Supporting Information

Synthetic Studies towards Leiodermatolide: Rapid Stereoselective Syntheses of Key Fragments

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Contents

Experimental details....................................................................................................... S2
Copies of NMR spectra................................................................................................. S15
Experimental section

**General.** Unless otherwise noted, all reactions were performed in oven-dried glassware. All solvents used in the reactions were purified before use. Dry diethyl ether (Et$_2$O), tetrahydrofuran, and toluene were distilled from sodium and benzophenone, whereas dry CH$_2$Cl$_2$, dimethylformamide, methanol, ethyl acetate, benzene, and triethylamine were distilled from CaH$_2$. Petroleum ether with a boiling range of 40–60 °C was used. Reactions were generally run under nitrogen atmosphere. All commercially available compounds (Acros, Aldrich, Fluka, Merck) were used without purification.

$^1$H and $^{13}$C NMR: Bruker Avance 400, spectra were recorded at 295 K in CDCl$_3$, benzene-$d_6$ or acetone-$d_6$; chemical shifts are calibrated to the residual proton and carbon resonance of the solvent. HRMS (FTyICR): Bruker Daltonic APEX 2 with electron spray ionization (ESI). Analytical LCyMS: HP 1100 Series connected with an ESI MS detector Agilent G1946C, positive mode with fragmentor voltage of 40 eV, column: Nucleosil 100-5, C-18 HD, 5 µm, 70 × 3 mm Machery Nagel, eluent: NaCl solution (5 mM)/acetonitrile, gradient: 0-10-15-17-20 min with 20-80-80-99-99% acetonitrile, flow: 0.5 mL min$^{-1}$. Flash chromatography: J. T. Baker silica gel 43–60 µm. Thin-layer chromatography Machery-Nagel Polygram Sil G/UV$_{254}$. Optical rotations: JASCO Polarimeter P-1020, sodium D line (589 nm), $c$ = g per 100 mL.

(2R,3R,4S,5S)-1-(tert-Butyldiphenylsilyloxy)-3,5-dimethyl-7-(trimethylsilyl)hept-6-yn-2,4-diol (8). A suspension of Pd(OAc)$_2$ (0.181 g, 0.810 mmol, 10 mol%) in abs. THF (50 mL) was cooled to –78 °C. Then finely powdered PPh$_3$ (0.212 g, 0.810 mmol, 10 mol%) was added under a slight flow of nitrogen. The resulting yellow solution was stirred for ca. 5 min. In separate flasks solutions of (R)-mesylate$^1$ 7 (3.58 g, 1.62 mmol) and aldehyde$^2$ 6 (2.90 g, 8.10 mmol) were prepared (both containing 2.0 mL of abs. THF). Then both were added dropwise to the solution of the prepared catalyst at the same time. The resulting yellow solution was stirred for 20 min at –78 °C before Et$_2$Zn (24.4 mL, 2.43 mmol, 1.0 M in hexane) was introduced over 30 min using a syringe pump. After complete addition, the reaction was allowed to warm to –10 °C (the cooling machine was switched off: in ca. 50 min the reaction reached –10 °C) and stirred for ca. 2 d (TLC and HPLC monitoring). During this time the color changed to dark brown. Work up was done by dropwise addition of sat. NH$_4$Cl solution (ca. 200 mL) directly to the reaction mixture. Then the mixture was warmed to room temperature, the layers were separated, and the aqueous phase extracted with Et$_2$O (3 × 50 mL). The combined organic layers were washed with saturated NaCl solution (100 mL) and dried over Na$_2$SO$_4$ containing norite decolorizing charcoal. After filtration and evaporation of the solvents the residue was purified by flash chromatography (petroleum ether/EtOAc, 10:1) to give diol 8 (2.38 g, 61%, 73% based on anti isomer) as a colorless oil. $R_f$ (petroleum ether/EtOAc, 5:1) 0.50; [α]$_D^{20}$ −1.4 (c 6.0, CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$): δ = 0.17 (s, 9H, TMS), 0.85 (d, $J$ = 7.1 Hz, 3H, 3-$CH_3$), 1.08 (s, 9H, C($CH_3$)$_3$), 1.14 (d, $J$ = 6.9 Hz, 3H, 5-$CH_3$), 1.88–1.91 (m, 1H, 3-$H$), 2.61–2.66 (m, 2H, 2 × $OH$), 3.05–3.07 (m, 1H, 5-$H$), 3.65–3.70 (m, 1H, 6-$H$), 3.76–3.81 (m, 1H, 7-$H$), 4.46 (s, 1H, $OH$).

1 For preparation, see: Marshall, J. A.; Chobanian, H. *Org. Synth.* 2005, 82, 43-54; *Org. Synth.* 2009, Coll. Vol. 11, 1056-1067. The ee value of (R)-mesylate 7 was determined to be >99%.

2 Smith, A. B.; Tomioka, T.; Risatti, C. A.; Sperry, J. B.; Sfouggatakis, C. *Org. Lett.* 2008, 10, 4359-4362. The aldehyde 6 was additionally purified by passing it through a short column of silica (petroleum ether/ethyl acetate, 9:1).
3H, 2H, CH2), 7.38–7.46 (m, 6H, mCH, pCH ar Ph), 7.67–7.69 m, 4H, oCH ar Ph). 13C NMR (100 MHz, CDCl3): δ = 0.1 (TMS), 9.2 (3-CH3), 17.2 (5-CH3), 19.2 (C(CH3)3), 26.8 (C(CH3)3), 32.0 (C-5), 35.8 (C-3), 65.9 (CH2), 73.9 (C-4), 74.4 (C-2), 87.2 (C≡CTMS), 108.5 (C≡CTMS), 127.7, 129.8, 133.1, 135.5 (C of SiPh2); HRMS (ESI): [M+Na]⁺ calcd for C28H42O3Si2Na 505.25647, found 505.25627.

(4S,5R,6R)-6-((tert-Butyldiphenylsilyloxy)methyl)-4-((S)-(trimethylsilyl)but-3-yn-2-yl)-2,2,5-trimethyl-1,3-dioxane (9). To a solution of diol 8 (2.88 g, 5.97 mmol) in a mixture of abs. CH2Cl2 (8.0 mL) and 2,2-dimethoxypropane (3.0 mL) was added CSA (0.139 g, 0.60 mmol, 10 mol%) and the resulting solution stirred for 24 h at ambient temperature. After this time, the reaction mixture was diluted with CH2Cl2 (30 mL) and shaken with NaHCO3 solution (10 mL). The aqueous layer was extracted with CH2Cl2 (15 mL). The combined organic layers were washed with saturated NaCl solution (50 mL), dried over Na2SO4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 40:1) to give acetonide 9 (2.32 g, 82%) as a colorless oil. Rf (petroleum ether/EtOAc, 20:1) 0.43; [α]D²⁰ +25.8 (c 8.2, CH2Cl2); 1H NMR (400 MHz, CDCl3): δ = 0.13 (s, 9H, TMS), 0.74 (d, J = 6.6 Hz, 3H, 5yCH3), 1.05–1.06 (m, 12H, C(CH3)3, 2’yCH3), 1.37 (s, 6H, 2’yCH3), 1.70 (app. ddq, J = 13.6, 11.2, 6.7 Hz, 1H, 5yH), 2.48 (app. dq, J = 10.7, 6.7 Hz, 1H, 2’yH), 3.37 (dd, J = 6.7, 3.9 Hz, 1H, 1H, 4-H), 3.58–3.66 (m, 2H, CH2, 6-H), 3.71–3.76 (m, 1H, CH2), 7.35–7.45 (m, 6H, mCH, pCH ar Ph), 7.68–7.70 (m, 4H, oCH ar Ph); 13C NMR (100 MHz, CDCl3): δ = 0.2 (TMS), 11.4 (5yCH3), 16.5 (2’yCH3), 19.3 (C(CH3)3), 23.7 (2-CH3), 24.9 (2-CH3), 26.8 (C(CH3)3), 28.1 (C-2’), 31.1 (C-5), 65.9 (CH2), 72.5 (C-6), 75.9 (C-4), 84.4 (C≡CTMS), 101.1 (C-2), 109.5 (C≡CTMS), 127.6, 129.6 × 2, 133.6, 133.8, 135.7 (C of SiPh2); HRMS (ESI): [M+Na]⁺ calcd for C31H46O3Si2Na 545.28777, found 545.288039.

(4S,5R,6R)-4-((S)-But-3-yn-2-yl)-6-((tert-butyldiphenylsilyloxy)-2,2,5-trimethyl-1,3-dioxane (10). A solution of acetonide 9 (0.082 g, 0.16 mmol) in dry MeOH (2.0 mL) and K2CO3 (0.044 g, 0.32 mmol) was stirred for 12 h at room temperature. Thereafter, the reaction mixture was poured into a separatory funnel containing saturated NH4Cl (5 mL) solution and Et2O (10 mL). The water layer was extracted with Et2O (2 × 20 mL). The combined organic layers were dried over MgSO4, filtered, and the solvent was evaporated to give alkyne 10 (0.069 g, 97%) as a colorless oil. The resulting compound was pure enough to be used for the next step. Rf (petroleum ether/EtOAc, 20:1) 0.40; [α]D²⁰ +19.8 (c 2.0, CH2Cl2); 1H NMR (400 MHz, CDCl3): δ = 0.76 (d, J = 6.8 Hz, 3H, 5-CH3), 1.06 (s, 9H, C(CH3)3), 1.09 (d, J = 6.8 Hz, 3H, 2’-CH3), 1.38 (s, 6H, 2 × 2-CH3), 1.73 (m, 1H, 3H, 4-CH3); 13C NMR (100 MHz, CDCl3): δ = 0.1 (TMS), 8.2 (3-CH3), 20.1 (5-CH3), 32.0 (C(CH3)3), 35.8 (C-3), 65.9 (CH2), 73.9 (C-4), 74.6 (C-2), 87.2 (C≡CTMS), 108.5 (C≡CTMS), 127.7, 129.8, 133.1, 135.5 (C of SiPh2); HRMS (ESI): [M+Na]⁺ calcd for C28H42O3Si2Na 505.25647, found 505.25627.
5-H), 2.03 (d, J = 2.0 Hz, 1H, 4'-H), 2.50 (m, 1H, 2'-H), 3.38 (dd, J = 6.7, 4.0 Hz, 1H, 4-H), 3.60–3.67 (m, 2H, 6-H, CH₂), 3.72–3.76 (m, 1H, CH₂), 7.35–7.44 (m, 6H, m-CH, p-CH ar Ph), 7.69–7.70 (m, 4H, o-CH ar Ph); ¹³C NMR (100 MHz, CDCl₃): δ = 11.5 (5-yCH₃), 16.7 (2-yCH₃), 19.3 (C(CH₃)₃), 23.7 (2-CH₃), 24.9 (2-CH₃), 26.8 (C(CH₃)₃), 27.1 (C-5), 34.1 (C-2'), 65.9 (CH₂), 68.6 (C-3'), 72.3 (C-6), 75.8 (C-4'), 101.1 (C-2), 127.6, 129.6 × 2, 133.6, 133.7, 135.7 (C of SiPh₂); HRMS (ESI): [M+Na]+ calcd for C₂₈H₃₈O₃SiNa 473.24824, found 473.24794.

1. (Cp)₂TiCH₂ClAl(Me)₂, THF, –40 °C (92%)
2. TBAF, THF 0 °C (85%)

(R)-3-((4R,5R,6R)-6-((tert-Butyldiphenylsilyloxy)methyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)butan-2-one (11). To a solution of alkyne 10 (2.06 g, 4.60 mmol) in acetone (49 mL), PPTS (1.68 g, 6.90 mmol), Hg(OAc)₂ (0.427 g, 1.38 mmol) and water (0.158 mL, 9.2 mmol) were added. The resulting clear solution was stirred for 18 h at ambient temperature. After this time the mixture was diluted with Et₂O (ca. 20 mL). White precipitates were removed by filtration through a short pad of silica gel and washed with Et₂O (2 × 20 mL). The filtrate was concentrated in vacuo, and residue purified by flash chromatography (petroleum ether/EtOAc, 10:1) to give methylketone 11 (1.62 g, 76%) as a colorless oil. Rf (petroleum ether/EtOAc, 10:1) 0.30; [α]D²⁰ +2.6 (c 2.7, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ = 0.77 (d, J = 6.9 Hz, 3H, 3-yCH₃), 0.89 (d, J = 6.9 Hz, 3H, 5-yCH₃), 1.05 (s, 9H, C(CH₃)₃), 1.24 (s, 3H, 2'-CH₃), 1.28 (s, 3H, 2'-CH₃), 1.72 (app. td, J = 6.9, 6.9, 4.5 Hz, 1H, 5'-H), 2.14 (s, 3H, 2-yCH₃), 2.67 (app. dq, J = 10.9, 6.9, 6.9, 6.9 Hz, 1H, 3-yH), 3.37 (app. td J = 6.7, 6.7, 4.1 Hz, 1H, 6'-H), 3.70 (m, 2H, CH₂OTBDPS), 3.83 (dd, J = 10.7, 4.3 Hz, 1H, 4'-H), 7.35–7.43 (m, 6H, m-CH, p-CH ar Ph), 7.68–7.69 (m, 4H, o-CH ar Ph); ¹³C NMR (100 MHz, CDCl₃): δ = 11.8 (5-yCH₃), 12.3 (3-CH₃), 19.3 (C(CH₃)₃), 23.6 (2'-CH₃), 24.9 (2'-CH₃), 26.8 (C(CH₃)₃), 30.2 (2-CH₃), 33.4 (C-5'), 46.6 (C-3), 65.9 (CH₂), 71.2 (C-6'), 75.8 (C-4'), 100.7 (C-2'), 127.6, 129.6 × 2, 133.6, 133.7, 135.7 (C of SiPh₂), 211.8 (C-2); HRMS (ESI): [M+Na]+ calcd for C₂₈H₄₀O₄SiNa 491.25881, found 491.258623.

((4R,5R,6S)-2,2,5-Trimethyl-6-((S)-3-methylbut-3-en-2-yl)-1,3-dioxan-4-yl)methanol (12). Tebbe olefination: A solution of ketone 11 (0.577 g, 1.2 mmol) in abs. THF (4.0 mL) was cooled to –40 °C. Then a solution of Tebbe reagent³ (6.70 mL, 4.8 mmol, 1.0M in toluene) was added dropwise. After complete addition (ca. 20 min), the cooling bath was removed and stirring continued for an additional h. The reaction mixture was diluted with Et₂O (10 mL), and then 1N NaOH (ca. 2 mL) was added very slowly, followed by anhydrous Na₂SO₄ (for drying).

resulting suspension was transferred onto a wet silica column (ca. 10 cm long) and eluted with a petroleum ether/EtOAc mixture (40:1) to give Tebbe olefination product (0.527 g, 92%, Rf 0.28, petroleum ether/EtOAc, 40:1) which was pure enough to be used for the next step.

**Deprotection:** To cooled solution (ice/salt bath) of foregoing silyl ether in abs. THF (5 mL) was added TBAF·3H2O in one portion followed by stirring of the resulting solution for 12 h. Saturated NH4Cl solution was added, the layers were separated, and the aqueous layer extracted with EtOAc (3 × 5 mL). The combined organics layers were washed with saturated NaCl solution, dried over MgSO4, filtered, and the filtrate concentrated in vacuo. The residue was purified via flash chromatography (petroleum ether/EtOAc, 5:1) to give alcohol 12 (0.30 g, 85%, 78% over 2 steps). Rf (petroleum ether/EtOAc, 5:1) 0.24; [α]D20 +16.3 (c 1.3, CH2Cl2); 1H NMR (400 MHz, CDCl3): δ = 0.89 (d, J = 2.3 Hz, 3H, 2'-CH3), 0.91 (d, J = 2.3 Hz, 3H, 5-CH3), 1.28 (s, 3H, 2-CH3), 1.32 (s, 3H, 2-CH3), 1.68 (s, 3H, 3'-CH3), 1.76 (m, 1H, 2'-H), 2.17 (br. s, 1H, OH), 2.29 (m, 1H, 5-H), 3.38 (ddd, J = 7.3, 7.3, 2.9 Hz, 1H, 4-H), 3.53–3.66 (m, 3H, CH2), 4.74 (d, J = 7.1 Hz, 3H, 5yCH3), 7.3, 7.3, 2.9 Hz, 1H, 4-H), 3.53–3.66 (m, 3H, CH2), 4.74 (d, J = 7.1 Hz, 3H, 5yCH3).

**13C NMR (100 MHz, CDCl3): δ = 11.8 (5yCH3), 16.0 (C-1''), 19.3 (3'-CH3), 23.9 (2-CH3), 25.1 (2-CH3), 33.5 (C-2''), 41.0 (C-5), 64.4 (CH2), 71.3 (C-4), 75.8 (C-6), 100.9 (C-2), 110.6 (C-4''), 148.1 (C-3''); HRMS (ESI): [M+Na]+ calcd for C13H24O3Na 251.32822, found 251.32856.

(4R,5R,6S)-4-Ethynyl-2,2,5-trimethyl-6-((S)-3-methylbut-3-en-2-yl)-1,3-dioxane (4). **Oxidation:** To a cooled solution (ice/salt bath) of alcohol 12 (0.290 g, 1.27 mmol) in abs. CH2Cl2 (2.0 mL) were added solid NaHCO3 (0.640 g, 7.62 mmol) and Dess-Martin periodinane (0.638 g, 1.52 mmol). After being stirred for 20 min, the cooling bath was removed and the mixture stirred for additional 2 h. After this time, the resulting suspension was transferred to a beaker, which already contained a mixture of saturated solutions of Na2S2O3 and NaHCO3 (1:1, 5 mL). This mixture was stirred for 10 min and then extracted with CH2Cl2 (3 × 10 mL). The combined organic layers were washed with saturated NaCl solution, dried with Na2SO4, filtered, and concentrated in vacuo to give the corresponding aldehyde and white solids, which were removed by filtration through a cotton plug and washing with Et2O (ca. 3 mL). Rf (petroleum ether/EtOAc, 5:1) 0.57.

**Alkyne formation:** To a solution of the foregoing aldehyde in MeOH (5 mL) was added diethyl-1-diazo-2-oxopropylphosphonate4 (0.620 g, 2.54 mmol) and K2CO3 (0.701 g, 5.01 mmol). The resulting yellow solution was stirred for 6 h at room temperature. The reaction mixture was diluted with Et2O (20 mL) and washed with an aqueous 5% NaHCO3 solution. The layers were separated and the organic layer was washed with saturated NaCl solution and dried over Na2SO4. After filtration and evaporation of the solvent, the residue was purified by flash chromatography (petroleum ether/EtOAc, 80:1) to give alkyne 4 (0.113 g, 40% over 2 steps) as a colorless oil. Rf (petroleum ether/EtOAc, 40:1) 0.52; [α]D20 +6.4 (c 1.1, CH2Cl2); 1H NMR (400 MHz, CDCl3): δ = 0.93 (d, J = 7.1 Hz, 3H, 2'-CH3), 1.07 (d, J = 7.1 Hz, 3H, 5-CH3), 1.33 (s, 3H, 2-CH3), 1.53 (s, 3H, 2-CH3), 1.70 (s, 3H, 3'-CH3), 1.92 (app. qt, J = 6.9, 6.9, 6.9, 3.7, 3.5 Hz, 1H, 5-H), 2.29 (app. dq, J = 10.3, 7.0, 7.0 Hz, 1H, 2'-H), 2.50 (d, J = 2.5 Hz, 1H, C=CH), 4.01 (dd, J = 10.4, 3.0 Hz, 1H, 6-H), 4.33 (dd, J = 3.9, 2.4 Hz, 1H, 4-H), 4.74 (d, J = 6.3 Hz, 2H, 4'-H); 13C NMR (100 MHz, CDCl3): δ = 11.3 (5-CH3), 15.6 (C-1''), 19.2 (C-4''), 23.2 (2-CH3), 28.2 (2-CH3), 36.5 (C-6), 41.8 (C-2''), 66.9 (C-4), 70.1 (C-5), 73.8 (C=CH), 84.4 (C=CH), 100.8 (C-2), 110.8 (C-4''), 147.9 (C-3''); HRMS (ESI): [M+Na]+ calcd for C14H22O2Na 245.31308, found 245.31315.

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(3S,4S,E)-7-(4-Methoxybenzyloxy)-3,5-dimethyl-1-(trimethylsilyl)hept-5-en-1-yn-4-ol (14). A suspension of Pd(OAc)$_2$ (0.072 g, 0.32 mmol, 5 mol%) in abs. THF (40 mL) was cooled to –78 °C. Then finely powdered PPh$_3$ (0.085 g, 0.32 mmol, 5 mol%) was added under a slight flow of nitrogen. The yellow solution was stirred for ca. 5 min. In separate flasks solutions of (R)-mesylate 7 (2.13 g, 9.67 mmol) and aldehyde 13 (1.42 g, 6.45 mmol) were prepared (both containing 1.5 mL of abs. THF). Then both solutions were added dropwise to a solution of prepared catalyst at the same time. The yellow solution was stirred for 20 min at –78 °C before Et$_2$Zn (19.3 mL, 19.3 mmol, 1.0 M in THF) was introduced over 30 min using syringe pump. After complete addition, the reaction mixture was allowed to warm to –5 °C (the cooling machine was switched off: within ca. 50 min the reaction mixture reached –5 °C) and stirred for ca. 1 d (TLC and HPLC monitoring). During this time the color changed to dark brown. For the work-up saturated NH$_4$Cl solution (ca. 100 mL) was added dropwise directly to the reaction mixture. After the mixture was warmed to room temperature, the layers were separated and the aqueous layer extracted with Et$_2$O (3 × 30 mL). The combined organic layers were washed with saturated NaCl solution and dried over Na$_2$SO$_4$ containing norite decolorizing charcoal. After filtration and evaporation of solvents, the residue was purified by flash chromatography (petroleum ether/EtOAc, 5:1) to give alcohol 14 (1.30 g, 58%) as a colorless oil. $[\alpha]_D^{20} +10.6$ (c 3.4, CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 0.15 (s, 9H, TMS), 1.10 (d, $J$ = 7.1 Hz, 3H, $3\gamma$CH$_3$), 1.61 (s, 3H, $5\gamma$CH$_3$), 2.67 (dq, $J$ = 7.2, 7.0 Hz, 1H, 3-H), 3.79–3.80 (m, 4H, 4-H, OCH$_3$), 4.05 (d, $J$ = 6.4 Hz, 2H, CH$_2$OPMB), 4.43 (s, 2H, CH$_2$PMP), 5.64 (dd, $J$ = 6.2, 6.2 Hz, 1H, 6-H), 6.86 (d, $J$ = 8.7 Hz, 2H, mCH ar Ph), 7.23 (d, $J$ = 8.7 Hz, 2H, oCH ar Ph); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 0.1 (TMS), 11.7 (5-CH$_3$), 17.3 (3-CH$_3$), 32.5 (C-3), 55.2 (OCH$_3$), 65.9 (C-7), 71.8 (CH$_2$PMP), 80.0 (C-4), 87.7 (C-1), 107.6 (C-2), 113.7 (oCH ar PMB), 125.6 (C-6), 129.3 (mCH ar PMB), 130.3 (CCH$_2$ ar PMB), 137.8 (C-5), 159.2 (COCH$_3$); HRMS (ESI): [M+K]$^+$ calcd for C$_{20}$H$_{34}$O$_3$SiK 385.15958, found 385.18061. According to Mosher analysis the ee of 14 was 96%.

4.2 mmol). The cooling bath was removed and the mixture allowed to stir overnight. Then it was diluted with water and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic extracts were washed with 1N HCl solution, saturated solutions of NaHCO₃ (20 mL) and NaCl (20 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. Flash chromatography (petroleum ether/EtOAc, 20:1) of the residue gave silyl ether 15 (1.04 g, 70%) as a colorless oil. Rₛ (petroleum ether/EtOAc, 10:1) 0.51; [α]₂⁰D +9.9 (c 9.1, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ = 0.01 (s, 3H, Si(CH₃)₂Bu), 0.09 (s, 3H, Si(CH₃)₂Bu), 0.12 (s, 9H, TMS), 0.89 (s, 9H, tBu), 1.00 (d, J = 7.1 Hz, 3H, 3-CH₃), 1.56 (s, 3H, 5-CH₃), 2.57 (m, 1H, 3-H), 3.80 (s, 3H, OCH₃), 3.88 (d, J = 8.1 Hz, 1H, 4-H), 4.03 (d, J = 4.0 Hz, 2H, CH₂OPMB), 4.41 (s, 2H, CH₂PMP), 5.52 (dd, J = 6.1, 6.1 Hz, 1H, 6-H), 6.87 (d, J = 8.7 Hz, 2H, mCH ar Ph), 7.24 (d, J = 8.7 Hz, 2H, oCH ar Ph); ¹³C NMR (100 MHz, CDCl₃): δ [ppm] = −4.8 (Si(CH₃)₂Bu), −4.7 (Si(CH₃)₂Bu), 0.2 (TMS), 11.4 (5-CH₃), 17.7 (3-CH₃), 18.3 (C(CH₃)₃), 25.9 (C(CH₃)₃), 32.8 (C-3), 55.3 (OCH₃), 65.9 (C-7), 71.5 (CH₂OPMB), 81.6 (C-4), 84.8 (C-1), 110.4 (C-2), 113.8 (oCH ar PMB), 125.0 (C-6), 129.3 (mCH ar PMB), 130.5 (CCH₂ ar PMB), 139.2 (C-5), 159.1 (COCH₃); HRMS (ESI): [M+H⁺] calcd for C₂₆H₄₅O₃SiNa 539.14489, found 539.145186.

1-(((2E,4S,5S,6Z)-4-tert-Butyldimethylsilyloxy-7-iodo-3,5-dimethylhepta-2,6-dienyloxy)methyl)-4-methoxybenzene (5).

Iodination: To a solution of silyl acetylene 15 (0.627 g, 1.36 mmol) in dry DMF (2 mL) were added NIS (0.470 g, 1.92 mmol) and AgNO₃ (0.054 g, 0.32 mmol). The resulting solution was protected from light and stirred for 5 h at ambient temperature. Then the reaction mixture was diluted with EtOAc (20 mL), washed with water (2 × 10 mL) and saturated NaCl solutions. The organic layer was dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 40:1) to give the corresponding iodoalkyne (0.767 g, 94%) as slightly yellow oil. It was introduced directly to the next step.

Z-selective reduction: To a solution of the foregoing iodoalkyne (0.767 g, 0.77% over 2 steps) in abs. MeOH (6.0 mL) were added pyridine (0.725 mL, 8.95 mmol) and KO₂CN=NCO₃K (1.49 g, 7.45 mmol) followed by the slow addition of acetic acid (0.5 mL, 8.95 mmol) over 6 h (syringe pump used). After this time, the mixture was diluted with EtOAc (20 mL), washed with water (2 × 20 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 40:1) to give Z-iodoalkene 5 (0.629 g, 82%, 77% over 2 steps) as a slightly yellow oil. Rₛ (petroleum ether/EtOAc, 20:1) 0.45; [α]₂⁰D −15.6 (c 2.3, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ = −0.01 (s, 3H, Si(CH₃)₂Bu), 0.04 (s, 3H, Si(CH₃)₂Bu), 0.90 (s, 9H, tBu), 0.94 (d, J = 6.9 Hz, 3H, 3-CH₃), 1.61 (s, 3H, 5-CH₃), 2.67–2.76 (m, 1H, 5-H), 3.80 (s, 3H, OCH₃), 3.91 (d, J = 5.1 Hz, 1H, 4-H), 4.06 (d, J = 6.4 Hz, 2H, CH₂OPMB), 4.42 (s, 2H, CH₂PMP), 5.54 (dd, J = 6.4, 6.4 Hz, 1H, 2-H), 6.07 (dd, J = 8.9, 7.4 Hz, 1H, 6-H), 6.15 (d, J = 7.4 Hz, 1H, 7-H), 6.88 (d, J = 8.7, 2H, mCH ar Ph), 7.26 (d, J = 8.7, 2H, oCH ar Ph); ¹³C NMR (100 MHz, CDCl₃): δ = −5.1 (Si(CH₃)₂Bu), −4.5 (Si(CH₃)₂Bu), 12.6 (5-CH₃), 16.6 (3-CH₃), 18.1 (C(CH₃)₃), 25.8 (C(CH₃)₃), 44.1 (C-5), 55.2 (OCH₃), 65.9 (C-1), 71.3 (CH₂PMP), 80.6 (C-7), 81.7 (C-4), 113.7 (oCH ar PMB), 123.5 (C-2), 129.2 (mCH ar PMB), 130.6 (CH₂ ar PMB), 139.8 (CH₂OPMB), 143.7 (C-6), 159.1 (COCH₃); HRMS (ESI): [M+Na⁺] calcd for C₂₆H₄₅O₃SiNa 539.14489, found 539.145186.
Methyl (3S)-3-hydroxypentanoate\(^6\) (16). A solution of benzeneruthenium(II) chloride (38.3 mg, 0.076 mmol, 0.0002 equiv) and (S)-BINAP (100.0 mg, 0.161 mmol, 0.0004 equiv) in dry degassed DMF (4.7 mL) was stirred for 10 min at 100 °C until a clear red-brown solution appears. The reaction mixture was cooled to 50 °C and the solvent was removed in high vacuum under vigorously stirring. The red-brown residue was dried in high vacuum for 1 h before a solution of methyl-3-oxo-pentanoate (47.0 g, 0.391 mol, 1.0 equiv) in degassed methanol (47 mL) was added. The resulting yellow-orange solution was degassed again three times and the mixture was set under hydrogen atmosphere (6 bar) at 100 °C for 16 h under vigorously stirring. The dark-orange solution was concentrated in vacuo. Purification of the residue by distillation (16 mbar, 70 °C) afforded 3-hydroxy ester 16 (44.8 g, 94%) as a colorless oil. \(\alpha_D\)\(^{20}\) +31.7 (c 1.0, CH\(_2\)Cl\(_2\)); ee = 99.4% (HewlletPackard HP6890/HP5973, column 25 m × 0.25 mm internal diameter, d\(_F\) = 0.13 \(\mu\)m, 30% Lipodex E (octakis-(2,6-di-n-pentyl-3-butyl-\(\gamma\)-cyclodextrin) in dimethyl polysiloxane PS 255 (70%); split injection, injection temperature = 230 °C, 50 °C, 8 min isotherm, 2.5 °C min\(^{-1}\) to 95 °C). \(\delta\) = 0.90 (t, \(J\) = 7.5 Hz, 3H, 5H), 1.35–1.55 (m, 2H, 4H), 2.35 (dd, \(J\) = 16.4, 9.1 Hz, 1H, 2-H), 2.46 (dd, \(J\) = 16.4, 3.0 Hz, 1H, 2-H), 2.65 (br s, 1H, 4-OH), 3.65 (s, 3H, OCH\(_3\)), 3.86 (m, 1H, 3-H); \(\delta\) = 10.2 (C-5), 29.8 (C-4), 41.1 (C-2), 52.1 (OCH\(_3\)), 69.7 (C-3), 173.9 (C-1); HRMS (ESI): calcd for C\(_6\)H\(_{12}\)O\(_3\)Na [M+Na\(^+\)] 155.06787, found 155.067993.

Methyl (2S,3S)-3-hydroxy-2-methylpentanoate\(^7\) (17). To a cooled (–10 °C) solution of diisopropylamine (46.8 mL, 0.333 mol, 2.2 equiv) in dry THF (60 mL) was added nBuLi (127 mL, 0.318 mmol, 2.5M in hexane, 2.1 equiv) dropwise under nitrogen atmosphere and the resulting yellow solution was stirred for 30 min at –10 °C. The mixture was cooled to –60 °C and a solution of hydroxy ester 16 (20.0 g, 151 mmol, 1.0 equiv) in dry THF (60 mL) was added dropwise. The reaction was stirred at –30 °C for 1 h, and was then cooled to –80 °C before HMPA (30 mL) was added and stirred for 2 h. The reaction mixture was allowed to warm to room temperature overnight. The mixture was poured into precooled HCl solution (1M, 300 mL). After separation of the layers, the aqueous phase was extracted with Et\(_2\)O (3 × 300 mL). The combined organic layers were washed with saturated NaCl solution (30 mL), dried over MgSO\(_4\), filtered and concentrated in vacuo. Purification by flash chromatography (petroleum ether/diethylthether, 3:1) afforded 2-methyl-3-hydroxy ester 17 (15.3 g, 70%) as a colorless oil. \(\alpha_D\) (petroleum ether/ethyl acetate, 3:1) 0.46; \([\alpha]_D^{20}\) +8.2 (c 1.0, CH\(_2\)Cl\(_2\)); dr = 85:15;


\[\text{MeO}_2\text{C} \quad \text{TBSCI, DMAP} \quad \text{imidazole, DMF} \quad \text{MeO}_2\text{C} \quad \text{OTBS}\]

Methyl (2S,3S)-3-(tert-butyldimethylsilyloxy)-2-methylpentanoate\(^7\) (18). To a cooled (0 °C) solution of 2-methyl-3-hydroxy ester 17 (14.60 g, 100 mmol, 1.0 equiv) in dry DMF (200 mL) were added TBDMS chloride (22.6 g, 150 mmol, 1.5 equiv), DMAP (244 mg, 2.0 mmol, 0.02 equiv) and imidazole (20.4 g, 300 mmol, 3.0 equiv) under nitrogen atmosphere. After stirring for 16 h at ambient temperature, saturated NaCl solution (200 mL) and Et\(_2\)O (200 mL) were added. After separation of the layers, the aqueous phase was extracted with Et\(_2\)O (3 × 300 mL). The combined organic layers were washed with saturated NaCl solution (150 mL), dried over MgSO\(_4\), filtered and concentrated in vacuo. Purification by flash chromatography (petroleum ether/Et\(_2\)O, 30:1) afforded 2-methyl-3-silyloxy ester 18 (24.3 g, 93%) as a colorless oil. R\(_f\) (petroleum ether/ethyl acetate, 15:1) 0.16; \([\alpha]_D^{20} +31.5\) (c 1.0, CH\(_2\)Cl\(_2\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 0.00\) (s, 3H, Si(CH\(_3\))\(_2\), 0.03 (s, 3H, Si(CH\(_3\))\(_2\), 0.85 (t, J = 7.2 Hz, 3H, 5-H), 0.85 (s, 9H, C(CH\(_3\))\(_3\)), 1.04 (d, J = 7.1 Hz, 3H, 2-CH\(_3\)), 1.38–1.52 (m, 1H, 4-H), 2.57–2.68 (m, 1H, 2-H), 3.63 (s, 3H, OCH\(_3\)), 3.85–3.92 (m, 1H, 3-H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 4.5\) (Si(CH\(_3\))\(_3\)), 4.7 (Si(CH\(_3\))\(_3\)), 8.3 (C-5), 12.2 (2-CH\(_3\)), 18.0 (C(CH\(_3\))\(_3\)), 25.7 (C(CH\(_3\))\(_3\)), 25.7 (C-4), 44.8 (C-2), 51.4 (OCH\(_3\)), 74.3 (C-3), 175.6 (C-1); HRMS (ESI): calcd for C\(_{13}\)H\(_{28}\)O\(_3\)SiNa [M+Na]\(^+\) 283.16999, found 283.169711.

\[\text{MeO}_2\text{C} \quad \text{MeONHMe-HCl} \quad \text{iPrMgCl, THF} \quad (88\%) \quad \text{MeO}_2\text{C} \quad \text{OTBS}\]

3-[(tert-Butyl(dimethyl)silyl)oxy]-N-methoxy-N,2-dimethylpentanamide (19). To a cooled (−10 °C) suspension of N,O-dimethylhydroxymine hydrochloride (13.12 g, 134.5 mmol, 2.0 equiv) in dry THF (250 mL) was added isopropyl magnesium bromide (134.5 mL, 269 mmol, 2.0 equiv) dropwise under nitrogen atmosphere and the mixture was stirred for 15 min at −10 °C. Then a solution of 2-methyl-3-siloxy ester 18 (14.0 g, 53.8 mmol, 1.0 equiv) in dry THF (250 mL) was added and the yellow solution was allowed to warm to room temperature over 2 h, before saturated NH\(_4\)Cl solution (200 mL) and Et\(_2\)O (200 mL) were added. After separation of the layers, the aqueous phase was extracted with Et\(_2\)O (3 × 250 mL). The combined organic layers were dried over MgSO\(_4\), filtered and concentrated in vacuo. Purification by flash chromatography (petroleum ether/Et\(_2\)O, 7:1) afforded Weinreb amide 19 (13.5 g, 88%) as a colorless oil. R\(_f\) (petroleum ether/Et\(_2\)O, 5:1) 0.26; \([\alpha]_D^{20} +37.6\) (c 1.0, CH\(_2\)Cl\(_2\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 0.01\) (s, 3H, Si(CH\(_3\))\(_2\)), 0.04 (s, 3H, Si(CH\(_3\))\(_2\)), 0.84 (s, 9H, C(CH\(_3\))\(_3\)), 0.88 (t, J = 7.3 Hz, 3H, 5-H), 0.98 (d, J = 7.1 Hz 3H, 2-CH\(_3\)), 1.52–1.59 (m, 2H, 4-H), 3.04–3.16 (m, 1H, 2-H), 3.15 (s, 3H, NCH\(_3\)), 3.69 (s, 3H, NOCH\(_3\)), 3.96 (dt, J = 8.7, 4.2 Hz, 1H, 3-H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 4.8\) (Si(CH\(_3\))\(_3\)), 7.3 (C-5), 13.2 (2-CH\(_3\)), 18.1 (NCH\(_3\)), 25.6 (C-4), 25.8 (C(CH\(_3\))\(_3\)), 31.9 (C(CH\(_3\))\(_3\)), 39.4 (C-2), 61.3
(NOCH), 73.8 (C-3), 176.3 (C-1); HRMS (ESI): calcd for C\textsubscript{14}H\textsubscript{31}NO\textsubscript{3}SiNa [M+Na]\textsuperscript{+} 312.19654, found 312.196636.

\[ \text{19} \xrightarrow{\text{vinylMgCl, THF}} \text{OTBS} \quad \text{10}^\circ \text{C to } 0^\circ \text{C} \quad (90\%) \]

**To a cooled (0 °C) solution of Weinreb amide 19 (9.11 g, 31.5 mmol, 1.0 equiv) in dry THF (180 mL) was added vinyl magnesium bromide (112.5 mL, 78.8 mmol, 2.5 equiv) dropwise under nitrogen atmosphere and the mixture was stirred for 15 min at −10 °C. After stirring of the mixture for 2 h at 0 °C, saturated NH\textsubscript{4}Cl solution (250 mL) and Et\textsubscript{2}O (250 mL) were added. After separation of the layers, the aqueous phase was extracted with Et\textsubscript{2}O (3 × 300 mL). The combined organic layers were washed with saturated NaCl solution (200 mL), dried over MgSO\textsubscript{4}, filtered and concentrated in vacuo. Purification by flash chromatography (petroleum ether/ethyl acetate, 50:1) afforded enone 20 (7.26 g, 90%) as a colorless oil. R\textsubscript{f} (petroleum ether/Et\textsubscript{2}O, 40:1) 0.23; [α]\textsubscript{D}\textsuperscript{20} +61.8 (c 1.0, CH\textsubscript{2}Cl\textsubscript{2}); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ = 0.03 (s, 3H, Si(CH\textsubscript{3})\textsubscript{2}), 0.04 (s, 3H, Si(CH\textsubscript{3})\textsubscript{2}), 0.83 (s, 9H, C(CH\textsubscript{3})\textsubscript{3}), 0.88 (t, J = 7.3 Hz, 3H, 7\textsubscript{y}H), 0.99 (d, J = 7.1 Hz, 3H, 4\textsubscript{y}CH\textsubscript{3}), 1.39–1.56 (m, 2H, 6\textsubscript{y}H), 3.00–3.10 (m, 1H, 3\textsubscript{y}H), 3.88–3.96 (m, 1H, 5\textsubscript{y}H), 5.74 (dd, J = 10.6, 1.3 Hz, 1H, 1\textsubscript{y}H), 6.22 (dd, J = 17.4, 1.3 Hz, 1-H), 6.43 (dd, J = 17.6, 10.5 Hz, 1H, 2-H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): δ = 4.92 (Si(CH\textsubscript{3})\textsubscript{2}), 4.5 (Si(CH\textsubscript{3})\textsubscript{2}), 4.92 (Si(CH\textsubscript{3})\textsubscript{2}), 7.9 (Cy7), 12.4 (4\textsubscript{y}CH\textsubscript{3}), 18.0 (C(CH\textsubscript{3})\textsubscript{3}), 25.8 (C(CH\textsubscript{3})\textsubscript{3}), 26.1 (C-6), 47.7 (C-4), 74.4 (C-5), 127.8 (C-1), 136.6 (C-2), 203.7 (C-3); HRMS (ESI): calcd for C\textsubscript{14}H\textsubscript{28}O\textsubscript{2}SiNa [M+Na]\textsuperscript{+} 179.17563, found 179.17538.

**To a solution of enone 20 (5.56 g, 21.7 mmol, 1.0 equiv) in distilled benzyl alcohol (6.74 mL, 65 mmol, 3.0 equiv) was added 1,1,3,3-tetramethylguanidine (1.36 g, 11 mmol, 0.5 equiv) under nitrogen atmosphere. After stirring for 2 h at ambient temperature, water (200 mL) and Et\textsubscript{2}O (200 mL) were added. After separation of the layers, the aqueous phase was extracted with Et\textsubscript{2}O (3 × 250 mL). The combined organic layers were washed with saturated NaCl solution (200 mL), dried over MgSO\textsubscript{4}, filtered and concentrated in vacuo. Purification by flash chromatography (petroleum ether/ethyl acetate, 15:1) afforded benzyloxyketone 21 (5.9 g, 76%) as a colorless oil. R\textsubscript{f} (petroleum ether/Et\textsubscript{2}O, 20:1) 0.32; [α]\textsubscript{D}\textsuperscript{20} +41.8 (c 1.0, CH\textsubscript{2}Cl\textsubscript{2}); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ = 0.03 (s, 3H, Si(CH\textsubscript{3})\textsubscript{2}), 0.04 (s, 3H, Si(CH\textsubscript{3})\textsubscript{2}), 0.85 (s, 9H, C(CH\textsubscript{3})\textsubscript{3}), 0.88 (t, J = 7.3 Hz, 3H, 7\textsubscript{y}H), 0.99 (d, J = 7.1 Hz, 3H, 4\textsubscript{y}CH\textsubscript{3}), 1.34–1.54 (m, 2H, 6\textsubscript{y}H), 2.70–2.86 (m, 3H, 2\textsubscript{y}H, 4\textsubscript{y}H), 3.66–3.78 (m, 2H, 1\textsubscript{y}H), 3.86–3.93 (m, 1H, 5\textsubscript{y}H), 4.49 (d, J = 1.8 Hz, 2H, CH\textsubscript{2}Ph), 7.23–7.37 (m, 5H, ar-H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): δ = 4.6 (Si(CH\textsubscript{3})\textsubscript{2}), 4.92 (Si(CH\textsubscript{3})\textsubscript{2}), 7.9 (Cy7), 12.4 (4-CH\textsubscript{3}), 18.0 (C(CH\textsubscript{3})\textsubscript{3}), 25.8 (C(CH\textsubscript{3})\textsubscript{3}), 26.1 (C-6), 43.7 (C-2), 50.7 (C-4), 65.2 (C-1), 73.2 (CH\textsubscript{2}Ph), 74.4 (Cy-C-5), 127.7 (ar-C), 128.3 (ar-C), 212.1 (C-3); HRMS (ESI): calcd for C\textsubscript{21}H\textsubscript{36}O\textsubscript{3}SiNa [M+Na]\textsuperscript{+} 387.23314, found 387.23341.
(4S,5S)-1-(Benzyloxy)-5-hydroxy-4-methylheptan-3-one (22). To a cooled (0 °C) solution of silyl ether 21 (2.66 g, 7.30 mmol, 1.0 equiv) in methanol (60 mL) was added conc. HCl solution (3 mL). After stirring for 2 h at ambient temperature, water (150 mL) and Et$_2$O (150 mL) were added. After separation of the layers, the aqueous phase was extracted with Et$_2$O (3 × 200 mL). The combined organic layers were washed with saturated NaCl solution (200 mL), dried over MgSO$_4$, filtered and concentrated in vacuo. Purification by flash chromatography (petroleum ether/ethyl acetate, 3:2) afforded hydroxyketone 22 (1.68 g, 89%) as a colorless oil. $R_f$ (petroleum ether/Et$_2$O, 1:1) 0.21; $[\alpha]_D^{20} +4.20$ (c 1.0, CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 0.96$ (t, $J = 7.5$ Hz, 3H, 7H), 1.07 (d, $J = 7.1$ Hz, 3H, 4H), 1.27–1.41 (m, 1H, 6H), 1.44–1.58 (m, 1H, 6H), 2.44 (br s, 1H, 5H), 2.56–2.71 (m, 2H, 2H), 2.72–2.82 (m, 1H, 1H), 3.52–3.60 (m, 1H, 5H), 3.63–3.76 (m, 2H, 1H), 4.44 (s, 2H, CH$_2$Ph), 7.17–7.33 (m, 5H, aryH); $^13$C NMR (100 MHz, CDCl$_3$): $\delta = 9.7$ (7C), 13.6 (4CH$_3$), 27.3 (Cy6), 42.4 (Cy2), 51.8 (Cy4), 65.3 (Cy1), 73.3 (Cy5), 74.9 (CH$_2$Ph), 127.7 (ar-H), 138.0 (ar-C), 214.2 (3-C); HRMS (ESI): calecd for C$_{15}$H$_{22}$O$_3$Na [M+Na]$^+$ 273.14612, found 273.145971.

(1S,2S)-5-(Benzyloxy)-1-ethyl-2-methyl-3-oxopentyl bromoacetate (23). To a cooled (−78 °C) solution of hydroxyketone 22 (1.50 g, 6.0 mmol, 1.0 equiv), pyridine (0.72 mL, 9.0 mmol, 1.5 equiv) and DMAP (73.3 mg, 0.60 mmol, 0.1 equiv) in dry CH$_2$Cl$_2$ was added bromoacetyl chloride (0.95 mL, 9.0 mmol, 1.5 equiv) dropwise under nitrogen atmosphere and the mixture was stirred for 15 min at −78 °C. Then the mixture was allowed to warm to −10 °C within 1 h, before water (100 mL) and CH$_2$Cl$_2$ (100 mL) were added. After separation of the layers, the aqueous phase was extracted with CH$_2$Cl$_2$ (3 × 100 mL). The combined organic layers were washed with saturated NaCl solution (50 mL), dried over MgSO$_4$, filtered and concentrated in vacuo. Purification by flash chromatography (petroleum ether/Et$_2$O, 1:1) afforded bromoacetate 23 (2.22 g, 100%) as a colorless oil. $R_f$ (petroleum ether/Et$_2$O, 3:2) 0.47; $[\alpha]_D^{20} +12.2$ (c 1.0, CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 0.94$ (t, $J = 7.1$ Hz, 3H, 2H), 1.00 (d, $J = 7.3$ Hz, 3H, 2H), 1.48–1.62 (m, 1H, 1H, 1H), 1.62–1.75 (m, 1H, 1H), 2.77 (dt, $J = 6.1$, 2.9 Hz, 1H, 4H), 2.87–2.97 (m, 1H, 2H), 3.66–3.80 (m, 4H, 5H), 4.48 (s, 2H, CH$_2$Ph), 5.13 (dt, $J = 7.7$, 3.5 Hz, 1H, 1H), 7.23–7.37 (m, 5H, ar-H); $^13$C NMR (100 MHz, CDCl$_3$): $\delta = 8.9$ (C-2'), 11.9 (2-CH$_3$), 23.6 (C-1'), 25.7 (CH$_2$Br), 42.1 (C-4), 49.2 (C-2), 65.0 (C-5), 73.3 (CH$_2$Ph), 77.6 (C-1), 127.7 (ar-C), 128.4 (ar-C), 138.0 (ar-C), 166.6 (CO$_2$), 209.6 (C-3); HRMS (ESI): calecd for C$_{17}$H$_{23}$BrO$_4$Na [M+Na]$^+$ 393.06719, found 393.067568.
(4S,5S,6S)-4-(2-(Benzyloxy)ethyl)-6-ethyl-4-hydroxy-5-methyl-tetrahydropyran-2-one (24). To a cooled (0 °C) black suspension of samarium (4.96 g, 33.0 mmol, 5.5 equiv) in dry THF (70 mL) was added diiodomethane (2.41 mL, 30.0 mmol, 5.0 equiv) dropwise under nitrogen atmosphere and the mixture was stirred for 2.5 h at ambient temperature. The green-blue suspension was cooled to −78 °C and a solution of bromide 23 (2.22 g, 6.0 mmol, 1.0 equiv) in dry THF (30 mL) was added dropwise. The resulting yellow-green suspension was stirred for 15 min at −78 °C, before saturated NaHCO₃ solution (150 mL) and Et₂O (200 mL) were added. After separation of the layers, the aqueous phase was extracted with Et₂O (3 × 200 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. Purification by flash chromatography (petroleum ether/ Et₂O, 1:4) afforded lactone 24 (1.48 g, 88%) as a colorless oil. Rₛ (petroleum ether/Et₂O, 1:2) 0.16; [α]Dⁿ²⁰ −7.5 (c 1.0, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ = 0.93 (t, J = 6.5 Hz, 2H, CH₂CH₃), 0.95 (d, J = 7.0 Hz, 3H, 5-CH₃), 1.38–1.58 (m, 3H, 3H, 5-CH₃), 1.80 (dq, J = 14.7, 7.5 Hz, 2H, CH₂CH₃), 2.14 (dt, J = 15.1, 10.6 Hz, 1H, 1'-H'), 2.37 (d, J = 17.2 Hz, 1H, 3-H), 2.73 (d, J = 16.9 Hz, 1H, 3-H), 3.58–3.75 (m, 2H, 2'-H'), 4.25 (dt, J = 10.4, 7.3 Hz, 1H, 6-H), 4.46 (d, J = 4.6 Hz, 2H, CH₂Ph), 7.18–7.34 (m, 5H, aryH); ¹³C NMR (100 MHz, CDCl₃): δ = 8.5 (CH₃), 9.8 (CH₃), 25.7 (CH₂CH₃), 37.7 (C-1’), 40.7 (C-5), 42.2 (C-3), 66.2 (C-2’), 71.3 (CH₂Ph), 73.7 (C-4), 82.1 (C-6), 127.8 (ar-C), 128.1 (ar-C), 128.6 (ar-C), 137.0 (ar-C), 170.8 (C-2); HRMS (ESI): calcd for C₁₇H₂₃O₂Na [M+Na]⁺ 315.15668, found 315.156699.

To a cooled (0 °C) solution of lactone 24 (1.2 g, 3.42 mmol, 1.0 equiv) in dry CH₂Cl₂ (20 mL) was added imidazole (1.17 g, 17.1 mmol, 5.0 equiv), DMAP (0.21 g, 1.71 mmol, 0.5 equiv) and TMSCl (0.93 g, 8.56 mmol, 2.5 equiv) before saturated NH₄Cl solution (100 mL) and Et₂O (100 mL) were added. After separation of the layers, the aqueous phase was extracted with Et₂O (3 × 100 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. Purification by flash chromatography (petroleum ether/ Et₂O, 1:2) afforded protected lactone 25 (1.48 g, 88%) as a colorless oil. Rₛ (petroleum ether/Et₂O, 1:2) 0.25; [α]Dⁿ²⁰ −7.5 (c 1.0, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ = 0.11 (s, 9H, Si(CH₃)₃), 0.86 (d, J = 6.6 Hz, 3H, 5-CH₃), 0.98 (t, J = 7.3 Hz, 3H, CH₂CH₃), 1.46–1.67 (m, 2H, CH₂CH₃, 5-H), 1.76–1.86 (m, 1H, CH₂CH₃), 1.86–1.94 (m, 1H, 1'-H'), 1.97–2.07 (m, 1H, 1'-H'), 2.60 (d, J = 17.4 Hz, 1H, 3-H), 2.76 (d, J = 16.7 Hz, 1H, 3-H), 3.40–3.52 (m, 2H, 2'-H'), 4.13–4.22 (m, 1H, 6-H), 4.46 (d, J = 6.8 Hz, 2H, CH₂Ph), 7.21–7.39 (m, 5H, ar-H); ¹³C NMR (100 MHz, CDCl₃): δ = 2.3 (Si(CH₃)₃), 8.7 (CH₃), 10.2 (CH₃), 25.8 (CH₂CH₃), 38.4 (C-5), 39.1 (C-1’), 43.5 (C-3), 66.0 (C-2’), 73.3 (CH₂Ph), 74.9 (C-4), 82.7 (C-6), 127.7 (ar-C), 127.8 (ar-C), 128.5 (ar-C), 137.7 (ar-C), 170.8 (C-2); HRMS (ESI): calcd for C₂₀H₃₂O₄SiNa [M+Na]⁺ 387.19621, found 387.195881.
To a solution of benzyl ether 25 (1.2 g, 3.30 mmol, 1.0 equiv) in dry THF (20 mL) was added a catalytic amount of palladium on charcoal (10% Pd/C). The black reaction mixture was stirred vigorously under a balloon of hydrogen at room temperature. After 2 h the reaction mixture was filtered through a pad of celite, the filter cake was washed with THF (total 200 mL) and the filtrate concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/Et₂O, 1:10) afforded primary alcohol 26 (0.72 g, 80%) as a colorless oil. 

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\alpha_D^{20} = -15.6 \ (c \ 1.0, \ CH_2Cl_2);
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\begin{align*}
^1H \text{ NMR (400 MHz, CDCl}_3\text{):} & \ \\
\delta &= 0.13 (s, 9H, Si(CH}_3)_3), 0.90 (d, J = 6.6 Hz, 3H, 5-CH(CH}_3)_2), 1.00 (t, J = 7.3 Hz, 3H, CH(CH}_3)_2), 1.48–1.72 (m, 2H, CH(CH}_3)_2, 5'-H), 1.77–1.89 (m, 2H, CH(CH}_3)_2, 1',H), 1.95–2.06 (m, 1H, 1'-H), 2.63 (d, J = 17.2 Hz, 1H, 3-H), 2.76 (d, J = 17.2, 1H, 3-H), 3.60–3.77 (m, 1H, 2'-H), 4.15–4.22 (m, 2H, 6'-H); \\
\end{align*}
\]

\[
13C \text{ NMR (100 MHz, CDCl}_3\text{):} & \\
\delta &= 2.3 (Si(CH}_3)_3), 8.8 (CH(CH}_3)_2), 10.2 (CH(CH}_3)_2), 25.8 (CH(CH}_3)_2), 39.0 (C-3), 41.8 (C-1'), 43.5 (C-5), 58.6 (C-2') \text{ ppm.}
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(4R,5S,6S)-6-Ethyl-5-methyl-4-(2-(1-phenyl-1H-tetrazol-5-ylthio)ethyl)-4-(trimethylsilyloxy)-tetrahydropyran-2-one (28). To a cooled (0 °C) solution of alcohol 26 (45.0 mg, 0.16 mmol, 1.0 equiv) in dry THF (3 mL) was added 1-phenyl-1H-tetrazole-5-thiol (27) (35.1 mg, 0.18 mmol, 1.2 equiv) and triphenylphosphine (172.2 mg, 0.66 mmol, 4.0 equiv) under nitrogen atmosphere followed by dropwise addition of N,N-diethyl azodicarboxylate (0.30 mL, 40% in toluene, 0.66 mmol, 4.0 equiv). The reaction mixture was stirred for 1 h at ambient temperature, before water (50 mL) and Et₂O (50 mL) were added. After separation of the layers, the aqueous phase was extracted with Et₂O (3 × 50 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. Purification by flash chromatography (petroleum ether/ethyl acetate, 5:2) afforded thioether 28 (65.6 mg, 92%) as a colorless oil. 

\[
\alpha_D^{20} = -14.5 \ (c \ 1.0, \ CH_2Cl_2);
\]

\[
\begin{align*}
^1H \text{ NMR (400 MHz, CDCl}_3\text{):} & \ \\
\delta &= 0.13 (s, 9H, Si(CH}_3)_3), 1.00 (d, J = 6.6 Hz, 3H, 5-CH(CH}_3)_2), 1.02 (t, J = 7.5 Hz, 3H, 2'-H), 1.51–1.64 (m, 1H, CH(CH}_3)_2), 1.65–1.76 (m, 1H, 5-H), 1.87 (dq, J = 14.8, 7.5 Hz, 1H, CH(CH}_3)_2), 2.03 (dt, J = 12.8, 4.6 Hz, 1H, 1'-H), 2.29 (dq, J = 12.9, 5.1 Hz, 1H, 1'-H), 2.68 (dd, J = 22.7, 17.2 Hz, 2H, 3-H), 3.16 (dt, J = 12.6, 4.6 Hz, 2'-H), 3.39 (dt, J = 12.5, 4.8, 1H, 2'-H), 4.16–4.24 (m, 1H, 6-H), 7.53–7.60 (m, 5H, ar-H); \\
\end{align*}
\]

\[
13C \text{ NMR (100 MHz, CDCl}_3\text{):} & \\
\delta &= 2.3 (Si(CH}_3)_3), 8.7 (CH(CH}_3)_2), 10.1 (CH(CH}_3)_2), 25.8 (CH(CH}_3)_2), 28.0 (C-2'), 39.1 (C-5), 39.6 (C-1'), 42.5 (C-3), 75.2 (C-4), 82.7 (C-6), 123.7 (ar-C), 130.0 (ar-C), 130.3 (ar-C), 133.5 (ar-C), 153.6 (ar-C), 170.0 (C-2); HRMS (ESI): calcd for C₂₀H₃₀N₄O₃SiNa [M+Na]⁺ 457.17056, found 457.17027.
(4R,5S,6S)-6-Ethyl-5-methyl-4-((2-(1-phenyl-1H-tetrazol-5-ylsulfonyl)ethyl)-4-(trimethylsilyloxy)-tetrahydropyran-2-one (29). To a cooled (0 °C) solution of thioether 28 (50.0 mg, 0.115 mmol, 1.0 equiv) in ethanol (0.8 mL) was added a solution of (NH₄)Mo₇O₂₄·4H₂O (61.0 mg, 0.035 mmol, 0.3 equiv) in H₂O₂ (0.08 mL, 30% in water, 20.0 equiv) dropwise. The reaction mixture was stirred for 2 h at ambient temperature, before water (50 mL) and Et₂O (50 mL) were added. After separation of the layers, the aqueous phase was extracted with Et₂O (3 × 50 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. Purification by flash chromatography (petroleum ether/ethyl acetate, 3:1) afforded sulfone 29 (52.0 mg, 97%) as a colorless oil. Rf (petroleum ether/ethyl acetate, 2:1) 0.49; [a]D²⁰ −16.9 (c 1.0, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ = 0.16 (s, 9H, Si(CH₃)₃), 0.98 (d, J = 6.8 Hz, 5-CH₃), 1.02 (t, J = 7.3 Hz, 2'-H), 1.52–1.70 (m, 2H, CH₂CH₃, 5-H), 1.88 (dq, J = 14.7, 7.5 Hz, 1H, CH₂CH₃), 2.18–2.33 (m, 2H, CH₂CH₃), 2.56 (d, J = 16.7 Hz, 1H, 3-H), 2.75 (d, J = 16.7 Hz, 1H, 3-H), 3.60–3.81 (m, 2H, 2'-H), 4.17 (dt, J = 10.0, 7.1 Hz, 1H, 6-H), 7.56–7.73 (m, 5H, ar-H); ¹³C NMR (100 MHz, CDCl₃): δ = 2.3 (Si(CH₃)₃), 8.7 (CH₃), 10.2 (CH₃), 25.7 (CH₂CH₃), 32.4 (C-1'), 40.0 (C-5), 42.5 (C-3), 52.0 (C-2'), 74.4 (C-4), 82.5 (C-6), 124.9 (ar-C), 129.8 (ar-C), 131.6 (ar-C), 132.8 (ar-C), 153.2 (ar-C), 169.2 (C-2); HRMS (ESI): calcd for C₁₇H₂₂N₄O₅SNa [M+Na]⁺ 417.12031, found 417.120664.
The image contains a 1H NMR spectrum of compound 25. The spectrum shows resonances at various ppm values, indicating the chemical shifts of different protons in the molecule. The compound structure is shown with the following labels:

- Me₃SiO
- O
- OBn
- Me
- 3
- SiO
- 25

The structure includes a carbon backbone with labeled positions 1'-2' and 4-6. The spectrum provides detailed information about the chemical environment of each proton, aiding in the identification and analysis of the compound's molecular properties.