

SYNTHESIS OF 4'-PHENYLATED PYRIMIDINE C-NUCLEOSIDES¹

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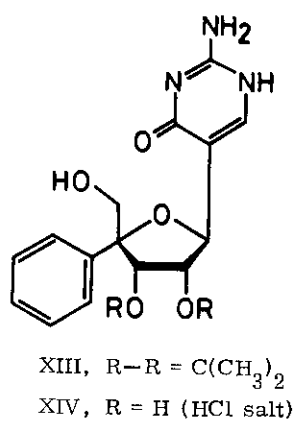
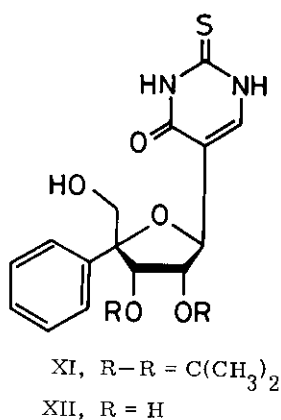
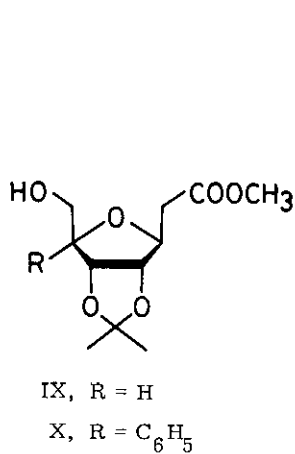
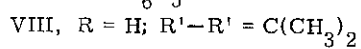
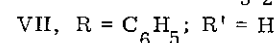
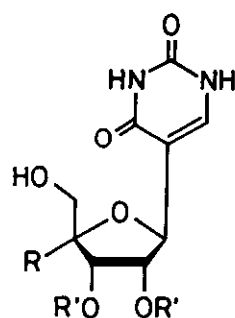
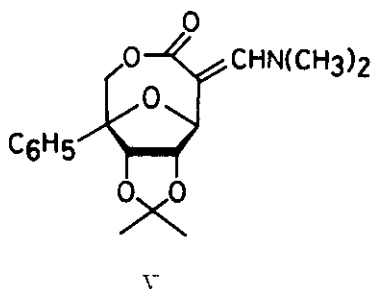
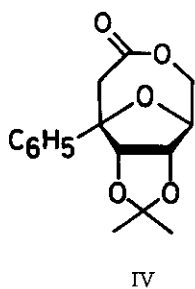
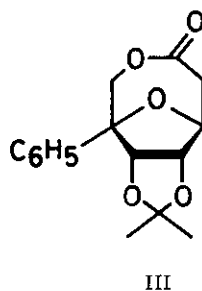
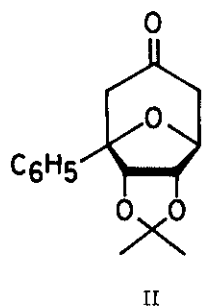
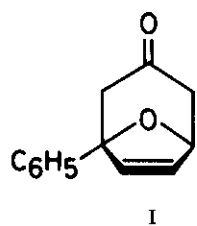
Abstract — 4'-Phenylated pyrimidine C-nucleosides have been prepared for the first time via the tetrabromoacetone/furan cyclocoupling approach.

The recently developed oxabicyclic ketone route to C-nucleosides² is synthetically quite flexible and permits the preparation of various analogues containing branched-chain sugar moieties. Described herein is its application to the direct synthesis of pyrimidine C-nucleosides possessing an aromatic substituent at the C-4' position.

The Fe₂(CO)₉-promoted reductive [3 + 4] cyclocoupling of $\alpha, \alpha, \alpha', \alpha'$ -tetrabromoacetone and 2-phenylfuran (iron carbonyl/bromide/furan = 1.5:2:1, benzene, 60 °C, 5 h)³ followed by treatment with Zn/Cu couple (excess, CH₃OH saturated with NH₄Cl, 25 °C, 1 h) gave the adduct I in 63% yield, which was converted specifically to the α acetonide II⁴ under the standard reaction conditions (1 mol % of OsO₄-30% H₂O₂ in 10:1:1 acetone-t-C₄H₉OH-ether, 25 °C, 24 h; then CuSO₄-acetone-p-CH₃C₆H₄SO₃H, 25 °C, 24 h; 51% yield). Its Baeyer-Villiger oxidation with CF₃CO₃H (5 equiv, CH₂Cl₂) proceeded smoothly at 25 °C to give a mixture of the lactones III⁵ and IV⁶ in 93% yield. Here eminent cation-supporting ability of the β phenyl substituent appeared to favor strongly the formation of the regioisomer III (III/IV = 88:12). Subsequent condensation of III with t-butoxybis(dimethylamino)methane (excess, DMF, 70 °C, 1 h) produced the dimethylaminomethylene lactone V (Z/E = 37:63, 92% yield). Exposure of V to 1 M ethanolic C₂H₅ONa containing urea (10 equiv, reflux, 2 h) afforded the uracil derivative VI⁷ (29%), which was subjected to deblocking under acidic conditions (10% HCl in CH₃OH, 25 °C, 15 min) to form 4'-phenylpseudouridine (VII).⁸ Features of the NMR (¹H and ¹³C) signal shift observed in going from 2',3'-O-isopropylidene-pseudouridine (VIII)⁹ to the phenyl derivative VI are quite similar to those induced by the structural change, IX¹⁰ → X,¹¹ compatible with the assigned β stereochemistry at C-1'.

Condensation of V with thiourea or guanidine in ethanolic C₂H₅ONa gave rise to the 2-thiouracil (XI, 58%) and isocytosine derivative (XIII, 78%), respectively. Removal of the isopropylidene protective group completed the synthesis of the corresponding 4'-phenylated C-nucleosides XII¹² and XIV.¹³

Thus the otherwise inaccessible aryl-substituted pyrimidine C-nucleoside analogues have been prepared in a general and completely stereocontrolled manner.



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REFERENCES AND NOTES

1. C-Nucleoside Synthesis. 11. Part 10: T. Sato, H. Kobayashi, and R. Noyori, Tetrahedron Lett., submitted for publication.
2. R. Noyori, T. Sato, and Y. Hayakawa, J. Am. Chem. Soc., 1978, **100**, 2561.
3. R. Noyori, Acc. Chem. Res., 1979, **12**, 61.
4. Mp 166–168 °C. IR (CHCl₃) 1720 cm⁻¹ (C=O). ¹H NMR (CDCl₃) δ 1.24 and 1.34 (s, isopropylidene CH₃), 2.3–3.0 (m, H₅ and H_{5'}), 4.61 (d, \underline{J} = 5.5 Hz, H_{2'}), 4.69 (d, \underline{J} = 5.5 Hz, H_{3'}), 4.77 (dd, \underline{J} = 1.5, 5.5 Hz, H_{1'}), 7.2–7.6 (m, C₆H₅).
5. Mp 156–158 °C. IR (CHCl₃) 1735 cm⁻¹ (C=O). ¹H NMR (C₆D₆) δ 1.13 and 1.30 (s, isopropylidene CH₃), 2.45 (m, H₅), 3.75 (d, \underline{J} = 13.5 Hz, H_{5'a}), 4.01 (d, \underline{J} = 13.5 Hz, H_{5'b}), 4.13 (m, H_{1'}), 4.61 (d, \underline{J} = 6.0 Hz, H_{2'}), 4.95 (d, \underline{J} = 6.0 Hz, H_{3'}), 7.0–7.5 (m, C₆H₅).
6. Mp 153–154 °C. IR (CHCl₃) 1733 cm⁻¹ (C=O). ¹H NMR (C₆D₆) δ 0.99 and 1.10 (s, isopropylidene CH₃), 2.62 (d, \underline{J} = 15.5 Hz, H_{5'a}), 3.15 (d, \underline{J} = 15.5 Hz, H_{5'b}), 3.44 (dd, \underline{J} = 4.1, 13.5 Hz, H_{5'a}), 3.69 (d, \underline{J} = 13.5 Hz, H_{5'b}), 4.11 (d, \underline{J} = 4.1 Hz, H_{4'}), 4.79 (d, \underline{J} = 5.8 Hz, H_{3'}), 4.85 (d, \underline{J} = 5.8 Hz, H_{2'}), 7.0–7.5 (m, C₆H₅).
7. Mp 282–285 °C. ¹H NMR (dimethyl-d₆ sulfoxide) δ 1.02 and 1.21 (s, isopropylidene CH₃), 3.50 (m, H_{5'}), 4.78 (d, \underline{J} = 5.1 Hz, H_{1'}), 4.84 (m, H_{2'}), 5.08 (d, \underline{J} = 5.1 Hz, H_{3'}), 7.32 (m, C₆H₅), 7.77 (s, H₆), 11.20 (br, NH). ¹³C NMR (dimethyl-d₆ sulfoxide) δ 25.59, 26.72, 68.29, 80.40, 83.38, 83.81, 89.50, 109.64, 112.51, 126.43, 127.24, 139.90, 141.34, 151.01, 164.00. UV λ_{\max} (CH₃OH) 263 nm (ϵ 7990), λ_{\max} (0.1 N NaOH) 285 nm (ϵ 7640).
8. Mp 245–249 °C. ¹H NMR (C₅D₅N) δ 4.07 (d, \underline{J} = 11.9 Hz, H_{5'a}), 4.17 (d, \underline{J} = 11.9 Hz, H_{5'b}), 5.28 (d, \underline{J} = 5.2 Hz, H_{1'}), 5.35 (d, \underline{J} = 7.5 Hz, H_{3'}), 5.62 (dd, \underline{J} = 5.2, 7.5 Hz, H_{2'}), 5.92 (br, OH), 7.2–8.0 (m, C₆H₅), 8.08 (s, H₆), 13.30 (br, NH). UV λ_{\max} (CH₃OH) 264 nm (ϵ 5380), λ_{\max} (0.1 N HCl) 263 nm (ϵ 8790), λ_{\max} (0.1 N NaOH) 288 nm (ϵ 5150).
9. Prepared from pseudouridine according to the reported procedure: A. M. Michelson and W. E. Cohn, Biochem., 1962, **1**, 490. ¹H NMR (dimethyl-d₆ sulfoxide) δ 1.27 and 1.49 (s, isopropylidene CH₃), 3.53 (m, H_{5'}), 3.91 (q-like, \underline{J} = 4.0 Hz, H_{4'}), 4.6–5.0 (m, H_{1'}, H_{2'}, and H_{3'}), 7.55 (s, H₆), 10.93 (br, H₁), 11.14 (br, H₃). ¹³C NMR (dimethyl-d₆ sulfoxide) δ 25.45, 27.42, 61.74, 80.30, 81.55, 83.91, 84.83, 110.40, 112.81, 140.03, 151.05, 163.27.
10. For ¹H NMR and ¹³C NMR data, see H. Ohrui, G. H. Jones, J. G. Moffatt, M. L. Maddox, A. T. Christensen, and S. K. Byram, J. Am. Chem. Soc., 1975, **97**, 4602.
11. ¹H NMR (CDCl₃) δ 1.04 and 1.28 (s, isopropylidene CH₃), 2.75 (dd, \underline{J} = 6.0, 14.5 Hz, H_aH_bCCOOCH₃), 2.96 (dd, \underline{J} = 4.8, 14.5 Hz, H_aH_bCCOOCH₃), 3.62 (d, \underline{J} = 12.5 Hz, H_{5'a}), 3.77 (s, OCH₃), 3.86 (d, \underline{J} = 12.5 Hz, H_{5'b}), 4.40 (m, H_{1'}), 4.56 (t-like, \underline{J} = 6.0 Hz, H_{2'}), 5.02 (br, OH), 5.16 (d, \underline{J} = 6.0 Hz, H_{3'}), 7.35 (m, C₆H₅). ¹³C NMR (CDCl₃) δ 25.80, 26.70, 37.21, 51.94, 69.33, 79.65, 83.86, 84.06, 90.23, 114.44, 126.50, 127.27, 127.82, 138.12, 171.69.

12. Mp 249–250 °C. ^1H NMR (dimethyl- d_6 sulfoxide) δ 3.36 (br s, $\text{H}_{5\text{a}}$), 4.34 (m, H_1 , and H_2), 4.57 (m, H_3), 7.30 (m, C_6H_5), 7.66 (d, $\underline{J} = 5.5$ Hz, H_6), 12.43 (d, $\underline{J} = 5.5$ Hz, H_1), 12.57 (br s, H_3). UV λ_{max} (CH_3OH) 276 nm (ϵ 16620), 290 (14970), λ_{max} (0.1 N HCl) 276 nm (ϵ 13620), 289 (13790), λ_{max} (0.1 N NaOH) 216 nm (ϵ 19540), 264 (13910), 289 (13790).
13. Mp 218–221 °C. ^1H NMR (dimethyl- d_6 sulfoxide) δ 3.40 (d, $\underline{J} = 11.9$ Hz, $\text{H}_{5\text{a}}$), 3.69 (d, $\underline{J} = 11.9$ Hz, $\text{H}_{5\text{b}}$), 4.35 (m, H_1 , and H_2), 4.69 (d, $\underline{J} = 6.0$ Hz, H_3), 7.30 (m, C_6H_5), 7.98 (s, H_6), 8.48 (br, NH_2). UV λ_{max} (CH_3OH) 217 nm (ϵ 17630), 262 (9530), λ_{max} (0.1 N HCl) 263 nm (ϵ 7880), λ_{max} (0.1 N NaOH) 231 nm (ϵ 14130), 276 (9740).

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