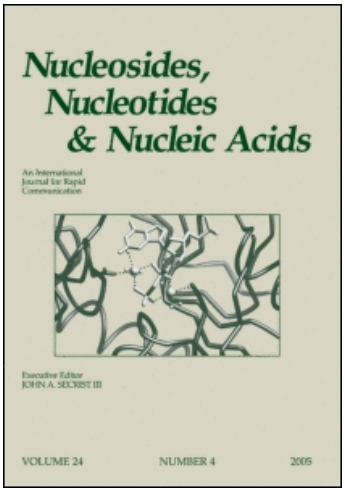

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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Online publication date: 09 August 2003

To cite this Article Serebryany, V. and Beigelman, L.(2003) 'Synthesis of 2'-*O*-Substituted Ribonucleosides', Nucleosides, Nucleotides and Nucleic Acids, 22: 5, 1007 — 1009
To link to this Article: DOI: 10.1081/NCN-120022724
URL: http://dx.doi.org/10.1081/NCN-120022724

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Vol. 22, Nos. 5–8, pp. 1007–1009, 2003

Synthesis of 2′-*O*-Substituted Ribonucleosides

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ABSTRACT

An efficient synthesis of 2′-*O*-substituted ribonucleosides, including 2′-*O*-TBDMS and 2′-*O*-TOM protected as well as 2′-*O*-Me and 2′-*O*-allyl derivatives is presented. Di-*t*-butylsilylene group was employed for simultaneous protection of 3′- and 5′- hydroxyl functions of nucleoside on the first step. Subsequent silylation or alkylation of free 2′-OH followed by introduction of suitable protection on the base moiety and removal of cyclic silyl protection gave target compounds in a high yield.

Increasing demand for synthetic RNA-based therapeutics has stimulated a search for efficient routes toward 2′-*O*-protected or other 2′-*O*-substituted ribonucleosides. However, large-scale preparation of such compounds is usually complicated due to the necessity of the separation of 2′- and 3′-isomers by chromatography. This complication could be overcome if suitable protecting group for simultaneous protection of 3′- and 5′-hydroxyl groups of starting nucleosides is employed. It has been shown that di-*tert*-butylsilylene protection[1,2] of 5′- and 3′-hydroxyls can be orthogonal to TBDMS protecting group.[3] We were interested if this synthetic methodology could be applied for the preparative synthesis of 2′-*O*-substituted nucleosides.

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DOI: 10.1081/NCN-120022724
1525-7770 (Print); 1532-2335 (Online)

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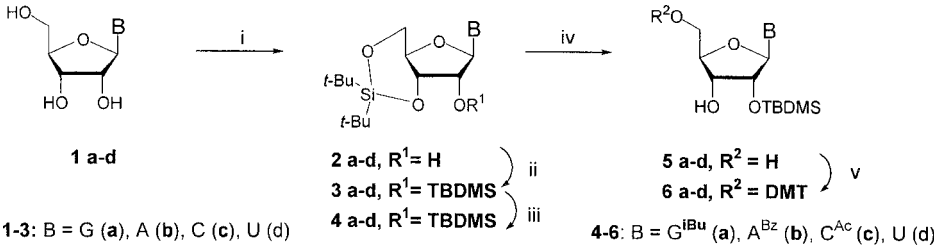
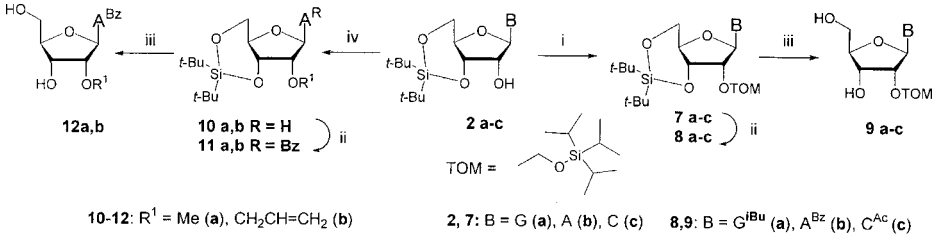


Scheme 1. Reagents & Conditions: i) t-$Bu_2Si(OTf)_2$, Im, DMF, 0°C; ii) t-$BuMe_2SiCl$, Im, DMF, 60°C, 80–87% (two steps); iii) **4a**: *i*Bu-Cl, Py-CH_2Cl_2, then $MeNH_2$, 96%; **4b**: Bz-Cl, Py, then morpholine, 77%; **4c**: Ac_2O, Py, 76% from **1c**; iv) HF-Py, CH_2Cl_2, 0°C, 90–95%; v) DMT-Cl, Py, 0°C, 90%.

2′-*O*-TBDMS-5′-*O*-DMT-protected nucleosides **6a–d** were obtained according to the Sch. 1.[4] Starting nucleosides **1–d** were reacted with t-$Bu_2Si(OTf)_2$ as described[3] to afford 3′,5′-*O*-protected intermediates **2a–d**. Without isolation from the reaction mixture, compounds **2a–c** were silylated to produce derivatives **3a–d** as crystalline solids in 80–87% yield. Acylation of base amino functions gave fully protected crystalline compounds **4a–c.** Subsequently, di-*tert*-butylsilylene protection was removed using HF-Py in dichloromethane to obtain diols **5a–d**, which were treated with DMT-Cl in pyridine to give **6a–d,** no significant 2′ → 3′-silyl migration was observed. Overall yield of target compounds **6a–d** from the starting nucleosides **1a–d** is 60–66%. All key intermediates, as well as the final compounds **6a** and **6c** are crystalline thus eliminating chromatographic purification steps. In the synthesis of **6b,d** only final chromatography step is necessary. A similar sequence of reactions was used for the preparation of 2′-*O*-TOM nucleosides[5] (Sch. 2). 5′,3′-*O*-Silylated nucleosides **2a–c** were reacted with TOM-Cl in the presence of DBU, resulting in protected derivatives **7a–c**. Subsequent acylation of base amino functions in **7a–c** provided fully protected intermediates **8a–c**. We found that the treatment of compounds **8a–c** with HF-Py in CH_2Cl_2 at 0°C leads to completely selective removal of 5′,3′-protection, leaving TOM group intact. Unfortunately, in the case of uridine, only products of base alkylation were detected in the reaction with TOM-Cl/DBU.



Scheme 2. Reagents & Conditions: i) TOM-Cl, DBU, THF, 0°C, 70–75%; ii) **8a**: *i*Bu-Cl, Py, then $MeNH_2$, 80%; **8b**: Bz-Cl, Py, then morpholine, 77%; **8c**: Ac_2O, Py, 75%; iii) HF-Py, CH_2Cl_2, 0°C, 95%, iv) Me_2SO_4 or allyl iodide, NaH, DMF, −20°C, 65%.

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Analogous approach was also used for the synthesis of 2′-*O*-Me and 2′-*O*-allyl adenosine. Treatment of **2b** with dimethyl sulfate or allyl iodide in the presence of NaH provided 2′-alkylated adenosines **10a,b** in 60–65% yield. Subsequent benzoylation followed by removal of 5′,3′-protection resulted in the target adenosine derivatives **12a,b**. It is important to note, that synthesis of 2′-*O*-Me adenosine **12a** does not require any chromatography purification – all intermediates (**2b**, **10a**, **11a**) as well as the final compound **12a** were isolated by crystallization.

In summary, an efficient methodology for the preparation of 2′-*O*-TBDMS, 2′-*O*-TOM protected as well as 2′-*O*-alkyl nucleosides using di-*t*-butylsilylene protection for 5′,3′-hydroxyl groups has been developed.

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