Lewis Acid Mediated Reductive Ring Opening of 2-Methoxyethylidene Acetals: A New Approach to 2-Methoxyethyl (MOE) Ethers of *cis*-Diols

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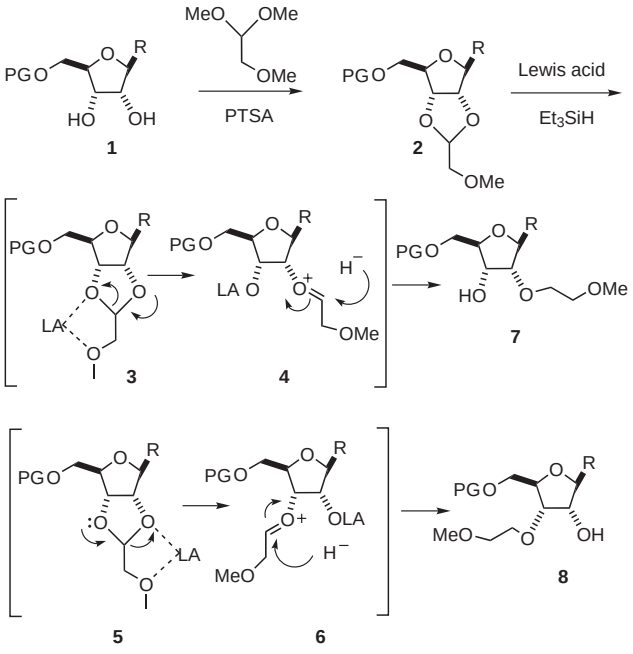
Abstract: The reductive opening of 2-methoxyethylidene acetals of vicinal diols in uridine and 1,4-anhydro-D-ribitol in the presence of $TiCl_4$ and Et_3SiH was investigated. The 3′-*O*-(2-methoxyethyl) ether of uridine and the 2′-*O*-(2-methoxyethyl) ether of 1,4-anhydro-D-ribitol were isolated and characterized. The results were rationalized based on coordination effects involving proximal substituents.

Key words: acetal, reductive opening, nucleoside, antisense

Selective etherification of vicinal diols has been an area of extensive study over the years, especially with the emergence of nucleoside 2′-*O*-alkyl ethers as modified subunits for the development of antisense therapeutic applications.[1,2] In particular, 2′-*O*-(2-methoxyethyl) nucleosides have gained considerable importance because their incorporation into antisense oligonucleotides has conferred high resistance to various nucleases, in addition to offering distinct advantages over non-modified counterparts as second-generation clinical candidates.[3–5] The potential of modified oligonucleotides as antiviral and anticancer agents is under intense study.[6]

There are several methods for the selective 2′-O-methylation of various purine and pyrimidine nucleosides.[1] There are comparatively fewer methods for the formation of the corresponding 2′-*O*-(2-methoxyethyl) ethers. One of the earliest reports by Martin[2a] utilized D-ribose as a starting material. Elaboration of known synthetic steps led to purine and pyrimidine nucleosides in which the 2′-OH group was unprotected. A similar sequence was also developed from D-glucose.[7] Alkylation of the 2′-OH group afforded the desired 2′-*O*-(2-methoxyethyl) ethers after deprotection. More recently, other approaches have been devised using appropriately O-protected nucleosides. Thus, Reese and coworkers[2b] developed an efficient ring opening of a 2,2′-anhydrouridine with aluminum 2-methoxyethoxide as a 'soft' nucleophile. Practical syntheses of 2′-*O*-(2-methoxyethyl) uridine and cytidine were thus developed. Theodorakis and coworkers[8] developed a new bis-silylating reagent [methylene bis(diisopropylsilyl)chloride] which engaged the 3′,5′-hydroxyls of guanosine, thereby allowing efficient alkylation of the 2′-OH group with 2-methoxyethyl bromide in the presence of NaHMDS. Ross and coworkers[1b] have described a highly efficient, two-step method to prepare 2′-*O*-anhydrouridine intermediate.

We considered a hitherto unexplored approach for the synthesis of 2′-*O*-(2-methoxyethyl) ether nucleosides such as **1** (Scheme 1) relying on the reductive opening of a 2-methoxymethyl-1,3-dioxolane unit in **2**. Thus, bidentate coordination of the 2- or 3-oxygen atoms in **3** or **5** with a Lewis acid would lead to the oxocarbenium ions **4** and **6**, respectively, which can undergo in situ reduction with triethylsilane to afford **7** or **8** as preponderant products or as a mixture. In the case of a purine or a pyrimidine analogue corresponding to **2**, the preferred product would be **7** in the context of antisense chemistry.



Scheme 1

In actual practice we chose uridine **9** as a model nucleoside. Thus, protection of the primary hydroxyl group as a *tert*-butyldiphenylsilyl ether[9] (**10**), followed by treatment with 2-methoxyacetaldehyde dimethyl acetal in the presence of PTSA in refluxing toluene gave the corresponding 2′,3′-*O*-(2-methoxyethylidene) acetal **11** as a single diastereomer in 75% yield (Scheme 2). We tentatively assign an *endo*-orientation for the methoxymethyl group based on NOE studies.[10] A smooth reaction took place in the

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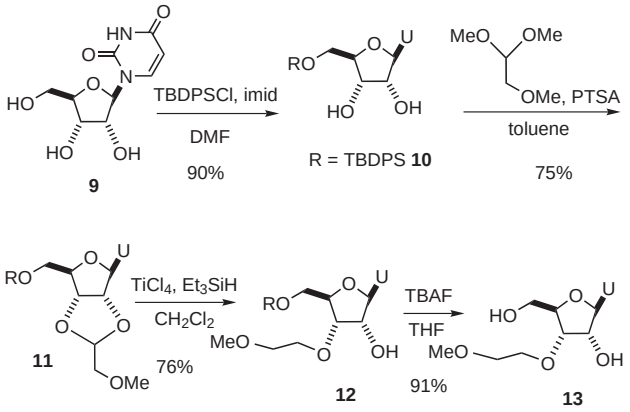
presence of $TiCl_4$ and triethylsilane to afford 5′-*O*-TBDPS uridine 3′-*O*-(2-methoxyethyl) ether **12** in 76% yield.[10] Treatment with TBAF gave uridine 3′-*O*-(2-methoxyethyl) ether **13** in excellent overall yield. A survey of several Lewis acids and reducing agents revealed $TiCl_4$ and Et_3SiH to be the best combination.[11] Dichloromethane was found to be the best solvent since precipitation or decomposition was observed with more polar solvents or solvent mixtures.[12]



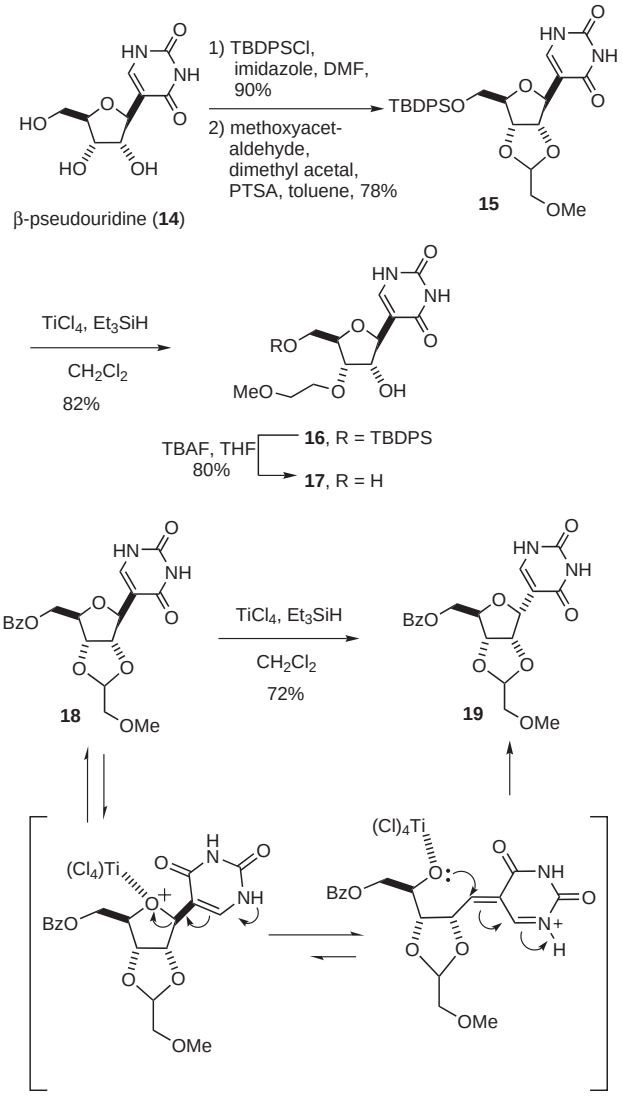
Scheme 2

A study of effect of substituents and protective groups on the reductive opening was hampered by insolubility. Thus, various 5′-esters of uridine (benzoate, acetate, pivaloate, methyl carbonate) were recovered unchanged after work up, reflecting on the possible formation of $TiCl_4$ complexes or aggregates involving the polar carbonyl groups in conjunction with the acetal oxygens.

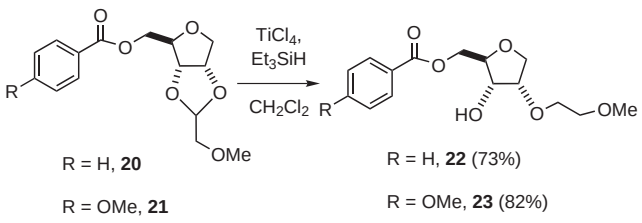
Suspecting an influence of the nucleobase on the reactivity of the C-2′–O atom in the initial coordination, we attempted the same reaction with β-pseudouridine[13] (**14**, Scheme 3). Once again, treatment of the corresponding acetal **15** with $TiCl_4$ and Et_3SiH gave the 3′-*O*-(2-methoxyethyl) ether **16** in 82% yield. Curiously, the corresponding 5′-benzoate **18** gave the anomerized *C*-nucleoside **19** without ring-opening. Evidently, in this case, activation of the furanosyl ring oxygen by the Lewis acid triggered ring-opening via an azadienium intermediate, which undergoes face-selective cycloetherification to α-pseudouridine (**19**, Scheme 3).

In an effort to probe the effect of the aglycone further, we conducted the reductive ring opening with the 5′-benzoate and *p*-bromobenzoate esters of 1,5-anhydro-D-ribitol acetals **20** and **21** (Scheme 4), which were also assigned as being *endo*-oriented according to NOE studies similar to the ones performed on **11**. In this case the corresponding 2′-*O*-(2-methoxyethyl) ethers **22** and **23** were obtained in 73% and 82% yields, respectively. The corresponding 5-*p*-nitrobenzoate, 5-*p*-methoxybenzyl, 5-TBDPS ethers, as well as various aliphatic 5-esters led to precipitates from which starting acetals could be recovered.

Clearly, the formation of insoluble complexes with $TiCl_4$ hampered our study of the effect of 1- and 5-substituents



Scheme 3



Scheme 4

on the regioselectivity of the reductive ring-opening reaction of furanosyl acetals. Nevertheless, a plausible explanation for the formation of the 3′-*O*-methoxyethyl ethers of 5′-*O*-TBDPS uridine acetals can be given in Figure 1. The prevalence of Ti-coordinated species such as **A** and **B** can be influenced by steric effects (TBDPS), and in addition by coordination to the pyrimidine group carbonyl as in **A** (or its dimer, etc.). The desired acetal coordination in **B** may not be prevalent in the equilibrium due to the steric effect of the TBDPS group, and more importantly, due to the lesser basicity of the C-2′ oxygen on account of its

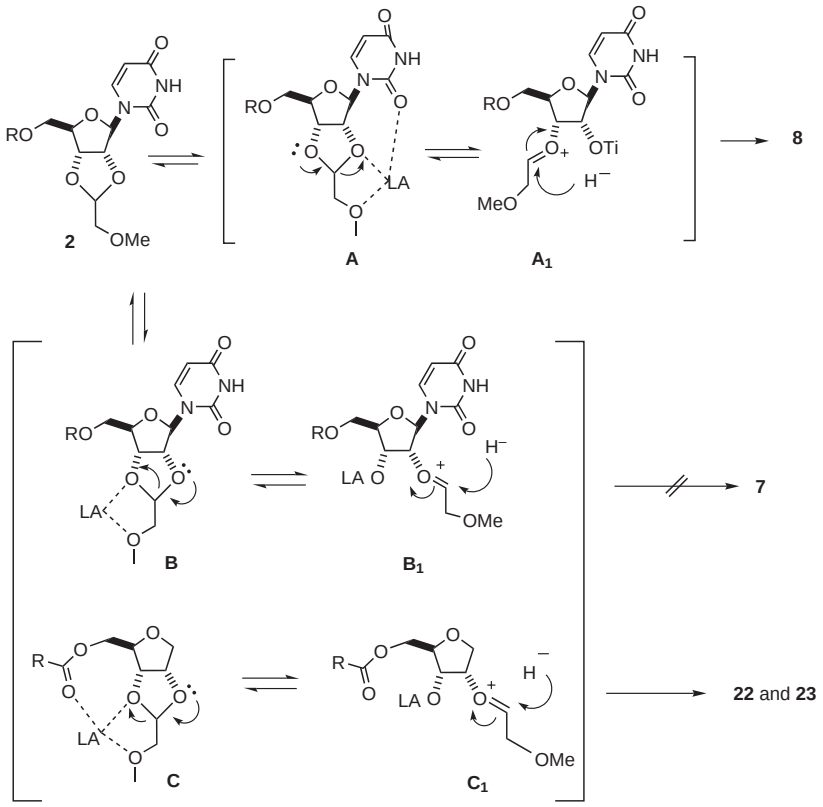


Figure 1

proximity to the anomeric carbon and a lower tendency to participate in oxocarbenium ion formation as in **B** → **B**$_1$. Evidently, a cooperative effect of the methoxy and uracilyl carbonyl group with the Lewis acid can sustain a weaker interaction with the C-2′ acetal oxygen in the formation of **8** via **A** → **A**$_1$.

This hypothesis is substantiated by the regioselective reversal of reductive opening in the case of the 1,5-anhydro-D-ribitol acetals **20** and **21**, where coordination can now occur between the ethylenedioxy moiety in conjuction with an additional anchoring with the ester carbonyl as in **C** en route to formation of the oxocarbenium **C**$_1$ and the observed 2′-*O*-(2-methoxyethyl) ethers **22** and **23**. The non-reactivity of the corresponding TBDPS ether under the same conditions demonstrates the importance of the 'third' coordination site involving the ester carbonyl. Presumably, this is compensated in the case of **2** by the uracilyl C-2 carbonyl. Thus, a combination of electronic, and to some extent steric effects seems to dictate the course of these $TiCl_4$-mediated reductive openings of 2′,3′-*O*-(2-methoxyethylidene) acetals.

There are a number of reported Lewis acid mediated ring openings of 1,3-dioxolane acetals,[14] but none, to the best of our knowledge, involving an 2-methoxyethylidene acetal as reported herein.

In conclusion, we have reported on the synthesis and reductive ring opening of 2′,3′-(2-methoxyethyl) ethylidene acetals of uridine, pseudouridine and the corresponding 1,4-anhydro-D-ribitol derivatives. The regioselectivity of opening depends on the presence of a proximal coordinative site such as an ester or a uracil carbonyl.

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(c) Typical Procedure **10** → **11** → **12**.
Compound **11**: to a mixture of **10** (4.5 g, 9.32 mmol) and PTSA (90 mg, 0.466 mmol) in toluene (65 mL) was added methoxyacetaldehyde dimethyl acetal (1.95 mL, 27.35 mmol). The mixture was stirred at 125 °C for 1 h, cooled to r.t. and concentrated. The crude product was purified by flash chromatography (5:1, EtOAc–hexane) to afford **11** (3.7 g, 6.87 mmol, 75%) as a white solid. R_f = 0.46 (5:1, EtOAc–hexane); mp 60–63 °C; $[\alpha]_D$ +4.9 (*c* 0.45, MeOH).
Compound **12**: to **11** (50 mg, 0.092 mmol) in CH_2Cl_2 (1.5 mL) at –78 °C was added $TiCl_4$ (0.92 mL, 0.92 mmol, 1 M CH_2Cl_2). The mixture was stirred at this temperature for 10 min, followed by the addition of Et_3SiH (0.6 mL, 3.68 mmol). The mixture was then slowly brought to r.t. over a period of 18 h. Then, H_2O (1.5 mL) and CH_2Cl_2 (1.5 mL) were added and the mixture and stirred for 10 min. The two phases were separated, the aqueous phase was extracted with CH_2Cl_2 (2 × 2 mL) and the organic phase was washed with NaCl (5 mL) and dried over Na_2SO_4. The organic layer was then concentrated and purified by flash chromatography (5:1, EtOAc–hexane) to afford **12** as a colorless oil (38 mg, 0.070 mmol, 76%). R_f = 0.19 (5:1, EtOAc–hexane); $[\alpha]_D$ +0.78 (*c* 7.00, MeOH).
(11) We have also used a combination of $ZnCl_2$/L-Selectride, $BF_3{\cdot}OEt_2/Et_3SiH$, however, no opening of the acetal was observed under these conditions.
(12) Decomposition was observed when MeCN and nitromethane were used as solvent.
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