Studies Towards the Total Synthesis of Epothilones: Asymmetric Synthesis of the Key Fragments

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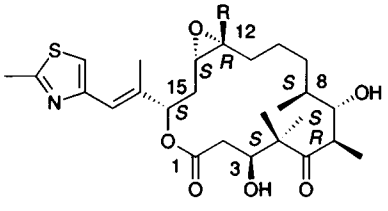
Abstract: Members of a new class of macrolide—the so-called epothilones (**1**)—showing a taxol-like biological activity have recently been isolated. A convergent approach to **1** is presented, and the asymmetric syntheses of the three key intermediates **3**, **4**, and **8** are reported.

Keywords
asymmetric syntheses · epothilones · macrolides · natural products

Introduction

Very recently, a new class of macrolide, the so-called epothilones (**1**, Scheme 1), was isolated by Höfle et al.[1, 2] These compounds show a striking stabilizing effect on the polymerization of microtubules and are very active against mouse leukemia cell lines. In addition, a strong immune suppression in human cells has been reported.[3] The biological activity spectrum is very close to that of taxol, and both compounds probably compete for the same receptor and replace each other. They are "equipotent" in in vitro tests, show similar kinetics and provide closely similar microscopic pictures of microtubule structure and cell damage.[1] There is a major difference in their effect on cell lines showing multiple drug resistance; epothilones are between about 2000 and 5000 times more active than taxol in these experiments.[2, 4]



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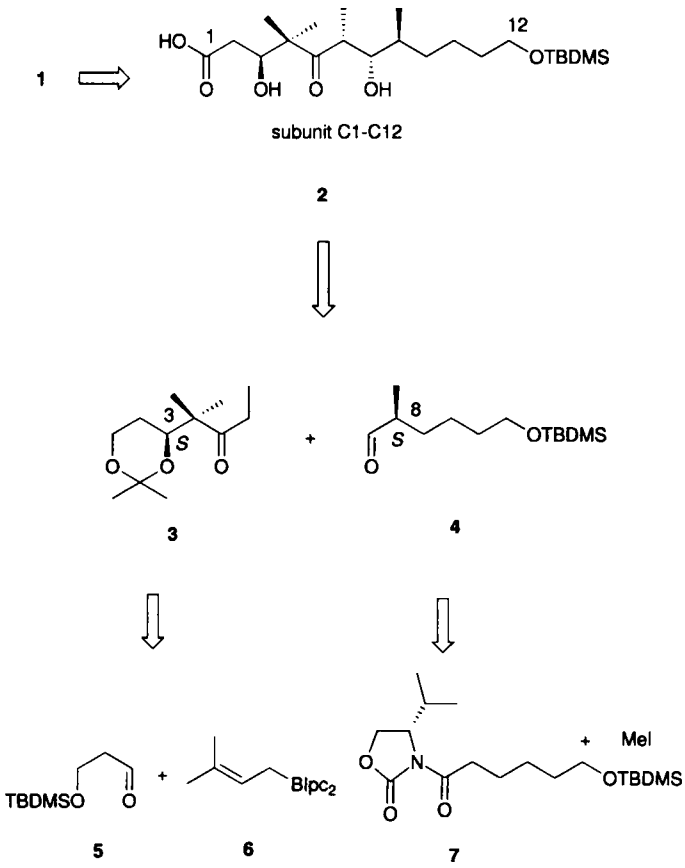
Scheme 1. Epothilones. **A**: R = H, **B**: R = Me.

In this full paper we wish to report our efforts focusing on the total synthesis of epothilones **1**. Following our retrosynthetic analysis, **1** can be split into three major fragments—**3**, **4** and **8** (Schemes 2 and 3): **3** and **4** can be coupled through a stereoselective aldol reaction to provide subunit **2**. Key intermediate **8** is obtained from the same starting material as intermediate **3** by employing a Sharpless resolution to obtain the optically active allyl alcohol **11**.



Scheme 2. Retrosynthetic analysis for key fragments **3** and **4**.

Results and Discussion

Starting from propane-1,3-diol, 3-(*tert*-butyldimethylsilyloxy)propanal (**5**) was obtained in two steps by monosilylation and Swern oxidation (Scheme 4).[5, 6] Reaction with (−)-Ipc_2B-prenyl, prepared in situ, yielded the functionalized homoallylic alcohol **15** in 95% *ee* with the correct absolute configuration.[7]

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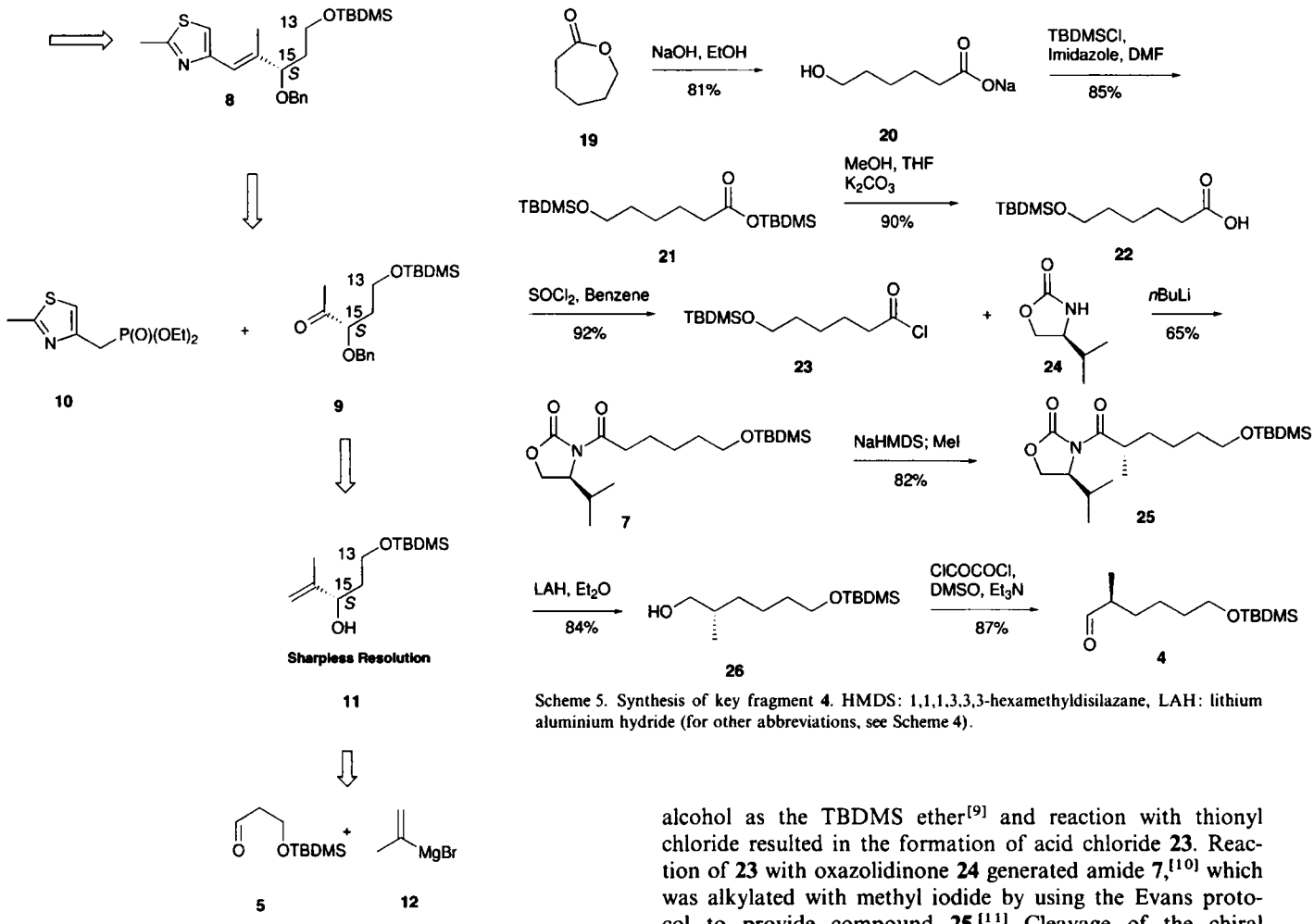


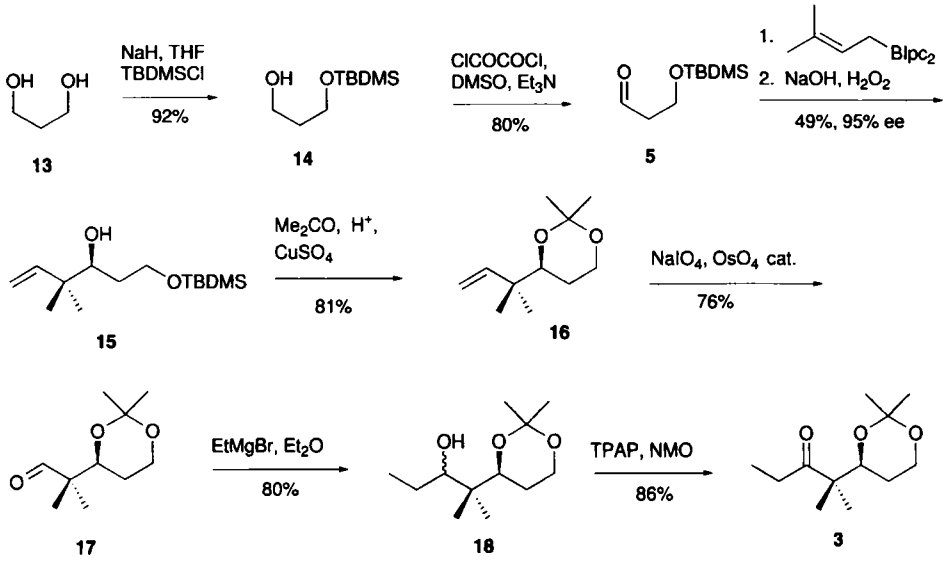
Scheme 3. Retrosynthetic analysis for key fragment **8**.

Deprotection of **15** followed by protection as the acetonide **16**, oxidative cleavage of the double bond, Grignard addition and final oxidation with TPAP/NMO[8] gave key fragment **3** in high overall yield.

Key aldehyde **4** was synthesized starting from ω-caprolactone (**19**) (Scheme 5). Lactone-opening, protection of the resulting alcohol as the TBDMS ether[9] and reaction with thionyl chloride resulted in the formation of acid chloride **23**. Reaction of **23** with oxazolidinone **24** generated amide **7**,[10] which was alkylated with methyl iodide by using the Evans protocol to provide compound **25**.[11] Cleavage of the chiral auxiliary with LAH and reoxidation to the α-chiral aldehyde **4** under Swern conditions provided the desired key fragment **4**.

Scheme 5. Synthesis of key fragment **4**. HMDS: 1,1,1,3,3,3-hexamethyldisilazane, LAH: lithium aluminium hydride (for other abbreviations, see Scheme 4).

Subunit **8** was synthesized from compound **5**, the same starting material as for the synthesis of key fragment **3** (Scheme 6). Addition of propenyl Grignard reagent **12** gave the functionalized allylic alcohol **27** in high yield.[12] Sharpless resolution provided alcohol **11** with the desired (*S*) configuration in 80% *ee*.[13–15] Benzylation followed by oxidative cleavage of the double bond with $NaIO_4/OsO_4$ gave methyl ketone **9**. Thiazole derivative **29** was synthesized in a straightforward way, by condensation of cysteine methyl ester hydrochloride with acetaldehyde and dehydrogenation with manganese dioxide.[16] Compound **29** was transformed into bromide **30**.[17] An Arbuzov reaction then gave phosphonate **10**.[18] Deprotonation of phosphonate **10** with *n*BuLi and reaction with methyl ketone **9** under Horner–Emmons conditions[19] yielded the desired trisubstituted olefin **8** as a single stereoisomer. The olefin configuration in **8** was unambiguously confirmed by NOE experiments.[1, 20]



Scheme 4. Synthesis of key fragment **3**. TBDMS: *tert*-butyldimethylsilyl, Ipc: isopinocampheyl, TPAP: tetrapropylammonium perruthenate(VII), NMO: 4-methylmorpholine *N*-oxide.

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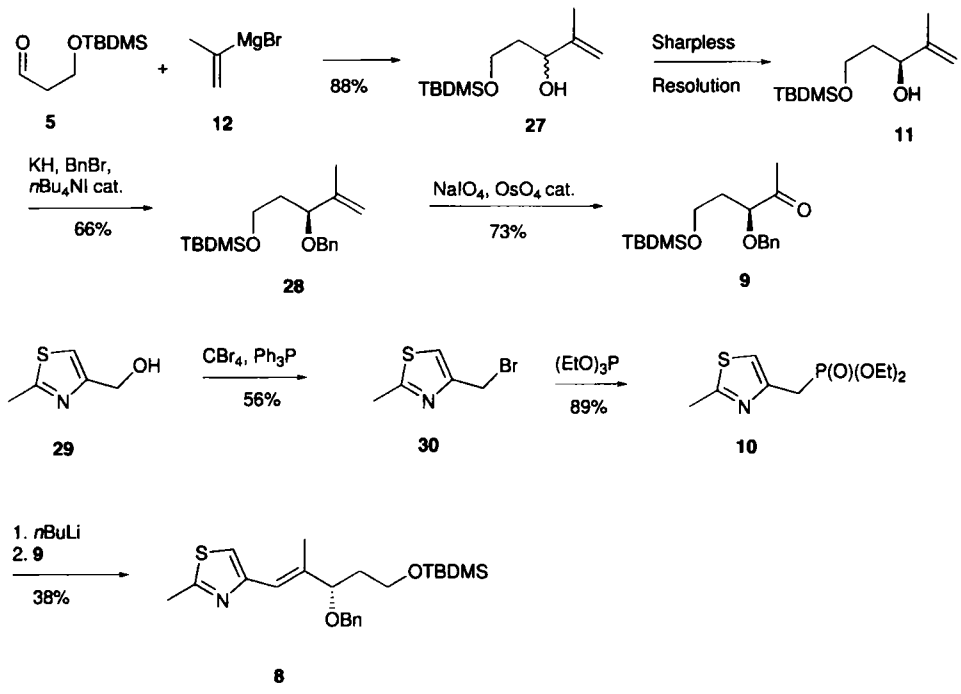

5 12 27 11 28 9 29 30 10 8

Scheme 6. Synthesis of key fragment **8**.

Conclusion

We have used a convergent approach to synthesize the desired key intermediates **3**, **4** and **8** for the cytotoxic macrolides epothilone **A** and **B** (Scheme 1). Starting with very simple compounds, we obtained important precursors enantiomerically pure with good overall yield. The final step in this total synthesis of epothilones, the coupling of fragments **3**, **4** and **8**, is under investigation and will be reported in due course.

Experimental Section

High-resolution mass spectra were obtained on Finnigan MAT 312 and MAT 8430 spectrometers (reference PFK, peak matching method, accuracy ±2 ppm). IR spectra were recorded on Perkin-Elmer 580, FT 1710 and Nicolet 320 FT-IR spectrometers. UV spectra were recorded on a Hewlett-Packard 8452 A spectrometer. NMR spectra were recorded on Bruker AC 200, AM 400 and DMX 600 spectrometers. All organometallic reactions were performed under nitrogen, and pure products were obtained after flash chromatography on Merck silica gel 60 (40–63 μm). Additions were carried out by means of a syringe pump. Optical rotations were recorded with a Perkin Elmer 241 polarimeter. GC analysis was performed with a Macherey-Nagel column (50 m, OV 1) on a Dani 86.10 HT GC.

(*S*)-1-(*tert*-Butyldimethylsilyloxy)-4,4-dimethylhex-5-en-3-ol (15): 3-Methyl-1,2-butadiene (500 mg, 7.34 mmol, 1 equiv) was slowly added to a cooled suspension (−25 °C) of Ipc_2BH (7.34 mmol), derived from (−)-α-pinene [99%, 97% *ee*], in THF (2.6 mL). The reaction mixture was stirred at that temperature for 6 h. The THF was evaporated at RT (14 mm Hg/1 h and 0.5 mm Hg/2 h), and the crude product was dissolved in ether (10 mL). The solution was cooled to −78 °C, and aldehyde **5** (1.382 g, 7.34 mmol, 1 equiv) added. The mixture was stirred for 12 h at −78 °C and warmed to RT. The reaction mixture was quenched with 3 N NaOH solution (10.7 mL) and 30% H_2O_2 solution (4.4 mL) and refluxed for 2 h. The organic layer was washed with water (15 mL) and brine (25 mL), and dried over $MgSO_4$. The solvent was removed, and the crude product purified by flash chromatography (ether:pentane = 1:2) to yield alcohol **15** as a colourless oil (922 mg, 49%, 95% *ee*), $[\alpha]_D^{20} = -1.6$ ($c = 1.0$, $CHCl_3$). The enantiomeric excess (*ee*) was determined by GC analysis of the diastereomeric esters formed with (1*R*)-(−)-camphanic chloride. The absolute configuration of **15** was determined by the method of Mosher [14,15]. IR (film): $\tilde{\nu}_{max}$ = 3512 (m), 2958 (s), 2931 (s), 2859 (s), 1638 (w), 1473 (m), 1257 (m), 1086 (s), 837 (s), 777 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.86 (dd, ^3J = 17.4 Hz, ^3J = 11.0 Hz, 1H, H-5), 5.02 (dd, ^3J = 11.0 Hz, ^2J = 1.5 Hz, 1H, H-6), 5.00 (dd, ^3J = 17.4 Hz, ^2J = 1.5 Hz, 1H, H′-6), 3.89–3.74 (m, 2H, H-1), 3.51 (dd, ^3J = 10.2, 1.6 Hz, 1H, H-3), 3.19 (br s, 1H, OH), 1.66–1.48 (m, 2H, H-2), 1.01 (s, 3H), 1.00 (s, 3H, C4-$(CH_3)_2$), 0.88 (s, 9H, Si*t*Bu), 0.06 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.69 (d), 112.27 (t), 78.52 (d), 63.29 (t), 41.19 (s), 33.39 (t), 25.89 (q), 22.85 (q), 22.43 (q), 18.17 (s), −5.52 (q); MS (70 eV, EI): *m/z* (%): 201 (3) [M^+ − *t*Bu], 189 (37), 131 (50), 109 (100), 105 (41), 101 (34), 89 (37), 75 (92) [$HOSi(CH_3)_2^+$], 73 (52), 67 (35); HRMS (EI): calcd for $C_{10}H_{21}O_2Si$ [M^+ − *t*Bu] 201.1311, found 201.131.

(*S*)-4-(1,1-Dimethylallyl)-2,2-dimethyl-[1,3]dioxane (16): Anhydrous $CuSO_4$ (400 mg, 2.51 mmol, 2.3 equiv) was added to a solution of alcohol **15** (278 mg, 1.08 mmol) in acetone (13 mL). A solution (20 drops) of glacial acetic acid (0.1 mL) in CH_2Cl_2 (1 mL) was added. The mixture was stirred for 12 h at RT, poured into a saturated solution of $NaHCO_3$ (30 mL) and extracted with ether (30 mL). The organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (ether:pentane = 1:2) to yield the acetonide **16** (161 mg, 81%) as a colourless oil; $[\alpha]_D^{20} = -1.7$ ($c = 1.0$, $CHCl_3$); IR (film): $\tilde{\nu}_{max}$ = 3084 (w), 2966 (s), 2866 (s), 1640 (w), 1381 (s), 1271 (m), 1197 (s), 1159 (m), 1107 (s), 973 (m), 855 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.91–5.84 (m, 1H, H-2′), 4.98–4.94 (m, 2H, H-3′), 3.93–3.86 (m, 1H), 3.83–3.78 (m, 1H, H-6), 3.51 (dd, ^3J = 11.7, 2.6 Hz, 1H, H-4), 1.65–1.50 (m, 1H, H-5), 1.40 (s, 3H), 1.35 (s, 3H, C2-$(CH_3)_2$), 1.32–1.24 (m, 1H, H′-5), 0.97 (s, 3H), 0.96 (s, 3H, C1′-$(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.10 (d), 111.88 (t), 98.19 (s), 75.32 (d), 60.10 (t), 39.97 (s), 29.80 (q), 25.88 (t), 22.86 (q), 22.45 (q), 19.11 (q); MS (70 eV, EI): *m/z* (%): 184 (0.003) [M^+], 169 (14), 115 (100), 109 (36), 81 (14), 73 (15), 67 (20), 59 (54), 57 (22), 43 (35); HRMS (EI): calcd for $C_{10}H_{17}O_2$ [$M^+ - CH_3$] 169.1229, found 169.122.

(*S*)-2-(2,2-Dimethyl-[1,3]dioxan-4-yl)-2-methylpropionaldehyde (17): Aqueous phosphate buffer (pH 7, 14 mL) was added to a solution of **16** (286 mg, 1.55 mmol) in THF (18 mL). OsO_4 solution (2.5% in *tert*-butanol; 400 μL, 31 μmol, 0.02 equiv) was then added to the vigorously stirred reaction mixture. After 10 min $NaIO_4$ (996 mg, 4.66 mmol, 3 equiv) was added in portions over a period of 20 min. The mixture was stirred at RT, and after 24 h and 48 h another two portions of $NaIO_4$ (332 mg, 1.55 mmol, 2 × 1.0 equiv) were added. After 55 h the layers were separated, the aqueous phase was extracted twice with ether (30 mL), the combined organic layers were dried with $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (ether:pentane = 1:1) to give aldehyde **17** (221 mg, 76%) as a colourless oil; $[\alpha]_D^{20} = +10.7$ ($c = 1.0$, $CHCl_3$); IR (film): $\tilde{\nu}_{max}$ = 2991 (s), 2940 (s), 2876 (s), 2707 (m), 1726 (s), 1468 (m), 1382 (s), 1273 (m), 1199 (s), 1107 (s), 970 (m), 854 (m) cm^{-1}; UV/Vis (CH_3CN): $\lambda_{max}(lg\varepsilon)$ = 202 nm (2.7); ^1H NMR (400 MHz, C_6D_6): δ = 9.55 (s, 1H, H-1), 3.98–3.91 (m, 2H, H-6′), 3.84 (ddd, J = 11.8, 5.5, 1.9 Hz, 1H, H-4′), 1.71–1.60 (m, 1H, 1H-5′), 1.40 (s, 3H, C2′-CH_3), 1.37–1.32 (m, 1H, 1H-5′), 1.31 (s, 3H, C2′-CH_3), 1.04 (s, 3H), 0.99 (s, 3H, H-3 and C2-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.09 (d), 98.43 (s), 72.94 (d), 59.75 (t), 48.84 (s), 29.57 (q), 25.57 (t), 18.96 (q), 18.62 (q), 16.46 (q); MS (70 eV, EI): *m/z* (%): 171 (4) [$M^+ - CH_3$], 133 (27), 105 (52), 75 (100); HRMS (EI): calcd for $C_9H_{15}O_3$ [$M^+ - CH_3$] 171.1021, found 171.102.

(3*RS*)-2-((4*S*)-2,2-Dimethyl-[1,3]dioxan-4-yl)-2-methylpentan-3-ol (18): A solution of EtMgBr (3 M in ether; 528 μL, 1.58 mmol, 1.1 equiv) was added to a solution of aldehyde **17** (268 mg, 1.44 mmol) in ether (4 mL) at 0 °C. The mixture was stirred for 2 h at 0 °C, warmed up to RT and stirred for 1 h. The mixture was quenched with a saturated solution of NH_4Cl (30 mL) and extracted twice with ether (30 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (ether:pentane = 1:1) to yield pure alcohol **18** (251 mg, 80%) as a colourless oil. Diastereomer **a**: IR (film): $\tilde{\nu}_{max}$ = 3484 (s), 2967 (s), 2939 (s), 2877 (s), 1468 (m), 1381 (s), 1273 (m), 1199 (s), 1100 (s), 973 (s), 856 (m) cm^{-1}; UV/Vis (CH_3CN): $\lambda_{max}(lg\varepsilon)$ = 202 nm (2.7); ^1H NMR (400 MHz, C_6D_6): δ = 3.70–3.59 (m, 3H, H-4′ and H-6′), 3.37 (br d, ^3J = 10.3 Hz, 1H, H-3), 2.85 (br s, 1H, OH), 1.62–1.30 (m, 3H, H-4 and H-5′), 1.41 (s, 3H), 1.29 (s, 3H, C2′-$(CH_3)_2$), 1.14 (t, ^3J = 7.2 Hz, 3H, H′-5), 1.01 (s, 3H), 0.65 (s, 3H, H-1 and C2-CH_3), 0.97–0.92 (m, 1H, H′-5′); ^{13}C NMR (100 MHz, C_6D_6): δ = 98.41 (s), 79.95 (d), 76.65 (d), 60.10 (t), 40.60 (s), 30.04 (q), 25.73 (t), 24.64 (t), 20.03 (q), 19.25 (q), 15.99 (q), 11.67 (q); MS (70 eV, EI): *m/z* (%): 216 (0.08) [M^+], 201 (17), 141 (17), 129 (16), 115 (100), 89 (18), 83 (54), 70 (19), 59 (93), 57 (41), 43 (33).

Diastereomer **b**: *IR* (film): $\tilde{\nu}_{max}$ = 3508 (s), 2966 (s), 2939 (s), 2877 (s), 1468 (m), 1381 (s), 1200 (s), 1100 (s), 967 (s), 853 (m) cm^{-1}; UV/Vis (CH_3CN): λ_{max}(lgε) = 198 nm (1.9), 226 nm (1.7); ^1H NMR (400 MHz, C_6D_6): δ = 3.66–3.53 (m, 3H, H-4′ and H-6′), 3.45 (brd, J = 9.1 Hz, 1H, H-3), 3.31 (brs, 1H, OH), 1.68–1.58 (m, 1H, H-5′), 1.47–1.37 (m, 2H, H-4), 1.35 (s, 3H, C2′–CH_3), 1.25 (t, ^3J = 7.2 Hz, 3H, H-5), 1.22 (s, 3H, C2′–CH_3'), 0.85 (s, 3H), 0.81 (s, 3H, H-1 and C2–CH_3), 0.83–0.78 (m, 1H, H′-5′); ^{13}C NMR (100 MHz, C_6D_6): δ = 98.57 (s), 78.85 (d), 76.46 (d), 60.08 (t), 39.93 (s), 30.02 (q), 25.41 (t), 25.08 (t), 20.85 (q), 20.30 (q), 18.90 (q), 11.95 (q); MS (70 eV, EI): *m/z* (%): 216 (0.007) [M^+], 201 (17), 141 (21), 129 (23), 115 (82), 89 (19), 83 (49), 70 (21), 59 (100), 57 (40), 43 (34); HRMS (EI): calcd for $C_{11}H_{21}O_3$ [$M^+ - CH_3$] 201.1491, found 201.149.

(*S*)-2-(2,2-Dimethyl-[1,3]dioxan-4-yl)-2-methylpentan-3-one (*3*): A trace of 4 Å molecular sieves and NMO (66 mg, 0.48 mmol, 1.5 equiv) were added to a solution of alcohol **18** (70 mg, 0.32 mmol) in CH_2Cl_2 (5 mL). After the mixture had been stirred for 10 min, TPAP (6 mg, 16 μmol, 0.05 equiv) was added, and the mixture was stirred for an additional 4 h at RT. The solvent was removed under reduced pressure, and the crude product purified by flash chromatography (ether:pentane = 1:1) to yield ethyl ketone **3** (60 mg, 86%) as a colourless oil; $[\alpha]_D^{24}$ = +12.4 (*c* = 1.0, $CHCl_3$); IR (film): $\tilde{\nu}_{max}$ = 2990 (s), 2973 (s), 2940 (s), 2877 (m), 1707 (s), 1462 (m), 1381 (s), 1198 (s), 1106 (s), 971 (s), 855 (w) cm^{-1}; UV/Vis (CH_3CN): λ_{max}(lgε) = 288 nm (1.9); ^1H NMR (400 MHz, C_6D_6): δ = 3.90 (dd, J = 11.7, 2.5 Hz, 1H, H-4′), 3.66–3.56 (m, 2H, H-6′), 2.34–2.23 (m, 2H, H-4), 1.52–1.43 (m, 1H, H-5′), 1.41 (s, 3H), 1.27 (s, 3H, C2′-(CH_3)$_2$), 1.12 (s, 3H), 0.90 (s, 3H, H-1 and C2-CH_3), 1.08 (t, J = 7.2 Hz, 3H, H-5), 0.89–0.84 (m, 1H, H′-5′); ^{13}C NMR (100 MHz, C_6D_6): δ = 213.23 (s), 98.42 (s), 74.18 (d), 59.82 (t), 50.44 (s), 31.70 (t), 30.03 (q), 25.55 (t), 20.97 (q), 19.35 (q), 19.04 (q), 8.16 (q); MS (70 eV, EI): *m/z* (%): 199 (24) [$M^+ - CH_3$], 156 (28), 139 (23), 127 (9), 115 (41), 99 (14), 83 (48), 57 (100), 43 (41); HRMS (EI): calcd for $C_{11}H_{19}O_3$ [$M^+ - CH_3$] 199.1334, found 199.133. Anal. calcd for $C_{12}H_{22}O_3$ (214.30): C 67.26%; H 10.35%. Found: C 67.21%; H 10.08%.

Sodium 6-hydroxyhexanoate (**20**) was synthesized according to a procedure from Wulff et al. [9] starting from ω-caprolactone (**19**).

***tert*-Butyldimethylsilyl 6-(*tert*-butyldimethylsilyloxy)hexanoate** (**21**): A mixture of the salt **20** (2.00 g, 13.0 mmol), DMF (25 mL), TBDMSCl (5.87 g, 38.9 mmol, 3 equiv) and imidazole (5.30 g, 77.85 mmol, 6 equiv) was stirred for 48 h at RT. The reaction mixture was filtered through a short pad of silica gel, and the product purified by flash chromatography (ether:pentane = 1:4) to yield compound **21** (3.99 g, 85%) as a colourless oil. IR (film): $\tilde{\nu}_{max}$ = 2956 (s), 2932 (s), 2888 (m), 2860 (s), 1722 (s), 1473 (m), 1363 (w), 1256 (s), 1102 (s), 837 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.58 (t, ^3J = 6.5 Hz, 2H, H-6), 2.30 (t, ^3J = 7.4 Hz, 2H, H-2), 1.64–1.56 (m, 2H), 1.55–1.48 (m, 2H), 1.38–1.30 (m, 2H, H-3, H-4, H-5), 0.91 (s, 9H, C1-OSi*t*Bu), 0.87 (s, 9H, C6-OSi*t*Bu) 0.24 (s, 6H, C1-OSiCH_3), 0.02 (s, 6H, C6-OSiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.17 (s), 63.00 (t), 36.02 (t), 32.53 (t), 25.95 (q), 25.55 (q), 25.40 (t), 24.91 (t), 18.33 (s), 17.57 (s), −4.83 (q), −5.32 (q); MS (70 eV, EI): *m/z* (%): 360 (0.2) [M^+], 345 (7), 303 (87), 287 (18), 189 (19), 171 (24), 147 (100), 133 (14), 117 (10), 97 (17), 75 (85) [$HOSi(CH_3)_2^+$], 69 (26); HRMS (EI): calcd for $C_{18}H_{40}O_3Si_2$ [$M^+ - t$Bu] 303.1812, found 303.181.

6-(*tert*-Butyldimethylsilyloxy)hexanoic acid (**22**) [21]: A solution of **21** (3.25 g, 9.02 mmol) in methanol (130 mL) and THF (44 mL) was mixed with a solution of K_2CO_3 (4.40 g, 31.8 mmol, 3.5 equiv) in water (44 mL) and stirred for 1 h at RT. The solution was concentrated to one quarter of its original volume under reduced pressure, diluted with brine (130 mL) and acidified with a 1 M $KHSO_4$ solution to pH 4–5. The solution was extracted with ether (100 mL), the organic layer dried over $MgSO_4$, and the solvent removed under reduced pressure to give acid **22** (2.01 g, 90%) as a colourless oil. IR (film): $\tilde{\nu}_{max}$ = 3038 (m), 2932 (s), 2859 (s), 1712 (s), 1473 (m), 1256 (s), 1102 (s), 837 (s), 776 (s) cm^{-1}; UV/Vis (CH_3CN): λ_{max} (lgε) = 198 nm (2.7), 218 nm (1.9); ^1H NMR (400 MHz, $CDCl_3$): δ = 3.59 (t, ^3J = 6.4 Hz, 2H, H-6), 2.34 (t, ^3J = 7.5 Hz, 2H, H-2), 1.68–1.60 (m, 2H), 1.56–1.49 (m, 2H), 1.41–1.33 (m, 2H, H-3, H-4, H-5), 0.87 (s, 9H, Si*t*Bu), 0.03 (s, 6H, Si$(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.09 (s), 62.90 (t), 34.05 (t), 32.37 (t), 25.93 (q), 25.31 (t), 24.46 (t), 18.32 (s), −5.33 (q); MS (70 eV, EI): *m/z* (%): 360 (0.2) [M^+], 345 (7), 303 (87), 287 (18), 189 (19), 171 (24), 147 (100), 133 (14), 117 (10), 97 (17), 75 (85) [$HOSi(CH_3)_2^+$], 69 (26); HRMS (EI): calcd for $C_9H_{17}O_3Si$ [$M^+ - t$Bu] 189.0947, found 189.094.

6-(*tert*-Butyldimethylsilyloxy)hexanoyl chloride (**23**): A solution of acid **22** (500 mg, 2.03 mmol) in benzene (4 mL) was mixed with $SOCl_2$ (362 mg, 3.04 mmol, 1.5 equiv) and refluxed for 2 h. The mixture was cooled to RT, and the solvent removed under reduced pressure. In order to remove excess $SOCl_2$ from the mixture, benzene (5 mL) was added and the solvent removed again under reduced pressure to give acid chloride **23** (494 mg, 92%). The product was used directly without further purification.

3-[6-(*tert*-Butyldimethylsilyloxy)hexanoyl]-(*S*)-4-isopropyloxazolidin-2-one (**7**): To a solution of (4*S*)-4-isopropyl-2-oxazolidinone (**24**) [22] (755 mg, 5.85 mmol) in THF (8 mL) at −78 °C was added a solution of *n*BuLi (1.6 M in hexane; 4.0 mL, 6.43 mmol, 1.1 equiv). Within 2 min a solution of acid chloride **23** (1.703 g, 6.43 mmol, 1.1 equiv) in THF (7 mL) was added at −78 °C. The mixture was warmed to RT and, after addition of a 1 M solution of K_2CO_3 (11 mL), stirred for 15 min. The mixture was extracted with CH_2Cl_2 (30 mL), the organic layer dried over $MgSO_4$, and the solvent removed under reduced pressure. The crude product was purified by flash chromatography (ether:pentane = 1:1) to give compound **7** (1.352 g, 65%) as a colourless oil. IR (film): $\tilde{\nu}_{max}$ = 2956 (s), 2932 (s), 2858 (s), 1785 (s), 1705 (s), 1472 (m), 1388 (s), 1252 (s), 1206 (s), 1101 (s), 837 (s), 776 (m) cm^{-1}; UV/Vis (CH_3CN): λ_{max} (lgε) = 204 nm (3.9); ^1H NMR (400 MHz, $CDCl_3$): δ = 4.44–4.39 (m, 1H, H-4), 4.26–4.16 (m, 2H, H-5), 3.58 (t, ^3J = 6.5 Hz, 2H, H-6′), 3.00–2.93 (m, 1H), 2.87–2.80 (m, 1H, H-2′), 2.37–2.32 (m, 1H, C4-CH), 1.69–1.61 (m, 2H), 1.56–1.50 (m, 2H), 1.49–1.35 (m, 2H, H-3′, H-4′, H-5′), 0.89 (d, ^3J = 7.2 Hz, 3H, C4-CH–CH_3), 0.86 (s, 9H, Si*t*Bu), 0.84 (d, ^3J = 6.9 Hz, 3H, C4-CH–CH_3'), 0.01 (s, 6H, Si$(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.22 (s), 154.02 (s), 63.26 (t), 62.94 (t), 58.32 (d), 35.47 (t), 32.52 (t), 28.32 (d), 25.92 (q), 25.36 (t), 24.18 (t), 18.29 (s), 17.92 (q), 14.61 (q), −5.34 (q); MS (70 eV, EI): *m/z* (%): 357 (0.06) [M^+], 342 (3) [$M^+ - CH_3$], 300 (86) [$M^+ - t$Bu], 229 (15), 186 (25), 171 (62), 129 (19), 91 (100); HRMS (EI): calcd for $C_{14}H_{26}NO_4$ [$M^\bullet - t$Bu] 300.1631, found 300.163.

(2*S*)-3-[6-(*tert*-Butyldimethylsilyloxy)-2-methylhexanoyl]-(4*S*)-4-isopropyloxazolidin-2-one (**25**): A solution of NaHMDS (1.0 M in THF; 1.23 mL, 1.23 mmol, 1.1 equiv) was cooled to −78 °C, and a precooled solution (0 °C) of oxazolidinone **7** (400 mg, 1.12 mmol) in THF (3.5 mL) was added. The reaction mixture was stirred for 30 min at −78 °C, and a solution of MeI (793 mg, 5.59 mmol, 5 equiv) in THF (2 mL) was added. After 4 h of stirring at −78 °C, the mixture was quenched with a saturated solution of NH_4Cl (30 mL) and extracted with ether (40 mL). The organic layer was dried over $MgSO_4$, and the solvent removed under reduced pressure. The crude product (15:1 ratio of diastereomers) was purified by flash chromatography (ether:pentane = 1:2) to give pure **25** (328 mg, 82%) as a colourless oil. IR (film): $\tilde{\nu}_{max}$ = 2958 (s), 2933 (s), 2859 (m), 1784 (s), 1702 (s), 1463 (m), 1386 (s), 1242 (m), 1205 (s), 1098 (s), 837 (m), 776 (m) cm^{-1}; UV/Vis (CH_3CN): λ_{max} (lgε) = 204 nm (4.0); ^1H NMR (400 MHz, $CDCl_3$): δ = 4.43–4.39 (m, 1H, H-4), 4.25–4.15 (m, 2H, H-5), 3.73–3.68 (m, 1H, H-2′), 3.58–3.54 (m, 2H, H-6′), 2.35–2.30 (m, 1H, C4-CH), 1.72–1.68 (m, 1H), 1.50–1.26 (m, 5H, H-3′, H-4′, H-5′), 1.17 (d, ^3J = 6.9 Hz, 3H, C2′-CH_3), 0.88 (d, ^3J = 7.0 Hz, 3H, C4-CH–CH_3), 0.86–0.84 (m, 3H, C4-CH–CH_3'), 0.85 (s, 9H, Si*t*Bu), 0.01 (s, 6H, Si$(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.13 (s), 153.60 (s), 63.13 (t), 62.95 (t), 58.38 (d), 37.63 (d), 32.83 (t), 32.78 (t), 28.37 (d), 25.92 (q), 23.50 (t), 18.29 (s), 17.89 (q), 17.76 (q), 14.63 (q), −5.33 (q); MS (70 eV, EI): *m/z* (%): 371 (0.18) [M^+], 356 (3) [$M^+ - CH_3$], 314 (100) [$M^+ - t$Bu], 243 (16), 186 (76), 130 (14), 75 (23) [$HOSi(CH_3)_2^+$]; HRMS (EI) calcd for $C_{16}H_{31}NO_4Si$ [$M^+ - t$Bu] 314.1788, found 314.178.

(*S*)-6-(*tert*-Butyldimethylsilyloxy)-2-methylhexane-1-ol (**26**): A slurry of LAH (1 M in ether; 452 μL, 0.452 mmol, 1 equiv) was added over 40 min by syringe pump to a cooled solution (0 °C) of compound **25** (168 mg, 0.45 mmol) in ether (3 mL). The mixture was quenched by addition of water (17 μL), 15% aqeous NaOH (17 μL) and water (52 μL). The mixture was filtered through a short plug and purified by flash chromatography (ether:pentane = 1:1) to give alcohol **26** (94 mg, 84%) as a colourless oil; $[\alpha]_D^{20}$ = −7.4 (*c* = 1.0, $CHCl_3$); IR (film): $\tilde{\nu}_{max}$ = 3348 (s), 2955 (s), 2931 (s), 2859 (s), 1472 (s), 1388 (w), 1256 (m), 1101 (s), 836 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.59 (t, ^3J = 6.4 Hz, 2H, H-6), 3.44 (ddd, J = 10.4, 6.5, 5.8 Hz, 2H, H-1), 1.62–0.98 (m, 7H, H-2, H-3, H-4, H-5), 0.90 (d, ^3J = 6.8 Hz, 3H, C2-CH_3), 0.87 (s, 9H, Si*t*Bu), 0.03 (s, 6H, Si$(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 68.25 (t), 63.12 (t), 35.72 (d), 33.03 (t), 32.84 (t), 25.94 (q), 23.13 (t), 18.34 (s), 16.51 (q), −5.29 (q); MS (70 eV, EI): *m/z* (%): 247 (0.7) [$M^+ + H$], 189 (6) [$M^+ - t$Bu], 143 (6), 115 (9), 105 (27), 97 (70), 75 (57) [$HOSi(CH_3)_2^+$], 69 (34), 55 (100); HRMS (EI): calcd for $C_{13}H_{30}O_2Si$ [$M^+ - t$Bu] 189.1311, found 189.131. Anal. calcd for $C_{13}H_{30}O_2Si$ (246.46): C 63.35%; H 12.27%. Found: C 62.98%; H 12.23%.

(*S*)-6-(*tert*-Butyldimethylsilyloxy)-2-methylhexanal (**4**): A solution of oxalyl chloride (64 mg, 0.505 mmol, 1.4 equiv) in CH_2Cl_2 (2 mL) was cooled to −78 °C and DMSO (79 mg, 1.01 mmol, 2.8 equiv) was added. After 5 min a solution of alcohol **26** (89 mg, 0.361 mmol) in CH_2Cl_2 (1 mL) was added. The mixture was stirred for 30 min at −78 °C, and NEt_3 (161 mg, 1.59 mmol, 4.4 equiv) was added. The mixture was stirred for an additional hour at −30 °C. The reaction mixture was diluted with pentane (5.2 mL) and washed with a 1 M aqueous solution of $NaHSO_4$ (3.4 mL) and with water (3 × 3.4 mL). The organic layer was dried over $MgSO_4$, and the solvent removed under reduced pressure. The crude product was purified by flash chromatography (ether:pentane = 1:2) to give aldehyde **4** (77 mg, 87%) as a colourless oil; $[\alpha]_D^{20}$ = +13.5 (*c* = 1.0, $CHCl_3$); IR (film): $\tilde{\nu}_{max}$ = 2956 (s), 2932 (s), 2859 (s), 2709 (w), 1730 (s), 1463 (w), 1256 (m), 1100 (s), 837 (s), 776 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 9.60 (d, ^3J = 2.0 Hz, 1H, H-1), 3.59 (t, ^3J = 6.4 Hz, 2H, H-6), 2.35–2.30 (m, 1H, H-2), 1.74–1.67 (m, 1H), 1.55–1.34 (m, 5H, H-3, H-4, H-5), 1.08 (d, ^3J = 7.2 Hz, 3H, C2-CH_3), 0.87 (s, 9H, Si*t*Bu), 0.02 (s, 6H, Si$(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.24 (d), 62.81 (t), 46.30 (d), 32.73 (t), 30.25 (t), 25.93 (q), 23.25 (t), 18.33 (s), 13.25 (q), −5.32 (q); MS (70 eV, EI): *m/z* (%): 245 (1.1) [$M^+ + H$], 243 (1.0) [$M^+ - H$], 227 (5), 203 (38), 185 (100), 143 (12), 131 (7), 101 (8), 83 (26), 75 (62) [$HOSi(CH_3)_2^+$], 55 (22).

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1-(*tert*-Butyldimethylsilyloxy)-4-methylpent-4-en-3-ol (27): To a suspension of Mg (700 mg, 28.8 mmol, 1.3 equiv) in THF (1.5 mL) was added 2-bromopropene (0.2 mL, 2.3 mmol, 0.1 equiv). After the reaction had started a solution of 2-bromopropene (2.5 mL, 28.9 mmol, 1.3 equiv) in THF (10 mL) was slowly added under ice-cooling until all the magnesium was dissolved. A solution of **5** (4.136 g, 22.0 mmol) in THF (10 mL) was added, and the mixture stirred for 20 h at RT. The mixture was poured into a saturated aqueous solution of NH_4Cl (200 mL) and stirred for 10 min. The mixture was extracted four times with ether (50 mL), and the combined organic layers were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude product purified by flash chromatography (ether:pentane = 1:6) to give **27** (4.462 g, 88%) as a colourless oil. IR (Film): $\tilde{\nu}_{max}$ = 3425 (br s), 3088 (w), 2956 (vs), 2930 (vs), 2886 (s), 2859 (s), 1652 (w), 1473 (m), 1389 (m), 1256 (s), 1098 (vs), 939 (m), 899 (m), 836 (vs), 777 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.01 (m, 1H, H-5), 4.84 (m, 1H, H'-5), 4.24 (m, 1H, H-3), 3.86 (ddd, J = 10.1, 5.8, 4.6 Hz, 1H, H-1), 3.78 (ddd, J = 10.1, 7.3, 4.6 Hz, 1H, H'-1), 3.34 (d, ^3J = 3.1 Hz, 1H, OH), 1.78–1.72 (m, 3H, C4-CH_3), 0.89 (s, 9H, Si*t*Bu), 0.07, 0.06 (2 s, 6H, Si-CH_3 and Si-CH_3'); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.10 (s), 110.39 (t), 75.21 (d), 62.17 (t), 36.79 (t), 25.89 (q), 18.41 (q), 18.17 (s), −5.49 (q), −5.53 (q); MS (PCI,NH_3): m/z (%) = 248 (3) $[M+NH_4^+]$, 231 (94) $[M+H^+]$, 213 (100) $[M^+ - OH]$, 132 (5) [TBDMSO + H^+], 92 (9); Anal. calcd for $C_{12}H_{26}O_2Si$ (230.43): C 62.55%; H 11.37%. Found: C 62.28%; H 11.32%.

(*S*)-1-(*tert*-Butyldimethylsilyloxy)-4-methylpent-4-en-3-ol (11): To a solution of **27** (800 mg, 3.47 mmol) and (−)-diisopropyltartrate (244 mg, 1.04 mmol, 0.3 equiv) in CH_2Cl_2 (14 mL) were added powdered and freshly activated molecular sieves 4 Å (250 mg). As internal GC standard *n*-decane (140 µL) was added. The mixture was cooled to −20 °C. Titanium(IV) isopropylate (197 mg, 0.694 mmol, 0.2 equiv) was added with stirring. After 30 min an aliquot of ca. 4 drops was removed, mixed with ether (0.15 mL) at 0 °C and quenched into an aqueous solution of $FeSO_4$ and citric acid to provide a GC t_0 sample. The reaction mixture was then treated with a solution of *tert*-butyl hydroperoxide (3M in isooctane; 1.07 mL, 2.43 mmol, 0.7 equiv). It was stirred at −22 °C and worked up after 50% conversion (46 h) by quenching with 10 mL of an aqueous solution containing 3.3 g of $FeSO_4 \cdot 7H_2O$ and 1.1 g of citric acid monohydrate. The mixture was stirred vigorously without cooling for 30 min, extracted three times with CH_2Cl_2 (30 mL) and washed with brine (50 mL). The combinded organic layers were dried over $MgSO_4$. The crude product was purified by flash chromatography (ether:pentane = 1:6) to yield **11** (274 mg, 46%) as a colourless oil. The enantiomeric excess (*ee*) was determined by analysis of the (+)-Mosher ester of **11**. $[\alpha]_D^{20}$ = −4.6 (*c* = 1, $CHCl_3$); 80% *ee*. The absolute configuration of **11** was determined by the method of Mosher [14,15].

(*S*)-3-Benzyloxy-1-(*tert*-butyldimethylsilyloxy)-4-methyl-4-pentene (28): Benzyl bromide (4.15 mL, 34.9 mmol, 25 equiv) was added at 0 °C to a suspension of potassium hydride (35% in mineral oil; 192 mg, 1.67 mmol, 1.2 equiv) in THF (4.2 mL). Alcohol **11** (322 mg, 1.40 mmol) and tetra-*n*-butylammonium iodide (8 mg, 21 µmol, 0.015 equiv) in THF (1 mL) were added with stirring. After 15 min the mixture was warmed to RT and stirred for an additional 41 h. The reaction mixture was quenched with an aqueous saturated solution of NH_4Cl (22 mL), extracted twice with ether (30 mL), washed with brine (30 mL), and dried over $MgSO_4$. The solvent and excess benzyl bromide were removed under reduced pressure, and the crude product was purified by flash chromatography (ether:petroleum ether = 1:80) to give **28** (297 mg, 66%) as a colourless oil. IR (Film): $\tilde{\nu}_{max}$ = 3070 (w), 3033 (w), 2955 (vs), 9292 (vs), 2884 (s), 2858 (vs), 1650 (w), 1472 (m), 1389 (m), 1361 (m), 1256 (s), 1096 (vs), 939 (m), 902 (m), 835 (vs), 776 (s), 733 (m), 697 (s) cm^{-1}; UV/Vis (CH_3CN): λ_{max} (lgε) = 210 nm (sh, 1.9); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.21 (m, 5H, Ar-H), 4.94 (m, 2H, H-5 und H'-5), 4.47 (d, ^2J = 11.6 Hz, 1H, Ar-C*H*H'O), 4.23 (d, ^2J = 11.6 Hz, 1H, Ar-CH*H'*O), 3.92 (dd, ^3J = 8.1, 5.3 Hz, 1H, H-3), 3.68 (ddd, J = 10.1, 7.5, 6.0 Hz, 1H, H-1), 3.62 (ddd, J = 10.1, 6.0, 6.0 Hz, 1H, H'-1), 1.90–1.82 (m, 1H, H-2), 1.71–1.64 (m, 1H, H'-2), 1.70 (m, 3H, C4-CH_3), 0.86 (s, 9H, Si*t*Bu), 0.02, 0.01 (2 s, 6H, Si-CH_3 and Si-CH_3'); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.70 (s), 138.87 (s), 128.33 (d), 127.78 (d), 127.40 (d), 113.54 (t), 80.03 (d), 70.07 (t), 59.71 (t), 37.18 (t), 25.97 (q), 18.30 (s), 16.75 (q), −5.28 (q), −5.31 (q); MS (EI): m/z (%) = 195 (23), 165 (21), 157 (7), 135 (8), 105 (6), 91 (100) [$C_7H_7^+$], 75 (14) [$C_2H_7OSi^+$], 57 (5) [tBu$^+$]; HRMS (NCI, NH_3): calcd for $C_{19}H_{32}O_2Si$ [$M - H^-$] 319.2093, found 319.209.

(*S*)-3-Benzyloxy-5-(*tert*-butyldimethylsilyloxy)-pentan-2-one (9): Alkene **28** (200 mg, 0.624 mmol) was added to a mixture of THF (8 mL) and water (8 mL). A mixture of OsO_4 (2.5% in *tert*-butanol; 127 mg, 12.5 µmol, 0.02 equiv) and THF (8 mL) was added. The mixture was stirred for 3 min, and $NaIO_4$ (400 mg, 1.87 mmol, 3.0 equiv) was added. After 22 h of stirring at RT, $NaIO_4$ (133 mg, 0.624 mmol, 1 equiv) was added. After being stirred for 40 h at RT, the reaction mixture was poured into ether (20 mL) and diluted with water (5 mL). The mixture was extracted twice with ether (20 mL), the combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (ether:pentane = 1:8) to give **9** (146 mg, 73%) as a colourless oil. IR (film): $\tilde{\nu}_{max}$ = 3065 (w), 3032 (w), 3008 (w), 2956 (vs), 2929 (vs), 2884 (s), 2857 (vs), 1718 (vs), 1498 (w), 1472 (m), 1420 (w), 1407 (w), 1390 (m), 1256 (s), 1098 (vs), 1028 (m), 1006 (w), 836 (s) cm^{-1}; UV/Vis (CH_3CN): λ_{max} (lgε) = 206 nm (sh, 2.9); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 5H, Ar-H), 4.58 (d, ^2J = 11.5 Hz, 1H, Ar-C*H*H'O), 4.44 (d, ^2J = 11.5 Hz, 1H, Ar-CH*H'*O), 3.98 (dd, ^3J = 7.8, 4.9 Hz, 1H, H-3), 3.74–3.71 (m, 2H, H-5), 2.18 (s, 3H, H-1), 1.93–1.81 (m, 2H, H-4), 0.87 (s, 9H, Si*t*Bu), 0.03 (2s, 6H, Si-CH_3 and Si-CH_3'); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.00 (s), 137.67 (s), 128.51 (d), 127.94 (d), 127.90 (d), 82.00 (d), 72.59 (t), 58.68 (t), 35.23 (t), 25.94 (q), 25.68 (q), 18.30 (s), −5.38 (q), −5.43 (q); MS (PCI, NH_3): m/z (%) = 340 (23) $[M+NH_4]^+$, 323 (100) $[M+H^+]$, 233 (4), 191 (14) [M^+ − TBDMSO], 108 (9), 91 (3) [$C_7H_7^+$]; HRMS (NCI, NH_3): calcd for $C_{18}H_{30}O_3Si$ [$M - H^-$] 321.1886, found 321.188.

4-Bromomethyl-2-methylthiazole (30): To a solution of **29** (484 mg, 3.75 mmol) in ether (8 mL) was added under stirring triphenyl phosphine (1.376 g, 5.24 mmol, 1.4 equiv) and tetrabromomethane (1.740 g, 5.24 mmol, 1.4 equiv). The mixture was stirred for 16 h at RT, filtered and washed with ether (30 mL). The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography (ether:pentane = 1:5) to yield **30** (401 mg, 56%) as a greenish yellow oil. IR (film): $\tilde{\nu}_{max}$ = 3465 (w), 3406 (w), 3106 (m), 3043 (s), 2979 (vs), 2847 (w), 1568 (w), 1487 (s), 1463 (m), 1375 (m), 1342 (s), 1231 (s), 1194 (m), 1139 (m), 845 (m), 747 (s), 614 (m) cm^{-1}; UV/Vis (CH_3CN): λ_{max} (lgε) = 216 nm (sh, 2.9), 240 nm (sh, 2.7); ^1H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.14 (s, 1H, H-5), 4.54 (s, 2H, C4-CH_2Br), 2.71 (s, 3H, C2-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.91 (s), 151.63 (s), 117.25 (d), 27.11 (t), 19.25 (q); MS (EI): m/z (%) = 191/193 (11/11) [M^+], 112 (100) [M^+ − Br], 71 (47), 69 (12), 45 (15) [HCS$^+$]; HRMS (EI): calcd for C_5H_6BrNS 190.9404, found 190.940.

Diethyl (2-methylthiazol-4-yl)methanephosphonate (10): A mixture of **30** (150 mg, 0.78 mmol) and triethyl phosphite (0.3 mL, 1.75 mmol, 2.2 equiv) was heated for 1.5 h at 160 °C. The reaction mixture was cooled and excess triethyl phosphite was removed under reduced pressure. The crude product was purified by flash chromatography (methanol:ether = 1:19) to give **10** (173 mg, 89%) as a colourless oil. IR (Film): $\tilde{\nu}_{max}$ = 3455 (s br), 2986 (s), 2927 (m), 2909 (m), 1655 (w); 1521 (m), 1444 (w), 1395 (w), 1323 (w), 1244 (s), 11187 (m), 1164 (m), 1053 (vs), 1026 (vs), 968 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.06 (d, ^4J(H,P) = 3.9 Hz, 1H, H-5), 4.09 (dq, ^3J(H,H) = 7.0 Hz, ^3J(H,P) = 7.8 Hz, 4H, PO-CH_2-CH_3), 3.35 (d, ^2J(H,P) = 21.4 Hz, 2H, P-CH_2-), 2.69 (s, 3H, C2-CH_3), 1.29 (t, ^3J(H,H) = 7.0 Hz, 6H, O-CH_2-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.44 (s), 145.96 (ds, ^2J(C,P) = 8.2 Hz), 115.67 (dd, ^3J(C,P) = 7.4 Hz), 62.19 (dt, 2C, ^2J(C,P) = 6.4 Hz), 29.35 (dt, ^1J(C,P) = 141 Hz), 19.05 (q), 16.35 (dq, 2C, ^3J(C,P) = 6.0 Hz); ^{31}P NMR (81 MHz, $CDCl_3$, H_3PO_4 ext.): δ = 26 (s); MS (70 eV, EI): m/z (%) = 249 (45) [M^+], 221 (6) [$M^+ - C_2H_4$], 204 (8) [M^+ − OEt], 176 (9), 175 (10), 152 (12), 140 (12), 126 (23), 113 (100) [$C_5H_7NS^+$], 112 (38) [$C_5H_6NS^+$], 81 (13), 71 (28), 45 (15).

(*S*,*E*)-3-Benzyloxy-1-(*tert*-butyldimethylsilyloxy)-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-ene (8): A solution of **10** (33 mg, 132 µmol) in THF (2 mL) was cooled to −78 °C, and *n*BuLi (15% in hexane; 78 µL, 125 µmol, 0.95 equiv) added. The mixture was stirred for 45 min. A solution of methyl ketone **9** (35 mg, 109 µmol) in THF (1 mL) was added at −78 °C. The reaction mixture was warmed slowly to RT, stirred for 40 h, quenched with a saturated solution of NH_4Cl (10 mL), extracted three times with ether (15 mL) and washed with brine (30 mL). The combined organic layers were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude product purified by flash chromatography (dichloromethane:pentane = 1:1) to give **4** (17 mg, 38%) as a colourless oil; $[\alpha]_D^{20}$ = −9.5 (*c* = 1.0, $CDCl_3$). IR (film): $\tilde{\nu}_{max}$ = 3064 (w), 3031 (w), 2955 (vs), 2928 (vs), 2883 (s), 2857 (s), 1506 (m), 1471 (m), 1463 (m), 1455 (m), 1388 (m), 1361 (w), 1256 (s), 1183 (m), 1094 (vs), 1028 (m), 940 (w), 835 (vs), 776 (s), 733 (m), 697 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.18 (m, 5H, Ar-H), 6.93 (s, 1H, H-5'), 6.49 (br s, 1H, H-5), 4.47 (d, ^2J = 11.8 Hz, 1H, Ar-C*H*H'O), 4.24 (d, ^2J = 11.8 Hz, 1H, Ar-CH*H'*O), 3.99 (dd, ^3J = 8.3, 5.0 Hz, 1H, H-3), 3.69 (ddd, J = 10.0, 7.7, 5.6 Hz, 1H, H-1), 3.62 (ddd, J = 10.0, 5.8, 5.8 Hz, 1H, H'-1), 2.67 (s, 3H, C2'-CH_3), 1.99 (d, ^4J = 1.2 Hz, 3H, C4-CH_3), 1.93–1.85 (m, 1H, H-2), 1.76–1.69 (m, 1H, H'-2), 0.83 (s, 9H, Si*t*Bu), −0.02 (2s, 6H, Si-CH_3 and Si-CH_3'); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.4 (s), 152.90 (s), 139.74 (s), 138.84 (s), 128.33 (d), 127.77 (d), 127.41 (d), 121.33 (d), 115.67 (d), 82.00 (d), 70.30 (t), 59.69 (t), 37.58 (t), 25.98 (q), 19.26 (q), 18.30 (s), 13.44 (q), −5.25 (q), −5.31 (q); MS (70 eV, EI): m/z (%) = 417 (9) [M^+], 360 (37) [M^+ − tBu], 326 (12) [$M^+ - C_7H_7$], 254 (15), 226 (13), 194 (2 165 (26), 140 (27), 91 (100) [$C_7H_7^+$], 89 (17), 73 (21), 57 (6) [tBu$^+$]; HRMS (EI): calcd for $C_{23}H_{35}NO_2SSi$ 417.2158, found 417.215. Anal. calcd for $C_{23}H_{35}NO_2SSi$ (417.69): C 66.15%; H 8.45%; N 3.36%; S 7.66%. Found: C 66.48%; H 8.44%; N 3.19%; S 7.73%.

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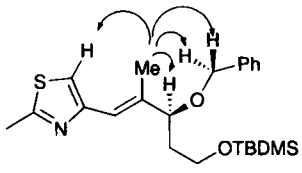
[20] The structure of **8** is unambiguously confirmed by the NOE relationships shown in Scheme 7 (see also ref. [1]).



Scheme 7.

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