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A Reverse Strategy for synthesis of nucleosides based on *n*-pentenyl orthoester donors†

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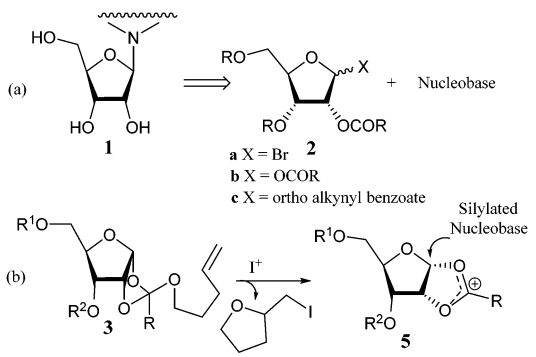
Strategically derivatized NPOE glycosyl donors, are able to efficiently glycosylate silylated nucleobases under mild conditions, even as low as −78 °C if necessary. Ensuring *trans*-1,2 glycosylation, thus permitting, unlike classical procedures, a Reverse Strategy for the synthesis of ribonucleosides, where glycosylation occurs late, rather than early, and convergency is optimized.

Ribonucleosides, **1**, are arguably the most prominent family of organic compounds employed in the broad spectrum of biological and medicinal chemistry.[1] Structurally, they may be regarded as ribosylamines and so direct combination of ribose and nucleobase sub-units have benefitted from donor/acceptor developments in glycosidation chemistry. Thus Hilbert and Johnson in 1929,[2] employed the seminal 1901 Koenigs and Knorr process,[3] which had shown that *solid* reaction partners could be combined (a) efficiently and (b) with high stereoselectivity. However, the use of heavy metal promoters was not tolerated well and by 1933, Helferich and Schmitz-Hillebrecht had developed glycosidation by glycosyl acetates, **2b**.[4] Forty years later, these donors were adapted by Vorbruggen *et al.*[5] providing the basis of today's preeminent protocol.[6]



However, nucleobases are weak nucleophiles and therefore compete poorly with the acyloxy unit released by glycosyl ester donors, **2b**. Unfortunately replacement with favoured glycosidation leaving groups[7–9] have had limited success. A recent variation of the Vorbruggen ribosyl ester, introduced by Yu and coworkers,[10] uses an *ortho*-alkynyl benzoate as leaving group, **2c**, which upon treatment with a gold catalyst is removed from competition by formation of an isocoumarin.

Stereoselectivity of the Koenings–Knorr coupling (item b), was not rationalized until 1939,[11] when Isbell discovered the phenomenon of neighboring group participation.[12] Use of a 2′-*O*-acyl group in donor **2** with EARLY installation of the nucleobase, to optimize β-D orientation, has become standard operational practice. However ester protecting groups disarm donors,[13,14] and coupling with non-nucleophilic acceptors, being unfavorable, usually requires Lewis acids with heating.[15] But this is fraught, because the reactants are sensitive, densely and differently functionalized, and inter-domain interactions, rearrangements, departure/reassembly phenomena, *etc.* may result.

In this manuscript we report that ribofuranosyl *n*-pentenyl orthoesters (NPOE) donors, *e.g.* **3**, described recently by us,[16] can be coupled with silylated nucleobase acceptors under the agency of iodonium ion at room temperature – or as low as −78 °C if required (*see below*). The process, eqn (b), is facilitated by sequestration of the released *n*-pentenyloxy as volatile 2-iodomethyl tetrahydrofuran, **4**,[17] leaving behind the dioxolenium intermediate **5**, poised for stereoselective β-D coupling to the nucleobase. The procedure allows ready protecting group differentiation between positions 3′ and 5′, and a free C3′–OH can be accommodated. Efficiency in glycosylation by the NPOE donor emanates from the substantial strain energy of the bicyclo [3.3.0] framework of **3**, which enables such mild reaction conditions, that extensive manipulations to sugar or nucleobase domain can be carried out *prior to* coupling. As a result, the process is highly convergent. Furthermore, bothersome emulsions are never encountered during work-up.[18]

Exploratory studies in glycosylation conditions with NPOE **6** revealed 0 °C to rt in CH_3CN to be optimal.[19] Thus results for

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‡ An independent non-profit research facility with laboratories at CiVentiCHEM, P.O. Box 12041, Research Triangle Park, NC 27709, USA.

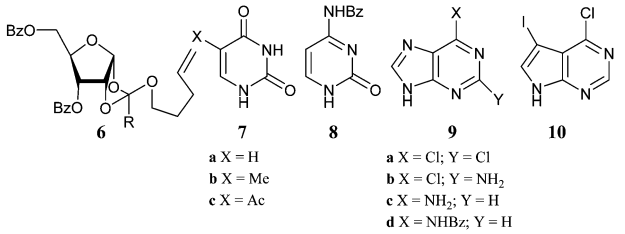


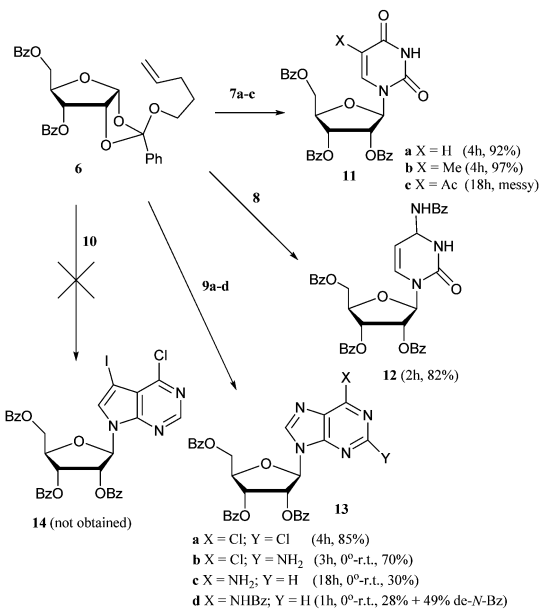
Fig. 1 *n*-Pentenyl orthoester (NPOE) **6** and nucleobases **7–10**.

reactions with nucleobases, **7–10** are (Fig. 1) shown in Schemes 1–3, where *the last reaction in all cases was installation of the nucleobase*. Uracil and thymine, **7a** and **7b**, gave excellent yields of nucleoside **11a** (92%) and **11b** (97%) after 4 hours. By contrast, the reaction of nucleobase **7c** was messy, an outcome that we attributed to the deactivating effect of the electron-withdrawing acyl group on the pyrimidine ring. Indeed, the electron-rich counterpart, **8**, gave nucleoside **12** in 82% yield in two hours. Extension to purine nucleobases was considered to be a critical test, because Yu and coworkers[10] noted recently that purine acceptors are "much more poorly nucleophilic".

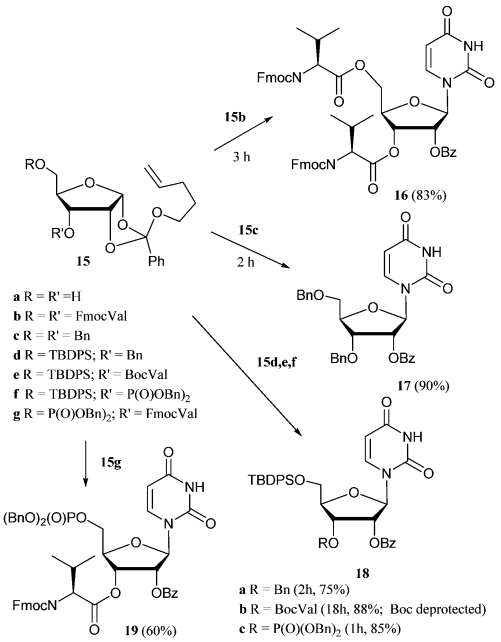
However our results with purine nucleobases were informative (Scheme 1). The 2,6-dichloro derivative, **9a**, afforded nucleoside **13a** in 85% yield after 4 hours. The 2-amino-6-chloro analog **9b** also underwent very good glycosylation to give **13b**. The results with substrate **9c** suggest that a free amino group has an inhibiting effect, and so overnight reaction at room temperature was required to effect glycosylation – albeit modest. On the other hand, the *N*-benzoylated analog, nucleobase **9d** afforded nucleoside **13d** in good yield. Interestingly, we did not obtain product **14** when we attempted to glycosylate the N-7 carba purine **10**.

Removal of the C3′ and C5′ benzoates gave NPOE diol **15a** and thus the bis-valinoyl donor **15b** which glycosylated uracil smoothly to give nucleoside **16** (Scheme 2).

The dibenzylated NPOE **15c** was of particular interest because the corresponding glycosyl ester donors perform poorly under



Scheme 1 Dibenzoylated ribo-NPOE **6** in *N*-glycosylations.



Scheme 2 Assembly of uracil (**7a**) with C3′ and C5′ differentiated ribo-NPOEs **15**.

Vorbruggen conditions, which makes it difficult to obtain the corresponding nucleosides. By contrast nucleoside **17** was obtained from NPOE **15c** in 90% yield after two hours.

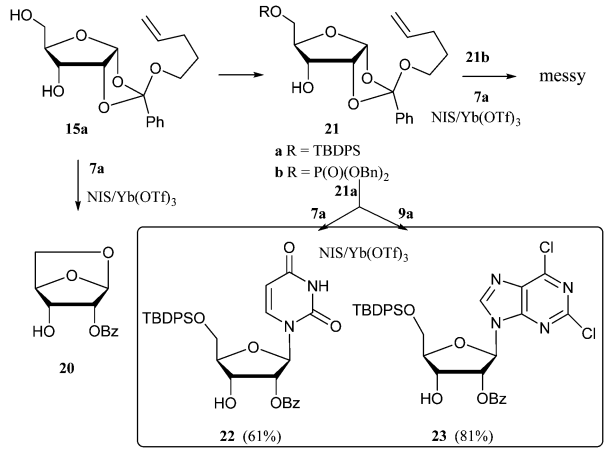
NPOE donors **15d, e and f**, differentially protected at C3′ and C5′, which were prepared routinely from diol **15a** gave nucleosides **18a, b and c** respectively in excellent yields. Similarly, differentiated donor **15g** gave nucleoside **19**.

The results with the phosphorylated NPOEs **15f** and **15g** are noteworthy because, to our knowledge, they represent the first examples of glycosylation by a donor with a C3′ or C5′-phosphate in place. The excellent yield of nucleoside **18c** (85%) after only 1 hour is very reassuring and is formation of the C5′-monophosphate, **19**.

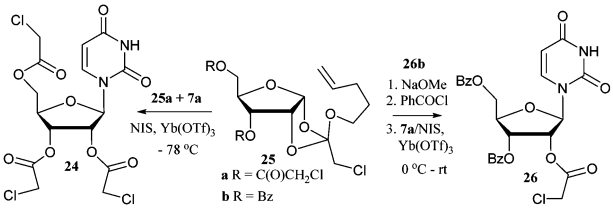
In our oligosaccharide syntheses,[20] we have shown that NPOEs with unprotected hydroxyl groups can be excellent donors; but not surprisingly NPOE diol **15a** gave the 1,5-anhydro sugar **20** exclusively (Scheme 3). The C5′–OH was therefore selectively protected to give donors, **21a and b**. The former when challenged with uracil, **7a**, gave nucleoside **22**, the structure of which was assigned based on 2D ^{1}H-NMR experiments. Similarly, glycosylation of the dichloropurine **9a**, gave product **23** (along with some N7 isomer).

The examples in Schemes 2 and 3 indicate that NPOE's allow ready differentiation between C3′ and C5′ sites. However, there may be occasions where chemospecific access to the C2′ site is also desired. Fortunately, the Reverse Strategy can accommodate this contingency as exemplified with the study in Scheme 4. Thus, chloroacetyl NPOE **25a** was prepared from methyl ribofuranoside by our recently described strategy.[16] Attempts to glycosylate uracil at 0 °C resulted in a mixture. The temperature was reduced, eventually, to −78 °C, whereupon nucleoside **24** was obtained in excellent yield. Alternatively, the acyl groups were switched, **25a** → **25b**, and reaction of the latter under standard conditions[19] gave triester **26**, the C2′ site of which is available for chemoselective dechloroacetylation.[21]

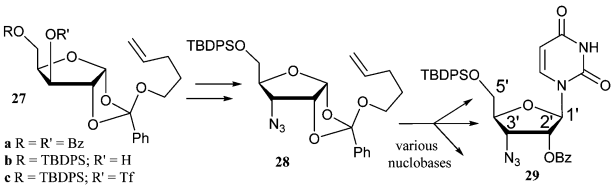
Finally, modification of C3′–OH in the hope of preventing oligomerization, has had a long history in medicinal chemistry.[2,22,23]



Scheme 3 NPOE donors with free C3′–OH in nucleoside assembly.



Scheme 4 C2′ differentiated ribo-glycosyl donors.



Scheme 5 Xylo-NPOE precursors for ribo-glycosyl donors and thence to different 3′-substituted ribonucleosides.

The Reverse Strategy facilitates syntheses of such fraudulent nucleosides as shown in Scheme 5. Thus, the xylofuranose NPOE **27a**, (readily available from xylose the least expensive furanose sugar),[16] gave differentiated **27c** smoothly. As exemplified with azide, a single inversion leads to C3′ substituted ribofuranosyl donors such as **28**. We then divided the latter into several portions, each of which was used to glycosylate a different nucleobase so as to obtain an assortment of nucleosides differing only at the aglycon. One of the products so obtained was the 3′-azido 3′-deoxy-ribonucleoside **29**.

In summary, we have shown that readily-prepared strategically functionalized *n*-pentenyl orthoesters (NPOEs) can be coupled to nucleobases efficiently at temperatures as low as −78 °C, such that functional groups at C5′, C3′ and C2′ are tolerated, as is a free C3′–OH. This Reverse Strategy therefore permits prior extensive structural modifications to the ribose sub-unit, and late installation of the nucleobase, confident of β-D orientation. Convergent assembly is therefore optimized.

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