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Direct One-Pot Synthesis of Nucleosides from Unprotected or 5-*O*-Monoprotected D-Ribose

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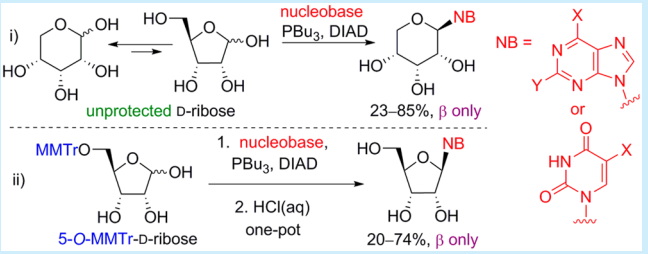
Supporting Information

ABSTRACT: New, improved methods to access nucleosides are of general interest not only to organic chemists but to the greater scientific community as a whole due their key implications in life and disease. Current synthetic methods involve multistep procedures employing protected sugars in the glycosylation of nucleobases. Using modified Mitsunobu conditions, we report on the first direct glycosylation of purine and pyrimidine nucleobases with unprotected D-ribose to provide β-pyranosyl nucleosides and a one-pot strategy to yield β-furanosides from the heterocycle and 5-*O*-monoprotected D-ribose.

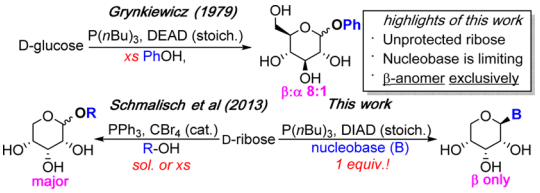


Nucleosides are the key to life as they make up DNA and RNA in Nature. In medicine, many drugs contain synthetic nucleosides or nucleoside analogues for the treatment of disease, especially cancer and viral infection.[1] As a result, designing expeditious routes to obtain nucleosides is of paramount importance to organic and medicinal chemists, and the glycosylation step between nucleobase and carbohydrate is often the trickiest. To date, all reported nonenzymatic methods to synthesize nucleosides have required the use of protecting groups on the carbohydrate component to deactivate the inherently reactive hydroxyl groups on the sugar ring and often on the heterocycle (nucleobase) to squelch reactivity at nonglycosylating nitrogens.[2] Three general glycosylation methods dominate in nucleoside synthesis. The Fischer method[3] employs nucleophilic displacement of an α-halogenose by the metal salt of a heterocycle to furnish the nucleoside.[4] The fusion method consists of heating a per-acylated sugar with a nucleobase.[5] The most popular and mildest is the Vorbrüggen variant[6] of the Hilbert–Johnson reaction making use of a fully protected sugar and coupling it with a silylated nucleobase in the presence of Lewis acids (typically $SnCl_4$ and TMSOTf), but other possibilities exist[7] to provide the protected nucleoside. Depending on the nucleobase and sugar, the regio- and stereoselectivity of the glycosylation reactions can be problematic often leading to mixtures difficult to separate.[8] Taking into account the protection, glycosylation, and deprotection sequences, the procedures are laborious and inefficient.

It is worth noting that several protecting group-free strategies to synthesize *O*-glycosides have been reported typically operating under heavily acidic conditions and date back to the Fischer glycosylation.[9] Modern examples typically employ Lewis acids but are hampered by the need to use stoichiometric or excessive quantities of the often toxic acid as well as long reaction times and high temperature.[10] Only a handful of examples describe direct *O*-glycosylation under mild[11] or organocatalytic[12] conditions, but none provide any insight on amenability to nucleoside synthesis. N-9 alkylation to synthesize nucleoside analogues using primary and secondary alcohols (containing only one hydroxyl group) has been reported under Mitsunobu conditions.[13]

We drew our inspiration from the pioneering work of Grynkiewicz[11b] (Scheme 1), who subjected D-glucose to

Scheme 1. Neutral Protecting Group-Free Glycosylation Strategies



Mitsunobu conditions in the presence of an excess of phenol to yield the phenyl glycoside in moderate yield and good diastereoselectivity. Recently, Schmalisch et al.[12b] developed neutral catalytic conditions to react unprotected D-ribose in the presence of an excess of alcohol acceptor to provide the thermodynamic β-anomer as the major product. It is crucial to note that in both examples the alcohol acceptor was used in excess. This is impractical for nucleoside synthesis as the

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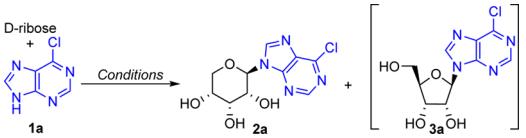
nucleobase is too precious to be used in excess. Herein we report on a novel method to synthesize nucleosides from unprotected or 5-*O*-monoprotected ribose on a preparative scale where the valuable nucleobase is the limiting reagent.

We chose 6-chloropurine (**1a**) as an appropriate nucleobase to begin our investigation as it is a very common precursor in the synthesis of diverse purine nucleosides. As a starting point, we reacted **1a** and D-ribose under the Mitsunobu conditions proposed by Grynkiewicz[11b] (Table 1, entry 1). We were able to isolate *β*-pyranosyl nucleoside **2a** in 22% yield, albeit contaminated with *n*-tributylphosphine oxide, thus confirming our prediction that the reaction would provide the thermodynamic product. Encouraged that this stereoselectively leads to *β*-configured nucleosides, we sought to optimize the conditions to allow the nucleobase to be the limiting reagent. We tried various electron acceptors including CCl_4, CBr_4, diisopropyl azodicarboxylate (DIAD), and 1,1′-(azodicarbonyl)dipiperidine (ADDP) (Table 1, entries 2−9) as well as Ag_2CO_3 (Table 1, entry 8), a well-known catalyst in the Koenigs−Knorr reaction.[14] This led to the formation of furanoside **3a** as a minor byproduct (12%), but the ultimately low combined yield of both isomers left us to abandon this strategy.

Table 1. Optimization of Glycosylation Conditions for Synthesis of 2a



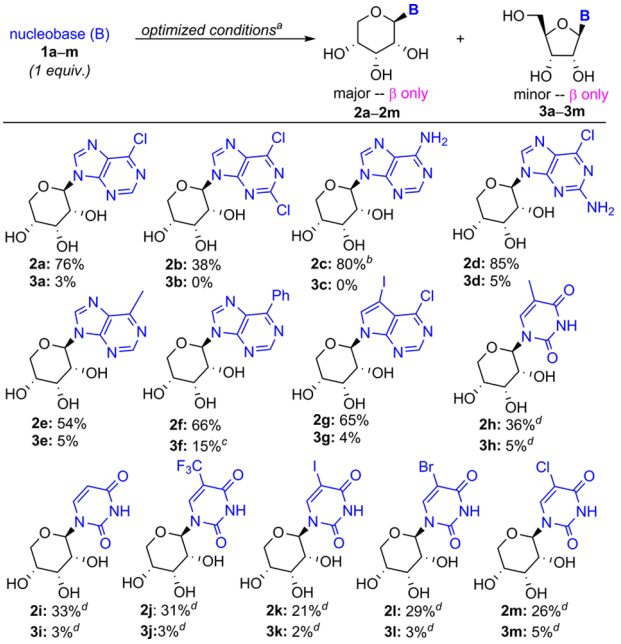
entry	base	conditions	yield[a] (%)
1	none	**1a** (1.5 eq), P(*n*-Bu)$_3$ (1.5 eq), DEAD (1.5 eq), DMF, 1 h, rt	22[b]
2	NaH	P(*n*-Bu)$_3$ (1.05 eq), CCl_4 (10.0 eq), THF, 1 h, rt	24[b]
3	none	PPh_3, (1.6 eq) CBr_4 (2 eq), ribose (1.5 eq), DMF, 1 h, rt	27[b]
4	NaH	P(*n*-Bu)$_3$ (1.2 eq), CCl_4 (2 eq), DMF, 12 h, rt	26[b]
5	$CsCO_3$	P(*n*-Bu)$_3$ (1.2 eq), CCl_4 (2 eq), DMF, 12 h, rt	trace
6	NaH	P(*n*-Bu)$_3$ (1.2 eq), DIAD (2 eq), DMF, 12 h, rt	12
7	NaH	P(*n*-Bu)$_3$ (1.2 eq), CCl_4 (2 eq), MeCN, 12 h, rt	33
8	NaH	P(*n*-Bu)$_3$ (1.2 eq), CCl_4 (2 eq), MeCN, $AgCO_3$ (1 eq), 12 h, rt	23[c]
9	NaH	P(*n*-Bu)$_3$ (1.2 eq), ADDP (2 eq), ribose (2 eq), MeCN, 12 h, 0 °C to rt	trace
10	**DBU**	**P(*n*-Bu)$_3$ (2 eq), DIAD (2.1 eq), ribose (2 eq), MeCN, 12 h, 0 °C to rt**	**52[d] (76)[e]**
11	DBU	P(*n*-Bu)$_3$ (3 eq), DIAD (3.1 eq), ribose (2 eq), MeCN, 12 h, 0 °C to rt	29[b]

[a]Isolated yield. [b]Product contaminated with phosphine oxide. [c]Furanoside **3a** was also isolated in 12% yield. [d]Furanoside **3a** was also isolated in 3% yield. [e]Yield after triturating crude reaction through Et_2O−petroleum ether prior to purification.

The conditions reported by Schmalisch et al.[12b] were also attempted at both catalytic (no reaction, not shown) and stoichiometric proportions (Table 1, entry 3) but proved inferior. Ultimately, the correct selection of base proved most crucial: Utilizing DBU offered great improvement over NaH, Cs_2CO_3, or none at all, and the isolated yield improved 2-fold (Table 1, entry 10). Furanoside **3a** was also present, albeit in very small amounts (3% yield). We postulated that the yield could be further improved by increasing the amount of Mitsunobu reagents; however, isolation of pure product proved impossible (Table 1, entry 11). To further improve the yield, we found triturating the crude reaction oil through an Et_2O−petroleum ether mixture removed excessive quantities of *n*-tributylphosphine oxide and dramatically enhanced the isolated yield as a result. In all instances through the optimization study the *α*-isomer never appeared.

With the optimized conditions in hand, we examined the ability of these reagents to provide a series of nucleosides containing common synthetic precursors or naturally occurring nucleobases. In all instances, the thermodynamic pyranoside product was observed as the sole product or in large excess over the furanoside, and only the *β*-anomer was observed both by NMR analysis of the crude reaction mixture and after purification (Scheme 2). In general, purine nucleobases (**1a−g**) were more reactive (moderate to good yield) and the products easier to purify than in the case of the pyrimidines (**1h−m**). The pyridimines were less reactive (low to moderate yield), and the mixtures of pyrano- and furanosides proved to be inseparable when purified by chromatography on silica gel. However, NMR analysis of the crude reaction mixtures confirmed that the low to moderate yields of the pyrimidines were due to the failure of the parent nucleobase to react, rather than due to competing unwanted side reactions at other hydroxyl groups. These conditions were also compatible with 7-deazapurine **1g** and alkylated analogues **1e** and **1f** all in good yield. Naturally occurring nucleobases in RNA and DNA (**1c**, **1h**, and **1i**) were reactive as well. Unfortunately, guanine, a notoriously poor substrate due to its very low solubility in most solvents and competing glycosylation at N-7,[15] and cytosine (not shown) failed to react to form isolatable product under our conditions.

Scheme 2. Substrate Scope of Direct Glycosylation of Nucleobase with D-Ribose



[a]Isolated yields. Conditions: DBU (1.0 equiv), **1** (1.0 equiv), MeCN, rt, 15 min, then DIAD (2.1 equiv), P(*n*-Bu)$_3$ (2.0 equiv), 0 °C, 5 min, then D-ribose (2.0 equiv), 0 °C to rt, 12 h. [b]DMF was used as solvent. [c]Furanoside isolated was a 1:1 inseparable mixture of N-9 and N-3 glycosylated products. [d]As determined by ^{1}H NMR. The products were inseparable when purified by chromatography on silica gel.

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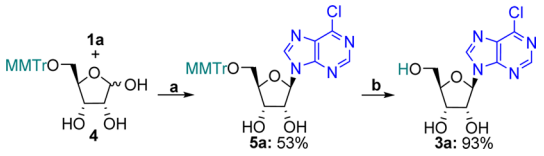
The direct synthesis of the pyranosyl nucleosides[16] from unprotected D-ribose and nucleobase served as a good proof-of-concept by exemplifying the possibility of synthesizing nucleosides in the complete absence of protecting groups; however, for most biological applications the furanoside is the desired isomer. We tried a number of direct Lewis acid mediated glycosylation strategies using $SnCl_4$,[17] TMSOTf,[18] and $Ti(O\text{-}i\text{-}Pr)_4$;[12c] however, no reaction or complex mixtures always resulted. Undaunted, we proposed that by careful selection of a labile protecting group for the primary position of ribose to lock ribose in the furanose form and inactivate the 5-OH group, we could still furnish the desired furanosyl nucleosides in a one-pot process where the protecting group could be removed in situ after the Mitsunobu glycosylation. Obvious choices were the trityl and 4-methoxytrityl (MMTr) protecting groups. We were concerned that the trityl ether would be too stable so we selected the MMTr group to begin our investigation. 5-*O*-MMTr-D-ribose (**4**) was synthesized in one step and 62% yield from D-ribose (see the Supporting Information, Figure S1).

We first tested the glycosylation followed by acid cleavage as a two-step process using 6-chloropurine (**1a**) as our model nucleobase (Scheme 3). We attempted the same glycosylation

Scheme 3. Two-Step Approach to Compound 3a via Isolation of 5′-*O*-MMTr Intermediate 5a[a]

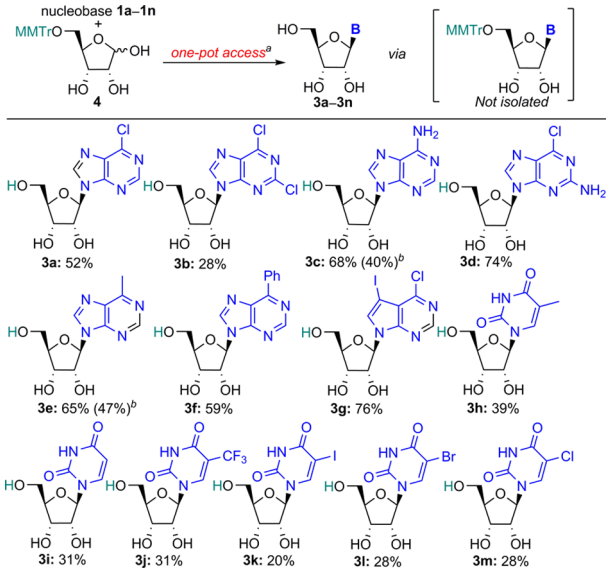


[a]Reagents and conditions: (a) DBU (1.0 equiv), **1a** (1.0 equiv), MeCN, rt, 15 min, then DIAD (2.1 equiv), $P(n\text{-}Bu)_3$ (2.0 equiv), 0 °C, 5 min, then **4** (1.0 equiv), 0 °C to rt, 12 h; (b) 1 M HCl(aq), pH = 1, MeCN, rt, 15 min.

conditions as in the pyranoside series, with the exception of utilizing equimolar amounts of 5-*O*-protected ribose **4** as the donor to improve the atom economy of the reaction. We were pleased to discover that the glycosylation proceeded smoothly to give desired MMTr-protected furanoside **5a** in 53% isolated yield. NMR analysis of the crude reaction mixture prior to purification showed only one product present with the remaining, unreacted 6-chloropurine making up the balance. Unfortunately, attempts to improve the yield by heating led only to the presence of undesired side-products (glycosylation at other nucleobase nitrogens). The MMTr group was then very easily removed after stirring an acidified solution (1 M HCl(aq), pH = 1) of 5′-*O*-protected nucleoside **5a** in MeCN at room temperature for 15 min to give ribonucleoside **3a** in 93% yield.

With these results in hand, we expanded this reaction into a one-pot process as a general method to access desired furanosyl nucleosides (Scheme 4). We found that the *n*-tributylphosphine oxide and the reduced DIAD hydrazine tended to buffer the reaction and that cleavage of the MMTr group was better effected by heating at 60 °C (purines) or prolonging stirring at room temperature (pyrimidines). We were pleased to find that the reactivity trends of the nucleobases were consistent with those obtained in the pyranoside series. The conditions still provided deazapurine **3h** in good yield as well as cytostatic[19] analogues **3f** and **3g** in moderate yield. Particularly interesting is that adenosine **3d** (68%) and uridine **3i** (31%) are both still accessible using this method, which stands as the shortest nonenzymatic synthesis of

Scheme 4. One-Pot Synthesis of Nucleosides Containing the Naturally Occurring Furanosyl Conformation of Ribose



[a]Isolated yields. Reaction conditions: (i) DBU (1.0 equiv), **1** (1.0 equiv), MeCN, rt, 15 min, then DIAD (2.1 equiv), $P(n\text{-}Bu)_3$ (2.0 equiv), 0 °C, 5 min, then **4** (1.0 or 1.5 equiv), 0 °C to rt, 12 h; (ii) 1 M HCl(aq), pH = 1, 60 °C or rt, 15 or 60 min. [b]Products contained trace impurities consisting primarily of DBU after chromatographic purification. Yield in parentheses is after crystallization from MeOH.

adenosine known (except for hypothetical prebiotic syntheses[20] which give very low yields of 2−15%). Once again, the reactivity of the pyrimidines was decreased over that of the purine series, but by increasing the amount of 5-*O*-MMTr-ribose **4** to 1.5 equiv we could obtain the furanoside products in virtually the same yield as in the pyranoside series. In all cases, only the desired furanoside was isolated with no pyranoside detected. Most importantly, this one-pot, two-step procedure is practical and efficient: it gives several previously described purine furanosides **3a** (32% vs 19%[21]), **3c** (42% vs 25%[22]), **3d** (46% vs 7.3%[22]), **3e** (40% vs 14%[23]), **3f** (30% vs 27%[24]), and **3g** (47% vs 27%[25]) in significantly better overall yields than precedented approaches based on the Vorbrüggen glycosylation followed by deprotection when calculating the total yield from D-ribose and nucleobase to the free nucleoside.[26]

We also confirmed that all reagents were required for reaction suggesting at least a Mitsunobu-like reaction pathway (see the Supporting Information, Figure S2). To account for the formation of the exclusive *β*-stereoselectivity in all cases, we postulated that the *C*2-OH may have a directing effect or a neighboring group effect on the reaction. In order to test this, 2-deoxy-D-ribose (**6**), isopropylidene **7**, tribenzoylated analogue **8**, and D-arabinose (**9**) were reacted with **1a** under our conditions (Figure 1). 2-Deoxy-D-ribose **6** gave a complex mixture of products that proved impossible to purify. This indicated that the *C*2-OH is needed to control the reaction. Furthermore,

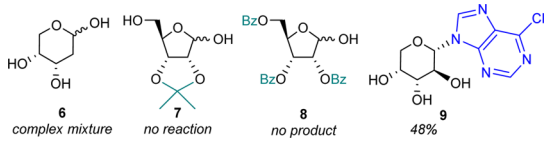


Figure 1. Structures of other sugars subjected to glycosylation.

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isopropylidene ribose **7** failed to react at all. Benzoylated analogue **8**, known to provide a neighboring group effect via formation of an acetoxonium ion under Vorbrüggen conditions, also failed to react to any extent with the nucleobase and only traces of any reaction occurring at all were evident by TLC and crude NMR analysis. Reaction with D-arabinose yielded selectively the predicted α-anomer **9** in 48% yield accompanied by only traces of the β-anomer (~2.5%) and the α-furanoside (~2%) side products as confirmed by ROESY analysis (see the Supporting Information). These results suggest that the unprotected, unhindered *C*2-OH of the sugar is crucial to dictating the final stereochemistry either through a directing effect or neighboring group effect.

In conclusion, we report a conceptually novel direct glycosylation strategy for nucleoside synthesis using Mitsunobu conditions and either unprotected or 5-*O*-monoprotected ribose. The reaction of ribose with nucleobases gives preferentially β-ribopyranosyl nucleosides in moderate to good yield. The method is applicable to both purine- and pyrimidine-based heterocycles, and the β-anomer is formed exclusively. We then applied the same conditions to provide purine or pyrimidine β-ribofuranosides in a one-pot method. This was achieved by coupling the nucleobase with MMTr-protected D-ribose and subsequent in situ cleavage of the MMTr group. A more in-depth mechanistic study, including why the anomeric alcohol reacts preferentially, has certainly been necessitated and has already begun but is beyond the scope of this communication. Expanding this operationally simple protocol to include larger nitrogenous heterocycles or modified sugars with medicinal implications is obvious, and efforts are underway. The results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02332.

Experimental procedures, analytical data, and comparison of purine nucleoside yield (PDF)
NMR spectra for obtained compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For recent reviews on the medical applications of synthetic nucleosides and nucleoside analogs, see: (a) Jordheim, L.; Durantel, D.; Zoulim, F.; Dumontet, C. *Nat. Rev. Drug Discovery* **2013**, *12*, 447. (b) De Clercq, E. *Annu. Rev. Pharmacol. Toxicol.* **2011**, *51*, 1. (c) De Clercq, E.; Holý, A. *Nat. Rev. Drug Discovery* **2005**, *4*, 928.

(2) For an expansive review on known glycosylation strategies in nucleoside chemistry, see: Romeo, G.; Chiacchio, U.; Corsaro, A.; Merino, P. *Chem. Rev.* **2010**, *110*, 3337.

(3) Fischer, E.; Helferich, B. *Ber. Dtsch. Chem. Ges.* **1914**, *47*, 210.

(4) Kazimierczuk, Z.; Cottam, H. B.; Revankar, G. R. *J. Am. Chem. Soc.* **1984**, *106*, 6379.

(5) Diekmann, E.; Friedrich, K.; Fritz, H. G. *J. Prakt. Chem./Chem.-Ztg.* **1993**, *335*, 415.

(6) (a) Bennua-Skalmowski, B.; Krolikiewicz, K.; Vorbrüggen, H. *Tetrahedron Lett.* **1995**, *36*, 7845. (b) Niedballa, U.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 461.

(7) For a recent gold(I)-catalyzed glycosylation strategy, see: Zhang, Q. J.; Sun, J. S.; Zhu, Y. G.; Zhang, F. Y.; Yu, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 4933.

(8) Framski, G.; Gdaniec, Z.; Gdaniec, M.; Boryski, J. *Tetrahedron* **2006**, *62*, 10123 and references cited therein.

(9) (a) Capon, B. *Chem. Rev.* **1969**, *69*, 407. (b) Fischer, E. *Ber. Dtsch. Chem. Ges.* **1895**, *28*, 1145. (c) Fischer, E. *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 2400. (d) Park, T.-J.; Weïwer, M.; Yuan, X.; Baytas, S. N.; Munoz, E. M.; Murugesan, S.; Linhardt, R. J. *Carbohydr. Res.* **2007**, *342*, 614.

(10) (a) Ferrières, V.; Bertho, J. N.; Plusquellec, D. *Tetrahedron Lett.* **1995**, *36*, 2749. (b) Bertho, J. N.; Ferrières, V.; Plusquellec, D. *J. Chem. Soc., Chem. Commun.* **1995**, 1391. (c) Velty, R.; Benvegnu, T.; Gelin, M.; Privat, E.; Plusquellec, D. *Carbohydr. Res.* **1997**, *299*, 7. (d) Regeling, H.; Zwanenburg, B.; Chittenden, G. J. F.; Plusquellec, D.; Mackenzie, G.; Watson, M. J.; Haley, J. A.; Goodby, J. W.; Pindak, R.; Durbin, M. K. *Carbohydr. Res.* **1998**, *314*, 267. (e) Ferrières, V.; Benvegnu, T.; Lefeuvre, M. *J. Chem. Soc., Perkin Trans. 2* **1999**, 951. (f) Ferrières, V.; Bertho, J. N.; Plusquellec, D. *Carbohydr. Res.* **1998**, *311*, 25. (g) Joniak, D.; Poláková, M. *J. Serb. Chem. Soc.* **2001**, *66*, 81.

(11) (a) Takeuchi, H.; Mishiro, K.; Ueda, Y. *Angew. Chem., Int. Ed.* **2015**, *54*, 6177. (b) Grynkiewicz, G. *Pol. J. Chem.* **1979**, *53*, 1571.

(12) (a) Matviitsuk, A.; Berndt, F.; Mahrwald, R. *Org. Lett.* **2014**, *16*, 5474. (b) Schmalisch, S.; Mahrwald, R. *Org. Lett.* **2013**, *15*, 5854. (c) Pfaffe, M.; Mahrwald, R. *Org. Lett.* **2012**, *14*, 792.

(13) (a) Lu, W. B.; Sengupta, S.; Petersen, J. L.; Akhmedov, N. G.; Shi, X. D. *J. Org. Chem.* **2007**, *72*, 5012. (b) Fletcher, S.; Shahani, V. M.; Lough, A. J.; Gunning, P. T. *Tetrahedron* **2010**, *66*, 4621.

(14) (a) Temeriusz, A.; Piekarska, B.; Radomski, J.; Stępiński, J. *Carbohydr. Res.* **1982**, *108*, 298. (b) Igarashi, K. *Adv. Carbohydr. Chem. Biochem.* **1977**, *34*, 243.

(15) Robins, M. J.; Zou, R.; Hansske, F.; Madej, D.; Tyrrell, D. L. J. *Nucleosides, Nucleotides Nucleic Acids* **1989**, *8*, 725.

(16) (a) Kritzyn, A. M.; Holý. *Collect. Czech. Chem. Commun.* **1975**, *40*, 3211. (b) Pitsch, S.; Wendeborn, S.; Krishnamurthy, R.; Holzner, A.; Minton, M.; Bolli, M.; Miculca, C.; Windhab, N.; Micura, R.; Stanek, M.; Jaun, B.; Eschenmoser, A. *Helv. Chim. Acta* **2003**, *86*, 4270.

(17) Zhong, M.; Nowak, I.; Robins, M. J. *Org. Lett.* **2005**, *7*, 4601.

(18) Moreau, C.; Kirchberger, T.; Zhang, B.; Thomas, M. P.; Weber, K.; Guse, A. H.; Potter, B. V. L *J. Med. Chem.* **2012**, *55*, 1478.

(19) (a) Van Aerschot, A. A.; Mamos, P.; Weyns, N. J.; Ikeda, S.; De Clercq, E.; Herdewijn, P. *J. Med. Chem.* **1993**, *36*, 2938. (b) Hocek, M.; Nauš, P.; Pohl, R.; Votruba, I.; Furman, P. A.; Tharnish, P. M.; Otto, M. J. *J. Med. Chem.* **2005**, *48*, 5869.

(20) Review: (a) Cafferty, B. J.; Hud, N. V. *Curr. Opin. Chem. Biol.* **2014**, *22*, 146. Recent example: (b) Singh, P.; Singh, A.; Kaur, J.; Holzer, W. *RSC Adv.* **2014**, *4*, 3158.

(21) Yadav, V.; Chu, C. K.; Rais, R. H.; Al Safarjalani, O. N.; Guarcello, V.; Naguib, F. N. M.; el Kouni, M. H. *J. Med. Chem.* **2004**, *47*, 1987.

(22) Bookser, B. C.; Raffaele, N. B. *J. Org. Chem.* **2007**, *72*, 173.

(23) Marasco, C. J.; Pera, P. J.; Spiess, A. J.; Bernacki, R.; Sufrin, J. R. *Molecules* **2005**, *10*, 1015.

(24) Hocek, M.; Holý, A.; Votruba, I.; Dvořáková, H. *J. Med. Chem.* **2000**, *43*, 1817.

(25) Kim, Y. A.; Sharon, A.; Chu, C. K.; Rais, R. H.; Al Safarjalani, O. N.; Naguib, F. N. M.; el Kouni, M. H. *J. Med. Chem.* **2008**, *51*, 3934.

(26) A more in depth summary and comparison of the yields is provided in the Supporting Information (Figure S3).

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