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Preliminary communication

Synthesis of C-4 branched-chain furanoses by free radical-mediated cyclization

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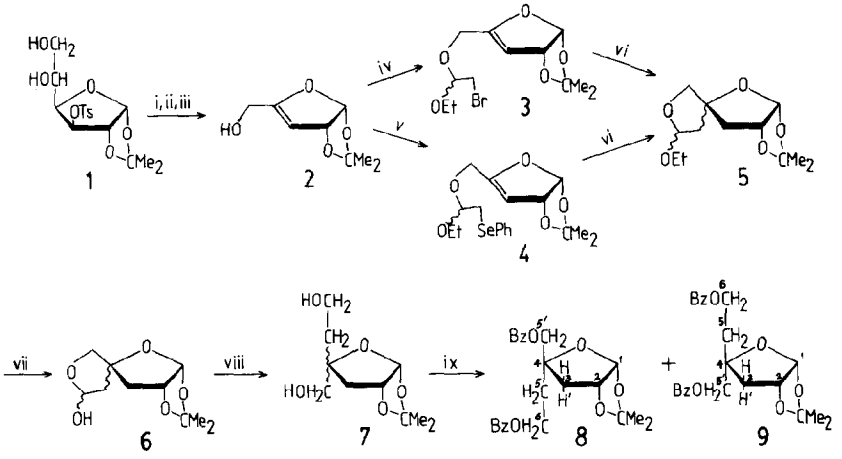
Since the elucidation of the structure of the nucleoside antibiotic nucleocidin[1] as 4′-fluoro-5′-*O*-sulfamoyladenosine, several methods[2–6] have been developed for the synthesis of 4′-substituted nucleosides. Nevertheless, unlike the synthesis of C-2 or C-3 branched-chain furanoses, the introduction of substituents at C-4 of furanose sugars and at C-4′ of nucleosides still remains a difficult problem.

We report here a new method for the incorporation of a substituent at C-4 of a furanose sugar by employing radical-mediated cyclization[7]. Diol **1** was transformed into allylic alcohol **2** by the sequence: (*a*) cleavage of the vicinal diol **1** with $NaIO_4$ to afford an aldehyde in almost quantitative yield, (*b*) elimination of the



(i) $NaIO_4$; (ii) Et_3N, benzene, heat; (iii) $LiAlH_4$, Et_2O, −78° ; (iv) $BrCH_2CHBrOEt$, Et_3N, CH_2Cl_2, 0° (v) $PhSeCH_2CHBrOEt$, $(i\text{-}Pr)_2NH$, THF, 25° ; (vi) Bu_3SnH, AIBN, benzene, heat; (vii) 30% HOAc; (viii) $LiAlH_4$, THF, −78° ; (ix) BzCl, Et_3N, CH_2Cl_2, 0° .

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tosyloxy group of the aldehyde using Et_3N in refluxing benzene to give an α,β-unsaturated aldehyde[8] in 90% yield, (*c*) reduction of the α,β-unsaturated aldehyde with $LiAlH_4$ in ether at −78° to provide allylic alcohol **2** in 72% yield. Treatment of **2** with 1,2-dibromo-1-ethoxyethane[9] (generated *in situ* from ethyl vinyl ether and bromine) in the presence of Et_3N at 0° gave rise to an isomeric mixture of bromoacetals **3** in 45% yield. Reaction of **3** with Bu_3SnH in the presence of AIBN in refluxing benzene afforded a mixture of C-4 branched-chain cyclic acetals **5** in 66% yield. Free-radical cyclization of phenylselenoacetal **4** (prepared by the reaction of **2** with 1-bromo-2-phenylseleno-1-ethoxyethane[10]) also afforded **5**, but in much lower yield. The mixture of isomers **5** was carried through to benzoates **8** and **9** without separation. Thus, the mixture **5** was hydrolyzed with 30% aq. HOAc at room temperature to give a mixture of hemiacetals **6** in 65% yield, which was then reduced with $LiAlH_4$ to afford a mixture of diols **7** in 40% yield. Benzoylation of **7** with BzCl in the presence of Et_3N afforded the C-4 branched-chain sugar benzoates **8** and **9** in 70% yield, which were separated by reversed-phase h.p.l.c. The ratio of major epimer to the minor one was 3:1, regardless whether the radical-cyclization was performed with **3** or with **4**. Compound **8** was assigned as the major epimer and **9** as the minor one on the basis of their ^{1}H-n.m.r. and ^{13}C-n.m.r. spectra*.

The ^{1}H-n.m.r. coupling constants $J_{1,2}$ 4.0, $J_{2,3}$ 5.7, and $J_{2,3'}$ 0 Hz of the minor epimer are consistent with the $^3T_4$ conformation, which is also known to be the stable conformation of 1,2-*O*-isopropylidene-α-D-glucofuranose[11]. On the other hand, the favored conformation of the major epimer was found to be close to $^3T_2$ based on $J_{1,2}$ 3.8, $J_{2,3}$ 5.0, and $J_{2,3'}$ 2.3 Hz. In the $^3T_4$ conformation, the α-substituent at C-4 is in the proximity of the *endo* methyl group on the 1,3-dioxolane ring, while in the $^3T_2$ conformation, in which the 1,3-dioxolane ring would also exist in the twist conformation, the distance between the *endo* methyl group and the α-substituent at C-4 is a little further than that in $^3T_4$ conformation. Therefore, compound **8**, which has the bulkier CH_2CH_2OBz group in the α-position at C-4, was tentatively assigned as the major epimer. The ^{13}C-n.m.r. chemical shifts, especially those of C-5, C-5′, and the carbons of the isopropylidene methyl group, also support this assignment. Thus, C-5 of **8** and C-5′ of **9** are more shielded than C-5 of **9** and C-5′ of **8**, respectively.

Although the reason for the α-side attack of the free radical on the double

*^{1}H-N.m.r. data ($CDCl_3$, 300 MHz): compound **8**, δ 1.34 and 1.60 (2 s, 6 H, $OCCH_3$), 2.20–2.39 (m, 2 H, H-3, H-3′), 2.50–2.59 (m, 2 H, H_2-5), 4.34 (ABq, 2 H, J 11.6 Hz, H_2-5′), 4.56–4.60 (m, 2 H, H_2-6), 4.85 (add, 1 H, $J_{1,2}$ 3.8, $J_{2,3}$ 5.0, $J_{2,3'}$ 2.3 Hz, H-2), 5.92 (d, 1 H, H-1), 7.33–7.60 (m, 6 H, Ph), and 7.97–8.03 (m, 4 H, Ph); compound **9**, δ 1.31 and 1.62 (2 s, 6 H, $OCCH_3$), 2.10–2.41 (m, 4 H, H-3, H-3′, H_2-5), 4.51 (dt, 2 H, J 2.2, J 6.6 Hz, H_2-6), 4.57 (s, 2 H, H_2-5′), 4.82 (dd, 1 H, $J_{1,2}$ 4.0, $J_{2,3}$ 5.7 Hz, H-2), 5.90 (d, 1 H, H-1), 7.35–7.58 (m, 6 H, Ph), 7.96–8.05 (m, 4 H, Ph); ^{13}C-n.m.r. data ($CDCl_3$, 75 MHz): compound **8**, δ 21.67 and 27.12 (2 $OCCH_3$), 36.25 (C-5), 38.91 (C-3), 61.24 (C-6), 69.00 (C-5′), 81.47 (C-2), 85.38 (C-4), 106.55 (C-1), 112.69 ($OCCH_3$), 128.34–130.22 (Ph), 166.09 (C=O), and 166.40 (C=O); compound **9**, δ 25.67 and 26.67 (2 $OCCH_3$), 36.74 (C-5), 38.96 (C-3), 60.92 (C-6), 67.91 (C-5′), 81.07 (C-2), 85.54 (C-4), 106.46 (C-1), 112.22 ($OCCH_3$), 128.34–130.12 (Ph), 166.04 (C=O), and 166.47 (C=O).

bond is unclear as yet, it may be speculated, based on inspection of molecular models, that chelation of the tributyltin salt with oxygen atoms of both the ethoxy group and the 1,3-dioxolane ring of compounds **3** and **4** might lead to stereoselective α-side addition.

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