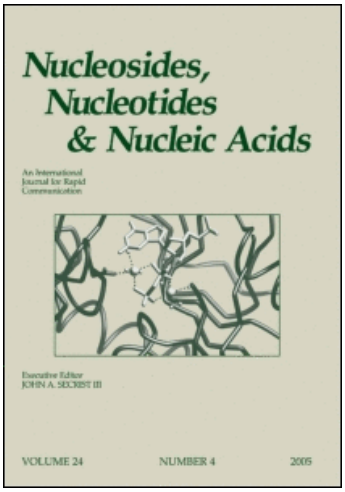

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Ex-Novo and *Revisum* Procedures for the Preparation of C-1' Branched Nucleosides

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EX-NOVO AND REVISUM PROCEDURES FOR THE PREPARATION OF C-1' BRANCHED NUCLEOSIDES

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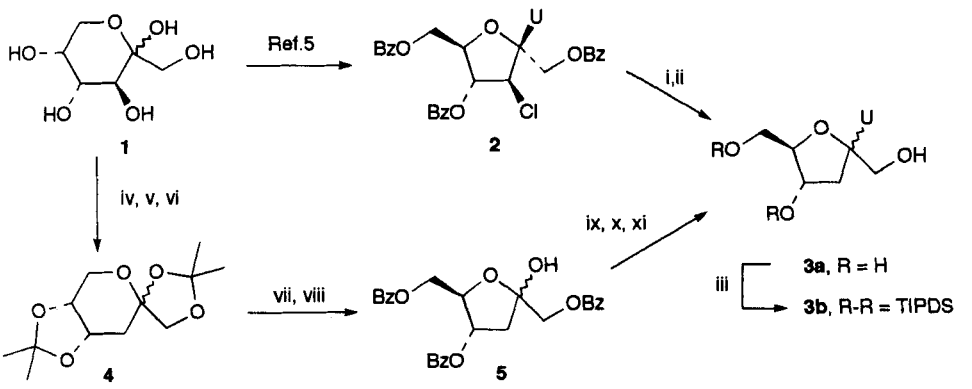
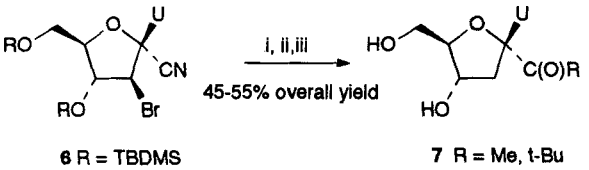
ABSTRACT: C-1' acylated derivatives of 2'-deoxyuridine were obtained either by revising the existing procedures or by introducing a new methodology.

C-1' branched nucleosides have attracted attention for their pharmacological and biological applications. In particular, the *tert*-butyl ketone at the C-1' position of 2'-deoxyuridine (7 R = t-Bu) has recently been applied to model studies of DNA damage.[2,3] In connection with these studies, we wish to briefly report the *revisum* and *ex novo* procedures for the synthesis of **7**, via derivatives **3**[4] and **6**, respectively.

Scheme 1 summarizes our innovations to the published strategies[5,6] for the preparation of **3**. The steps i and vi were carried out by using $(TMS)_3SiH$ as the radical based reducing agent.[7] The reaction products precipitated from the reaction mixture by the addition of n-pentane, thus overcoming tedious purification procedures and contamination problems due to toxic tin compounds. In the coupling step between the sugar and base moieties, only the furanose form of the sugar is able to react. Therefore, by steps vii and viii,[8] we obtained tribenzoylated 3-deoxyfructose **5** in good yield exclusively in the furanose form. It is worth noting that the coupling between the sugar and uracil (step x) gave an anomeric α/β ratio of 5/1, which was recognized by comparison with the ^1H NMR spectrum of the pure β-anomer. This result is in conflict with the previous report.[6] The protection of **3a** has been accomplished by a novel $PdCl_2$-catalyzed procedure (step iii),[9] which utilizes the less expensive TIPDS hydride.



SCHEME 1 *Reagents and conditions:* i) $(TMS)_3SiH$, AIBN, benzene, 80°C, 3 hrs (92% yield); ii) MeONa, MeOH, r.t.; iii) TIPDS-H_2, CCl_4, 2% $PdCl_2$ then 0.15M of **3a** in Py, -35°C to r.t./overnight (33% yield of **3b** + 52% of other separable regioisomers); iv) 0.25% H_2SO_4, acetone; v) PhOC(S)Cl, DMAP, CH_3CN; vi) $(TMS)_3SiH$, AIBN, benzene, 80°C, 3 hrs (97% yield); vii) 1N HCl, THF, r.t.; viii) BzCN, Py, 67°C, 3 hrs; ix) 0.25% (v/v) H_2SO_4, MeOH, 24 hrs; x) uracil, $NH(TMS)_2$, TMSCl, $SnCl_4$, $ClCH_2CH_2Cl$, -20°C; xi) MeONa, MeOH, r.t.



6 R = TBDMS

7 R = Me, t-Bu

SCHEME 2 *Reagents and conditions* : i) $(TMS)_3SiH$, AIBN, benzene, 80°C, 3 hrs (92% yield); ii) RLi, THF, -78°C, then work up and silica gel chromat.; iii) NH_4F, MeOH, 60°C.

A new synthesis of C-1' acylated derivatives is reported in Scheme 2. The precursor **6**, readily available from 1',2'-didehydro-2'-deoxyuridine by literature procedures,[10] was reduced using again $(TMS)_3SiH$ and then treated with organolithium reagents, to the desired products after deprotection.

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