Syntheses of (−)-Epothilone B

Dieter Schinzer,* Armin Bauer, and Jennifer Schieber[a]

Abstract: Two efficient routes for the total synthesis of (−)-epothilone B are reported. One strategy is based on ring-closing metathesis, and a second synthesis on a macrolactonization. The key fragments are available on large scale to provide sufficient material for biological tests. Thiazole fragment **4** was obtained by an improved route starting from (*S*)-malic acid. The first synthesis is based on our preceding paper. The critical trisubstituted double bond C12–13 in our second approach was constructed by a highly efficient Pd-mediated coupling reaction. Ring closure was achieved by macrolactonization.

Keywords: cytotoxic agents · epothilones · macrolides · natural products

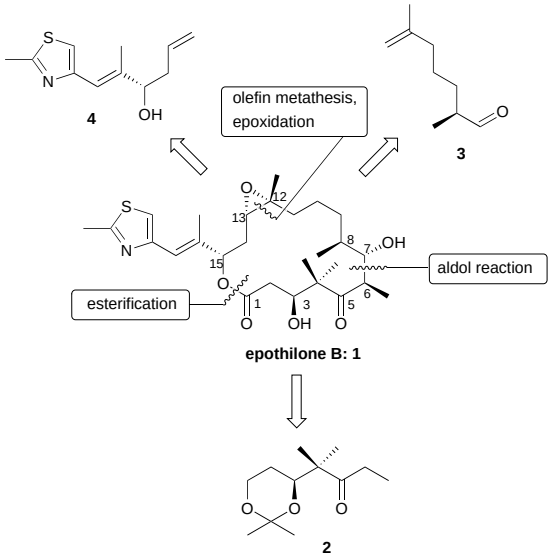
Introduction

The discovery that the bacterial macrolides epothilone A and epothilone B[1] act as biological analogues of paclitaxel has induced intense research activity,[2] resulting in several total syntheses of epothilone A[3] and B,[4] partial syntheses,[5] and numerous derivatives.[6] In various biochemical assays, paclitaxel and the epothilones were found to be almost identical in their effect on microtubule stabilization and cytotoxic properties. However, being tested on multiple-drug resistant (MDR) human carcinoma cell lines, the epothilones were significantly more potent than paclitaxel. They may even prove to be more promising anticancer drugs than paclitaxel with less undesired side effects.[7] Recent studies with MDR cell lines indicate that epothilone B is the most potent of the epothilones in vitro, whereas deoxyepothilone B (epothilone D) exhibited the best therapeutic results in vivo and is thus regarded as a lead compound for potential clinical development.[8]

In the preceding paper,[9] we described the synthesis of epothilone A by an approach based on ring-closing metathesis. Here we report two routes to epothilone B. The first approach proceeds along a similar path developed for epothilone A, representing, together with the work of Danishefsky et al.,[3b] a formal total synthesis of (−)-epothilone B (**1**). This olefin metathesis approach, however, suffers from unsactisfactory stereocontrol in the ring-closure step. In view of the importance of sufficient quantities of epothilone B and its analogues for drug development, we have elaborated an alternative, selective access to this series of compounds based on highly efficient aldol and transition-metal mediated coupling reactions leading to a seco acid precursor of Nicolaou's macrolactonization route[3g, 4d] to (−)-epothilone B.

Results and Discussion

The metathesis approach to epothilone B: The retrosynthetic analysis of our olefin metathesis approach to epothilone B is outlined in Scheme 1. Building blocks **2** and **4** are identical to the thiazole and ethyl ketone fragments employed in the



Scheme 1. Retrosynthetic analysis of epothilone B—the olefin metathesis approach.

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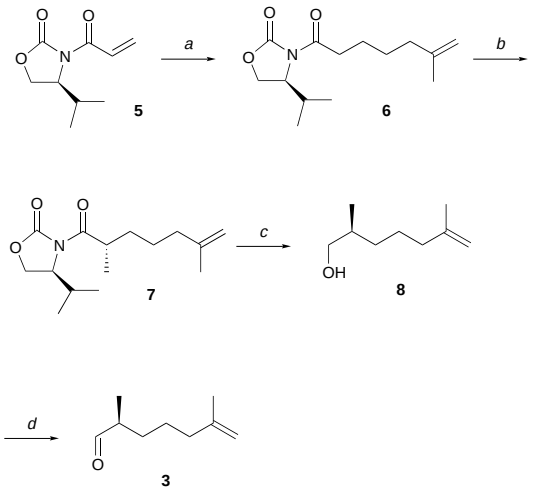
preceding epothilone A synthesis.[9] They were assembled with the aldehyde building block **3** in the same manner to afford the desired olefin metathesis precursor, which was first published by Danishefsky et al.,[3b] as outlined below.

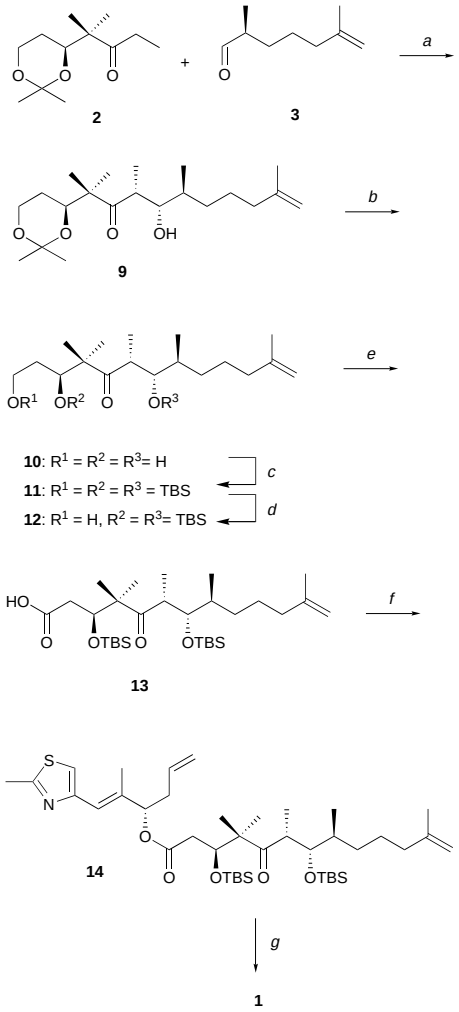
Again, an Evans asymmetric alkylation was chosen for the introduction of the chiral center in the aldehyde building block **3**. 1,4-Addition of a homoallylcuprate derived from commercially available 3-methyl-3-buten-1-ol[10] to the acryloyl oxazolidinone **5**[11] in the presence of TMSCl and LiI[12] gave 6-methylheptenoyl oxazolidinone **6** in 60% yield (Scheme 2).



Scheme 2. Synthesis of the aldehyde building block **3**. a) $CH_2{=}CH(CH_3)CH_2CH_2MgBr$ (1.8 equiv), $CuBr \cdot Me_2S$ (1.1 equiv), LiI (1.1 equiv), TMSCl (2.07 equiv), THF, $-78\,^{\circ}C$, 6 h, 60%; b) NaHMDS (1.1 equiv), THF, $-78\,^{\circ}C$, 30 min; then MeI (5 equiv), $-78\,^{\circ}C$, 11 h, 87%; c) LAH, Et_2O, RT, 24 h, 94%; d) Dess–Martin periodinane[13] (1.2 equiv), CH_2Cl_2, RT, 5 min, 80%; NaHMDS = sodium hexamethyldisilazane.

Its enolate was generated by the action of NaHMDS in THF at $-78\,^{\circ}C$, followed by the reaction with excess methyl iodide to afford alkylation product **7**, which was isolated in 87% yield (diastereoselectivity of the alkylation 10:1 by ^1H NMR spectroscopy of the crude product). Reductive removal (LAH) of the auxiliary furnished alcohol **8**, which was converted to the aldeyde **3** by Dess–Martin oxidation (78% over two steps).

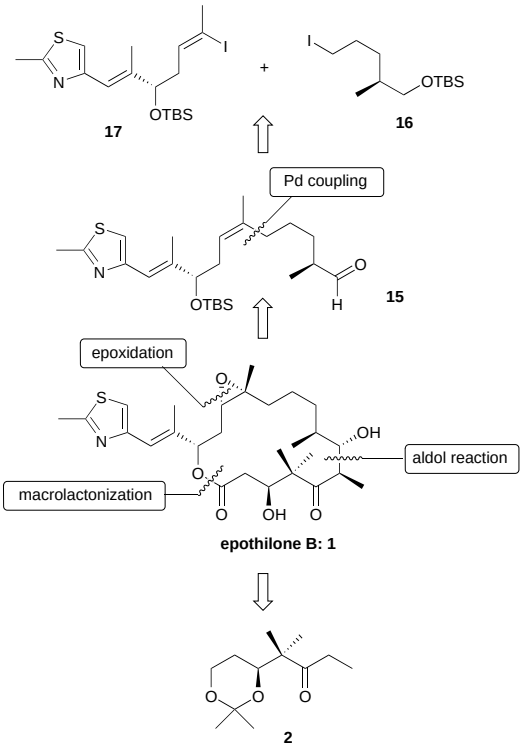
The conditions employed for the assembly of the corresponding fragments in the epothilone A synthesis proved to be optimal for the coupling of building blocks **2** and **3** (Scheme 3). Again, the *anti* Cram (6*R*,7*S*) isomer **9** was favored in this crossed aldol reaction, the diastereoselectivity being somewhat lower (10:1) than for the epothilone A synthesis. Transformation of the aldol product **9** to the acid **13** needed for the synthesis of the metathesis precursor required protective group manipulations and C1 oxidation: Thus, acid cleavage of the dioxolane and persilylation of the resulting triol **10** yielded tris-silyl ether **11**. Selective desilylation gave alcohol **12**, which was converted to acid **13** by PDC oxidation. DMAP-catalyzed DCC coupling of **13** with the thiazole building block **4** resulted in the formation of ester **14**, whose spectroscopical data ([α], IR, MS, ^1H and ^{13}C NMR) were consistent with the olefin metathesis precursor described by Danishefsky et al.[3b] Attempts to cyclize **14** in the presence of



Scheme 3. Assembly of the building blocks **2** and **3** and completion of the synthesis. a) Ketone **2**, LDA (0.95 equiv), THF, $-78\,^{\circ}C$, 1 h; then aldehyde **3**, $-78\,^{\circ}C$, 45 min, 68%; b) PPTS (1.0 equiv), MeOH, RT, 24 h, 88%; c) TBSOTf (1.5 equiv/OH), 2,6-lutidine (2.5 equiv/OH), CH_2Cl_2, $-50\,^{\circ}C$ to $+10\,^{\circ}C$, 4 h, 99%; d) CSA (0.2 equiv), $MeOH/CH_2Cl_2$ (1:1), $0\,^{\circ}C$, 5 h, 84%; e) PDC (9 equiv), DMF, RT, 36 h, 91%; f) DCC (1.1 equiv), DMAP (0.15 equiv), CH_2Cl_2, RT, 16 h, 61%; g) 1. $[Mo(CHMe_2Ph)\{N(2,6\text{-}i Pr_2C_6H_3)\}\{OCMe(CF_3)_2\}_2]$ (ring-closing olefin metathesis); 2. separation of *E* and *Z* isomers; 3. desilylation; 4. epoxidation, see ref. [3b]; PPTS = pyridinium *p*-toluenesulfonate, TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate, CSA = camphorsulfonic acid, PDC = pyridinium dichromate, DCC = dicyclohexyl carbodiimide, DMAP = 4-dimethylaminopyridine

the Grubbs catalyst $[RuCl_2(=CHPh)(PCy_3)]$[14] under various conditions were unsuccessful. However, Danishefsky et al.[3b] have shown that **14** can be transformed into epothilone B with the Schrock catalyst $[Mo(CHMe_2Ph)\{N(2,6\text{-}i Pr_2C_6H_3)\}\{OCMe(CF_3)_2\}_2]$[15] followed by deprotection and epoxidation.[3b]

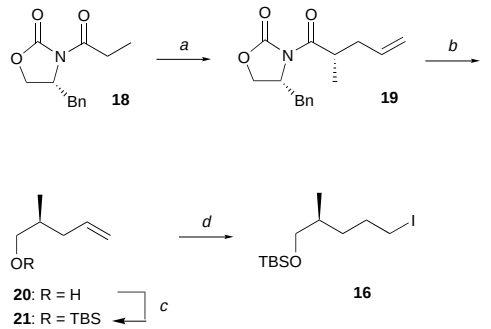
The macrolactonization approach to epothilone B: Scheme 4 depicts the retrosynthetic analysis that led to the macrolactonization-based strategy for the synthesis of epothilone B. The key step for the formation of a seco acid needed for cyclization to deoxy-**1** by macrolactonization[3g, 4d] would be an aldol reaction of the ethyl ketone **2** employed in the metathesis approach and the Nicolaou[3g, 4d] aldehyde **15**. Further disconnection of **15** led to the thiazole fragment **17** and a



Scheme 4. Retrosynthetic analysis of epothilone B—the macrolactonization approach.

C7–C11 building block **16**. An efficient palladium-mediated Negishi-type coupling reaction[16] was envisioned for the assembly of **16** and **17** to a precursor of aldehyde **15**.

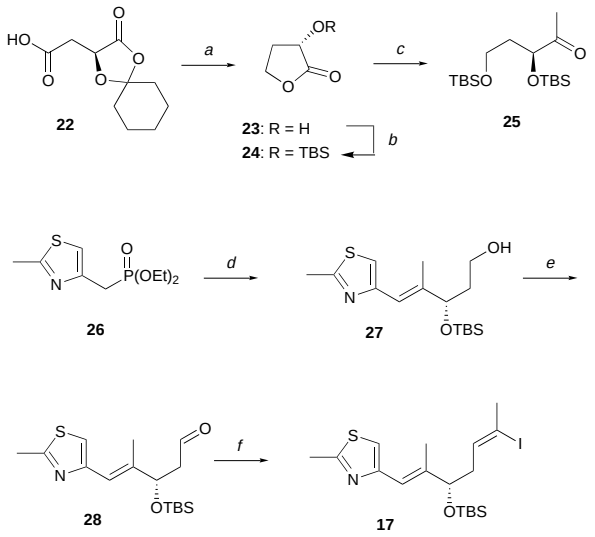
An approach to the C7–C11 fragment **16** was originally developed by Evans et al. for a synthesis of the polyether antibiotic X-206 using diastereoselective alkylation and hydrozirconation as the key steps.[17a] The phenylalanine-derived oxazolidinone **18**[18] is the starting material for our synthesis of **16** which furnishes this compound in multigram quantities. Alkylation of the Na enolate of **18** with 3-iodopropene (allyl iodide) gave crystalline amide **19** in 61% yield (Scheme 5); only one stereoisomer was detected by ^{1}H and ^{13}C NMR spectroscopy. Action of LAH resulted in the formation of alcohol **20** which was protected as its TBS ether



Scheme 5. Synthesis of the C7–C11 fragment **16**. a) NaHMDS (1.05 equiv), THF, −78 °C, 1 h; then 3-iodopropene (1.5 equiv), −78 °C, 4 h, 61%; b) LAH (7 equiv), Et_2O, RT, 5 h; c) TBSCl (1.3 equiv), imidazole (2.6 equiv), DMF, RT, 24 h, 80% over two steps; d) $BH_3 \cdot THF$ (1.2 equiv), THF, 0 °C, 1 h; then MeOH, NaOAc (1.0 equiv), ICl (1.0 M solution in CH_2Cl_2, 1.0 equiv), 0 °C, 30 min, 60%.

21 under standard conditions (80% yield for two steps). Finally, the known alkyl iodide **16**[17] was obtained by a one-pot hydroboration/iodination reaction[19] in 60% yield.

The thiazole building block **17** was synthesized according to an improved sequence which was amenable to a multigram scale-up. In the preceding synthesis,[5a, 9] the stereocenter in this fragment had been established by a Sharpless resolution, which gave **25** in 80% *ee*. In this sequence, (*S*)-malic acid was chosen as the source of chirality. Its cyclohexylidene ketal **22**[20] was selectively reduced with $BH_3 \cdot Me_2S$ (Scheme 6). The reduction product was transformed into the known lactone



Scheme 6. Synthesis of the thiazole building block **17**. a) 1. $BH_3 \cdot Me_2S$ (2.85 equiv), $B(OMe)_3$ (2.85 equiv), THF, 24 h; 2. *p*TsOH · H_2O (0.1 equiv), CH_2Cl_2, RT, 24 h, 72% over two steps; b) TBSCl (1.1 equiv), imidazole (2.2 equiv), DMF, RT, 24 h, 93%; c) 1. MeLi (1.1 equiv), THF, −78 °C, 3 h; 2. TBSCl (1.1 equiv), imidazole (2.2 equiv), DMF, RT, 24 h, 73% over two steps; d) 1. *n*BuLi, THF, −78 °C, then **25**; 2. HF, MeCN/Et_2O, glass, 69% over two steps, see preceding paper; e) Swern oxidation, 82%; f) $Ph_3P{=}C(H)I$ (1.8 equiv), THF, −30 °C, 20 min, 54%.

23[21] by acid catalysis. Protection of compound **23** afforded silyl ether **24** in 93% yield. Addition of MeLi[22] gave a lactol which opened under standard TBS protection conditions to the enantiomerically pure ketone **25** (49% from **22**). Alcohol **27** was obtained following the Horner–Emmons reaction and desilylation protocol from our synthesis of epothilone A.[9] Oxidation of **27** to the aldehyde **28** was performed under Swern conditions (82%). A *Z*-selective Wittig reaction of **28** with iodomethyltriphenylphosphorane[23] then led to the desired vinyl iodide **17** as the only stereoisomer in 54% yield.

An efficient palladium-mediated coupling[16a] of vinyl iodide **17** with the organozinc species[24] derived from **16** led to the bis-silyl ether **29** in 84% yield (Scheme 7). Selective deprotection to the alcohol **30** was achieved by CSA in $MeOH/CH_2Cl_2$ (82%). Reaction of **30** with Dess–Martin periodinane as the reagent of choice provided aldehyde **15** needed for the aldol reaction with ketone **2** in 97% yield.

In contrast to our metathesis approach to the epothilones, the conditions for the aldol reaction of ethyl ketone **2** and the aldehyde **15** had to be slightly changed (Scheme 8). In order to ensure complete conversion of the aldehyde to the desired

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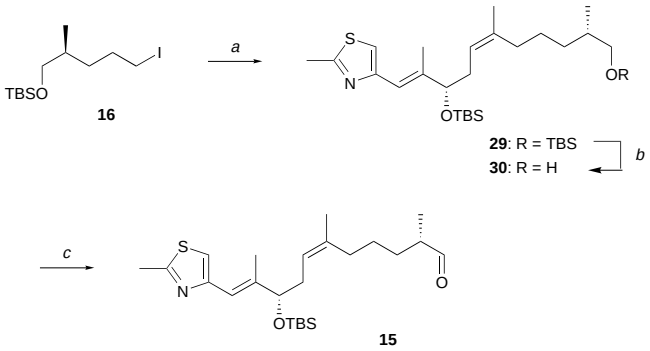
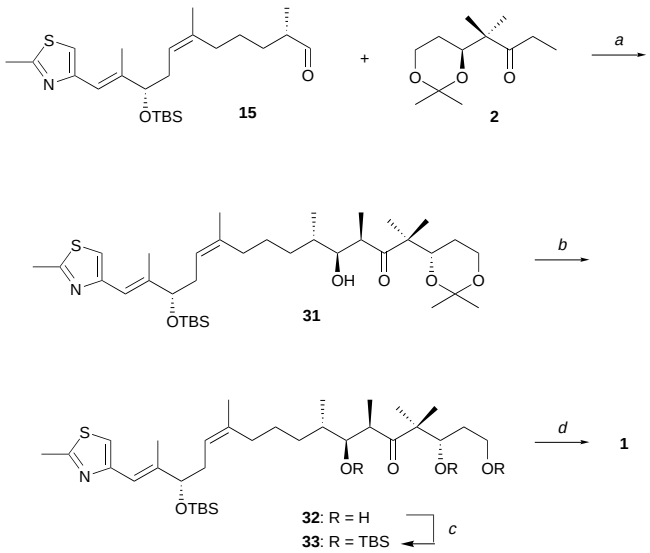


Scheme 7. Pd coupling of building blocks **16** and **17** and transformation to the aldehyde **15**. a) Zn (1.5 equiv), benzene/DMAc (7:1), 60 °C, 2.5 h; then **17** (0.67 equiv), $[Pd(PPh_3)_4]$ (4 mol %), 60 °C, 30 min, 84 %; b) CSA (1.05 equiv), $MeOH/CH_2Cl_2$ (1:1), 0 °C, 30 min, RT, 30 h, 82 %; c) Dess–Martin periodinane (1.3 equiv), pyridine (1.3 equiv), CH_2Cl_2, 97 %; DMAc = *N*,*N*-dimethyl acetamide.



Scheme 8. Final steps of the macrolactonization approach to epothilone B—synthesis of a seco acid precursor. a) Ketone **2** (1.0 equiv), LDA (0.98 equiv), THF, −78 °C, 1 h; then aldehyde **15** (0.5 equiv), −78 °C, 15 min, 85 %; b) PPTS (1.0 equiv), MeOH, RT, 72 h, 86 %; c) TBSOTf (1.5 equiv/OH), 2,6-lutidine (2.5 equiv/OH), CH_2Cl_2, −50 °C to 0 °C, then 0 °C, 2 h, 95 %; d) 1. C1-OH deprotection; 2. C1 oxidation to carboxylic acid; 3. C15-OH deprotection; 4. Yamaguchi macrolactonization; 5. desilylation; 6. epoxidation, see ref. [3g].

aldol product **31**, two equivalents of the lithium enolate generated from ketone **2** had to be employed in the reaction. The product ratio *anti* Cram (6*R*,7*S*) to Cram (6*S*,7*R*) was determined as 9:1 by HPLC. The aldol product **31** was isolated in 85 % yield from the reaction mixture. Transformation of intermediate **31** into the known seco acid precursor **33**[3g] required cleavage of the ketal protecting group by the action of PPTS in MeOH, leading to the triol **32**. Finally, silylation of compound **32** with TBSOTf and 2,6-lutidine led to the known tetrakis-silyl ether **33** identical ([α], IR, MS, ^{1}H and ^{13}C NMR) to an intermediate from Nicolaou's synthesis of epothilone B. Nicolaou et al.[3g] have shown that this precursor can be converted to (−)-epothilone B by a seven-step sequence consisting of selective deprotection steps, C1 oxidation, Yamaguchi macrolactonization, and epoxidation.[3g]

Conclusions

In summary, we have presented two formal total syntheses of epothilone B and D. Especially our aldol reaction offers the best and efficient method to date for the acyclic stereocontrol of the configurations at C6 and C7, which represents the major stereochemical issue in the field of epothilones. In addition, we have presented a straightforward synthesis to construct the tricyclic double bond at C12–C13 by a palladium-mediated coupling. Finally, our methods allow the synthesis of designed analogues for in vitro and in vivo testing.

Experimental Section

General techniques: See preceding article.[9]

(4*S*)-4-Isopropyl-3-(6-methyl-6-heptenoyl)-oxazolidin-2-one (6): 4-Bromo-2-methyl-1-butene[10] (997 mg, 0.2 equiv) was added to a suspension of Mg (76.0 mmol, 2.0 equiv) in THF (5 mL). After the reaction had started a solution of 4-bromo-2-methyl-1-butene (8.973 g, 1.8 equiv) in THF (45 mL) was added at such a rate that the mixture gently refluxed. Refluxing was continued for 20 min after the addition of the alkyl bromide was complete. The mixture was cooled to room temperature and added dropwise to a solution of $CuBr \cdot Me_2S$ (7.561 g, 36.8 mmol, 1.1 equiv) and LiI (4.923 g, 36.8 mmol, 1.1 equiv) in THF (60 mL) at −60 °C. The resulting brown cuprate suspension was stirred for 15 min at −60 °C, and TMSCl (9.6 mL, 76.0 mmol, 2.07 equiv) was added dropwise. Stirring was continued for 10 min at −60 °C. A solution of (*S*)-3-acryloyl-4-isopropyl-1,3-oxazolidin-2-one (**5**)[11] (6.126 g, 33.4 mmol) in THF (50 mL) was added at −78 °C within 1 h. The reaction mixture was stirred at −78 °C for 5 h. NEt_3 (13.9 mL, 100.3 mmol, 3 equiv) was added dropwise and stirring was continued for 3 h at −78 °C. Saturated aqueous NH_4Cl solution (40 mL) was added and the mixture was warmed to room temperature. The organic phase was separated and the aqueous layer was extracted with Et_2O (4 × 200 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography (pentane/Et_2O 5:1) gave oxazolidinone **6** (5.068 g, 60 %) as a colorless oil. $[\alpha]_D^{20} = +64.3$, $[\alpha]_{546}^{20} = +75.7$ ($c = 1.15$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3543$, 3074, 2966, 1782, 1701, 1650, 1464, 1387, 1302, 1206, 1073, 888 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.72–4.66$ (m, 2H; H-7′), 4.47–4.41 (m, 1H; H-4), 4.27 (t, ^2J = 8.7 Hz, 1H; H-5), 4.21 (dd, $^2J = 9.2$ Hz, $^3J = 3.1$ Hz, 1H; H-5), 3.05–2.82 (m, 2H; H-2′), 2.42–2.33 (m, 1H; C4-CH), 2.05 (t, $^3J = 7.5$ Hz, 2H; H-5′), 1.71 (s, 3H; C6′-CH_3), 1.70–1.61 (m, 2H), 1.55–1.46 (m, 2H)(H-3′, H-4′), 0.92 (d, $^3J = 7.0$ Hz, 3H; C4-CHCH_3), 0.87 (d, $^3J = 6.9$ Hz, 3H; C4-CHCH_3); ^{13}*C NMR (100 MHz, CDCl$_3$)*: $\delta = 173.2$, 154.0, 145.5, 109.9, 63.3, 58.3, 37.4, 35.3, 28.3, 26.9, 24.0, 22.3, 17.9, 14.6; MS (70 eV, EI): *m*/*z* (%): 253 (14) $[M]^+$, 198 (4), 184 (21), 171 (74), 130 (100), 125 (26), 99 (36), 97 (29), 85 (42), 83 (63), 69 (38), 68 (39), 55 (88); HRMS (EI): calcd for $C_{14}H_{23}NO_3$ 253.1678, found 253.167; $C_{14}H_{23}NO_3$ (253.3) calcd C 66.37, H 9.15, N 5.53; found C 66.41, H 9.24, N 5.19.

(4*S*,2′*S*)-4-Isopropyl-3-(2,6-dimethyl-6-heptenoyl)-oxazolidin-2-one (7): A solution of NaHMDS (1.0 M in THF; 17.6 mL, 17.6 mmol, 1.1 equiv) was cooled to −78 °C, and a precooled (0 °C) solution of **6** (4.059 g, 16.0 mmol) in THF (17 mL) was added. The reaction mixture was stirred for 30 min at −78 °C, and a solution of MeI (5 mL, 80.0 mmol, 5 equiv) in THF (2 mL) was added. After 11 h of stirring at −78 °C, the mixture was quenched with saturated NH_4Cl solution (20 mL), and extracted with Et_2O (4 × 200 mL). The combined organic extracts were dried over $MgSO_4$, and concentrated in vacuo. Purification of the crude product (10:1 ratio of diastereomers by ^{1}H NMR) by flash chromatography (pentane/Et_2O 7:1) furnished **7** (3.739 g, 87 %) as a colorless oil. $[\alpha]_D^{20} = +88.8$, $[\alpha]_{546}^{20} = +105.0$ ($c = 1.04$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 2967$, 1782, 1700, 1460, 1386, 1301, 1205, 1058, 888 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.72–4.66$ (m, 2H; H-7′), 4.48–4.42 (m, 1H; H-4), 4.27 (t, $^2J = 8.7$ Hz, 1H; H-5), 4.20 (dd, $^2J = 9.1$ Hz, ^3J = 3.1 Hz, 1H; H-5), 3.80–3.70 (m, 1H; H-2′), 2.41–2.30 (m, 1H; C4-CH), 2.01 (t, $^3J = 7.3$ Hz, 2H; H-5′), 1.70 (s, 3H; C6′-CH_3), 1.60–1.32 (m, 4H; H-3′, H-4′), 1.21 (d, $^3J = 6.9$ Hz, 3H; C2′-CH_3), 0.92 (d, $^3J = 7.0$ Hz, 3H; C4-CHCH_3), 0.87 (d, $^3J = 6.9$ Hz, 3H; C4-CHCH_3); ^{13}C NMR (100 MHz,

$CDCl_3$): $\delta = 177.2$, 153.7, 145.6, 110.0, 63.2, 58.4, 37.7, 37.6, 32.6, 28.4, 25.2, 22.3, 17.9, 17.8, 14.7; MS (70 eV, EI): *m/z* (%): 267 (0.6) $[M]^+$, 198 (10), 185 (100), 156 (6), 139 (109, 130 (44), 110 (10), 95 (209, 85 (20), 69 (36), 55 (28), 43 (11); $C_{15}H_{25}NO_3$ (267.4) calcd C 67.38, H 9.42, N 5.24; found C 67.53, H 9.46, N 5.06.

(*S*)-2,6-Dimethyl-6-hepten-1-ol (8): LAH (850 mg, 22.4 mmol, 3.4 equiv) was added in small portions to a solution of oxazolidinone **7** (3.517 g, 13.15 mmol) in Et_2O (85 mL) within a period of 3 h. The reaction mixture was stirred for 24 h at room temperature, quenched by dropwise addition of water (0.85 mL), 15 % aqueous NaOH (0.85 mL), and water (2.25 mL). The mixture was stirred for 4 h at room temperature until a white precipitate formed, which was filtered off by suction through a small plug of celite. The precipitate was washed with Et_2O (4×40 mL). The filtrate and washings were combined, and concentrated in vacuo. Purification of the residue by flash chromatography (pentane/Et_2O 5:1) afforded alcohol **8** (1.753 g, 94 %) as a colorless liquid. $[\alpha]_D^{20} = -11.8$, $[\alpha]_{546}^{20} = -13.6$ ($c = 1.0$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3334$, 2934, 1650, 1455, 1375, 1042, 886 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.73 - 4.65$ (m, 2H; H-7), 3.52 – 3.38 (m, 2H; H-1), 2.05 – 1.97 (m, 2H; H-5), 1.71 (s, 3H; C6-CH_3), 1.69 – 1.35 (m, 5H), 1.16 – 1.05 (m, 1H)(H-2, H-3, H-4, OH), 0.93 (d, $^3J = 6.7$ Hz, 3H; C2-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 146.0$, 109.8, 68.3, 38.0, 35.7, 32.7, 24.9, 22.3, 16.5; MS (70 eV, EI): *m/z* (%): 142 (18) $[M]^+$, 124 (12) $[M - H_2O]^+$, 109 (60), 95 (40), 82 (71), 69 (97), 68 (100), 56 (92); HRMS (EI): calcd for $C_9H_{18}O$ 142.1358, found 142.135.

(*S*)-2,6-Dimethyl-6-heptenal (3): Dess – Martin periodinane[13] (4.581 g, 10.8 mmol, 1.2 equiv) was added to a solution of alcohol **8** (1.280 g, 9.0 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred for 5 min. Flash chromatography (pentane/Et_2O 10:1) of the reaction mixture provided aldehyde **3** (1.000 g, 80 %) as a colorless liquid. $[\alpha]_D^{20} = +12.9$, $[\alpha]_{546}^{20} = +16.2$ ($c = 1.0$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 2937$, 2815, 1728, 1650, 1458, 1376, 888 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.62$ (d, $^3J = 2.0$ Hz, 1H; H-1), 4.73 – 4.65 (m, 2H; H-7), 2.40 – 2.30 (m, 1H; H-2), 2.03 (t, $^3J = 7.4$ Hz, 2H; H-5), 1.71 (s, 3H; C6-CH_3), 1.53 – 1.18 (m, 4H; H-3, H-4), 1.10 (d, $^3J = 7.0$ Hz, 3H; C2-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 205.2$, 145.3, 110.2, 46.2, 37.6, 30.0, 24.8, 22.2, 13.3; MS (70 eV, EI): *m/z* (%): 140 (0.6) $[M]^+$, 122 (4) $[M - H_2O]^+$, 107 (14), 93 (16), 82 (100), 69 (40), 67 (41), 55 (61), 43 (50); HRMS (EI): calcd for $C_9H_{16}O$ 140.1201, found 140.119.

(4*R*,5*S*,6*S*,4′*S*)-2-(2,2-Dimethyl-1,3-dioxan-4-yl)-5-hydroxy-2,4,6,10-tetramethylundec-10-en-3-one (9): A solution of ethyl ketone **2** (1.179 g, 5.5 mmol) in THF (5.0 mL) was added dropwise at $-78\,^\circ C$ to a freshly prepared solution of LDA [*n*BuLi (3.27 mL, 1.6 M solution in hexanes, 5.23 mmol, 0.95 equiv) was added to a solution of diisopropylamine (741 μL, 5.23 mmol) in THF (5.5 mL) at $0\,^\circ C$]. The mixture was stirred for 1 h at $-78\,^\circ C$. Aldehyde **3** (772 mg, 5.5 mmol, 1.0 equiv) was added dropwise and stirring was continued for 45 min at $-78\,^\circ C$. The reaction mixture was quenched by dropwise addition of saturated aqueous NH_4Cl solution at $-78\,^\circ C$. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined extracts were dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (pentane/Et_2O 10:1) of the residue afforded *anti* Cram aldol product **9** (1.326 g, 68 %) and Cram aldol product (136 mg, 7 %) as colorless oils. *anti* Cram diastereomer: $[\alpha]_D^{20} = -23.3$, $[\alpha]_{546}^{20} = -28.1$ ($c = 1.0$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3508$, 2969, 2361, 1685, 1458, 1373, 1273, 1197, 1107, 971, 882 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.72 - 4.64$ (m, 2H; H-11), 4.06 (dd, $^3J = 11.8$ Hz, $^3J = 2.5$ Hz, 1H; H-4′), 3.96 (dt, $^2J = 11.9$ Hz, $^3J = 2.7$ Hz, 1H; H-6′), 3.86 (ddd, $^3J = 11.7$ Hz, $^3J = 5.4$ Hz, $^3J = 1.6$ Hz, 1H; H-6′), 3.50 (s, 1H; OH), 3.37 (d, $^3J = 9.3$ Hz, 1H; H-5), 3.29 (dq, $^3J = 7.0$ Hz, $^3J = 1.2$ Hz, 1H; H-4), 2.09 – 1.94 (m, 2H; H-9), 1.82 – 1.48 (m, 4H; H-6, H-7, H-8, H-5′), 1.71 (s, 3H; C10-CH_3), 1.41 (s, 3H; C2′-CH_3), 1.40 – 1.31 (m, 2H; H-8, H-5′), 1.33 (s, 3H; C2′-CH_3), 1.21 (s, 3H; H-1), 1.16 – 1.05 (m, 1H; H-7), 1.09 (s, 3H; C2-CH_3), 1.02 (d, $^3J = 7.0$ Hz, 3H; C4-CH_3), 0.84 (d, $^3J = 7.0$ Hz, 3H; C6-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 222.9$, 146.2, 109.5, 98.4, 74.7, 74.3, 59.8, 51.5, 41.2, 38.2, 35.3, 32.6, 29.7, 25.1, 24.7, 22.3, 21.5, 19.0, 18.5, 15.3, 9.2; MS (70 eV, EI): *m/z* (%): 354 (3) $[M]^+$, 339 (6), 296 (9), 278 (5), 214 (6), 197 (10), 185 (26), 156 (84), 141 (28), 127 (26), 123 (65), 115 (78), 82 (100); $C_{21}H_{38}O_4$ (354.5): calcd C 71.15, H 10.80; found C 71.21, H 10.88.

(3*S*,6*R*,7*S*,8*S*)-1,3,7-Trihydroxy-4,4,6,8,12-pentamethyl-12-tridecen-5-one (10): A solution of aldol product **9** (1.102 g, 3.11 mmol) in MeOH (20 mL) was added to a solution of PPTS (469 mg, 1.87 mmol, 0.6 equiv) in MeOH (130 mL). The mixture was stirred at room temperature for 14 h. PPTS (312 mg, 0.4 equiv) was added and stirring was continued for 10 h. Water (4.5 mL) and saturated aqueous $NaHCO_3$ solution (4.5 mL) were added, and the mixture was concentrated under reduced pressure. The residue was dissolved in Et_2O (300 mL) and the resulting solution was washed with brine (20 mL). The organic layer was separated and dried over $MgSO_4$. After removal of the solvent in vacuo and flash chromatography (Et_2O) of the residue, triol **10** (863 mg, 88 %) was obtained as a colorless oil. $[\alpha]_D^{20} = -40.3$, $[\alpha]_{546}^{20} = -49.7$ ($c = 1.0$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3402$, 2937, 1685, 1649, 1467, 1376, 1329, 1055, 979, 885 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.72 - 4.66$ (m, 2H; H-13), 4.08 – 4.01 (m, 1H; H-3), 3.94 – 3.83 (m, 2H; H-1), 3.35 (d, $^3J = 9.0$ Hz, 1H; H-7), 3.34 (s, 1H; C7-OH), 3.27 (dq, $^3J = 6.9$ Hz, $^3J = 1.6$ Hz, 1H; H-6), 2.58 (br s, 1H; OH), 2.09 – 1.93 (m, 2H; H-11), 1.79 – 1.48 (m, 5H; H-2, H-8, H-9, H-10), 1.71 (s, 3H; C12-CH_3), 1.42 – 1.30 (m, 1H; H-10), 1.21, 1.12 (2 s, 2×3H; C4-CH_3), 1.14 – 1.04 (m, 1H; H-9), 1.07 (d, $^3J = 6.9$ Hz, 3H; C6-CH_3), 0.86 (d, $^3J = 6.8$ Hz, 3H; C8-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 223.8$, 146.2, 109.7, 76.4, 74.7, 62.2, 52.6, 40.9, 38.2, 35.5, 32.5, 32.4, 24.8, 22.4, 21.5, 18.5, 15.5, 10.1; MS (70 eV, EI): *m/z* (%): 314.0 (1) $[M]^+$, 297.6 (100) $[M+H-H_2O]^+$, 279.1 (35), 239.9 (17), 222.9 (33), 214.9 (21), 197.0 (36), 184.9 (29), 173.9 (24), 156.7 (78), 141.0 (52), 122.6 (44), 99.9 (50), 81.9 (48), 69.0 (43); HRMS (EI) calcd for $C_{18}H_{34}O_4$ 296.2351, found 296.235.

(3*S*,6*R*,7*S*,8*S*)-1,3,7-Tri-(*tert*-butyldimethylsilyloxy)-4,4,6,8,12-pentamethyl-12-tridecen-5-one (11): 2,6-Lutidine (2.39 mL, 20.6 mmol, 7.5 equiv) and TBSOTf (2.83 mL, 7.5 mmol, 4.5 equiv) were added dropwise at $-50\,^\circ C$ to a solution of triol **10** (863 mg, 2.74 mmol) in CH_2Cl_2 (8.2 mL). The mixture was allowed to warm to $10\,^\circ C$ within 4 h. Flash chromatography (pentane/Et_2O 20:1) of the reaction mixture gave tris-silyl ether **11** (1.783 g, 99 %) as a colorless oil. $[\alpha]_D^{20} = -31$, $[\alpha]_{546}^{20} = -38$ ($c = 1.0$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3075$, 2955, 1698, 1652, 1473, 1388, 1361, 1255, 1104, 986, 838, 775, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.71 - 4.64$ (m, 2H; H-13), 3.89 (dd, $^3J = 7.5$ Hz, $^3J = 2.8$ Hz, 1H; H-3), 3.77 (dd, $^3J = 6.6$ Hz, $^3J = 2.2$ Hz, 1H; H-7), 3.67 (dt, $^2J = 9.4$ Hz, $^3J = 5.0$ Hz, 1H; H-1), 3.62 – 3.54 (m, 1H; H-1), 3.14 (dq, $^3J = 9.4$ Hz, $^3J = 5.0$ Hz, 1H; H-6), 2.05 – 1.92 (m, 2H; H-11), 1.70 (s, 3H; C12-CH_3) 1.64 – 1.01 (m, 7H; H-2, H-8, H-9, H-10), 1.22 (s, 3H; C4-CH_3), 1.05 (d, $^3J = 6.9$ Hz, 3H; C6-CH_3), 1.03 (s, 3H; C4-CH_3), 0.92 (d, $^3J = 6.9$ Hz, 3H; C8-CH_3), 0.91, 0.90, 0.88 (3 s, 9H; $OSiC(CH_3)_3$), 0.09, 0.07, 0.06, 0.06, 0.03, 0.02 (6 s, 6×3H; $OSi(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 218.2$, 145.9, 109.8, 77.4, 74.04, 61.0, 53.7, 45.0, 38.9, 38.4, 38.1, 30.7, 26.2, 26.1, 26.0, 25.7, 24.5, 22.4, 19.4, 18.5, 18.4, 18.3, 17.5, 15.2, −3.7, −3.7, −3.8, −4.0, −5.2, −5.3 ; MS (PCI, CH_4): *m/z* (%): 657.2 (50) $[M+H]^+$, 641.5 (5) $[M - CH_3]^+$, 545.2 (2), 403.3 (4), 373.3 (13), 311.2 (14), 303.8 (100), 255.1 (52), 123.2 (37); HRMS (EI): calcd for $C_{32}H_{67}O_4Si_3$ $[M - t\mathrm{Bu}]^+$ 599.4347, found 599.432.

(3*S*,6*R*,7*S*,8*S*)-3,7-Di-(*tert*-butyldimethylsilyloxy)-1-hydroxy-4,4,6,8,12-penta-methyl-12-tridecen-5-one (12): A solution of CSA (121 mg, 0.52 mmol, 0.2 equiv) in MeOH (20 mL) was added at $0\,^\circ C$ to a solution of tris-silyl ether **11** (1.696 g, 2.58 mmol) in MeOH (70 mL) and CH_2Cl_2 (50 mL). The reaction mixture was stirred for 5 h at $0\,^\circ C$ and quenched with saturated aqueous $NaHCO_3$ solution (20 mL). Precipitated solid $NaHCO_3$ was filtered off. The filtrate was concentrated under reduced pressure, diluted with Et_2O (200 mL) and washed with brine (20 mL). The phases were separated and the aqueous layer was extracted with Et_2O (2×40 mL). The combined organic phases were dried over $MgSO_4$ and the solvents were removed in vacuo. The residue was purified by flash chromatography (pentane/Et_2O 5:1) to give alcohol **12** (1.175 g, 84 %) as a colorless oil. $[\alpha]_D^{20} = -19.4$, $[\alpha]_{546}^{20} = -22.8$ ($c = 1.0$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3449$, 2931, 1691, 1473, 1388, 1255, 1103, 987, 837, 775, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.71 - 4.64$ (m, 2H; H-13), 4.07 (dd, $^3J = 6.1$ Hz, $^3J = 4.1$ Hz, 1H; H-3), 3.80 (dd, $^3J = 7.3$ Hz, $^3J = 1.7$ Hz, 1H; H-7), 3.66 – 3.57 (m, 2H; H-1), 3.13 (dq, $^3J = 7.1$ Hz, $^3J = 7.1$ Hz, 1H; H-6), 2.05 – 1.91 (m, 2H; H-11), 1.87 (t, $^3J = 5.4$ Hz, 1H; OH), 1.70 (s, 3H; C12-CH_3), 1.66 – 0.96 (m, 7H; H-2, H-8, H-9, H-10), 1.22 (s, 3H; C4-CH_3), 1.06 (d, $^3J = 6.9$ Hz, 3H; C6-CH_3), 1.06 (s, 3H; C4-CH_3), 0.93 (d, $^3J = 6.9$ Hz, 3H; C8-CH_3), 0.90 (2 s, 2×9H; $OSiC(CH_3)_3$), 0.11, 0.07, 0.06, 0.06 (4 s, 4×6H; $OSi(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 219.6$, 145.9, 109.9, 77.6, 73.1, 60.3, 53.8, 45.1, 38.7, 38.4, 38.3, 30.4, 26.2, 26.1, 25.7, 24.9, 22.4, 18.5, 18.3, 17.7, 17.6, 15.7, −3.6, −3.8, −3.9; MS (70 eV, EI): *m/z* (%): 542.1 (<0.5) $[M]^+$, 525.1 (51) $[M+H-H_2O]^+$, 485.0 (28) $[M - t\mathrm{Bu}]^+$, 412.9 (11), 393.0 (5), 373.0 (11), 353.0 (27), 345.0 (100), 311.0 (66), 303.0 (12), 271.0 (87), 255.0 (72), 212.9 (18), 190.1 (74), 172.8 (46), 145.0 (60), 130.9 (92); $C_{30}H_{62}O_4Si_2$ (543.0) calcd C 66.36, H 11.51; found C 66.22, H 11.42.

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(3*S*,6*R*,7*S*,8*S*)-3,7-Di-(*tert*-butyldimethylsilyloxy)-4,4,6,8,12-pentamethyl-5-oxo-12-tridecenoic acid (13): A solution of PDC (5.886 g, 15.65 mmol, 9.0 equiv) in DMF (15 mL) was added to a solution of alcohol **12** (944 mg, 1.74 mmol) in DMF (10 mL). The reaction mixture was stirred for 36 h at room temperature, mixed with brine (100 mL), diluted with water (100 mL), and extracted with CH_2Cl_2 (6 × 100 mL). The combined extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (pentane/Et_2O 2:1) to afford acid **13** (885 mg, 91 %) as a viscous, colorless oil. $[\alpha]_D^{20} = -28.6$, $[\alpha]_{546}^{20} = -33.4$ (c = 1.0, $CHCl_3$); IR (film): $\tilde{\nu}_{max}$ = 2936, 2710, 1719, 1460, 1389, 1303, 1255, 1099, 986, 843, 774, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.70–4.58 (m, 2H; H-13), 4.38 (dd, ^3J = 6.8 Hz, ^3J = 3.0 Hz, 1H; H-3), 3.79 (dd, ^3J = 7.2 Hz, ^3J = 1.7 Hz, 1H; H-7), 3.14 (dq, ^3J = 7.0 Hz, ^3J = 7.0 Hz, 1H; H-6), 2.49 (dd, ^2J = 16.4 Hz, ^3J = 3.1 Hz, 1H; H-2), 2.30 (dd, ^2J = 16.4 Hz, ^3J = 6.8 Hz, 1H; H-2), 2.04–1.91 (m, 2H; H-11), 1.69 (s, 3H; C12-CH_3), 1.57–0.96 (m, 5H; H-8, H-9, H-10), 1.23, 1.09 (2s, 2 × 3H; C4-CH_3), 1.05 (d, ^3J = 6.9 Hz, 3H; C6-CH_3), 0.92 (d, ^3J = 7.1 Hz, 3H; C8-CH_3), 0.90, 0.88 (2s, 2 × 9H; $OSiC(CH_3)_3$), 0.09, 0.05, 0.05, 0.04 (4s, 4 × 3H; $OSi(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 218.1, 178.2, 145.9, 109.8, 77.6, 73.5, 53.5, 45.2, 40.2, 38.7, 38.3, 30.4, 26.2, 26.0, 25.7, 23.7, 22.3, 19.1, 18.5, 18.2, 17.7, 15.7, −3.6, −3.8, −4.3, −4.6; MS (PCI, CH_4): m/z (%): 557.5 (46) $[M+H]^+$, 541.5 (89) $[M-CH_3]^+$, 499.4 (100) $[M-t\mathrm{Bu}]^+$, 453.4 (7), 445.4 (9), 425.4 (48), 417.4 (68), 409.4 (22), 401.4 (44); $C_{30}H_{60}O_5Si_2$ (557.0) calcd C 64.69, H 10.86; found C 64.89, H 10.96.

(1*S*)-1-[(*E*)-1-Methyl-2-(2-methyl-1,3-thiazol-4-yl)-1-ethenyl-3-butenyl (3*S*,6*R*,7*S*,8*S*)-3,7-di-[*tert*-butyldimethylsilyloxy]-4,4,6,8,12-pentamethyl-5-oxo-12-tridecenoate (14): DCC (91 mg, 0.44 mmol, 1.1 equiv) was added at 0 °C to a solution of acid **13** (223 mg, 0.40 mmol), thiazole alcohol **4** (84 mg, 0.40 mmol) and DMAP (7.3 mg, 0.06 mmol, 0.15 equiv) in CH_2Cl_2 (5 mL). The mixture was stirred for 10 min at 0 °C and for 16 h at room temperature The solvent was removed in vacuo and the residue was purified by flash chromatography (pentane/Et_2O 20:1) to afford ester **14** (183 mg, 61 %) as a colorless oil. $[\alpha]_D^{20} = -38.8$, $[\alpha]_{546}^{20} = -46.9$ (c = 0.1, $CHCl_3$) [Lit.:[3b] $[\alpha]_D = -55.1$ (c = 0.85, $CHCl_3$)]; IR (film): $\tilde{\nu}_{max}$ = 2930, 1737, 1697, 1472, 1377, 1254, 1179, 1085, 989, 836, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.94 (s, 1H; thiazole H-5), 6.49 (s, 1H; H-2″), 5.78–5.65 (m, 2H; H-3′), 5.30 (t, ^3J = 6.7 Hz, 1H; H-1′), 5.13–5.00 (m, 2H; H-4′), 4.70–4.62 (m, 2H; H-13), 4.34 (dd, ^3J = 6.0 Hz, ^3J = 3.6 Hz, 1H; H-3), 3.73 (dd, ^3J = 6.8 Hz, ^3J = 2.0 Hz, 1H; H-7), 3.19–3.11 (m, 1H; H-6), 2.70 (s, 3H; thiazole CH_3), 2.53 (dd, ^2J = 17.0 Hz, ^3J = 3.6 Hz, 1H; H-2), 2.53–2.40 (m, 2H; H-2′), 2.29 (dd, ^2J = 17.0 Hz, ^3J = 6.1 Hz, 1H; H-2), 2.07 (d, ^4J = 1.2 Hz, 3H; C1″-CH_3), 2.01–1.94 (m, 2H; H-11), 1.69 (s, 3H; C12-CH_3), 1.61–0.94 (m, 5H; H-8, H-9, H-10), 1.23 (s, 3H; C4-CH_3), 1.04 (d, ^3J = 6.8 Hz, 3H; C6-CH_3), 1.03 (s, 3H; C4-CH_3), 0.89 (d, ^3J = 7.1 Hz, 3H; C8-CH_3), 0.89, 0.88 (2s, 2 × 9H; $OSiC(CH_3)_3$), 0.10, 0.05, 0.03, 0.03 (4s, 4 × 3H; $OSi(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 217.7, 171.2, 164.5, 152.6, 146.0, 136.8, 133.4, 121.1, 117.8, 116.4, 109.8, 78.7, 77.6, 74.1, 53.3, 45.2, 40.3, 38.8, 38.3, 37.5, 30.6, 26.2, 26.0, 25.7, 23.2, 22.3, 20.4, 19.2, 18.5, 18.2, 17.6, 15.4, 14.6, −3.6, −3.8, −4.3, −4.7; MS (PCI, NH_3): m/z (%): 748 (85) $[M+H]^+$, 520 (12), 447 (75), 419 (51), 391 (57), 363 (12), 192 (100), 123 (11); $C_{41}H_{73}NO_5SSi_2$ (748.3) calcd C 65.81, H 9.83, N 1.87, S 3.93; found C 66.30, H 10.06, N 1.92, S 3.91.

(4*R*)-4-Benzyl-3-[(2*S*)-2-methyl-4-pentenoyl]-1,3-oxazolidin-2-one (19): A solution of NaHMDS (1.0 M in THF, 47.25 mL, 47.25 mmol, 1.05 equiv) was added dropwise to a solution of (4*R*)-4-benzyl-3-propionyl-1,3-oxazolidin-2-one (**18**)[18] (10.50 g, 45.0 mmol) in THF (120 mL) at −78 °C. The reaction mixture was stirred for 1 h at −78 °C, and 3-iodopropene (6.20 mL, 67.5 mmol, 1.5 equiv) was added dropwise. The mixture was stirred for 4 h at −78 °C, allowed to warm to room temperature, and quenched with saturated NH_4Cl solution (45 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 90 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude product (10:1 ratio of diastereomers by ^1H NMR) by flash chromatography (pentane/Et_2O 4:1) gave oxazolidinone **19** (7.56 g, 61 %) as a colorless oil, which crystallized upon standing. M.p. 28 °C; $[\alpha]_D^{20} = -41.7$ (c = 1.0, $CHCl_3$); IR (film): $\tilde{\nu}_{max}$ = 2982, 1782, 1699, 1381, 1243, 1210, 1102, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.20 (m, 5H; Ar-H), 5.88–5.77 (m, 1H; H-4′), 5.15–5.04 (m, 2H; H-5′), 4.73–4.64 (m, 1H; H-4), 4.20 (dd, ^2J = 9.1 Hz, ^3J = 0.7 Hz, 1H; H-5), 4.15 (dd, ^2J = 9.1 Hz, ^3J = 3.4 Hz, 1H; H-5), 3.91–3.82 (m, 1H; H-2′), 3.29 (dd, ^2J = 13.3 Hz, ^3J = 3.3 Hz, 1H; C4-CH_2), 2.70 (dd, ^2J = 13.3 Hz, ^3J = 9.8 Hz, 1H; C4-CH_2), 2.57–2.49 (m, 1H; H-3′), 2.29–2.20 (m, 1H; H-3′), 1.19 (d, ^3J = 6.8 Hz, 3H; C2′-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.5, 153.1, 135.4, 135.3, 129.4, 128.9, 127.3, 117.2, 66.0, 55.4, 38.1, 38.0, 37.1, 16.4; MS (70 eV, EI): m/z (%): 273.1 (10) $[M]^+$, 244.1 (1), 117.0 (4), 97.0 (12), 91.0 (17), 69.1 (100), 67.0 (36), 53.0 (29); $C_{16}H_{19}NO_3$ (241.3): calcd C 70.31, H 7.01, N 5.12; found C 70.64, H 7.09, N 5.21.

(2*S*)-2-Methyl-4-penten-1-ol (20): LAH (3.343 g, 88.1 mmol, 7 equiv) was added in small portions to a solution of oxazolidinone **19** (6.967 g, 25.5 mmol) in Et_2O (120 mL) within a period of 4 h. The reaction mixture was stirred for 1 h at room temperature and quenched by dropwise addition of water (3.34 mL), 15 % aqueous NaOH (3.34 mL), and water (8.35 mL) at 0 °C. The mixture was stirred for 4 h at room temperature until a white precipitate formed, which was filtered off by suction through a small plug of celite. The precipitate was washed with Et_2O (200 mL) and CH_2Cl_2 (200 mL). The filtrate and the washings were combined and concentrated in vacuo. (4*R*)-4-benzyl-1,3-oxazolidin-2-one (2.639 g, 58 %) precipitated as colorless needles. The solid was filtered off by suction and washed with Et_2O (5 mL) and pentane (5 mL). The filtrate and the washings were combined. After evaporation of the solvent crude alcohol **20**[17a] (2.922 g) was obtained as a colorless liquid, which was used for the preparation of silyl ether **21** without further purification. An analytical sample was obtained by flash chromatography (pentane/Et_2O 5:1). $[\alpha]_D^{20} = -2.1$, $[\alpha]_{546}^{20} = -2.5$ (c = 1.0, $CHCl_3$); IR (film): $\tilde{\nu}_{max}$ = 3337, 2916, 1641, 1457, 1044, 993, 912 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.86–5.75 (m, 1H; H-4), 5.17–4.99 (m, 2H; H-5), 3.53–3.40 (m, 2H; H-1), 2.22–2.14 (m, 1H; H-3), 2.04 (br s, 1H; OH), 1.97–1.89 (m, 1H; H-3), 1.78–1.66 (m, 1H; H-2), 0.92 (d, ^3J = 6.8 Hz, 3H; C2-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.9, 116.0, 67.7, 37.8, 35.5, 16.3; MS (PCI, CH_4): m/z (%): 101 (21) $[M+H]^+$, 99 (32), 83 (100) $[M+H-H_2O]^+$, 81 (34), 71 (11), 55 (12).

***tert*-Butyldimethyl-{[(2*S*)-2-methyl-4-pentenyl]oxy}silane (21)**: Imidazole (4.121 g, 60.5 mmol, 2.6 equiv) and TBSCl (30.3 mmol, 1.3 equiv) were added to a solution of the crude alcohol **20** (2.669 g ≈ 23.3 mmol) in DMF (15 mL). The mixture was stirred for 24 h at room temperature. Flash chromatography of the reaction mixture (pentane/Et_2O 20:1) gave silyl ether[17a] **22** (3.991 g, 80 % over two steps) as a colorless oil. $[\alpha]_D^{20} = -1.0$, $[\alpha]_{546}^{20} = -1.2$ (c = 1.0, $CHCl_3$); IR (film): $\tilde{\nu}_{max}$ = 2957, 2858, 1472, 1256, 1095, 911, 838, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.85–5.73 (m, 1H, H-4), 5.04–4.96 (m, 2H; H-5), 3.44 (dd, ^2J = 9.8 Hz, ^3J = 6.2 Hz, 1H; H-1), 3.40 (dd, ^2J = 9.8 Hz, ^3J = 6.2 Hz, 1H; H-1), 2.23–2.15 (m, 1H; H-3), 1.90–1.81 (m, 1H; H-3), 1.73–1.61 (m, 1H; H-2), 0.90 (s, 9H, $OSiC(CH_3)_3$), 0.87 (d, ^3J = 6.7 Hz, 3H; C2-CH_3), 0.04 (s, 6H, $OSi(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.4, 115.6, 67.8, 37.7, 35.7, 26.0, 18.3, 16.4, −5.4; MS (PCI, CH_4): m/z (%): 215.2 (22) $[M+H]^+$, 213.1 (72), 208.9 (100), 199.1 (34) $[M-CH_3]^+$, 157.0 (21) $[M-t\mathrm{Bu}]^+$, 145.0 (14), 133.0 (38), 82.8 (32).

1-(*tert*-Butyldimethylsilyl) [(2*S*)-5-iodo-2-methylpentyl] ether (16): $BH_3\cdot$THF (1.0 M solution in THF, 5.94 mL, 1.2 equiv) was added dropwise at 0 °C to a solution of silyl ether **21** (3.184 g, 14.85 mmol) in THF (5 mL) was added. The mixture was stirred for 1 h at room temperature. MeOH (0.5 mL) and NaOAc (1.0 M solution in MeOH, 14.85 mL, 1 equiv) were added at 0 °C, followed by the addition of ICl (1.0 M solution in CH_2Cl_2, 14.85 mL, 1 equiv) within 30 min at 0 °C. The reaction mixture was stirred for 30 min at room temperature, quenched with $Na_2S_2O_3$ (1.0 M aqueous solution, 40 mL), and extracted with pentane/Et_2O (20:1, 3 × 100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude product by flash chromatography (pentane/Et_2O 20:1) gave known[17a] alkyl iodide **16** (3.067 g, 60 %) as a colorless oil. $[\alpha]_D^{20} = -5.8$, $[\alpha]_{546}^{20} = -7.2$ (c = 1.0, $CHCl_3$); IR (film): $\tilde{\nu}_{max}$ = 2956, 2857, 1472, 1256, 1095, 837, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.42 (dd, ^2J = 9.8 Hz, ^3J = 6.3 Hz, 1H; H-1), 3.39 (dd, ^2J = 9.8 Hz, ^3J = 6.2 Hz, 1H; H-1), 3.23–3.13 (m, 2H; H-5), 1.96–1.76 (m, 2H), 1.66–1.44 (m, 2H), 1.33–1.12 (m, 1H)(H-2, H-3, H-4), 0.89 (s, 9H, $OSiC(CH_3)_3$), 0.88 (d, ^3J = 6.5 Hz, 3H; C2-CH_3), 0.04 (s, 6H, $OSi(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 68.1, 35.0, 34.3, 31.3, 25.9, 18.3, 16.7, 7.3, −5.4; MS (PCI, CH_4): m/z (%): 343.0 (100) $[M+H]^+$, 327.0 (63) $[M-CH_3]^+$, 284.9 (71) $[M-t\mathrm{Bu}]^+$, 215.1 (79), 210.9 (33), 83.0 (7).

(3*S*)-3-Hydroxytetrahydrofuranone (23): A solution of (5*S*)-(2,2-cyclohexylidene-4-oxo-1,3-dioxolan-5-yl)acetic acid **22**[20] (15.04 g, 70.2 mmol) in THF (70 mL) was added dropwise to a mixture cooled to 0 °C of $BH_3\cdot Me_2S$ complex (100 mL, 200.0 mmol, 2.0 M) and $B(OMe)_3$ (24.2 mL, 200.0 mmol) in THF (175 mL). The reaction mixture was stirred for 24 h at room temperature and cooled to 0 °C. MeOH (70 mL) was added dropwise. The

mixture was stirred for 1 h at room temperature, and the solvents were removed under reduced pressure to afford a thick oil. This process was repeated twice with MeOH (105 mL) to afford a colorless oil. The crude product (a mixture of lactone **23** and (5*S*)-(1′-hydroxyethyl)-2,2-cyclohexylidene-1,3-dioxolan-4-one) was dissolved in CH_2Cl_2 (175 mL). *p*TsOH · H_2O (1.335 g, 7.02 mmol, 0.1 equiv) was added and the mixture was stirred for 24 h at room temperature. NEt_3 (0.98 mL) was added and the mixture was concentrated in vacuo. Purification of the residue by flash chromatography (Et_2O) gave lactone[21] **23** (5.160 g, 72 %) as a colorless oil. $[\alpha]_D^{20} = -60.1$, $[\alpha]_{546}^{20} = -71.3$ ($c = 0.67$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3400, 1773, 1378, 1221, 1185, 1128, 1015, 947, 719\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.54$ (t, $^3J = 9.2$ Hz, 1H; H-3), 4.43 (td, $^3J = 9.0$ Hz, $^3J = 2.1$ Hz, 1H; H-5), 4.29 – 4.22 (m, 1H; H-5), 3.90 (s, 1H, OH), 2.66 – 2.58 (m, 1H; H-4), 2.35 – 2.26 (m, 1H; H-4); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 178.2, 67.4, 65.2, 30.8$; MS (PCI, CH_4): *m*/*z* (%): 116.9 (6) $[M+CH_4]^+$, 102.9 (100) $[M]^+$, 84.9 (3).

(3*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]tetrahydrofuranone (24): Imidazole (241 mg, 3.54 mmol, 2.2 equiv) and TBSCl (267 mg, 1.77 mmol, 1.1 equiv) were added to a solution of lactone **23** (164 mg, 1.61 mmol) in DMF (1.5 mL). The mixture was stirred for 24 h at room temperature. Flash chromatography (pentane/Et_2O 10:1) of the reaction mixture afforded silyl ether **24** (321 mg, 93 %) as a colorless oil. $[\alpha]_D^{20} = -31.7$, $[\alpha]_{546}^{20} = -37.4$ ($c = 0.86$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 2931, 2859, 1790, 1473, 1362, 1254, 1154, 1022, 840, 781\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.43 - 4.35$ (m, 2H; H-5, H-3), 4.22 – 4.15 (m, 1H; H-5), 2.49 – 2.41 (m, 1H; H-4), 2.27 – 2.21 (m, 1H; H-4), 0.91 (s, 9H, $OSiC(CH_3)_3$), 0.17, 0.14 (2s, 2 × 3H; $OSi(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 175.8, 68.2, 64.7, 32.3, 25.6, 18.2, -4.8, -5.3$; MS (70 eV, EI): *m*/*z* (%): 217.1 (20) $[M+H]^+$, 201.0 (81) $[M - CH_3]^+$, 189.0 (6), 171.0 (78), 159.2 (79) $[M - t\mathrm{Bu}]^+$, 146.8 (13), 145.0 (16), 130.9 (100), 114.9 (92), 102.9 (35), 100.9 (37); HRMS (EI): calcd for $C_6H_{11}O_3Si$ $[M - t\mathrm{Bu}]^+$ 159.0477, found 159.047.

(3*S*)-3,5-Di-[(*tert*-butyldimethylsilyl)oxy]pentan-2-one (25): MeLi (0.67 mL, 1.11 mmol, 1.1 equiv of a 1.65 M solution in Et_2O) was added dropwise to a stirred solution cooled to −78 °C of silyl ether **24** (218 mg, 1.01 mmol) in THF (4 mL). After stirring at −78 °C for 3 h, the reaction was quenched by the addition of glacial acetic acid (72 μL, 1.26 mmol, 1.25 equiv). Et_2O (20 mL) and saturated aqueous $NaHCO_3$ solution (10 mL) were added. The organic layer was separated after stirring for 5 min, and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give crude (3*S*)-3-[(*tert*-butyldimethylsilyl)oxy]-2-methyl-tetrahydrofuran-2-ol (235 mg, 93 %) as a colorless crystalline solid (mixture of diastereomers), which was used for the synthesis of ketone **25** without further purification: Imidazole (125 mg, 1.84 mmol, 2.2 equiv) and TBSCl (139 mg, 0.92 mmol, 1.1 equiv) were added to a solution of (3*S*)-3-[(*tert*-butyldimethylsilyl)oxy]-2-methyl-tetrahydrofuran-2-ol (194 mg, 0.83 mmol) in DMF (0.80 mL). The mixture was stirred for 24 h at room temperature. Purification of the reaction mixture by flash chromatography (pentane/Et_2O 20:1) afforded ketone **25** (226 mg, 78 %) as a colorless oil. $[\alpha]_D^{20} = -11.8$, $[\alpha]_{546}^{20} = -14.1$ ($c = 1.0$, $CHCl_3$), identical (^1H and ^{13}C NMR, IR, EI-MS) with **25** obtained by the Sharpless resolution protocol described in the preceding paper.[9] Compound **25** was transformed to thiazole alcohol **27** by Horner – Emmons reaction and selective desilylation according to the method applied in the preceding paper.[9]

(3*S*,4*E*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4-methyl-5-(2-methyl-1,3-thiazol-4-yl)-4-pentenal (28): A solution of DMSO (2.04 mL, 28.8 mmol, 2.4 equiv) in CH_2Cl_2 (6 mL) was added dropwise at −78 °C to a stirred solution of $(COCl)_2$ (1.14 mL, 13.2 mmol, 1.1 equiv) in CH_2Cl_2 (30 mL) within 5 min. The mixture was stirred for 10 min at −70 °C. A solution of thiazole alcohol **27** (3.93 g, 12.0 mmol) in CH_2Cl_2 (5 mL) was added dropwise within 5 min. The mixture was stirred for 30 min at −70 °C. The reaction was quenched by dropwise addition of NEt_3 (8.4 mL, 60.0 mmol). The mixture was warmed to room temperature within 45 min. Water (30 mL) was added and the mixture was stirred for 10 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography (pentane/Et_2O 5:2) afforded aldehyde **28** (3.21 g, 82 %) as a pale yellow oil. $[\alpha]_D^{20} = -19.2$, $[\alpha]_{546}^{20} = -22.1$ ($c = 1.0$, $CHCl_3$), identical (^1H and ^{13}C NMR, IR, EI-MS) with **28** obtained by the Dess – Martin oxidation protocol.[9]

***tert*-Butyldimethylsilyl {(1*S*,3*Z*)-4-iodo-1-[(*E*)-1-methyl-2-(2-methyl-1,3-thiazol-4-yl)-1-ethenyl]-3-pentenyl} ether (17)**: *n*BuLi (5.14 mL, 12.86 mmol, 1.96 equiv of a 2.5 M solution in hexanes) was added at 0 °C to a stirred suspension of ethyl triphenylphosphonium iodide (13.12 mmol, 2.0 equiv) in THF (60 mL). The resulting clear red ylide solution was added dropwise to a rapidly stirred solution of iodine (3.163 g, 12.46 mmol, 1.90 equiv) in THF (90 mL) cooled to −78 °C. The resulting yellow suspension was stirred vigorously for 10 min at −78 °C and for 30 min at −30 to −40 °C. A solution of NaHMDS (1.0 M in THF, 11.81 mL, 11.81 mmol, 1.80 equiv) was added dropwise within 10 min at −30 °C. The mixture was stirred for 15 min at −30 °C. A solution of aldehyde **28** (2.137 g, 6.56 mmol) in THF (30 mL) was added dropwise within 10 min. The mixture was stirred for 10 min at −30 °C and quenched with saturated aqueous NH_4Cl solution (10 mL). Pentane (150 mL) was added and the mixture was filtered through a small plug of silica. The column was eluted with pentane/Et_2O (4:1, 400 mL). The filtrate was concentrated in vacuo. Purification of the residue by flash chromatography (pentane/Et_2O 10:1) gave vinyl iodide **17** (1.640 g, 54 %) as a pale yellow oil. $[\alpha]_D^{20} = +14.2$, $[\alpha]_{546}^{20} = +18.5$ ($c = 1.0$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 2955, 2857, 1652, 1507, 1472, 1252, 1184, 1067, 837, 777\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.91$ (s, 1H; H-5″), 6.49 (s, 1H; H-2′), 5.46 (td, $^3J = 6.7$ Hz, $^4J = 1.5$ Hz, 1H; H-3), 4.21 (t, $^3J = 6.3$ Hz, 1H; H-1), 2.71 (s, 3H; C2″-CH_3), 2.48 (d, $^4J = 1.4$ Hz, 3H; H-5), 2.44 – 2.29 (m, 2H; H-2), 2.02 (d, $^4J = 1.1$ Hz, 3H; C1′-CH_3), 0.90 (s, 9H, $OSiC(CH_3)_3$), 0.06, 0.02 (2s, 2 × 3H; $OSi(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 164.4, 153.1, 141.7, 132.1, 118.9, 115.2, 102.3, 77.3, 43.7, 33.7, 25.8, 19.2, 18.2, 14.1, -4.7, -5.0$; MS (PCI, CH_4): *m*/*z* (%): 464.4 (100) $[M+H]^+$, 448.3 (32) $[M - CH_3]^+$, 423.3 (3), 406.2 (16) $[M - t\mathrm{Bu}]^+$, 369.2 (5), 332.0 (50), 282.1 (63), 232.3 (11), 229.1 (23), 205.1 (28); $C_{18}H_{30}INOSSi$ (463.5): calcd C 46.65, H 6.52, N 3.02, S 6.92; found C 46.67, H 6.77, N 3.12, S 6.57.

4-[(1*E*,3*S*,5*Z*,10*S*)-3,11-Di-(*tert*-butyldimethylsilyloxy)-2,6,10-trimethyl-1,5-undecadienyl]-2-methyl-1,3-thiazole (29): 1,2-Dibromoethane (35 μL) was added to a suspension of powdered Zn/Cu couple[25] (477 mg, 7.27 mmol, 2.3 equiv) in benzene (11 mL). The mixture was heated for a few seconds under reflux. After cooling to room temperature, TMSCl (35 μL) was added and the mixture was stirred for 5 min. DMAc (0.75 mL) and alkyl iodide **16** (1.623 g, 4.74 mmol, 1.5 equiv) in benzene (4 mL) were added. The mixture was stirred for 2.5 h at 60 °C. TESOTf (20 μL) and DMAc (0.75 mL) were added and the mixture was heated under reflux for 1 h. After cooling to room temperature, $[Pd(PPh_3)_4]$ (140 mg, 4 mol %) was added and the mixture was stirred for 5 min. A solution of vinyl iodide **17** (1.463 g, 3.16 mmol) in benzene (3 mL) was added. The mixture was stirred for 30 min at 60 °C, cooled to room temperature, and quenched with saturated aqueous NH_4Cl solution (5 mL). The organic layer was separated and the aqueous layer was extracted with MeO*t*Bu (3 × 30 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography (pentane/Et_2O 25:1) afforded coupling product **29** (1.458 g, 84 %) as a colorless oil. $[\alpha]_D^{20} = +12.2$, $[\alpha]_{546}^{20} = +9.3$ ($c = 1.25$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 2930, 2858, 1472, 1361, 1256, 1184, 1092, 940, 837, 776\ cm^{-1}$; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 6.92$ (s, 1H; H-5′), 6.45 (s, 1H; H-11), 5.18 – 5.06 (m, 1H; H-5), 4.07 – 4.03 (m, 1H; H-3), 3.44 (dd, $^2J = 9.8$ Hz, $^3J = 5.8$ Hz, 1H; H-11), 3.34 (dd, $^2J = 9.7$ Hz, $^3J = 6.6$ Hz, 1H; H-11), 2.70 (s, 3H; C2′-CH_3), 2.31 – 2.17 (m, 2H; H-4), 2.04 – 1.95 (m, 2H; H-7), 1.99 (d, $^4J = 1.2$ Hz, 3H; C2-CH_3), 1.58 (s, 3H; C6-CH_3), 1.66 – 1.53 (m, 2H), 1.46 – 0.95 (m, 3H)(H-8, H-9, H-10), 0.89 (s, 18H, $OSiC(CH_3)_3$), 0.87 (d, $^3J = 7.0$ Hz, 3H; C10-CH_3), 0.04, 0.03, 0.03, 0.00 (4s, 4 × 3H; $OSi(CH_3)_2$); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 164.4, 153.3, 142.6, 136.9, 121.4, 118.6, 114.9, 79.0, 68.4, 35.8, 35.3, 33.2, 32.3, 26.0, 25.8, 25.4, 23.5, 19.2, 18.3, 18.2, 16.7, 13.9, -4.7, -4.9, -5.3$; MS (70 eV, EI): *m*/*z* (%): 551 (0.5) $[M]^+$, 536 (1.7) $[M - CH_3]^+$, 494 (3.5) $[M - t\mathrm{Bu}]^+$, 282 (100) $[C_{14}H_{24}NOSSi]^+$, 173 (2), 91 (22), 73 (21); HRMS (EI): calcd for $C_{29}H_{54}NO_2SSi_2$ $[M - CH_3]^+$ 536.3414, found 536.342.

(2*S*,6*Z*,9*S*,10*E*)-9-(*tert*-Butyldimethylsilyloxy)-2,6,10-trimethyl-11-(2-methyl-1,3-thiazol-4-yl)-undeca-6,10-dien-1-ol (30): CSA (366 mg, 1.56 mmol, 1.05 equiv) was added over a 5 min period at 0 °C to a solution of the coupling product **29** (828 mg, 1.5 mmol) in a mixture of CH_2Cl_2 (15 mL) and MeOH (15 mL). The mixture was stirred for 30 min at 0 °C and for 3 h at room temperature, quenched with NEt_3 (0.22 mL, 1.56 mmol, 1.05 equiv) and concentrated in vacuo. After flash chromatography (pentane/Et_2O 1:1) of the residue, alcohol **30** (582 mg, 82 %) was obtained as a colorless oil. $[\alpha]_D^{20} = +7.6$, $[\alpha]_{546}^{20} = +10.5$ ($c = 1.0$, $CHCl_3$); IR (film):

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$\tilde{\nu}_{max}$ = 3362, 2930, 2857, 1463, 1361, 1253, 1186, 1075, 940, 837, 776 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.92 (s, 1H; H-5′), 6.45 (s, 1H; H-11), 5.18–5.12 (m, 1H; H-7), 4.11–4.06 (m, 1H; H-9), 3.50 (dd, ^2J = 10.5 Hz, ^3J = 5.9 Hz, 1H; H-1), 3.41 (dd, ^2J = 10.4 Hz, ^3J = 6.4 Hz, 1H; H-1), 2.70 (s, 3H; C2′-CH_3), 2.32–2.17 (m, 2H; H-8), 2.09–1.92 (m, 2H; H-5), 1.98 (d, ^4J = 1.2 Hz, 3H; C10-CH_3), 1.67 (s, 3H; C6-CH_3), 1.65 (br s, 1H; OH), 1.64–1.52 (m, 2H), 1.48–1.30 (m, 2H), 1.13–1.03 (m, 1H)(H-2, H-3, H-4), 0.89 (s, 9H, OSiC$(CH_3)_3$), 0.89 (d, ^3J = 6.9 Hz, 3H; C2-CH_3), 0.04, 0.00 (2s, 2 × 3H; OSi$(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.4, 153.1, 142.7, 136.8, 121.7, 118.7, 114.8, 79.2, 68.2, 35.7, 35.5, 33.1, 32.2, 25.8, 25.3, 23.5, 19.1, 18.2, 16.6, 13.9, −4.7, −4.9; MS (70 eV, EI): *m*/*z* (%): 437.4 (0.2) $[M]^+$, 422.2 (0.4) $[M-CH_3]^+$, 380.2 (0.6) $[M-t\mathrm{Bu}]^+$, 297.1 (2), 282.1 (100) $[C_{14}H_{24}NOSSi]^+$, 240.0 (3), 165.9 (8), 73.0 (79); HRMS (EI): calcd for $C_{24}H_{43}NO_2SSi$ 437.2784, found 437.275.

(2*S*,6*Z*,9*S*,10*E*)-9-(*tert*-Butyldimethylsilyloxy)-2,6,10-trimethyl-11-(2-methyl-1,3-thiazol-4-yl)-undeca-6,10-dienal (15): Pyridine (73 μL, 0.91 mmol) was added to a stirred solution of Dess–Martin periodinane[13] (386 mg, 0.91 mmol, 1.3 equiv) in CH_2Cl_2 (5 mL). The mixture was cooled to 0 °C and a solution of alcohol **30** (306 mg, 0.7 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The mixture was stirred for 30 min at room temperature. Et_2O (30 mL), pyridine (146 μL, 1.82 mmol), and buffered aqueous $Na_2S_2O_3$ solution (10 mL, 0.5 M, pH 7) were added. The organic layer was separated and the aqueous layer was extracted with MeO*t*Bu (2 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by flash chromatography (pentane/Et_2O 5:1) gave aldehyde[3g] **15** (295 mg, 97%) as a pale yellow oil. $[\alpha]_D^{20}$ = +19.9, $[\alpha]_{546}^{20}$ = +25.5 (*c* = 1.7, $CHCl_3$) [Lit.:[3g] $[\alpha]_D$ = +14.7 (*c* = 1.7, $CHCl_3$)]; IR (film): $\tilde{\nu}_{max}$ = 2930, 2857, 1727, 1507, 1463, 1389, 1255, 1184, 1076, 940, 837, 777 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.60 (d, ^3J = 2.0 Hz, 1H; H-1), 6.91 (s, 1H; H-5′), 6.45 (s, 1H; H-11), 5.19–5.13 (m, 1H; H-7), 4.11–4.06 (m, 1H; H-9), 2.71 (s, 3H; C2′-CH_3), 2.35–2.17 (m, 3H), 2.10–1.95 (m, 2H), 2.00 (d, ^4J = 1.1 Hz, 3H; C10-CH_3), 1.66 (d, ^4J = 1.0 Hz, 3H; C6-CH_3), 1.72–1.61 (m, 1H), 1.45–1.22 (m, 3H)(H-2, H-3, H-4, H-8), 1.08 (d, ^3J = 7.0 Hz, 3H; C2-CH_3), 0.88 (s, 9H, OSiC$(CH_3)_3$), 0.04, 0.00 (2s, 2 × 3H; OSi$(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.1, 164.4, 153.2, 142.5, 136.1, 122.1, 118.7, 115.0, 78.9, 46.3, 35.4, 31.8, 30.4, 25.8, 25.2, 23.4, 19.2, 18.2, 14.0, 13.3, −4.7, −4.9; MS (70 eV, EI): *m*/*z* (%): 435 (0.48) $[M]^+$, 420 (0.90) $[M-CH_3]^+$, 378 (0.82) $[M-t\mathrm{Bu}]^+$, 303 (3), 282 (100) $[C_{14}H_{24}NOSSi]^+$, 75 (8), 73 (6); HRMS (EI): calcd for $C_{24}H_{41}NO_2SSi$ 435.2627, found 435.263.

(4*S*,5*S*,6*S*,7*S*,10*Z*,13*S*,14*E*)-13-[(*tert*-Butyldimethylsilyl)oxy]-2-[(4*R*)-2,2-dimethyl-1,3-dioxan-4-yl]-5-hydroxy-2,4,6,10,14-pentamethyl-15-(1,3-thiazol-4-yl)-10,14-pentadecadien-3-one (31): A solution of ethyl ketone **2** (64 mg, 0.3 mmol, 1 equiv) in THF (0.5 mL) was added dropwise at −78 °C to a freshly prepared solution of LDA [*n*BuLi (118 μL, 0.294 mmol, 0.98 equiv of a 2.5 M solution in hexanes) was added to a solution of diisopropylamine (41.6 μL, 0.294 mmol) in THF (0.5 mL) at 0 °C]. The mixture was stirred for 30 min at 0 °C. The solution was stirred for 1 h at −78 °C. A solution of aldehyde **15** (65 mg, 0.15 mmol, 0.5 equiv) in THF (0.6 mL) was added dropwise and stirring was continued for 20 min at −78 °C. The mixture was quenched by dropwise addition of saturated NH_4Cl solution (2 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by flash chromatography (pentane/Et_2O 10:1, then 5:1) afforded *anti* Cram (6*R*,7*S*) aldol product **31** (83 mg, 85%) and its corresponding Cram (6*S*,7*R*) diastereomer (9 mg, 9.5%) (ratio 9:1 by HPLC) as colorless oils. (6*R*,7*S*) Isomer: $[\alpha]_D^{20}$ = −25, $[\alpha]_{546}^{20}$ = −27 (*c* = 0.1, $CHCl_3$); IR (film): $\tilde{\nu}_{max}$ = 3505, 2931, 2858, 1686, 1472, 1373, 1255, 1197, 1098, 971, 837, 777 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.91 (s, 1H, H-5″), 6.45 (s, 1H; H-15), 5.17–5.09 (m, 1H; H-11), 4.10–4.06 (m, 1H; H-13), 4.04 (dd, ^3J = 11.8 Hz, ^3J = 2.5 Hz, 1H; H-4′), 3.96 (dt, ^2J = 11.9 Hz, ^3J = 2.7 Hz, 1H; H-6′), 3.86 (ddd, ^2J = 11.7 Hz, ^3J = 5.4 Hz, ^3J = 1.7 Hz, 1H; H-6′), 3.50 (br s, 1H; OH), 3.36 (d, ^3J = 9.3 Hz, 1H; H-5), 3.27 (dq, ^3J = 7.0 Hz, ^3J = 1.4 Hz, 1H; H-4), 2.71 (s, 3H; C2″-CH_3), 2.34–2.14 (m, 2H; H-12), 2.06–1.93 (m, 2H; H-9), 1.99 (d, ^4J = 1.2 Hz, 3H; C14-CH_3), 1.82–1.71 (m, 1H; H-7), 1.67 (d, ^4J = 1.1 Hz, 3H; C10-CH_3), 1.66–1.22 (m, 5H; H-6, H-8, H-5′), 1.40 (s, 3H; C2′-CH_3), 1.33 (s, 3H; C2′-CH_3), 1.20 (s, 3H; H-1), 1.16–1.05 (m, 1H; H-7), 1.09 (s, 3H; C2-CH_3), 1.02 (d, ^3J = 7.0 Hz, 3H; C4-CH_3), 0.88 (s, 9H; OSiC$(CH_3)_3$), 0.82 (d, ^3J = 6.8 Hz, 3H; C6-CH_3), 0.04, 0.00 (2s, 2 × 3H; OSi$(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 222.8, 164.3, 153.3, 142.6, 136.9, 121.4, 118.6, 114.9, 98.5, 79.1, 74.7, 74.4, 59.9, 51.6, 41.3, 35.4, 35.3, 33.0, 32.4, 29.8, 25.8, 25.2, 25.1, 23.5, 21.6, 19.2, 19.0, 18.6, 18.2, 15.4, 13.9, 9.3, −4.7, −4.9; MS (70 eV, EI): *m*/*z* (%): 650 (3) $[M]^+$, 436 (5), 282 (100) $[C_{14}H_{24}NOSSi]^+$, 167 (10), 149 (21), 115 (12), 73 (25); $C_{36}H_{63}NO_5SSi$ (650.0): C 66.46, H 9.69, N 2.15, S 4.99; found C 66.37, H 9.34, N 2.42, S 4.72.

(3*S*,6*S*,7*S*,8*S*,12*Z*,15*S*,16*E*)-1,3,7-Trihydroxy-15-[(*tert*-butyldimethylsilyl)oxy]-4,4,6,8,12,16-hexamethyl-17-(2-methyl-1,3-thiazol-4-yl)-12,16-heptadecadien-5-one (32): PPTS (6.0 mg, 24 μmol, 0.6 equiv) was added to a solution of aldol product **31** (26 mg, 0.04 mmol) in MeOH (0.5 mL). The mixture was stirred for 22 h at room temperature. Another portion of PPTS (4.0 mg, 16 μmol, 0.4 equiv) was added and stirring was continued for 50 h at room temperature. The solvent was removed in vacuo and the residue was purified by flash chromatography (Et_2O) to give triol **32** (21 mg, 86%) as a colorless oil. $[\alpha]_D^{20}$ = −7.0, $[\alpha]_{546}^{20}$ = −8.0 (*c* = 0.3, $CHCl_3$); IR (film): $\tilde{\nu}_{max}$ = 3396, 2930, 2857, 1687, 1470, 1374, 1257, 1060, 973, 836, 776 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.92 (s, 1H, H-5′), 6.44 (s, 1H; H-17), 5.18–5.12 (m, 1H; H-13), 4.10–4.03 (m, 2H; H-15, H-3), 3.94–3.91 (m, 2H; H-1), 3.51 (br d, ^3J = 3.7 Hz, 1H; C7-OH), 3.36 (d, ^3J = 8.9 Hz, 1H; H-7), 3.30 (br s, 1H; OH), 3.28 (dq, ^3J = 6.9 Hz, ^3J = 1.8 Hz, 1H; H-6), 2.77 (br s, 1H; OH), 2.72 (s, 3H; C2′-CH_3), 2.26–2.15 (m, 2H; H-14), 2.05–1.93 (m, 2H; H-11), 1.98 (d, ^4J = 1.3 Hz, 3H; C16-CH_3), 1.78–1.40 (m, 5H; H-2, H-8, H-9, H-10), 1.67 (d, ^4J = 1.1 Hz, 3H; C12-CH_3), 1.38–0.91 (m, 2H; H-9, H-10), 1.22, 1.13 (2s, 2 × 3H; C4-CH_3), 1.06 (d, ^3J = 6.9 Hz, 3H; C6-CH_3), 0.89 (s, 9H; OSiC$(CH_3)_3$), 0.86 (d, ^3J = 6.8 Hz, 3H; C8-CH_3), 0.05, 0.00 (2s, 2 × 3H; OSi$(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 223.3, 164.5, 153.1, 142.7, 136.8, 121.6, 118.7, 114.8, 79.2, 76.3, 74.4, 62.1, 52.7, 41.1, 35.6, 35.4, 32.8, 32.5, 32.3, 25.8, 25.1, 23.5, 21.6, 19.1, 18.5, 18.2, 15.5, 13.8, 10.1, −4.0, −4.3; MS (PCI, CH_4): *m*/*z* (%): 610.7 (0.2) $[M]^+$, 536.5 (1.0) $[M-t\mathrm{Bu}]^+$, 464.3 (10), 420.3 (13), 378.2 (11), 304.1 (81), 282.0 (42) $[C_{14}H_{24}NOSSi]^+$, 175.9 (15), 157.0 (22), 139.0 (17), 100.9 (100), 83.0 (50), 57.0 (70); HRMS (EI): calcd for $C_{32}H_{56}NO_5SSi$ $[M-CH_3]^+$ 594.3649, found 594.361.

(3*S*,6*S*,7*S*,8*S*,12*Z*,15*S*,16*E*)-1,3,7,15-Tetra[(*tert*-butyl-dimethylsilyl)oxy]-4,4,6,8,12,16-hexamethyl-17-(2-methyl-1,3-thiazol-4-yl)-12,16-heptadecadien-5-one (33): 2,6-Lutidine (29 μL, 247.5 μmol, 2.5 equiv) was added to a solution of triol **32** (20.0 mg, 33 μmol) in CH_2Cl_2 (0.2 mL). The mixture was cooled to −50 °C and TBSOTf (34 μL, 148.5 μmol, 1.5 equiv) was added. The mixture was allowed to warm to 0 °C and stirring was continued for 2 h at 0 °C. The solvent was removed in vacuo and the residue was purified by flash chromatography (pentane/Et_2O 20:1). The tetrakis-silyl ether[3g] **33** (30 mg, 95%) was obtained as a colorless oil. $[\alpha]_D^{20}$ = −13.7, $[\alpha]_{546}^{20}$ = −15.7 (*c* = 0.1, $CHCl_3$) [Lit.:[3g] $[\alpha]_D$ = −10.8 (*c* = 0.5, $CHCl_3$)]; IR (film): $\tilde{\nu}_{max}$ = 2929, 2857, 1698, 1473, 1388, 1362, 1256, 1093, 986, 836, 775, 669 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.91 (s, 1H, H-5′), 6.45 (s, 1H; H-17), 5.17–5.10 (m, 1H; H-13), 4.10–4.05 (m, 1H; H-15), 3.88 (dd, ^3J = 7.5 Hz, ^3J = 2.7 Hz, 1H; H-3), 3.76 (dd, ^3J = 6.7 Hz, ^3J = 1.9 Hz, 1H; H-7), 3.71–3.64 (m, 1H), 3.62–3.54 (m, 1H; H-1), 3.18–3.11 (m, 1H; H-6), 2.71 (s, 3H; C2′-CH_3), 2.31–2.17 (m, 2H; H-14), 2.01–1.93 (m, 2H; H-11), 1.99 (d, ^4J = 1.1 Hz, 3H; C16-CH_3), 1.66 (s, 3H; C12-CH_3), 1.64–1.01 (m, 7H; H-2, H-8, H-9, H-10), 1.22 (s, 3H; C4-CH_3), 1.04 (d, ^3J = 6.9 Hz, 3H; C6-CH_3), 1.02 (s, 3H; C4-CH_3), 0.93–0.86 (m, 39H; C8-CH_3, 4 × OSiC$(CH_3)_3$), 0.09, 0.07, 0.06, 0.04, 0.03, 0.02 (6s, 6 × 3H; OSi$(CH_3)_3$), 0.00 (s, 6H; OSi$(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 218.3, 164.3, 153.3, 142.5, 136.8, 121.6, 118.7, 114.9, 79.0, 77.5, 74.0, 61.0. 53.7, 45.0, 39.0, 38.1, 35.3, 32.6, 31.0, 29.7, 26.2, 26.1, 26.0, 25.9, 24.5, 23.5, 19.4, 19.2, 18.5, 18.3, 18.2, 18.1, 17.6, 15.2, 13.9, −3.6, −3.7, −3.8, −4.0, −4.6, −4.9, −5.2, −5.3; MS (PCI, CH_4): *m*/*z* (%): 952.7 (27) $[M+H]^+$, 936.7 (14) $[M-CH_3]^+$, 894.6 (5) $[M-t\mathrm{Bu}]^+$, 820.6 (16), 634.4 (16), 624.4 (9), 550.4 (100), 435.6 (16), 303.1 (67), 282.0 (95) $[C_{14}H_{24}NOSSi]^+$, 231.0 (10), 188.9 (16), 132.9 (22); HRMS (EI): calcd for $C_{47}H_{92}NO_5SSi_4$ 894.5773, found 894.577.

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