

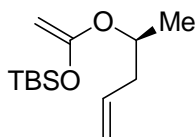
Concise Synthesis of the Bacterial DNA Primase Inhibitor (+)-Sch 642305

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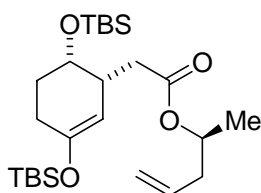
Supporting Information

General Methods. All reactions were carried out under an inert N₂ atmosphere in oven-dried glassware. Reactions were monitored by thin-layer chromatography (TLC) which was performed using Merck® silica gel 60 F₂₅₄ pre-coated plates (0.25 mm) and visualized by UV absorbance (254 or 366 nm), potassium permanganate, or anisaldehyde stain. Flash column chromatography was carried out with EcoChrom ICN SiliTech 32-63 D 60 Å silica gel using the indicated solvent system as eluent. Methylene chloride (CH₂Cl₂) was purified by passage over activated alumina. Tetrahydrofuran (THF) was distilled from benzophenone and sodium immediately prior to use. Benzene (PhH), diisopropylamine (*i*-Pr₂NH), triethylamine, and acetonitrile (CH₃CN) were distilled from CaH₂ immediately prior to use. *n*-Butyllithium was titrated with diphenylacetic acid prior to use. All other reagents and solvents were used without further purification from commercial sources. NMR spectra were measured on Bruker DRX-500, Av-500, AVQ-400, AVB-400 and Av-300 instruments, ¹H: 500 MHz, 400 MHz or 300 MHz and ¹³C:125 MHz or 100 MHz. ¹H chemical shifts are reported using residual undeuterated solvent as an internal standard (CHCl₃: 7.26 ppm, MeOH: 4.78 ppm). The abbreviations used for the multiplicity are: s = singlet, d = doublet, t = triplet. ¹³C chemical shifts are reported using the central peak of deuteriochloroform or deuteromethanol as an internal standard (77.2 and 49.0, respectively). HPLC purification was performed using a Dynamax Microsorb 60Si column (21 x 250mm, 8 μm, 60 Å) with isopropanol and hexanes. IR spectra were measured with a Genesis FT-IR or Nicolet FT-IR spectrometer by thin film on NaCl plates. Melting points were determined with an electrothermal apparatus and are uncorrected.

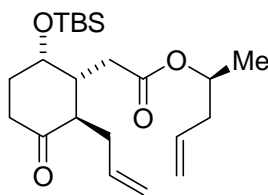


(-)-(S-Pent-4-en-2-yl)-(tert-butyldimethylsilyl)-ketenacetal (11). To a solution of LDA in THF (50 mL, 1.22 M) at -78°C, was added ester **10** (7.1 g, 55.4 mmol) dropwise over 15 min. The solution was stirred at the addition temperature for 50 min., HMPA (5.54 mL, 45.2 mmol) was added, and the reaction was stirred an additional 5 min. A solution of TBSCl in *n*-pentane (15 mL, 4.1 M) was added over 10 min. The solution was left to

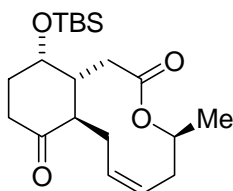
stir at -78°C for 1 h, was warmed to 0°C, and quenched with cold water (50 mL). The organics were extracted with n-pentane (3 x 50 mL), washed with brine (20 mL), dried over MgSO₄, and concentrated *in vacuo*. The crude liquid was purified via Kugelrohr distillation (130°C, 0.5 mm Hg) to provide **11** as a clear colorless liquid (9.5 g, 39.0 mmol, 70%): $[\alpha]_D^{25}$ -2.3 (*c* 1.1, CHCl₃); IR (NaCl) 2958, 2859, 1652, 1472, 1271 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 5.83-5.75 (m, 1H), 5.11-5.06 (m, 2H), 4.09 (m, 1H), 3.28 (d, 1H, *J* = 2.5 Hz), 3.11 (d, 1H, *J* = 2.0 Hz), 2.47-2.40 (m, 1H), 2.28-2.23 (m, 1H), 1.22 (d, 3H, *J* = 6.0 Hz), 0.93 (s, 9H), 0.17 (s, 6H); ¹³C NMR (CDCl₃, 125 MHz) δ 159.7, 134.3, 117.6, 73.0, 62.0, 40.4, 25.8, 18.9, 18.2, -4.3; HRMS (FAB⁺) calcd for C₁₃H₂₇O₂Si (M + H⁺): 243.1780, found: 243.1787.



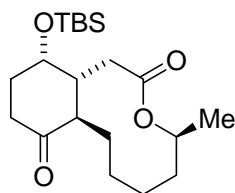
(-)-S-Pent-4-en-2-yl (1R,6S)[3,6-Bis(*tert*-butyldimethylsilyloxy)-2-cyclohexen-1-yl]acetate (12**).** To a solution of (**4**) (3.5 g, 15.5 mmol) and TBSOTf (0.2 mL, 0.87 mmol) in DCM at 0°C was added silyl ketene acetal **11** (5.63 g, 23.3 mmol) in DCM in one portion. The reaction was stirred for 15 min. then quenched by stirring with 2-pyridinol (0.08 mL, 0.87 mmol) for 15 min. The solution was warmed to room temperature then filtered over a plug of silica gel (deactivated with 1% TEA, eluted with 10% EtOAc in hexanes). The residue was concentrated *in vacuo* and purified flash silica column chromatography (deactivated with 1% TEA, eluted a gradient of hexanes to 1% EtOAc in hexanes) to provide **12** as a colorless oil as a 3.7:1 mixture of *syn* : *anti* stereoisomers (5.4 g, 11.5 mmol, 81%). The isomers could be separated only on an analytical scale by HPLC. Stereochemical assignments were based on NOE correlations. *Syn* isomer: $[\alpha]_D^{25}$ -20.2 (*c* 0.26, CHCl₃); IR (NaCl) 2957, 2930, 2858, 1737, 1667, 1640, 1472, 1463, 1379, 1260, 1181, 1098, 1015 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 5.80-5.71 (m, 1H), 5.10-5.05 (m, 2H), 4.96 (sextet, 1H, *J* = 6.2 Hz), 4.69 (d, 1H, *J* = 6.0 Hz), 3.97 (m, 1H), 2.71 (m, 1H), 2.62 (dd, 1H, *J* = 15.5, 5.5 Hz), 2.35 (dt, 1H, *J* = 14.0, 7.0 Hz), 2.26 (dt, 1H, *J* = 14.0, 6.9 Hz), 2.11 (dd, 1H, *J* = 15.5, 9.3 Hz), 2.15-2.09 (m, 1H), 2.01 (dt, 1H, *J* = 17.3, 6.8 Hz), 1.75 (quintet, 1H, *J* = 6.8 Hz), 1.66-1.61 (m, 1H), 1.22 (d, 3H, *J* = 6.0 Hz), 0.90 (s, 9H), 0.88 (s, 9H), 0.88-0.86 (m, 1H), 0.11 (s, 6H), 0.05 (d, 6H, *J* = 5.5 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 173.2, 150.7, 133.9, 117.8, 105.5, 70.0, 68.2, 40.5, 37.2, 36.7, 28.7, 27.3, 26.0, 25.8, 19.7, 18.3, 18.2, -4.2, -4.4, -4.4, -4.8 ; HRMS (FAB⁺) calcd for C₂₅H₄₉O₄Si₂ (M + H⁺): 469.3169, found: 469.3167.



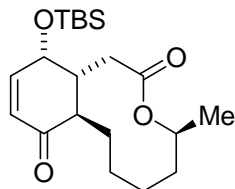
S-Pent-4-en-2-yl (1R,2R,6S)-[6-(*tert*-Butyldimethylsilyloxy)-2-(2-propenyl)-3-oxocyclohex-1-yl]acetate (3). A solution of silyl enol ether (mixture of C4-C5 isomers) **12** (3.52 g, 7.5 mmol) and allyl bromide (2.2 mL, 25.4 mmol) in dry THF (80 mL) was stirred for 20 min. over 4 Å MS. To the reaction solution at -35° C, was added TASf (2.350 g, 8.5 mmol, 2M in DMF) dropwise. The solution was stirred at the addition temperature for 30 min. then at 0° C for an additional 2 h. The reaction was diluted with H₂O (30 mL) then the organics were extracted with diethyl ether (3 x 30 mL), dried over MgSO₄, and concentrated *in vacuo*. The crude product was purified by flash silica column chromatography (20 : 1 hexanes : EtOAc) to afford **3** (mixture of inseparable 2.7:1 C4-C5 isomers) as a clear oil (1.65 g, 4.18 mmol, 56%) : IR (NaCl) 2929, 2856, 1727, 1700, 1650, 1250, 1080 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 5.80-5.70 (m, 2H), 5.11-4.94 (m, 5H), 4.179-4.17 (m, 0.73H), 4.15-4.11 (m, 0.27H), 2.70-1.99 (m, 11H), 1.86-1.83 (m, 0.74), 1.83-1.70 (m, 0.29H), 1.23-1.21 (m, 3H), 0.92 (s, 6.8H), 0.89 (s, 2.2H), 0.09 (s, 6H); ¹³C NMR (CDCl₃, 125 MHz) δ 211.1, 172.2, 135.9, 133.7, 118.0, 116.8, 70.5, 67.6, 48.7, 43.5, 40.4, 36.1, 34.2, 32.7, 30.5, 26.0, 19.5, 18.2, -4.2, -4.9; HRMS (FAB+) calcd for C₂₂H₃₉O₄Si (M + H⁺): 395.2618, found: 395.2627.



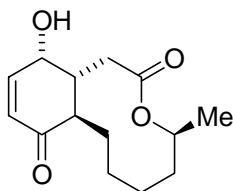
(-)-{(1R,2R,6S)-6-(*tert*-Butyldimethylsilyloxy)-2-[(*S*)-5-hydroxy-hex-2-enyl]-3-oxocyclohex-1-yl}acetic acid lactone (13). To a solution of diene **3** (206 mg, 0.52 mmol) in DCM (100 mL), was added Grubbs II catalyst. The reaction was refluxed for 4h, cooled and filtered through celite. Purification of the crude residue by flash silica column chromatography (20 : 1 hexanes : EtOAc) afforded **13** as a white solid (120 mg, 0.34 mmol, 63%): mp 76-78°C; [α]_D²⁵ -20.8 (c 0.40, CHCl₃); IR (NaCl) 2927, 2856, 1727, 1700, 1461, 1250, 1080 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 5.66-5.52 (m, 2H), 5.03 (m, 1H), 4.02 (m, 1H), 2.94 (bs, 1H), 2.80-2.63 (m, 3H), 2.44 (m, 3H), 2.29-2.24 (m, 1H), 2.14-2.00 (m, 2H), 1.89-1.79 (m, 2H), 1.22 (d, 3H, *J* = 6.9 Hz), 0.92 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 210.5, 172.9, 132.1, 123.8, 71.6, 68.9, 50.6, 43.0, 41.8, 35.1, 31.8, 29.4, 26.0, 24.2, 18.2, 18.0, -4.2, -4.7; HRMS (FAB+) calcd for C₂₀H₃₄LiO₄Si (M + Li⁺): 373.2386, found: 373.2396.



(-)-{(1R,2R,6S)-6-(tert-Butyldimethylsilyloxy)-2-[(S)-5-hydroxyhexyl]-3-oxocyclohex-1-yl}acetic acid lactone (14**).** To a solution of **13** (113 mg, 0.31 mmol) in EtOAc (10 mL) was added 5% Pd/C (100 mg, 0.048 mmol). The flask was purged with H₂ several times and was left to stir at room temperature under an atmosphere of H₂ for 2 h. The reaction mixture was filtered over celite and concentrated *in vacuo* to provided **14** as white needles (108 mg, 0.29 mmol, 95%): mp 100-101°C; $[\alpha]_D^{25}$ -22.2 (*c* 0.37, CHCl₃); IR (NaCl) 2955, 2857, 1724, 1700, 1462, 1253, 1079 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 5.06 (m, 1H), 4.02 (m, 1H), 2.67 (td, 1H, *J* = 14.5, 6.5 Hz), 2.58-2.45 (m, 4H), 2.20 (m, 1H), 2.10 (m, 1H), 2.01 (m, 2H), 1.85-1.79 (m, 3H), 1.36-1.25 (m, 3H), 1.25 (d, 3H, *J* = 7.0 Hz), 0.91 (s, 9H), 0.91 (m, 1H), 0.10 (s, 3H), 0.08 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 211.0, 171.8, 73.2, 71.1, 50.2, 41.0, 40.4, 35.3, 32.1, 29.5, 26.0, 23.3, 23.0, 21.7, 18.4, 18.2, -4.2, -4.7; HRMS (FAB+) calcd for C₂₀H₃₇O₄Si (*M* + H⁺): 369.2461, found: 369.2453.



(+)-O-(tert-Butyldimethylsilyl)Sch 642305 (15**).** To a solution of **14** (46.6 mg, 0.13 mmol) in dry THF (0.8 mL) at -78° C was added TESCl (24.1 mg, 0.16 mmol) in THF (0.2 mL). The reaction was stirred for 30 min. then loaded directly on a plug of silica gel eluting with 4 : 1 hexanes : EtOAc and concentrated *in vacuo*. The TES enol ether was redissolved in CH₃CN (5 mL) to which was added Pd(OAc)₂ (157 mg, 0.7 mmol). The reaction mixture stirred at room temperature for 24 hrs then was filtered through a plug of celite and concentrated. Purification of the crude residue by flash silica column chromatography (4 : 1 hexanes : EtOAc) afforded **15** as a white solid (28.1 mg, 0.08 mmol, 61%): $[\alpha]_D^{25}$ +52.1 (*c* 0.48, CHCl₃); IR (NaCl) 2955, 1725, 1679, 1462, 1251, 1085, 1034, 1006 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 6.85 (dd, 1H, *J* = 10.0, 5.6 Hz), 5.97 (d, 1H, *J* = 10.0 Hz), 5.10-5.08 (m, 1H), 4.22 (dd, 1H, *J* = 5.6, 3.2 Hz), 2.85-2.78 (m, 1H), 2.74-2.70 (m, 1H), 2.62-2.55 (m, 1H), 2.51-2.46 (m, 1H), 2.25-2.09 (m, 2H), 1.84-1.76 (m, 1H), 1.65-1.56 (m, 1H), 1.39-1.32 (m, 1H), 1.26 (d, 4H, *J* = 6.8 Hz), 0.87 (s, 9H), 0.11 (s, 3H), 0.07 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 200.6, 171.7, 146.9, 130.2, 73.3, 67.7, 46.7, 39.4, 37.5, 29.5, 25.9, 22.9, 21.7, 18.3, 18.2, -3.7, -4.6; HRMS (FAB+) calcd for C₂₀H₃₄LiO₄Si (*M* + Li⁺): 373.2386, found: 373.2389.



(+)-Sch 642305 (1). To a solution of TBS ether **15** (24 mg, 0.07 mmol) in THF (2 mL) at room temperature, was added a solution of TBAF (0.79 mL of a 1M sol. in THF, 0.79 mmol) and acetic acid (47 mg, 0.79 mmol). The reaction was stirred for 12 h then poured into saturated NH_4Cl (2 mL) and extracted with ether (3 x 4 mL). The organics were washed with NaHCO_3 sat., brine (3 mL), dried over MgSO_4 , and were concentrated *in vacuo*. The crude material was purified by flash silica column chromatography (2 : 1 hexanes : EtOAc) to afford **1** as a white solid (12 mg, 0.05 mmol, 73%): $[\alpha]_D^{25} +76.1$ (*c* 0.92, MeOH); IR (NaCl) 3423, 2917, 2850, 1720, 1676, 1460, 1386, 1279, 1249, 1202, 1076, 1061 cm^{-1} ; ^1H NMR (MeOD, 500 MHz) δ 7.04 (dd, 1H, $J = 10.0, 5.5$ Hz), 5.97 (d, 1H, $J = 10.0$ Hz), 5.06 (m, 1H), 4.23 (dd, 1H, $J = 5.5, 3.5$ Hz), 2.83 (tdd, 1H, $J = 11.5, 3.5, 2.4$ Hz), 2.69 (dd, 1H, $J = 17.0, 2.5$ Hz), 2.66 (dt, 1H, $J = 11.5, 4.0$ Hz), 2.54 (dd, 1H, $J = 17.0, 11.5$ Hz), 2.21-2.10 (m, 2H), 1.89-1.82 (m, 1H), 1.61-1.53 (m, 1H), 1.44-1.21 (m, 3H), 1.29 (d, 3H, $J = 6.5$ Hz), 1.10 (ddd, 1H, $J = 14.8, 11.0, 3.5$ Hz); ^{13}C NMR (MeOD, 125 MHz) δ 202.3, 173.7, 149.4, 130.6, 74.7, 67.1, 47.7, 39.7, 37.8, 30.7, 24.2, 24.1, 22.6, 18.6; HRMS (FAB+) calcd for $\text{C}_{14}\text{H}_{21}\text{O}_4$ ($\text{M} + \text{H}^+$): 253.1440, found: 253.1443.

