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Total Synthesis of Epothilone D: the Nerol/Macroaldolization Approach

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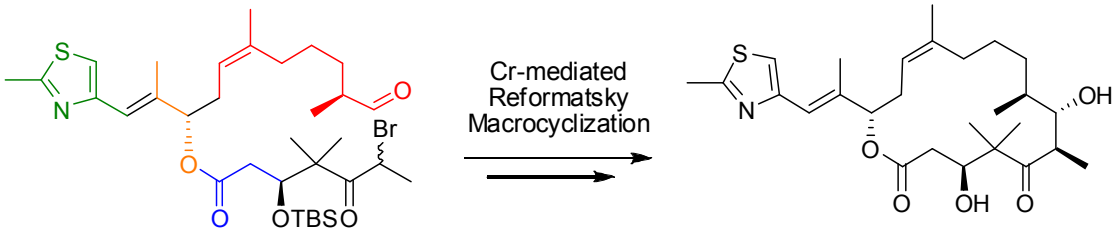


Epothilone D

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.

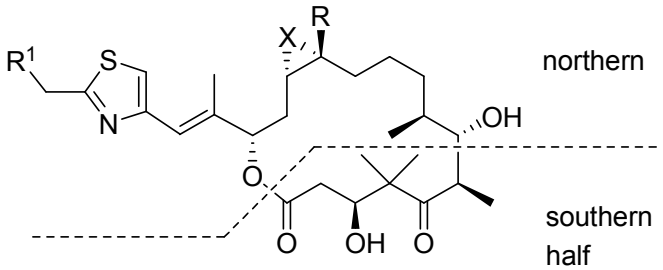
Footnote:

[†]part of this work was performed at the Vrije University Amsterdam, NL

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 polymerisation 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 published.[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.

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 taxanes, they express non-overlapping 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]



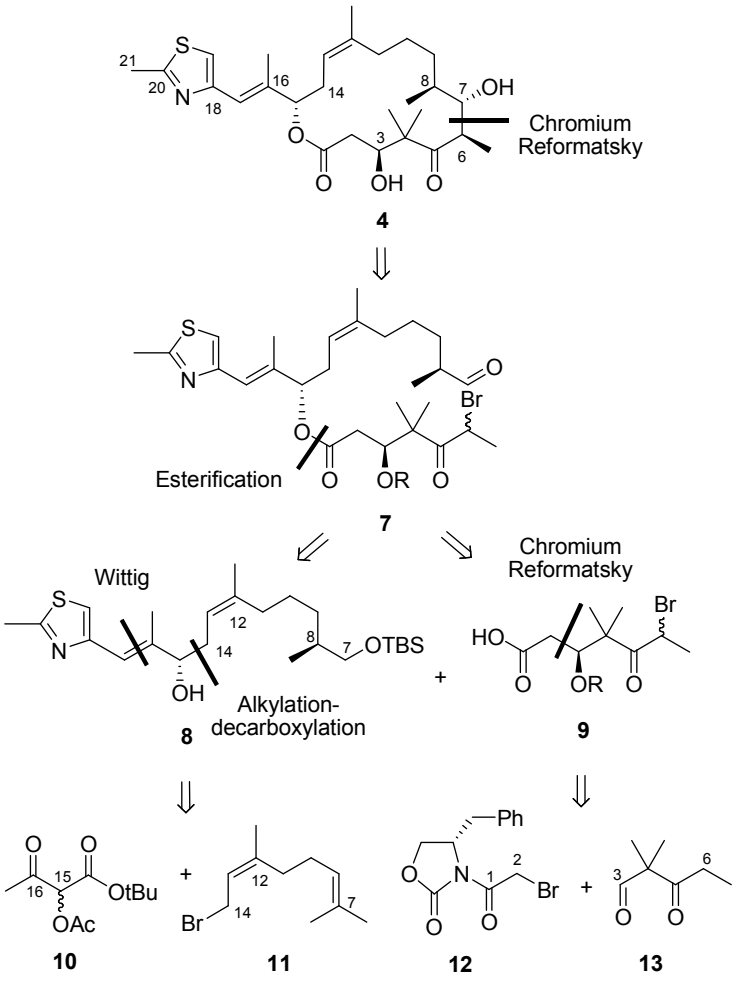
1 Epothilone A, R = H, R^1 = H, X = O
2 Epothilone B, R = Me, R^1 = H, X = O
3 Epothilone C, R = H, R^1 = H, X = bond
4 Epothilone D, R = Me, R^1 = H, X = bond
5 Epothilone E, R = H, R^1 = H, X = O
6 Epothilone F, R = Me, R^1 = OH, X = O

Figure 1. Structures of epothilones A–F.

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 re-occuring 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 C6–C7 bond *via* a novel chromium-Reformatsky-macrocyclization of the linear epothilone precursor **7** (Scheme 1).



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).[12]

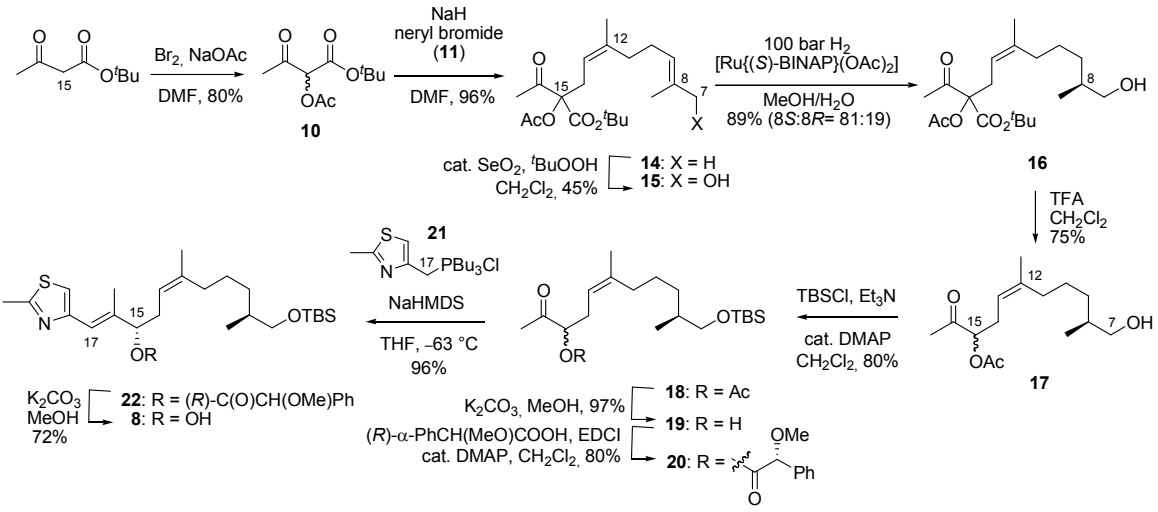
The other disconnections cut the ester moiety in compound **7**, which separates the epothilones northern and southern halves (**8** and **9**, respectively). Further disconnection of compound **8** through a Wittig-reaction and alkylation-decarboxylation sequence leads back to acetoacetate **10** and 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 is lower yielding than the overstoichiometric use of SeO_2, up 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 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.



Scheme 2. Synthesis of northern half (showing resolution of *O*-methyl mandelates)

Hydrogenation of the C8–C9 double bond of allylic alcohol **15** utilizing Noyori-catalyst [Ru{(*S*)-BINAP}$(OAc)_2$] (1.5 mol%) in methanol-water (95:5) at >100 bar hydrogen 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 hampers the catalyst to dock to surrounding potential ligand positions. Without the bulky substituents, the hydrogenation gives mixtures (saturation of double bonds 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 ester of compound **16**. The ratio between 8*S*:8*R* is 81:19 in 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 original northern half (courtesy of Prof. Höfle), obtained by degradation of natural epothilone. Acidic decarboxylation of **16** using TFA takes place without

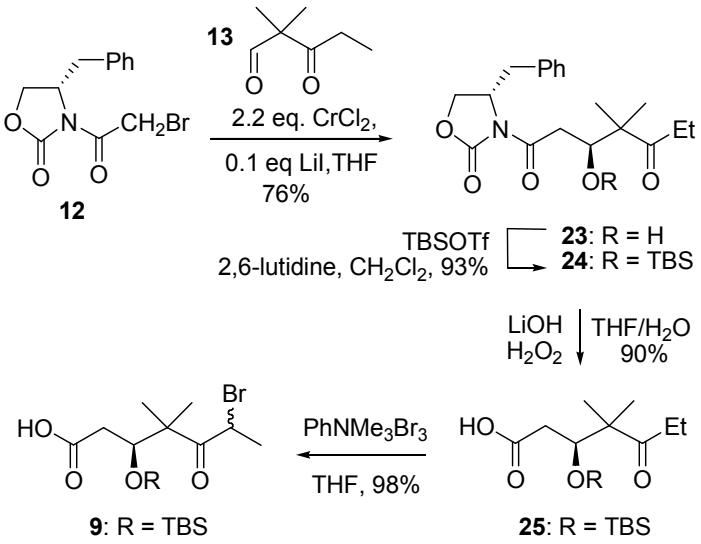
detectable isomerization of the remaining double bond, in contrast to classic Krapcho decarboxylation conditions. The trade-in, however, is a partial trifluoroacetylation of the ω-alcohol, which can be reverted quantitatively by work up with aqueous $NaHCO_3$.

The obtained free primary alcohol **17** was subsequently protected as 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 Evans auxiliary, or enzymatic resolution (e.g. by *Candida antarctica* lipase B).[4e] Since the C15 stereocenter of **20** is in α-position 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 the Wittig olefination using thiazole phosphonium salt **21** in the presence of NaHMDS yielding olefin **22** without racemization in excellent yield.[4n,17] Other ylids show worse reactivity or purification behavior.[18] Finally, ester saponification gave access to the northern half building block **8**.

The stereoselective formation of 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,4g,9,19] in contrast to lithium or other counter ions.

In the presence of 2.2 equivalents of $CrCl_2$, bromoacetate **12** reacts exclusively at the aldehyde portion with β-keto aldehyde **13** to 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 retro-aldolization. Retroaldolization is commonly observed in sterically compressed non-cyclic double aldolates like **23**, which re-open at the C3-C4 bond during reaction if, e.g. 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]

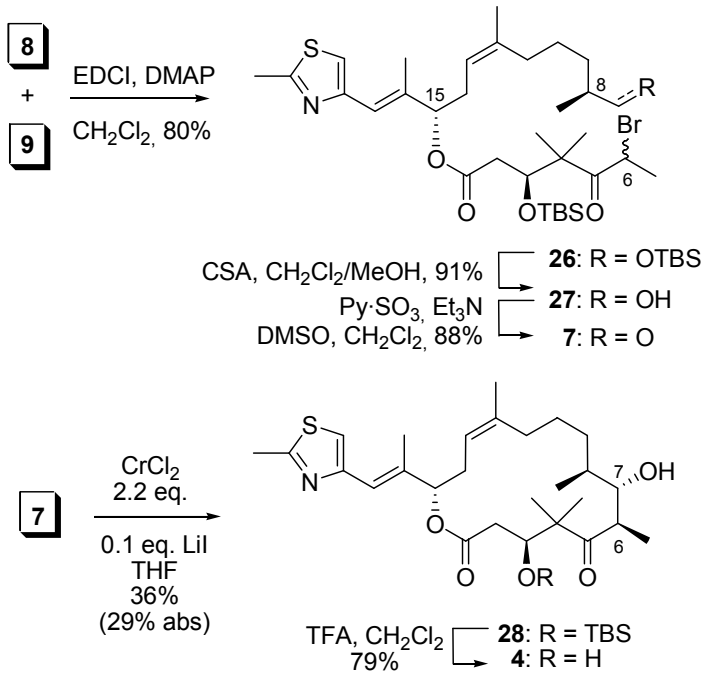


Scheme 3. Synthesis of Southern half

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 provides α-bromoketone **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 cyclic byproduct was observed.

Esterification of southern half carboxylic acid **9** with nothern 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%).



Scheme 4. Macrocyclization and completion of the synthesis

In a 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 stereo differentiation between C7 and C8[21] and, ideally in such a way, that only the 8*S*-diastereomer (shown) is reacting, and not the residual 20% 8*R*-epimer (not shown). Induction for this selection must come from the fully defined C3 or the C15 stereocenter. But not only stereoselection is crucial, 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 6-membered ring Claisen product rather than a macroaldol. Indeed, the latter reaction occurs with all other tested counterions (Li, Zn, In, Sm etc.) different than chromium(III).

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 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 Supporting Inormation page S52). Other spectroscopic and chromatographic properties, and eventually the antimitotic activity on human and plant cells proved to be identical.[22]

Also an inverted order for the connection of southern and northern half was successfully performed, i.e. a C6–C7-chromium aldol reaction with C1-methyl ester gave 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 one, but this is counterbalanced by a lower selectivity towards 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 approach, 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-bromo-acetoacetate (59.27 g, 250 mmol) was added dropwise to a suspension of sodium acetate (30.76 g, 375 mmol) in DMF (250 mL). After stirring 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), dried over anhydrous Na_2SO_4 and after filtration, the solvent was removed in 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-dimethyl-deca-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, nerylbromide (19.6 g, 90 mmol) was added dropwise at 0 °C. The solution was warmed to room temperature and then allowed to stir for 16 h. The resulting mixture was diluted with ether (750 mL), washed with water (3 × 200 mL), brine (1 × 200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in 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-dimehtyl-10-hydroxy-deca-4,8-dienoic-acid-*tert*-butyl ester (15). Powdered seleniumdioxide (0.16 g, 1.42 mmol) was suspended in CH_2Cl_2 (50 mL), followed by the addition of 70% *tert*-butylhydroperoxide 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 further 48 h and then concentrated under reduced pressure. Toluene (3 × 50 mL) was added to it and subsequently removed in vacuum (for the removal of excess *tert*-butylhydroperoxide). Slightly yellow oil was obtained and purified by flash chromatography (ethyl acetate/petroleum ether, 1:2; yield 4.65 g, 44%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 1.67 (s, 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-hydroxy-deca-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 nitrogen atmosphere together with a magnetic stirring bar. After threefold purging with hydrogen (5.0 quality) the autoclave was set under a pressure of 100 bar hydrogen (5.0 quality) and stirred at room temperature for 22 h. The hydrogen pressure was carefully released and the solution was concentrated in vacuum to yield 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 allowed to stir for 2 h at room temperature. After completion of reaction all volatile matter was removed in vacuum and the remaining oil was dissolved in methanol (28 mL). 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), brine (50 mL) and dried over anhydrous Na_2SO_4. Filtration and removal of the solvents in vacuum gave slightly yellow oil which was purified by flash chromatography (ethyl acetate/petroleum ether, 2:3; yield 568 mg, 75%): $[\alpha]_D^{22} = -4.95°$ (*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) $[2M + Na]^+$, 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 over night at room temperature. After completion of reaction, methanol (460 μL) was added to the reaction mixture and was allowed to stir 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 in 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 allowed to stir for 14 min at ambient temperature. After completion of reaction the solvent was removed under reduced pressure and extracted with diethylether (5 × 30 mL), washed with brine (30 mL) and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent in 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-dimethylaminopropyl)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 allowed to stir for 2 h at ambient temperature followed by the extraction with diethylether (250 mL), 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 abs. THF (19.0 mL) at –65 °C. After stirring for 10 min, a solution of compound **22** (1.19 g, 2.43 mmol) in abs. THF (8.0 mL) was added slowly and then allowed to stir 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), 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 solvents were removed in vacuum. The residue

was dissolved in ethyl acetate (40 mL) and washed with water (3 × 10 mL), brine (10 mL), dried over anhydrous Na_2SO_4, filtered and then concentrated under reduced pressure. The slightly yellow oil 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-benzyl-oxazolidin-2-on (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-on (2.55 g, 14.4 mmol) in 50 mL 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 allowed to come 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 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*-butyl-dimethylsilanyloxy)-heptyl]-4-benzyl-oxazolidin-2-on (24). 2,6-Lutidin (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 CH_2Cl_2 at 0 °C. The solution was allowed to stir for 1.5 h at 0 °C and then diluted with CH_2Cl_2 (30 mL) followed by the addition of 2N NaOH (4 mL). The organic layer was separated and washed with 2N HCl (30 mL), brine (30 mL) and subsequently dried over anhydrous $MgSO_4$. Filtration and removal of the solvents in vacuum gave 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*-butyl-dimethylsilanyloxy)-4,4-dimethyl-5-oxo-heptanoic acid (25). 30% Hydrogen peroxide (1.11 mL, 9.66 mmol) and lithiumhydroxide-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 sulphite (1.4 g) in water (20 mL) and then buffered with $NaHCO_3$. The volatile solvent was removed in vacuum and the remaining aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The aqueous phase was acidified to pH 1 with 2N 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 in 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*-butyl-dimethylsilanyloxy)-4,4-dimethyl-5-oxo-heptanoic 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 allowed to come to room temperature followed by an additional stirring for 1 h. Water (13 mL) was added to the reaction mixture and the organic layer was separated while aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with 1N HCl (25 mL), brine (25 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The remaining oil was purified by flash 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-oxo-heptanoic 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 18 h at room temperature. The reaction mixture was extracted with diethyl ether (50 mL). The combined organic extracts were washed with a half concentrated NaCl solution (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in 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-oxo-heptanoic acid (3*Z*,1*S*, 8*S*)-9-hydroxy-4,8-dimethyl-1-[*E*-methyl-2-(2-methyl-thiazol-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 allowed to stir 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 residue 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*-butyl-dimethyl-silanyloxy)-4,4-dimethyl-5-oxo-heptanoic acid (1*S*,3*Z*,8*S*)-9-hydroxy-4,8-dimethyl-1-[(1*E*)-methyl-2-(2-methyl-thiazol-4-yl)-vinyl]-9-oxo- non-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), washed with water (2 × 50 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and

concentrated in vacuum to yield 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 concentrated NH_4Cl (20 mL). The organic phase was extracted with ether (5 × 15 mL), washed with demineralised water (2 × 15 mL), brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue 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), brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue 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.

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Supporting Information

General experimental procedures and copies of ^{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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