Total Synthesis of (−)-Epothilone A

Dieter Schinzer,* Armin Bauer, Oliver M. Böhm, Anja Limberg, and Martin Cordes[a]

Abstract: The total synthesis of (−)-epothilone A by a convergent route is reported. The synthesis of the required key intermediates has been improved with respect to stereoselectivity and availability. The access to ethyl ketone **2** has been significantly improved by employment of chiral acetate equivalents, which provided higher optical and chemical yields. Key intermediate **3** was obtained by oxazolidinone auxiliary techniques and stereoselectively coupled with **2** by an aldol reaction. After esterification with thiazole fragment **4**, (−)-epothilone A was finally constructed by using ring-closing metathesis.

Keywords: cytotoxic agents · epothilones · macrolides · natural products

Introduction

The fascinating biological activities of the epothilones, a new class of macrolides isolated from the myxobacterium *Sorangium cellulosum* by Höfle, Reichenbach, and co-workers at the Gesellschaft für Biotechnologische Forschung (GBF), Braunschweig (Germany)[1] have created tremendous excitement in the scientific community.[2] Following a screening program aimed at the identification of substances with a taxol-like mode of action, Daniel M. Bollag and co-workers at the Merck research laboratories in West Point, PA, found in 1995 that the epothilones are powerful cytotoxic agents which function through stabilization of cellular microtubules in the same mode of action like paclitaxel and its analogues. The biological activity spectrum of the epothilones is very close to that of paclitaxel. Both compounds supposedly compete for the same receptor, paclitaxel being displaced from the binding site by the epothilones. They show similar kinetics in in vitro tests and provide closely similar pictures of microtubule structure and cell damage; the major difference in their effect on cell lines is their efficacy against multiple-drug resistance. Epothilones are between 2000 and 5000 times more active than paclitaxel in these experiments.[3] Their important antitumor activity combined with their relative structural simplicity compared with paclitaxel, and a much better water solubility of the epothilones define exciting opportunities for synthetic chemists, biologists, and clinicians for the development of new, powerful anti-cancer drugs. Owing to the impressive biological profile of those compounds, several groups engaged in synthetic-organic and natural product chemistry focused their efforts on developing strategies for the total synthesis of epothilones and their synthetic analogues. Several total syntheses of epothilone A[4] and epothilone B[5] as well as various partial syntheses have already been achieved.[6]

In this paper, we report on the details of an improved total synthesis of (−)-epothilone A based on our previously communicated olefin metathesis approach,[6a] with a metathesis reaction as the ring-closing step.[4e] The structure of epothilone A (**1**) is characterized by a 16-membered macrocyclic lactone carrying a *cis*-epoxide moiety, seven stereocenters, and two geometrical elements that have to be built up during the course of the synthesis. Disconnection gives three key fragments which can be assembled in a convergent manner: as shown in Scheme 1, the ester and the β-hydroxy keto functions in **1** allow the indicated disconnection to the ethyl ketone fragment **2**, aldehyde **3**, and thiazole fragment **4** as potential precursors.

Results and Discussion

The synthesis of the ethyl ketone fragment **2** was accomplished as depicted in Scheme 2. In contrast to our previously described asymmetric prenylborane synthesis of fragment **2**, the construction of the stereocenter at C3 in the epothilone macrocycle is achieved by a diastereoselective aldol reaction with the chiral acetate equivalent (*S*)-(−)-HYTRA (1,1,2-triphenyl-1,2-ethanediol acetate) (**9**).[7] Aldehyde **8** required for this aldol reaction was obtained starting from a Reformatsky reaction of α-bromo ester **5** and 3-pentanone which

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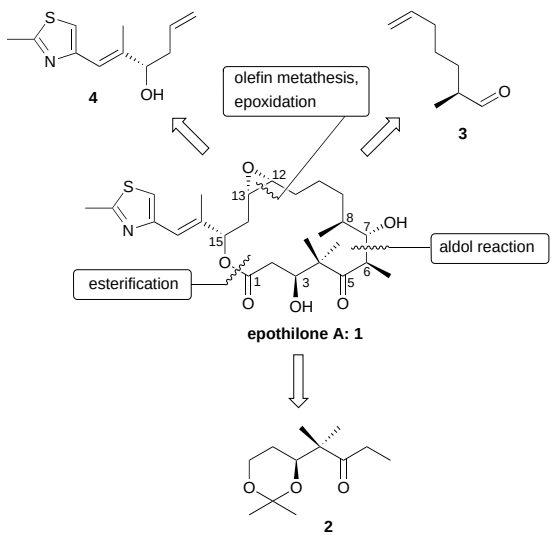
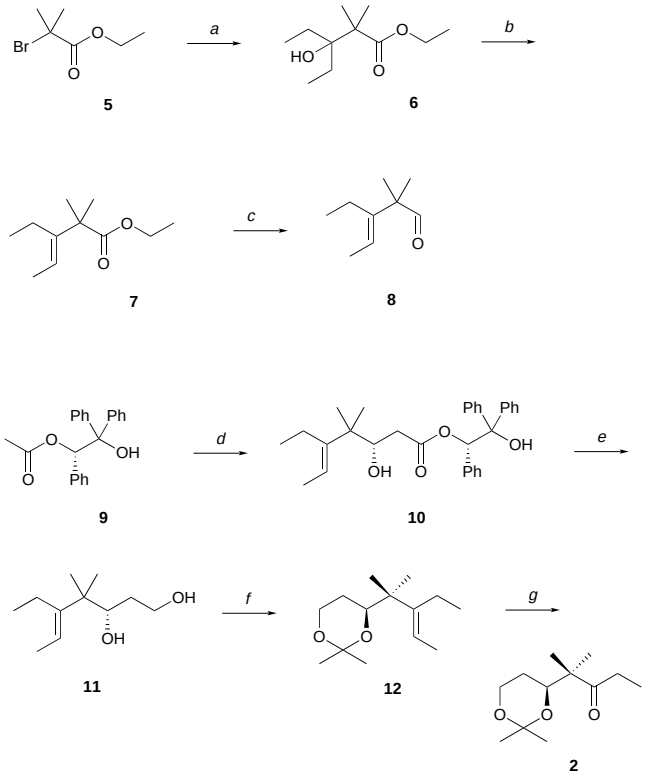


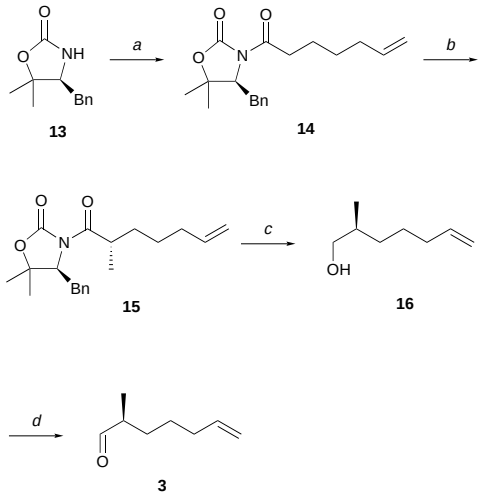
Scheme 1. Retrosynthetic analysis of epothilone A.



Scheme 2. Synthesis of the ethyl ketone fragment **2**. a) 1.1 equiv Zn dust, 3-pentanone, THF/B(OMe)$_3$ (1:1), reflux, 2 h, then RT, 20 h, 65%; b) Sicapent[9], cyclohexane, reflux, 20 min, 80%; c) 1. LAH (2 equiv), THF, reflux, 2 h; 2. Swern oxidation, 63%; d) LDA (2 equiv), THF, 0 °C, 1 h; then 1.2 equiv **8**, −78 °C, 1.5 h, 75%; e) LAH (7 equiv), Et$_2$O, reflux, 2.5 h, 90%; f) acetone, CuSO$_4$ anhydr. (1.5 equiv), *p*TsOH·H$_2$O (0.2 equiv), pyridine (0.15 equiv), RT, 24 h, 90%; g) O$_3$, CH$_2$Cl$_2$, −78 °C; then PPh$_3$ (1.2 equiv), −78 °C to RT, 4 h, 85%; LDA = lithium diisopropylamide, LAH = lithium aluminium hydride.

furnished *β*-hydroxyester **6** in 65% yield.[8] Dehydration with P_4O_{10} gave ester **7** (80%, only the *E* isomer was detected by ^{1}H and ^{13}C NMR spectroscopy), which then was converted to the aldehyde **8** by LAH reduction and subsequent Swern oxidation in 63% yield. Addition of the dianion of **9** to **8** in THF at −78 °C resulted in the formation of crystalline ester **10** in excellent diastereoselectivity (96% *de*, by HPLC) and good yield (75%). LAH reduction allowed the auxiliary to be removed nearly quantitatively and led to the diol **11** (90%). Finally, **11** was protected as the 1,3-dioxolane **12** (90%) and ozonolysis gave the desired building block **2** in 85% yield, identical with **2** prepared according to the prenyl borane protocol.[6a]

Aldehyde building block **3** was prepared by employing an Evans asymmetric-alkylation strategy, starting from SuperQuat oxazolidinone **13**,[10] which was deprotonated with *n*BuLi and treated with 6-heptenoyl chloride to afford amide **14** in 65% yield. Alkylation of the sodium enolate of **14** with MeI in THF at −78 °C provided compound **15** (85%, only one isomer was detected by ^{1}H and ^{13}C NMR spectroscopy). Alcohol **16** was then obtained in 88% yield after reductive removal (LAH)[11] of the auxiliary (recovery: 89%); subsequent oxidation with TPAP/NMO[12] gave the desired *α*-chiral aldehyde **3** (89%).



Scheme 3. Synthesis of aldehyde **3**. a) 1.15 equiv *n*BuLi, THF, −78 °C, 30 min; then 6-heptenoyl chloride, −78 °C to RT, 65%; b) 1.15 equiv NaHMDS, THF, −78 °C, 30 min; then MeI (5 equiv), −78 °C, 30 min, 85%; c) LAH (4 equiv), Et$_2$O, 0 °C, 88%; d) NMO (1.5 equiv), TPAP (0.05 equiv), CH$_2$Cl$_2$, 10 min, 89%; NaHMDS = sodium hexamethyldisilazane, NMO = *N*-methylmorpholine *N*-oxide, TPAP = tetra-*n*-propylammonium perruthenate.

Alcohol **17** (80% *ee*, provided by the previously described Sharpless resolution)[6a] was used as the starting material for the construction of the thiazole fragment **4**. Silylation followed by ozonolysis gave methyl ketone **19** (68% over two steps). Deprotonation of phosphonate **20**[6a] with *n*BuLi and reaction with **19** under Horner–Emmons conditions[13] yielded the desired trisubstituted olefin **21** as a single stereoisomer in good yield (79%). Selective desilylation of the primary hydroxy group from **21** was achieved by the action of aqueous HF and catalytic amounts of H_2SiF_6[14] in MeCN/Et$_2$O, leading to hydroxy compound **22** (92%). Dess–Martin oxidation[15] then gave aldehyde **23** in 84% yield, which was converted to the required thiazole alcohol **4** by the action of the Wittig reagent $Ph_3P{=}CH_2$ and subsequent desilylation with TBAF in THF (84% over two steps).

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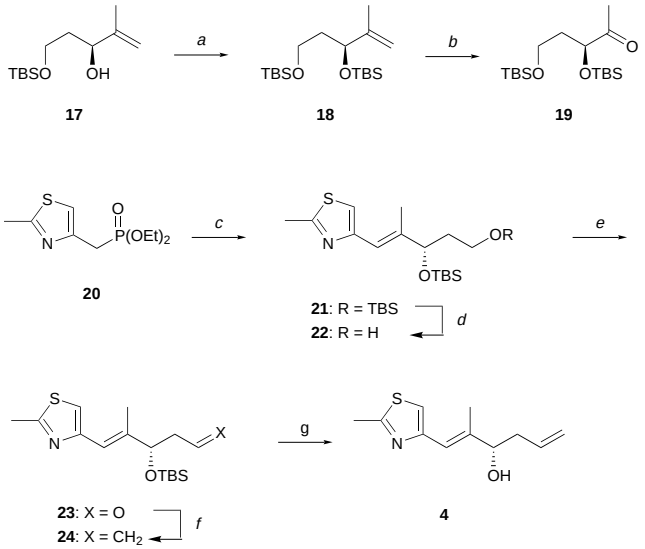
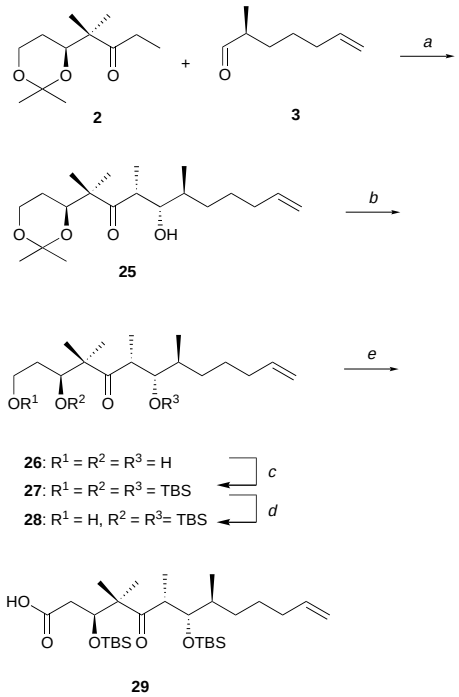
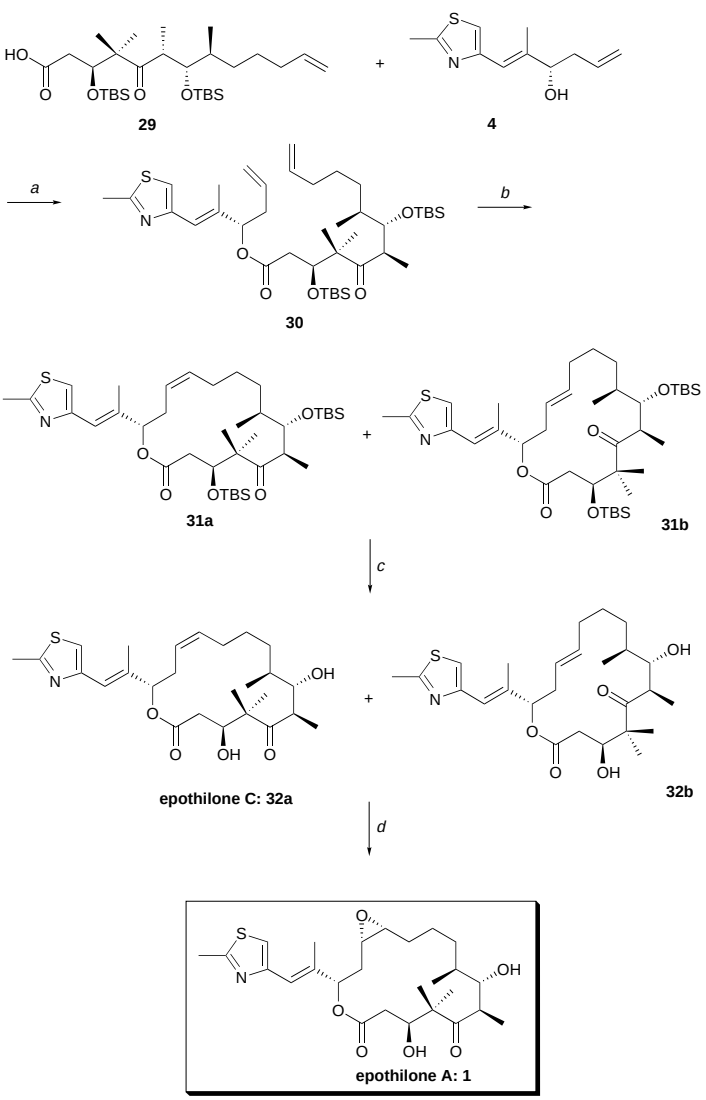


Scheme 4. Synthesis of the thiazole fragment **4**. a) 1.3 equiv TBSCl, 2.6 equiv imidazole, DMF, RT, 10 h, 98%; b) O_3, CH_2Cl_2, $-78\,^{\circ}C$; then PPh_3 (3 equiv), $-78\,^{\circ}C$ to RT, 69%; c) 1.2 equiv *n*BuLi, THF, $-78\,^{\circ}C$, 1 h; then **18** (1.0 equiv), $-78\,^{\circ}C$ to RT, 12 h, 79%; d) HF aq. (40%), glass splinters, MeCN/Et_2O (1:1), $0\,^{\circ}C$, 3 h, 92%; e) Dess–Martin periodinane (1.3 equiv), CH_2Cl_2, RT, 30 min, 84%; f) $MePPh_3Br/NaNH_2$ (1.85 equiv), THF, RT, 25 min, 85%; g) TBAF (3 equiv), MS 4 Å, THF, $0\,^{\circ}C$, 80 min, 99%; TBSCl = *tert*-butyldimethylchlorosilane, TBAF = tetra-*n*-butylammonium fluoride.

The coupling of building blocks **2**, **3**, and **4**, and the total synthesis of epothilone A (**1**) are shown in Schemes 5 and 6. Ethyl ketone **2** and aldehyde **3** were coupled in an aldol



Scheme 5. Coupling of building blocks **2** and **3**. a) LDA (0.98 equiv), THF, $-78\,^{\circ}C$, 1 h; then **3**, $-78\,^{\circ}C$, 45 min, 73%; b) PPTS (1.3 equiv), MeOH, RT, 36 h, 88%; c) TBSOTf (6 equiv), 2,6-lutidine (12 equiv), CH_2Cl_2, $-78\,^{\circ}C$, 30 min, then $0\,^{\circ}C$, 3 h, 99%; d) CSA (0.2 equiv), MeOH/CH_2Cl_2 (1:1), $0\,^{\circ}C$, 5 h, 83%; e) PDC (11 equiv), DMF, RT, 36 h, 79%; PPTS = pyridinium *p*-toluenesulfonate, TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate, CSA = camphorsulfonic acid, PDC = pyridinium dichromate.



Scheme 6. Final steps in the total synthesis of epothilone A. a) DCC (1.3 equiv), DMAP (0.2 equiv), CH_2Cl_2, RT, 16 h, 80%; b) $[RuCl_2(=CHPh)(PCy_3)]$ (0.06 equiv), CH_2Cl_2, RT, 16 h, 94%, (Z/E = 1.7:1); c) HF aq. (40%), glass splinters, MeCN/Et_2O (1:1), RT, 12 h, 65%; d) dimethyl dioxirane, CH_2Cl_2, $-35\,^{\circ}C$, 2 h, 48%; DCC = dicyclohexyl carbodiimide, DMAP = 4-dimethylaminopyridine.

reaction, which proceeds with remarkable diastereoselectivity (20:1) in favor of the desired anti Cram (6*R*,7*S*) [16] isomer **25** in high yield (73%). The optimum conditions for this coupling reaction required generation of the *syn*-lithium enolate of **2** with 0.98 equivalents of LDA in THF at $-78\,^{\circ}C$, followed by the addition of aldehyde **3**, resulting almost exclusively in the formation of **25**, which was transformed to acid **29** by a four-step sequence: Thus, cleavage of the dioxolane protective group with PPTS in MeOH led to the triol **26** in 88% yield.[17] Exposure of **26** to excess of TBSOTf and 2,6-lutidine gave trissilyl ether **27** almost quantitatively (99%). Selective deprotection of the primary TBS group of **27** was achieved by the action of CSA in MeOH/CH_2Cl_2 (1:1), leading to alcohol **28** in 83% yield.[18] Finally, acid **29** was obtained from **28** by oxidation with PDC in DMF in 79% yield.[19]

Acid **29** was coupled with thiazole building block **4** in the presence of DCC and DMAP to afford the metathesis

precursor **30** in 80% yield. The olefin-metathesis reaction of **30** with 6 mol% of the Grubbs catalyst $[RuCl_2(=CHPh)(PCy_3)]$[20] in CH_2Cl_2 gave a mixture of cyclic systems **31a** and **31b** in 94% yield, the desired *Z* isomer being slightly favored ($Z/E = 1.7:1$). As the isomers could not be separated by flash chromatography, they were subjected to the following deprotection step with HF in $MeCN/Et_2O$ as a mixture, leading to a mixture of **32a**, whose spectroscopical data were identical with the naturally occurring epothilone C, and **32b** in 65% yield. This mixture was treated with a freshly prepared solution of dimethyl dioxirane[21] in CH_2Cl_2 at $-35\,^{\circ}C$ leading to a mixture of epoxidation products. (−)-epothilone A (**1**) with properties (TLC, $[\alpha]_D$, ^1H and ^{13}C NMR, MS) identical to an authentic sample could be chromatographically isolated from this mixture in 48% yield.

Conclusions

We have presented a very flexible and efficient route to (−)-epothilone A (**1**). The asymmetric syntheses of the three key fragments have been achieved in a straightforward way. The coupling of the ketone and aldehyde fragment by a kinetically controlled aldol reaction provided stereochemically homogeneous material with outstanding facial selectivity. Finally, esterification, ring-closing metathesis, and selective epoxidation gave (−)-epothilone A (**1**) in high optical purity. In summary, our strategy offers the possibility to synthesize epothilone analogues in sufficient quantities for in vitro and in vivo biological studies.

Experimental Section

General: Solvents were dried by standard procedures and redistilled under N_2 atmosphere prior to use. All organometallic reactions were run under nitrogen. The products were purified by flash chromatography on Merck silica gel 60 (40–63 μm). Melting points are uncorrected. Mass spectra were recorded on Finnigan MAT 312, 8430, and SSQ 7000 spectrometers; high-resolution mass spectra were obtained on the latter spectrometers (reference PFK, peak matching method, accuracy ±2 ppm). IR spectra were recorded on Perkin–Elmer 2000, 580, FT 1710, and Nicolet 320 FT-IR spectrometers. UV spectra were recorded on Hewlett–Packard 8452 A and Perkin–Elmer Lambda 19 spectrometers. NMR spectra were recorded on Bruker AC 200, AM 400, and DPX 400 spectrometers. Optical rotations were recorded with a Perkin–Elmer 241 polarimeter.

Ethyl 3-ethyl-3-hydroxy-2,2-dimethylpentanoate (6): A suspension of zinc dust (10.79 g, 0.165 mol) in THF (40 mL) and $B(OMe)_3$ (40 mL) was activated with 1,2-dibromoethane (0.26 mL, 3.0 mmol) and TESOTf (0.34 mL, 1.5 mmol). A mixture of 3-pentanone (15.9 mL, 0.15 mol) and ethyl 2-bromo-2-methylpropanoate **5** (23.4 mL, 0.165 mol) was added slowly to the activated zinc suspension. The reaction mixture was heated gently in a hot air stream until the reaction started. The addition was performed at such a rate that the mixture gently refluxed. After addition of the reactants, the mixture was refluxed for 2 h and stirred at room temperature for 20 h. The reaction was quenched by addition of 25% aqueous NH_3 solution (45 mL) at 0 °C. Glycerine (45 mL) and Et_2O (40 mL) were added and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 × 40 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by vacuum distillation afforded β-hydroxy alcohol **6** (19.72 g, 65%) as a colorless liquid. B.p. 108–110 °C 10 mbar^{-1}; IR (film): $\tilde{\nu}_{max} = 3492$, 2982, 1699, 1472, 1390, 1271, 1153, 1026, 968, 857, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.17$ (q, $^3J = 7.1$ Hz, 2H; CH_3CH_2OCO), 3.78 (s, 1H; OH), 1.56 (m, 4H; H-4), 1.29 (t, $^3J = 7.1$ Hz, 3H; CH_3CH_2OCO), 1.22 (s, 6H; C2-CH_3), 0.93 (t, $^3J = 7.5$ Hz, 6H; H-5); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 179.2$, 76.2, 60.9, 50.3, 28.2, 21.6, 14.1, 8.9; MS (PCI, CH_4): *m/z* (%): 203.4 (100) $[M+H]^+$, 185.4 (78) $[M+H-H_2O]^+$, 171.1 (11), 155.1 (23), 145.1 (24), 111.1 (16); $C_{11}H_{22}O_3$ (202.3): calcd C 65.31, H 10.96; found C 65.09, H 11.35.

Ethyl (*E*)-3-ethyl-2,2-dimethyl-3-pentenoate (7): Hydroxy ester **6** (9.74 g, 48.1 mmol) was heated under reflux with Sicapent[9] (11.84 g) in cyclohexane (40 mL) for 20 min. The solvent was removed by distillation. Vacuum distillation of the residue afforded ester **7** (7.10 g, 80%) as a colorless liquid. B.p. 60–63 °C 3 mbar^{-1}; IR (film): $\tilde{\nu}_{max} = 2976$, 1776, 1730, 1472, 1383, 1255, 1134, 1027, 823, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.41$ (q, $^3J = 6.8$ Hz, 1H; H-4), 4.11 (q, $^3J = 7.2$ Hz, 2H; CH_3CH_2OCO), 2.06 (q, $^3J = 7.6$ Hz, 2H; $CH_3CH_2C{=}C$), 1.65 (d, $^3J = 6.8$ Hz, 3H; H-5), 1.28 (s, 6H; C2-CH_3), 1.23 (t, $^3J = 7.1$ Hz, 3H; CH_3CH_2OCO), 0.97 (t, $^3J = 7.5$ Hz, 3H; $CH_3CH_2C{=}C$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 177.2$, 144.1, 118.5, 60.3, 48.4, 24.9, 21.7, 14.1, 13.9, 13.5; MS (PCI, CH_4): *m/z* (%): 185.1 (69) $[M+H]^+$, 169.1 (14), 157.1 (100), 153.0 (16), 139.0 (9), 124.9 (15), 111.0 (30), 57.0 (38); HRMS (EI): calcd for $C_{11}H_{20}O_2$ 184.1463, found 184.146.

(*E*)-3-Ethyl-2,2-dimethyl-3-pentenal (8): LAH (2.95 g, 77.6 mmol, 2.0 equiv) was added to a solution of ester **7** (7.15 g, 38.8 mmol) in THF (40 mL). The mixture was refluxed for 2 h. After cooling to 0 °C, Et_2O (30 mL) was added, and the mixture was quenched by dropwise addition of water (2.95 mL), 15% aqueous NaOH (2.95 mL), and water (4.50 mL). Celite (400 mg) was added, and the mixture was stirred for 30 min at room temperature. The precipitate was filtered off by suction and washed with Et_2O (4 × 40 mL). The filtrate and the washings were combined and concentrated in vacuo to furnish crude (*E*)-3-ethyl-2,2-dimethyl-3-penten-1-ol as a colorless liquid, which was used for the preparation of aldehyde **8** without further purification. An analytical sample of the alcohol was obtained by vacuum distillation: B.p. 105–106 °C 30 mbar^{-1}; IR (film): $\tilde{\nu}_{max} = 3393$, 2970, 1702, 1476, 1377, 1046, 960, 822, 643 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.43$ (q, $^3J = 6.7$ Hz, 1H; H-4), 3.35 (s, 2H; H-1), 2.07 (q, $^3J = 7.6$ Hz, 2H; $CH_3CH_2C{=}C$), 1.67 (d, $^3J = 6.7$ Hz, 3H; H-5), 1.34 (br s, 1H; OH), 1.04 (s, 6H; C2-CH_3), 1.00 (t, $^3J = 7.5$ Hz, 3H; $CH_3CH_2C{=}C$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 145.2$, 120.5, 69.7, 42.0, 24.0, 20.0, 14.2, 13.6; MS (70 eV, EI): *m/z* (%): 142.1 (7) $[M]^+$, 125.1 (48), 111.0 (34), 96.2 (14), 83.0 (35), 71.1 (37), 69.1 (100), 57.0 (42), 55.0 (66).

DMSO (6.59 mL, 93.0 mmol, 2.0 equiv) in CH_2Cl_2 (20 mL) was added dropwise at −78 °C to a stirred solution of $(COCl)_2$ (3.71 mL, 42.7 mmol, 1.1 equiv) in CH_2Cl_2 (97 mL) within 5 min. The mixture was stirred for 10 min at −70 °C. The crude (*E*)-3-ethyl-2,2-dimethyl-3-penten-1-ol dissolved in CH_2Cl_2 (38 mL) was added dropwise within 5 min. The mixture was then stirred for 1 h at −70 °C. The reaction was quenched by dropwise addition of NEt_3 (27 mL, 194.0 mmol, 5.0 equiv). The mixture was warmed to room temperature within 45 min. Water (97 mL) was added, and the mixture was stirred for 10 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by vacuum distillation afforded aldehyde **8** (3.43 g, 63% over two steps) as a colorless liquid. B.p. 85–86 °C 28 mbar^{-1}; IR (film): $\tilde{\nu}_{max} = 3403$, 2974, 1728, 1472, 1376, 1144, 1086, 975, 825 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.27$ (s, 1H; H-1), 5.41 (q, $^3J = 6.8$ Hz, 1H; H-4), 2.02 (q, $^3J = 7.6$ Hz, 2H; $CH_3CH_2C{=}C$), 1.69 (d, $^3J = 6.9$ Hz, 3H; H-5), 1.17 (s, 6H; C2-CH_3), 0.96 (t, $^3J = 7.6$ Hz, 3H; $CH_3CH_2C{=}C$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 203.5$, 141.4, 122.6, 52.7, 24.2, 20.9, 14.1, 13.8; MS (PCI, CH_4): *m/z* (%): 141.0 (29) $[M+H]^+$, 127.1 (98), 111.1 (100), 97.1 (2), 83.1 (3); HRMS (EI): calcd for $C_9H_{16}O$ 140.1201, found 140.116.

(1*S*)-2-Hydroxy-1,2,2-triphenylethyl (3*S*,5*E*)-5-ethyl-3-hydroxy-4,4-dimethyl-5-heptenoate (10): *n*BuLi (3.20 mL, 8.0 mmol, 2.5 M solution in hexanes) was added at −78 °C to a solution of diisopropylamine (1.28 mL, 8.0 mmol) in THF (10 mL) cooled to −78 °C. This LDA solution was stirred for 30 min at 0 °C and added dropwise to a solution of (*S*)-(−)-2-hydroxy-1,2,2-triphenyl acetate (**9**) (1.330 g, 4.0 mmol) in THF (25 mL) at −78 °C. The mixture was stirred for 1 h at 0 °C. The resulting orange-red solution was cooled to −78 °C, and a solution of aldehyde **8** (673 mg, 4.8 mmol, 1.2 equiv) in THF (5.0 mL) was added dropwise. The mixture was stirred for 90 min. The reaction was quenched with saturated aqueous NH_4Cl solution (30 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification of the

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residue by flash chromatography (pentane/Et_2O 3:1) afforded β-hydroxy ester **10** (1.41 g, 75%, 94% *de*) as a colorless crystalline solid. M.p. 144–145 °C, $[\alpha]_D^{20} = -163.3$, $[\alpha]_{546}^{20} = -195.5$ ($c = 1.0$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} =$ 3548, 3465, 2972, 1724, 1494, 1450, 1290, 1153, 990, 890, 751, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.59-7.54$ (m, 2H; $H_{arom.}$), 7.38–7.02 (m, 13H; $H_{arom.}$), 6.70 (s, 1H; PhC*H*), 5.30 (q, $^3J = 6.8$ Hz, 1H; H-6), 3.78 (ddd, $^3J = 10.0$ Hz, $^3J = 2.7$ Hz, $^3J = 2.5$ Hz, 1H; H-3), 2.86 (s, 1H; Ph_2CO*H*), 2.31 (dd, $^2J = 15.7$ Hz, $^3J = 2.2$ Hz, 1H; H-2), 2.21 (dd, $^2J = 15.7$ Hz, $^3J = 10.0$ Hz, 1H; H-2), 2.03 (d, $^3J = 3.1$ Hz, 1H; C3-OH), 1.98 (dq, $^4J = 2.2$ Hz, $^3J =$ 7.5 Hz, 2H; CH_3CH_2C≡C), 1.60 (d, $^3J = 6.8$ Hz, 3H; H-7), 0.98, 0.91 (2s, 2 × 3H; C2-CH_3), 0.91 (t, $^3J = 7.6$ Hz, 3H; CH_3CH_2C≡C); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 172.2, 146.0, 144.7, 142.6, 135.6, 128.4, 128.3, 128.0, 127.8, 127.5, 127.3, 127.1, 126.3, 126.2, 120.3, 80.4, 78.9, 72.3, 44.0, 37.4, 22.9, 21.3, 20.2, 14.3, 13.6; MS (70 eV, EI): *m*/*z* (%): 472.3 (< 0.4) $[M]^+$, 455.2 (0.4), 290.3 (4), 273.1 (70), 256.1 (12), 195.1 (17), 183.1 (100), 167.2 (12), 112.0 (16), 105.0 (26), 69.2 (10); $C_{31}H_{36}O_4$ (472.6): calcd C 78.78, H 7.68; found C 78.87, H 7.73.

(3*S*,5*E*)-5-Ethyl-4,4-dimethyl-5-heptene-1,3-diol (11): LAH (1.325 g, 35.0 mmol, 7.0 equiv) was added portionwise to a refluxing solution of ester **10** (2.364 g, 5.0 mmol) in Et_2O (50 mL) within a period of 2 h. Refluxing was continued for 30 min. After cooling to 0 °C, the reaction was quenched by dropwise addition of water (1.35 mL) and 15% aqueous NaOH (1.35 mL). Et_2O (40 mL) and water (1.35 mL) were added. The mixture was stirred for 1 h at room temperature until a white precipitate formed which was filtered off by suction through a small plug of celite. The precipitate was washed with Et_2O (4 × 40 mL). The filtrate and washings were combined, and concentrated in vacuo. Purification of the residue by flash chromatography (pentane/Et_2O 2:1) afforded (*S*)-2,2,1-triphenylethane-1,2-diol (**9**) (922 mg, 99%) as a colorless crystalline solid, and alcohol **11** (836 mg, 90%) as a colorless oil. $[\alpha]_D^{20} = -30.7$, $[\alpha]_{546}^{20} = -37.5$ ($c = 1.0$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} =$ 3313, 2969, 1472, 1382, 1312, 1053, 956, 822, 659 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.43$ (q, $^3J = 6.8$ Hz, 1H; H-6), 3.86–3.76 (m, 2H; H-1), 3.68 (dd, $^3J = 10.3$ Hz, $^3J = 2.1$ Hz, 1H; H-3), 3.00 (br s, 1H; OH), 2.20 (br s, 1H; OH), 2.17–2.02 (m, 2H; CH_3CH_2C≡C), 1.67 (d, $^3J = 6.8$ Hz, 3H; H-7), 1.71–1.52 (m, 2H; H-2), 1.03, 1.01 (2s, 2 × 3H; C4-CH_3), 0.91 (t, $^3J = 7.6$ Hz, 3H; CH_3CH_2C≡C); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 146.2, 121.1, 75.8, 62.6, 44.4, 32.7, 22.8, 21.1, 20.1, 14.3, 13.6; MS (70 eV, EI): *m*/*z* (%): 186.0 (0.6) $[M]^+$, 177.0 (1), 141.0 (3), 112.0 (100), 96.9 (19), 83.0 (75), 74.9 (13), 68.9 (60), 54.9 (34); HRMS (EI): calcd for $C_{11}H_{22}O_2$ 186.1620, found 186.157.

(4*S*)-4-[(*E*)-2-Ethyl-1,1-dimethyl-2-butenyl]-2,2-dimethyl-1,3-dioxane (12): Anhydrous $CuSO_4$ (478 mg, 3.0 mmol, 1.5 equiv), *p*$TsOH \cdot H_2O$ (76 mg, 0.4 mmol, 0.2 equiv), and pyridine (24 μL, 0.3 mmol, 0.15 equiv) was added to a solution of diol **11** (372 mg, 2.0 mmol) in acetone (30 mL). The mixture was stirred for 24 h at room temperature. Saturated aqueous $NaHCO_3$ solution (40 mL) was added and the aqueous layer was extracted with Et_2O (4 × 60 mL). The combined organic extracts were dried over $MgSO_4$ and carefully concentrated in vacuo. Purification of the residue by flash chromatography (pentane/Et_2O 40:1) gave acetonide **12** (812 mg, 90%) as a colorless oil. $[\alpha]_D^{20} = +14.3$, $[\alpha]_{546}^{20} = +17.0$ ($c = 1.0$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} =$ 2970, 1475, 1380, 1271, 1197, 1108, 971, 860, 765 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.32$ (q, $^3J = 6.8$ Hz, 1H; H-3′), 3.88 (dt, $^2J =$ 11.8 Hz, $^3J = 2.9$ Hz, 1H; H-6), 3.80 (ddd, $^2J = 11.6$ Hz, $^3J = 5.5$ Hz, $^3J =$ 2.0 Hz, 1H; H-6), 3.70 (dd, $^3J = 11.6$ Hz, $^3J = 2.5$ Hz, 1H; H-4), 2.18–2.00 (m, 2H; CH_3CH_2C≡C), 1.62 (d, $^3J = 6.8$ Hz, 3H; H-4′), 1.59–1.46 (m, 1H; H-5), 1.41, 1.35 (2s, 2 × 3H; C2-CH_3), 1.18 (ddd, $^2J = 13.1$ Hz, $^3J = 4.7$ Hz, $^3J = 2.6$ Hz, 1H; H-5), 1.03, 1.00 (2s, 2 × 3H; C1′-CH_3), 0.98 (t, $^3J = 7.5$ Hz, 3H; CH_3CH_2C≡C); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 146.1, 119.2, 98.3, 74.2, 60.4, 42.9, 29.9, 26.1, 24.2, 21.2, 20.8, 19.1, 14.4, 13.6; MS (70 eV, EI): *m*/*z* (%): 226.1 (8) $[M]^+$, 211.1 (14), 205.1 (3), 151.0 (14), 114.9 (100), 94.7 (10), 72.9 (32), 58.9 (60); HRMS (EI): calcd for $C_{14}H_{26}O_2$ 226.1933, found 226.193.

2-[(4*S*)-2,2-dimethyl-1,3-dioxan-4-yl]-2-methyl-3-pentanone (2): A stream of ozone in oxygen was bubbled through a solution of acetonide **12** (226 mg, 1.0 mmol) in CH_2Cl_2 (40 mL) at −78 °C until the blue color of the solution persisted. PPh_3 (262 mg, 1.2 equiv) was added at −78 °C, the mixture was allowed to warm to room temperature within 4 h and concentrated in vacuo. Purification of the residue by flash chromatography (pentane/Et_2O 5:1) furnished ethyl ketone **2** (182 mg, 85%) as colorless crystals, m.p. 37 °C, identical ([α], IR, ^1H NMR, ^{13}C NMR) with substance obtained from the previously described prenyl borane protocol.[6a]

(4*S*)-4-Benzyl-5,5-dimethyl-3-(6-heptenoyl)-1,3-oxazolidin-2-one (14): Oxalyl chloride (822 μL, 9.43 mmol, 2.0 equiv) was added dropwise at room temperature to a solution of 6-heptenoic acid (604 mg, 4.71 mmol) in CH_2Cl_2 (15 mL). The mixture was stirred for 3 h and then refluxed for another 15 min. Evaporation at 40 mbar yielded the crude 6-heptenoyl chloride, which was used without further purification for the synthesis of oxazolidinone **14**: SuperQuat **13** (774 mg, 3.77 mmol) was dissolved in THF (40 mL) and cooled to −78 °C. *n*BuLi (1.73 mL, 2.5 M in hexanes, 4.34 mmol, 1.15 equiv) was added and stirring was continued at −78 °C for 30 min. A solution of the crude 6-heptenoyl chloride in THF (10 mL) was added dropwise to the reaction mixture. The mixture was allowed to warm to room temperature, quenched with saturated aqueous $NaHCO_3$ solution (40 mL), and extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (pentane/Et_2O 4:1) to yield oxazolidinone **14** (969 mg, 65% over two steps) as a colorless oil. $[\alpha]_D^{20} = -31.5$ ($c = 1.68$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} =$ 2934, 1779, 1699, 1457, 1357, 1278, 1209, 1160, 100, 914, 734, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.33-7.20$ (m, 5H; Ar-H), 5.86–5.74 (m, 1H; H-6′), 5.05–4.92 (m, 2H; H-7), 4.51 (dd, $^3J = 9.5$ Hz, $^3J = 4.0$ Hz, 1H; H-4), 3.14 (dd, $^2J = 14.3$ Hz, $^3J = 4.0$ Hz, 1H; C4-CH_2), 2.98–2.86 (m, 1H; H-2′), 2.88 (dd, $^2J = 14.3$ Hz, $^3J = 9.5$ Hz, 1H; C4-CH_2), 2.12–2.03 (m, 2H, H-5′), 1.69–1.58 (m, 3H), 1.49–1.40 (m, 2H)(H-2′, H-3′, H-4′), 1.37, 1.35 (2s, 2 × 3H; C5-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 173.4, 152.6, 138.4, 137.0, 129.1, 128.6, 126.8, 114.7, 82.1, 63.5, 35.5, 35.4, 33.4, 28.5, 28.3, 23.8, 22.3; MS (PCI, CH_4): *m*/*z* (%): 316.1 (100) $[M+H]^+$, 300.1 (7), 272.1 (19), 234.0 (3); HRMS (EI): calcd for $C_{19}H_{25}NO_3$ 315.1834, found 315.184.

(4*S*)-4-Benzyl-5,5-dimethyl-3-[(2*S*)-2-methyl-6-heptenoyl]-1,3-oxazolidin-2-one (15): A solution of oxazolidinone **14** (949 mg, 3.01 mmol) in THF (10 mL) was added slowly to a solution of NaHMDS (3.46 mL, 1.0 M in Et_2O, 3.46 mmol) in THF (4 mL) at −78 °C. The mixture was stirred for 1 h at −78 °C. MeI (937 μL, 15.0 mmol, 5.0 equiv) was added and stirring was continued for 30 min at −78 °C. The reaction was quenched by addition of saturated NH_4Cl solution (30 mL), warmed to room temperature and extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The crude product was purified by flash chromatography (pentane/Et_2O 6:1) to obtain alkylated amide **15** (841 mg, 85%) as a viscous, colorless oil. $[\alpha]_D^{20} = -5.7$ ($c = 1.06$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} =$ 2976, 2935, 1774, 1698, 1457, 1353, 1277, 1242, 1099, 991, 915, 734, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.33-7.20$ (m, 5H; Ar-H), 5.84–5.72 (m, 1H; H-6′), 5.03–4.91 (m, 2H; H-7), 4.51 (dd, $^3J = 9.3$ Hz, $^3J = 4.1$ Hz, 1H; H-4), 3.79–3.68 (m, 1H; H-2′), 3.08 (dd, $^2J =$ 14.3 Hz, $^3J = 4.0$ Hz, 1H; C4-CH_2), 2.88 (dd, $^2J = 14.3$ Hz, $^3J = 9.3$ Hz, 1H; C4-CH_2), 2.10–1.97 (m, 2H; H-5), 1.76–1.64 (m, 1H), 1.46–1.38 (m, 3H)(H-3′, H-4′), 1.38, 1.36 (2s, 2 × 3H; C5-CH_3), 1.13 (d, $^3J = 6.8$ Hz, 3H; C2-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 177.3, 152.3, 138.4, 136.9, 129.1, 128.6, 126.8, 114.7, 81.9, 63.6, 37.6, 35.5, 33.7, 33.0, 28.4, 26.5, 22.2, 17.4; MS (PCI, CH_4): *m*/*z* (%): 330.2 (100) $[M+H]^+$, 314.2 (6) $[M-CH_3]^+$, 286.1 (14), 261.0 (1), 234.0 (3); HRMS (EI): calcd for $C_{20}H_{27}NO_3$ 329.1991, found 329.199.

(*S*)-2-Methyl-6-hepten-1-ol (16): A solution of compound **15** (827 mg, 2.51 mmol) in Et_2O (12 mL) was titrated at 0 °C with portions of a suspension of LAH (approx. 250 mg consumed, 4 equiv) in Et_2O until TLC showed complete conversion of the starting material. Water (0.8 mL) was added dropwise, and stirring was continued until the precipitate appeared white. The suspension was filtered over celite, and the residue was washed with Et_2O (150 mL). The solvent was removed carefully under reduced pressure. Flash chromatography (pentane/Et_2O 3:1) yielded SuperQuat **13** (459 mg, 89%) as colorless crystals and alcohol **16** (282 mg, 88%) as a colorless liquid. $[\alpha]_D^{20} = -12.5$ ($c = 1.03$, $CDCl_3$); IR (film): $\tilde{\nu}_{max} =$ 3347, 2929, 2874, 1642, 1462, 1379, 1035, 910 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.89-5.79$ (m, 1H; H-6), 5.06–4.95 (m, 2H; H-7), 3.55–3.42 (m, 2H; H-1), 2.34 (s; OH), 2.12–2.03 (m, 2H; H-5), 1.70–1.33 (m, 5H; H-2, H-3, H-4), 0.94 (d, $^3J = 6.8$ Hz, 3H; C2-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 138.9, 114.4, 68.2, 35.6, 34.0, 32.6, 26.3, 16.5; MS (70 eV, EI): *m*/*z* (%): 130 (1) $[M]^+$, 128 (5), 110 (9), 97 (12), 95 (44), 81 (44), 71 (28), 69 (34), 68 (46), 67 (35), 56 (33), 55 (100), 54 (51), 43 (20); HRMS (EI): calcd for $C_8H_{16}O$ 128.1201, found 128.108.

(*S*)-2-Methyl-6-heptenal (3): Dess–Martin periodinane[15] (1.27 g, 2.99 mmol, 1.3 equiv) was added to a solution of alcohol **16** (295 mg,

2.30 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred for 25 min at room temperature and quenched with phosphate buffer solution (7 mL, 0.1M, pH 7.0). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were dried over $MgSO_4$ and concentrated carefully in vacuo. Flash chromatography (pentane/Et_2O 10:1) of the residue afforded aldehyde **3** (224 mg, 77%) as a colorless liquid. Alternative procedure: Freshly activated molecular sieves (500 mg, 4 Å) were added to a solution of alcohol **16** (275 mg, 2.15 mmol) and NMO (377 mg, 3.22 mmol, 1.5 equiv) in CH_2Cl_2 (10 mL). The mixture was stirred vigorously for 10 min, and TPAP (38 mg, 0.107 mmol, 0.05 equiv) was added. After 10 min, the mixture was flash-filtered with CH_2Cl_2 over a short silica gel column. The solvent was removed under ambient pressure to yield aldehyde **3** (239 mg, 89%) as a colorless liquid. $[\alpha]_D^{20} = +25.7$ ($c = 1.0$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 2977$, 2935, 2861, 2711, 1728, 1642, 1461, 998, 913 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.62$ (d, $^3J = 1.9$ Hz, 1H; H-1), 5.84–5.74 (m, 1H; H-6), 5.04–4.95 (m, 2H; H-7), 2.38–2.32 (m, 1H; H-2), 2.10–2.05 (m, 2H; H-5), 1.77–1.33 (m, 4H; H-3, H-4), 1.10 (d, $^3J = 7.2$ Hz, 3H; C2-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 205.0$, 138.1, 114.8, 46.1, 33.6, 29.8, 26.1, 13.3; MS (EI, 70 eV): m/z (%) = 126 (4) $[M]^+$, 125 (18) $[M-H]^+$, 111 (24), 97 (39), 95 (18), 82 (21), 74 (42), 71 (26), 69 (100), 67 (20), 55 (90), 43 (31), 41 (50); HRMS (EI): calcd for $C_8H_{14}O$ 126.1045, found 126.100.

(*S*)-1,3-Di-(*tert*-butyldimethylsilyloxy)-4-methyl-4-pentene (18): Imidazole (77 mg, 1.1 mmol, 2.6 equiv) and TBSCl (85 mg, 0.56 mmol, 1.3 equiv) were added to a solution of alcohol **17** (100 mg, 0.43 mmol) in DMF (1.5 mL). The mixture was stirred for 10 h at room temperature. Flash chromatography (pentane/Et_2O 20:1) of the reaction mixture yielded bis-silyl ether **18** (146 mg, 98%) as a colorless oil. $[\alpha]_D^{20} = -10.0$ ($c = 1.0$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 2956$, 2859, 1472, 1256, 1091, 836, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.89-4.84$ (m, 1H; H-5), 4.76–4.70 (m, 1H; H-5), 4.21 (dd, $^3J = 7.6$ Hz, $^3J = 5.0$ Hz, 1H; H-3), 3.67–3.55 (m, 2H; H-1), 1.76–1.58 (m, 2H; H-2), 1.68 (s, 3H; C2-CH_3), 0.89, 0.88 (2s, 2 × 9H; $OSiC(CH_3)_3$), 0.01, 0.00 (4s, 4 × 3H; $OSi(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 147.8$, 110.4, 73.4, 59.8, 39.5, 25.9, 25.8, 18.3, 18.2, 17.1, −4.8, −5.2, −5.3; MS (PCI, isobutane): m/z (%): 345 (100) $[M+H]^+$, 329 (4) $[M-CH_3]^+$, 287 (28) $[M-t\mathrm{Bu}]^+$, 259 (8), 213 (95), 206 (26), 164 (12), 132 (7), 98 (15); HRMS (EI): calcd for $C_{18}H_{40}O_2Si_2$ 344.2567, found 344.343.

(*S*)-3,5-Di-(*tert*-butyldimethylsilyloxy)-2-pentanone (19): A solution of bis-silyl ether **18** (146 mg, 0.424 mmol) in CH_2Cl_2 (70 mL) was cooled to −78 °C. A stream of ozone in oxygen was bubbled through the solution until the blue color persisted, then the excess of ozone was removed by bubbling N_2 through the solution. PPh_3 (333 mg, 1.27 mmol, 3.0 equiv) was added, and the mixture was allowed to warm to room temperature. Stirring was continued until TLC indicated conversion of the intermediate product. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (pentane/Et_2O 19:1) to yield methyl ketone **19** (101 mg, 69%) as a colorless oil. $[\alpha]_D^{20} = -8.9$ ($c = 1.0$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 2957$, 2859, 1720, 1473, 1361, 1256, 1106, 838, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.15$ (dd, $^3J = 6.8$ Hz, $^3J = 5.3$ Hz, 1H; H-3), 3.75–3.58 (m, 2H; H-5), 2.16 (s, 3H; H-1), 1.88–1.70 (m, 2H; H-4), 0.92, 0.88 (2s, 2 × 9H; $OSiC(CH_3)_3$), 0.06, 0.06, 0.04, 0.03 (4s, 4 × 3H; $OSi(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 212.0$, 75.8, 58.4, 37.8, 25.9, 25.7, 25.4, 18.3, 18.1, −5.0, −5.1, −5.4; MS (PCI, NH_3): m/z (%): 347 (100) $[M+H]^+$, 324 (17), 279 (93), 231 (4), 215 (7), 157 (8), 94 (11); HRMS (EI): calcd for $C_{17}H_{38}O_3Si_2$ 346.2360, found 346.235.

(3*S*,4*E*)-1,3-Di-(*tert*-butyldimethylsilyloxy)-4-methyl-5-(2-methyl-1,3-thiazol-4-yl)-4-pentene (21): *n*BuLi (23.5 mL, 58.7 mmol, 1.2 equiv of a 2.5M solution in hexanes) was added dropwise to a stirred solution of phosphonate **20** (14.64 g, 58.7 mmol, 1.2 equiv) in THF (150 mL) cooled to −78 °C. After the mixture was stirred at −78 °C for 1 h, a solution of methyl ketone **19** (16.96 g, 48.9 mmol, 1.0 equiv) in THF (100 mL) was added dropwise at −78 °C. The mixture was allowed to warm to room temperature within 12 h. The reaction was quenched with saturated aqueous NH_4Cl solution (100 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (CH_2Cl_2, then Et_2O) yielded unconverted methyl ketone **19** (3.22 g, 22%) and *E* olefin **21** (17.07 g, 79%) as colorless oils. $[\alpha]_D^{20} = -0.7$ ($c = 0.46$, CH_2Cl_2); IR (film): $\tilde{\nu}_{max} = 2956$, 2858, 1472, 1256, 1099, 836, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.91$ (s, 1H; H-5′), 6.47 (s, 1H; H-5), 4.31 (dd, $^3J = 8.0$ Hz, $^3J = 4.6$ Hz, 1H; H-3), 3.71–3.58 (m, 2H; H-1), 2.70 (s, 3H; C2′-CH_3), 1.99 (d, $^4J = 1.1$ Hz, 3H; C4-CH_3), 1.83–1.75 (m, 2H; H-2), 0.89, 0.88 (2s, 2 × 9H; $OSiC(CH_3)_3$), 0.06, 0.00 (2s, 2 × 3H; $OSi(CH_3)_2$), 0.03 (s, 6H; $OSi(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 164.3$, 153.2, 142.6, 118.6, 115.0, 75.0, 59.6, 39.8, 25.9, 25.8, 19.2, 18.2, 13.8, −4.6, −5.1, −5.3, −5.4; MS (70 eV, EI): m/z (%): 441.2 (35) $[M]^+$, 384.1 (89) $[M-t\mathrm{Bu}]^+$, 356.1 (80), 309.1 (49), 282.1 (65) $[C_{14}H_{24}NOSSi]^+$, 252.0 (70), 178.0 (38), 147.0 (71), 73.1 (100); HRMS (EI): calcd for $C_{22}H_{43}NO_2SSi_2$ 441.2553, found 441.255.

(3*S*,4*E*)-3-(*tert*-Butyldimethylsilyloxy)-4-methyl-5-(2-methyl-1,3-thiazol-4-yl)-4-penten-1-ol (22): In a PE bottle, silyl ether **21** (13.255 g, 30.0 mmol) was dissolved in a mixture of Et_2O (120 mL) and MeCN (120 mL). Aqueous 40% hydrofluoric acid (20 mL) and finely ground splinters of glass (133 mg) were added at 0 °C to the vigorously stirred mixture. The mixture was stirred for 2 h at 0 °C. Hydrofluoric acid (20 mL) was added and stirring was continued for 1 h at 0 °C. The reaction was quenched by carefully adding solid $NaHCO_3$ (84.0 g, 1.0 mol) within 15 min at 0 °C. After the mixture was stirred for 30 min at 0 °C, water was added until the solids dissolved (the pH was adjusted to 6–8 by further addition of $NaHCO_3$, if necessary). The mixture was extracted with CH_2Cl_2 (4 × 200 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (pentane/Et_2O 4:1) afforded alcohol **22** (9.041 g, 92%) as a viscous, colorless oil. $[\alpha]_D^{20} = -5.7$ ($c = 1.0$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3357$, 2955, 2857, 1472, 1252, 1074, 837, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.92$ (s, 1H; H-5′), 6.52 (s, 1H; H-5), 4.38 (dd, $^3J = 7.4$ Hz, $^3J = 4.5$ Hz, 1H; H-3), 3.80–3.67 (m, 2H; H-1), 2.70 (s, 3H; C2′-CH_3), 2.40 (s, 1H; OH), 2.01 (d, $^4J = 1.2$ Hz, 3H; C4-CH_3), 1.93–1.76 (m, 2H; H-2), 0.91 (s, 9H; $OSiC(CH_3)_3$), 0.10, 0.03 (2s, 2 × 3H; $OSi(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 164.5$, 153.0, 141.6, 118.8, 115.4, 77.5, 60.4, 38.2, 25.8, 19.2, 18.1, 14.4, −4.6, −5.2; MS (70 eV, EI): m/z (%): 327 (18) $[M]^+$, 282 (39), 270 (94) $[M-t\mathrm{Bu}]^+$, 268 (29), 252 (12), 240 (14), 178 (41), 168 (100), 164 (23), 105 (27), 75 (59), 73 (42); HRMS (EI): calcd for $C_{16}H_{29}NO_2SSi$ 327.1688, found 327.168.

(3*S*,4*E*)-3-(*tert*-Butyldimethylsilyloxy)-4-methyl-5-(2-methyl-1,3-thiazol-4-yl)-4-pentenal (23): Dess–Martin periodinane[15] (478 mg, 2.91 mmol, 1.3 equiv) was added to a solution of alcohol **22** (732 mg, 2.24 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred for 30 min at room temperature. The solvent was removed under reduced pressure. Flash chromatography (pentane/Et_2O 4:1) yielded aldehyde **23** (614 mg, 84%) as a pale yellow oil. $[\alpha]_D^{20} = -11.9$ ($c = 1.0$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 2956$, 2857, 1727, 1472, 1389, 1254, 1085, 838, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.79$ (t, $^3J = 2.7$ Hz, 1H; H-1), 6.94 (s, 1H; H-5′), 6.56 (s, 1H; H-5), 4.69 (dd, $^3J = 8.2$ Hz, $^3J = 4.0$ Hz, 1H; H-3), 2.75 (ddd, $^2J = 15.5$ Hz, $^3J = 7.7$ Hz, $^3J = 2.9$ Hz, 1H; H-2), 2.70 (s, 3H; C2′-CH_3), 2.51 (ddd, $^2J = 15.5$ Hz, $^3J = 4.0$ Hz, $^3J = 2.1$ Hz, 1H; H-2), 2.04 (d, $^4J = 1.2$ Hz, 3H; C4-CH_3), 0.88 (s, 9H; $OSiC(CH_3)_3$), 0.08, 0.03 (2s, 2 × 3H; $OSi(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 201.5$, 164.8, 152.6, 140.5, 119.3, 115.9, 73.9, 50.1, 25.7, 19.2, 18.1, 14.1, −4.6, −5.2; MS (70 eV, EI): m/z (%): 325 (6) $[M]^+$, 282 (24), 268 (98) $[M-t\mathrm{Bu}]^+$, 250 (17), 194 (13), 176 (100), 164 (19), 135 (15), 101 (20), 75 (32), 73 (31); HRMS (EI): calcd for $C_{16}H_{27}NO_2SSi$ 325.1532, found 325.153.

(1*E*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-methyl-1-(2-methyl-1,3-thiazol-4-yl)-1,5-hexadiene (24): A mixture of methyl triphenyl phosphonium bromide (1.197 g, 3.35 mmol, 1.85 equiv), $NaNH_2$ (131 mg, 3.35 mmol, 1.85 equiv), and THF (10 mL) was stirred for 30 min at room temperature. A solution of aldehyde **23** (589 mg, 1.81 mmol) in THF (5 mL) was added dropwise over 10 min. The mixture was stirred for 15 min at room temperature, poured into saturated aqueous $NaHCO_3$ solution (60 mL), and extracted with Et_2O. The combined organic layers were washed with brine and dried over $MgSO_4$. After removal of the solvents under reduced pressure, flash chromatography (pentane/Et_2O 19:1) of the residue afforded olefin **24** (498 mg, 85%) as a pale yellow oil. $[\alpha]_D^{20} = +2.3$ ($c = 1.0$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 2929$, 2857, 1472, 1255, 1076, 914, 836, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.92$ (s, 1H; H-5′), 6.46 (s, 1H; H-1), 5.83–5.72 (m, 1H; H-5), 5.08–4.97 (m, 2H; H-6), 4.15 (t, $^3J = 6.4$ Hz, 1H; H-3), 2.70 (s, 3H; C2′-CH_3), 2.40–2.25 (m, 2H; H-4), 2.00 (d, $^4J = 1.0$ Hz, 3H; C2-CH_3), 0.89 (s, 9H; $OSiC(CH_3)_3$), 0.06, 0.01 (2s, 2 × 3H; $OSi(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 164.4$, 153.1, 142.0, 135.3, 118.8, 116.5, 115.1, 78.5, 41.4, 25.8, 19.2, 18.2, 13.9, −4.6, −5.0; MS (PCI, NH_3): m/z (%): 324 (100) $[M+H]^+$, 308 (1) $[M-CH_3]^+$, 282 (7), 266 (1) $[M-t\mathrm{Bu}]^+$, 192 (4), 94 (3); HRMS (EI): calcd for $C_{17}H_{29}NOSSi$ 323.1739, found 323.173.

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(1*E*,3*S*)-2-Methyl-1-(2-methyl-1,3-thiazol-4-yl)-1,5-hexadien-3-ol (4): TBAF (4.0 mL, ~1.0 M in THF, 4 mmol, 3 equiv) was added at 0 °C to freshly activated molecular sieves 4 Å in THF (16 mL). The mixture was stirred for 45 min at room temperature. A solution of silyl ether **24** (444 mg, 1.37 mmol) in THF (2 mL) was added, and stirring was continued for 80 min at 0 °C. The mixture was poured into saturated aqueous NH_4Cl solution (35 mL) and extracted with Et_2O (4 ×). The combined organic layers were washed with brine and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure, followed by flash filtration with Et_2O over a short silica gel column afforded alcohol **4** (283 mg, 99 %) as a colorless oil. $[\alpha]_D^{20} = -11.4$ ($c = 1.0$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3078, 2931, 1642, 1507, 1473, 1361, 1256, 1076, 914, 836, 777, 728, 670\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.91$ (s, 1H; H-5′), 6.53 (s, 1H; H-1), 5.86–5.73 (m, 1H; H-5), 5.18–5.06 (m, 2H; H-6), 4.18 (dd, $^3J = 7.4$ Hz, $^3J = 5.5$ Hz, 1H; H-3), 2.68 (s, 3H; C2′-CH_3), 2.48 (br s, 1H; OH), 2.46–2.30 (m, 2H; H-4), 2.01 (d, $^4J = 1.1$ Hz, 3H; C2-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 164.6, 152.7, 141.5, 134.6, 119.0, 117.7, 115.4, 76.4, 40.0, 19.1, 14.3$; MS (70 eV, EI): *m*/*z* (%): 209 (41) $[M]^+$, 190 (24), 168 (100), 142 (40), 100 (16), 75 (4); HRMS (EI): calcd for $C_{11}H_{15}NOS$ 209.0874, found 209.087; $C_{17}H_{29}NSSiO$ (323.2): calcd C 63.10, H 9.03, N 4.33, S 9.91; found C 62.91, H 8.95, N 4.73, S 9.65.

(4*R*,5*S*,6*S*,4′*S*)-2-(2,2-dimethyl-1,3-dioxan-4-yl)-5-hydroxy-2,4,6-trimethyl-10-undecen-3-one (25): A solution of ethyl ketone **2** (1.17 g, 5.45 mmol) in THF (1.0 mL) was added to a freshly prepared solution of LDA [*n*BuLi (3.34 mL, 1.6 M solution in hexanes, 5.35 mmol, 0.98 equiv) was added to a solution of diisopropylamine (749 μL, 5.35 mmol) in THF (4.0 mL) at 0 °C] dropwise at −78 °C. The solution was stirred for 1 h at −78 °C. Aldehyde **3** (688 mg, 5.45 mmol, 1.0 equiv) was added dropwise and stirring was continued for 45 min at −78 °C. The reaction mixture was quenched by dropwise addition of saturated aqueous NH_4Cl solution at −78 °C. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined extracts were dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (pentane/Et_2O 10:1) of the residue afforded *anti* Cram aldol product **25** (1.36 g, 73 %) and Cram aldol product (57 mg, 3 %) as colorless oils. *anti* Cram diastereomer: $[\alpha]_D^{20} = -25.7$ ($c = 1.0$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3509, 2970, 2938, 2876, 1685, 1467, 1381, 1372, 1272, 1197, 1107, 971\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.83–5.75$ (m, 1H, H-10), 5.00–4.89 (m, 2H, H-11), 4.02 (dd, $^3J = 11.8$ Hz, $^3J = 2.5$ Hz, 1H; H-4′), 3.94 (dt, $^3J = 11.9$ Hz, $^3J = 2.7$ Hz, 1H; H-6), 3.84 (ddd, $^2J = 11.7$ Hz, $^3J = 5.4$ Hz, $^3J = 1.8$ Hz, 1H; H-6′), 3.48 (s, 1H; OH), 3.35 (d, $^3J = 9.3$ Hz, 1H; H-5), 3.26 (dq, $^3J = 7.0$ Hz, $^3J = 1.4$ Hz, 1H; H-4), 2.11–1.96 (m, 2H; H-9), 1.80–1.72 (m, 1H; H-7), 1.66–1.42 (m, 3H; H-5′, H-6, H-8), 1.38, 1.31 (2s, 2 × 3H; C2′-CH_3), 1.35–1.22 (m, 2H; H-5′, H-8), 1.18 (s, 3H; H-1), 1.15–1.05 (m, 1H; H-7), 1.07 (s, 3H; C2-CH_3), 1.00 (d, $^3J = 7.0$ Hz, 3H; C4-CH_3), 0.81 (d, $^3J = 6.8$ Hz, 3H; C6-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 223.0, 139.1, 114.2, 98.4, 74.8, 74.3, 59.9, 51.6, 41.2, 35.3, 34.2, 32.5, 29.7, 26.1, 25.1, 21.6, 19.0, 18.5, 15.3, 9.3$; MS (70 eV, EI): *m*/*z* (%): 340 (6) $[M]^+$, 325 (9) $[M - CH_3]^+$, 282 (3), 264 (20), 214 (8), 185 (20), 183 (14) $[M - (\text{dioxanyl}\cdot C(CH_3)_2)]^+$, 156 (86), 147 (72), 127 (38), 115 (82), 109 (63), 99 (28), 83 (68), 82 (100), 69 (24), 57 (24); HRMS (EI) calcd for $C_{20}H_{36}O_4$ 340.2614, found 340.261; $C_{20}H_{36}O_4$ (340.5) calcd C 70.55, H 10.66; found C 70.36, H 10.69.

(3*S*,6*R*,7*S*,8*S*)-1,3,7-Trihydroxy-4,4,6,8-tetramethyl-12-tridecen-5-one (26): PPTS (250 mg, 0.993 mmol, 1.3 equiv) was added to a solution of the aldol product **25** (260 mg, 0.764 mmol) in MeOH (22.0 mL). The mixture was stirred at room temperature for 36 h. Saturated aqueous $NaHCO_3$ solution was added, and the solvent was removed in vacuo. The residue was dissolved in Et_2O, and the resulting solution was washed with brine and extracted with Et_2O. The combined extracts were dried over $MgSO_4$. After removal of the solvent in vacuo and flash chromatography (Et_2O) of the residual alcohol, **26** (202 mg, 88 %) was obtained as a colorless oil. $[\alpha]_D^{20} = -45.4$, $[\alpha]_{546}^{20} = -56.0$ ($c = 1.0$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3419, 2971, 2935, 2882, 1685, 1470, 1383, 1330, 1056, 996, 910\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.85–5.61$ (m, 1H; H-12), 5.00–4.90 (m, 2H; H-13), 4.04–4.01 (m, 1H; H-3), 3.88–3.80 (m, 2H; H-1), 3.35 (br d, $J = 9.2$ Hz, 3H; H-7, C3-OH, C7-OH), 3.25 (q, $^3J = 6.9$ Hz, 1H; H-6), 2.69 (br s, 1H; C1-OH), 2.07–1.98 (m, 2H; H-11), 1.78–1.70 (m, 1H; H-9), 1.63–1.42 (m, 4H; H-2, H-8, H-10), 1.35–0.96 (m, 2H; H-9, H-10), 1.19, 1.12 (2s, 2 × 3H; C4-CH_3), 1.04 (d, $^3J = 6.9$ Hz, 3H; C6-CH_3), 0.84 (d, $^3J = 6.8$ Hz, 3H; C8-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 223.7, 139.0, 114.3, 76.3, 74.6, 62.1, 52.6, 40.9, 35.5, 34.2, 32.5, 32.2, 26.1, 21.5, 18.5, 15.5, 10.1$; MS (70 eV, EI): *m*/*z* (%): 300 (<1) $[M]^+$, 267 (1) $[M - H_2O - CH_3]^+$, 201 (13), 183 (19) $[M - CH_2(OH)CH_2CH(OH)CH(CH_3)_2]^+$, 165 (10), 156 (11), 127 (23), 109 (47), 100 (100), 82 (80), 69 (46), 57 (45), 43 (30); $C_{17}H_{32}O_4$ (300.4): calcd C 67.96, H 10.74; found C 67.83, H 11.04.

(3*S*,6*R*,7*S*,8*S*)-1,3,7-Tri-(*tert*-butyldimethylsilyloxy)-4,4,6,8-tetramethyl-12-tridecen-5-one (27): 2,6-Lutidine (1.05 mL, 9.0 mmol, 12.0 equiv) and TBSOTf (1.03 mL, 4.5 mmol, 6.0 equiv) were slowly added at −78 °C to a solution of triol **26** (225 mg, 0.75 mmol) in CH_2Cl_2 (13.0 mL). The mixture was stirred at −78 °C for 30 min and at 0 °C for 3 h. Saturated aqueous $NaHCO_3$ solution was added and the mixture was extracted with CH_2Cl_2. The combined extracts were dried over $MgSO_4$ and concentrated in vacuo. Tris-silyl ether **27** (476 mg, 99 %) was obtained as a colorless oil after purification of the residue by flash chromatography (pentane/Et_2O 20:1). $[\alpha]_D^{20} = -33.6$, $[\alpha]_D^{20} = -41.0$ ($c = 1.0$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 2957, 2931, 2886, 2858, 1697, 1473, 1256, 1103, 987, 836, 775\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.83–5.73$ (m, 1H; H-12), 5.00–4.91 (m, 2H; H-13), 3.88 (dd, $^3J = 7.6$ Hz, $^3J = 2.7$ Hz, 1H; H-3), 3.76 (dd, $^3J = 6.7$ Hz, $^3J = 2.1$ Hz, 1H; H-7), 3.69–3.63 (m, 1H; H-1), 3.59–3.53 (m, 1H; H-1), 3.15–3.11 (m, 1H; H-6), 2.05–1.99 (m, 2H; H-11), 1.58–1.32 (m, 5H), 1.19–1.11 (m, 2H)(H-2, H-8, H-9, H-10), 1.21 (s, 3H; C4-CH_3), 1.03 (d, $^3J = 6.9$ Hz, 3H; C6-CH_3), 1.01 (s, 3H; C4-CH_3), 0.90 (d, 3H; C8-CH_3), 0.89 (2s, 2 × 9H; OSiC$(CH_3)_3$), 0.87 (s, 9H; OSiC$(CH_3)_3$), 0.08, 0.05, 0.02, 0.01 (4s, 4 × 3H; OSi$(CH_3)_2$), 0.05 (s, 6H; OSi$(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 218.3, 138.9, 114.4, 77.4, 74.0, 61.0, 53.7, 45.0, 38.9, 38.1, 34.3, 30.5, 27.1, 26.2, 26.1, 26.0, 24.5, 19.3, 18.5, 18.3, 18.3, 17.5, 15.2, −3.7, −3.7, −3.8, −4.0, −5.2, −5.3; MS (70 eV, EI): *m*/*z* (%): 643 (<1) $[M+H]^+$, 546 (2), 413 (3), 373 (8), 303 (100), 241 (54), 187 (9), 171 (16), 145 (28), 115 (19), 109 (98), 89 (84), 73 (64); $C_{35}H_{74}O_4Si_3$ (643.2): calcd C 65.36, H 11.60; found C 65.36, H 11.85.

(3*S*,6*R*,7*S*,8*S*)-3,7-Di-(*tert*-butyldimethylsilyloxy)-1-hydroxy-4,4,6,8-tetramethyl-12-tridecen-5-one (28): CSA (11 mg, 48 μmol, 0.2 equiv) was added at 0 °C to a solution of tris-silyl ether **27** (156 mg, 0.243 mmol) in MeOH (6.5 mL) and CH_2Cl_2 (6.5 mL). The reaction mixture was stirred for 5 h at 0 °C and quenched with saturated aqueous $NaHCO_3$ solution. The phases were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (pentane/Et_2O 3:1) to give alcohol **28** (106 mg, 83 %) as a colorless oil. $[\alpha]_D^{20} = -23.6$, $[\alpha]_{546}^{20} = -27.0$ ($c = 1.0$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3444, 2957, 2931, 2886, 2858, 1693, 1463, 1255, 1094, 987, 836, 775\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.83–5.73$ (m, 1H; H-12), 5.01–4.91 (m, 2H; H-13), 4.06 (dd, $^3J = 6.3$ Hz, $^3J = 4.0$ Hz, 1H; H-3), 3.79 (dd, $^3J = 7.3$ Hz, $^3J = 1.8$ Hz, 1H; H-7), 3.64–3.63 (m, 2H; H-1), 3.14–3.10 (m, 1H; H-6), 2.05–2.00 (m, 2H; H-11), 1.87–1.85 (m, 1H; OH), 1.61–1.55 (m, 2H; H-2), 1.48–1.30 (m, 3H), 1.24–1.09 (m, 2H)(H-8, H-9, H-10), 1.21, 1.05 (2s, 2 × 3H; C4-$(CH_3)_2$), 1.05 (d, $^3J = 6.9$ Hz, 3H; C6-CH_3), 0.89 (d, 3H; C8-CH_3), 0.89 (s, 18H; C3-OSiC$(CH_3)_3$, C7-OSiC$(CH_3)_3$), 0.10, 0.06 (2s, 2 × 3H; C7-OSi$(CH_3)_2$), 0.05 (s, 6H; C3-OSi$(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 219.6, 138.9, 114.4, 77.6, 73.0, 60.3, 53.8, 45.1, 38.7, 38.4, 34.3, 30.3, 27.1, 26.2, 26.0, 24.9, 18.5, 18.3, 17.7, 17.7, 15.7, −3.6, −3.8, −3.9$; MS (EI, 70 eV): *m*/*z* (%) = 472 (3) $[M+H-t\text{Bu}]^+$, 413 (4), 345 (11), 299 (4), 271 (10), 241 (48), 189 (100), 145 (26), 109 (90), 75 (46), 73 (63); HRMS (EI) calcd for $C_{29}H_{60}O_4Si_2$ 528.4030, found 528.402; $C_{29}H_{60}O_4Si_2$ (529.0) calcd C 65.85, H 11.43; found C 65.51, H 11.83.

(3*S*,6*R*,7*S*,8*S*)-3,7-Di-(*tert*-butyldimethylsilyloxy)-4,4,6,8-tetramethyl-5-oxo-12-tridecenoic acid (29): A solution of PDC (2.37 g, 6.30 mmol, 11.0 equiv) in DMF (3 mL) was added to a solution of alcohol **28** (303 mg, 0.573 mmol) in DMF (6 mL). The reaction mixture was stirred for 36 h at room temperature, mixed with brine (50 mL), diluted with water, and extracted with CH_2Cl_2. The combined extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (pentane/Et_2O 2:1) to furnish acid **29** (247 mg, 79 %) as a viscous, colorless oil. $[\alpha]_D^{20} = -31.7$, $[\alpha]_{546}^{20} = -37.6$ ($c = 1.0$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 2957, 2931, 2858, 1713, 1473, 1389, 1361, 1303, 1254, 1092, 989, 836, 776\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.83–5.73$ (m, 1H; H-12), 5.01–4.91 (m, 2H; H-13), 4.37 (dd, $^3J = 6.7$ Hz, $^3J = 3.1$ Hz, 1H; H-3), 3.77 (dd, $^3J = 7.3$ Hz, $^3J = 1.9$ Hz, 1H; H-7), 3.14–3.11 (m, 1H; H-6), 2.48 (dd, $^2J = 16.5$ Hz, $^3J = 3.1$ Hz, 1H; H-2), 2.29 (d, $^2J = 16.5$ Hz, $^3J = 6.8$ Hz, 1H; H-2), 2.05–1.99 (m, 2H; H-11), 1.48–1.29 (m, 3H), 1.24–1.11 (m, 2H)(H-8, H-9, H-10), 1.22, 1.07 (2s, 2 × 3H; C4-$(CH_3)_2$), 1.04 (d, $^3J =$ 6.9 Hz, 3H; C6-CH_3), 0.90 (d, 3H; C8-CH_3), 0.89, 0.87 (2s, 2 × 9H; OSiC$(CH_3)_3$), 0.08, 0.04 (2s, 2 × 3H; OSi$(CH_3)_2$), 0.04 (s, 6H; OSi$(CH_3)_2$);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 218.2, 178.0, 138.9, 114.4, 77.6, 73.4, 53.5, 45.2, 40.2, 38.7, 34.3, 30.3, 27.1, 26.2, 26.0, 23.7, 19.0, 17.7, 15.7, 18.5, 18.2, −3.6, −3.8, −4.3, −4.6; MS (70 eV, EI): *m*/*z* (%): 528 (<1) [*M*+H−CH_3]$^+$, 359 (14), 353 (13), 283 (14), 241 (20), 203 (100), 185 (12), 149 (16), 115 (58), 109 (32), 75 (36), 73 (51); $C_{29}H_{58}O_5Si_2$ (542.9) calcd C 64.15, H 10.77; found C 63.96, H 11.12.

(1*S*)-1-[(*E*)-1-Methyl-2-(2-methyl-1,3-thiazol-4-yl)-1-ethenyl]-3-butenyl (3*S*,6*R*,7*S*,8*S*)-3,7-di-[*tert*-butyldimethylsilyloxy]-4,4,6,8-tetramethyl-5-oxo-12-tridecenoate (30): DCC (72 mg, 0.35 mmol, 1.3 equiv) was added at 0 °C to a solution of acid **29** (145 mg, 0.27 mmol), alcohol **4** (56 mg, 0.27 mmol), and DMAP (6.5 mg, 0.054 mmol, 0.2 equiv) in CH_2Cl_2 (1.5 mL). The mixture was stirred for 10 min at 0 °C and for 16 h at room temperature. The solvent was removed in vacuo and the product was purified by flash chromatography (pentane/Et_2O 20:1) to afford ester **30** (157 mg, 80%) as a colorless oil. $[\alpha]_D^{20} = -45.0$, $[\alpha]_{546}^{20} = -53.8$ (*c* = 1.0, $CHCl_3$) [Lit.:[4b] $[\alpha]_D = -41.2$ (*c* = 3.1, $CHCl_3$)]; IR (film): $\tilde{\nu}_{max}$ = 3079, 2931, 1736, 1698, 1473, 1256, 1179, 989, 832, 777 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$); δ = 6.94 (s, 1H; thiazole H-5), 6.49 (s, 1H; H-2″), 5.85–5.66 (m, 2H; H-12, H-3′), 5.30 (t, ^3J = 6.7 Hz, 1H, H-1′), 5.14–4.91 (m, 4H; H-13, H-4′), 4.34 (dd, ^3J = 6.0 Hz, ^3J = 3.6 Hz, 1H; H-3), 3.74 (dd, ^3J = 6.8 Hz, ^3J = 2.3 Hz, 1H; H-7), 3.15 (dq, ^3J = 6.8 Hz, ^3J = 6.8 Hz, 1H; H-6), 2.70 (s, 3H; thiazole CH_3), 2.57–2.41 (m, 3H; H-2, H-2′), 2.29 (dd, ^2J = 17.0 Hz, ^3J = 6.0 Hz, 1H; H-2′), 2.07 (d, ^4J = 1.3 Hz, 3H; C1″-CH_3), 2.06–1.97 (m, 2H; H-11), 1.52–1.29 (m, 3H), 1.27–1.06 (m, 2H)(H-8, H-9, H-10), 1.24, 1.04 (2s, 2 × 3H; C4-CH_3), 1.04 (d, ^3J = 6.8 Hz, 3H; C6-CH_3), 0.90 (d, ^3J = 6.4 Hz, 3H; C8-CH_3), 0.90, 0.88 (2s, 2 × 9H; $OSiC(CH_3)_3$), 0.11, 0.06, 0.04, 0.03 (4s, 4 × 3H; $OSi(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$); δ = 217.6, 171.1, 164.5, 152.6, 138.9, 136.8, 133.4, 121.1, 117.7, 116.4, 114.4, 78.7, 77.6, 74.1, 53.4, 45.2, 40.3, 38.9, 37.5, 34.3, 30.5, 27.1, 26.2, 26.0, 23.2, 20.4, 19.2, 18.5, 18.2, 17.6, 15.4, 14.6, −3.7, −3.8, −4.3, −4.7; MS (PCI, CH_4): *m*/*z* (%): 734.5 (15) [*M*+H]$^+$, 399.2 (10), 241.1 (14), 191.9 (100); $C_{40}H_{71}NO_5SSi_2$ (734.2): calcd C 65.43, H 9.75, N 1.91, S 4.37; found C 65.36, H 9.65, N 2.29, S 4.25.

(4*S*,7*R*,8*S*,9*S*,16*S*)-4,8-Di-*tert*-butyldimethylsilyloxy-5,5,7,9-tetra-methyl-1-6-[(*E*)-1-methyl-2-(2-methyl-1,3-thiazol-4-yl)-1-ethenyl]-1-oxa-13-cyclohexadecen-2,6-dione, mixture of the (13*Z*) and (13*E*) isomers, (31a) and (31b): Bis(tricyclohexylphosphine)benzylideneruthenium dichloride ($[RuCl_2(=CHPh)(PCy_3)_2]$[20a] 7.4 mg, 9 μmol, 0.06 equiv) was added to a solution of diene **30** (110 mg, 0.15 mmol) in CH_2Cl_2 (75 mL, 0.002 M), and the reaction mixture was stirred for 16 h at room temperature. The solvent was removed in vacuo and the crude product was purified by flash chromatography (pentane/Et_2O 20:1) to give a mixture of diastereomers **31a** and **31b** (*Z*/*E* = 1.7:1, 99 mg, 94%, colorless viscous oil). IR (*Z*/*E* mixture, film): $\tilde{\nu}_{max}$ = 2929, 2858, 1739, 1695, 1464, 1362, 1251, 828, 673 cm^{-1}; ^{1}H NMR (*Z* isomer **31a**, 400 MHz, $CDCl_3$): δ = 6.96 (s, 1H; H-19), 6.57 (brs, 1H; H-17), 5.53 (dt, ^3J = 11.2 Hz, ^3J = 3.5 Hz, 1H; H-12), 5.49–5.31 (m, 1H; H-13), 5.02 (d, ^3J = 10.0 Hz, 1H; H-15), 4.04 (dd, ^3J = 10.2 Hz, ^3J = 1.3 Hz, 1H; H-3), 3.90 (d, ^3J = 8.6 Hz, 1H; H-7), 3.01 (dq, ^3J = 8.6 Hz, ^3J = 6.9 Hz, 1H; H-6), 2.82 (dd, ^2J = 16.4 Hz, ^3J = 1.3 Hz, 1H; H-2), 2.81–2.69 (m, 1H; H-14), 2.71 (s, 3H; H-21), 2.67 (dd, ^2J = 16.6 Hz, ^3J = 10.3 Hz, 1H; H-2), 2.42–2.32 (m, 1H; H-10), 2.12 (d, ^4J = 1.2 Hz, 3H; H-27), 2.11–2.05 (m, 1H; H-14), 1.92–1.81 (m, 1H; H-10), 1.63–1.46 (m, 3H; H-8, H-9, H-11), 1.19–1.00 (m, 2H; H-9, H-11), 1.19, 1.15 (2s, 2 × 3H; H-22, H-23), 1.09 (d, ^3J = 6.8 Hz, 3H; H-24), 0.96 (d, ^3J = 6.8 Hz, 3H; H-25), 0.94, 0.84 (2s, 2 × 9H; $OSiC(CH_3)_3$), 0.12, 0.10, 0.08, −0.09 (4s, 4 × 3H; $OSi(CH_3)_2$); ^{13}C NMR (*Z* isomer **31a**, 100 MHz, $CDCl_3$): δ = 215.0, 171.2, 164.6, 152.5, 138.6, 135.0, 122.8, 119.5, 116.0, 79.5, 79.2, 76.4, 53.4, 47.9, 38.9, 37.9, 31.8, 31.4, 29.2, 28.4, 26.4, 26.2, 24.9, 24.2, 19.2, 19.0, 18.7, 18.6, 17.6, 15.2, −3.2, −3.3, −3.7, −5.7; ^{1}H NMR (*E* isomer **31b**, 400 MHz, $CDCl_3$): δ = 6.94 (s, 1H; H-19), 6.54 (brs, 1H; H-17), 5.49–5.31 (m, 2H; H-12, H-13), 5.24 (dd, ^3J = 7.8 Hz, ^3J = 3.1 Hz, 1H; H-15), 4.42 (dd, ^3J = 6.6 Hz, ^3J = 4.3 Hz, 1H; H-3), 3.93 (dd, ^3J = 6.9 Hz, ^3J = 1.5 Hz, 1H; H-7), 3.07 (dq, ^3J = 6.9 Hz, ^3J = 6.9 Hz, 1H; H-6), 2.71 (s, 3H; H-21), 2.66 (dd, ^2J = 15.7 Hz, ^3J = 4.2 Hz, 1H; H-2), 2.58–2.42 (m, 2H; H-14); 2.56 (dd, ^2J = 15.7 Hz, ^3J = 6.6 Hz, 1H; H-2), 2.21–2.11 (m, 1H; H-11), 2.15 (d, ^4J = 1.1 Hz, 3H; H-27), 1.96–1.88 (m, 1H; H-11), 1.60–1.37 (m, 3H; H-8, H-9, H-10), 1.18 (s, 3H; H-22), 1.18–1.14 (m, 1H; H-10), 1.15 (d, ^3J = 6.9 Hz, 3H; H-24), 1.09 (s, 3H; H-23), 1.02–0.99 (m, 1H; H-9), 0.94 (d, ^3J = 8.0 Hz, 3H; H-25), 0.90, 0.88 (2s, 2 × 9H; $OSiC(CH_3)_3$), 0.11, 0.08, 0.07, 0.05 (4s, 4 × 3H; $OSi(CH_3)_2$); ^{13}C NMR (*E* isomer **31b**, 100 MHz, $CDCl_3$): δ = 216.3, 170.5, 164.6, 152.7, 137.8, 134.2, 125.7, 119.6, 116.2, 78.5, 77.0, 73.8, 53.9, 45.3, 41.4, 39.8, 36.4, 32.4, 30.0, 27.1, 26.2, 26.1, 23.5, 21.4, 19.3, 16.9, 18.5, 18.4, 17.1, 15.5, −3.5, −3.8, −4.0, −4.5; MS (*Z*/*E* mixture, PCI, CH_4): *m*/*z* (%): 706.4 (100) [*M*+H]$^+$, 690.4 (39), 648.3 (34), 478.2 (14), 404.2 (5), 225.0 (8), 152.9 (15), 75.1 (17); HRMS (EI): calcd for $C_{38}H_{67}NO_5SSi_2$ 705.4279, found 705.428.

(4*S*,7*R*,8*S*,9*S*,16*S*)-4,8-Dihydroxy-5,5,7,9-tetramethyl-16-[(*E*)-1-methyl-2-(2-methyl-1,3-thiazol-4-yl)-1-ethenyl]-1-oxa-cyclohexadec-13-en-2,6-dione, mixture of the (13*Z*) and (13*E*) isomers, (32a) and (32b): A solution of bissilyl ethers **31a** and **31b** (*Z*:*E* = 1.7:1, 35.3 mg, 0.05 mmol) in MeCN/Et_2O (1:1, 2.4 mL) at 0 °C was treated with aqueous hydrofluoric acid (0.27 mL, 40%) and some ground glass splinters, and the mixture was stirred for 12 h at room temperature. The mixture was then poured slowly into saturated $NaHCO_3$ solution (10 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo. Flash chromatography (Et_2O) of the residue gave diols **32a** (epothilone C) and **32b** as a mixture of diastereomers (*Z*/*E* = 1.7:1, 16.5 mg, 65%, colorless viscous oil). IR (*Z*/*E* mixture, film): $\tilde{\nu}_{max}$ = 3456, 2927, 1733, 1690, 1471, 1377, 1251, 978, 882, 731 cm^{-1}; ^{1}H NMR (*Z* isomer **32a**, 400 MHz, $CDCl_3$): δ = 6.96 (s, 1H; H-19), 6.60 (brs, 1H; H-17), 5.56–5.34 (m, 2H; H-12, H-13), 5.29 (dd, ^3J = 9.8 Hz, ^3J = 1.7 Hz, 1H; H-15), 4.23 (dd, ^3J = 11.2 Hz, ^3J = 2.3 Hz, 1H; H-3), 3.76–3.71 (m, 1H; H-7), 3.33 (brs, 1H; OH), 3.14 (dq, ^3J = 6.8 Hz, ^3J = 2.1 Hz, 1H; H-6), 3.05 (brs, 1H; OH), 2.74–2.63 (m, 1H; H-14), 2.70 (s, 3H; H-21), 2.48 (dd, ^2J = 15.1 Hz, ^3J = 11.2 Hz, 1H; H-2), 2.35 (dd, ^2J = 15.1 Hz, ^3J = 2.6 Hz, 1H; H-2), 2.09 (d, ^4J = 1.2 Hz, 3H; H-27), 2.30–2.12 (m, 2H; H-15, H-11), 2.08–1.97 (m, 1H; H-11), 1.79–1.60 (m, 2H; H-9, H-10), 1.36–1.13 (m, 3H; H-8, H-9, H-10), 1.33 (s, 3H; H-22), 1.19 (d, ^3J = 6.8 Hz, 3H; H-24), 1.08 (s, 3H; H-23), 1.00 (d, ^3J = 6.8 Hz, 3H; H-25); ^{13}C NMR (*Z* isomer **32a**, 100 MHz, $CDCl_3$): δ = 220.5, 170.3, 165.0, 152.0, 138.6, 133.4, 125.0, 119.5, 115.8, 78.4, 74.1, 72.4, 53.3, 41.8, 39.2, 38.5, 32.5, 31.7, 27.6, 27.5, 22.7, 19.0, 18.7, 15.8, 15.5, 13.5; ^{1}H NMR (*E* isomer **32b**, 400 MHz, $CDCl_3$): δ = 6.98 (s, 1H; H-19), 6.57 (brs, 1H; H-17), 5.45–5.34 (m, 3H; H-12, H-13, H-15), 4.19 (dd, ^3J = 10.2 Hz, ^3J = 2.9 Hz, 1H; H-3), 3.76–3.71 (m, 1H; H-7), 3.29–3.20 (m, 2H; H-7, OH), 2.78 (brs, 1H; OH), 2.71 (s, 3H; H-21), 2.56 (dd, ^2J = 15.1 Hz, ^3J = 10.1 Hz, 1H; H-2), 2.49 (dd, ^2J = 15.1 Hz, ^3J = 3.0 Hz, 1H; H-2), 2.48–2.42 (m, 2H; H-14), 2.21–2.10 (m, 1H; H-11), 2.08 (d, ^4J = 1.1 Hz, 3H; H-27), 1.99–1.91 (m, 1H; H-11), 1.72–1.57 (m, 2H; H-9, H-10), 1.52–1.40 (m, 1H; H-9), 1.28 (s, 3H; H-22), 1.27–1.15 (m, 2H; H-8, H-10), 1.18 (d, ^3J = 4.8 Hz, 3H; H-24), 1.07 (s, 3H; H-23), 0.99 (d, ^3J = 6.4 Hz, 3H; H-25); ^{13}C NMR (*E* isomer **32b**, 100 MHz, $CDCl_3$): δ = 219.9, 170.5, 164.9, 152.1, 137.1, 134.3, 125.7, 119.8, 116.0, 77.6, 75.8, 72.4, 52.5, 43.6, 38.9, 37.7, 36.2, 32.4, 30.5, 27.2, 21.0, 20.7, 19.1, 16.4, 15.7, 14.8; MS (*Z*/*E* mixture, 70 eV, EI): *m*/*z* (%): 477.3 (22) [*M*]$^+$, 459.3 (7), 405.2 (6), 290.1 (24), 168.0 (100), 151.0 (17), 111.0 (16); HRMS (EI): calcd for $C_{26}H_{39}NO_5S$ 477.2549, found 477.255.

Epothilone A (1): A freshly prepared solution of dimethyl dioxirane in acetone[21] (1.3 equiv) was added dropwise at −35 °C with stirring to a solution of **32a** and **32b** (14.3 mg, 0.03 mmol, 1.7:1–*Z*:*E* mixture) in CH_2Cl_2 (2.5 mL). Stirring was continued for 2 h at −35 °C. Aqueous iron(II) sulfate solution (10%, 5.0 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were concentrated in vacuo and the residue was purified by flash chromatography with Et_2O to give epothilone A (**1**) (7.1 mg, 48%; 76% based on pure *Z* isomer) as a colorless foam. $[\alpha]_D^{20} = -43.8$, $[\alpha]_{546}^{20} = -59.4$ (*c* = 0.17, MeOH) [Lit.:[1a] $[\alpha]_D^{20} = -47.1$ (*c* = 1.0, MeOH)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.98 (s, 1H; H-19), 6.60 (brs, 1H; H-17), 5.44 (dd, ^3J = 9.8 Hz, ^3J = 1.7 Hz, 1H; H-15), 4.20 (dd, ^3J = 10.8 Hz, ^3J = 3.0 Hz, 1H; H-3), 4.04 (brs, 1H; OH), 3.79 (dd, ^3J = 4.4 Hz, ^3J = 4.3 Hz, 1H; H-7), 3.23 (dq, ^3J = 6.9 Hz, ^3J = 4.7 Hz, 1H; H-6), 3.04 (ddd, ^3J = 8.1 Hz, ^3J = 4.2 Hz, ^3J = 4.0 Hz, 1H; H-13), 2.92 (ddd, ^3J = 7.8 Hz, ^3J = 4.0 Hz, ^3J = 3.7 Hz, 1H; H-12), 2.70 (s, 3H; H-21), 2.63 (brs, 1H; OH), 2.54 (dd, ^2J = 14.4 Hz, ^3J = 10.6 Hz, 1H; H-2), 2.41 (dd, ^2J = 14.4 Hz, ^3J = 3.2 Hz, 1H; H-2), 2.14 (ddd, ^2J = 15.1 Hz, ^3J = 7.0 Hz, ^3J = 2.8 Hz, 1H; H-14), 2.09 (d, ^4J = 0.9 Hz, 3H; H-27), 1.88 (ddd, ^2J = 15.1 Hz, ^3J = 8.5 Hz, ^3J = 8.4 Hz, 1H; H-14), 1.81–1.66 (m, 2H; H-10, H-11), 1.61–1.19 (m, 5H; H-8, H-9, H-10, H-11), 1.37 (s, 3H; H-22), 1.18 (d, ^3J = 6.9 Hz, 3H; H-24), 1.10 (s, 3H; H-23), 1.00 (d, ^3J = 7.0 Hz, 3H; H-25); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 220.2, 170.6, 165.2, 151.8, 137.6, 119.8, 116.2, 76.6, 74.5, 73.3, 57.5, 54.6, 52.9, 43.4, 38.9, 36.2, 31.5, 30.6, 27.2, 23.5, 21.6, 20.6, 19.2, 17.2, 15.7, 14.1; MS (PCI, CH_4,): *m*/*z* (%): 494.5 (10) [*M*+H]$^+$, 394.3 (7), 334.2 (6), 324.2 (53), 306.1 (100), 171.0 (12), 153.0 (18).

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