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Synthesis of a New Furanoid Glycal Auxiliary

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Summary. A route is investigated for the synthesis of 3-*O*-allyl-1,4-anhydro-5-*O*-*tert*-butyldiphenylsilyl-2-deoxy-*D*-*erythro*-pent-1-enitol. The highest overall yield was obtained when 5′-*O*-(*tert*-butyldiphenylsilyl)thymidine was converted to the corresponding furanoid glycal and subsequently 3-*O*-allylated.

Keywords. 1,4-Anhydropentenitols; Elimination; Carbohydrates; Furanoid glycals; Nucleosides.

Introduction

The synthesis of furanose glycals has received great attention because they have been used as key intermediates in the preparation of structurally diverse biologically active compounds such as polyether antibiotics [1], 6-*epi*-leukotrienes *C* and *D* [2], antiviral and antitumor C-nucleosides [3], α-*arabino* nucleosides [4], 2′,3′-dideoxynucleosides [5], and 2′-deoxynucleosides [6] with remarkable antiviral and antitumor activities [7].

Electrophilic addition reactions to a furanoid glycal have been used as key steps in the synthesis of 2′,3′-dideoxyadenine (*ddA*) and 2′,3′-didehydro-2′,3′-dideoxythymidine (*d4T*) [8]. Glycals can be used for the synthesis of aryl C-glycosides and C-nucleosides which have potential antiviral and antitumor activity [9] and for the synthesis of novel base pairing moieties in oligonucleotides [10]. Several methods have been reported for the synthesis of substituted glycals [1, 11–16]. The simplest method was described by the group of *Pedersen* in 1994 [17], and this method was used by *Hammer et al.* [18] and later by *Quirion et al.* [19], and *Beigelman* and coworkers [20] to prepare additional furanoid glycals. The method is highly effective and is based on elimination of thymine base upon heating

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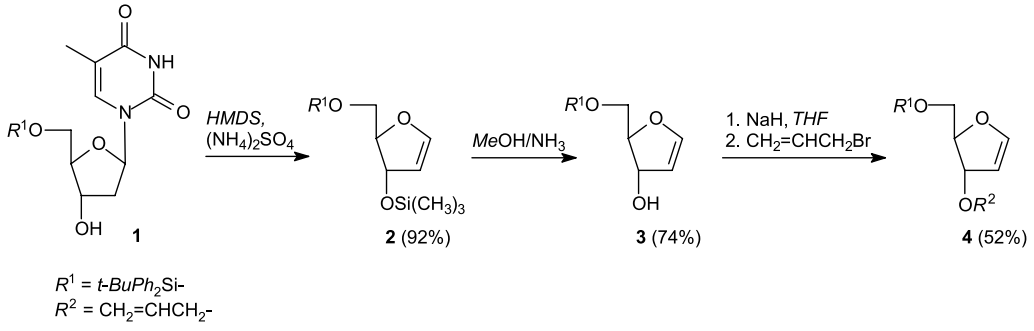

Scheme 1

thymidine nucleosides in 1,1,1,3,3,3-hexamethyldisilazane (*HMDS*) under reflux in the presence of ammonium sulfate.

A literature survey showed that our glycal synthesis has been well accepted by the chemistry community and has been used in the synthesis of C-nucleosides [21–27], *D*-ribitol [20], Buergerinin [28], cyclic phosphonomethylphosphinates [29], and 2′-C-branched nucleosides [19, 30]. Due to the interest of furanoid glycals we describe in this paper the synthesis of a new silyl and allyl protected furanoid glycal, which we think is a suitable auxiliary for the synthesis of glycosides and nucleosides.

Results and Discussions

The glycal **4** was prepared in three steps starting from the nucleoside **1**. Refluxing **1** with *HMDS* in the presence of ammonium sulfate for 6 h under nitrogen afforded the 5′-*O* silyl protected glycal **2** having an additional protection with a 3′-*O* trimethylsilyl group [17]. The latter protecting group was removed by treatment with ammonia in methanol at room temperature to give the glycal **3** [18]. This compound was converted to the target glycal **4** by reaction with allyl bromide in the presence of sodium hydride in dry *THF* under nitrogen at room temperature in 35% overall yield from compound **1** (Scheme 1).

It was also attempted to use a reverse reaction sequence by 3-*O*-allylation of the silylated thymidine **1** before formation of the glycal. Although the last step produced the glycal **4** in 38% yield, the overall yield was only 6% due to formation of a complex mixture of triallyl (3-N, 3′-O, 5′-O), diallyl (3-N, 3′-O and 3′-O, 5′-O), and monoallyl (3′-O) thymidine derivatives in the allylation step. The latter only being formed in 15% yield.

Experimental

NMR spectra were recorded on a Varian Gemini 2000 NMR spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C with *TMS* as an internal standard. MALDI mass spectra were recorded on an IonSpec Fourier Transform Ion Cyclotron Resonance Mass Spectrometer. Melting points were determined on a *Büchi* melting point apparatus. The progress of reactions was monitored by TLC (DC-alufolio 60 F_{254}) from Merck. For column chromatography Merck silica gel (0.040–0.063 mm) was used. Solvents used for column chromatography were distilled prior to use, while reagents were used as purchased.

1,4-Anhydro-5-O-(tert-butyldiphenylsilyl)-2-deoxy-D-erythro-pent-1-enitol (**3**)
A solution of 8.52 g **2** [17] (20.0 mmol) in 50 cm^3 *Me*OH/NH_3 was stirred at room temperature for 48 h. The solvent was removed *in vacuo*, and the residue chromatographed on a silica gel column using petroleum ether (60–80°C): *Et*OA*c* (8:2, *v*:*v*) to give 5.24 g (74%) **3**. NMR spectra were in accordance with Ref. [17].

3-O-Allyl-1,4-anhydro-5-O-tert-butyldiphenylsilyl-2-deoxy-D-erythro-pent-1-enitol
(**4**, $C_{24}H_{30}O_3Si$)
To a solution of **3** (1.74 g, 4.9 mmol) in 60 cm^3 of dry *THF* was added 588 mg NaH (60%, 25.4 mmol) and 1.22 g of allyl bromide (10 mmol) under N_2. After the reaction had been stirred at room temperature for 24 h the reaction mixture was quenched with 1 cm^3 *Me*OH and the solvent was removed *in vacuo*. The residue was diluted with 200 cm^3 *Et*OA*c* and filtered. The solvent was removed *in vacuo*, and the residue chromatographed on a silica gel column using petroleum ether (60–80°C): *Et*OA*c* (3:2, *v*:*v*) to give 980 mg (52%) **4**. Pale yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.06$ (s, 9H, $3 \times CH_3$), 3.59 (dd, 1H, $J = 10.6$, 6.1 Hz, 5-H), 3.75 (dd, 1H, $J = 10.8$, 5.3 Hz, 5-H), 3.99 (m, 2H, OCH_2), 4.48–4.50 (m, 3H, 4-H, OCH_2), 5.13 (t, 1H, $J = 2.4$ Hz, 3-H), 5.17–5.18 (m, 3H, CH_2=CH, 2-H), 5.86–5.95 (m, 1H, CH=CH_2), 6.53 (d, 1H, $J = 2.5$ Hz, 1-H), 7.37–7.68 (m, 10H, H_{arom}) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 19.23$ ($(CH_3)_3C$), 26.75 ($3 \times CH_3$), 63.51 (C-5), 68.59 (C-3), 82.54 (OCH_2), 86.07 (C-4), 100.47 (C-2), 116.85 (CH_2=CH), 127.70, 129.76, 133.17, 134.85 (C_{arom}), 135.57 (CH=CH_2), 150.39 (C-1) ppm; HRMS (MALDI, peak matching): $m/z = 417.1853$ ($M + Na^+$; calcd. 417.1856).

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