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SYNTHESIS OF 4'-HYDROXYMETHYLATED PYRIMIDINE RIBO-C-NUCLEOSIDES[1]

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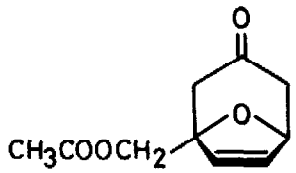
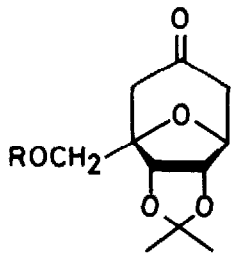
Summary: A stereocontrolled synthesis of 4'-hydroxymethylated ribo-C-nucleosides and a new psico-C-nucleoside has been accomplished on the basis of the [3 + 4] reductive cyclocoupling reaction of $\alpha,\alpha,\alpha',\alpha'$-tetrabromoacetone and furfuryl acetate.

The 4'-hydroxymethylation of ribonucleosides has received considerable attention in recent years as a means to obtain biologically more effective agents.[2] Disclosed herein is a straightforward entry to 4'-hydroxymethylated pyrimidine C-nucleosides via the polybromo ketone/furan cyclocoupling approach.[3]

Reaction of $\alpha,\alpha,\alpha',\alpha'$-tetrabromoacetone and furfuryl acetate with the aid of Zn/Ag couple[4] (1:5:1.5 ratio, THF, 20 °C, 12 h), followed by Zn/Cu couple reduction of the cycloadduct in CH_3OH saturated with NH_4Cl (20 °C, 1 h) gave rise to the bicyclic ketone I in 46% yield.[5] When I was treated with 30% H_2O_2 and a catalytic amount of OsO_4 in a 10:1:1 mixture of acetone, ether, and t-C_4H_9OH (25 °C, 12 h) and then with p-TsOH and anhydrous $CuSO_4$ in acetone (25 °C, 12 h), the acetonide II[6] possessing α configuration was obtained in 62% yield as a single stereoisomer. The acetyl group was removed by LiOH in CH_3OH (20 °C, 12 h, 96%) and replaced by a silyl protective group[7] (1.5 equiv of t-$C_4H_9(CH_3)_2SiCl$ and 3 equiv of imidazole, DMF, 25 °C, 12 h, 100%) to give III. The Baeyer-Villiger oxidation was then effected by 3 equiv of CF_3CO_3H (9 equiv of Na_2HPO_4, CH_2Cl_2, 25 °C, 12 h) to produce a 55:45 mixture of the regioisomers IV[8] and V[9] quantitatively. The major isomer IV was converted to the benzoate VI by treatment with $(n\text{-}C_4H_9)_4N^+F^-$ in THF (20 °C, 30 min) and then C_6H_5COCl (2 equiv, pyridine, 15 °C, 12 h, 90%). Condensation of the lactone VI with an excess of t-butoxybis(dimethylamino)methane in DMF (90 °C, 30 min) provided the dimethylaminomethylene lactone VIII in 91% yield. This compound was susceptible to base catalyzed cyclization with urea (5 equiv, 1 M C_2H_5ONa in C_2H_5OH, reflux, 5 h) and simultaneous removal of the benzoyl moiety to lead to the uracil derivative IX (39%).[10] Finally, the isopropylidene protective group was removed by 10% HCl in CH_3OH to form 5-(4-hydroxymethyl-β-ribofuranosyl)uracil (X) in 89% yield.[11,12] Similarly, treatment of VIII with 7 equiv of thiourea in ethanolic C_2H_5ONa gave XI in 63% yield. Acid removal of the isopropylidene blocking group afforded 5-(4-hydroxymethyl-β-ribofuranosyl)-2-thiouracil (XII) (90%).[12,13]

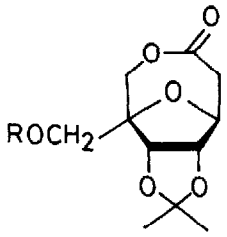


I



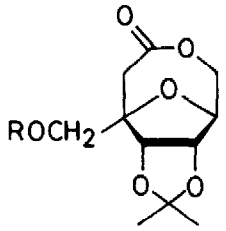
II, R = $COCH_3$

III, R = $Si(CH_3)_2$-t-C_4H_9



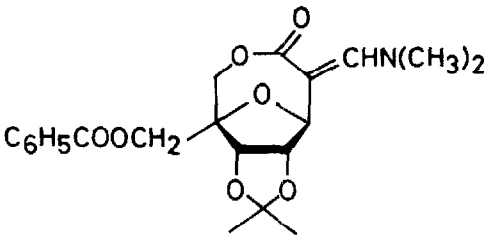
IV, R = $Si(CH_3)_2$-t-C_4H_9

VI, R = COC_6H_5

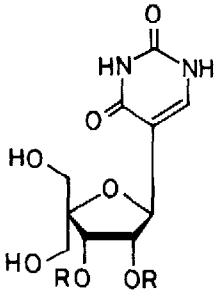


V, R = $Si(CH_3)_2$-t-C_4H_9

VII, R = COC_6H_5

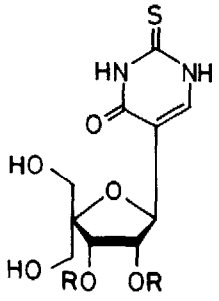


VIII



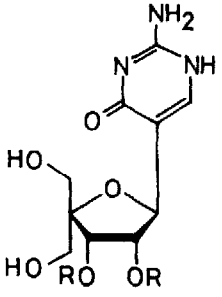
IX, R—R = $C(CH_3)_2$

X, R = H



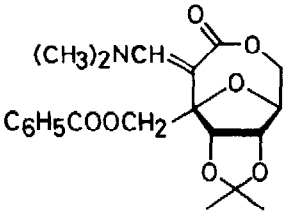
XI, R—R = $C(CH_3)_2$

XII, R = H

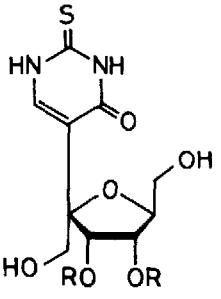


XIII, R—R = $C(CH_3)_2$

XIV, R = H (HCl salt)



XV



XVI, R—R = $C(CH_3)_2$

XVII, R = H

The base promoted cyclization of VIII with guanidine, giving XIII, followed by deprotection of the isopropylidene moiety completed the synthesis of 5-(4-hydroxymethyl-β-ribofuranosyl)-isocytosine (XIV) (41%).[12,14] Thus the desired 4'-hydroxymethylated analogues of pseudouridine possessing β-C-glycoside linkage were prepared under complete stereochemical control.

The lactone VII obtained from V can be transformed to 1'-hydroxymethylated C-nucleosides.[15] For instance, 5-(1-hydroxymethyl-β-ribofuranosyl)-2-thiouracil (XVII) was prepared by way of XV and XVI.[12,16] Condensation of VII with an excess of t-butoxybis-(dimethylamino)methane (DMF, 60 °C, 4 h) produced XV, which in turn was subjected to the base catalyzed heterocycle formation with thiourea (1.0 M C_2H_5ONa in C_2H_5OH, reflux, 3 h, 51% yield) and acid catalyzed removal of the isopropylidene group to give the new C-nucleoside XVII consisting of psicose and a pyrimidine base.

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REFERENCES AND NOTES

1. C-Nucleoside Synthesis. 13. Part 12: T. Sato, M. Watanabe, and R. Noyori, Chem. Lett., submitted for publication.

2. Synthesis of 4'-hydroxymethylated nucleosides: D. L. Leland and M. P. Kotick, Carbohydr. Res., 38, C9 (1974); R. D. Youssefyeh, D. Tegg, J. P. H. Verheyden, G. H. Jones, and J. G. Moffatt, Tetrahedron Lett., 435 (1977); R. D. Youssefyeh, J. P. H. Verheyden, and J. G. Moffatt, J. Org. Chem., 44, 1301 (1979); G. H. Jones, M. Taniguchi, D. Tegg, and J. G. Moffatt, ibid., 44, 1309 (1979).

3. R. Noyori, T. Sato, and Y. Hayakawa, J. Am. Chem. Soc., 100, 2561 (1978).

4. T. Sato and R. Noyori, Bull. Chem. Soc. Jpn., 51, 2745 (1978).

5. R. Noyori, Acc. Chem. Res., 12, 61 (1979).

6. Mp 84–86 °C. IR ($CHCl_3$) 1732 and 1720 cm^{-1} (C=O). ^1H NMR ($CDCl_3$) δ 1.30 and 1.50 (s, isopropylidene CH_3), 2.12 (s, CH_3C=O), 2.2–2.9 (m, H_5 and $H_{5'}$), 4.36 (s, CH_2OC=O), 4.46 (d, J = 6.0 Hz, $H_{3'}$), 4.56 (d, J = 6.0 Hz, $H_{2'}$), 4.63 (m, $H_{1'}$).

7. E. J. Corey and A. Venkateswarlu, J. Am. Chem. Soc., 94, 6190 (1972).

8. Mp 75–76 °C. IR ($CHCl_3$) 1735 cm^{-1} (C=O). ^1H NMR ($CDCl_3$) δ 0.08 and 0.91 (s, t-$C_4H_9(CH_3)_2Si$), 1.32 and 1.49 (s, isopropylidene CH_3), 2.99 (m, H_5), 3.61 (d, J = 10.5 Hz, H_aH_bCOSi), 3.95 (d, J = 10.5 Hz, H_aH_bCOSi), 4.30 (d, J = 13.2 Hz, $H_{5'a}$), 4.31 (t-like, J = 3.8 Hz, $H_{1'}$), 4.58 (d, J = 13.2 Hz, $H_{5'b}$), 4.68 (d, J = 6.0 Hz, $H_{2'}$), 4.86 (d, J = 6.0 Hz, $H_{3'}$).

9. Mp 64—65 °C. IR ($CHCl_3$) 1738 cm^{-1} (C=O). ^1H NMR ($CDCl_3$) δ 0.09 and 0.92 (s, t-$C_4H_9(CH_3)_2Si$), 1.32 and 1.49 (s, isopropylidene CH_3), 2.92 (d, J = 16.0 Hz, H_{5a}), 3.23 (d, J = 16.0 Hz, H_{5b}), 3.65 (d, J = 10.5 Hz, H_aH_bCOSi), 3.90 (d, J = 10.5 Hz, H_aH_bCOSi), 4.29—4.53 (m, $H_{4'}$ and $H_{5'}$), 4.60 (d, J = 5.9 Hz, $H_{2'}$), 5.00 (d, J = 5.9 Hz, $H_{3'}$).
10. Foam. ^1H NMR (dimethyl-d_6 sulfoxide) δ 1.23 and 1.46 (s, isopropylidene CH_3), 3.50 (m, $H_{5'}$ and CH_2OH), 4.53—4.86 (m, $H_{1'}$, $H_{2'}$, and $H_{3'}$), 7.51 (s, H_6). UV λ_{max} (CH_3OH) 263 nm (ε 4910), λ_{max} (0.1 N NaOH) 284 nm (ε 4670).
11. Mp 76—79 °C. ^1H NMR (dimethyl-d_6 sulfoxide) δ 3.46 (d-like, J = 6.0 Hz, $H_{5'}$ and CH_2OH), 4.33 (m, $H_{1'}$, $H_{2'}$, and $H_{3'}$), 4.0—5.0 (br, OH), 7.43 (d, J = 5.8 Hz, H_6), 10.87 (d, J = 5.8 Hz, H_1), 11.05 (br s, H_3). UV λ_{max} (CH_3OH) 264 nm (ε 6580), λ_{max} (0.1 N HCl) 264 nm (ε 6090), λ_{max} (0.1 N NaOH) 287 nm (ε 6780).
12. All new compounds described herein are racemic mixtures. The optical resolution may be attained at the lactone stage.[3]
13. Mp 84—87 °C. ^1H NMR (dimethyl-d_6 sulfoxide) δ 3.48 (d-like, J = 5.9 Hz, $H_{5'}$ and CH_2OH), 4.06 (m, $H_{2'}$), 4.61 (m, $H_{1'}$ and $H_{3'}$), 4.3—5.0 (br, OH), 7.52 (d, J = 5.9 Hz, H_6), 11.84 (d, J = 5.9 Hz, H_1), 11.98 (br s, H_3). UV λ_{max} (CH_3OH) 213 nm (ε 14110), 275 (15840), 296 (sh, 13120), λ_{max} (0.1 N HCl) 214 nm (ε 13500), 273 (13500), 292 (sh, 12080), λ_{max} (0.1 N NaOH) 265 nm (ε 13620), 285 (12920).
14. Mp 177—182 °C. ^1H NMR (dimethyl-d_6 sulfoxide) δ 3.51 (d-like, J = 6.1 Hz, $H_{5'}$ and CH_2OH), 4.08 (m, $H_{2'}$ and $H_{3'}$), 4.57 (m, $H_{1'}$), 5.0—6.4 (br, OH), 7.82 (br s, H_6), 8.50 (br, NH_2). UV λ_{max} (CH_3OH) 224 nm (ε 9250), 263 (7870), λ_{max} (0.1 N HCl) 222 nm (ε 9580), 263 (7520), λ_{max} (0.1 N NaOH) 233 nm (ε 10870), 278 (8510).
15. For 1'-hydroxymethylated ribonucleosides such as angustmycin A and C, see R. J. Suhadolnik, "Nucleoside Antibiotics", Wiley-Interscience, New York, N.Y., 1970, pp 96—122.
16. Foam. ^1H NMR (dimethyl-d_6 sulfoxide) δ 1.26 and 1.48 (s, isopropylidene CH_3), 3.3—3.8 (br, OH), 3.52 (d-like, J = 7.5 Hz, $H_{5'}$ and CH_2OH), 4.56—4.88 (m, $H_{2'}$, $H_{3'}$, and $H_{4'}$), 7.52 (s, H_6). UV λ_{max} (CH_3OH) 214 nm (ε 8780), 276 (11350), 293 (10040), λ_{max} (0.1 N NaOH) 223 nm (ε 12910), 264 (8430), 289 (7080).

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