

Synthesis of Carbocyclic Nucleoside Analogues by Palladium-Mediated Coupling¹

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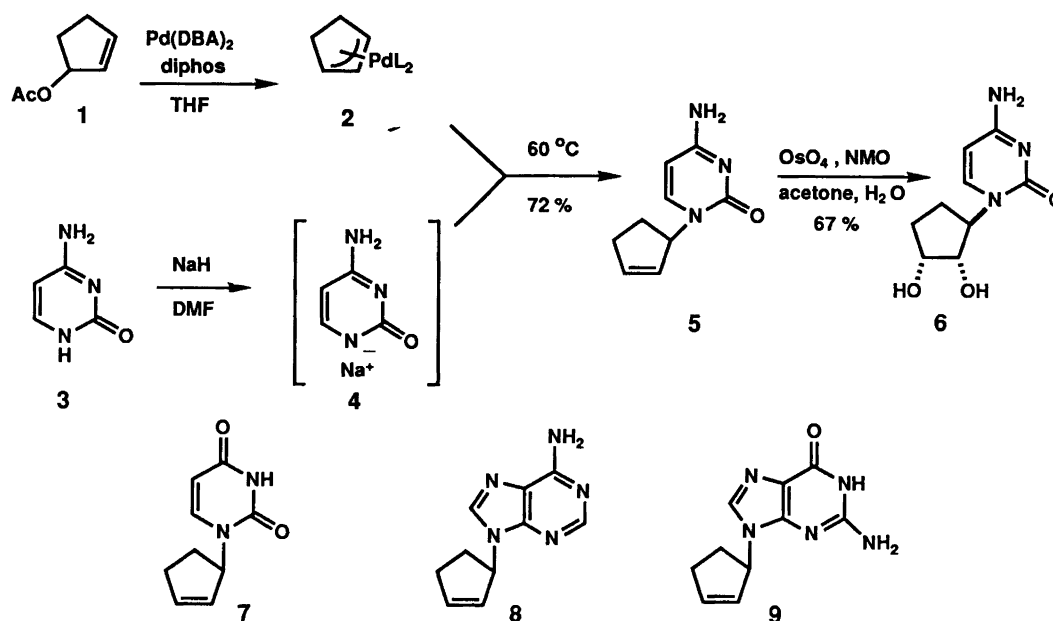
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Dedicated to Professor Lars Skattebøl on the occasion of his 65th birthday.

The enzyme ribonuclease A is well elucidated from a mechanistic and structural point of view, however, its usefulness as a tool in bioorganic synthesis has not been exploited. The potential to achieve stereoselective hydrolysis of cyclic phosphate esters of *cis*-1,2-diols with RNase A encouraged this group to investigate the scope and limitation of this enzyme as a bioorganic catalyst. Appropriate substrate analogues for such an investigation were effectively prepared by a palladium-mediated coupling reaction described herein.

The coupling of a nitrogen nucleophile with a (1-3- η^3 -cyclopentenyl)palladium complex has been developed for

N-alkylations.³⁻⁷ This procedure may be a general method for the synthesis of various carbocyclic nucleosides and their analogues that generally elaborate the heterocyclic ring in a sequential process from aminocarbocyclic synthons, and provides a simple, convenient, convergent route to the target analogue.⁸⁻¹¹ Cytosine anion (**4**), generated with sodium hydride in DMF, was coupled with (1-3- η^3 -cyclopentenyl)palladium complex **2**, prepared *in situ* from bis(dibenzylideneacetone)palladium, 1,2-bis(diphenylphosphino)ethane and 3-acetoxycyclopentene, to afford 1-(2-cyclopentenyl)cytosine (**5**). Subsequent oxidation¹² of the cyclopentene moiety of the cytidine analogue with *N*-



Scheme 1.

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Table 1. Palladium-mediated reaction of nucleoside bases with cyclopentenyl acetate (**1**).

Nucleoside base	Product	Yield (%) ^a
Cytosine (3)	5	72
Uracil	7	70
Adenine	8	68
Guanine	9	22

^aRefers to isolated yield after gradient chromatography.

methylmorpholine *N*-oxide, catalysed by osmium tetroxide, provided 1-(*cis*-2,3-dihydroxycyclopentyl)cytosine (**6**) (Scheme 1). A minor diastereomeric isomer, which is believed to be the all *cis* isomer, was detected. However, there is evidence that the ratio of stereoisomer **6** to the (1 β ,2 β ,3 β)-isomer is dependent on temperature and concentration of osmium tetroxide. Therefore it is possible to maximize the yield of the desired diol by careful control of the reaction conditions.¹³

Adenine, uracil and guanine anions were also used as nucleophiles in this palladium-mediated coupling reaction (Table 1). The yields of the 1-(2-cyclopentenyl) derivatives of adenine and uracil were similar (68–72%) to that of the cytidine analogue whereas the yield of the guanine derivative was somewhat lower (22%). Optimization of these reaction conditions should improve these yields.

This palladium-mediated coupling reaction seems to be a general and expedient method for the synthesis of carbocyclic nucleoside analogues and should be a useful procedure for the preparation of potential antiviral and antitumour agents.

Experimental¹⁴

All glassware was oven dried, cooled to ambient temperature in a desiccator, quickly assembled, and flushed with argon. The reaction assembly consisted of a reflux condenser mounted on a two-necked, round-bottomed flask containing a magnetic stir bar. All reactions were monitored by thin layer chromatography (TLC, CH₂Cl₂–MeOH, 9:1) on aluminium-backed silica gel plates, and visualization was accomplished with UV light. Tetrahydrofuran (THF, Aldrich Chemical Co.) was freshly distilled under a nitrogen atmosphere from a dark blue THF solution containing sodium diphenylketyl (from sodium–benzophenone). *N,N*-Dimethylformamide (DMF, anhydrous, packaged under nitrogen in a Sure Seal bottle), *N*-methylmorpholine *N*-oxide (NMO), cytosine, uracil, guanine and adenine were from Aldrich. 1,2-Bis(diphenylphosphino)ethane (diphos) was from Fluka and bis(dibenzylideneacetone)palladium [Pd(dba)₂] was prepared.¹⁵ The purification of products by gradient chromatography [CH₂Cl₂ to CH₂Cl₂–MeOH (6:4)] was accomplished on silica gel.¹⁶

1-(2-Cyclopentenyl)cytosine (5). After addition of 20 ml of anhydrous THF to a mixture of 91 mg (0.16 mmol) of bis(dibenzylideneacetone)palladium [Pd(dba)₂], 84 mg (0.22 mmol) of 1,2-bis(diphenylphosphino)ethane (diphos), and 501 mg (4.0 mmol) of 3-acetoxycyclopentene under an argon atmosphere, the resultant purple solution was warmed (oil bath, 45 °C) until a yellow colour was established (ca. 5 min). Then a white frothy suspension of the sodium salt of cytosine [prepared by adding 103 mg (4.0 mmol) of sodium hydride to 484 mg (4.4 mmol) of cytosine in 20 ml of DMF in a conical flask under an argon atmosphere and followed by heating (oil bath, 70 °C) for 30 min] was added to the palladium complex with a syringe (wide bore needle, 15-gauge) and the resultant bright yellow reaction mixture was stirred at 60 °C for 24 h. When the tan reaction mixture had cooled to ambient temperature, the solvents were removed at reduced pressure, and the crude solid was subjected to gradient chromatography to afford **5** as a tan solid. The regiochemistry of the alkylated product follows from its NMR data and from comparisons of these data with those of related cytosine derivatives. Yield: 510 mg (72%).

IR (KBr): 3346, 3052, 2959, 2935, 2854, 2807, 1673, 1627, 1524, 1626, 1525, 1486, 1398, 1353, 1271, 1227, 1178, 1148, 787, 715, 656, 620 cm⁻¹.

¹H NMR: δ 7.24 (1 H, d, *J* = 7.2 Hz), 6.97 (2 H, br d, *J* = ca. 14.7 Hz; exchanges with D₂O), 6.16 (1 H, dd, *J* = 5.3, 2.0 Hz), 5.66 (1 H, d, *J* = 7.1 Hz) superimposed on 5.68–5.65 (1 H, m; apparent dd with added D₂O), 5.55 (1 H, m) 2.51–2.44 (1 H, m), 2.38–2.28 (2 H, m), 1.48 (1 H, tt, *J* = ca. 13.2, 4.3 Hz). ¹³C NMR: δ 165.3, 155.3, 141.7, 136.8, 129.7, 93.7, 61.0, 30.9, 30.4.

1-(2-Cyclopentenyl)uracil (7). Similar treatment of 449 mg (4.0 mmol) of uracil, as described for **5**, afforded **7** as a white solid. The position of alkylation was unambiguously assigned using NMR spectroscopy. Yield: 500 mg (70%).

IR (KBr): 3196, 3170, 3097, 3050, 2984, 2944, 2877, 2818, 2784, 1702, 1650, 1616, 1476, 1383, 1370, 1350, 1257, 1444, 1091, 925, 845, 805, 766, 680 cm⁻¹.

¹H NMR: δ 11.23 (1 H, br s), 7.25 (1 H, d, *J* = 7.9 Hz), 6.20 (1 H, dq, *J* = 5.6, 2.0 Hz), 5.69 (1 H, dd, *J* = 5.6, 2.2 Hz), 5.54 (1 H, apparent dd, *J* = 7.9, 2.3 Hz), 5.48 (1 H, complex m), 2.56–2.44 (1 H, m), 2.38–2.29 (2 H, m), 1.64–1.579 (1 H, m). ¹³C NMR: δ 163.3, 150.9, 141.6, 137.8, 128.8, 101.5, 60.9, 31.1, 29.7.

9-(2-Cyclopentenyl)adenine (8). Similar treatment of 543 mg (4.0 mmol) of adenine, as described for **5**, afforded **8** as a white solid. Alkylation of N9 of adenine is consistent with other base-promoted coupling reactions of adenine with Pd-allyl complexes.^{5,7} Yield: 550 mg (68%).

IR (KBr): 3309, 3143, 3050, 2937, 2910, 2851, 1662, 1602, 1576, 1476, 1416, 1310, 1244, 1198, 1078, 985, 912, 905, 799, 726 cm⁻¹.

¹H NMR: δ 8.12 (1 H, s), 7.97 (1 H, s), 7.19 (2 H, br s), 6.22 (1 H, dq, *J* = 5.6, 1.9 Hz), 5.90 (1 H, apparent dq,

$J = 5.6, 2.2$ Hz), 5.59 (1 H, complex m), 2.69–2.61 (1 H, m), 2.52–2.38 (2 H, m), 1.97–1.90 (1 H, m). ^{13}C NMR: δ 155.8, 152.2, 149.0, 138.6, 136.7, 129.0, 118.9, 59.3, 31.1, 30.7.

9-(2-Cyclopentenyl)guanine (**9**). Similar treatment of 601 mg (4.0 mmol) of guanine, as described for **5**, afforded **9** as a white solid. The theoretically possible alkylation at N7 was ruled out by the ^{13}C NMR data:¹⁷ Yield: 191 mg (22%).

IR (KBr): 3442, 3154, 2850, 2728, 1674, 1630, 1571, 1536, 1474, 1413, 1386, 1312, 1233, 1176, 1082, 1024, 982, 921, 856, 784, 754, 720, 680, 644 cm^{-1} .

^1H NMR: δ 10.54 (1 H, br s), 7.50 (1 H, s), 6.42 (1 H, br s), 6.19 (1 H, apparent dd, $J = 5.5, 2.1$ Hz), 5.85 (1 H, apparent dd, $J = 5.5, 2.1$ Hz), 5.33 (1 H, complex m), 2.65–2.58 (1 H, m), 2.44–2.35 (2 H, m), 1.87–1.80 (1 H, m). ^{13}C NMR: δ 158.8, 153.4, 150.9, 138.8, 134.9, 129.1, 116.9, 58.9, 31.1, 31.0.

1-(cis-2,3-Dihydroxycyclopentyl)cytosine (**6**). To a stirred mixture of 107 mg (0.91 mmol) of *N*-methylnorpholine *N*-oxide, 5 ml of water, 2 ml of acetone and 21 mg (0.083 mmol) of osmium tetroxide (OsO_4) in 8 ml of *t*-butyl alcohol were added 147 mg (0.83 mmol) of 1-(2-cyclopentenyl)cytosine (**5**). The reaction mixture was stirred at ambient temperature for 24 h, at which point the reaction was quenched by the addition of sodium hydrosulfite (250 mg) and neutralized with acetic acid. Silica gel (6.5 g) was added and the solvents evaporated. The crude product was purified by gradient chromatography to afford **6**, yield: 117 mg (67%).

IR (KBr): 3343, 3183, 2944, 1895, 1735, 1662, 1603, 1530, 1480, 1369, 1284, 1177, 1180, 1091, 1044, 951, 832, 792, 669, 613 cm^{-1} .

^1H NMR: δ 8.26 (1 H, br s), 7.82 (1 H, d, $J = 7.5$ Hz), 7.71 (1 H, br s), 5.87 (1 H, d, $J = 7.4$ Hz), 4.88 (1 H, br s), 4.61 (1 H, br s), 4.54 (1 H, q, $J = 8.9$ Hz), 4.05 (1 H, apparent dd, $J = 8.8, 4.2$ Hz), 3.89 (1 H, apparent d, $J = 4.0$ Hz), 2.05–1.91 (2 H, m), 1.58–1.22 (2 H, m). ^{13}C NMR: δ 165.4, 156.6, 144.3, 93.7, 75.0, 70.6, 62.6, 28.9, 25.1.

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