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Straightforward synthesis of 3′-deoxy-3′,4′-didehydronucleoside-5′-aldehydes via 2′,3′-*O*-orthoester group elimination: a simple route to 3′,4′-didehydronucleosides

Magdalena Petrová, Miloš Buděšínský, Ivan Rosenberg *

Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, v. v. i., Flemingovo nám. 2, 166 10 Prague 6, Czech Republic

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ABSTRACT

Straightforward, high-yielding syntheses of 3′-deoxy-3′,4′-didehydronucleoside-5′-aldehydes and 3′-deoxy-3′,4′-didehydronucleosides starting from 2′,3′-*O*-orthoester derivatives of ribonucleosides are described.

Nucleoside analogs containing an unsaturated sugar part are generally recognized as an important class of biologically active compounds with significant antiviral (anti-HIV, anti-HVB, anti-HCV, etc.) and antitumor activities.[1–4] Whereas several 2′,3′-unsaturated derivatives are in use or in clinical trials,[4] the 3′,4′-unsaturated nucleosides have been reported only rarely, mostly as intermediates of multistep synthetic routes (for adenine,[5–9] hypoxanthine,[6,7] and uracil[10] nucleosides). Recently, 3′-deoxy-3′,4′-didehydrocytidine was identified in a mixture with 2′-deoxy-1′,2′-didehydrocytidine as a tumor supressor.[11,12] Although formation of the corresponding 3′-deoxy-3′,4′-didehydronucleoside-5′-aldehydes upon prolonged treatment of the 2′,3′-*O*-acetal or ketal derivatives of ribonucleoside-5′-aldehydes with either silica gel or with a base has been patented,[10,13] no synthetic use for this approach has been reported in the literature. Later, 2′-deoxy-3′,4′-didehydropyrimidine nucleosides were prepared by treatment of a 2′-deoxy-5′-ethoxycarbonyl-3′-*O*-mesylnucleoside derivative with a base in DMF.[14] In the ribo series, the reported synthetic approaches employed conventional dehydrohalogenation of 3′-deoxy-3′-halo derivatives[6,8,15–17] prepared from nucleoside 2′,3′-*O*-orthoesters,[5] or oxidative elimination of 3′-deoxy-3′-phenylseleno derivatives obtained by a multistep procedure.[18] The formation of 3′-deoxy-3′,4′-didehydronucleoside derivatives as minor side products was observed upon Wittig reaction of nucleoside-5′-aldehydes protected with 2′,3′-*O*-orthoester or 2′,3′-*O*-isopropylidene moieties.[19–21]

In our study on oxidation of the 5′-OH group of ribonucleosides with various 2′,3′-*O*-protecting groups we found that upon Moffat oxidation (DMSO/DCC/TFA/pyridine) of 2′,3′-*O*-methoxymethylidene ribonucleosides **1**, two major products were formed: the expected 2′,3′-*O*-methoxymethylidene-5′-aldehyde **2** and a more polar compound, the structure of which was assigned, according to NMR spectra, as 3′-deoxy-3′,4′-didehydronucleoside-5′-aldehyde **3** (Scheme 1). The rapid conversion of **2** into **3** was achieved by addition of triethylamine to the reaction mixture. The resulting aldehydes **3** are stable upon isolation and characterization. In order to overcome work-up difficulties involving removal of excess DMSO and the side product dicyclohexyl urea, and to increase the isolated yields of aldehydes **3**, the Moffat oxidation procedure was modified using DMF as the solvent, a six-molar excess of DMSO with respect to the nucleoside, and EDC instead of DCC. The crude oxidation mixture was then treated briefly with Et_3N to complete the elimination, quenched using oxalic acid to decompose excess EDC, and concentrated at 35 °C in vacuo (13 Pa). No formation of by-products during this work-up was detected. This procedure afforded 3′,4′-didehydro-5′-aldehydes **3a–e**, both in the purine and pyrimidine series, in isolated yields of 69–89% (Scheme 1). A lower yield of cytosine derivative **3c** was due to partial loss of the *N*-benzoyl group during work-up of the oxidation mixture. Therefore, we performed, in three cases, the reduction step without isolation of aldehydes **3**, providing 3′,4′-didehydronu-

* Corresponding author.
E-mail address: ivan@uochb.cas.cz (I. Rosenberg).

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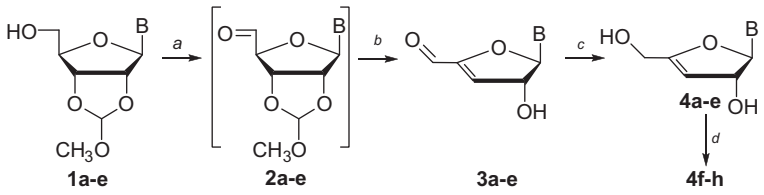
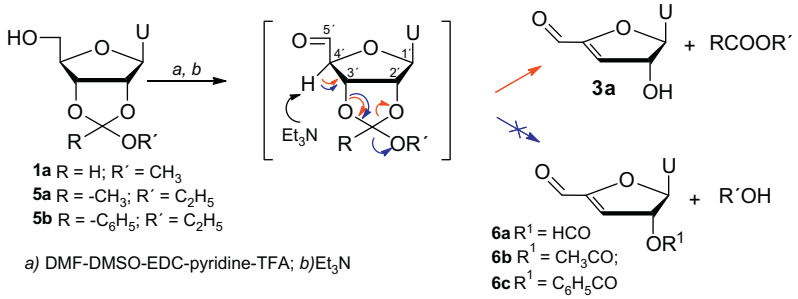


a) DMF-DMSO-EDC-pyridine-TFA; *b)* Et_3N; *c*) $NaBH_4$, MeOH, DMF; *d*) for **4b-d** CH_3NH_2-EtOH

B	U **a**	A^{Bz} **b**	C^{Bz} **c**	G^{iBu} **d**	T **e**	A **f**	C **g**	G **h**
1 → **3**	89	78	69	87	87			
3 → **4**	80	82	76	94	-			
1 → **4**	71[a]	64[a]	52[a]	82[a]	-			
1 → **4**	-	-	82[b]	87[b]	72[b]			
4 → **4**	-	-	-	-	-	93	85	86

[a] Yield from **1** over two steps with isolation of aldehyde **3**.
[b] Yield from **1** over two steps without isolation of aldehyde **3**.

Scheme 1. Synthesis and isolated yields (%) of 3′,4′-didehydronucleoside derivatives **3** and **4**.



1a R = H; R′ = CH_3
5a R = -CH_3; R′ = C_2H_5
5b R = -C_6H_5; R′ = C_2H_5

a) DMF-DMSO-EDC-pyridine-TFA; *b)*Et_3N

6a R^1 = HCO
6b R^1 = CH_3CO;
6c R^1 = C_6H_5CO

Scheme 2. Proposed elimination mechanisms.

cleosides **4c–e** in excellent yields of 82%, 87%, and 72%, respectively (Scheme 1).

The isolated 3′,4′-didehydro-5′-aldehydes **3a–d** were reduced into the corresponding 3′,4′-didehydro-nucleosides **4a–d** in high yields (76–94%; Scheme 1) by treatment with $NaBH_4$ in ice-cold DMF, containing a five-molar excess of methanol with respect to the aldehyde. Under these conditions, the *N*-acyl protecting groups on the nucleobase were stable. Their subsequent removal using an 8 M ethanolic solution of methylamine provided 3′,4′-didehydro-nucleosides **4f–h** (Scheme 1) in high yields (85–93%).

Considering the elimination mechanism, Zhang et al.[19] explained the observed minor formation of a 3′-deoxy-3′,4′-didehydroadenosine derivative during the Wittig reaction of 2′,3′-*O*-ethoxymethylideneadenosine-5′-aldehyde via orthoester moiety elimination, enabled by the increased acidity of H4′ resulting from the presence of a neighboring 5′-aldehyde group. Deprotonation of H4′ by the action of a base triggers elimination of the orthoester moiety upon cleavage of the C3′–O3′ linkage and formation of the 3′,4′-double bond to give 3′-deoxy-3′,4′-didehydronucleoside **3** possessing a free 2′-hydroxy group (Scheme 2, red arrows). However, another mechanism involving the formation of 2′-*O*-acylnucleoside **6** and an alcohol (Scheme 2, blue arrows) can also be considered since, in the case of 2′,3′-*O*-alkoxymethylidenenucleoside **1**, the formed labile 2′-*O*-formyl derivative **6a** would be prone to rapid deformylation during isolation. In order to decide which mechanism is likely, we subjected 2′,3′-*O*-1-ethoxyethylideneuridine (**5a**) and 2′,3′-*O*-ethoxybenzylideneuridine (**5b**) to the oxidation–elimination reaction and carefully analyzed the products. No formation of 2′-*O*-acetyl **6b** and 2′-*O*-benzoyl **6c** derivatives, respectively, was observed (Scheme 2) and compound **3a** possessing a free 2′-hydroxy group was isolated as the only nucleoside product. Since both 2′-*O*-acetyl and 2′-*O*-benzoyl groups would be stable under the nearly aprotic conditions of the oxidation–elimination reaction, the plausibility of the reaction mechanism originally proposed by Zhang[19] was confirmed unambiguously.

In conclusion, we have found that 2′,3′-*O*-orthoester derivatives of ribonucleoside-5′-aldehydes undergo base-catalyzed elimination of the orthoester moiety resulting in a quantitative yield of 3′-deoxy-3′,4′-didehydronucleoside-5′-aldehydes. The 5′-aldehyde group can be smoothly and rapidly reduced to give 3′-deoxy-3′,4′-didehydronucleosides using $NaBH_4$ in DMF with a limited amount of methanol, without the loss of *N*-acyl protecting groups. Moreover, the 3′-deoxy-3′,4′-didehydronucleoside-5′-aldehydes themselves represent useful and challenging synthons, offering a wide range of chemical transformations either on the 5′-aldehyde group (e.g., Wittig reactions and nucleophilic additions[22,23]) or on the vinyl ether type double bond (electrophilic reactions providing a variety of C4′-branched nucleoside derivatives[9,15,18]). Further study is underway.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.117.

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