (dd, $J = 4.3$, 2.8 Hz, 1H), 2.59 (q, $J = 7.1$ Hz, 2H), 1.10 (s, 3H), 1.07 (s, 3H), 1.05 (t, $J = 7.1$ Hz, 3H); MS: *m*/*z* (%): 142 (1.81) [M^+], 113 (2.55), 85 (16), 69 (18), 57 (100), 55 (44), 41 (24); HRMS(EI): calcd for $C_8H_{14}O_2$: 142.0994; found: 142.1035.

Hydrolytic kinetic resolution of racemic epoxide 20: A mixture of racemic epoxide **20** (7.0 g, 49.2 mmol), salen-Co^{III}OAc catalyst (670 mg, 0.98 mmol, 1.99 mol %) and H_2O (531 mg, 29.5 mmol, 0.60 equiv) was stirred for 36 h at RT. The reaction mixture was bulb-to-bulb distilled under reduced pressure to give a mixture of the chiral epoxide **21** and diol **22**. The crude product was purified by flash chromatography to give **21** (3.384 g, 48.3 %) and diol **22** (3.192 g, 40.5 %).

2-[(2*R*)-Oxiran-2-yl]-2-methylpentan-3-one (21): $[\alpha]_D^{20} = +16.1$ ($c = 2.2$, $CHCl_3$); >99% *ee* (determined by HPLC analysis with a Chiralpak AS column, λ 284 nm); IR (film): $\tilde{\nu}_{max} = 2980, 1711, 1378, 1365, 1101, 974, 834\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.05$ (dd, $J = 4.3, 2.8$ Hz, 1H), 2.75 (dd, $J = 8.7, 4.3$ Hz, 1H), 2.64 (dd, $J = 4.3, 2.8$ Hz, 1H), 2.59 (q, $J = 7.1$ Hz, 2H), 1.10 (s, 3H), 1.07 (s, 3H), 1.05 (t, $J = 7.1$ Hz, 3H); MS: *m/z* (%): 142 (1.81) [M^+], 113 (2.55), 85 (15.83), 69 (18.52), 57 (100), 55 (43.58), 41 (23.72); elemental analysis calcd for $C_8H_{14}O_2$ (142.20): C 67.57, H 9.92; found: C 67.61, H 9.86.

(5*S*)-5,6-Dihydroxy-4,4-dimethylhexan-3-one (22): $[\alpha]_D^{20} = +10.4$ ($c = 1.9$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3416, 2976, 1702, 1469, 1388, 1089, 1019, 972\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 4.14$ (dd, $J = 4.9$ Hz, 10.3 Hz, 1H), 3.86 (d, $J = 10.3$ Hz, 1H), 3.81–3.72 (m, 1H), 3.71–3.58 (m, 2H), 2.53 (q, $J = 7.4$ Hz, 1H), 1.63 (q, $J = 7.4$ Hz, 1H), 1.18 (s, 6H), 1.10–0.89 (m, 3H); MS: *m/z* (%): 161 (5.59) [M^++H], 143 (100), 131 (2), 85 (15), 71 (29), 57 (47); elemental analysis calcd for $C_8H_{16}O_3$ (160.21): C 59.98, H 10.06; found: C 60.29, H 10.00.

Conversion of diol 22 to epoxide 21: Benzoyl chloride (0.9 mL, 7.5 mmol, 1.5 equiv) was added to a solution of diol **22** (0.8 g, 5.0 mmol) in dry pyridine (20 mL) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C, then allowed to warm to RT and stirred for additional 12 h, after which time no starting material was detected by TLC. Methanol (1 mL) was added to quench the reaction. The mixture was diluted with EtOAc (20 mL), washed with H_2O, saturated aqueous $CuSO_4$ solution and brine. The organic phase was dried over Na_2SO_4, filtered and concentrated in vacuo. Flash chromatography of the residue provided pure benzoylate of **22** (0.538 g, 92.1%) as a wax-like product. $[\alpha]_D^{20} = +22.9$ ($c = 1.3$, $CHCl_3$); 90% *ee* (determined by chiral HPLC); MS: *m/z* (%): 264 (0.14) [M^+], 247 (15.69), 143 (57.88), 105 (100), 77 (88.36), 68 (23.61), 57 (31.43); IR (film): $\tilde{\nu}_{max} = 3491, 3066, 2978, 1720, 1603, 1452, 1276, 1121, 713\ cm^{-1}$; ^1H NMR (300 MHz, CDCl3): $\delta = 8.03$ (d, $J = 7.8$ Hz, 2H), 7.57 (t, $J = 7.5$ Hz, 1H), 7.46 (dd, $J = 7.5, 7.8$ Hz, 2H), 4.55 (dd, $J = 2.8, 11.7$ Hz, 1H), 4.32 (dd, $J = 7.3, 11.7$ Hz, 1H), 4.11 (dd, $J = 2.8, 7.3$ Hz, 1H), 2.56 (q, $J = 7.1$ Hz, 2H), 1.27 (s, 3H), 1.26 (s, 3H), 1.02 (t, $J = 7.1$ Hz, 3H); elemental analysis calcd for $C_{15}H_{20}O_4$ (264.32): C 68.16, H 7.63; found: C 67.99, H7.43.

Triethylamine (1 mL, 7.2 mmol, 4.5 equiv) and tosyl chloride (0.5 mL, 6.4 mmol, 4.0 equiv) were added at 0 °C to a solution of benzoylate of **22** (0.417 g, 1.58 mmol) in CH_2Cl_2 (50 mL). The reaction mixture was allowed to warm to RT and stirred for 12 h. After completion of the reaction, methanol (1 mL) was added, followed by H_2O (10 mL). The organic phase was separated, washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the tosylate (0.392 g) as a yellowish oil, which was used in the next step without further purification.

Thus, the tosylate (0.392 g, 1.14 mmol) prepared above was dissolved in MeOH (20 mL). K_2CO_3 (0.275 g, 2.0 mmol, 1.8 equiv) was added at RT. The reaction mixture was vigorously stirred for 1 h, and H_2O (20 mL) was added. Most of methanol was removed under reduced pressure, and the resulting residue was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over ($MgSO_4$) and concentrated in vacuo. Purification of the residue by flash chromatography gave pure **21** (0.163 g, 72.6% from **11a**) as a colorless oil. $[\alpha]_D^{20} = +15.0$ ($c = 1.6$, $CHCl_3$); 90% *ee* (determined by chiral HPLC).

Methyl (*S*)-3-hydroxy-4,4-dimethyl-5-oxo-heptanoate 23: An autoclave was charged under air with $Co_2(CO)_8$ (1.0 g, 2.93 mmol) and 3-hydroxypyridine (0.555 g, 5.84 mmol). THF (20 mL) and MeOH (20 mL) were added, followed by chiral epoxide **21** (8.5 g, 59.8 mmol). The reaction vessel was flushed three times with CO gas and then charged to a pressure of 750 psi (≈50 bar). After the reaction mixture was heated and stirred for 24 h at 65 °C, the autoclave was cooled to RT, and the excess gas was released carefully; the reaction mixture was poured into Et_2O (200 mL) to precipitate the catalyst mixture. The suspension was stirred under air for 2 h and then filtered through a plug of Celite. The solvents was removed under reduced pressure, and the crude product was purified by flash chromatography to give pure β-hydroxyester **23** (7.238 g, 65%) as a colorless oil. $[\alpha]_D^{20} = -32.4$ ($c = 1.4$, $CHCl_3$), 99.8% *ee* [determined by chiral HPLC with an Chiralpak OJ column; mobile phase: *n*-hexane/*i*PrOH (80:20)]; λ 214nm); MS: *m/z* (%): 203 (37.98) [M^++H], 185 (7.71), 143 (9.30), 103 (10.10), 91 (72.14), 71 (79.13), 57 (96.67), 43 (100); IR (film): $\tilde{\nu}_{max} = 3511, 2978, 1740, 1703, 1439, 1369, 1175, 973\ cm^{-1}$; ^1H MNR (300 MHz, $CDCl_3$): $\delta = 4.22–4.16$ (m, 1H, CHOH), 3.67 (s, 3H, CO_2CH_3), 3.35 (d, $J = 4.5$ Hz, 1H, OH), 2.60–2.44 (m, 2H), 2.40–2.34 (m, 2H), 1.12 [s, 3H, $C(CH_3)_2$], 1.09 [s, 3H, $C(CH_3)_2$], 0.98 (t, $J = 7.1$ Hz, 3H, CH_3CH_2); elemental analysis calcd for $C_{10}H_{18}O_4$ (202.25): C 59.39, H 8.97; found: C 59.35, H 9.08.

Methyl (3*S*)-3-(4-methoxybenzyloxy)-4,4-dimethyl-5-oxo-heptanoate (24): A solution of **23** (1.011 g, 5 mmol) in CH_2Cl_2 (5 mL) and cyclohexane (10 mL) was added $Cl_3CC(=NH)OPMB$ (10.5 mL, 0.955 M in CH_2Cl_2, 10 mmol, 2 equiv) and CF_3SO_3H (22 μL, 0.25 mmol). The reaction mixture was stirred for 30 min at RT and then filtered. The filtrate was diluted with Et_2O, and washed with water, sat. $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography to yield **24** (1.533 g, 95.1%) as a colorless oil. $[\alpha]_D^{20} = -9.8$ ($c = 1.45$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 2970, 1739, 1704, 1614, 1515, 1250, 1089, 822\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.16$ (d, $J = 8.2$ Hz, 2H), 6.84 (d, $J = 8.2$ Hz, 2H), 4.51, 4.36 (AB, $J_{AB} = 10.8$ Hz, 2H), 4.22 (t, $J = 5.8$ Hz, 1H), 3.78 (s, 3H), 3.67 (s, 3H), 2.50 (q, $J = 7.1$ Hz, 2H), 2.45 (d, $J = 5.8$ Hz, 2H), 1.12 (s, 3H), 1.07 (s, 3H), 1.0 (t, $J = 7.1$ Hz, 3H); MS: *m/z* (%): 322 (0.34) [M^+], 321 (1.65) [$M^+ - H$], 248 (4), 1.86 (2), 121 (100), 57 (12); elemental analysis calcd for $C_{18}H_{26}O_5$ (322.40): C 67.06, H 8.13; found: C 67.32, H 8.43.

Methyl (3*S*)-3-(*tert*-butyldimethylsilyloxy)-4,4-dimethyl-5-oxo-heptanoate (25): 2,6-Lutidine (1.0 mL, 8.6 mmol, 2.1 equiv) and TBSOTf (1.2 mL, 5.2 mmol, 1.3 equiv) were slowly added at 0 °C to a solution of β-hydroxyester **23** (0.831 g, 4.1 mmol) in CH_2Cl_2 (30 mL). The reaction mixture was allowed to warm to RT and stirred for 30 min. The mixture was diluted with EtOAc (30 mL) and washed with 1% HCl aqueous solution and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography afforded **25** (1.254 g, 96.4%) as a colorless oil. $[\alpha]_D^{20} = -22.5$ ($c = 1.0$, $CHCl_3$); MS: *m/z* (%): 317 (81.41) [M^++H], 301 (24.21) [$M^+ - Me$], 285 (9.96), 259 (93.42), 243 (25.69), 217 (100), 187 (21.73), 159 (23.16), 57 (10.51); IR (film): $\tilde{\nu}_{max} = 2956, 2859, 1743, 1707, 1473, 1256, 1092, 838, 778\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 4.48$ (dd, $J = 3.8, 7.0$ Hz, 1H, CHOSi), 3.66 (s, 3H, CO_2CH_3), 2.62–2.40 (m, 3H, CH_2CO_2Me, CH_2CH_3), 2.29 (q, $J = 7.0$ Hz, 1H, CH_2CH_3), 1.12 [s, 3H, $C(CH_3)_2$], 1.07 [s, 3H, $C(CH_3)_2$], 0.99 (t, $J = 7.1$ Hz, 3H, CH_3CH_2), 0.83 [s, 9H, $C(CH_3)_3$], 0.054 [s, 3H, $Si(CH_3)_2$], −0.0007 (s, 3H, $Si(CH_3)_2$); HRMS: calcd for $C_{12}H_{23}O_4Si$ ($C_{16}H_{32}O_4Si - t$Bu): 259.1367; found: 259.1396.

(3*S*)-3-(*tert*-Butyldimethylsilyloxy)-4,4-dimethylheptane-1,5-diol (26): $NaBH_4$ (48 mg, 1.27 mmol, 4.0 equiv) and $CaCl_2$ (70 mg, 0.63 mmol, 2.0 equiv) were added to a solution of **25** (100 mg, 0.32 mmol) in THF/EtOH (4:6, 10 mL). The reaction mixture was stirred for 18 h at RT and quenched with saturated aqueous NH_4Cl solution. The phases were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography to furnish diol **26** (90 mg, 98%) as a viscous, colorless oil. MS: *m/z* (%): 291 (6.99), 273 (9.05), 257 (7.68), 215 (42.79), 189 (77.54), 131 (91.46), 89 (35.57), 75 (100), 59 (44.36); IR (film): $\tilde{\nu}_{max} = 3321, 2960, 1473, 1388, 1257, 1099, 1082, 837, 776, 669\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.74–3.55$ (m, 4H), 3.29 (br d, $J = 10.3$ Hz, 1H), 2.45 (br s, 1H), 1.97–1.93 (m, 1H), 1.90–1.70 (m, 1H), 1.52–1.46 (m, 1H), 1.27–1.18 (1H), 0.96–0.89 (m, 3H), 0.84 (s, 9H), 0.83 (s, 3H), 0.70 (s, 3H), 0.058 (s, 3H), 0.009 (s, 3H).

[(2*S*,3*R*)-3-Methyloxiran-2-yl]methyl tosylate (16):[9] Crushed, activated 3 Å molecular sieves (3.0 g) were introduced into a flame-dried 500 mL flask under nitrogen. After the flask was flushed for several minutes with N_2, CH_2Cl_2 (200 mL) was added and the flask was cooled to −20 °C. L-(+)-Diisopropyl tartrate (DIPT) (1.42 g, 6.0 mmol), (*E*)-2-buten-1-ol (7.21 g, 100 mmol), and $Ti(OiPr)_4$ (1.42 g, 5.0 mmol) were added sequentially. The mixture was stirred for 15 min at −20 °C, and a solution of *tert*-butyl hydroperoxide (TBHP) (5.0 M in CH_2Cl_2, 40 mL, 200 mmol, 2 equiv) was added dropwise. The reaction mixture was stirred for 2 h at −20 °C. Careful quenching of the excess TBHP was accomplished by the slow addition of tri-*n*-butylphosphine (24.9 mL, 100 mmol, 1 equiv) at −20 °C. A solution of trimethylamine (21 mL, 149 mmol), 4-DMAP (1.5 g, 12 mmol), and *p*-toluenesulfonyl chloride (19.1 g, 100 mmol) in CH_2Cl_2 (100 mL) was then added. After being stirred for 30 h at −10 °C, the reaction mixture was filtered through Celite and washed with CH_2Cl_2. The filtrate was then washed with 10% tartaric acid, saturated $NaHCO_3$, and saturated NaCl.

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The organic layer was dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure, and the crude oil was re-crystallized twice (Et_2O/petroleum ether) to yield **16** (16.696 g, 69%) as white needles. $[\alpha]_D^{20} = -33.7$ ($c = 1.0$, $CHCl_3$); [lit:[8] $[\alpha]_D^{20} = -34.1$ ($c = 2.90$, $CHCl_3$); 99.5% *ee* (determined by chiral HPLC); MS: *m/z* (%): 243 [M^++H] (1.61), 199 (3.53), 155 (92.15), 139 (5.49), 91 (100), 71 (19.66), 65 (27.11), 43 (23.32); IR (KBr): $\tilde{\nu}_{max} = 3009$, 2957, 1597, 1494, 1450, 1176, 958, 877, 826, 814, 790, 668 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.79$ (d, $J = 8.2$ Hz, 2H, Ar-H), 7.31 (d, $J = 8.2$ Hz, 2H, Ar-H), 4.17 (dd, $J = 3.8$, 11.8 Hz, 1H, TsO-CH_2), 3.97 (dd, $J = 5.8$, 11.8 Hz, 1H, TsO-CH_2), 3.06–2.80 (m, 2H), 2.44 (s, 3H, Ar-CH_3), 1.29 (d, $J = 5.2$ Hz, 3H, CH_3CH); elemental analysis calcd for $C_{11}H_{14}O_4S$ (242.29): C 54.53, H 5.82; found: C 54.35, H 5.71.

(2*R*,3*S*,10*S*)-2-Benzyloxy-10-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-undec-5-yn-3-ol (28): A solution of **8** (2.891 g, 14.738 mmol) in THF (15 mL) was cooled to $-78\,^\circ C$, and *n*BuLi (1.6 M in cyclohexane, 9.2 mL, 14.73 mmol, 1 equiv) was added. After being stirred for 15 min, the solution was allowed to warm to $-40\,^\circ C$, and after 40 min at that temperature, it was re-cooled to $-78\,^\circ C$. $BF_3 \cdot Et_2O$ (1.12 mL, 8.34 mmol, 0.57 equiv) was added. A solution of epoxide **5** (1.312 g, 7.36 mmol, 0.50 equiv) was added dropwise after 10 min, and the resulting mixture was stirred for 30 min at $-78\,^\circ C$, and then quenched with saturated aqueous NH_4Cl solution (5 mL). The mixture was warmed to RT and extracted with EtOAc (3×30 mL). The combined organic layers were washed with water, 10% aqueous $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4, and filtered. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography to furnish alcohol **24** (2.470 g, 89.6%) as a colorless oil. $[\alpha]_D^{20} = -40.3$ ($c = 0.5$, $CHCl_3$); MS: *m/z* (%): 374 (0.88) [M^+], 359 (1.35) [$M^+ -$ Me], 317 (11.18), 299 (40.49), 209 (15.22), 181 (17.72), 135 (17.35), 91 (100), 43 (13.48); IR (film): $\tilde{\nu}_{max} = 3470$, 3065, 3032, 2936, 1497, 1455, 1379, 1370, 1214, 1072, 862, 738, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.34$–7.24 (m, 5H, Ph), 4.62, 4.50 (AB, $J_{AB} = 11.6$ Hz, 2H, OCH_2-Ph), 3.99 (dd, $J = 7.2$, 6.8 Hz, 1H), 3.88 (dd, $J = 6.6$, 13.2 Hz, 1H), 3.84–3.75 (m, 1H), 3.60 (t, $J = 7.2$ Hz, 2H), 2.43 (br s, 1H, OH), 2.30–2.14 (m, 4H, $CH_2C{\equiv}CCH_2$), 1.58–1.13 [m, 5H, $CH(CH_3)$, $2 \times CH_2$], 1.43 [s, 3H, $C(CH_3)_2$], 1.37 [s, 3H, $C(CH_3)_2$], 1.21 (d, $J = 6.3$ Hz, 3H, CH_3CHOBn), 0.95 (d, $J = 6.7$ Hz, 3H, CH_3CH); elemental analysis calcd for $C_{23}H_{34}O_4$ (374.52): C 73.76, H 9.15; found: C 73.75, H 9.30.

(2*R*,3*S*,10*S*,5*Z*)-2-Benzyloxy-10-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]undec-5-en-3-ol (29): Lindlar catalyst (197 mg, 10% wt) was added to a solution of **28** (1.973 g, 5.27 mmol) in MeOH (50 mL), and the mixture was hydrogenated for 1.5 h at RT. The reaction mixture was filtered, and the filtrate was concentrated. Purification of the residue by flash chromatography gave **29** (1.848 g, 93%) as a colorless oil. $[\alpha]_D^{20} = -29.8$ ($c = 2.05$, $CHCl_3$); MS: *m/z* (%): 361 (1.08) [$M^+ -$ Me], 101 (11.62), 92 (18.05), 91 (100), 81 (10.59), 72 (10.28), 59 (9.51), 43 (28.19); IR (film): $\tilde{\nu}_{max} = 3475$, 2984, 2934, 1497, 1455, 1379, 1370, 1214, 1071, 736, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.36$–7.26 (m, 5H, Ph), 5.50–5.44 (m, 2H, HC=CH), 4.63, 4.52 (AB, $J_{AB} = 11.7$ Hz, 2H, OCH_2Ph), 3.99 (dd, $J = 6.2$, 7.7 Hz, 1H), 3.88 (dd, $J = 6.8$, 13.6 Hz, 1H), 3.80–3.70 (m, 1H), 3.62–3.52 (m, 2H), 2.27–2.40 (m, 2H, CH_2CH=), 2.08–2.03 (m, 2H, CH_2CH=), 1.63–1.56 (m, 2H), 1.45–1.12 (m, 3H), 1.40 [s, 3H, $C(CH_3)_2$], 1.35 [s,3H, $C(CH_3)_2$], 1.20 (d, $J = 6.4$ Hz, 3H, CH_3CHOBn), 0.98 (d, $J = 5.1$ Hz, 3H, CH_3CH); elemental analysis calcd for $C_{23}H_{36}O_4$ (376.54): C 73.37, H 9.64; found: C 73.13, H 9.71.

(2*R*,3*S*,10*S*,5*Z*)-2-Benzyloxy-3-(1-ethoxyethyloxy)-10-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]undec-5-ene (30): Vinyl ethyl ether (2.55 mL, 26.56 mmol, 10 equiv) and PPTS (46.5 mg, 0.185 mmol, 7 mol%) were added to a solution of alcohol **29** (1.0 g, 2.66 mmol) in CH_2Cl_2 (10 mL). After being stirred for 2 h at RT, the mixture was quenched with Na_2CO_3 (200 mg). The solution was filtered, and the filtrate was concentrated, and the residue was purified by flash chromatography to give **30** (1.112 g, 96%) as a colorless oil. $[\alpha]_D^{20} = -18.9$ ($c = 1.95$, $CHCl_3$); MS: *m/z* (%): 433 (2.91) [$M^+ -$ Me], 403 (15.68), 345 (15.41), 251 (22.44), 193 (29.17), 91 (70.67), 73 (100), 45 (30.86); IR (film): $\tilde{\nu}_{max} = 3090$, 3066, 2983, 1652, 1497, 1455, 1378, 1370, 1214, 1097, 1068, 862, 736, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.36–7.24 (m, 5H, Ph-H), 5.46–5.41 (m, 2H, CH=CH), 4.89 [q, $J = 5.3$ Hz, ½H, $OCH(CH_3)O$], 4.81 [q, $J = 5.3$ Hz, ½H, $OCH(CH_3)O$], 4.62–4.52 (m, 2H, $PhCH_2O$), 3.98 (dd, $J = 6.2$, 7.6 Hz, 1H), 3.85 (dd, $J = 6.0$, 12.7 Hz, 1H), 3.76–3.51 (m, 5H), 2.35–2.32 (m, 2H, CH_2CH=CH), 2.03 (br s, 2H, CH_2CH=CH), 1.65–1.19 (m, 14H), 1.39 [s, 3H, $C(CH_3)_2$], 1.35 [s, 3H, $C(CH_3)_2$], 0.95 (d, $J = 6.7$ Hz, 3H, CH_3CH); elemental analysis calcd for $C_{27}H_{44}O_5$ (448.64): C 72.28, H 9.88; found: C 72.29, H 9.65.

(2*R*,3*S*,10*S*,5*Z*)-3-(1-Ethoxyethyloxy)-10-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]undec-5-en-2-ol (31): Liquid ammonium (80 mL) was collected at $-78\,^\circ C$, and Na (1.338 g, 58.15 mmol, 10 equiv) added to give a blue solution. To this solution was added THF (20 mL) and a solution of **30** (2.609 g, 5.82 mmol) in THF (10 mL). After being stirred for 30 min at $-78\,^\circ C$, the reaction mixture was quenched by carefully adding MeOH (5 mL); after the blue color disappeared, saturated aqueous NH_4Cl solution (5 mL) was added. The mixture was allowed to RT to remove most of NH_3, and the residue was extracted with EtOAc (100 mL). The organic layer was washed with water and brine, dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure. The residue was purified by flash chromatography to give pure **31** (2.041 g, 97.9%) as a colorless oil. $[\alpha]_D^{20} = -3.0$ ($c = 1.25$, $CHCl_3$); MS: *m/z* (%): 313 (1.80), 297 (6.70), 255 (4.06), 175 (9.24), 101 (31.62), 73 (100), 43 (26); IR (film): $\tilde{\nu}_{max} = 3478$, 2983, 2935, 1458, 1379, 1370, 1215, 1058, 946, 861 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 5.46$–5.42 (m, 2H, CH=CH), 4.83 [q, $J = 5.3$ Hz, 1H, $OCH(CH_3)$], 3.99 (dd, $J = 6.4$, 7.7 Hz, 1H), 3.91–3.85 (m, 2H), 3.72–3.50 (m, 4H), 2.48 (br s, 1H, OH), 2.40–2.20 (m, 2H, CH_2CH=CH), 2.05 (br s, 2H, CH_2CH=CH), 1.60–1.25 (m, 5H), 1.40 [s, 3H, $C(CH_3)_2$], 1.35 [s, 3H, $C(CH_3)_2$], 1.34 (d, $J = 5.3$ Hz, 3H, CH_3CHO), 1.22 (t, $J = 7.1$ Hz, 3H, CH_3CH_2O), 1.19 (d, $J = 7.1$ Hz, 3H, CH_3CHO), 0.96 (d, $J = 6.9$ Hz, 3H, CH_3CH); elemental analysis calcd for $C_{20}H_{38}O_5$ (358.52): C 67.00, H 10.68; found: C 67.47, H 10.44.

(3*S*,10*S*,5*Z*)-3-(*tert*-Butyldimethylsilyoxy)-10-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]undec-5-en-2-one (32): A solution of oxalyl chloride (1 mL, 11.50 mmol, 2 equiv) in CH_2Cl_2 (20 mL) was cooled to $-78\,^\circ C$, and a solution of DMSO (1.8 mL, 25.15 mmol, 4.4 equiv) added dropwise. The reaction mixture was stirred for 30 min at $-78\,^\circ C$, and a solution of **31** (2.041 g, 5.69 mmol, 1 equiv) in CH_2Cl_2 (15 mL) was added. After 2 h of stirring at $-78\,^\circ C$, the mixture was quenched with Et_3N (4 mL, ≈ 6 equiv) and was allowed to warm to RT. The mixture was diluted with EtOAc (100 mL) and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to afford ketone **32** as colorless oil, which was used directly in next step without further purification.

Ketone **32** was dissolved in *n*-propanol (30 mL), and PPTS (450 mg) added. The mixture was stirred for 2 h at RT and quenched with Na_2CO_3. After being vigorously stirred for 10 min, the mixture was diluted with EtOAc (50 mL), and washed with water and brine, dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure, and the residue was dissolved in DMF (30 mL). Imidazole (3.379 g, 49.69 mmol, 8.7 equiv) and TBSCl (2.247 g, 14.91 mmol, 2.6 equiv) were added at $0\,^\circ C$. The reaction mixture was allowed to warm to RT and stirred for additional 5 h. To the mixture was added ice water (20 mL) and Et_2O (20 mL), and two phases separated. The aqueous phase was extracted with Et_2O (3×20 mL), and the combined organic layers were washed with water and brine, dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure, and the crude product was purified by flash chromatography to yield compound **34** (1.935 g, 85.3%) as a colorless oil. $[\alpha]_D^{20} = -16.0$ ($c = 1.5$, $CHCl_3$); MS: *m/z* (%): 383 (1.05) [$M^+ -$ Me], 355 (1.97), 283 (5.98), 171 (12.00), 157 (21.26), 101 (16.02), 73 (100), 43 (52.64); IR (film): $\tilde{\nu}_{max} = 2957$, 1718, 1464, 1379, 1369, 1254, 1103, 838, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 5.55$–5.48 (m, 1H, CH=CH), 5.48–5.42 (m, 1H, CH=CH), 4.01 (dd, $J = 7.3$, 13.5 Hz, 2H), 3.87 (dd, $J = 6.9$, 13.6 Hz, 1H), 3.59 (t, $J =$ 7.5 Hz, 1H), 2.45–2.37 (m, 1H), 2.37–2.20 (m, 1H), 2.16 (s, 3H, CH_3CO), 1.98 (br d, $J = 6.2$ Hz, 2H), 1.64–1.20 (m, 4H), 1.40 [s, 3H, $C(CH_3)_2$], 1.35 [s, 3H, $C(CH_3)_2$], 1.20–0.90 (m, 1H), 0.96 (d, $J = 6.7$ Hz, 3H, CH_3CH), 0.92 [s, 9H, $(CH_3)_3$C-Si], 0.099 [s, 3H, $Si(CH_3)_2$], 0.066 [s, 3H, $Si(CH_3)_2$]; elemental analysis calcd for $C_{22}H_{42}O_4Si$ (398.66): C 66.28, H 10.62; found: C 66.49, H 10.15.

(1*S*,8*S*,3*Z*)-1-[(1*E*)-1-Methyl-2-(2-methyl-1,3-thiazol-4-yl)vinyl]-8-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-1-(*tert*-butyldimethylsilyloxy)non-3-ene (35): A solution of **6** (5.267 g, 15.05 mmol, 3 equiv) in THF (50 mL) was cooled to $0\,^\circ C$, and *t*BuOK (1.405 g, 12.54 mmol, 2.5 equiv) added. The mixture was stirred for 30 min to obtain an orange solution. A solution of ketone **34** (2.0 g, 5.02 mmol, 1 equiv) was added at $0\,^\circ C$, and result mixture was warmed slowly to RT. After being stirred for 2 h at RT, the reaction mixture was quenched with a saturated solution of NH_4Cl (10 mL), extracted with EtOAc (3×20 mL). The organic layer was washed with

water and brine, dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure, and the crude product was purified by flash chromatography to give **35** (2.279 g, 92%) as a colorless oil. $[\alpha]_D^{20} = -7.1$ ($c = 2.8$, $CHCl_3$); MS: m/z (%): 494 (10.46) [M^++H], 478 (7.11) [M^+ − Me], 362 (1.69), 282 (100), 151 (1.88), 73 (9.93), 43 (3.83); IR (film): $\tilde{\nu}_{max} =$ 3095, 2985, 2858, 1506, 1472, 1463, 1378, 1369, 1253, 1071, 837, 776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.93$ (s, 1H, SCH=C), 6.46 (s, 1H, $CH{=}CCH_3$), 5.42 – 5.37 (m, 2H, CH=CH), 4.16 – 4.09 (m, 1H, CHOSi), 3.99 (dd, $J = 6.5$, 7.8 Hz, 1H), 3.86 (dd, $J = 6.6$, 13.4 Hz, 1H), 3.59 (t, $J = 7.6$ Hz, 1H), 2.71 (s, 3H, $N{=}C(CH_3)S$), 2.33 – 2.28 (m, 2H, $CH_2CH{=}CH$), 2.05 – 1.98 (m, 5H, $CH_2CH{=}CH$, $CH_3C{=}CH$), 1.56 – 1.10 [m, 5H, $CH(CH_3)$, 2 × CH_2], 1.40 [s, 3H, $C(CH_3)_2$], 1.35 [s, 3H, $C(CH_3)_2$], 0.95 (d, $J = 6.6$ Hz, 3H, CH_3CH), 0.89 [s, 9H, $SiC(CH_3)_3$)], 0.054 [s, 3H, $Si(CH_3)_2$], 0.021 [s, 3H, $Si(CH_3)_2$]; elemental analysis calcd for $C_{27}H_{47}O_3NSSi$ (493.82): C 65.67, H 9.59, N 2.83; found: C 65.40, H 9.60, N 2.90.

(2*R*,3*S*,10*S*,7*Z*,11*E*)-10-(*tert*-Butyldimethylsilyloxy)-3,11-dimethyl-12-(2-methyl-1,3-thiazol-4-yl)dodeca-7,11-diene-1,2-diol (36): $CuCl_2 \cdot H_2O$ (385 mg, 2.26 mmol, 3 equiv) was added to a solution of **35** (372 mg, 0.75 mmol) in CH_3CN (10 mL). The reaction mixture was stirred for 2 h at RT, quenched with H_2O (20 mL), extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with water, saturated solution of NH_4Cl and brine, dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography to give corresponding diol of **35** (272 mg, 79.6%) as a colorless oil. $[\alpha]_D^{20} = -0.70$ ($c = 3.3$, $CHCl_3$); MS: m/z (%): 454 (3.76) [M^++H], 438 (1.87) [M^+ − Me], 422 (3.58), 394 (6.37), 322 (10.09), 282 (100), 151 (2.96), 73 (12.38); IR (film): $\tilde{\nu}_{max} =$ 3369, 3013, 2955, 1656, 1508, 1472, 1253, 1075, 837, 776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.94$ (s, 1H, SCH=C), 6.45 (s, 1H, $CH{=}CCH_3$), 5.42 – 5.38 (m, 2H, CH=CH), 4.12 (br t, $J = 6.3$ Hz, 1H, CHOSi), 3.67 – 3.50 (m, 3H), 2.88 (br s, 2H), 2.70 [s, 3H, $N{=}C(CH_3)S$], 2.32 – 2.27 (m, 2H), 2.05 – 1.95 (m, 2H), 1.97 (s, 3H, $CH_3C{=}CH$), 1.52 – 1.10 [m, 5H, $CH(CH_3)$, 2 × CH_2], 0.91 (d, $J = 7.0$ Hz, 3H, CH_3CH), 0.88 [s, 9H, $SiC(CH_3)_3$], 0.055 [s, 3H, $Si(CH_3)_2$], 0.001 [s, 3H, $Si(CH_3)_2$]; elemental analysis calcd for $C_{24}H_{43}O_3NSSi$ (453.76): C 63.53, H 9.55, N 3.09; found: C 63.27, H 9.37, N 3.07.

A solution of the diol of **35** (91 mg, 0.20 mmol) in CH_2Cl_2 (2 mL) was added to a suspension of $NaIO_4$/silica gel (1.0 g) in CH_2Cl_2 (5 mL). The mixture was vigorously stirred for 15 min at RT, and filtered. The filtrate was concentrated to give **36** (84 mg, quant.) as a colorless oil. The product was used directly without further purification. $[\alpha]_D^{20} = +12.3$ ($c = 1.6$, $CHCl_3$). [lit:[3b] $[\alpha]_D^{20} = +13.3$ ($c = 0.7$, $CHCl_3$)]; MS: m/z (%): 422 (0.91) [M^++H], 284 (10.76), 283 (24.71), 282 (100), 75 (19.42), 73 (43.15), 45 (5.55); IR (film): $\tilde{\nu}_{max} =$ 2955, 2930, 2858, 1727, 1507, 1472, 1463, 1253, 1184, 1076, 938, 837, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 9.59$ (d, $J = 2.1$, 1H; CHO), 6.92 (s, 1H, SCH=C), 6.45 (s, 1H, $CH{=}CCH_3$), 5.41 – 5.38 (m, 2H, CH=CH), 4.11 (dd, $J = 6.4$, 6.3 Hz, 1H; CHOSi), 2.70 (s, 3H, thiazole CH_3), 2.33 – 2.28 (m, 3H), 2.05 – 1.99 (m, 2H), 1.99 (s, 3H, $CH{=}CCH_3$), 1.72 – 1.64 (m, 1H), 1.41 – 1.33 (m, 3H), 1.06 (d, $J = 7.0$ Hz, 3H, CH_3CHO), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.05 (s, 3H, $Si(CH_3)_2$), − 0.002 (s, 3H, $Si(CH_3)_2$).

Aldol reaction of keto acid 7a with aldehyde 36: A solution of keto acid **7a** (185 mg, 0.60 mmol, 3 equiv) in THF (1 mL) was added dropwise to a freshly prepared solution of LDA [diisopropylamine (0.2 mL, 0.14 mmol) was added to *n*BuLi (0.75 mL, 1.6 M solution in hexanes, 1.20 mmol) in THF (1 mL) at 0 °C] at − 78 °C. After being stirred for 15 min, the solution was allowed to warm to − 40 °C, and after 30 min at that temperature, it was re-cooled to − 78 °C. A solution of aldehyde **36** (84 mg, 0.20 mmol, 1 equiv) in THF (1 mL) was added dropwise, and the resulting mixture was stirred for 10 min and then quenched with a saturated aqueous NH_4Cl solution (1 mL). The reaction mixture was warmed to 0 °C, and acetic acid (0.1 mL) was added, followed by addition of EtOAc (10 mL). The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with saturated aqueous NH_4Cl solution and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a mixture of aldol products **37a,b** in ≈1:1 ratio and un-reacted keto acid **7a**. The mixture was dissolved in CH_2Cl_2 (8 mL) and treated with 2,6-lutidine (0.23 mL, 2.0 mmol, 10 equiv) and TBSOTf (0.27 mL, 1.2 mmol, 6.0 equiv) at 0 °C. After the reaction mixture was stirred for 2 h, aqueous 10% HCl (3 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were washed with saturated NH_4Cl solution and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was dissolved in MeOH (5 mL), and K_2CO_3 (166 mg, 1.20 mmol, 6 equiv) was added at 25 °C. The reaction mixture was vigorously stirred for 15 min, and acidified with a 1 M $KHSO_4$ solution to pH 4 – 5. Most of MeOH was removed under reduced pressure, and the residue was extracted with EtOAc (3 × 10 mL). The organic solution was washed with saturated aqueous NH_4Cl solution and brine, dried over Na_2SO_4, filtered, and concentrated to furnish a mixture of carboxylic acids **39a,b**, and keto acid **7a**. Purification of the mixture by flash chromatography gave **39a,b** (122 mg, 72.2%) as a 1:1 mixture (^1H NMR) as a colorless oil. $[\alpha]_D^{20} = -3.8$ ($c = 1.0$, $CHCl_3$); ESI-MS: m/z: 845 [M^++H], 639, 604, 580, 544; MS: m/z (%): 844 [M^+], 698 (0.74), 516 (3.26), 478 (5.01), 284 (11.01), 282 (100), 121 (23.69), 75 (13.96); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.20$ (d, $J = 8.6$ Hz, 2H, Ar-H), 6.91 (s, 1H, H-19), 6.82 (d, $J = 8.6$ Hz, 2H, Ar-H), 6.57 (s, ½H, H-17), 6.47 (s, ½H, H-17), 5.42 – 5.38 (m, 2H, CH=CH), 4.65, 4.45 (AB, $J_{AB} = 10.6$ Hz, 2H, $ArCH_2O$), 4.33 – 4.25 (m, 1H, H-3), 4.12 (dd, $J = 7.1$, 14.2 Hz, 1H, H-15), 3.87 (d, $J = 8.6$ Hz, 1H, H-7), 3.78 (s, 3H, CH_3OAr), 3.18 – 3.14 (m, 1H, H-6), 2.77 (s, ½ × 3H, H-21), 2.72 (s, ½ × 3H, H-21), 2.58 – 2.49 (m, 2H), 2.37 – 2.25 (m, 2H), 2.08 – 1.95 (m, 2H), 1.95 (s, ½ × 3H, H-27), 1.93 (s, ½ × 3H, H-27), 1.48 – 1.03 (m, 8H), 1.20 (s, 3H, H-22), 1.16 (s, 3H, H-23), 1.04 (d, $J = 6.8$ Hz, 3H, H-25), 0.89 [s, 18H, 2 × $SiC(CH_3)_3$], 0.085 – 0.049 [m, 12H, 2 × $Si(CH_3)_2$].

Hydroxy acids 40a, b: A solution of **39a,b** (122 mg, 0.14 mmol) in THF (3 mL) at 25 °C was treated with TBAF (0.9 mL, 1 M solution in THF, 0.9 mmol, 6.4 equiv). After being stirred for 8 h, the reaction mixture was diluted with EtOAc (10 mL) and washed with aqueous solution of HCl (10 mL, 1 N solution). The aqueous phase was extracted with EtOAc (4 × 10 mL), and the combined organic phases were washed with saturated aqueous NH_4Cl solution and brine, dried over $MgSO_4$. After filtration, solvent was removed under reduced pressure, and the residue was purified by flash chromatography to give **40a,b** (90 mg, 85.3%, 1:1 mixture) as a colorless oil. Mixture of **40a,b**: MS: m/z (%): 730 (1.35) [M^+], 715 (1.63) [M^+ − Me], 712 (16.00) [$M^+ - H_2O$], 566 (10.81), 168 (12.83), 121 (100), 75 (8.22); IR (film):$\tilde{\nu}_{max} =$ 2934, 2858, 1614, 1515, 1472, 1250, 1040, 986, 836, 775 cm^{-1}.

Compound **40a**: $[\alpha]_D^{20} = -12.2$ ($c = 1.2$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.17$ (d, $J = 8.5$ Hz, 2H), 6.93 (s, 1H), 6.80 (d, $J = 8.5$ Hz, 2H), 6.56 (s, 1H), 5.56 – 5.47 (m, 1H), 5.40 – 5.32 (m, 1H), 4.57, 4.40 (AB, $J_{AB} =$ 10.7 Hz, 2H), 4.31 (br t, $J = 6.0$ Hz, 1H), 4.18 – 4.06 (m, 2H), 3.84 (br d, $J =$ 8.6 Hz, 1H), 3.75 (s, 3H), 3.11 (dq, $J = 7.2$, 8.1 Hz, 1H), 2.70 (s, 3H), 2.51 – 2.30 (m, 4H), 2.05 – 1.98 (m, 2H), 1.98 (s, 3H), 1.84 – 1.82 (m, 1H), 1.32 – 1.14 (m, 8H), 1.08 (s, 3H), 1.01 (d, $J = 6.8$ Hz, 3H), 0.88 (s, 9H), 0.77 (d, $J =$ 5.8 Hz, 3H), 0.050 (s, 3H), 0.039 (s, 3H).

Compound **40b**: $[\alpha]_D^{20} = -5.6$ ($c = 2.7$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.20$ (d, $J = 8.5$ Hz, 2H), 6.96 (s, 1H), 6.81 (d, $J = 8.5$ Hz, 2H), 6.63 (s, 1H), 5.60 – 5.48 (m, 1H), 5.45 – 5.32 (m, 1H), 4.64, 4.42 (AB, $J_{AB} = 10.7$ Hz, 2H), 4.37 – 4.32 (m, 1H), 4.17 (br t, $J = 6.6$ Hz, 1H), 3.87 (br d, $J = 8.6$ Hz, 1H), 3.77 (s, 3H), 3.15 (dq, $J = 5.7$, 8.2 Hz, 1H), 2.84 (br s, 2H), 2.77 (s, 3H), 2.48 – 2.39 (m, 4H), 2.02 (br s, 5H), 1.48 – 0.98 (m, 8H), 1.26 (s, 3H), 1.12 (s, 3H), 0.93 (s, 9H), 0.80 (d, $J = 6.1$ Hz, 3H), 0.064 (s, 6H).

Macrolactonization of hydroxy acids 40a,b: A solution of hydroxy acids **40a,b** (43 mg, 0.06 mmol) in THF (2 mL) was treated at RT with Et_3N (70 μL, 0.5 mmol, 8.3 equiv) and 2,4,6-trichlorobenzoyl chloride (70 μL, 0.45 mmol, 7.5 equiv). The mixture was stirred for 15 min, diluted with toluene (20 mL), and then added dropwise to a solution of 4-DMAP (73 mg, 0.6 mmol, 10 equiv) in toluene (10 mL) within 3 h at 80 °C. The reaction mixture was stirred for an additional 1 h at 80 °C, and concentrated under reduced pressure to a small volume and filtered through silica gel. The residue was washed with 40% Et_2O in hexanes, and the resulting solution was concentrated. Purification by flash chromatography (silica gel, 3% acetone in hexanes) gave pure lactone **41** (17 mg, 40.5%) and **42** (17 mg, 40.5%) as colorless oils.

Lactone 41: $R_f = 0.33$ (30% Et_2O in hexanes); $[\alpha]_D^{20} = -38$ ($c = 0.75$, $CHCl_3$); MS: m/z (%): 712 (5.46) [M^++H], 645 (16.46), 566 (11.59), 446 (8.21), 346 (4.71), 164 (7.93), 121 (100), 75 (9.00); IR (film): $\tilde{\nu}_{max} =$ 3004, 2956, 2857, 1720, 1697, 1614, 1514, 1470, 1376, 1361, 1246, 1123, 837, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.14$ (d, $J = 8.3$ Hz, 2H, Ar-H), 6.94 (s, 1H, H-19), 6.78 (d, $J = 8.3$ Hz, 2H, Ar-H), 6.65 (s, 1H, H-17), 5.39 (br s, 3H, CH=CH, H-17), 4.60, 4.50 (AB, 2H, $ArCH_2O$, $J_{AB} = 10.8$ Hz),

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4.08 (dd, $J = 3.8, 8.5$ Hz, 1H, H-3), 3.78 (s, 4H, H-7, CH_3OAr), 3.01 (dq, $J =$ 5.5, 6.9 Hz, 1H, H-6), 2.79–2.68 (m, 2H), 2.70 (s, 3H, H-21), 2.27–2.02 (m, 4H), 2.12 (s, 3H, H-27), 1.66–1.38 (m, 5H), 1.25 (s, 3H, H-22), 1.15 (s, 3H, H-23), 1.06 (d, $J = 6.8$ Hz, 3H, H-24), 0.95 [s, 9H, $SiC(CH_3)_3$], 0.88 (d, $J =$ 6.9 Hz, 3H, H-25), 0.07 [s, 3H, $Si(CH_3)_2$], 0.03 [s, 3H, $Si(CH_3)_2$]; HRMS: calcd for $C_{40}H_{61}NO_6SSi$: 711.3992; found: 711.3988.

Lactone 42: $R_f = 0.35$ (30% Et_2O in hexanes); $[\alpha]_D^{20} = -62$ ($c = 0.70$, $CHCl_3$); MS: *m/z* (%): 712 (18.57) [M^++H], 654 (21.18), 566 (17.67), 446 (7.33), 405 (14.16), 346 (3.86), 121 (100), 75 (9.06); IR (film): $\tilde{\nu}_{max} = 2958$, 2857, 1737, 1691, 1515, 1387, 1250, 1039, 984, 836, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.17$ (d, $J = 8.6$ Hz, 2H, Ar-H), 6.95 (s, 1H, H-19), 6.82 (d, $J = 8.6$ Hz, 2H, Ar-H), 6.53 (s, 1H, H-17), 5.44–5.34 (m, 2H, CH=CH), 5.35 (br d, 1H, H-15), 4.58, 4.46 (AB, $J_{AB} = 10.2$ Hz, 2H, $ArCH_2O$), 3.99 (dd, $J = 3.9$, 8.4 Hz, 1H, H-3), 3.91 (br d, $J = 7.0$ Hz, 1H, H-7), 3.79 (s, 3H, CH_3OAr), 3.24 (dq, $J = 7.2$, 7.3 Hz, 1H, H-6), 2.69 (s, 3H, H-21), 2.71–2.40 (m, 2H), 2.39–2.00 (m, 4H), 2.15 (s, 3H, H-27), 1.64–1.23 (m, 5H), 1.20 (s, 3H, H-22), 1.11 (s, 3H, H-23), 1.04 (d, $J = 7.1$ Hz, 3H, H-24), 0.90 [s, 9H, $SiC(CH_3)_3$], 0.61 (d, $J = 6.2$ Hz, 3H, H-25), 0.09 [s, 3H, $Si(CH_3)_2$], 0.07 [s, 3H, $Si(CH_3)_2$]; HRMS: calcd for $C_{40}H_{61}NO_6SSi$: 711.3992; found: 711.4014.

Preparation of epothilone C (3a): To lactone **41** (22 mg, 0.031 mmol) cooled to $-20\,^\circ C$, was added a freshly prepared 20% (*v*/*v*) CF_3COOH solution in CH_2Cl_2 (2 mL). The reaction mixture was allowed to reach $0\,^\circ C$ and was stirred for 1 h. The solvents were evaporated under reduced pressure, and the residue was purified by flash chromatography to give pure epothilone C (**3a**; 13 mg, 88%) as white foam. $[\alpha]_D^{20} = -83.0$ ($c = 0.4$, $CHCl_3$); [lit:[3b] $[\alpha]_D^{22} = -80.2$ ($c = 1.7$, $CHCl_3$)]; MS: *m/z* (%): 477 (10.95) [M^+], 459 (4.43) [$M^+ - H_2O$], 389 (6.16), 290 (24.60), 168 (85.93), 121 (48.70), 97 (37.76), 57 (72.48), 43 (100); IR (KBr): $\tilde{\nu}_{max} = 3449$, 2964, 2930, 1733, 1687, 1649, 1467, 1262, 1093, 803, 757 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.97$ (s, 1H, H-19), 6.60 (s, 1H, H-17), 5.46–5.38 (m, 2H, CH=CH), 5.29 (dd, $J = 9.7$, 1.7 Hz, 1H, H-15), 4.25 (d, $J = 10.4$ Hz, 1H, H-3), 3.74 (br s, 1H, H-7), 3.39 (br s, 1H, OH), 3.14 (dq, $J = 6.7$, 1.9 Hz, 1H, H-6), 3.05 (br s, 1H, OH), 2.70 (s, 3H, H-21), 2.71–2.63 (m, 1H), 2.50 (dd, $J = 14.9$,11.2 Hz, 1H, H-2), 2.34 (dd, $J = 15.1$, 2.7 Hz, 1H, H-2), 2.30–2.10 (m, 2H), 2.09 (s, 3H, H-27), 2.10–1.95 (m, 1H), 1.90–1.60 (m, 2H), 1.34 (s, 3H, H-22), 1.45–1.15 (m, 3H), 1.19 (d, $J = 6.9$ Hz, 3H, H-24), 1.08 (s, 3H, H-23), 1.00 (d, $J = 7.0$ Hz, 3H, H-25); HRMS: calcd for $C_{26}H_{39}NO_5S$ 477.2551; found: 477.2553.

Preparation of epothilone A (1): A solution of **3a** (14 mg, 0.029 mmol) in CH_2Cl_2 (2 mL) was cooled to $-50\,^\circ C$, a freshly prepared 3,3-dimethyldioxirane (2 mL, ≈0.1M in acetone). The resulting solution was allowed to warm to $-30\,^\circ C$ for 1 h. A stream of nitrogen was then bubbled through the solution to remove excess 3,3-dimethyldioxirane. The residue was purified by flash chromatography (40% EtOAc in hexanes) to afford epothilone A (**1**; 7.5 mg, 52%) as a white solid and its β-epoxide diastereoisomer (1.5 mg, 10%).

Epothilone A (1): $[\alpha]_D^{20} = -41.5$ ($c = 0.20$, CH_3OH); [lit:[1] $[\alpha]_D^{20} = -47.1$ ($c = 1.0$, CH_3OH)]; MS: *m/z* (%): 493 (9.02) [M^+], 494 (7.03) [M^++H], 476 (3.42) [$M^+ - H_2O$], 322 (21.93), 306 (85.94), 304 (61.60), 164 (100), 57 (51.67), 43 (62.83); IR (film): $\tilde{\nu}_{max} = 3462$, 2960, 1737, 1690, 1506, 1467, 1260, 1153, 980, 757cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.98$ (s, 1H, H-19), 6.60 (s, 1H, H-17), 5.43 (dd, $J = 8.5$, 2.5 Hz, 1H, H-15), 4.20–4.17 (m, 1H, H-3), 3.96 (d, $J = 6.2$ Hz, 1H, 3-OH), 3.79 (dd, $J = 8.2$, 4.0 Hz, 1H, H-7), 3.49 (br s, OH), 3.23 (dq, $J = 11.6$, 7.0 Hz, 1H, H-6), 3.03 (m, 1H, H-13), 2.92 (m, 1H, H-12), 2.70 (s, 3H, H-21), 2.60 (br s, 1H, 7-OH), 2.57 (dd, $J = 14.4$, 10.4 Hz, 1H, H-2), 2.41 (dd, $J = 14.4$, 3.2 Hz, 1H, H-2), 2.17–2.11 (m, 1H, H-14), 2.09 (s, 3H, H-27), 1.93–1.85 (m, 1H, H-14), 1.75–1.67 (m, 2H, H-8, H-11), 1.52–1.40 (m, 5H, 2H-9, 2H-10, H-11), 1.37 (s, 3H, H-22), 1.18 (d, $J = 6.8$ Hz, 3H, H-24), 1.10 (s, 3H, H-23), 1.01 (d, 3H, $J = 7.0$ Hz, H-25); HRMS: calcd for $C_{26}H_{39}NO_6S$: 493.2498; found: 493.2487.

β-Epoxide isomer of epothilone A: $[\alpha]_D^{20} = -51$ ($c = 0.10$, CH_3OH); MS: *m/z* (%): 493 (2.93) [M^+], 405 (4.42), 380 (6.15), 306 (49.51), 164 (89.26), 151 (34.98), 57 (68.64), 43 (100); IR (film): $\tilde{\nu}_{max} = 3476$, 2929, 1736, 1689, 1509, 1459, 1257, 1152, 983, 913, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta =$ 6.98 (s, 1H, H-19), 6.61 (s, 1H, H-17), 5.70 (d, 1H, H-15, $J = 8.1$ Hz), 4.13 (br d, $J = 10.6$ Hz, 1H, H-3), 4.01 (br s, 1H, OH), 3.94 (br d, $J = 4.9$ Hz, 1H, H-7), 3.49 (s, 1H, OH), 3.32 (dd, $J = 2.3$, 7.1 Hz, 1H, H-6), 3.28–3.22 (dt, $J = 9.3$, 4.2 Hz, 1H, H-13), 2.97 (dt, $J = 3.3$, 10.1 Hz, 1H, H-12), 2.71 (s, 3H, H-21), 2.50 (dd, $J = 10.8$, 12.7 Hz, 1H, H-2), 2.40 (dd, $J = 2.6$, 12.7 Hz, 1H, H-2), 2.12 (s, 3H, H-27), 2.09–2.03 (m, 1H, H-14), 1.92–1.78 (m, 3H, H-14, 2H-11), 1.59–1.20 (m, 5H, 2H-10, 2H-9, H-8), 1.36 (s, 3H, H-22), 1.12 (d, $J = 7.0$ Hz, 3H, H-24), 1.05 (s, 3H, H-23), 0.95 (d, $J = 7.1$ Hz, 3H, H-25).

(4*S*,7*R*,8*S*,16*S*)-8-Hydroxy-4-(4-methoxybenzyloxy)-5,5,7,9-tetramethyl-16-[(*E*)-1-methyl-2-(2-methyl-1,3-thiazol-4-yl)-1-ethenyl]-1-oxacyclohexadec-13-en-2,6-dione (3b): HF·pyridine (0.6 mL) was added dropwise to a solution of lactone **41** (21 mg, 29.5 mmol) in THF (1.0 mL) at RT in a plastic vial. After being stirred for 2 h at RT, the reaction mixture was diluted with Et_2O (20 mL) and slowly added $NaCO_3$ until no further CO_2 was formed. The mixture was filtered, and the organic layer was washed with sat. aqueous $CuSO_4$, water and brine, dried over $NaSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography provided **3b** (16 mg, 91%) as a wax-like solid. $[\alpha]_D^{20} = -70.3$ ($c = 0.40$, $CHCl_3$); MS: *m/z* (%): 598 [M^++H] (1.24), 290 (5.57), 168 (12.25), 164 (21.25), 137 (21.61), 121 (100), 77 (10.91); IR (KBr): $\tilde{\nu}_{max} = 3563$, 3100, 3007, 2961, 2929, 2854, 1717, 1687, 1614, 1514, 1469, 1270, 1246, 1181, 1093, 1024, 824, 747 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.08$ (d, $J = 8.6$ Hz, 2H, Ar-H), 6.90 (s, 1H, H-19), 6.75 (d, $J = 8.6$ Hz, 2H, Ar-H), 6.60 (s, 1H, H-17), 5.42–5.33 (m, 3H, CH=CH, H-15), 4.53, 4.46 (AB, $J_{AB} = 10.4$ Hz, 2H, $ArCH_2O$), 4.09 (dd, $J = 10.4$, 1.9 Hz, 1H, H-3), 3.77 (s, 3H, CH_3OAr), 3.75–3.73 (m, 1H, H-7), 3.09–3.04 (m, 2H, H-6, OH), 2.81–2.71 (m, 2H, H-14), 2.69 (s, 3H, H-21), 2.54 (dd, $J = 15.5$, 2.7 Hz, 1H, H-2), 2.22–2.09 (m, 2H, H-2, H-11), 2.13 (s, 3H, H-27), 2.0–1.90 (m, 1H, H-11), 1.75–1.52 (m, 2H), 1.43–1.10 (m, 3H), 1.22 (s, 3H, H-22), 1.17 (s, 3H, H-23), 1.15 (d, $J =$ 6.7 Hz, 3H, H-24), 0.98 (d, $J = 7.0$ Hz, 3H, H-25).

(1*S*,3*S*,7*S*,10*R*,11*S*,12*S*,16*R*)-3-[(*E*)-1-Methyl-2-(2-methyl-1,3-thiazol-4-yl)-1-ethenyl]-11-hydroxy-7-(4-methoxybenzyloxy)-8,8,10,12-tetramethyl-4,17-dioxa-bicyclo[14.1.0]heptadecane-5,9-dione (43): A freshly prepared solution of 3,3-dimethyldioxirane (0.1M in acetone, 2 mL) was added at $-50\,^\circ C$ to a solution of **3b** (10 mg, 16.7 μmol) in CH_2Cl_2 (1.0 mL). The reaction mixture was allowed to warm to $-30\,^\circ C$ for 2 h. A stream of nitrogen gas was then bubbled through the solution to remove excess 3,3-dimethyldioxirane. The residue was purified by flash chromatography and afforded **43** (9 mg, 88%) as a wax-like solid. $[\alpha]_D^{20} = -60$ ($c = 0.20$, $CHCl_3$); MS: *m/z* (%): 614 [M^++H] (13.37), 306 (9.78), 164 (13.37), 137 (15.13), 121 (100), 57 (10.36); IR (KBr): $\tilde{\nu}_{max} = 3502$, 3107, 2960, 2929, 2858, 1736, 1687, 1614, 1515, 1465, 1388, 1371, 1302, 1251, 1180, 1155, 1036, 980, 823, 757 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.09$ (d, $J = 8.6$ Hz, 2H, Ar-H), 6.92 (s, 1H, H-19), 6.77 (d, $J = 8.6$ Hz, 2H, Ar-H), 6.60 (s, 1H, H-17), 5.53 (dd, $J = 8.4$, 1.8 Hz, 1H, H-15), 4.55, 4.48 (AB, $J_{AB} = 10.3$ Hz, 2H, $ArCH_2O$), 4.09 (dd, $J = 10.0$, 3.2 Hz, 1H, H-3), 3.81 (t, $J = 4.0$ Hz, 1H, H-7), 3.77 (s, 3H, CH_3O), 3.13 (dq, $J = 6.7$, 3.1 Hz, 1H, H-6), 2.99 (td, $J =$ 9.1, 3.6 Hz, 1H, H-13), 2.78–2.60 (m, 2H, H-12, H-2), 2.69 (s, 3H, H-21), 2.61 (dd, $J = 15.1$, 3.1 Hz, 1H, H-2), 2.18–2.10 (m, 1H, H-14), 2.14 (s, 3H, H-27), 2.05–2.00 (m, 1H, H-14), 1.95–1.85 (m, 1H, H-11), 1.80–1.55 (m, 1H, H-11), 1.45–1.20 (m, 5H, 2H-10, 2H-9, H-8), 1.24 (s, 3H, H-22), 1.21 (s, 3H, H-23), 1.15 (d, $J = 6.7$ Hz, 3H, H-24), 0.98 (d, $J = 7.0$ Hz, 3H, H-25).

Epothilone A (1): 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 4 mg, 17.6 μM) was added to a solution of **43** (4 mg, 6.62 μm) in CH_2Cl_2/H_2O (20:1, 1.0 mL). the reaction mixture was stirred at RT for 1 h, then diluted with EtOAc (20 mL). The organic solution was washed with saturated aqueous $NaCO_3$, water and brine, dried over $NaSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography gave epothilone A (**1**; 3 mg, 93%) as a white solid. $[\alpha]_D^{20} = -41.5$ ($c = 0.20$, CH_3OH); [lit:[1] $[\alpha]_D^{20} = -47.1$ ($c = 1.0$, CH_3OH)]; MS: *m/z* (%): 493 (9.02) [M^+], 494 (7.03) $M^+ + H$], 476 (3.42) [$M^+ - H_2O$], 322 (21.93), 306 (85.94), 304 (61.60), 164 (100), 57 (51.67), 43 (62.83); IR (film): $\tilde{\nu}_{max} = 3462$, 2960, 1737, 1690, 1506, 1467, 1260, 1153, 980, 757 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.98$ (s, 1H, H-19), 6.60 (s, 1H, H-17), 5.43 (dd, $J = 8.5$, 2.5 Hz, 1H, H-15), 4.20–4.17 (m, 1H, H-3), 3.96 (d, $J = 6.2$ Hz, 1H, 3-OH), 3.79 (dd, $J = 8.2$, 4.0 Hz, 1H, H-7), 3.49 (br s, OH), 3.23 (dq, $J = 11.6$, 7.0 Hz, 1H, H-6), 3.03 (m, 1H, H-13), 2.92 (m, 1H, H-12), 2.70 (s, 3H, H-21), 2.60 (br s, 1H, 7-OH), 2.57 (dd, $J = 14.4$, 10.4 Hz, 1H, H-2), 2.41 (dd, $J = 14.4$, 3.2 Hz, 1H, H-2), 2.17–2.11 (m, 1H, H-14), 2.09 (s, 3H, H-27), 1.93–1.85 (m, 1H, H-14), 1.75–1.67 (m, 2H, H-8, H-11), 1.52–1.40 (m, 5H, 2H-9, 2H-10, H-11), 1.37 (s, 3H, H-22), 1.18 (d, $J = 6.8$ Hz, 3H, H-24), 1.10 (s, 3H, H-23), 1.01 (d, 3H, $J = 7.0$ Hz, H-25); HRMS: calcd for $C_{26}H_{39}NO_6S$: 493.2498; found: 93.2487.

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