Tetrahedron Letters No. 45, pp 4403 - 4406. 0040-4039/78/1101-4403$02.00/0

SYNTHESIS OF PSEUDOURIDINES MODIFIED AT THE C-5' POSITION[1]

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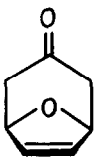
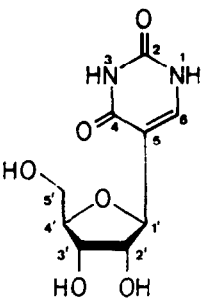
We have recently developed an efficient route to members of C-nucleoside antibiotics starting from acetone and furan.[1] Use of the oxabicyclooctenone I as the key intermediate permits the perfect stereochemical control throughout the overall transformation that consists of elaboration of the ribofuranosyl skeleton and introduction of the nitrogen bases into the C-1' position. Because of the versatility of the reductive 3 + 4 cyclocoupling reaction between polybromo ketones and furans,[2] this method finds a wide synthetic flexibility. Here we describe the first, ready structural modification of pseudouridine (II) at the C-5' position.



I

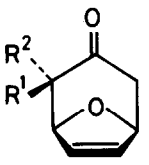


II

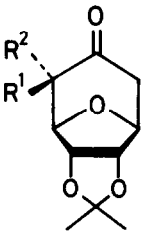
The bicyclic ketone IIIa, prepared from 1,1,3-tribromo-3-methylbutan-2-one and furan,[3] was converted with complete stereoselectivity to the α glycol acetonide IVa[4] by the standard procedure (30% H_2O_2—cat. OsO_4/acetone—ether—tert-butyl alcohol, 25 °C, 12 h, and then p-TsOH--$CuSO_4$/acetone, 25 °C, 12 h, 59% yield). Subsequent Baeyer—Villiger oxidation with CF_3CO_3H (3 equiv, CH_2Cl_2—phosphate buffer, 25 °C, 6 h) led regiospecifically to the lactone Va[5] in 81% yield, which was reacted with bis(dimethylamino)-tert-butoxymethane[6] (6.5 equiv, DMF, 50 °C, 3 h) to afford VIa[7] in 96% yield. Condensation of VIa with urea forming the uracil derivative VIIa[8] was accomplished with 2.4 M ethanolic C_2H_5ONa in 48% yield. This product was homogeneous on thin-layer chromatography with several solvent systems. The β stereochemistry at the anomeric 1' position was confirmed by the NMR spectrum.[9] Finally, acid

treatment of VIIa (10% HCl in CH_3OH, 25 °C, 10 min) furnished 5',5'-dimethylpseudouridine (VIIIa) in 97% yield.[12,13] No pyranose derivative was formed by this deprotection procedure.

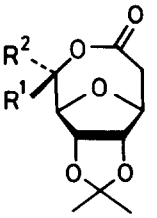
In a similar manner, the monoalkylated pseudouridines, VIIIb and VIIIc, as well as the phenyl substituted analogue VIIId[14] were prepared from the corresponding bicyclic ketones, IIIb–d. In addition to the complete stereo- and regiochemical control, configurational relationship between the carbonyl α position in III and the 5' carbon of VIII is noteworthy. Since the chiral center created in the initial 3 + 4 cyclocoupling reaction[3] remains intact during the transformation, the stereochemistry inherent in IIIb or IIIc, for example, led to 6'-deoxyallofuranosyl structures, VIIIb and VIIIc. Thus this approach provides a general method for the synthesis of pseudouridines possessing carbon substituent(s) and the 5' position.



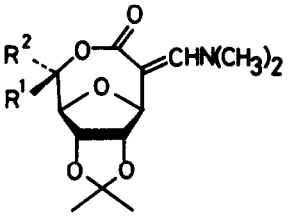
III



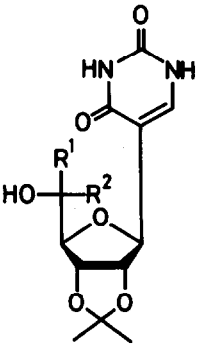
IV



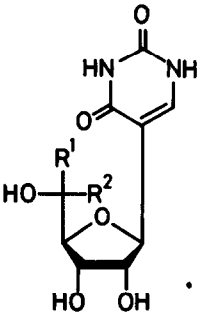
V



VI



VII



VIII

a, $R^1 = R^2 = CH_3$
b, $R^1 = CH_3$; $R^2 = H$
c, $R^1 = (CH_2)_4CH_3$; $R^2 = H$
d, $R^1 = C_6H_5$; $R^2 = H$

ACKNOWLEDGMENT

This work was supported in part by the Ministry of Education, the Japanese Government (Grant-in-Aid, No. 311709 and 354169), and the Kurata Science Foundation.

REFERENCES AND NOTES

1. C-Nucleoside Synthesis. IV. Part I: R. Noyori, T. Sato, and Y. Hayakawa, J. Am. Chem. Soc., 100, 2561 (1978). Part II: T. Sato, R. Ito, Y. Hayakawa, and R. Noyori, Tetrahedron Lett., 1829 (1978). Part III: T. Sato and R. Noyori, Bull. Chem. Soc. Japan, in press.
2. Review: R. Noyori, Ann. N.Y. Acad. Sci., 295, 225 (1977).
3. H. Takaya, S. Makino, Y. Hayakawa, and R. Noyori, J. Am. Chem. Soc., 100, 1765 (1978). See also Part III of this series (ref. 1).
4. Mp 109.5–110 °C. IR ($CHCl_3$) 1709 cm^{-1}. NMR ($CDCl_3$, pseudouridine numbering) δ 1.11, 1.31, 1.34, and 1.50 (s, CH_3), 2.20 (d, H_{5a}), 2.91 (dd, H_{5b}), 4.02 (s, $H_{4'}$), 4.44 (d, $H_{2'}$), 4.52 (d, $H_{1'}$), 4.60 (d, $H_{3'}$); $J_{1',2'} = J_{1',5a} = J_{3',4'}$ = ca. 0 Hz, $J_{1',5b}$ = 6.0 Hz, $J_{2',3'}$ = 5.5 Hz, $J_{5a,5b}$ = 16 Hz. The stereochemical assignment was based on the vicinal coupling constants, $J_{1',2'}$ and $J_{3',4'}$.
5. Mp 158.5–159.2 °C. IR ($CHCl_3$) 1730 cm^{-1}. NMR ($CDCl_3$, pseudouridine numbering) δ 1.34, 1.46, 1.50, and 1.56 (s, CH_3), 2.88 and 3.12 (dd, H_{5a} and H_{5b}), 4.10 (s, $H_{4'}$), 4.33 (dd, $H_{1'}$), 4.64 (d, $H_{2'}$), 4.97 (d, $H_{3'}$); $J_{1',2'} = J_{3',4'}$ = ca. 0 Hz, $J_{1',5a}$ = 4.0 Hz, $J_{1',5b}$ = 3.0 Hz, $J_{2',3'}$ = 6.0 Hz, $J_{5a,5b}$ = 17 Hz.
6. H. Bredereck, G. Simchen, S. Rebsdat, W. Kantlehner, P. Horn, R. Wahl, H. Hoffmann, and P. Grieshaber, Chem. Ber., 101, 41 (1968).
7. A 70:30 mixture of the (Z)- and (E)-isomers. IR ($CHCl_3$) 1670, 1590 cm^{-1}. NMR ($CDCl_3$) δ 1.33, 1.44, 1.47, and 1.51 (s, CH_3), 2.93 and 3.14 (s, $N(CH_3)_2$, 30:70 ratio), 6.58 and 7.39 (s, C=CH, 30:70 ratio). UV λ_{max} (CH_3OH) 300 nm (log ε 4.20).
8. Mp 153.1–156.8 °C. NMR (pyridine-d_5, pseudouridine numbering) δ 1.41, 1.48, 1.53, 1.67 (s, CH_3), 4.12 (d, $H_{4'}$), 5.08 (d, $H_{1'}$), 5.30 (m, $H_{2'}$ and $H_{3'}$), 7.93 (s, H_6); $J_{1',2'} = J_{3',4'}$ = 3.7 Hz. UV λ_{max} (CH_3OH) 263 nm (log ε 3.72), λ_{max} (0.1 N NaOH) 286 nm (3.73). TLC (silica gel, 7:1 $CHCl_3$–CH_3OH) R_f 0.42.
9. The spectrum taken in pyridine-d_5 gave the isopropylidene methyl signals at δ 1.41 and 1.67 (Δδ 0.26 ppm), indicating the β configuration of the uracil residue.[10] The coupling constant, $J_{3',4'}$ = 3.7 Hz, also supported this assignment.[11]
10. J. L. Imbach, Ann. N.Y. Acad. Sci., 255, 177 (1975).
11. H. Ohrui and S. Emoto, J. Org. Chem., 42, 1951 (1977).
12. Mp 221–225 °C. NMR (pyridine-d_5) δ 1.53 and 1.57 (s, CH_3), 4.2–4.4 (m, $H_{3'}$ and $H_{4'}$), 5.12 (dd, $H_{2'}$), 5.25 (d, $H_{1'}$), 5.75 (br, OH), 8.00 (s, H_6); $J_{1',2'}$ = 6.5 Hz, $J_{2',3'}$ = 5.0

Hz, $J_{3',4'}$ = 3.0 Hz. UV λ_{max} (CH_3OH) 212 (log ε 3.90), 263 nm (3.82), λ_{max} (0.1 N HCl) 264 nm (3.92), λ_{max} (0.1 N NaOH) 218 (3.92), 287 nm (3.80).

13. All compounds described herein are racemic. Stable compounds gave correct elemental analysis and/or exact mass spectral data.

14. VIIIb Mp 237–239 °C. NMR (dimethyl sulfoxide-d_6) δ 1.06 (d, CH_3), 3.50 (m, $H_{4'}$ and $H_{5'}$), 4.0 (m, $H_{2'}$ and $H_{3'}$), 4.37 (d, $H_{1'}$), 7.70 (d, H_6), 10.87 (d, H_1), 11.08 (s, H_2); $J_{1',2'} = J_{5',CH_3} = J_{1,6}$ = 6.0 Hz. UV λ_{max} (CH_3OH) 264 nm (log ε 3.75), λ_{max} (0.1 N HCl) 263 nm (3.91), λ_{max} (0.1 N NaOH) 287 nm (3.93). VIIIc Mp 193–198 °C. NMR (pyridine-d_5) δ 0.81 (t, CH_3), 1.1–1.9 (m, CH_2), 4.24 (m, $H_{5'}$), 4.54 (t-like, $H_{4'}$), 4.94 (dd, $H_{3'}$), 5.1–5.2 (m, $H_{1'}$ and $H_{2'}$), 5.50 (m, OH and NH), 7.95 (s, H_6); $J_{2',3'}$ = 4.3 Hz, $J_{4',5'}$ = 2.8 Hz, J_{CH_3,CH_2} = 6.0 Hz. UV λ_{max} (CH_3OH) 212 (log ε 3.93), 265 nm (3.84), λ_{max} (0.1 N HCl) 264 nm (3.74), λ_{max} (0.1 N NaOH) 217 (4.04), 286 nm (3.86). VIIId (wax) NMR (pyridine-d_5) δ 4.90 (m, $H_{4'}$ and $H_{5'}$), 5.24 (m, $H_{2'}$ and $H_{3'}$), 5.47 (d, $H_{1'}$), 7.83 (s, H_6), 7.2–7.5 (m, C_6H_5); $J_{1',2'}$ = 4.0 Hz. The β configuration of the C-1' appendage was determined at the stage of the acetonides, VIIb–d, using the Imbach rule.[10]

(Received in Japan 4 August 1978)