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A STEREOCONTROLLED SYNTHESIS OF C-4' ALKYLATED PYRIMIDINE C-NUCLEOSIDES[1]

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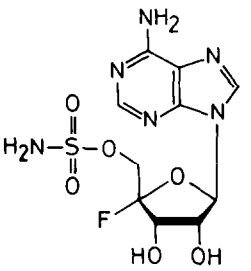
Summary: A general, stereocontrolled synthesis of pyrimidine C-nucleosides possessing an alkyl group at the C-1' or C-4' position is outlined.

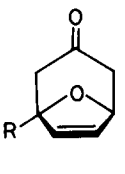
In the area of nucleoside synthesis, a variety of modifications of the carbohydrate moiety have been investigated in the hope of obtaining therapeutically useful agents. Powerful antitrypanosomal property of nucleocidin (I)[2] has stimulated interest in devising efficient methods allowing substituent incorporation at the C-4' position,[3] only very few modifications at this position have been reported.[4] Disclosed herein is the first stereospecific synthesis of C-4' alkylated pyrimidine C-nucleosides.



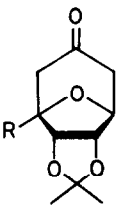
I

The bicyclic ketone IIa[5] was obtained in 70% yield by the $Fe_2(CO)_9$-aided [3 + 4] cyclocoupling reaction between $\alpha,\alpha,\alpha',\alpha'$-tetrabromoacetone and 2-methylfuran ($Fe_2(CO)_9$:halo ketone:furan = 1.5:2:1, benzene, 60 °C, 5 h),[6] followed by treatment with Zn/Cu couple in methanol saturated with NH_4Cl (25 °C, 1 h). In place of $Fe_2(CO)_9$, Zn/Ag couple may be employed (60% yield).[7] The unsaturated ketone IIa was then allowed to react with 30% H_2O_2 (2 equiv) and a catalytic amount of OsO_4 (ca. 1 mol %) in acetone–tert-butyl alcohol–ether (10:1:1 v/v) (25 °C, 12 h) and the crude product was treated with acetone–$CuSO_4$ (large excess) containing p-$CH_3C_6H_4SO_3H$ (25 °C, 12 h), leading to the acetonide IIIa[8] in a stereospecific manner (53% yield). When this compound was subjected to the Baeyer–Villiger oxidation with

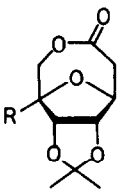
CF_3CO_3H (3 equiv) in CH_2Cl_2 containing Na_2HPO_4 and EDTA·2Na (0–20 °C, 10 h), there were obtained the regioisomeric lactones IVa[9] and Va[10] in a 53:47 ratio (90% combined yield). Treatment of the bicyclic lactone IVa with excess tert-butoxybis(dimethylamino)methane in DMF (70 °C, 3 h) gave the dimethylaminomethylene derivative VIa[11] in 70% yield. Conversion of VIa to an uracil VIIa[12] was accomplished by heating VIa with urea (10 equiv) in 1.6 N



II



III



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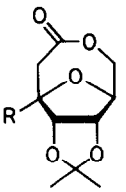
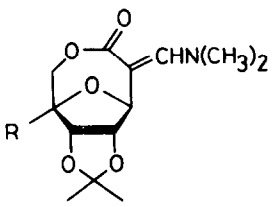
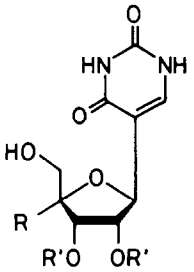


V

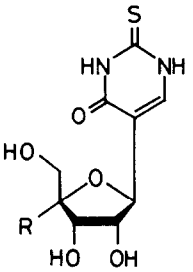


VI

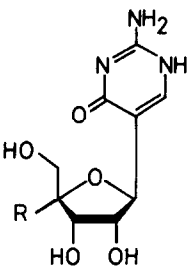


VII, R'–R' = $C(CH_3)_2$

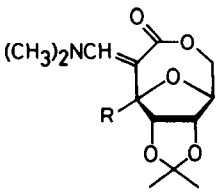
VIII, R' = H



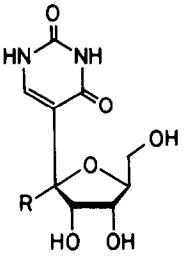
IX



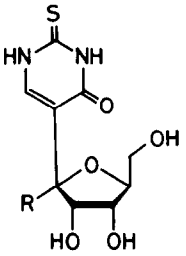
X (HCl salt)



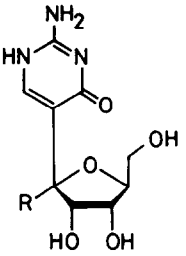
XI



XII



XIII



XIV (HCl salt)

a: R = CH_3 b: R = $(CH_2)_4CH_3$

ethanolic C_2H_5ONa (reflux, 2 h, 31%). The assignment of β configuration of the uracil appendage was made on the basis of the ^1H NMR spectrum, particularly the spin-spin coupling constant, $J_{1',2'} = 6.5$ Hz,[13] and chemical shift of the isopropylidene methyls, δ 1.40 and 1.66 ($\Delta\delta = 0.26$ ppm).[14] Finally, VIIa was exposed to 10% HCl in methanol (25 °C, 15 min) to form 4'-methylpseudouridine (VIIIa).[15,16] Preparation of 4'-methyl-2-thiopseudouridine (IXa) was effected by heating VIa with thiourea in 1.4 N ethanolic C_2H_5ONa (80 °C, 2 h), followed by dil HCl treatment (75%). When VIa was condensed with guanidine and then the isopropylidene protective group was removed, 4'-methylpseudoisocytidine (Xa) was produced in 64% yield.

When 2-pentylfuran was used as a C_4 component in the initial [3 + 4] cyclocoupling reaction, the bicyclic ketone IIb was obtained. This compound was also transformed to the corresponding pyrimidine C-nucleosides according to similar synthetic procedures.

Elaboration of heterocycles onto XI was achieved less effectively (10–20% yield) because of the severe steric hindrance of the alkyl group. In any event, this bicyclic lactone route marks the first synthesis of C-1' alkylated C-nucleosides.[17]

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REFERENCES AND NOTES

1. C-Nucleoside Synthesis. VI. Part V: T. Sato, M. Watanabe, and R. Noyori, Chem. Lett., 1297 (1978).
2. R. J. Suhadolnik, "Nucleoside Antibiotics", Wiley--Interscience, New York, N.Y., 1970, pp 246–256.
3. I. D. Jenkins, J. P. H. Verheyden, and J. G. Moffatt, J. Am. Chem. Soc., 93, 4323 (1971).
4. J. P. H. Verheyden, I. D. Jenkins, G. R. Owen, S. D. Dimitrijevich, C. M. Richards, P. C. Srivastava, N. Le-Hong, and J. G. Moffatt, Ann. N.Y. Acad. Sci., 255, 151 (1975); G. R. Owen, J. P. H. Verheyden, and J. G. Moffatt, J. Org. Chem., 41, 3010 (1976); R. Youssefyeh, D. Tegg, J. P. H. Verheyden, G. H. Jones, and J. G. Moffatt, Tetrahedron Lett., 435 (1977); J. A. Secrist III and W. J. Winter, Jr., J. Am. Chem. Soc., 100, 2554 (1978).
5. Reviews: R. Noyori, Ann. N.Y. Acad. Sci., 295, 225 (1977); R. Noyori, Acc. Chem. Res., 12, 61 (1979).
6. IR (neat) 1718 cm^{-1}. NMR ($CDCl_3$) δ 1.50 (s, CH_3), 2.1–2.9 (m, CH_2), 5.06 (ddd, J = 5.0, 1.8, 1.2 Hz, $OC\underline{H}CH_2C{=}O$), 6.05 (d, J = 5.8 Hz, $OC(CH_3)C\underline{H}{=}CH$), 6.20 (dd, J = 5.8, 1.8 Hz, $OCHC\underline{H}{=}CH$).
7. T. Sato and R. Noyori, Bull. Chem. Soc. Jpn., 51, 2745 (1978).
8. Mp 76–77 °C. IR ($CHCl_3$) 1719 cm^{-1}. NMR ($CDCl_3$, pseudouridine numbering) δ 1.30 and

1.52 (s, isopropylidene CH_3), 1.42 (s, CH_3), 2.2–2.8 (m, $H_{5'}$, H_5), 4.30 (d, $H_{2'}$), 4.51 (d, $H_{3'}$), 4.54 (dd, $H_{1'}$); $J_{1',2'}$ = ca. 0 Hz, $J_{2',3'}$ = 5.7 Hz, $J_{1',5a}$ = 1.8 Hz, $J_{1',5b}$ = 5.2 Hz.

9. Mp 100–102 °C. IR ($CHCl_3$) 1735 cm^{-1}. NMR (C_6D_6) δ 1.01 (s, CH_3), 1.07 and 1.40 (s, isopropylidene CH_3), 2.25 (dd, H_{5a}), 2.45 (dd, H_{5b}), 3.38 (d, $H_{5'a}$), 3.56 (d, $H_{5'b}$), 3.93 (dd, $H_{1'}$), 4.41 (d, $H_{2'}$), 4.48 (d, $H_{3'}$); $J_{1',2'}$ = ca. 0 Hz, $J_{2',3'}$ = 6.0 Hz, $J_{5'a,5'b}$ = 14.0 Hz, $J_{1',5a}$ = 2.9 Hz, $J_{1',5b}$ = 4.1 Hz, $J_{5a,5b}$ = 15.5 Hz.
10. Mp 100–101 °C. IR ($CHCl_3$) 1735 cm^{-1}. NMR (C_6D_6) δ 1.05 and 1.38 (s, isopropylidene CH_3), 1.16 (s, CH_3), 2.34 (d, H_{5a}), 2.54 (d, H_{5b}), 3.36 (dd, $H_{5'a}$), 3.60 (d, $H_{5'b}$), 3.91 (d, $H_{4'}$), 4.33 (d, $H_{2'}$), 4.67 (d, $H_{3'}$); $J_{2',3'}$ = 6.0 Hz, $J_{3',4'}$ = $J_{4',5'b}$ = ca. 0 Hz, $J_{4',5'a}$ = 4.0 Hz, $J_{5'a,5'b}$ = 13.8 Hz, $J_{5a,5b}$ = 16.0 Hz.
11. Mp 118–120 °C. IR ($CHCl_3$) 1680, 1590 cm^{-1}. UV λ_{max} (CH_3OH) 297 nm (ε 19800). The NMR spectrum ($CDCl_3$) exhibited characteristic signals at δ 1.26 (s, CH_3), 1.33 and 1.51 (s, isopropylidene CH_3), 2.94 and 3.11 ($N(CH_3)_2$, 33:67 ratio), 6.67 and 7.34 (=CH, 33:67 ratio).
12. Mp 200–205 °C. NMR (pyridine-d_5) δ 1.40 and 1.66 (s, isopropylidene CH_3), 1.50 (s, CH_3), 3.79 (d, $H_{5'a}$), 3.95 (d, $H_{5'b}$), 5.07 (d, $H_{3'}$), 5.15 (d, $H_{1'}$), 5.44 (dd, $H_{2'}$), 7.92 (s, H_6); $J_{1',2'}$ = 6.5 Hz, $J_{2',3'}$ = 5.5 Hz, $J_{5'a,5'b}$ = 11.0 Hz. UV λ_{max} (CH_3OH) 266 nm (ε 7230), λ_{max} (0.1 N NaOH) 285 nm (ε 7510).
13. H. Ohrui, G. H. Jones, J. G. Moffatt, M. L. Maddox, A. T. Christensen, and S. K. Byram, J. Am. Chem. Soc., 97, 4602 (1975); H. Ohrui and S. Emoto, J. Org. Chem., 42, 1951 (1977).
14. J.-L. Imbach, Ann. N.Y. Acad. Sci., 255, 177 (1975).
15. Mp 226–228 °C. NMR (pyridine-d_5) δ 1.69 (s, CH_3), 3.90 (d, $H_{5'a}$), 4.08 (d, $H_{5'b}$), 4.87 (m, $H_{3'}$), 5.26 (m, $H_{1'}$ and $H_{2'}$), 6.32 (br, OH), 7.98 (s, H_6), 12.50 and 13.20 (br, NH); $J_{5'a,5'b}$ = 11.5 Hz. UV λ_{max} (CH_3OH) 264 nm (ε 7760), λ_{max} (0.1 HCl) 264 nm (ε 7510), λ_{max} (0.1 N NaOH) 286 nm (ε 7540).
16. All compounds described herein are racemic. Stable compounds gave correct elemental analysis and/or exact mass spectral data.
17. For example, XIIIb UV λ_{max} (CH_3OH) 215 nm (ε 10910), 277 (14540), 291 (13190, s), λ_{max} (0.1 N HCl) 213 nm (ε 7280, s), 273 (8440), 295 (6160, s), λ_{max} (0.1 N NaOH) 220 nm (ε 9340, s), 262 (9420), 297 (4590, s). XIVa UV λ_{max} (CH_3OH) 222 nm (ε 9490), 262 (6290), 300 (1030, s), λ_{max} (0.1 N HCl) 221 nm (ε 8680), 262 (6450), λ_{max} (0.1 N NaOH) 230 nm (ε 11030), 278 (8250). The NMR spectra were consistent with the structures assigned.

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