

Synthesis of Pyrrolidine C-Nucleosides via *Heck* Reaction

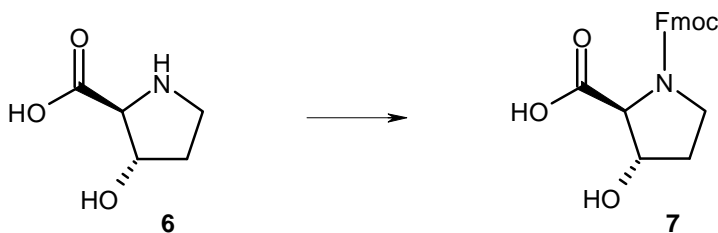
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Supporting Information

General. All experiments were carried out under Ar. Solvents were distilled prior to use. All moisture sensitive reactions were performed in oven-dried glassware. External bath temperatures were used to record all reaction temperatures. Spectral data (NMR, MS) were measured with standard equipment and are indicated in standard format. Flash chromatography (FC) was performed using silica gel with an average size of 40 μm . Thin-layer chromatography (TLC) was performed on silica gel plates (0.25 mm).

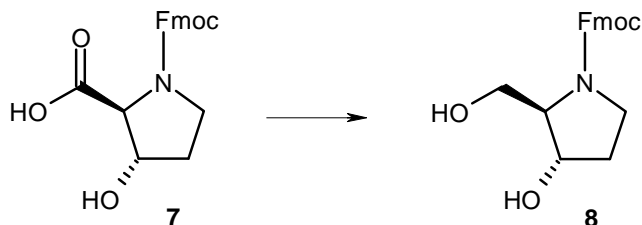
trans-N-(9-Fluorenylmethoxycarbonyl)-3-hydroxy-L-proline (**7**)



A soln. of 9-fluorenylmethyl chloroformate (11.0 g, 42.5 mmol) in dioxane (150 ml) was added to a suspension of *trans*-3-hydroxy-L-proline (**6**, 5.5 g, 41.9 mmol) in dioxane (300 ml) and 5 % aq. NaHCO_3 soln. (150 ml) at 0°C . After 2 h, the cooling bath was removed and stirring was continued for 7 h. Most of the dioxane was evaporated, the aq. layer washed twice with Et_2O , acidified with 2 N aq. HCl soln. to pH 3.0 and extracted with AcOEt (3 x). The combined org. layers were dried (MgSO_4) and evaporated to give 14.7 g (41.6 mmol, 98 %) of **7** as a white powder.

^1H -NMR (300 MHz, d_6 -DMSO): 1.80-1.98 (m, 2 H, $\text{H}_2\text{-C}(4)$); 3.48-3.54 (m, 2 H, $\text{H}_2\text{-C}(5)$); 4.05-4.37 (m, 5 H, H-C(2), H-C(3), Fmoc CH, Fmoc CH_2); 5.52, 5.59 (2 br s, 1 H, HO); 7.29-7.44 (m, 4 H, arom. Fmoc); 7.62-7.69 (m, 2 H, arom. Fmoc); 7.88-7.91 (m, 2 H, arom. Fmoc); 12.91 (br s, 1 H, HO_2C). ^{13}C -NMR (75 MHz, d_6 -DMSO): 34.38, 35.37 (2 t, C(4)); 47.33, 47.97 (2 t, C(5)); 49.61 (d, Fmoc CH); 69.70, 69.98 (2 t, Fmoc CH_2); 70.91, 71.18 (2 d, C(3)); 75.81, 76.91 (2 d, C(2)); 123.15 (d, arom. Fmoc); 128.14, 128.24 (2 d, arom. Fmoc); 130.16 (d, arom. Fmoc); 130.71 (d, arom. Fmoc); 143.66, 143.75 (2 s, arom. Fmoc); 146.69, 146.82 (2 s, arom. Fmoc); 157.03, 157.21 (2 s, NCO_2); 174.79, 175.09 (2 s, CO_2H). MS (FAB $^+$): 354 (26, $[\text{M} + \text{H}]^+$), 338 (24), 309 (100). HR-MS (FAB $^+$, $[\text{M} + \text{H}]^+$): 354.13574 (calc. 354.13415).

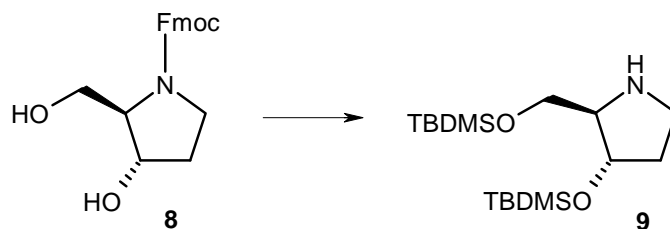
N-(9-Fluorenylmethoxycarbonyl)-(3*S*)-hydroxy-(2*R*)-(hydroxymethyl)-pyrrolidine (**8**)



To a soln. of **7** (13.0 g, 36.8 mmol) in dry THF (130 ml) were added $\text{BH}_3 \cdot (\text{CH}_3)_2\text{S}$ (2 M in THF, 96.2 ml, 192.4 mmol). The soln. was heated at reflux for 2 h, cooled to rt and quenched by addition of MeOH. The soln. was evaporated, the residue dissolved in AcOEt, washed with H_2O , dried (MgSO_4) and evaporated. FC (toluene/THF 1:1 to 5:6 gave 12.1 g (35.7 mmol, 97 %) of **8** as a white solid.

TLC (toluene/THF 1:1): R_f 0.24. $^1\text{H-NMR}$ (300 MHz, d_6 -DMSO): 1.66-1.75 (m, 1 H, H-C(4)); 1.94-2.07 (m, 1 H, H-C(4)); 3.08-3.20 (m, 1 H, $\text{CH}_2\text{-OH}$); 3.28-3.57 (m, 4 H, H-C(2), $\text{H}_2\text{-C}(5)$, $\text{CH}_2\text{-OH}$); 4.17-4.21 (m, 1 H, H-C(3)); 4.27 (s, 3 H, CH Fmoc, CH_2 Fmoc); 4.76-4.82 (m, 1 H, HO-CH_2); 4.92-4.94 (m, 1 H, $\text{HO-C}(3)$); 7.33 (t, 2 H, $J = 7.2$, arom. Fmoc); 7.42 (t, 2 H, $J = 7.0$, arom. Fmoc); 7.66 (d, 2 H, $J = 7.4$, arom. Fmoc); 7.90 (d, 2 H, $J = 7.4$, arom. Fmoc). MS (FAB^+): 340 (100, $[\text{M} + \text{H}]^+$), 309 (22), 179 (60), 155 (52), 119 (83). HR-MS (FAB^+ , $[\text{M} + \text{H}]^+$): 340.15485 (calc. 340.15488).

(3*S*)-(tert-Butyldimethylsilyloxy)-(2*R*)-(tert-butyldimethylsilyloxymethyl)-pyrrolidine (**9**)

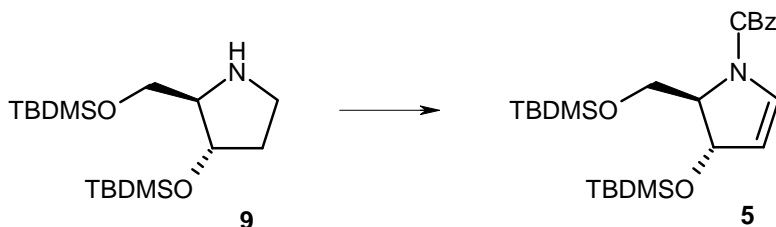


To a soln. of **8** (12.0 g, 35.4 mmol) and imidazole (8.4 g, 123 mmol) in dry THF (150 ml) was added *tert*-butyldimethylsilylchloride (11.7 g, 77.6 mmol). After 2 h, piperidine (23 ml, 233 mmol) was added and stirring was continued for 12 h. The soln. was evaporated and the residue distributed between AcOEt and H_2O . The org. layer was dried (MgSO_4) and evaporated. FC ($\text{CH}_2\text{Cl}_2/\text{MeOH}/25\%$ aq. NH_3 50:1:1 to 25:1:1) afforded 11.0 g (31.8 mmol, 90 %) of **9** as a yellow oil.

$^1\text{H-NMR}$ (300 MHz, CDCl_3): 0.06 (s, 12 H, 4 $\text{CH}_3\text{-Si}$); 0.88, 0.89 (2 s, 18 H, 2 $(\text{CH}_3)_3\text{C-Si}$); 1.63-1.72 (m, 1 H, H-C(4)); 1.83-1.95 (m, 1 H, H-C(4)); 2.22 (s, 1 H, HN); 2.90-3.11 (m, 3 H, H-C(2), $\text{H}_2\text{-C}(5)$); 3.54-3.64 (m, 2 H, $\text{CH}_2\text{-OTBDMS}$); 4.10-4.15 (m, 1 H, H-C(3)). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): -5.50, -5.45, -4.76, -4.59 (4 q, 4 $\text{CH}_3\text{-Si}$); 18.02, 18.27 (2 s, 2 $(\text{CH}_3)_3\text{C-Si}$); 25.82, 25.90 (2 q, 2 $(\text{CH}_3)_3\text{C-Si}$); 35.28 (t,

C(4)); 44.82 (t, C(5)); 63.12 (t, CH₂-OTBDMS); 68.14 (d, C(2)); 73.77 (d, C(3)). MS (FAB⁺): 346 (100, [M + H]⁺), 288 (8), 200 (17). HR-MS (FAB⁺, [M + H]⁺): 346.25998 (calc. 346.25976).

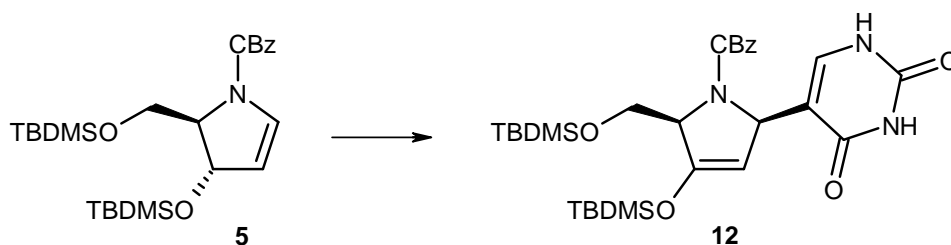
N-(Benzyloxycarbonyl)-(4*S*)-(tert-butyltrimethylsilyloxy)-(5*R*)-(tert-butyltrimethylsilyloxymethyl)-aza-2-cyclopenten (**5**)



To a soln. of **9** (7.0 g, 20.3 mmol) in hexane (250 ml) was added *N*-chlorosuccinimide (3.49 g, 26.1 mmol). After 1 h, the suspension was filtered over Celite and evaporated. The residue was dissolved in dry THF (350 ml) and cooled to -78°C . A soln. of tetramethylpiperidine (8.30 ml, 48.9 mmol) in THF (200 ml), previously treated with BuLi (1.6 M in hexane, 28.5 ml, 45.6 mmol) at 0°C and stirred for 30 min at 0°C , was added over 1 h to the soln. at -78°C until no *N*-chloro compound was detected by TLC. After 1 h, NEt₃ (12.6 ml, 90.4 mmol) was added followed by benzyl chloroformate (50 % in THF, 23.1 g, 67.8 mmol) and the mixture was warmed to rt over a period of 8 h. Most of the THF was evaporated and the residue distributed between *tert*-butylmethylether and H₂O. The org. layer was dried (MgSO₄) and evaporated. FC (hexane/*tert*-butylmethylether 25:1 to 15:1) gave 5.92 g (61 %, 12.4 mmol) of **5** as a yellow solid.

TLC (hexane/*tert*-butylmethylether 20:1): R_f 0.29. ¹H-NMR (300 MHz, CDCl₃): -0.04, -0.02, 0.04, 0.06, 0.10 (5 s, 12 H, 4 CH₃-Si); 0.85, 0.88, 0.90 (3 s, 18 H, 2 (CH₃)₃C-Si); 3.39 (t, 0.44 H, J = 9.2, H-C(5)); 3.61 (dd, 0.56 H, J = 7.4, 9.9, H-C(5)); 3.77-3.82, 3.89-3.92, 3.98-4.00 (3 m, 2 H, CH₂-OTBDMS); 4.88 (br s, 1 H, H-C(4)); 5.05-5.29 (m, 3 H, H-C(3), CH₂-C₆H₅); 6.71 (d, 0.56 H, J = 4.4, H-C(2)); 6.81 (d, 0.44 H, J = 4.1, H-C(2)); 7.37 (br s, 5 H, C₆H₅). ¹³C-NMR (75 MHz, CDCl₃): -5.51, -5.43, -4.40, -4.33 (4 q, 4 CH₃-Si); 18.09, 18.28 (2 s, 2 (CH₃)₃C-Si); 25.86 (2 q, 2 (CH₃)₃C-Si); 60.88, 61.37 (2 t, CH₂-C₆H₅); 67.21, 67.32 (2 t, CH₂-OTBDMS); 67.35 (d, C(4)); 75.80, 76.85 (2 d, C(5)); 110.27 (d, C(3)); 128.10, 128.17, 128.27, 128.32, 128.36, 128.50, 128.57 (7 d, C₆H₅); 131.66, 132.31 (2 d, C(2)); 136.14 (s, C₆H₅); 151.56 (s, NCO₂). MS (FAB⁺): 478 (24, [M + H]⁺), 434 (60), 376 (22), 342 (31), 286 (23), 147 (85), 133 (100), 115 (82). HR-MS (FAB⁺, [M + H]⁺): 478.28116 (calc. 478.28089).

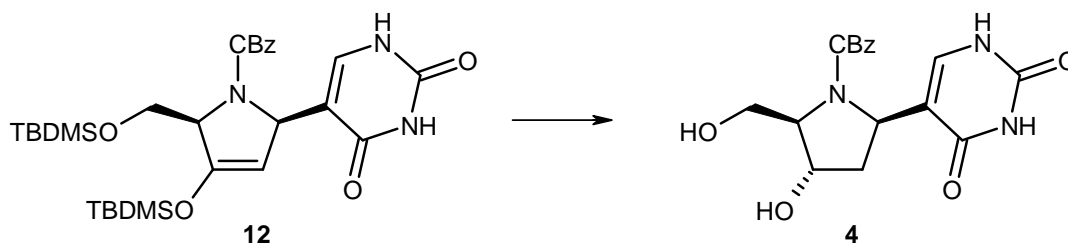
N-(Benzyloxycarbonyl)-(2*R*)-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-4-(*tert*-butyldimethylsilyloxy)-(5*R*)-(tert-butyldimethylsilyloxymethyl)-aza-3-cyclopenten (**12**)



A soln. of palladium(II) acetate (363 mg, 1.62 mmol) and triphenylarsine (951 mg, 3.11 mmol) in dry DMF (120 ml) was stirred for 30 min at rt. A soln. of **5** (4.50 g, 9.38 mmol), 5-iodouracil (5.58 g, 23.45 mmol) and tributylamine (3.60 ml, 15.1 mmol) in dry DMF (50 ml) was added and the yellow soln. was warmed to 65°C. After 20 h at 65°C, the dark red solution was evaporated to a smaller volume and distributed between AcOEt and H₂O. The org. layer was dried (MgSO₄) and evaporated. The residue was purified by FC (hexane/AcOEt 1:1 to 1:2) to give 3.19 g (5.41 mmol, 58 %) of **12** as a slightly yellow solid.

TLC (hexane/AcOEt 1:1): R_f 0.41. ¹H-NMR (300 MHz, CDCl₃): 0.04, 0.08, 0.17, 0.20 (4 s, 12 H, 4 CH₃-Si); 0.85, 0.92 (2 s, 18 H, 2 (CH₃)₃C-Si); 3.84 (d, 1 H, J = 10.3, CH₂-OTBDMS); 4.05 (d, 0.42 H, J = 10.3, H-C(5)); 4.22-4.30 (m, 1.58 H, H-C(5), CH₂-OTBDMS); 4.77 (s, 0.58 H, H-C(2)); 4.88 (s, 0.42, H-C(2)); 5.00-5.25 (m, 2 H, CH₂-C₆H₅); 5.48 (s, 1 H, H-C(3)); 7.29-7.37 (m, 5 H, C₆H₅); 7.53 (s, 0.42 H, pyrimidine H-C(6)); 7.59 (s, 0.58 H, pyrimidine H-C(6)). ¹³C-NMR (75 MHz, CDCl₃): -5.48, -5.33, -5.14, -4.76 (4 q, 4 CH₃-Si); 17.92, 18.55 (2 s, 2 (CH₃)₃C-Si); 25.49, 25.95 (2 q, 2 (CH₃)₃C-Si); 57.28, 58.02 (2 d, C(5)); 60.29, 60.98 (2 t, CH₂-OTBDMS); 65.01, 65.49 (2 d, C(2)); 66.93, 67.16 (2 t, CH₂-C₆H₅); 101.21 (d, C(3)); 114.70, 115.21 (2 s, pyrimidine C(5)); 127.77, 128.04, 128.38, 128.48 (4 d, C₆H₅); 136.20, 136.29 (2 s, C₆H₅); 138.63, 139.30 (2 d, pyrimidine C(6)); 148.04, 148.38 (2 s, C(4)); 152.56, 152.70 (2 s, NCO₂); 154.46, 154.68 (2 s, pyrimidine C(2)); 164.45, 164.59 (2 s, pyrimidine C(4)). MS (FAB⁺): 588 (100, [M + H]⁺), 530 (12), 454 (19), 412 (55), 320 (18). HR-MS (FAB⁺, [M + H]⁺): 588.29266 (calc. 588.29252).

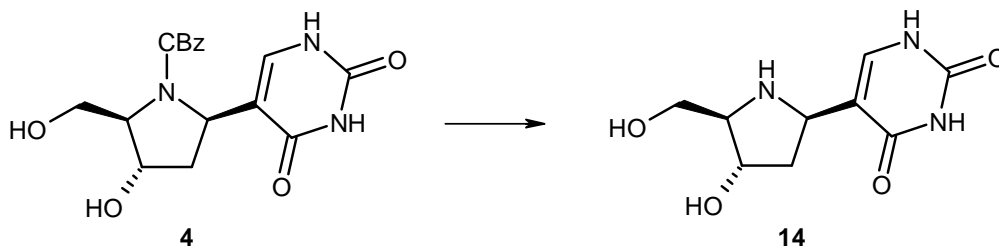
N-(Benzyloxycarbonyl)-(2*R*)-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-(4*S*)-hydroxy-(5*R*)-hydroxymethyl-pyrrolidine (**4**)



To a soln. of **12** (2.70 g, 4.58 mmol) in dry THF (135 ml) at -15°C was added acetic acid (2.61 ml, 45.6 mmol). After 15 min TBAF (1 M in THF, 23 ml, 23 mmol) was added dropwise and stirring was continued for 2 h at -15°C and then for 35 h at rt. The soln. was evaporated, the residue dissolved in acetonitrile (80 ml) and acetic acid (80 ml) and cooled to -15°C . $\text{NaB}(\text{OAc})_3\text{H}$ (1.89 g, 8.92 mmol) was added in portions. After 20 min the soln. was evaporated and the residue purified by FC (toluene/acetone/MeOH 20:20:3 to 10:10:3) to give 1.44 g (87 %, 3.99 mmol) of **4** as a white powder.

TLC (toluene/acetone/MeOH 20:20:3): R_f 0.38. $^1\text{H-NMR}$ (300 MHz, CD_3OD): 2.20-2.28 (m, 2 H, $\text{H}_2\text{-C}(3)$); 3.72-3.90 (m, 3 H, $\text{H-C}(5)$, CH_2OH); 4.35 (s, 1 H, $\text{H-C}(4)$); 4.84-5.29 (m, 3 H, $\text{H-C}(2)$, $\text{CH}_2\text{C}_6\text{H}_5$); 7.23-7.36 (m, 6 H, pyrimidine $\text{H-C}(6)$, C_5H_6). $^{13}\text{C-NMR}$ (75 MHz, $d_6\text{-DMSO}$): 37.97, 39.03 (2 t, $\text{C}(3)$); 53.99, 54.81 (2 d, $\text{C}(4)$); 60.48, 61.02 (2 t, $\text{CH}_2\text{-OH}$); 66.08 (t, $\text{CH}_2\text{C}_6\text{H}_5$); 68.91, 69.25, 70.26, 70.68 (4 d, $\text{C}(2)$, $\text{C}(5)$); 113.45, 114.34 (2 s, pyrimidine $\text{C}(5)$); 127.20, 127.67, 127.92, 128.45, 128.57, 128.71 (6 d, C_6H_5); 137.20 (s, C_6H_5); 137.69 (d, pyrimidine $\text{C}(6)$); 151.16 (s, pyrimidine $\text{C}(2)$), 155.10 (s, NCO_2); 163.67 (s, pyrimidine $\text{C}(4)$). MS (FAB^+): 362 (27, $[\text{M} + \text{H}]^+$), 346 (100), 338 (18), 309 (21). HR-MS (FAB^+ , $[\text{M} + \text{H}]^+$): 362.13586 (calc. 362.13521).

(2*R*)-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-(4*S*)-hydroxy-(5*R*)-hydroxymethyl-pyrrolidine (**14**)

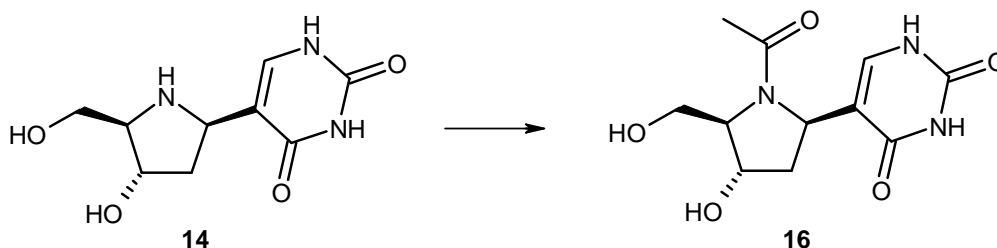


A mixture of **4** (500 mg, 1.38 mmol) and 10 % Pd/C (100 mg) in MeOH (75 ml) was vigorously stirred under an atmosphere of H_2 . After 4 h, the soln. was filtered over

Celite and evaporated to give 311 g (99 %, 1.36 mmol) of **14** as a yellow oil. The product was used for the next step without further purification.

¹H-NMR (300 MHz, D₂O): 1.86-1.98 (m, 2 H, H₂-C(3)); 3.06-3.11 (m, 1 H, H-C(5)); 3.47-3.58 (m, 2 H, CH₂OH); 4.07-4.17 (m, 2 H, H-C(2), H-C(4)); 7.37 (s, 1 H, pyrimidine H-C(6)). ¹³C-NMR (75 MHz, D₂O): 38.20 (t, C(3)); 54.42 (d, C(4)); 62.25 (t, CH₂OH); 67.66 (d, C(5)); 72.82 (d, C(2)); 112.04 (s, pyrimidine C(5)); 141.94 (d, pyrimidine C(6)); 154.80 (pyrimidine C(2)), 167.27 (pyrimidine C(4)). Difference-NOE (500 MHz, D₂O): 3.06-3.11 (H-C(5)) → 4.17 (H-C(2)); 3.47-3.58 (CH₂OH) → 3.06-3.11 (H-C(5)) / 4.12 (H-C(4)). MS (FAB⁺): 228 (100, [M + H]⁺), 195 (67), 177 (57). HR-MS (FAB⁺, [M + H]⁺): 228.09857 (calc. 228.09843).

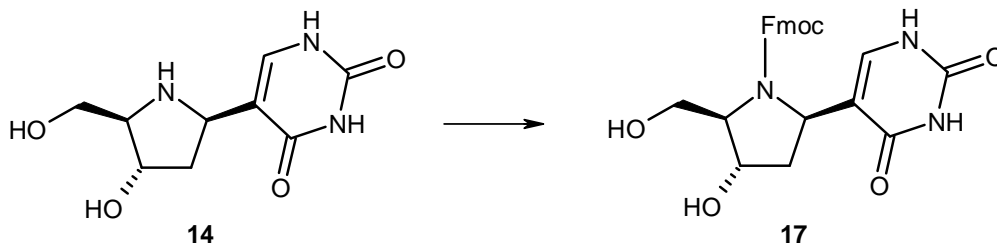
N-Acetyl-(2*R*)-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-(4*S*)-hydroxy-(5*R*)-hydroxymethyl-pyrrolidine (**16**)



To a soln. of **14** (50 mg, 0.22 mmol) in MeOH (3 ml) and H₂O (0.5 ml) at 0°C, acetic anhydride (0.15 ml, 1.59 mmol) was added dropwise. After 30 min at 0°C, the reaction was stirred 2 h at rt, evaporated and purified by FC (CH₂Cl₂/MeOH 5:2): 38 mg (65 %, 0.14 mmol) of **16** as a white solid.

TLC (CH₂Cl₂/MeOH 4:1): R_f 0.16. ¹H-NMR (300 MHz, D₂O): 1.87 (s, 1.20 H, CH₃CO); 1.92-2.05 (m, 1 H, H-C(3)); 2.09 (s, 1.80 H, CH₃CO); 2.29-2.40 (m, 1 H, H-C(3)); 3.51-3.66 (m, 2 H, CH₂-OH); 3.92-3.98 (m, 1 H, H-C(5)); 4.24-4.27 (m, 1 H, H-C(4)); 4.76-4.94 (m, 1 H, H-C(2)); 7.15 (s, 0.60 H, pyrimidine H-C(6)); 7.42 (s, 0.40 H, pyrimidine H-C(6)).

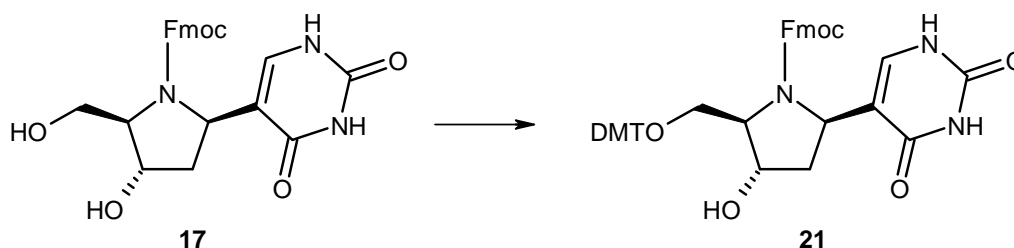
N-(9-Fluorenylmethoxycarbonyl)-(2*R*)-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-(4*S*)-hydroxy-(5*R*)-hydroxymethyl-pyrrolidine (**17**)



A soln. of *N*-(9-fluorenylmethoxycarbonyloxy)-succinimide (740 mg, 2.19 mmol) in THF (12 ml) was added to a suspension of **14** (250 mg, 1.10 mmol) in dioxane (12 ml) and 5 % aq. NaHCO₃ soln. (16 ml). After 3 h, sat. aq. NaCl soln. was added and the product was extracted with AcOEt (3x). The combined org. layers were dried (MgSO₄) and evaporated. FC (CH₂Cl₂/EtOH 5:1 to 5:2) afforded 448 mg (91 %, 1.00 mmol) of **17** as a white powder.

TLC (CH₂Cl₂/EtOH 5:1): R_f 0.30. ¹H-NMR (300 MHz, d₆-DMSO): 1.84-2.00 (m, 1 H, H-C(3)); 2.02-2.18 (m, 1 H, H-C(3)); 3.43-3.68 (m, 3 H, H-C(5), CH₂OH); 4.11-4.29 (m, 4 H, H-C(4), Fmoc CH, Fmoc CH₂); 4.62-4.76 (m, 1 H, H-C(2)); 4.94 (t, J = 5.2, 1 H, HOCH₂); 5.04 (d, J = 3.7, 1 H, HO-C(4)); 7.23-7.86 (m, 9 H, pyrimidine H-C(6), arom. Fmoc); 10.72 (br s, 1 H, HN); 11.11 (br d, J = 17.3, 1 H, HN). ¹³C-NMR (75 MHz, d₆-DMSO): 40.02, 40.43 (2 t, C(3)); 53.91, 54.82 (2 d, C(4)); 60.13, 61.02 (2 t, CH₂OH); 66.73, 67.11 (2 t, CH₂ Fmoc); 68.93, 69.68 (2 d, C(5)); 70.80, 72.41 (2 d, C(2)); 120.23, 120.35 (2 d, arom. Fmoc); 121.59 (d, arom. Fmoc); 125.08, 125.31 (2 s, pyrimidine C(5)); 127.51, 127.87 (2 d, arom. Fmoc); 129.14 (d, arom. Fmoc); 140.89 (d, pyrimidine C(6)); 143.75, 144.12 (2 s, arom. Fmoc); 151.27 (s, pyrimidine C(2)), 155.03, 155.40 (2 s, NCO₂); 167.27 (s, pyrimidine C(4)). MS (FAB⁺): 450 (15, [M + H]⁺), 391 (37), 287 (16), 150 (100), 136 (76). HR-MS (FAB⁺, [M + H]⁺): 450.16623 (calc. 450.16651).

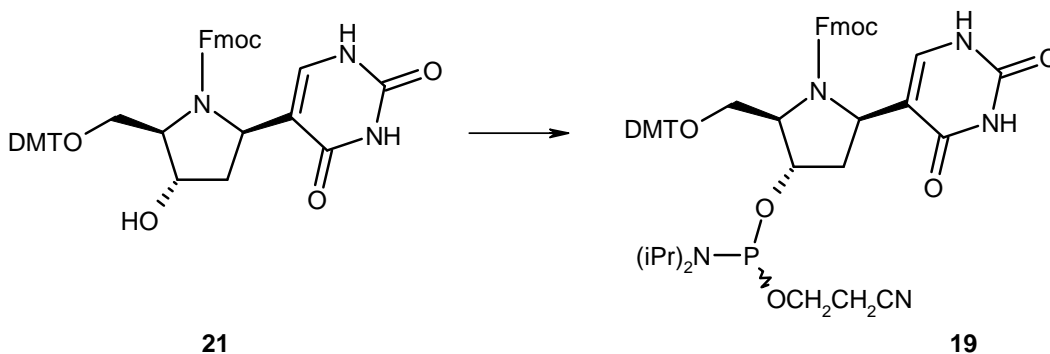
N-(9-Fluorenylmethoxycarbonyl)-(2*R*)-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-(4*S*)-hydroxy-(5*R*)-(dimethoxytrityl-hydroxymethyl)-pyrrolidine (**21**)



To a soln. of **17** (150 mg, 0.33 mmol) in dry pyridine (5 ml) was added in portions 4,4'-dimethoxytrityl chloride (146 mg, 0.43 mmol). After 2 h, the soln. was diluted with AcOEt, washed with water, dried (MgSO₄) and evaporated. The residue was purified by FC (CH₂Cl₂/EtOH/NEt₃ 20:1:0.03): 161 mg (65 %, 0.21 mmol) of **21** as a yellow solid.

TLC (toluene/EtOH 8:1): R_f 0.35. ¹H-NMR (300 MHz, d₆-DMSO): 1.67-2.18 (m, 2 H, H₂-C(3)); 3.01-3.18 (m, 3 H, H-C(5), CH₂OH); 3.68 (s, 6 H, 2 CH₃O); 4.10-4.29 (m, 4 H, H-C(4), Fmoc CH, Fmoc CH₂); 4.64 (br s, 1 H, H-C(2)); 5.14 (br s, 1 H, HO-C(4)); 6.84 (d, J = 8.1, 5 H, arom. DMT); 7.21-7.52 (m, 15 H, pyrimidine H-C(6), arom. DMT (8 H), arom. Fmoc (6 H)); 7.84-7.86 (m, 2 H, arom. Fmoc); 10.67 (br s, 1 H, HN); 11.10 (br s, 1 H, HN). HR-MS (ESI⁻, [M - H]⁻): 750.28130 (calc. 750.28209).

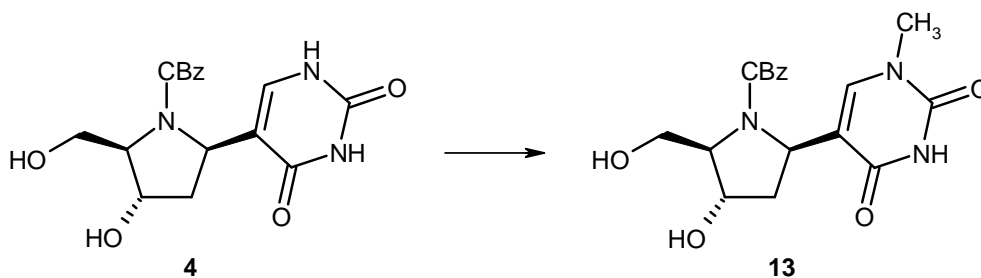
N-(9-Fluorenylmethoxycarbonyl)-(4*S*)-*O*-((β -cyanoethyl-*N,N'*-diisopropylphosphoramidite)oxy)-(5*R*)-(dimethoxytrityl-hydroxymethyl)-(2*R*)-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-pyrrolidine (**19**)



To a soln. of **21** (145 mg, 0.19 mmol) in dry THF (4 ml) was added EtN*i*Pr₂ (165 μ l, 0.96 mmol) followed by 2-cyanoethyl diisopropylchlorophosphoramidite (107 μ l, 0.48 mmol). After 2 h, 5 % aq. NaHCO₃ soln. was added and the product extracted twice with AcOEt. The combined org. layers were dried (MgSO₄) and evaporated. FC (CH₂Cl₂/EtOH/NEt₃ 30:1:0.1 to 20:1:0.1) gave 163 mg (88 %, 0.17 mmol) of **19** as a white foam.

TLC (CH₂Cl₂/EtOH/NEt₃ 20:1:0.1): R_f 0.43; 0.45. ³¹P-NMR (161.9 MHz, CDCl₃): 149.52, 149.81, 149.96. HR-MS (ESI⁺, [M - H]⁺): 950.39160 (calc. 950.38994).

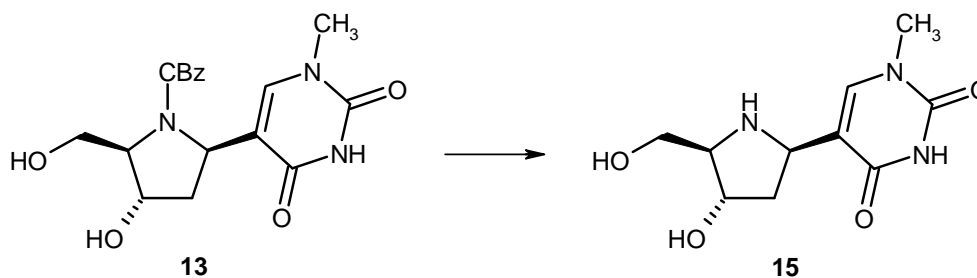
N-(Benzyloxycarbonyl)-(2*R*)-(2,4-dioxo-1-methyl-1,2,3,4-tetrahydropyrimidin-5-yl)-(4*S*)-hydroxy-(5*R*)-hydroxymethyl-pyrrolidine (**13**)



To a suspension of **4** (634 mg, 1.75 mmol) in dry CH₂Cl₂ (30 ml) was added dropwise *N,O*-bis(trimethylsilyl)acetamide (BSA, 2.57 ml, 10.5 mmol). After 1.5 h, CH₃I (4 ml, 64.3 mmol) was added to the soln. and stirring was continued for 70 h. The soln. was evaporated, the residue dissolved in sat. aq. NaCl soln. and extracted with AcOEt (3x). The combined org. layers were dried (MgSO₄) and evaporated. FC (toluene/acetone/MeOH 20/20/3 to 10/10/3) afforded 505 mg (77 %, 1.35 mmol) of **13** as a yellow solid.

TLC (toluene/acetone/MeOH 5:5:1): R_f 0.53. $^1\text{H-NMR}$ (300 MHz, d_6 -DMSO): 1.99-2.05 (m, 2 H, $\text{H}_2\text{-C}(3)$); 3.08 (br s, 1.7 H, CH_3N); 3.20 (br s, 1.3 H, CH_3N); 3.55 (br s, 2 H, CH_2OH); 3.69 (br s, 1 H, $\text{H-C}(5)$); 4.16 (s, 1 H, $\text{H-C}(4)$); 4.69-5.15 (m, 5 H, $\text{H-C}(2)$, $\text{HO-C}(4)$, HO-CH_2 , $\text{CH}_2\text{C}_6\text{H}_5$); 7.17-7.41 (m, 6 H, pyrimidine $\text{H-C}(6)$, C_5H_6), 11.26 (s, 1 H, HN). $^{13}\text{C-NMR}$ (75 MHz, d_6 -DMSO): 35.45 (q, CH_3N); 38.99, 39.81 (2 t, $\text{C}(3)$); 54.36, 54.90 (2 d, $\text{C}(4)$); 60.77, 61.15 (2 t, $\text{CH}_2\text{-OH}$); 66.11 (t, $\text{CH}_2\text{C}_6\text{H}_5$); 69.08, 69.48, 70.28, 70.68 (4 d, $\text{C}(2)$, $\text{C}(5)$); 113.75, 114.19 (2 s, pyrimidine $\text{C}(5)$); 127.43, 127.67, 127.91, 128.49 (4 d, C_6H_5); 137.07 (s, C_6H_5); 142.51 (d, pyrimidine $\text{C}(6)$); 150.80 (s, pyrimidine $\text{C}(2)$), 155.12 (s, NCO_2); 163.22 (s, pyrimidine $\text{C}(4)$). MS (FAB^+): 376 (100, $[\text{M} + \text{H}]^+$), 332 (19), 200 (20). HR-MS (FAB^+ , $[\text{M} + \text{H}]^+$): 376.15097 (calc. 376.15086).

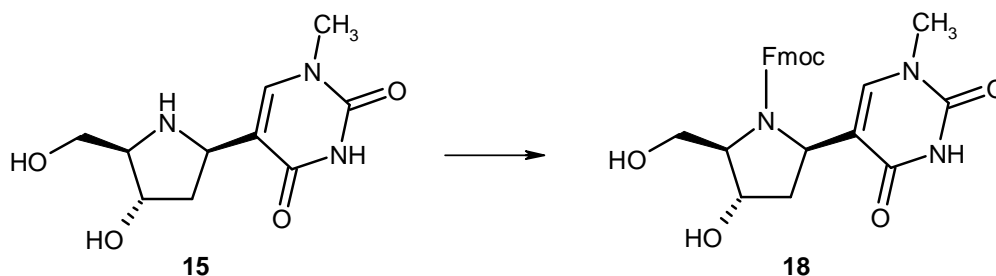
(2*R*)-(2,4-dioxo-1-methyl-1,2,3,4-tetrahydropyrimidin-5-yl)-(4*S*)-hydroxy-(5*R*)-hydroxymethyl-pyrrolidine (**15**)



A mixture of **13** (300 mg, 0.80 mmol) and 10 % Pd/C (60 mg) in MeOH (48 ml) was vigorously stirred under an atmosphere of H_2 . After 3 h, the soln. was filtered over Celite and evaporated to give 191 mg (99 %, 0.79 mmol) of **15** as a yellow oil. The product was used for the next step without further purification.

$^1\text{H-NMR}$ (300 MHz, D_2O): 1.85-1.95 (m, 2 H, $\text{H}_2\text{-C}(3)$); 3.01-3.07 (m, 1 H, $\text{H-C}(5)$); 3.22 (s, 3 H, CH_3N); 3.50-3.54 (m, 2 H, CH_2OH); 4.07-4.12 (m, 2 H, $\text{H-C}(2)$, $\text{H-C}(4)$); 7.43 (pyrimidine $\text{H-C}(6)$). $^{13}\text{C-NMR}$ (75 MHz, CD_3OD): 36.69 (q, CH_3N); 41.50 (t, $\text{C}(3)$); 55.90 (d, $\text{C}(4)$); 64.70 (t, $\text{CH}_2\text{-OH}$); 69.64 (d, $\text{C}(5)$); 74.67 (d, $\text{C}(2)$); 116.26 (s, pyrimidine $\text{C}(5)$); 144.66 (d, pyrimidine $\text{C}(6)$); 154.11 (s, pyrimidine $\text{C}(2)$); 167.15 (s, pyrimidine $\text{C}(4)$). Difference-NOE (500 MHz, D_2O): 3.22 (CH_3N) \rightarrow 7.43 (pyrimidine $\text{H-C}(6)$); 7.43 (pyrimidine $\text{H-C}(6)$) \rightarrow 3.22 (CH_3N) / 4.17 ($\text{H-C}(2)$). MS (FAB^+): 242 (100, $[\text{M} + \text{H}]^+$).

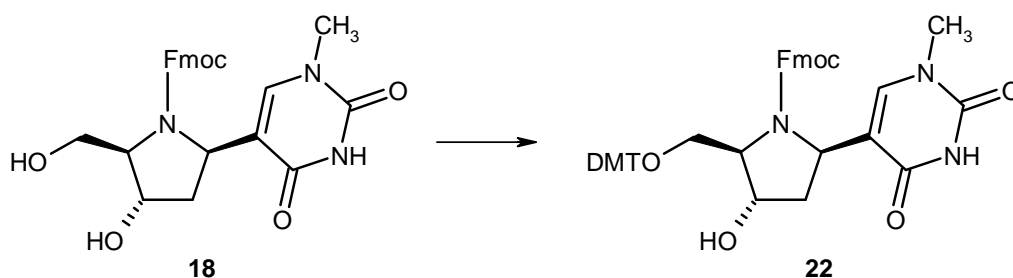
N-(9-Fluorenylmethoxycarbonyl)-(2*R*)-(2,4-dioxo-1-methyl-1,2,3,4-tetrahydropyrimidin-5-yl)-(4*S*)-hydroxy-(5*R*)-hydroxymethyl-pyrrolidine (**18**)



A soln. of *N*-(9-fluorenylmethoxycarbonyloxy)-succinimide (500 mg, 1.48 mmol) in THF (7 ml) was added to a suspension of **15** (178 mg, 0.74 mmol) in dioxane (7 ml) and 5 % aq. NaHCO₃ soln. (7 ml). After 3 h, sat. aq. NaCl soln. was added and the product was extracted with AcOEt (3x). The combined org. layers were dried (MgSO₄) and evaporated. FC (CH₂Cl₂/EtOH 5:1 to 4:1) afforded 223 mg (65 %, 0.48 mmol) of **18** as a white powder.

TLC (CH₂Cl₂/EtOH 5:1): R_f 0.35. ¹H-NMR (300 MHz, d₆-DMSO): 1.77-2.09 (m, 2 H, H₂-C(3)); 3.11 (s, 1.7 H, CH₃N); 3.21 (s, 1.3 H, CH₃N); 3.50-3.71 (m, 3 H, H-C(5), CH₂OH); 4.09-4.35 (m, 4 H, H-C(4), Fmoc CH, Fmoc CH₂); 4.53-4.70 (m, H-C(2)); 4.89-5.12 (m, 2 H, 2 HO); 7.18-7.92 (m, 9 H, pyrimidine H-C(6), arom. Fmoc); 11.28 (s, 1 H, HN). MS (FAB⁺): 464 (100, [M + H]⁺), 441 (47), 391 (46), 309 (23), 179 (70). HR-MS (FAB⁺, [M + H]⁺): 464.18222 (calc. 464.18216).

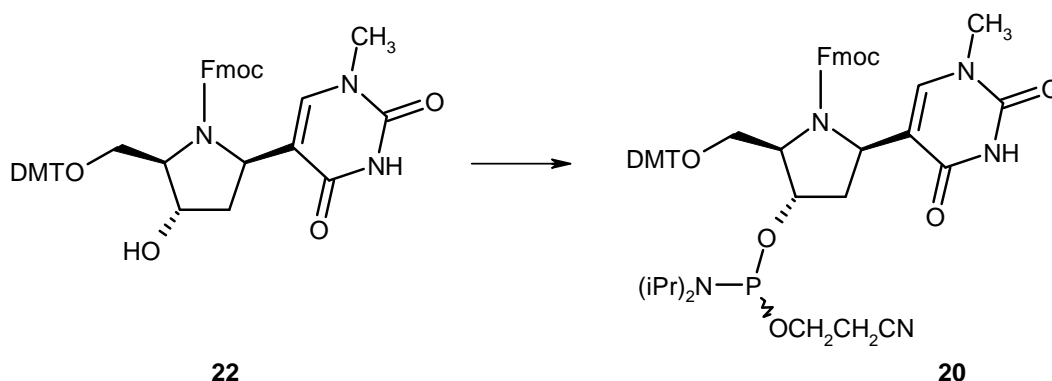
N-(9-Fluorenylmethoxycarbonyl)-(2*R*)-(2,4-dioxo-1-methyl-1,2,3,4-tetrahydropyrimidin-5-yl)-(4*S*)-hydroxy-(5*R*)-(dimethoxytrityl-hydroxymethyl)-pyrrolidine (**22**)



To a soln. of **18** (140 mg, 0.30 mmol) in dry pyridine (4 ml) was added in portions 4,4'-dimethoxytrityl chloride (127 mg, 0.38 mmol). After 2 h, the soln. was diluted with AcOEt, washed with water, dried (MgSO₄) and evaporated. The residue was purified by FC (CH₂Cl₂/EtOH/NEt₃ 20:1:0.03): 148 mg (64 %, 0.19 mmol) of **22** as a yellow solid.

TLC (CH₂Cl₂/EtOH/NEt₃ 20:1:0.1): R_f 0.31. HR-MS (ESI⁻, [M - H]⁻): 764.30110 (calc. 750.29774).

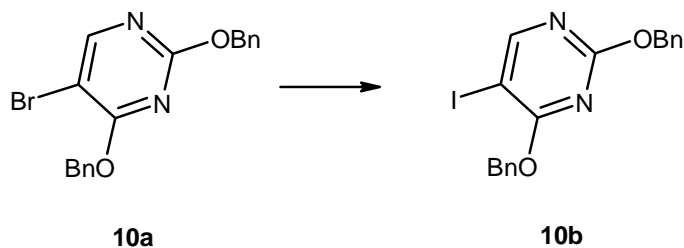
N-(9-Fluorenylmethoxycarbonyl)-(4*S*)-O-((β-cyanoethyl-*N,N'*-diisopropylphosphoramidite)oxy)-(2*R*)-(2,4-dioxo-1-methyl-1,2,3,4-tetrahydropyrimidin-5-yl)-(5*R*)-(dimethoxytrityl-hydroxymethyl)-pyrrolidine (**20**)



To a soln. of **22** (123 mg, 0.16 mmol) in dry THF (3.5 ml) was added EtN*i*Pr₂ (137 μl, 0.80 mmol) followed by 2-cyanoethyl diisopropylchlorophosphoramidite (90 μl, 0.40 mmol). After 2 h, 5 % aq. NaHCO₃ soln. was added and the product extracted twice with AcOEt. The combined org. layers were dried (MgSO₄) and evaporated. FC (CH₂Cl₂/EtOH/NEt₃ 20:1:0.1) gave 110 mg (71 %, 0.11 mmol) of **20** as a white foam.

TLC (CH₂Cl₂/EtOH/NEt₃ 20:1:0.1): R_f 0.48; 0.53. ³¹P-NMR (161.9 MHz, CDCl₃): 148.97, 149.41, 149.58. HR-MS (ESI⁻, [M - H]⁻): 964.40230 (calc. 964.40559).

2,4-Bis-benzyloxy-5-iodo-pyrimidine (**10b**)



To a soln. of **10a** (1.60 g, 4.31 mmol) in dry THF (30 ml) at -78°C was added dropwise BuLi (1.6 N in hexane, 2.70 ml, 4.32 mmol). After 1 h, a soln. of I₂ (1.22 g, 4.81 mmol) in dry THF (5 ml) was added dropwise. The soln. was warmed to rt overnight and poured into 5 % aq. Na₂S₂O₃ soln. (70 ml). The aq. layer was extracted twice with *t*BuMeO. The combined org. phases were washed with H₂O, dried

(MgSO₄) and evaporated. FC (hexane/AcOEt 20:1 to 12:1) and crystallisation from hexane/AcOEt afforded 1.62 g (90 %, 3.88 mmol) of **10b** as white needles.

TLC (hexane/AcOEt 10:1): R_f 0.52. ¹H-NMR (300 MHz, CDCl₃): 5.41, 5.47 (2 s, 4 H, CH₂C₆H₅); 7.34-7.48 (m, 10 H, CH₂C₆H₅); 8.50 (s, 1 H, H-C(6)). MS (FAB⁺): 419 (100, [M + H]⁺), 329 (14), 293 (52), 181 (36).