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A Ferrier-Type Allylic Rearrangement of 3′-Deoxy-3′,4′-didehydronucleosides Mediated by DMF Dimethyl Acetal: Direct Access to 4′-Alkoxy-2′,3′-didehydro-2′,3′-dideoxynucleosides

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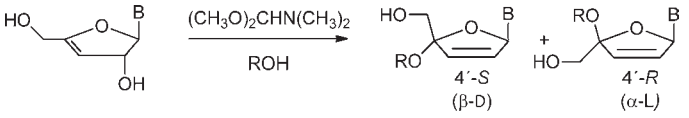
ABSTRACT



A straightforward synthesis of epimeric 4′-alkoxy-substituted 2′,3′-didehydro-2′,3′-dideoxynucleosides via a DMF dimethyl acetal mediated allylic rearrangement of 3′-deoxy-3′,4′-didehydronucleosides is described.

Nucleoside analogues possessing an unsaturated sugar moiety are an important class of biologically active compounds; d4T (Stavudine) has been approved for AIDS treatment, and β-L-d4FC (Elvucitabine) and β-D-2′-Fd4C are in clinical trials as anti-HIV and/or anti-HBV agents.[1] The recently reported 4′-ethynyl d4T derivative was more potent against HIV than stavudine and less toxic to CEM cell growth, whereas the 4′-cyano d4T analogue was 5 times less active than stavudine.[2] Various approaches at synthesizing 2′,3′-didehydro-2′,3′-dideoxynucleosides were reviewed,[3] as was the potential of 4′-*C*-substituted nucleosides (in ribo, 2′-deoxyribo, 2′,3′-dideoxy, and 2′,3′-didehydro-2′,3′-dideoxy series) for use in the treatment of HIV-1.[4] The design, synthesis, and properties of 4′-substituted ribonucleosides as inhibitors of HCV replication have been previously reported; in particular, 4′-azidocytidine has been shown to act as a potent and highly selective inhibitor.[5]

Epimeric 4′-alkoxy substituted derivatives have been previously prepared from O^2,4′-anhydronucleosides, 4′,5′-epoxy-, or 3′,4′-epoxynucleosides, in the presence of alcohol.[6] 4′-*C*-Branched 2′,3′-didehydro-2′,3′-dideoxyribonucleosides have been prepared by the treatment of 4′,5′-epoxynucleosides with various organosilicon or

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organoaluminum reagents,[7] or by the allylic substitution of 3′,4′-unsaturated nucleosides having a leaving group at the 2′-position.[8] Other synthetic approaches employ coupling reactions of sugar synthons with a nucleobase.[9]

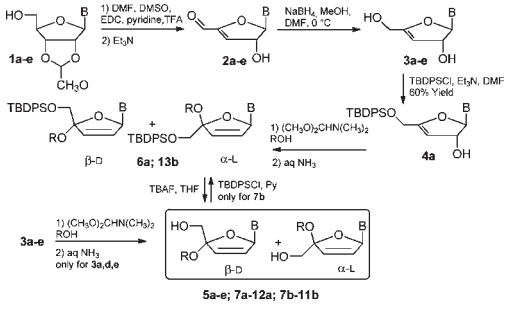
Given their broad interest and important applications discussed above, simplified synthetic pathways leading to various 4′-alkoxy substituted 2′,3′-unsaturated nucleoside derivatives would have a great impact, providing more facile access to potentially biologically active 4′-alkoxy derivatives. Herein, we describe a new, straightforward synthesis of epimeric 4′-alkoxy-substituted 2′,3′-didehydro-2′,3′-dideoxynucleosides from easily available 3′-deoxy-3′,4′-didehydronucleosides.[10]

Dialkylformamide acetals, in general, are useful reagents in nucleoside chemistry, e.g., for the selective introduction of the amidine-type protecting group for nucleobases,[11] for the transition protection of *cis*-diols in ribonucleosides,[12] and for the alkylation of the amide linkage of nucleobases.[13] The role of DMF acetals as leaving groups is well documented, for example, in the intramolecular displacement of the 5′-*O*-amidoacetal group by the 3-*N* atom of the xanthine nucleobase providing 3-*N*,5′-cyclo-xanthosine,[14] or in the decarboxylative elimination of the 3′-*O*-amidoacetal grouping of nucleoside-5′-carboxylate leading to dihydrofuryl nucleosides.[15] Upon heating, allylic DMF acetals undergo intramolecular rearrangement to β,γ-unsaturated dimethylamides.[16]

Having previously reported a straightforward, high-yielding synthesis of 3′-deoxy-3′,4′-didehydronucleosides **3** and the respective 5′-aldehydes **2** from nucleoside orthoesters **1** (Scheme 1),[10] we decided to further study their chemical transformations.[17] Surprisingly, our attempt to selectively protect the 6-*N*-amino group of 3′-deoxy-3′,4′-didehydroadenosine **3a** with a dimethylaminomethylene moiety using *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA)[18] in methanol resulted, apart from the formation of adenine, in the formation of 4′-epimeric β-D- and α-L-2′,3′-didehydro-2′,3′-dideoxy-4′-methoxyadenosine (**5a**) (see Table 1, entry 1). To the best of our knowledge, no DMF-DMA-mediated allylic rearrangement of nucleoside derivatives, as described above, has been reported so far. Typically, an acid catalyzed allylic rearrangement of optionally acylated 3-hydroxy glycals involving C-3 dehydroxylation with nucleophilic substitution is known as a Ferrier-type rearrangement and is applied to the transformation of glycals into 2,3-unsaturated glycosyl derivatives.[19] Alcohols, with the exception of phenols, generally undergo reaction with allyl acetates upon transesterification, and allylic alkylation is achieved only with complex metal catalysis.[20]

A series of 3′-deoxy-3′,4′-didehydronucleosides **3b**−**e** were treated with DMF-DMA in methanol (Scheme 1),[21] and 4′-methoxy derivatives **5b**−**e** were obtained in good to moderate yields (Table 1, entries 2−5). Whereas the transformation of pyrimidine derivatives proceeded smoothly (entries 2−4), providing better isolated yields, the use of purines (entries 1 and 5) was accompanied by substantial cleavage of the nucleoside bond (up to 50% according to the LCMS analyses of the crude reaction mixtures).

Scheme 1. Scope of Syntheses of 4′-Alkoxy-2′,3′-didehydro-2′,3′-dideoxynucleosides **5**−**13**



In addition, it was found that the rearrangement also proceeded with 3′,4′-didehydronucleoside-5′-aldehyde **2** as the starting compound; after *in situ* reduction using $NaBH_4$ in methanol and a subsequent treatment with DMF-DMA, 2′,3′-didehydro-2′,3′-dideoxy-4′-methoxy-5-methyluridine (**5b**) was prepared in good yield (entry 6). The recently published one-pot synthesis of 3′-deoxy-3′,4′-didehydronucleosides **3** starting from 2′,3′-*O*-methoxymethylideneribonucleosides **1**[10] encouraged us to adopt a one-flask approach (Scheme 1), including (a) the oxidation of 2′,3′-*O*-orthoester **1** with DMF-DMSO-EDC-pyridine-TFA to the 5′-aldehyde, (b) the Et_3N-mediated elimination upon formation of the 3′,4′-unsaturated 5′-aldehyde **2**, (c) the reduction of the 5′-aldehyde group using $NaBH_4$, (d) DMF-DMA-mediated allylic rearrangement of the 3′,

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(21) 5 Molar excess of DMF-DMA over the starting nucleoside was used, with subsequent removal of the exocyclic dimethylaminomethylene group from the cytosine and guanine nucleobase using aq ammonia treatment.

Table 1. Scope of Syntheses of 4′-Alkoxy-2′,3′-didehydro-2′,3′-dideoxynucleosides **5**–**13**

	starting compound		product			
entry	no.	B	no.	B	R	isolated yield β-D/α-L
1	**3a**	A	**5a**	A	CH_3	29/10
2	**3b**	T	**5b**	T	CH_3	39/32
3	**3c**	U	**5c**	U	CH_3	28/21
4	**3d**	C	**5d**	C	CH_3	42/13
5	**3e**	G	**5e**	G	CH_3	16/10
6	**2b**	T	**5b**	T	CH_3	38/28
7	**1a**	A^{Bz}	**5a**	A	CH_3	37/19
8	**1c**	U	**5c**	U	CH_3	20/7
9	**1d**	C^{Bz}	**5d**	C	CH_3	19/15
10	**1e**	G^{DMAM}	**5e**	G	CH_3	19/17
11	**3a**	A	**7a**	A	$CH_3OCH_2CH_2$	8/5
12	**3a**	A	**8a**	A	$CH_3SCH_2CH_2$	20/17
13	**3a**	A	**9a**	A	$HC{\equiv}CCH_2$	26/17
14	**4a**	A	**6a**	A	CH_3	38/22
15	**4a**	A	**10a**	A	$H_2C{=}CHCH_2$	29/19
16	**4a**	A	**11a**	A	F_3CCH_2	6/5
17	**4a**	A	**12a**	A	$N_3CH_2CH_2$	13/8
18	**3b**	T	**8b**	T	$CH_3SCH_2CH_2$	16/13
19	**3b**	T	**9b**	T	$HC{\equiv}CCH_2$	16/8
20	**3b**	T	**10b**	T	$H_2C{=}CHCH_2$	16/12
21	**3b**	T	**11b**	T	F_3CCH_2	25/11
22	**3b**	T	**7b**[a]	T	$CH_3OCH_2CH_2$	52
23	**7b**	T	**13b**	T	$CH_3OCH_2CH_2$	10/8[b]

[a] According to LCMS analysis, a nonseparable mixture of β-D/α-L. [b] Overall isolated yield starting from **3b**

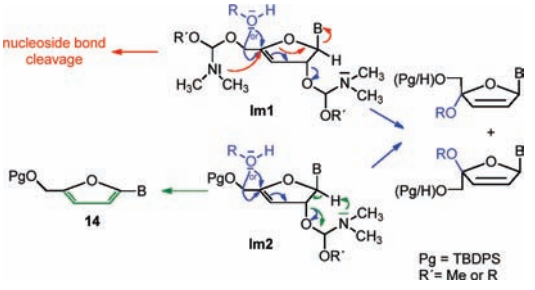
4′-didehydronucleosides **3**, and eventually (e) the final deprotection of the nucleobase exocyclic amino group using aq ammonia. Thus, pure epimers **5** of both purine and pyrimidine nucleosides were obtained in good isolated yields (over five reaction steps) (Table 1, entries 7–10). The only drawback of this one-flask approach was a rather laborious isolation of the final compounds from the reaction mixture, wherein both silica gel and reversed-phase chromatography had to be employed. To examine the possibility of introducing other 4′-alkoxy groups, the reaction of 3′-deoxy-3′,4′-didehydroadenosine (**3a**) with a series of alcohols was checked, and the desired epimeric 4′-alkoxy derivatives were obtained, although in lower yields, depending on the reactivity of the corresponding alcohol (Table 1, entries 11–13).[22] In all cases, LCMS analysis of the reaction mixture revealed, apart from the presence of the nucleobase and desired 4′-epimeric products, minor formation of epimeric 4′-methoxy derivatives **5a**, which likely arose due to the presence of methanol coming from the transacetalization reaction. An attempt to use DMF dineopentyl acetal as a less reactive reagent was unsuccessful; no desired product was formed, and substantial cleavage of the nucleosidic bond was instead observed.

(22) The respective alcohol was used as a solvent, or in a mixture with DMF to improve the solubility of the starting 3′,4′-didehydronucleoside.

To examine the role of the primary 5′-hydroxy group of the starting nucleoside **3** in the course of the rearrangement, we protected the 5′-hydroxy group with TBDPS.[23] As expected, the 2′,5′-bis-*O*-silylated compound remained intact when mixing with DMF-DMA and methanol, whereas the 5′-*O*-silyl derivative **4a** reacted smoothly, giving the 4′-methoxyadenosine derivative **6a** in very good yield (Table 1, entry 14). Next, the reactivity of allyl alcohol, trifluoroethanol, and 2-azidoethanol toward **4a** was examined, and after deprotection,[24] the desired epimerically pure 4′-alkoxyadenosine derivatives **10a**–**12a** were obtained, although in low yields (Table 1, entries 15–17). In these cases, according to LCMS analyses, a significant amount of furan derivative **14** was identified, as were minor amounts of the 4′-methoxyadenosine derivatives **5a**, as discussed above.

As a representative of pyrimidine derivatives more prone to this rearrangement, 3′-deoxy-3′,4′-didehydro-5-methyluridine (**3b**) was subjected to reaction with 2-methylthioethanol, propargyl alcohol, allyl alcohol, trifluoroethanol, and 2-methoxyethanol. According to LCMS analyses of the reaction mixtures, both thymine and the 4′-methoxy byproduct **5b** were identified, with the desired 4′-alkoxy derivatives **8b**–**11b** being the major products (entries 18–21). In contrast to all of the adenine 4′-alkoxy derivatives, which were conveniently separated by RP HPLC, the separation of the 4′-epimeric thymine derivatives proved to be more laborious; for example, the epimeric 4′-(2-methoxyethoxy) derivative **7b** was resolved into pure epimers only after a 5′-O-TBDPS group had been introduced (entry 23).[25]

Scheme 2. Proposed Reaction Mechanisms



As has been suggested by the diversity of the reaction byproducts obtained, the rearrangement reaction mechanism is rather complicated, involving several pathways leading to the various products. We propose that transacetalization of DMF-DMA with the unprotected 2′- and 5′-hydroxy groups of a 3′-deoxy-3′,4′-didehydronucleoside gives the 2′,5′-bis-*O*-dimethylamino(alkoxy)methyl intermediate **Im1**, which undergoes two main reactions

(23) TBDPSCl in pyridine gave the 2′,5′-bis-*O*-silylated derivative as the main product; TBDPSCl in DMF with Et_3N provided the 5′-*O*-silyl derivative **4a** in 60% isolated yield (with only 10% of the bis-silylated compound).

(24) Using aq ammonia followed by 0.5 M TBAF in THF.

(25) Separation conditions are discussed in detail in the Supporting Information

(Scheme 2): the desired allylic rearrangement (blue arrows), and nucleoside bond cleavage (red arrows). A "push−pull" mechanism, the simultaneous attack of the alcohol hydroxy group on a partially positively charged C4′ atom, and the withdrawal of the 2′-dimethylamino(alkoxy)methoxy group from **Im1**, seems to be the driving force of this allylic rearrangement. The 5′-*O*-dimethylamino(alkoxy)methyl group in **Im1** appears to be responsible for the nucleoside bond cleavage (red arrows). This is strongly supported by the finding that the 5′-*O*-TBDPS group-protected nucleoside intermediate **Im2** provided only traces of nucleobase even in the absence of alcohol. The extent of the nucleoside bond cleavage in **Im1** was found to depend strongly on the nucleophilicity of the alcohol used. The less reactive the alcohol, the more readily the nucleobase is formed. Treatment of the nucleoside **3a** with DMF-DMA in the absence of alcohol led to almost complete nucleoside bond cleavage. To support the proposed mechanism of the nucleoside bond cleavage (Scheme 2, the red route), we treated the 2′-*O*-TBDPS derivative of **3a** with DMF-DMA at rt for 16 h expecting the nucleoside bond cleavage. No nucleobase formation, however, was observed. This finding seems apparently to be in contradiction to the proposed mechanism (Scheme 2, the red route), but it is obvious that the nucleobase elimination proceeds only in connection with the allylic rearrangement. In contrast to pyrimidine nucleosides, the purine nucleosides were found to be more susceptible to nucleoside bond cleavage. The amount of the purine nucleobase formed depended on alcohol reactivity and varied from several to 50% (LCMS analyses).

The introduction of the 5′-*O*-TBDPS group reduced the nucleobase formation significantly; however, a new, furan-based nucleoside byproduct **14** was identified and presumably formed by a cyclic elimination mechanism of the **Im2** (Scheme 2, green arrows). We observed that furan **14** formation decreased with the increasing reactivity of the alcohol used, as was similarly observed for nucleoside bond cleavage.

As obvious from Table 1, the DMF-DMA mediated rearrangement proceeds with a moderate stereoselectivity for the β-D epimer. We can speculate that the 3′,4′-unsaturated sugar ring with the C4′-hydroxymethyl moiety is not strictly planar but can acquire two conformations with the O4′ atom oriented up and below the plane formed of the sugar ring carbon atoms. In this case, the dihedral angles C2′—C3′=C4′—O4′ of both conformers are different from zero, and thus, the C4′-hydroxymethyl substituent could be oriented either up or below the plane. Very likely, the "upper" orientation of the hydroxymethyl moiety is more advantageous, and thus, a preferential attack of the alcohol hydroxy group on the C4′ is from the less hindered "bottom" side, giving rise to a slight excess of the β-D epimer. The highest β-D/α-L ratio (> 2:1) was achieved for **5a**, **5d**, **5c**, and **11b**.

The structures of all of the nucleosides were confirmed by ^{1}H and ^{13}C NMR spectra.[26] The configuration at carbon atom C-4′ of nucleosides **5**−**13** was derived from NOE contacts detected in 2D-H,H-ROESY spectra. Observed NOE contacts of H-6 (pyrimidines) or H-8 (purines) with the H-atoms of the 4′-substituent proved its *cis*-orientation relative to the base (above the dihydrofuran ring), whereas the observed contacts of H-1′ with the H-atoms of the 4′-substituent indicated *cis*-orientation of that substituent relative to H-1′ (directed below the dihydrofuran ring). Very small vicinal coupling (J(1′,2′) = 1.5 Hz) and large allylic coupling (J(1′,3′) = 2 Hz), were observed in the whole series of C4′-epimers **5**−**13**, in agreement with the preferred ^{O}E form. Between the configuration at carbon atom C-4′ and chemical shifts of hydrogen H-1′, and carbon atoms C-1′ and C-4′, the following relation was found: $\delta_{\text{H-1}'}$ [4′*S*] > $\delta_{\text{H-1}'}$ [4′*R*]; $\delta_{\text{C-1}'}$ [4′*S*] > $\delta_{\text{C-1}'}$ [4′*R*]; and $\delta_{\text{C-4}'}$ [4′*S*] > $\delta_{\text{C-4}'}$ [4′*R*].

Significant differences in the IR spectra of all the studied nucleoside epimer pairs were observed in the region 1000−1200 cm^{-1}, with several bands of the β-D epimers occurring at higher frequencies than those of the α-L epimers.[27]

In conclusion, we have found that the exposure of 3′-deoxy-3′,4′-didehydronucleosides to DMF-DMA and alcohol at rt results in a Ferrier-type glycal allylic rearrangement upon formation of the C4′-epimeric 4′-alkoxy-2′,3′-didehydro-2′,3′-dideoxynucleosides. Although the formation of these compounds is accompanied by nucleoside bond cleavage and/or formation of a furan nucleoside, pure β-D and α-L epimers were obtained by means of preparative reversed-phase and/or silica gel chromatography. Moreover, a direct, one-pot synthesis of 4′-methoxy-2′,3′-didehydro-2′,3′-dideoxynucleosides was successfully elucidated, starting from the readily available 2′,3′-*O*-methoxymethylideneribonucleosides. We expect that this simple approach toward a wide range of 4′-alkoxy-2′,3′-didehydro-2′,3′-dideoxynucleosides will become a useful tool in the search for biologically active compounds. Despite the relatively low yields of the 4′-alkoxy derivatives in some cases, the reaction as introduced is worth further study because of the ready availability of the starting 3′,4′-unsaturated nucleosides. Studies on antiviral and anticancer properties of the prepared nucleoside analogues are in progress, and results will be reported in due course.

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Supporting Information Available. Full experimental and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

(26) See Tables 1S and 2S in the Supporting Information

(27) As illustrated in detail in the Supporting Information