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Total Synthesis of Epothilone D: The Nerol/Macroaldolization Approach

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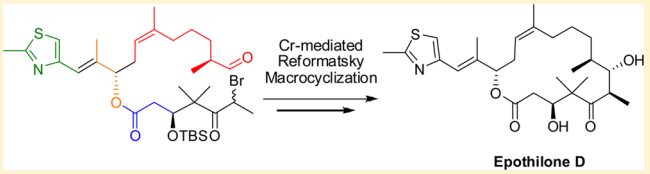
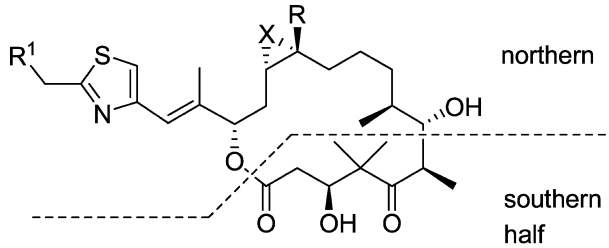
Supporting Information

ABSTRACT: A highly convergent and stereocontrolled synthesis of epothilone D (**4**) is reported. Key features are a cheap and *Z*-selective synthesis of the northern half based on nerol and acetoacetate and chromium(II)-mediated Reformatsky reactions as a powerful tool for chemoselective asymmetric carbon−carbon bond formations, including an unusual stereospecific macroaldolization.



INTRODUCTION

Epothilones are cytotoxic macrolides, first isolated by Höfle and co-workers from myxobacterium *Sorangium cellulosum* strain 90.[1] After the elucidation of the absolute stereochemistry of epothilone B (**2**) through a combination of X-ray crystallography and chemical degradation studies, various epothilones were discovered and eventually developed into marketed drugs. The high potency of epothilones against cancer cells results from their ability to intervene in tubulin polymerization dynamics, in which they stabilize formed microtubuli.[2] These are part of the cytoskeleton and are indespensible for cell division.[3] Several total and many partial syntheses of epothilones (Figure 1) using different strategies have been reported.[4] However, new syntheses are still in demand, as they can give easier access, allow new derivatives, or can be cheaper and provide freedom to operate: e.g., for generics production.



1 Epothilone A, R = H, R^1 = H, X = O
2 Epothilone B, R = Me, R^1 = H, X = O
3 Epothilone C, R = H, R^1 = H, X = bond
4 Epothilone D, R = Me, R^1 = H, X = bond
5 Epothilone E, R = H, R^1 = H, X = O
6 Epothilone F, R = Me, R^1 = OH, X = O

Figure 1. Structures of epothilones A−F.

In comparison to the well-known Taxotere and taxol (paclitaxel),[5] which are frontline anticancer agents, epothilones exhibit several important advantages. Some epothilones are available by fermentation with (genetically engineered) bacteria.[6] Furthermore, epothilones possess unique pharmacokinetic profiles and show activity against paclitaxel-resistant cell lines. Mechanistic investigations show that they competitively bind to the same pocket of β-tubulin as taxol.[7] This was confirmed by comparison of structural data of the tubulin polymer complexed to either taxol or epothilone A or B.[8] However, taxanes and epothilones each occupy the binding pocket in a unique and independent manner, which revokes the idea of a common pharmacophore for epothilones and taxol. Although epothilones have a microtubule-stabilizing mechanism of action similar to that of taxanes, they express nonoverlapping mechanisms of resistance.[9] Therefore, they were approved by the U.S. Food and Drug Administration for the treatment of taxane- and anthracycline-resistant breast cancer in 2007.[10]

Structure−activity relationships (SAR) of various epothilone analogues suggest that epothilones may not tolerate too many broad structural changes.[11] This renders access to the natural compound crucial. At first glance the arrangement of the functional groups in the macrocycle allows a variety of retrosynthetic disconnections. The majority of reports on epothilone syntheses follow very similar synthetic strategies. Often reoccurring features are the introduction of the thiazole side chain via a Wittig reaction,[4n] aldol connection of carbon atoms C6 and C7, and the Yamaguchi macrocyclization for the construction of the macrolactone scaffold.

RESULTS AND DISCUSSION

The retrosynthetic strategy to epothilone D (**4**) reported herein initially follows the classical northern−southern half strategy. The crucial step, however, is the unusal formation of a C6−C7 bond via a novel chromium Reformatsky macrocyclization of the linear epothilone precursor **7** (Scheme 1).

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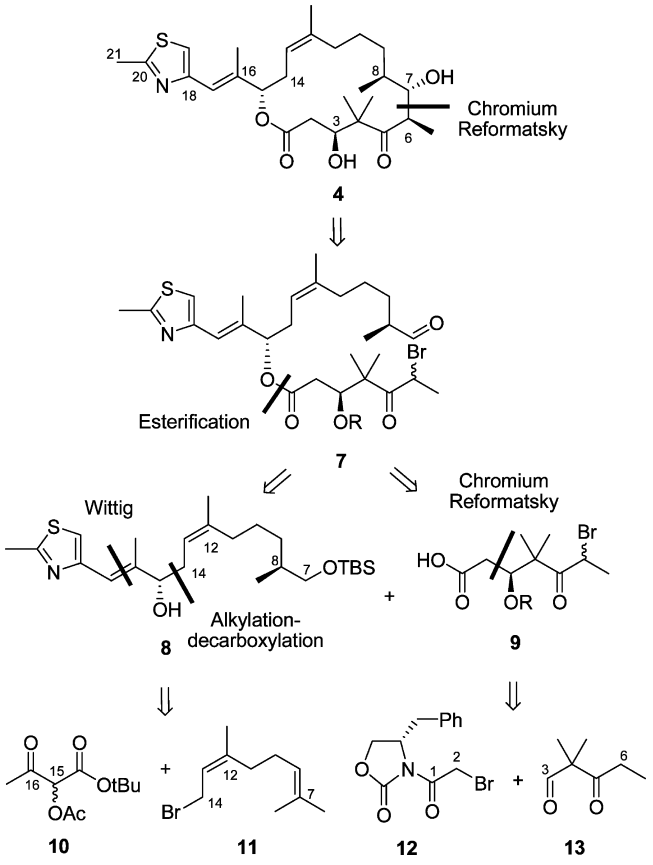
Scheme 1. Retrosynthetic Analysis of Epothilone D (4)



This chromium-mediated version of an aldol reaction exhibits extraordinary chemo- and diastereoselectivity.[4g,12] The behavior of chromium(III) enolates was thoroughly studied in our group, and thus we expected the reaction to provide the desired *syn*-aldol product (C6/C7) exclusively in combination with the correct *anti*-Cram selectivity (C7/C8).[4g,h,12]

The other disconnections cut the ester moiety in compound **7**, which separates the epothilone's northern and southern halves (**8** and **9**, respectively). Further disconnection of compound **8** through a Wittig reaction and alkylation–decarboxylation sequence leads back to acetoacetate **10** and the neryl backbone **11**. Retrosynthesis of the southern half (i.e., **9**) leads to a scission at C2–C3, leading to bromo acetimide **12** and keto aldehyde **13**, featuring another (auxiliary controlled) chromium Reformatsky reaction.

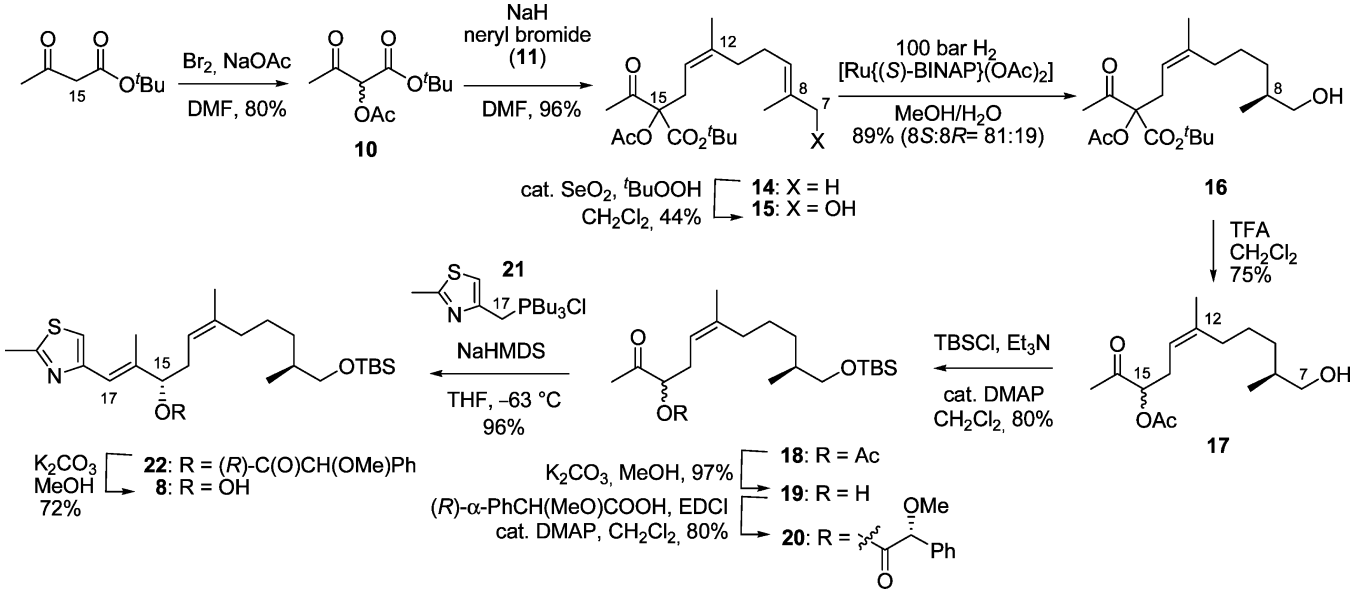
Commencing with the forward synthesis of the northern half (Scheme 2), oxidative acetoxylation of acetoacetate **10** was achieved via the bromination of *tert*-butyl acetoacetate with NBS followed by a nucleophilic substitution with sodium acetate, giving compound **10** in 68% yield.[13] Later this two-step process was reduced to a one-pot procedure, using elementary bromine in the presence of a sodium alkanoate. With *tert*-butyl acetoacetate and sodium acetate product **10** was obtained directly in 80% yield.

Deprotonation of **10** with NaH and subsequent alkylation with neryl bromide (**11**) gives the quaternary acetoacetate derivative **14** in 96% to quantitative yield.

For the introduction of the terminal hydroxyl group, Sharpless allylic oxidation with *t*-BuOOH and (usually 5%) catalytic SeO_2 was used.[14] Although the catalytic version give yields lower than those for the overstoichiometric use of SeO_2, to date it is still the only method that allows a regioselective catalytic oxidation of the terminal (*E*)-methyl group. The catalytic version provides a maximum yield of 44% of C7-oxidized products (**15**) but requires only 1.75 mol % of selenium dioxide. The catalytic process has the better overall performance, because the starting material is readily synthesized in large amounts, unreacted material can be recovered if desired, and, most importantly, the carryover of selenium residues is avoided. These were found to be detrimental even at very low concentration for the subsequent catalytic hydrogenation.

Hydrogenation of the C8–C9 double bond of allylic alcohol **15** utilizing the Noyori catalyst [Ru{(*S*)-BINAP}$(OAc)_2$] (1.5 mol %) in methanol/water (95/5) at >100 bar of hydrogen

Scheme 2. Synthesis of Northern Half (Showing Resolution of *O*-Methyl Mandelates)



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pressure led exclusively to the reduction of the C8−C9 double bond,[15] yielding compound **16** (89%). The regioselectivity results on one hand from the coordination of the allylic ω-hydroxy group to the catalyst. On the other hand, and most importantly, competing hydrogenation of the C12−C13 double bond is prevented by the bulky residues at the quaternary C15 that probably hamper the catalyst in docking to surrounding potential ligand positions. Without the bulky substituents, the hydrogenation gives mixtures (saturation of double bond C8−C9 or C12−C13 or both). The enantiomeric ratio was determined by ^{1}H NMR analysis of the C8 protons of both (*R*)- and (*S*)-Mosher esters of compound **16**. The ratio between 8*S* and 8*R* is 81:19 on average. A separation of the enantiomeric impurity is not required, as a later stereoselective reaction exclusively reacts with the desired 8*S* isomer (vide infra). The absolute stereochemistry at C8 was confirmed by comparison with the Mosher ester of the original northern half (courtesy of Prof. Höfle), obtained by degradation of natural epothilone. Acidic decarboxylation of **16** using TFA takes place without detectable isomerization of the remaining double bond, in contrast to classic Krapcho decarboxylation conditions. The tradeoff, however, is a partial trifluoroacetylation of the ω-alcohol, which can be reverted quantitatively by workup with aqueous $NaHCO_3$.

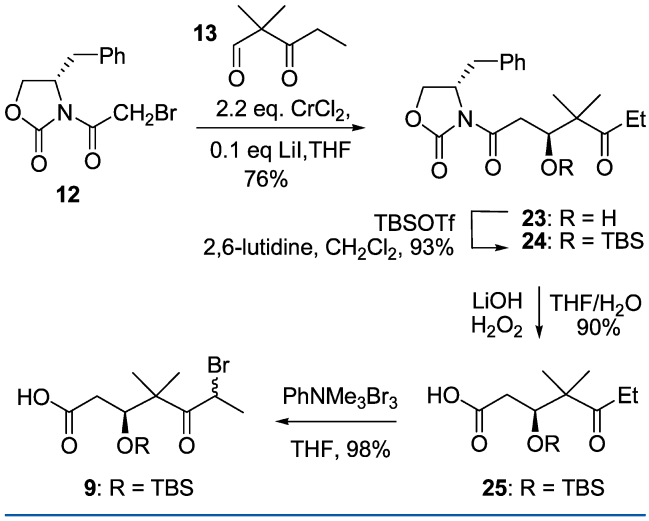
The obtained free primary alcohol **17** was subsequently protected as the TBS ether **18**, both present as inseparable diastereomers. The distant and independent stereocenter at C15 therefore requires enantioselective separation. One possibility is the transesterification of acetate **18** with (*R*)-α-methoxyphenylacetic acid, which allows the separation of the resulting diastereomers with standard chromatography (40% isolated yield, 80% based on theory). Alternative methods to obtain the correct diastereoisomer (**20**) are asymmetric synthesis applying an Evans auxiliary and enzymatic resolution (e.g., by *Candida antarctica* lipase B).[4e] Since the C15 stereocenter of **20** is in a position α to a keto group, the undesired diastereomer can be racemized and reused. A dynamic kinetic resolution therefore can be performed in a circular or phase-separated system without isolation of the undesired diastereomer, as has been reported elsewhere.[16]

Diastereomerically pure **20** was subjected to a Wittig olefination using thiazole phosphonium salt **21** in the presence of NaHMDS, yielding olefin **22** without racemization in excellent yield.[4n,17] Other ylides show worse reactivity or purification behavior.[18] Finally, ester saponification gave access to the northern half building block **8**.

The stereoselective formation of the C2−C3 aldol bond requires the chemoselective and asymmetric transfer of a carboxymethyl unit, i.e. an "acetate Cα anion" (ester enolate) to an aldehyde (Scheme 1). This transformation can be achieved by an auxiliary-controlled chromium Reformatsky reaction which allows β-induction with so-called non-Evans stereoselection,[4e,g,h,9,19] in contrast to lithium or other counterions.

In the presence of 2.2 equiv of $CrCl_2$, bromoacetate **12** reacts exclusively at the aldehyde portion with β-keto aldehyde **13** to give the desired product **23** (Scheme 3). In contrast to other approaches to the southern half, the aldol product already has the correct oxidation state at C1. This direct aldol reaction (without scavenging the aldolate) is only possible because the intermediate chromium(III) aldolates are insensitive to retroaldolization. Retroaldolization is commonly observed in sterically compressed noncyclic double aldolates such as **23**, which reopen at the C3−C4 bond during reaction if, for

Scheme 3. Synthesis of Southern Half



example, sodium or lithium aldolates would be the intermediates.[9] Please note that in the final macrocycle the limited conformational freedom allows a greater stability of the aldol portion, a fact that has been used by Danishefsky in his macroaldolization approach.[4k]

The N-acylation of the auxiliary with 2-bromoacetyl bromide was also successfully combined with the Reformatsky reaction in a two-step−one-pot process. TBS protection of the secondary alcohol **23** was followed by the cleavage of a chiral auxiliary to obtain carboxylic acid **25**. The synthesis of the southern half was completed by a quantitative bromination of **25** at C6 and provided α-bromo ketone **9**. Several brominating agents worked on **24** or **25**, but phenyltrimethylammonium tribromide applied on free acid **25** was found to be the best choice. In contrast to expectation, in **24** competing C2 bromination was not a problem, but under the basic auxiliary cleavage conditions, the formation of a cyclic byproduct was observed.

Esterification of the southern half carboxylic acid **9** with the northern half chiral alcohol **8** led to the linear epothilone precursor **26** in 80% yield (Scheme 4). The primary TBS ether was then selectively cleaved by treatment with (1*S*)-(+)-CSA to furnish alcohol **27** (91%).

In the next step, alcohol **27** was converted to aldehyde **7** using a Doering oxidation. Deviation from the reaction conditions or order of reagents, or other reactions such as Swern or Dess−Martin oxidation, gave lower yields apart from other disadvantages.

The linear macrocyclization precursor **7** was followed by a chromium(II)-mediated Reformatsky macrocyclization, the first one of its kind (Scheme 4) with challenging selectivity demands. Required are *syn* selectivity at C6−C7[20] and *anti*-Cram double stereodifferentiation between C7 and C8,[21] ideally in such a way that only the 8*S* diastereomer (shown) is reacting, not the residual 20% 8*R* epimer (not shown). Induction for this selection must come from the fully defined C3 or the C15 stereocenter. However, not only is stereoselection crucial but also chemoselectivity. Since C1 is an ester, and the C4-dimethyl group exerts a strong Thorpe−Ingold effect, any C6-enolate is bound to give a six-membered-ring Claisen product rather than a macroaldol. Indeed, the latter reaction occurs with all tested counterions (Li, Zn, In, Sm, etc.) other than chromium(III).

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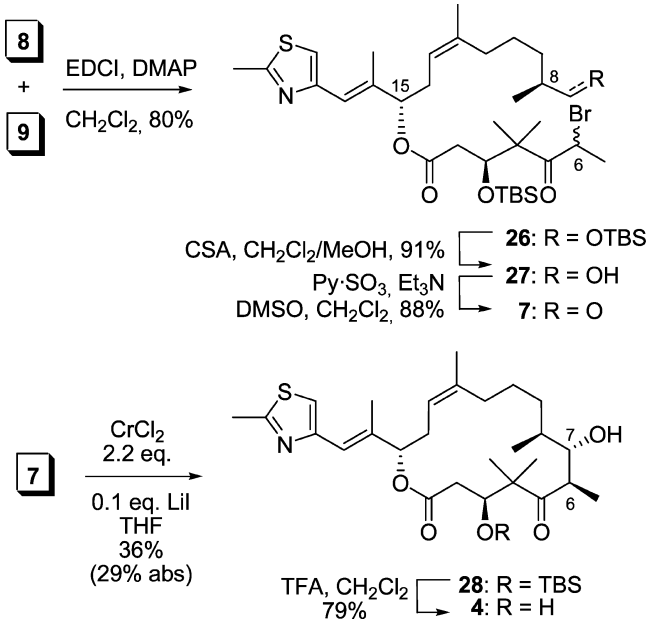
Scheme 4. Macrocyclization and Completion of the Synthesis



Fortunately, the addition of compound **7** in THF via syringe pump to a suspension of $CrCl_2$ and LiI in THF furnished the desired product (22% based on available (8*S*)-**7** as substrate) exclusively as the correct diastereomer: i.e. with C6−C7-*syn* and C7−C8-*anti*-Cram configuration. The other starting diastereomer did not cyclize to the epimeric epothilone within the reaction time and was not recovered. From the reaction mixture only compound **28** was isolated (see the Experimental Section), and its deprotection in the final step afforded epothilone D (**4**). NMR analysis confirmed the structure of compound **4** by comparison to the natural product and literature values of synthetic epothilone D (see the Supporting Information, page S52). Other spectroscopic and chromatographic properties, and eventually the antimitotic activity on human and plant cells, proved to be identical.[22]

In addition, an inverted order for the connection of the southern and northern halves was successfully performed: i.e., a C6−C7-chromium aldol reaction with C1-methyl ester gave a 97% yield of a diastereomeric mixture, from which 60% of the correct diastereomer and precursor for a more conventional order of construction was separated. After de- and reprotection, a standard Yamaguchi macrolactonization used in many former syntheses gave the product after a final deprotection. The intermolecular chromium Reformatsky reaction expectedly gave much higher yields than the cyclizing reaction, but this is counterbalanced by a lower selectivity toward the 8*S* isomer, requiring a subsequent separation effort and a lower yield of the macrolactonization vs the esterification. The macrolactonization variant also required additional protection/deprotection steps. Thus, despite higher yields in the C6−C7 aldol formation, of the macrolactonization approaches, the unusual chromium(II)-mediated macrocyclizing Reformatsky variant provides less purification effort, a better overall yield, and a reduced step count.

CONCLUSION

A highly convergent and stereocontrolled synthesis of epothilone D (**4**) is presented. Some crucial steps to the major building blocks and the unusual chromium(II)-mediated macroaldolization variant are clearly distinct from other syntheses. The use of cheap, available nerol avoids problems with C12−C13 *cis* selectivity, enzymatic (or other) resolution of a cheap 2-acetyl acetoacetate derivative gives perfect stereoselection at C15 (formally this is diastereoselection, but there is no influence of the remote C8 center on the process, which thus behaves like an enantioselection). The two chromium Reformatsky steps provide the perfect chemo- and diastereoselectivity in two aldolizations, which both fail with other counterions, one of them being the first chromium macroaldolization. In direct comparison with the macrolactonization approach, the macroaldolization route provided a better overall performance with respect to step count, separation effort, and overall yield.

EXPERIMENTAL SECTION

***tert*-Butyl 2-Acetoxyacetoacetate (10).** *tert*-Butyl 2-bromoacetoacetate (59.27 g, 250 mmol) was added dropwise to a suspension of sodium acetate (30.76 g, 375 mmol) in DMF (250 mL). After the mixture was stirred at ambient temperature for 90 min, water (415 mL) was added, followed by extraction with ethyl acetate (3 × 325 mL). The combined organic layers were washed with water (3 × 325 mL) and brine (325 mL) and dried over anhydrous Na_2SO_4, and after filtration, the solvent was removed under vacuum. The resulting oil was purified via distillation (12 mbar, 128 °C; yield 36.52 g, 68%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (s, 9H), 2.22 (s, 3H), 2.34 (s, 3H), 5.40 (s, 1H); ^{13}C NMR (APT, 75 MHz, $CDCl_3$) δ (−) 20.5, (−) 27.3, (−) 27.8, (−) 78.4, (+) 84.0, (+) 163.1, (+) 169.3, (+) 197.5; IR (KBr) 841 (w), 1094 (m), 1152 (s), 1221 (s), 1250 (s), 1395 (w), 1420 (w), 1456 (w), 1748 (s), 2938 (m), 2980 (m) cm^{-1}; $C_{10}H_{16}O_5$ (216.23, 216.10); MS (CI) *m*/*z* (%) 117 (19), 143 (12), 161 (100), 205 (43), 207 (12), 217 (18); HRMS (ESI) *m*/*z* [M + H]$^+$ calcd 217.1076, found 217.1046.

(*Z*)-2-Acetoxy-2-acetyl-5,9-dimethyldeca-4,8-dienoic Acid *tert*-Butyl Ester (14). *tert*-Butyl 2-acetoxyacetoacetate (**10**; 19.5 g, 90 mmol) was added dropwise to a stirred suspension of NaH (2.59 g, 108 mmol) in THF (180 mL) at 0 °C. After the complete liberation of hydrogen gas neryl bromide (19.6 g, 90 mmol) was added dropwise at 0 °C. The solution was warmed to room temperature and then stirred for 16 h. The resulting mixture was diluted with ether (750 mL), washed with water (3 × 200 mL) and brine (1 × 200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The crude product was used without further purification (yield 30.3 g, 96%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.58 (s, 3H), 1.65 (s, 3H), 1.67 (s, 3H), 1.90−2.05 (m, 4H), 2.16 (s, 3H), 2.28 (s, 3H), 2.75−2.90 (m, 2H), 4.95−5.09 (m, 2H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 18.1, 21.1, 24.0, 28.1, 26.8, 26.9, 28.1, 32.4, 32.8, 83.8, 88.1, 116.5, 124.0, 132.0, 140.2, 166.1, 169.6, 201.0; IR (KBr) 845 (w), 1024 (w), 1072 (w), 1086 (w), 1115 (w), 1157 (s), 1236 (s), 1256 (s), 1314 (w), 1370 (s), 1389 (w), 1437 (w), 1452 (w), 1746 (s), 2861 (w), 2882 (w), 2932 (m), 2976 (m) cm^{-1}; $C_{20}H_{32}O_5$ (352.47, 352.22); MS (CI) *m*/*z* (%) 353 (13), 298 (21), 297 (100), 279 (14), 255 (10), 253 (13), 237 (27), 219 (20), 209 (65), 193 (10), 175 (6), 153 (7), 137 (16); HRMS (ESI) *m*/*z* [M + H]$^+$ calcd 353.2328, found 353.2324.

(4*Z*,8*E*)-2-Acetoxy-2-acetyl-5,9-dimethyl-10-hydroxydeca-4,8-dienoic Acid *tert*-Butyl Ester (15). Powdered selenium dioxide (0.16 g, 1.42 mmol) was suspended in CH_2Cl_2 (50 mL), followed by the addition of 70% *tert*-butyl hydroperoxide solution (10.2 g, 79.5 mmol). The resulting mixture was stirred at room temperature for 30 min and then treated with compound **14** (10.0 g, 28.4 mmol). The reaction mixture was stirred for a further 48 h and then concentrated under reduced pressure. Toluene (3 × 50 mL) was added to it and subsequently removed under vacuum (for the removal of excess *tert*-butyl hydroperoxide). A slightly yellow oil was obtained and purified by flash chromatography (ethyl acetate/petroleum ether, 1/2; yield 4.65 g, 44%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 1.67 (s,

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3H), 1.71 (s, 3H), 1.90−2.15 (m, 4H), 2.16 (s, 3H), 2.31 (s, 3H), 2.85−2.88 (m, 2H), 3.99 (s, 2H), 5.01−5.03 (m, 1H), 5.36−5.38 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.7, 20.8, 23.5, 25.8, 27.1, 27.8, 31.6, 32.3, 68.7, 83.2, 87.9, 116.5, 124.8, 135.2, 139.5, 165.8, 169.4, 201.2; IR (KBr) 755 (w), 845 (w), 1018 (w), 1049 (w), 1072 (w), 1157 (m), 1236 (m), 1258 (m), 1371 (m), 1395 (w), 1435 (w), 1456 (w), 1742 (s), 2854 (w), 2934 (w), 2978 (w) cm^{-1}; $C_{20}H_{32}O_6$ (368.46, 368.22); MS (CI) m/z (%) 369 (6), 329 (6), 311 (26), 295 (100), 271 (11), 253 (24), 235 (14), 203 (10), 169 (9), 135 (10); HRMS (ESI) m/z [M + H]$^+$ calcd 369.2277, found 369.2288.

(*Z*)-(9*S*)-2-Acetoxy-2-acetyl-5,9-dimethyl-10-hydroxydeca-4-enoic Acid *tert*-Butyl Ester (16). Compound **15** (7.94 g, 21.6 mmol) was dissolved in a mixture of absolute methanol (15.0 mL) and water (750 μL). The solution was degassed with three freeze−thaw cycles before the addition of [Ru{(*S*)-BINAP}$(OAc)_2$] (185 mg, 1 mol %) and then placed in an autoclave under a nitrogen atmosphere together with a magnetic stirring bar. After 3-fold purging with hydrogen (5.0 quality) the autoclave was set under a pressure of 100 bar of hydrogen (5.0 quality) and the mixture stirred at room temperature for 22 h. The hydrogen pressure was carefully released, and the solution was concentrated under vacuum to yield a brown oil, which was purified by flash chromatography (ethyl acetate/petroleum ether, 1/2; yield 7.08 g, 88%): $[\alpha]_D^{25}$ = −5.2° (*c* = 0.62, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (d, 3H, *J* = 6.4 Hz), 1.24−1.27 (m, 2H), 1.33−1.42 (m, 2H), 1.45 (s, 9H), 1.55−1.66 (m, 1H), 1.68 (s, 3H), 1.99−2.03 (m, 2H), 2.16 (s, 3H), 2.31 (s, 3H), 2.56−2.95 (m, 2H), 3.41 (dd, 1H, *J* = 6.3 Hz, 10.5 Hz), 3.49 (dd, 1H, *J* = 5.9 Hz, 10.5 Hz), 5.00 (t, 1H, *J* = 6.0 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 16.6, 20.8, 23.6, 25.2, 27.1, 27.8, 32.0, 32.3, 32.9, 35.7, 68.2, 83.2, 87.9, 116.0, 140.2, 165.7, 169.4, 201.1; IR (KBr) 756 (w), 845 (w), 1045 (m), 1065 (m), 1080 (m), 1157 (s), 1235 (s), 1258 (s), 1371 (s), 1395 (w), 1429 (w), 1456 (w), 1744 (s), 2874 (w), 2934 (m), 2972 (m) cm^{-1}; $C_{20}H_{34}O_6$ (370.48, 370.24); MS (CI) m/z (%) 369 (6); HRMS (ESI) m/z [M + H]$^+$ calcd 371.2433, found 371.2420.

(*Z*)-(10*S*)-3-Acetoxy-11-hydroxy-6,10-dimethyl-5-undecen-2-one (17). TFA (2.80 mL) was added dropwise to a solution of compound **16** (1.03 g, 2.79 mmol) in CH_2Cl_2 (28 mL) and the mixture stirred for 2 h at room temperature. After completion of the reaction all volatile matter was removed under vacuum and the remaining oil was dissolved in methanol (28 mL). A saturated $NaHCO_3$ solution (5.6 mL) was added to the reaction mixture, and the suspension was stirred for 140 min at ambient temperature followed by dilution with ether (200 mL). The organic layer was separated, washed with water (2 × 50 mL) and brine (50 mL), and dried over anhydrous Na_2SO_4. Filtration and removal of the solvents under vacuum gave a slightly yellow oil which was purified by flash chromatography (ethyl acetate/petroleum ether, 2/3; yield 568 mg, 75%): $[\alpha]_D^{25}$ = −4.95° (*c* = 0.48, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (d, 3H, *J* = 6.6 Hz), 1.24−1.27 (m, 2H), 1.33−1.42 (m, 2H), 1.55−1.67 (m, 1H), 1.70 (s, 3H), 1.99−2.03 (m, 2H), 2.14 (s, 3H), 2.16 (s, 3H), 2.46−2.50 (m, 2H), 3.44−3.49 (m, 2H), 5.11 (t, 1H, *J* = 6.0 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 16.6, 20.8, 23.5, 25.2, 26.8, 29.1, 32.1, 33.0, 35.7, 68.2, 78.5, 117.7, 139.6, 170.4, 205.2; IR (KBr) 755 (w), 986 (w), 1047 (m), 1175 (w), 1242 (s), 1375 (m), 1435 (w), 1456 (w), 1730 (s), 1744 (s), 2872 (m), 2932 (s) cm^{-1}; $C_{15}H_{26}O_4$ (270.36, 270.18); MS (ESI-MS) m/z (%) 563.3 (100) [2 M + Na]$^+$, 293.0 (54) [M + Na]$^+$, 271.1 (7) [M + H]$^+$.

(*Z*)-(10*S*)-3-Acetoxy-11-*tert*-butyldimethylsilyloxy-6,10-dimethyl-5-undecen-2-one (18). Triethylamine (541 μL, 3.90 mmol) and 4-dimethylaminopyridine (DMAP, 12 mg, 0.10 mmol) were added to a solution of compound **17** (528 mg, 1.95 mmol) in absolute CH_2Cl_2 (10.0 mL). The mixture was cooled to 0 °C and stirred for 5 min at this temperature. TBDMSCl (368 mg, 2.44 mmol) was added to it, and the solution was stirred overnight at room temperature. After completion of the reaction, methanol (460 μL) was added to the reaction mixture and stirring was continued for another 30 min. All solvents were removed under reduced pressure, and the resulting residue was suspended in ether (15 mL) and saturated NH_4Cl solution (15 mL). The organic layer was separated, and the aqueous layer was extracted with ether (2 × 10 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum to yield an oil which was purified by flash chromatography (ethyl acetate/petroleum ether, 1/10; yield 597 mg, 80%): $[\alpha]_D^{25}$ = −2.38° (*c* = 0.68, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 6H), 0.83 (d, 3H, *J* = 6.4 Hz), 0.86 (s, 9H), 0.94−1.07 (m, 1H), 1.20−1.42 (m, 3H), 1.46−1.58 (m, 1H), 1.66 (s, 3H), 1.89−2.01 (m, 2H), 2.10 (s, 3H), 2.12 (s, 3H), 2.38−2.47 (m, 2H), 3.33 (dd, 1H, *J* = 6.4 Hz, 9.8 Hz), 3.39 (dd, 1H, *J* = 6.0 Hz, 10 Hz), 4.94 (t, 1H, *J* = 6.4 Hz), 5.03−5.07 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ −5.2, 16.8, 18.4, 20.8, 23.5, 25.3, 26.0, 26.7, 29.0, 32.2, 33.1, 35.8, 68.3, 78.5, 117.6, 139.7, 170.3, 205.0; IR (KBr) 775 (m), 837 (m), 1053 (w), 1092 (m), 1248 (s), 1373 (w), 1458 (w), 1472 (w), 1734 (s), 1748 (s), 2857 (m), 2891 (w), 2905 (w), 2932 (m), 2955 (m) cm^{-1}; $C_{21}H_{40}O_4Si$ (384.63, 384.27); MS (CI) m/z (%) 385 (13) [M + H]$^+$, 327 (13), 267 (26), 253 (6), 193 (40), 175 (62), 117 (100). HRMS (ESI) m/z [M + H]$^+$ calcd 385.2774, found 385.2785.

(*Z*)-(10*S*)-11-(*tert*-Butyldimethylsilyloxy)-3-hydroxy-6,10-dimethyl-5-undecen-2-one (19). Saturated potassium carbonate solution (400 μL) was added to a solution of compound **18** (1.94 g, 5.05 mmol) in methanol (20.0 mL) and stirred for 14 min at ambient temperature. After completion of the reaction the solvent was removed under reduced pressure and extracted with diethyl ether (5 × 30 mL), washed with brine (30 mL), and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent under vacuum, the remaining oil was purified via flash chromatography (ethyl acetate/petroleum ether, 1/4; yield 1.69 g, 97%): $[\alpha]_D^{25}$ = −2.13°(*c* = 0.72, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.87 (d, 3H, *J* = 6.4 Hz), 0.89 (s, 9H), 1.00−1.65 (m, 5H), 1.70 (s, 3H), 1.96−2.04 (m, 2H), 2.19 (s, 3H), 2.34−2.41 (m, 1H), 2.52−2.58 (m, 1H), 3.30−3.44 (m, 2H), 4.19−4.23 (m, 1H), 5.08−5.11 (m, 1H); ^{13}C NMR (APT, 75.5 MHz, $CDCl_3$) δ (−) −5.2, (−) 16.8, (+) 18.4, (−) 23.6, (+) 25.4, (−) 25.6, (−) 26.0, (+) 32.1, (+) 32.3, (+) 33.1, (−) 35.7, (+) 68.3, (−) 76.7, (−) 117.9, (+) 139.6, (+) 209.4; IR (KBr) 667 (w), 775 (m), 837 (s), 1006 (w), 1093 (s), 1147 (w), 1163 (w), 1249 (s), 1362 (m), 1373 (m), 1387 (w), 1419 (w), 1436 (w), 1457 (m), 1464 (m), 1472 (m), 1653 (w), 1684 (w), 1700 (w), 1733 (s), 1747 (s), 2855 (m), 2881 (w), 2902 (m), 2907 (m), 2929 (m), 2950 (m), 2956 (m) cm^{-1}; $C_{19}H_{38}O_3Si$ (342.59, 342.26); HRMS [M + H]$^+$ calcd. 342.2590, found 342.2583.

(*R*)-α-Methoxyphenylacetic Acid (*Z*)-(1*S*,8*S*)-1-Acetyl-9-(*tert*-butyldimethylsilyloxy)-4,8-dimethylnon-3-enyl Ester (20). 1-Ethyl-3-(3-(dimethylamino)propyl)carbodiimide (EDCI; 2.70 g, 14.09 mmol) was added to a solution of compound **19** (2.41 g, 7.04 mmol), (*R*)-α-methoxyphenylacetic acid (1.28 g, 7.75 mmol), and DMAP (86 mg, 0.70 mmol) in CH_2Cl_2 (72.0 mL). The reaction mixture was stirred for 2 h at ambient temperature, followed by extracting with diethyl ether (250 mL) and washing with water (2 × 100 mL) and brine (100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The remaining yellow oil contained two diastereomeric esters, which were separated by flash chromatography (ethyl acetate/petroleum ether, 1/10; yield of the desired diastereomer 2.796 g, 81%): $[\alpha]_D^{25}$ = −28.54° (*c* = 0.51, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 6H), 0.83 (d, 3H, *J* = 6.8 Hz), 0.86 (s, 9H), 1.12−1.62 (m, 5H), 1.52 (s, 3H), 1.84−2.01 (m, 2H), 2.07 (s, 3H), 2.25−2.45 (m, 2H), 3.35−3.39 (m, 2H), 3.41 (s, 3H), 4.35 (s, 1H), 4.93−5.30 (m, 2H), 7.35−7.49 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ −5.2, 16.8, 18.4, 23.4, 25.3, 26.0, 26.6, 29.2, 32.1, 33.1, 35.7, 57.5, 68.3, 79.0, 82.2, 117.3, 127.1, 128.5, 128.7, 135.8, 139.7, 170.1, 204.3; IR (KBr) 665 (w), 697 (w),733 (w), 756 (w), 776 (m), 814 (w), 837 (s), 916 (w), 939 (w), 1005 (w), 1032 (w), 1043 (w), 1098 (s), 1114 (s), 1171 (s), 1200 (m), 1254 (m), 1388 (m), 1459 (m), 1470 (m), 1731 (s), 1757 (s), 2855 (m), 2897 (m), 2929 (s), 2952 (s) cm^{-1}; $C_{28}H_{46}O_5Si$ (490.75, 490.31); HRMS (ESI) m/z [M + H]$^+$ calcd 490.3115, found 490.3107.

(*R*)-α-Methoxyphenylacetic Acid (*Z*)-(1*S*,8*S*)-9-(*tert*-Butyldimethylsilyloxy)-4,8-dimethyl-1-[(*E*)-1-methyl-2-(2-methylthiazol-4-yl)-vinyl]non-3-enyl Ester (22). Sodium hexamethyldisilazide (2 M solution in THF, 1.56 mL, 3.12 mmol) was added dropwise to a cooled solution of tributyl(2-methylthiazol-4-ylmethyl)phosphonium chloride (**21**; 1.02 g, 2.92 mmol) in absolute

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THF (19.0 mL) at −65 °C. After the mixture was stirred for 10 min, a solution of compound **22** (1.19 g, 2.43 mmol) in absolute THF (8.0 mL) was added slowly and then this mixture was stirred for 60 min at −65 °C. A saturated NH_4Cl solution (45 mL) was added to the reaction mixture and extracted with ether (5 × 25 mL). The combined organic extracts were washed with water (3 × 30 mL) and brine (1 × 50 mL), dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1/5; yield 1.37 g, 96%): $[\alpha]_D^{25}$ = −27.6° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.84 (d, 3H, *J* = 6.9 Hz), 0.89 (s, 9H), 0.95−2.05 (m, 7H), 1.51 (s, 3H), 2.05 (s, 3H), 2.29 (t, 2H, *J* = 7.2 Hz), 2.70 (s, 3H), 3.30−3.46 (m, 2H), 3.41 (s, 3H), 4.75−4.80 (m, 1H), 4.78 (s, 1H), 5.25 (t, 1H, *J* = 6.6 Hz), 6.48 (s, 1H), 6.90 (s, 1H), 7.32−7.37 (m, 3H), 7.43−7.46 (m, 2H); ^{13}C NMR (APT, 100.5 MHz, $CDCl_3$) δ (−) −5.3, (−) 14.9, (−) 16.7, (+) 18.4, (−) 19.2, (−) 23.3, (+) 25.2, (−) 25.9, (+) 31.5, (+) 32.1, (+) 33.0, (−) 35.7, (−) 57.3, (+) 68.3, (−) 79.7, (−) 82.6, (−) 116.3, (−) 118.9, (−) 120.4, (−) 127.2, (−) 128.5, (−) 128.4, (+) 136.4, (+) 137.2, (+) 138.5, (+) 152.5, (+) 164.6, (+) 169.9; IR (KBr) 665 (w), 697 (w), 757 (s), 774 (m), 837 (s), 1006 (w), 1032 (w), 1040 (w), 1098 (s), 1112 (s), 1153 (m), 1177 (s), 1198 (m), 1253 (m), 1340 (w), 1361 (w), 1375 (w), 1388 (w), 1459 (m), 1470 (m), 1497 (w), 1751 (s), 2855 (m), 2928 (s), 2952 (s) cm^{-1}; $C_{33}H_{51}NO_4Ssi$ (585.91, 585.33); HRMS (ESI) *m*/*z* $[M + H]^+$ calcd 586.3390, found 586.3381.

(1*E*,5*Z*,3*S*,10*S*)-11-(*tert*-Butyldimethylsilyloxy)-2,6,10-trimethyl-1-(2-methylthiazol-4-yl)undeca-1,5-dien-3-ol (8). K_2CO_3 (0.28 g, 2.00 mmol) was added to a solution of compound **22** (0.59 g, 1.00 mmol) in methanol (10.0 mL) at ambient temperature. The reaction mixture was stirred for 90 min at room temperature, and then the solvents were removed under vacuum. The residue was dissolved in ethyl acetate (40 mL) and the solution was washed with water (3 × 10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The slightly yellow oily residue was purified by flash chromatography (ethyl acetate/petroleum ether, 1/3; yield 0.31 g, 70%): $[\alpha]_D^{25}$ = −11.14° (*c* = 0.95, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.86 (d, 3H, *J* = 6.7 Hz,), 0.89 (s, 9H), 1.00−1.65 (m, 5H), 1.71 (s, 3H), 2.01−2.08 (m, 2H), 2.05 (s, 3H), 2.34−2.36 (m, 2H), 2.71 (s, 3H), 3.35 (dd, 1H, *J* = 6.5 Hz, 9.7 Hz), 3.44 (dd, 1H, *J* = 5.9 Hz, 9.7 Hz), 4.13−4.15 (m, 1H), 5.15−5.17 (m, 1H), 6.56 (s, 1H), 6.94 (s, 1H); ^{13}C NMR (APT, 75.5 MHz, $CDCl_3$) δ (−) −5.4, (−) 14.4, (−) 16.8, (+) 18.3, (−) 19.1, (−) 23.6, (+) 25.5, (−) 25.9, (+) 32.3, (+) 33.1, (+) 34.1, (−) 35.7, (+) 68.3, (−) 77.2, (−) 115.4, (−) 118.8, (−) 120.1, (+) 139.3, (+) 141.7, (+) 152.9, (+) 164.4; IR (KBr) 775 (s), 837 (s), 1007 (w), 1053 (m), 1092 (s), 148 (w), 1186 (w), 1254 (m), 1362 (w), 1375 (w), 1387 (w), 1420 (w), 1437 (w), 1462 (m), 1472 (m), 1507 (m), 2857 (s), 2899 (s), 2928 (s), 2953 (s) cm^{-1}; $C_{24}H_{43}NO_2SSi$ (437.75, 437.28); MS (CI) *m*/*z* (%) 438 (13) $[M + H]^+$, 420 (27), 396 (4), 380 (12), 364 (4), 259 (27), 213 (100); HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd 460.268, found 460.2676.

(4*S*)-3-[(3*S*)-4,4-Dimethyl-1,5-dioxo-3-hydroxyheptyl]-4-benzyloxazolidin-2-one (23). A butyllithium solution (1.6 M, 9 mL, 14.4 mmol) was added dropwise at −63 °C to a solution of (*S*)-4-benzyloxazolidin-2-one (2.55 g, 14.4 mmol) in 50 mL of THF. The reaction mixture was further treated with bromoacetyl bromide (1.25 mL, 14.4 mmol), stirred for 30 min at −63 °C, and then warmed to room temperature. To this reaction mixture were added 2,2-dimethyl-3-oxopentanal (2.03 g, 15.8 mmol), $CrCl_2$ (4.42 g, 36 mmol), and LiI (0.19 g, 1.44 mmol) under argon. The mixture was stirred for 8 h at ambient temperature, and after addition of brine (20 mL) it was vigorously stirred for additional 15 min. The organic phase was separated, and the aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to provide a dark oil which was purified by flash chromatography (ethyl acetate/petroleum ether, 1/1; yield 3.8 g, 76%): $[\alpha]_D^{22}$ = +13.6°; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (t, 3H, *J* = 7.2 Hz), 1.16 (s, 3H), 1.26 (s, 3H), 2.57 (dq, 2H, *J* = 1.5 Hz, 7.2 Hz), 2.79 (dd, 1H, *J* = 9.5 Hz, 13.4 Hz), 3.04−3.07 (m, 2H), 3.28−3.33 (m, 2H), 4.18−4.24 (m, 2H), 4.35 (ddd, 1H, *J* = 1.2 Hz, 5.6 Hz), 4.66−4.74 (m, 1H), 7.20−7.36 (m, 5H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 7.9, 19.6, 21.4, 31.2, 37.7, 38.1, 51.2, 55.2, 66.3, 72.6, 127.4, 129.0, 129.4, 135,1, 153.5, 172.6, 216.2; IR (KBr) 3522 (br), 3063 (w), 3029 (w), 2976 (w), 2938 (w), 2879 (w), 1783 (s), 1700 (s), 1498 (w), 1471 (w), 1454 (w), 1390 (m) 1354 (w), 1294 (w), 1213 (m), 1199 (m), 1111 (w), 1100 (w), 1076 (w), 1053 (w), 973 (w), 762 (w), 704 (w) cm^{-1}; $C_{19}H_{25}NO_5$ (347.41, 347.17); MS (ESI-MS) *m*/*z* (%) 348 (5) $[M + H]^+$, 329 (24), 273 (56), 248 (24), 178 (85), 153 (14), 117 (34), 100 (68), 96 (100). HRMS (ESI) *m*/*z* $[M + H]^+$ calcd 347.1733, found 347.1728.

(4*S*)-3-[(3*S*)-4,4-Dimethyl-1,5-dioxo-3-(*tert*-butyldimethylsilanyloxy)heptyl]-4-benzyloxazolidin-2-one (24). 2,6-Lutidine (1.11 mL, 9.5 mmol) and TBSOTf (1.49 mL, 6.48 mmol) were added to a cooled solution of compound **23** (1.5 g, 4.32 mmol) in 20 mL of CH_2Cl_2 at 0 °C. The solution was stirred for 1.5 h at 0 °C and then diluted with CH_2Cl_2 (30 mL) followed by the addition of 2 N NaOH (4 mL). The organic layer was separated and washed with 2 N HCl (30 mL) and brine (30 mL) and subsequently dried over anhydrous $MgSO_4$. Filtration and removal of the solvents under vacuum gave a yellow oil, which was purified by flash chromatography (ethyl acetate/petroleum ether, 5/1; yield 1.85 g, 93%); $[\alpha]_D^{22}$ = +15.8°; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.12 (s, 3H), 0.88 (s, 9H), 0.99 (t, 3H, *J* = 7.0 Hz), 1.14 (s, 3H), 1.17 (s, 3H), 2.55 (q, 2H, *J* = 7.0 Hz), 2.69 (dd, 1H, *J* = 10.3 Hz), 3.05 (d, 2H, *J* = 5.2 Hz), 3.38 (dd, 1H, *J* = 3.4 Hz, 13.2 Hz), 4.11−4.21 (m, 2H), 4.60−4.68 (m, 1H), 4.72 (t, 1H, *J* = 5.2 Hz), 7.09−7.24 (m, 5H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ −4.9, −4.2, 7.7, 18.2, 19.4, 22.2, 26.0, 31.5, 38.0, 40.7, 52.7, 55.4, 66.2, 71.9, 127.3, 129.0, 129.4, 135.5, 153.5, 171.3, 215.7; IR (KBr) 3027 (w), 2956 (m), 2931 (m), 2885 (w), 2858 (w), 1784 (s), 1702 (s), 1598 (w), 1572 (m), 1455 (w), 1378 (s) 1351 (m), 1309 (m), 1253 (m), 1216 (m), 1088 (s), 1054 (w), 1024 (w), 1006 (w), 972 (w) cm^{-1}; $C_{25}H_{39}NO_5Si$ (461.67, 461.26); MS (ESI-MS) *m*/*z* (%) 461 (2) $[M]^+$, 404 (98), 362 (18), 348 (9), 330 (13), 304 (100), 276 (10), 252 (25), 227 (20), 185 (17), 91 (9).

(3*S*)-3-(*tert*-Butyldimethylsilanyloxy)-4,4-dimethyl-5-oxoheptanoic Acid (25). Hydrogen peroxide (30%, 1.11 mL, 9.66 mmol) and lithium hydroxide hydrate (0.14 g, 3.22 mmol) were added to a cooled solution of compound **24** (0.74 g, 1.61 mmol) in THF/water (3/1, 36 mL) at 0 °C. The reaction mixture was stirred for 1 h, followed by the addition of a solution of sodium sulfite (1.4 g) in water (20 mL), and then buffered with $NaHCO_3$. The volatile solvent was removed under vacuum, and the remaining aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The aqueous phase was acidified to pH 1 with 2 N HCl and extracted again with CH_2Cl_2 (5 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The remaining oil was purified by flash chromatography (ethyl acetate/petroleum ether, 1/2 + 1% acetic acid; yield 0.44 g, 90%): $[\alpha]_D^{22}$ = −19.3°; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.06 (s, 3H), 0.85 (s, 9H), 1.00 (t, 3H, *J* = 7.1 Hz), 1.09 (s, 3H), 1.15 (s, 3H), 2.29−2.55 (m, 4H), 4.47 (dd, 1H, *J* = 3.6 Hz, 6.9 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ −4.9, −4.3, 7.7, 18.2, 20.6, 21.1, 25.9, 31.8, 39.3, 52.6, 73.5, 178.0, 215.2; IR (KBr) 3300 (br), 2956 (s), 2932 (s), 2887 (w), 1736 (s), 1712 (s), 1472 (m), 1410 (m), 1389 (m) 1363 (w), 1303 (w), 1255 (m), 1216 (w), 1092 (s), 1026 (w), 1006 (w), 973 (w) cm^{-1}; $C_{15}H_{30}O_4Si$ (302.48, 302.19); MS (CI, isobut.): *m*/*z* (%) 303 (6) $[M + H]^+$, 245 (95), 227 (58), 203 (25), 183 (18), 171 (43), 153 (60), 145 (79), 125 (46), 101 (100), 75 (94).

(3*S*)-6-Bromo-3-(*tert*-butyldimethylsilanyloxy)-4,4-dimethyl-5-oxoheptanoic Acid (9, Mixture of Diastereomers). Phenyltrimethylammonium bromide (0.42 mL, 1.13 mmol) was added to a cooled solution of compound **25** (0.33 g, 1.08 mmol) in THF at 0 °C. The reaction mixture was stirred for 15 min at 0 °C and then warmed to room temperature followed by additional stirring for 1 h. Water (13 mL) was added to the reaction mixture, and the organic layer was separated while the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with 1 N HCl (25 mL) and brine (25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The remaining oil was purified by flash

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chromatography (ethyl acetate/petroleum ether, 1/4 containing 2% acetic acid; yield 0.41 g, 98%): $[\alpha]_D^{22} = -40.8°$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.07 (s, 3H), 0.09 (s, 3H), 0.83 (s, 9H), 1.22 (s, 3H), 1.24 (s, 3H), 1.37 (s, 3H), 1.60−1.70 (m, 6H), 2.26 (dd, 1H, J = 6.2 Hz, 16.9 Hz), 2.41 (dd, 1H, J = 6.5 Hz, 16.8 Hz), 2.55 (dd, 1H, J = 3.6 Hz, 16.7 Hz), 2.69 (dd, 1H, J = 4.1 Hz, 16.9 Hz), 4.25 (dd, 1H, J = 4.2 Hz, 6.2 Hz), 4.49 (dd, 1H, J = 3.6 Hz, 6.5 Hz), 4.75−4.88 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ −4.7, −4.6, −4.5, −4.3, 18.1, 20.4, 20.5, 21.1, 21.6, 21.9, 22.7, 25.6, 26.0, 39.5, 39.7, 41.5, 41.7, 52.7, 53.3, 73.3, 75.4, 177.2, 177.5, 208.3, 208.5; $C_{15}H_{29}BrO_4Si$ (381.38, 380.10); MS (CI, isobut.) m/z (%) 383 (11) $[M + H]^+$, 303 (25), 137 (27), 135 (27), 105 (20), 93 (30), 88 (100), 76 (49), 71 (46); HRMS (ESI) m/z $[M + H]^+$ calcd 381.1907, found 381.1068.

(3*S*)-6-Bromo-3-(*tert*-butyldimethylsilyloxy)-4,4-dimethyl-5-oxoheptanoic Acid (3*Z*,1*S*,8*S*)-9-(*tert*-Butyldimethylsilyloxy)-4,8-dimethyl-1-[(*E*)-1-methyl-2-(2-methylthiazol-4-yl)-vinyl]-non-3-enyl Ester (26, Mixture of Diastereomers). EDCI (0.25 g, 1.29 mmol) was added to a cooled solution of compound **8** (0.28 g, 0.64 mmol), (3*S*)-6-bromo-3-(*tert*-butyldimethylsilanyloxy)-4,4-dimethyl-5-oxo-heptanoic acid (**9**, 26 g, 0.64 mmol), and DMAP (8 mg, 0.064 mmol) in CH_2Cl_2 (3.50 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C and then for 18 h at room temperature. The reaction mixture was extracted with diethyl ether (50 mL). The combined organic extracts were washed with a half-concentration NaCl solution (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The remaining oil was purified by flash chromatography (ethyl acetate/petroleum ether, 1/4; yield 0.36 g, 70%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.01−0.12 (m, 12H), 0.81−0.95 (m, 21H), 0.90−1.63 (m, 12H), 1.67 (s, 3H), 1.69 (dd, 3H, J = 4.4 Hz), 1.92−2.05 (m, 2H), 2.08 (s, 3H), 2.22 (dd, 1H, J = 5.6 Hz), 2.33−2.54 (m, 2H), 2.66 (dd, 1H, J = 4.8 Hz), 2.71 (s, 3H), 3.36 (dd, 1H, J = 6.8 Hz, 9.6 Hz), 3.45 (dd, 1H, J = 5.6 Hz, 9.6 Hz), 4.25 (dd, 1H), 4.56 (dd, 1H), 4.81−4.89 (m, 1H), 5.00−5.11 (m, 1H), 5.20 (dd, 1H, J = 3.2 Hz, 7.5 Hz), 6.50 (s, 1H), 6.96 (s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ −5.3, −4.8, −4.5, −4.2, −4.0, 14.9, 16.8, 18.1, 18.3, 19.2, 20.9, 21.3, 21.4, 21.5, 22.7, 22.9, 23.5, 26.0, 26.2, 31.6, 32.3, 33.2, 35.8, 39.8, 40.1, 41.7, 42.1, 52.6, 53.3, 68.3, 73.5, 75.6, 79.8, 116.3, 119.3, 121.0, 137.1, 138.6, 152.6, 164.5, 170.9, 208.3, 208.6; IR (KBr) 667 (w), 758 (s), 777 (s), 814 (w), 837 (s), 1005 (w), 1024 (w), 1094 (s), 1181 (m), 1215 (w), 1254 (m), 1294 (w), 1362 (w), 1375 (w), 1387 (w), 1447 (w), 1471 (m), 1507 (w), 1709 (m), 1734 (m), 2857 (s), 2928 (s) 2955 (s) cm^{-1}; $C_{39}H_{70}BrNO_5SSi_2$ (801.12, 799.37); MS (CI) m/z (%) 802 (0.9) $[M + H]^+$, 800 (0.6) $[M + H]^+$, 420 (75), 168 (100); HRMS (ESI) m/z $[M + Na]^+$ 824.3557, found 824.3568.

(3*S*)-6-Bromo-3-(*tert*-butyldimethylsilyloxy)-4,4-dimethyl-5-oxoheptanoic Acid (3*Z*,1*S*,8*S*)-9-Hydroxy-4,8-dimethyl-1-[(*E*)-methyl-2-(2-methylthiazol-4-yl)vinyl]non-3-enyl Ester (27, Mixture of Diastereomers). Compound **26** (0.32 g, 0.41 mmol) was dissolved in a 1/1 mixture of CH_2Cl_2 and MeOH (12.4 mL) and cooled to 0 °C. CSA (97 mg, 0.42 mmol) was added to this solution, and the mixture was stirred for 2.5 h at 0 °C. The reaction mixture was treated with triethylamine (64 mg, 87 μL, 0.63 mmol) and concentrated under reduced pressure. The residual oil was purified by flash chromatography (ethyl acetate/petroleum ether, 1/2; yield 0.24 g, 86%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.00−0.03 (m, 6H), 0.72−0.89 (m, 9H), 0.85 (d, 3H, J = 6.8 Hz), 0.99−1.67 (m, 4H), 1.07 (s, 3H), 1.17 (s, 3H), 1.37 (s, 3H), 1.57−1.63 (m, 3H), 1.60 (s, 3H), 1.72−1.88 (bs, 1H) 1.89−2.10 (m, 2H), 2.00 (s, 3H), 2.16 (dd, 1H, J = 5.6 Hz), 2.53−2.49 (m, 2H), 2.60 (dd, 1H, J = 4.8 Hz), 2.65 (s, 3H), 3.37 (dd, 1H, J = 6.8 Hz), 3.43 (dd, 1H, J = 6.0 Hz), 4.16−4.40 (m, 1H), 4.75−4.81 (m, 1H), 4.99−5.35 (m, 1H), 5.11−5.17 (m, 1H), 6.45 (s, 1H), 6.92 (s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ −5.1, −5.0, −4.6, −4.4, 14.5, 16.5, 19.0, 19.4, 20.2, 21.3, 21.5, 22.6, 22.9, 23.7, 25.8, 26.2, 31.5, 32.1, 33.9, 35.5, 39.7, 40.2, 41.5, 42.4, 52.4, 53.1, 67.8, 73.7, 75.5, 79.8, 116.2, 119.2, 121.0, 137.0, 138.3, 152.3, 164.5, 170.8, 208.2, 208.7; IR (KBr) 733 (s), 756 (w), 779 (m), 837 (s), 910 (w), 1003 (w), 1024 (w), 1061 (m), 1094 (m), 1182 (s), 1255 (m), 1294 (w), 1375 (m), 1386 (m), 1420 (w), 1437 (w), 1447 (w), 1456 (m), 1472 (m), 1507 (m), 1520 (w), 1541 (m), 1559 (m), 1653 (m), 1684 (w), 1701 (s), 1717 (s), 1734 (s), 2859 (m), 2934 (s), 2955 (s) cm^{-1}.; $C_{33}H_{56}BrNO_5SSi_2$ (686.86, 685.28); MS (CI) m/z (%) 688 (1.6) $[M + H]^+$, 686 (1.1) $[M + H]^+$, 306 (100), 168 (100); HRMS (ESI) m/z $[M + Na]^+$ calcd 710.2685, found 710.2704.

(3*S*)-6-Bromo-3-(*tert*-butyldimethylsilanyloxy)-4,4-dimethyl-5-oxoheptanoic Acid (1*S*,3*Z*,8*S*)-9-Hydroxy-4,8-dimethyl-1-[(1*E*)-methyl-2-(2-methylthiazol-4-yl)vinyl]-9-oxonon-3-enyl Ester (7, Mixture of Diastereomers). SO_3·(pyridine) complex (0.20 g, 1.22 mmol) was added to a cooled solution of compound **27** (0.18 g, 0.26 mmol), DMSO (1.72 mL), triethylamine (0.16 mg, 0.21 mL, 1.53 mmol), and CH_2Cl_2 (5.30 mL) at 0 °C. The resulting mixture was stirred for 60 min at 0 °C and then extracted with diethyl ether (40 mL) and washed with water (2 × 50 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum to yield a slightly yellow oil which was used in the following reaction step without any further purification (yield 0.15 g, 84%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.09 (s, 6H), 0.75 (s, 12H), 0.98−1.17 (m, 6H), 1.36−1.51 (m, 4H), 1.65 (s, 3H), 1.94−2.11 (m, 3H), 2.14−2.65 (m, 10H), 2.63 (s, 3H), 4.18−4.45 (m, 1H), 4.72−4.86 (m, 1H), 5.01−5.12 (m, 1H), 5.14−5.21 (m, 1H), 6.41 (s, 1H), 6.88 (s, 1H), 9.53 (d, 1H, J = 1.6 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ −4.5, −4.4, −4.0, −3.8, 13.8, 15.1, 18.5, 19.6, 20.8, 21.0, 21.1, 22.1, 22.6, 23.8, 25.6, 26.4, 30.7, 31.5, 32.3, 40.2, 41.1, 41.6, 42.6, 46.7, 53.0, 53.7, 73.9, 76.0, 80.2, 116.8, 120.3, 121.6, 124.7, 137.4, 137.7, 138.2, 152.9, 153.0, 164.6, 170.3, 205.3, 208.8, 209.0; $C_{33}H_{54}BrNO_5SSi$ (684.84, 683.27); MS (CI) m/z (%) 684 (4) $[M + H]^+$, 606 (16) $[M + H - Br]^+$, 474 (20), 372 (49), 355 (18), 306 (18), 304 (17), 271 (100); HRMS (ESI) m/z $[M + H]^+$ 684.2753, found 684.2753.

(13*Z*,4*S*,7*R*,8*S*,9*S*,16*S*)-4-(*tert*-Butyldimethylsilyloxy)-8-hydroxy-5,5,7,9,13-pentamethyl-16-[(*E*)-1-methyl-2-(2-methylthiazol-4-yl)vinyl]oxacyclohexadec-13-ene-2,6-dione (28). A solution of compound **7** (80 mg, 0.12 mmol) in THF (5.0 mL) was added to a suspension of $CrCl_2$ (35 mg, 0.28 mmol) and LiI (30 mg, 0.22 mmol) in dry THF (25 mL) over a period of 80 min via syringe pump. The resulting suspension was stirred a further 2 h at ambient temperature and then quenched with half-concentration NH_4Cl (20 mL). The organic phase was extracted with ether (5 × 15 mL), washed with demineralized water (2 × 15 mL) and brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residual oil was purified by flash chromatography (ethyl acetate/petroleum ether, 5/1; yield 16.2 mg, 22%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.12 (s, 3H), 0.83 (s, 9H), 0.86−1.86 (m, 7H), 1.03 (d, 3H, J = 7.2 Hz), 1.14−1.17 (m, 9H), 1.66 (s, 3H), 1.98−2.89 (m, 4H), 2.10 (s, 3H), 2.71 (s, 3H), 2.95−3.04 (bs, 1H), 3.03−3.07 (m, 1H), 3.80−3.89 (m, 1H), 4.06 (dd, 1H, J = 4.0 Hz, 8.8 Hz), 4.98 (dd, 1H, J = 10.0 Hz), 5.13−5.17 (m, 1H), 6.48 (s, 1H), 6.94 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ −4.3, −3.6, 13.0, 15.3, 15.8, 18.2, 19.3, 22.3, 22.9, 23.0, 25.9, 31.9, 32.5, 37.9, 34.2, 40.1, 41.4, 53.7, 72.8, 73.3, 79.6, 116.2, 120.1, 120.8, 137.7, 138.3, 152.6, 164.7, 170.3, 220.1; IR (KBr) 731 (m), 777 (s), 835 (s), 937 (w), 974 (w), 986 (w), 1063 (w), 1094 (m), 1134 (w), 1163 (m), 1179 (m), 1204 (w), 1252 (w), 1412 (m), 1451 (m), 1468 (s), 1501 (m), 1512 (m), 1530 (w), 1547 (m), 1564 (w), 1582 (w), 1688 (s), 1740 (s), 2857 (m), 2930 (s), 2959 (m) cm^{-1}; $C_{33}H_{55}NO_5SSi$ (605.94, 605.36); HRMS (ESI) m/z $[M + Na]^+$ 628.3452, found 628.3462.

(13*Z*,4*S*,7*R*,8*S*,9*S*,16*S*)-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[*E*-1-methyl-2-(2-methylthiazol-4-yl)vinyl]-oxacyclohexadec-13-ene-2,6-dione (Epothilone D, 4). TFA (200 μL) was added to a cooled solution of **28** (7 mg, 0.012 mmol) in methylene chloride (1 mL) at 0 °C. The solution was stirred at 0 °C over a period of 90 min and then extracted with methylene chloride (20 mL). The organic extract was washed with saturated $NaHCO_3$ solution (2 × 10 mL), water (10 mL), and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residual yellow oil was purified by flash chromatography (ethyl acetate/petroleum ether, 1/2; yield 4.1 mg, 69%): ^{1}H NMR (400 MHz, CD_3OD) δ 1.00 (s, 3H), 1.01 (d, 3H, J = 7.5 Hz), 1.20 (d, 3H, J = 7.0 Hz), 1.25−1.56 (m, 5H), 1.32 (s, 3H), 1.69 (s, 3H), 1.69−1.78 (m, 1H), 1.84−1.91 (m, 1H), 2.05 (s, 3H), 2.22 (dd, 1H, J = 6.0 Hz,

15.0 Hz), 2.35−2.16 (m, 2H), 2.69 (s, 3H), 2.68−2.75 (m, 1H), 3.23 (dq, 1H, J = 7.0 Hz), 3.30−3.31 (m, 2H), 3.65 (dd, 1H, J = 3.0 Hz, 6.7 Hz), 4.30 (dd, 1H, J = 4.0 Hz, 10.0 Hz), 5.18−5.23 (m, 2H), 6.57 (s, 1H), 7.22 (s, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 15.7, 16.2, 17.5, 18.6, 18.9, 19.3, 19.5, 23.4, 23.4, 32.8, 38.5, 39.9, 40.8, 45.5, 49.3, 72.5, 77.5, 80.7, 117.4, 120.0, 121.6, 140.2, 140.3, 166.0, 167.0, 220.3; $C_{27}H_{41}NO_5S$ (491.68, 491.27); HRMS (ESI) m/z [M + Na]$^+$ 614.2594, found 614.2598.

■ ASSOCIATED CONTENT

Supporting Information

Text and figures giving general experimental procedures and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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