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Efficient Synthesis of Methyl 3,5-Di-*O*-benzyl-α-D-ribofuranoside and Application to the Synthesis of 2′-*C*-*β*-Alkoxymethyluridines

Nan-Sheng Li,* Jun Lu, and Joseph A. Piccirilli*

Howard Hughes Medical Institute, Department of Biochemistry and Molecular Biology, and Department of Chemistry, University of Chicago, 929 East 57th Street, Chicago, Illinois 60637

nli@uchicago.edu; jpicciri@uchicago.edu

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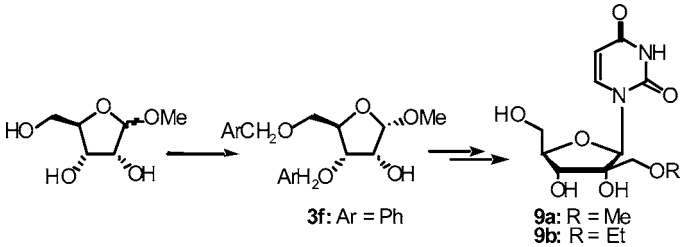
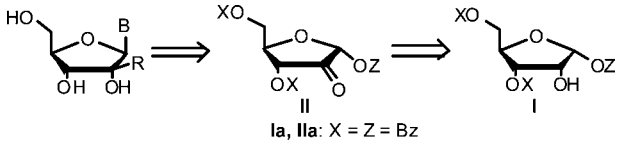
ABSTRACT



Methyl 3,5-di-*O*-arylmethyl-α-D-ribofuranosides have been used extensively as synthons to construct 2′-*C*-branched ribonucleosides. Herein, we describe efficient access to methyl 3,5-di-*O*-arylmethyl-α-D-ribofuranosides (aryl: 2-ClC$_6$H$_4$, 3-ClC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 2,4-Cl$_2$C$_6$H$_3$, Ph) in 72–82% yields from methyl D-ribofuranoside. We also demonstrate efficient access to the versatile precursor methyl 3,5-di-*O*-benzyl-α-D-ribofuranoside (3f) and the synthesis of 2′-*C*-*β*-methoxymethyl- and 2′-*C*-*β*-ethoxymethyluridine in six steps from 3f with overall yields of 18% and 32%, respectively.

2′-*C*-Branched ribonucleosides represent an important and diverse class of nucleoside analogues with potential both as therapeutic agents and as probes to define the relationship between nucleic acid structure and biological function.[1] In this work we sought to prepare 2′-*C*-*β*-methoxymethyl- and 2′-*C*-*β*-ethoxymethyluridines as members of a series of 2′-*C*-branched ribonucleosides for investigating the mechanism of RNA cleavage.[2] Construction of these nucleosides often begins with a partially protected ribose derivative such as **Ia**−**d** (Scheme 1). Perbenzylation of methyl ribofuranoside followed by tin(IV) chloride ($SnCl_4$)-mediated selective *O*-2 debenzylation allows access to **Ib** and **Ic**.[3] Subsequent oxidation, branch installation, and glycosylation after suitable protection has enabled synthesis of a variety of 2′-branched nucleosides.[1a,4] During our efforts to synthesize 2′-*C*-*β*-alkoxymethyluridines,[5] we encountered two apparent limitations with the selective debenzylation reaction. First, only

Scheme 1



Ia, IIa: X = Z = Bz
Ib, IIb: X = 2,4-Cl$_2$C$_6$H$_3$CH$_2$, Z = Me
Ic, IIc: X = 4-ClC$_6$H$_4$CH$_2$, Z = Me
Id, IId: X = PhCH$_2$, Z = Me

(1) (a) Harry-O'kuru, R. E.; Smith, J. M.; Wolfe, M. S. *J. Org. Chem.* **1997**, *62*, 1754 and references cited therein. (b) Gordon, P. M.; Fong, R.; Deb, S.; Li, N.-S.; Schwans, J. P.; Ye, J.-D.; Piccirilli, J. A. *Chem. Biol.* **2004**, *11*, 237. (c) Schwans, J. P.; Li, N.-S.; Piccirilli, J. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3033.

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the β anomer of methyl ribofuranoside has served as a substrate, thereby limiting the overall yield from D-ribose.[3] Second, $SnCl_4$ catalyzes intramolecular C-arylation when the benzyl group lacks electron-withdrawing groups,[6] apparently precluding access to the potentially more versatile, non-halogenated partially protected ribose derivative **Id**. Herein, we address these limitations to allow efficient access to methyl 3,5-di-*O*-benzyl-α-D-ribofuranoside (**3f**). We then use **3f** to access 2′-*C*-*β*-methoxymethyl- and 2′-*C*-*β*-ethoxymethyluridines.

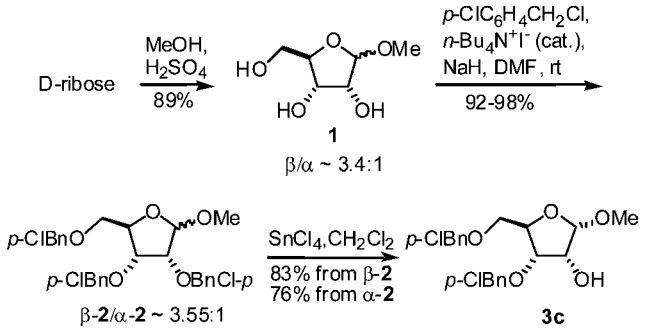
Beginning with the reaction conditions developed by O. Martin[3a] (Table 1; entry 1) and P. Martin[3b] for the synthesis of methyl 2,3,5-tri-*O*-(4-chlorobenzyl)-*β*-D-ribofuranoside (**2**) and methyl 2,3,5-tri-*O*-(2,4-dichlorobenzyl)-*β*-D-ribofuranoside, respectively, we optimized conditions for 4-chlorobenzylation of methyl ribofuranoside (Table 1). We found that inclusion of tetrabutylammonium iodide (3% equiv) improved yield significantly, possibly via in situ generation of 4-chlorobenzyl iodide, a more reactive benzylating agent than 4-chlorobenzyl chloride. Proceeding to the debenzylation step, we first tested whether the α anomer could serve as a substrate. We found that in the presence of $SnCl_4$ (0−4 °C for 36 h), α-**2** gives **3c** in 76% yield, similar to the yield from *β*-**2** (83%) (Scheme 2). Together with the improved synthesis of **2** (Table 1, no. 2), the ability to access **3c** from α-**2** increases the overall yield of **3c** from D-ribose compared to the previous synthesis[3a] (70% vs 51%).

Table 1. Preparation of **2**

no.[a]	molar ratio of **1**:NaH:4-ClBnCl	solvent	catalyst[b]	time (h)	yield[c] (%)
1[d]	1:9.3:9.5	DMSO	−	15[e]	81
2	1:6.0:6.0	DMF	+	3	98
3	1:4.5:4.5	DMF	+	3	93
4	1:3.3:3.3	DMF	+	9	92
5	1:4.5:4.5	DMF	−	3	85

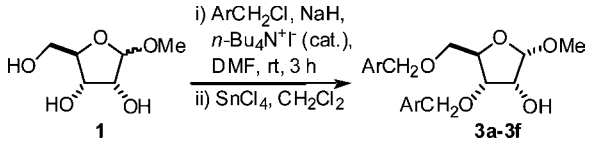
[a] All reactions were carried out under argon at room temperature. [b] *n*-$Bu_4N^+I^-$ (3% equiv) was used as catalyst. [c] Combined isolated yield of *β*-**2** plus α-**2**. [d] Reference 3a; dimsyl sodium was used as a base and prepared in situ from sodium hydride and dry Me_2SO at 60 °C for 45 min; methyl D-ribofuranoside ($\beta/\alpha \approx 10:1$) was prepared according to Barker and Fletcher (Barker, R.; Fletcher, H. G., Jr. *J. Org. Chem.* **1961**, *26*, 4605), and only *β*-**2** was isolated. [e] Overnight reaction.

Scheme 2



Finally, we used our optimized conditions[7] to synthesize a variety of methyl 3,5-di-*O*-arylmethyl-α-D-ribofuranosides (**3**) (Table 2). We first prepared methyl 2,3,5-tri-*O*-haloarylmethyl-α/*β*-D-ribofuranosides from **1** and the corresponding arylmethyl chlorides. After workup, the crude mixtures were treated with $SnCl_4$ (0 °C to room temperature over 24 h) to give **3a**−**e** in yields ranging from 75% to 82%.

Table 2. Preparation of **3a**−**f**



no.	product	Ar	conditions ii[a]	yield (%)[b]
1	**3a**	2-ClC_6H_4	0 °C to rt, 22 h	82
2	**3b**	3-ClC_6H_4	0 °C to rt, 23 h	75
3	**3c**	4-ClC_6H_4	0 °C to rt, 28 h	75
4	**3d**	4-BrC_6H_4	0 °C to rt, 24 h	75
5	**3e**	2,4-$Cl_2C_6H_3$	0 °C to rt, 24 h	75
6	**3f**	Ph	0 °C to rt, 18 h	61
7	**3f**	Ph	0−4 °C, 48 h	72

[a] Reaction conditions ii are for the $SnCl_4$-mediated reaction. [b] Isolated yield based on methyl ribofuranoside (**1**).

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(5) We focused on **Ib**−**d** (protected with benzyl ethers) as synthons for 2′-*C*-*β*-alkoxymethyluridines because the benzoate esters of **IIa** react with Grignard reagents used to install the alkoxymethyl branch at C-2.

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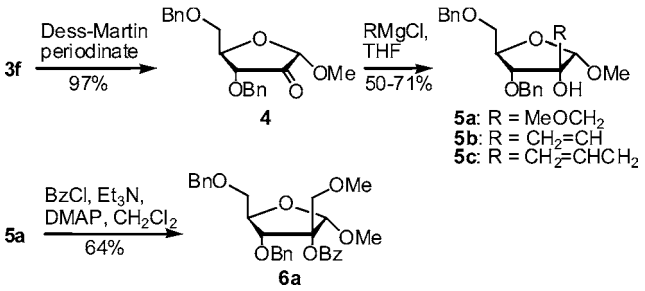
(7) Perbenzylation reactions were carried out with **1**:NaH:arylmethyl chloride:*n*-$Bu_4N^+I^-$ (1:4.5:3.0:0.03) in DMF at room temperature for 3 h. Our procedure eliminates the need to separate the anomers of 2,3,5-tri-*O*-halobenzyl-α/*β*-D-ribofuranosides.

Among the methyl 3,5-di-*O*-arylmethyl-α-D-ribofuranosides, methyl 3,5-di-*O*-benzyl-α-D-ribofuranoside (**3f**) may provide the most versatile intermediate for the synthesis of 2′-*C*-branched nucleosides, as benzyl ethers tolerate a greater variety of conditions than do halobenzyl ethers. Nevertheless, only one report has appeared in the literature describing the use of **3f** for the synthesis of nucleosides,[8] possibly because access to this compound has required a multistep synthesis (eight steps from D-xylose with 14% overall yield[8,9]). We know of no reported attempts to access **3f** via the perbenzylation/selective debenzylation reaction sequence, possibly due to anticipated problems with selective debenzylation. In the presence of $SnCl_4$, benzylated glycofuranosyl acetates undergo efficient intramolecular Friedel−Crafts alkylation rather than 2-*O*-debenzylation.[6] These observations led to the expectation that chemoselective 2-*O*-debenzylation requires deactivated benzyl substituents.[6] However, along with the *C*-arylation product (30% yield) methyl 2,3,5-tri-*O*-(3-methylbenzyl)-*β*-D-ribofuranoside gives some debenzylation product (49% yield)[6b] suggesting that the methyl glycoside may favor debenzylation. We examined $SnCl_4$-mediated debenzylation of methyl 2,3,5-tri-*O*-benzyl-α/*β*-D-ribofuranoside, reasoning that the less activated phenyl ring might resist C-arylation of the methyl glycoside. We prepared methyl 2,3,5-tri-*O*-benzyl-D-ribofuranoside as a mixture of anomers. Exposure to $SnCl_4$ at 0−25 °C for 18 h converted the anomeric mixture to **3f** in 61% yield with no evidence of the C-arylation product (Table 2, no. 6). Longer exposure at low temperature (0−4 °C for 48 h) increased the yield of **3f** to 72% (Table 2, no. 7). This synthesis allows more efficient access to **3f** (64% in three steps from D-ribose) than the previous synthesis (14% in eight steps from D-xylose[8,9]).

We used **3f** to construct alkoxymethyluridines for investigating the mechanism of RNA cleavage.[2] Dess−Martin periodinane oxidation of **3f** gave 3,5-di-*O*-benzyl-2-keto-1-α-*O*-methyl-D-ribofuranose (**4**) in 97% yield (Scheme 3).

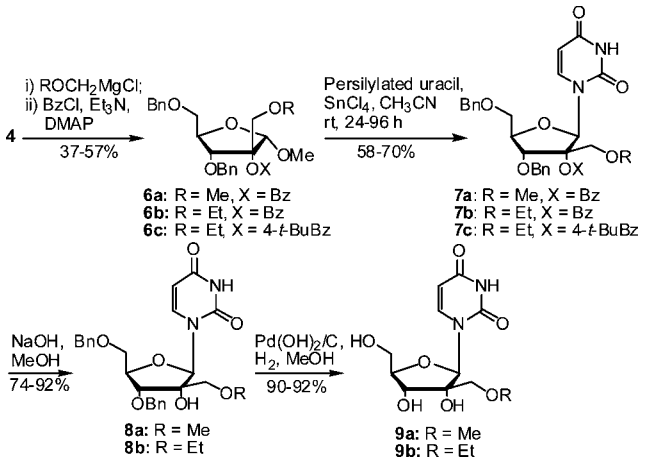
Scheme 3



Unstable alkoxymethylmagnesium chlorides such as methoxymethyl- and ethoxymethylmagnesium chlorides require in situ preparation from alkoxymethyl chlorides and magnesium at low temperature (−25 to −30 °C).[10] We obtained di-*O*-benzyl-2-*C*-*β*-methoxymethyl-1-α-*O*-methyl-D-ribofuranose (**5a**) in 50% yield by treating **4** with in situ prepared methoxymethylmagnesium chloride[11] at −78 °C for 1 h, then at room temperature for 48 h. Reactions of vinylmagnesium chloride and allymagnesium chloride with ketone **4** at −78 °C to room temperature for 16 h gave **5b** and **5c** in 57% and 71% yield, respectively.

To prepare the sugar for stereoselective glycosylation, we treated **5a** with BzCl in the presence of DMAP and obtained the corresponding benzoate ester **6a** in 64% yield (32% overall yield from **4**). Using crude **5a**, we obtained **6a** in 37% overall yield from **4** (Scheme 4). Analogously, using

Scheme 4



the crude addition product from reaction of ethoxymethylmagnesium chloride and ketone **4**, we obtained **6b** in 49% overall yield (Scheme 4).

Glycosylation of persilylated uracil with **6a** in the presence of $SnCl_4$ (at room temperature for 48 h) gave uridine derivative **7a** in 70% yield. With **6b** as the glycosyl donor, reactions required 96 h and gave uridine derivative **7b** in only 58% yield. As a possible strategy to improve the reaction, we prepared **6c** (57% yield), expecting that the electron-donating *tert*-butyl substituent might stabilize the 1,2-acyloxonium ion intermediate that putatively forms during the glycosylation reaction. **6c** reacted with persilated uracil within 24 h and gave **7c** in 68% yield. Although we could protect **5a** by reaction with acetic anhydride (6 equiv) (triethylamine (10 equiv) and DMAP (0.2 equiv) in the absence of solvent; ∼29% yield), the resulting 2′-*O*-acetate derivative reacted very slowly with persilylated uracil. Continuing with the synthesis of the target nucleosides, sodium hydroxide treatment converted **7a** to **8a** in 79% yield, and **7b** and **7c** to **8b** in 74% and 92% yield, respectively. Palladium(II) hydroxide-catalyzed hydrogenation removed

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(11) Ketone addition reactions usually give yields ranging from 35% to 82% depending upon the steric environment of the carbonyl group. See: De Botton, M. *Bull. Soc. Chim. Fr.* **1973**, 2472.

the benzyl groups efficiently to give the target nucleosides, 2′-*C*-*β*-methoxymethyluridine (**9a**) and 2′-*C*-*β*-ethoxymethyluridine (**9b**) in 92% and 90% yield, respectively.[12]

In summary, we have established an efficient strategy for acquisition of methyl 3,5-di-*O*-arylmethyl-α-D-ribofuranosides, which serve as valuable precursors for the synthesis of 2′-*C*-branched nucleosides. We improved the procedure for benzylation of methyl ribofuranoside and extended the scope of the subsequent O-2 selective debenzylation reaction to include α-anomers. Using this three-step strategy, we demonstrated efficient access to methyl 3,5-di-*O*-benzyl-D-ribofuranoside, a potentially more valuable intermediate for nucleoside synthesis. Benzyl ethers tolerate a wider range of reagents and conditions than do the corresponding chorobenzyl ethers, including organometallic reagents (RLi/E^+,[13] $ArB(OH)_2$/Pd(II) complex,[14] and $ArSnBu_3/Cu_2O$, etc.[15]). We used **3f** to develop efficient syntheses of 2′-*C*-*β*-methoxymethyluridine (**9a**) and 2′-*C*-*β*-ethoxymethyluridine (**9b**). In constructing these uridine analogues, we generated a series of glycosyl donors esterified at the C-2 hydroxyl group as the acetate, benzoate, or *tert*-butylbenzoate ester. Glycosylation efficiency followed the order 4-*t*-BuBz > Bz > Ac, presumably reflecting the relative stability of the corresponding 1,2-acyloxonium ion intermediates. This reactivity trend, which has not been reported previously, suggests a possible general strategy to improve glycosylation reactions involving sterically hindered or electron-poor glycosyl donors.

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Supporting Information Available: Experimental procedures, compound characterizations, ^1H and ^{13}C NMR spectra of **9a** and **9b**, and ^{13}C NMR spectra of all other compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) The 2′-*β*-configurations of **9a** and **9b** were confirmed by NOSEY experiment. We obsevered strong NOEs between H-6 and 2′-CH_2OR (R = Me, Et), suggesting that the nucleobase and 2′-CH_2OR are on the same side of the ribose ring.

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