SYNTHESIS OF 4'-PHENYLATED PYRIMIDINE C-NUCLEOSIDES[1]

T. Sato, M. Watanabe, and R. Noyori*
Department of Chemistry, Nagoya University, Chikusa, Nagoya 464, Japan

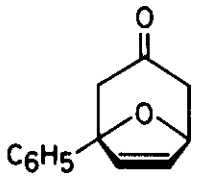
Abstract — 4'-Phenylated pyrimidine C-nucleosides have been prepared for the first time via the tetrabromoacetone/furan cyclocoupling approach.

The recently developed oxabicyclic ketone route to C-nucleosides[2] 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.

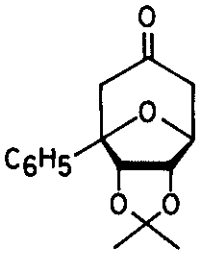
The $Fe_2(CO)_9$-promoted reductive [3 + 4] cyclocoupling of $\alpha,\alpha,\alpha',\alpha'$-tetrabromoacetone and 2-phenylfuran (iron carbonyl/bromide/furan = 1.5:2:1, benzene, 60 °C, 5 h)[3] followed by treatment with Zn/Cu couple (excess, CH_3OH saturated with NH_4Cl, 25 °C, 1 h) gave the adduct I in 63% yield, which was converted specifically to the α acetonide II[4] under the standard reaction conditions (1 mol % of OsO_4–30% H_2O_2 in 10:1:1 acetone–t-C_4H_9OH–ether, 25 °C, 24 h; then $CuSO_4$–acetone–p-$CH_3C_6H_4SO_3H$, 25 °C, 24 h; 51% yield). Its Baeyer–Villiger oxidation with CF_3CO_3H (5 equiv, CH_2Cl_2) proceeded smoothly at 25 °C to give a mixture of the lactones III[5] and IV[6] 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 C_2H_5ONa containing urea (10 equiv, reflux, 2 h) afforded the uracil derivative VI[7] (29%), which was subjected to deblocking under acidic conditions (10% HCl in CH_3OH, 25 °C, 15 min) to form 4'-phenylpseudouridine (VII).[8] Features of the NMR (^1H and ^{13}C) signal shift observed in going from 2',3'-O-isopropylidenepseudouridine (VIII)[9] to the phenyl derivative VI are quite similar to those induced by the structural change, IX[10] → X,[11] compatible with the assigned β stereochemistry at C-1'.

Condensation of V with thiourea or guanidine in ethanolic C_2H_5ONa 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 XII[12] and XIV.[13]

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



I



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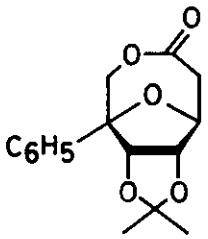
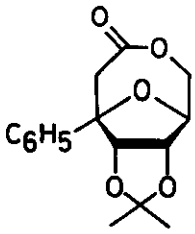
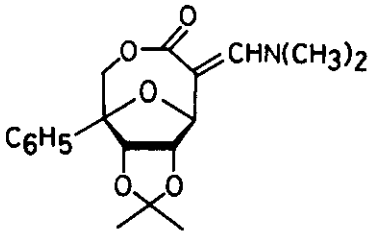


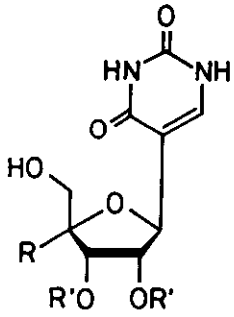
III



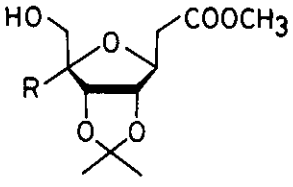
IV



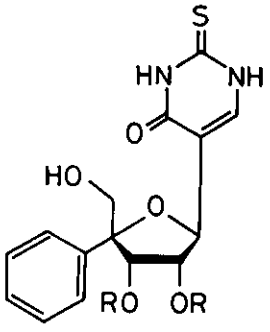
V



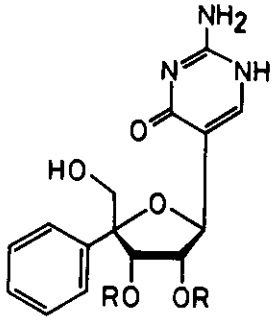
VI, R = C_6H_5;
R'—R' = $C(CH_3)_2$
VII, R = C_6H_5; R' = H
VIII, R = H; R'—R' = $C(CH_3)_2$



IX, R = H
X, R = C_6H_5



XI, R—R = $C(CH_3)_2$
XII, R = H



XIII, R—R = $C(CH_3)_2$
XIV, R = H (HCl salt)

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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 ($CHCl_3$) 1720 cm^{-1} (C=O). ^1H NMR ($CDCl_3$) δ 1.24 and 1.34 (s, isopropylidene CH_3), 2.3–3.0 (m, H_5 and $H_{5'}$), 4.61 (d, J = 5.5 Hz, $H_{2'}$), 4.69 (d, J = 5.5 Hz, $H_{3'}$), 4.77 (dd, J = 1.5, 5.5 Hz, $H_{1'}$), 7.2–7.6 (m, C_6H_5).
5. Mp 156–158 °C. IR ($CHCl_3$) 1735 cm^{-1} (C=O). ^1H NMR (C_6D_6) δ 1.13 and 1.30 (s, isopropylidene CH_3), 2.45 (m, H_5), 3.75 (d, J = 13.5 Hz, $H_{5'a}$), 4.01 (d, J = 13.5 Hz, $H_{5'b}$), 4.13 (m, $H_{1'}$), 4.61 (d, J = 6.0 Hz, $H_{2'}$), 4.95 (d, J = 6.0 Hz, $H_{3'}$), 7.0–7.5 (m, C_6H_5).
6. Mp 153–154 °C. IR ($CHCl_3$) 1733 cm^{-1} (C=O). ^1H NMR (C_6D_6) δ 0.99 and 1.10 (s, isopropylidene CH_3), 2.62 (d, J = 15.5 Hz, H_{5a}), 3.15 (d, J = 15.5 Hz, H_{5b}), 3.44 (dd, J = 4.1, 13.5 Hz, $H_{5'a}$), 3.69 (d, J = 13.5 Hz, $H_{5'b}$), 4.11 (d, J = 4.1 Hz, $H_{4'}$), 4.79 (d, J = 5.8 Hz, $H_{3'}$), 4.85 (d, J = 5.8 Hz, $H_{2'}$), 7.0–7.5 (m, C_6H_5).
7. Mp 282–285 °C. ^1H NMR (dimethyl-d_6 sulfoxide) δ 1.02 and 1.21 (s, isopropylidene CH_3), 3.50 (m, $H_{5'}$), 4.78 (d, J = 5.1 Hz, $H_{1'}$), 4.84 (m, $H_{2'}$), 5.08 (d, J = 5.1 Hz, $H_{3'}$), 7.32 (m, C_6H_5), 7.77 (s, H_6), 11.20 (br, NH). ^{13}C NMR (dimethyl-d_6 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} (CH_3OH) 263 nm (ε 7990), λ_{max} (0.1 N NaOH) 285 nm (ε 7640).
8. Mp 245–249 °C. ^1H NMR (C_5D_5N) δ 4.07 (d, J = 11.9 Hz, $H_{5'a}$), 4.17 (d, J = 11.9 Hz, $H_{5'b}$), 5.28 (d, J = 5.2 Hz, $H_{1'}$), 5.35 (d, J = 7.5 Hz, $H_{3'}$), 5.62 (dd, J = 5.2, 7.5 Hz, $H_{2'}$), 5.92 (br, OH), 7.2–8.0 (m, C_6H_5), 8.08 (s, H_6), 13.30 (br, NH). UV λ_{max} (CH_3OH) 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-d_6 sulfoxide) δ 1.27 and 1.49 (s, isopropylidene CH_3), 3.53 (m, $H_{5'}$), 3.91 (q-like, J = 4.0 Hz, $H_{4'}$), 4.6–5.0 (m, $H_{1'}$, $H_{2'}$, and $H_{3'}$), 7.55 (s, H_6), 10.93 (br, H_1), 11.14 (br, H_3). ^{13}C NMR (dimethyl-d_6 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 ^{13}C 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 ($CDCl_3$) δ 1.04 and 1.28 (s, isopropylidene CH_3), 2.75 (dd, J = 6.0, 14.5 Hz, $H_aH_bCCOOCH_3$), 2.96 (dd, J = 4.8, 14.5 Hz, $H_aH_bCCOOCH_3$), 3.62 (d, J = 12.5 Hz, $H_{5'a}$), 3.77 (s, OCH_3), 3.86 (d, J = 12.5 Hz, $H_{5'b}$), 4.40 (m, $H_{1'}$), 4.56 (t-like, J = 6.0 Hz, $H_{2'}$), 5.02 (br, OH), 5.16 (d, J = 6.0 Hz, $H_{3'}$), 7.35 (m, C_6H_5). ^{13}C NMR ($CDCl_3$) 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. ^{1}H NMR (dimethyl-d_6 sulfoxide) δ 3.36 (br s, $H_{5'}$), 4.34 (m, H_1, and $H_{2'}$), 4.57 (m, $H_{3'}$), 7.30 (m, C_6H_5), 7.66 (d, J = 5.5 Hz, H_6), 12.43 (d, 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. ^{1}H NMR (dimethyl-d_6 sulfoxide) δ 3.40 (d, J = 11.9 Hz, $H_{5'a}$), 3.69 (d, J = 11.9 Hz, $H_{5'b}$), 4.35 (m, H_1, and $H_{2'}$), 4.69 (d, 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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