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A GENERAL, STEREOCONTROLLED ENTRY TO PYRIMIDINE HOMO-C-NUCLEOSIDES[1]

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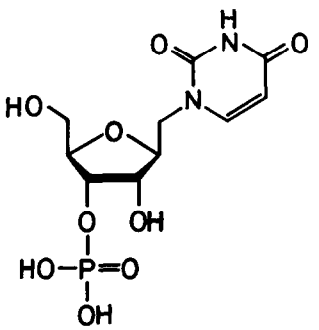
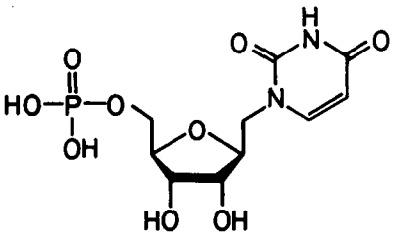
Summary: A simple synthesis of nucleoside analogues with a methylene group between the ribose and 5-position of pyrimidine appendages is outlined.

The unique activities displayed by the homonucleotides I and II[2] prompted us to prepare homo-C-nucleosides,[3] in which the ribofuranosyl moiety and sp^2-hybridized carbon of the heterocyclic nuclei are linked via a methylene unit. We present here the first stereocontrolled synthesis of pyrimidine homo-C-nucleosides that starts with the readily accessible chiral bicyclic lactone III[4] possessing a rigid C-β-glycoside structure.



I



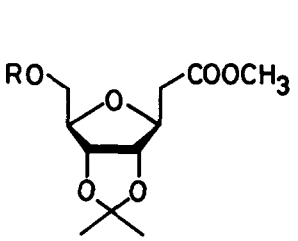
II

The lactone III was treated with 0.2 M methanolic CH_3ONa at 0 °C for 45 min to give the methyl ester IV.[5] The hydroxyl group was protected by treating with trityl chloride in pyridine leading to V,[5,6] which was then reduced with $LiAlH_4$ (1.0 mol, THF, -20 °C, 1 h) to produce the primary alcohol VI (83% yield based on III).[7] The reaction conditions were so mild that the original β configuration at the anomeric C-1 position was retained throughout the transformation. The alcohol VI was converted to the tosylate VII (1.3 equiv p-$CH_3C_6H_4SO_2Cl$/pyridine, 0 °C, 15 h) and then to the cyanide VIII (3 equiv KCN and 0.1 equiv dicyclohexano-18-crown-6/CH_3CN, 82 °C, 15 h) (59% yield). Hydrolysis of VIII was conducted in ethylene glycol containing KOH (120 °C, 20 h) and the resulting carboxylic acid was methylated by diazomethane to afford IX (74% yield).[8] Sequential treatment of the methyl ester IX in THF with lithium di-

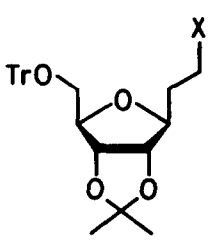
isopropylamide (2 equiv, -78 °C, 30 min) and then methyl formate (5 equiv, 0 °C, 4 h) led to the formylated derivative as a lithium salt, which was subjected to methylation with methyl iodide (5 equiv) to give the (E)-enol ether X. When a 1:7 mixture of X and urea was heated at reflux in 1 M ethanolic C_2H_5ONa, the 5-substituted uracil XI was produced in 35% yield.[9] The β stereochemistry at the C-1' position is indicated by the NMR spectra. The isopropylidene methyls show two ^1H signals at δ 1.30 and 1.50, and Δδ value, 0.20 ppm, is clearly in the β range.[10] The corresponding ^{13}C NMR signals ($CDCl_3$) occur at δ 25.79 and 27.58 (Δδ 1.79 ppm), again consistent with the β structure.[3b,5] Finally, the protective groups of XI were removed by exposure to 10% HCl in CH_3OH at 20 °C for 40 min to provide homopseudouridine (5-(β-D-ribofuranosyl)methyluracil) (XII).[11]

In a like manner, elaboration of a 2-thiouracil ring was effected facilely by treatment of X with thiourea in refluxing ethanolic C_2H_5ONa for 12 h. Compound XIII thus obtained (68% yield) was deprotected by the standard procedure (10% HCl/CH_3OH) to afford homo-2-thiopseudouridine (5-(β-D-ribofuranosyl)methyl-2-thiouracil) (XIV).[12] Condensation of X with

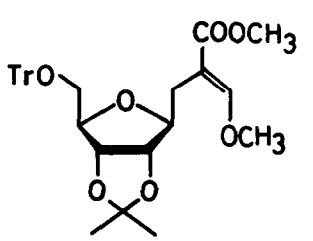
III



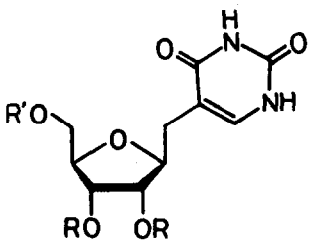
IV, R = H
V, R = $C(C_6H_5)_3$



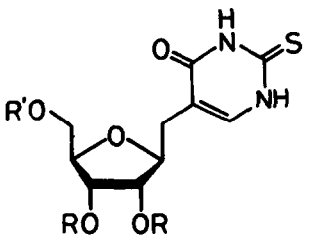
VI, X = OH
VII, X = $OSO_2C_6H_4CH_3$-p
VIII, X = CN
IX, X = $COOCH_3$



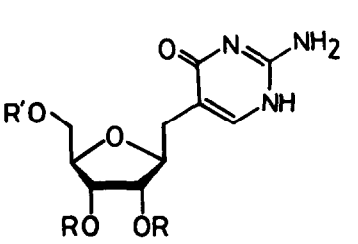
X



XI, R—R = $C(CH_3)_2$; R' = Tr
XII, R = R' = H



XIII, R—R = $C(CH_3)_2$; R' = Tr
XIV, R = R' = H



XV, R—R = $C(CH_3)_2$; R' = Tr
XVI, R = R' = H (HCl salt)

guanidine (1 M C_2H_5ONa/C_2H_5OH, 78 °C, 19 h), giving XV, followed by treatment with 10% HCl—CH_3OH formed homopseudoisocytidine (5-(β-D-ribofuranosyl)methylisocytosine) (XVI) as HCl salt.[13]

Since a variety of bicyclic lactones of type III are available[14] using the [3 + 4] reductive cyclocoupling reaction of polybromo ketones and furans[15] as the key step, this method in principle provides a general procedure for the synthesis of pyrimidine homo-C-nucleosides containing branched sugar moieties.

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5. 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).
6. T. J. Cousineau and J. A. Secrist III, J. Carbohydr., Nucleosides, Nucleotides, 3, 185 (1976).
7. IR ($CHCl_3$) 3560 cm^{-1} (OH). ^1H NMR ($CDCl_3$) δ 1.33 and 1.53 (s, isopropylidene CH_3), 1.95 (m, CH_2CH_2OH), 2.24 (br, OH), 3.17 (dd, J = 4.8, 10.5 Hz, $H_{5'a}$), 3.32 (dd, J = 4.2, 10.5 Hz, $H_{5'b}$), 3.83 (m, $H_{4'}$ and CH_2OH), 4.12 (m, $H_{1'}$), 4.42 (dd, J = 5.2, 6.2 Hz, $H_{2'}$), 4.60 (dd, J = 3.5, 6.2 Hz, $H_{3'}$), 7.36 (m, Tr).
8. IR ($CHCl_3$) 1732 cm^{-1} (C=O). ^1H NMR ($CDCl_3$) δ 1.33 and 1.54 (s, isopropylidene CH_3), 1.99 (m, $CH_2CH_2COOCH_3$), 2.52 (t-like, J = 7.2 Hz, CH_2COOCH_3), 3.17 (dd, J = 5.0, 10.0 Hz, $H_{5'a}$), 3.30 (dd, J = 4.1, 10.0 Hz, $H_{5'b}$), 3.68 (s, OCH_3), 3.93 (m, $H_{4'}$), 4.12 (m, $H_{1'}$), 4.36 (dd, J = 5.0, 6.2 Hz, $H_{2'}$), 4.59 (dd, J = 3.5, 6.2 Hz, $H_{3'}$), 7.30 (m, Tr).
9. Foam. ^1H NMR ($CDCl_3$) δ 1.30 and 1.50 (s, isopropylidene CH_3), 2.66 (m, CH_2-uracil), 3.26 (m, $H_{5'}$), 4.13 (m, $H_{1'}$ and $H_{4'}$), 4.44 (dd, J = 4.1, 6.3 Hz, $H_{2'}$), 4.62 (dd, J = 3.5, 6.3 Hz, $H_{3'}$), 7.30 (m, Tr). UV λ_{max} (CH_3OH) 264 nm (ε 6850).
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11. Mp 184—186 °C. $[\alpha]^{20}_D$ -8.2° (c 0.14, CH_3OH). ^1H NMR (dimethyl sulfoxide-d_6) δ 2.36 (m, CH_2-uracil), 3.43 (m, $H_{5'}$), 3.62 (m, $H_{1'}$ and $H_{4'}$), 3.74 (m, $H_{2'}$ and $H_{3'}$), 3.1—4.9

(br, OH), 7.27 (m, H_6), 10.69 and 11.00 (br, NH). ^{13}C NMR (dimethyl sulfoxide-d_6) δ 30.06 (CH_2-uracil), 62.00 ($C_{5'}$), 71.11, 74.33, 81.10, 84.09 ($C_{1'}$—$C_{4'}$ of ribose), 127.79, 139.14, 151.23, 164.60. UV λ_{max} (CH_3OH) 265 nm (ε 7130), λ_{max} (1 N HCl) 266 nm (ε 7080), λ_{max} (1 N NaOH) 285 nm (ε 7100).

12. ^{1}H NMR (dimethyl sulfoxide-d_6) δ 2.41 (m, CH_2-2-thiouracil), 3.42 (m, $H_{5'}$), 3.61 (m, $H_{1'}$ and $H_{4'}$), 3.76 (m, $H_{2'}$ and $H_{3'}$), 4.03 (br, OH), 7.31 (m, H_6), 12.17 and 12.36 (br, NH). ^{13}C NMR (dimethyl sulfoxide-d_6) δ 30.12 (CH_2-2-thiouracil), 61.65 ($C_{5'}$), 70.86, 74.15, 80.14, 83.96 ($C_{1'}$—$C_{4'}$ of ribose), 114.49, 139.08, 161.45, 174.42. UV λ_{max} (CH_3OH) 216 nm, 277, 290 (sh), λ_{max} (1N HCl) 216 nm, 277, 290 (sh), λ_{max} (1N NaOH) 222 nm, 261, 288. This compound was so hygroscopic that optical extinction (ε value) could not be obtained.

13. Mp 185—188 °C. $[\alpha]^{20}_D$ -49° (c 0.37, CH_3OH). ^{1}H NMR (dimethyl sulfoxide-d_6) δ 2.47 (m, CH_2-isocytosine), 3.44 (m, $H_{5'}$), 3.64 (m, $H_{1'}$ and $H_{4'}$), 3.80 (m, $H_{2'}$ and $H_{3'}$), 3.8—5.0 (br, OH), 7.59 (s, H_6), 8.49 (br, NH). ^{13}C NMR (dimethyl sulfoxide-d_6) δ 29.85 (CH_2-isocytosine), 61.79 ($C_{5'}$), 71.00, 74.23, 80.07, 84.30 ($C_{1'}$—$C_{4'}$ of ribose), 113.82, 138.05, 152.28, 160.27. UV λ_{max} (CH_3OH) 224 nm (ε 11500), 263 (7830), λ_{max} (1N HCl) 223 nm (ε 12300), 264 (9420), λ_{max} (1N NaOH) 232 nm (ε 11300), 281 (9100).

14. For example, T. Sato, M. Watanabe, and R. Noyori, Tetrahedron Lett., 4403 (1978).

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