JOC The Journal of Organic Chemistry

Article

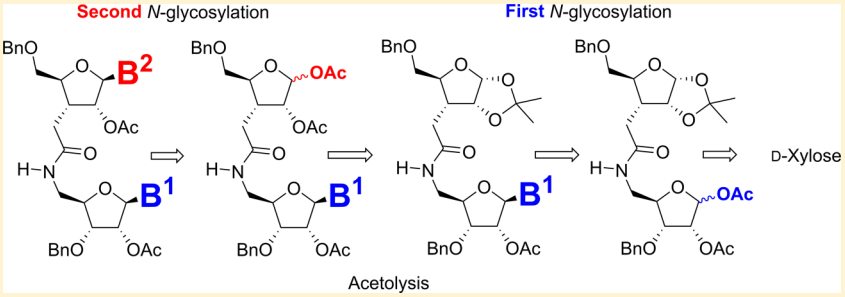
pubs.acs.org/joc

Synthesis of Ribonucleosidic Dimers with an Amide Linkage from D-Xylose

Laurence Arzel, Didier Dubreuil, Fabrice Dénès, Virginie Silvestre, Monique Mathé-Allainmat,* and Jacques Lebreton*

Université de Nantes, CEISAM-UMR CNRS 6230, Faculté des Sciences et des Techniques, 2 rue de la Houssinière, BP 92208, 44322 Nantes Cedex 3, France

Supporting Information



ABSTRACT: An original and efficient stereocontrolled synthesis of ribonucleosidic homo- and heterodimers has been achieved from inexpensive D-xylose. This successful strategy involved the sequential introduction of nucleobases, using two stereocontrolled *N*-glycosidation reactions, from a common two-furanoside amide-linked scaffold offering the possibility of obtaining any given base sequence. The pertinence of this approach is illustrated through the preparation of the homodimers UU-**34** and TT-**35** in 18 steps with an excellent overall yield of more than 10% from D-xylose, while the heterodimer route led to UT-**39** in 19 steps with around 10% overall yield.

1. INTRODUCTION

Since the pioneering work of Zamecnik and Stephenson[1] major advances have been made in the development of chemically modified oligonucleotides as a novel strategy for drug discovery[2] in various gene silencing technologies, such as antisense,[3] antigene[4] and RNA interference.[4,5] In 1998, the first antisense drug, the phosphorothioate oligonucleotide Vitravene (ISIS 2922), was approved for the treatment of AIDS-related cytomegalovirus (CMV) retinitis.[6] Five years later, a second antisense phosphorothioate oligonucleotide drug Kynamro (ISIS 301012) was approved to treat homozygous familial hypercholesterolemia (HoFH), a genetic defect that leads to high cholesterol levels.[7] Currently, more than 40 antisense therapies are in clinical trials for diseases such as cancer, diabetes and neurodegenerative diseases.[8]

In the last two decades, a large variety of chemically modified oligonucleotides have been designed, synthesized and evaluated in order to improve properties such as nuclease resistance to degradation in biological fluids, biodistribution and pharmacokinetics, while keeping the affinity and specificity toward the targeted RNA messenger or RNA interference.[9] Among these, the oligonucleotides modified with nonionic phosphate linkage mimics offered various advantages, especially an increase in hydrophobicity due to the reduced global charge.[10] In this context, earlier studies showed that the C3′-CH_2-CO-NH-C5′ internucleoside amide linkage (**C**, Figure 1), first synthesized and patented[11] by De Mesmaeker and co-workers at CIBA in 1992, does not disturb the thermal stability of DNA/RNA duplexes.[11,12] In fact, with oligodeoxynucleotides, this amide linkage improved the binding affinity by Watson–Crick base pairing for RNA complements, as measured by increased duplex stability in thermal denaturation experiments (ΔT_m per modification: +0.4 to +0.9 °C). Moreover, these modified oligodeoxynucleotides displayed remarkable resistance to enzymatic degradation relative to reference strands. It was

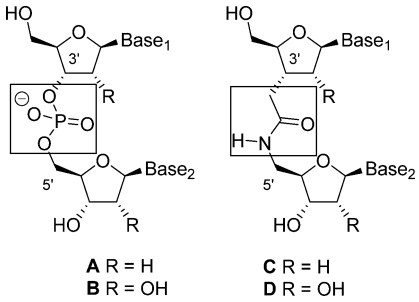
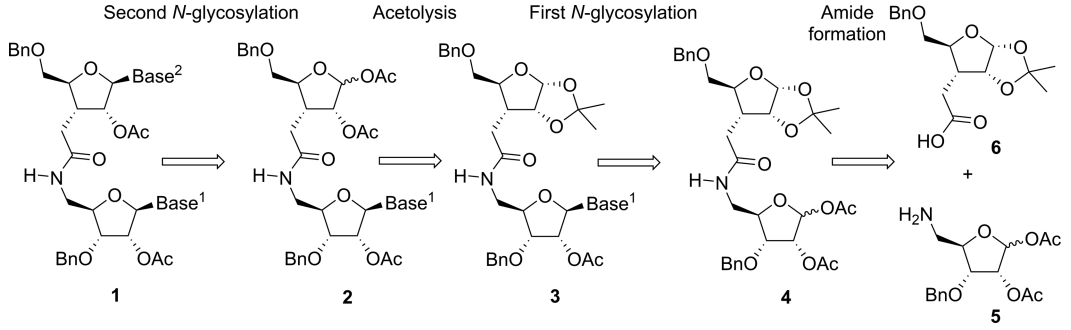


Figure 1. Natural phosphodiester linkage in natural DNA **A** and RNA **B** strands and amide linkages **C** and **D** proposed as a substitute for the phosphodiester in oligodeoxynucleotides and oligoribonucleotides, respectively.

Received: July 28, 2016
Published: October 21, 2016

DOI: 10.1021/acs.joc.6b01822
J. Org. Chem. 2016, 81, 10742–10758

Scheme 1. Retrosynthetic Analysis of Protected Amide-Linked Ribonucleoside Dimers 1



also reported that this modified internucleoside amide linkage, such as in **C**, with an additional methyl substituent at C5′ having the S configuration improved the thermal stability of duplexes with RNA (ΔT_m per modification: +1.0 to +1.4 °C) compared to the R configuration (ΔT_m per modification: −3.6 to −4.9 °C).[13] It should also be pointed out that the other four possible structural isomers of amide dimers between the C3′ of the upper base and the C5′ of the lower base have been prepared and evaluated by the same group.[11,14] More recently, Rozners[15] and Iwase[16] showed that this same internucleoside amide linkage C3′-CH_2-CO-NH-C5′, such as in dimer **D** in RNA strands, does not disturb the A-type structure of the corresponding RNA/RNA duplexes (ΔT_m per modification: −0.2 to +0.7 °C). As previously mentioned for the DNA series, amide-linked RNA is remarkably resistant to nuclease-mediated cleavage.

In the quest for ideal backbone replacements, various neutral linkages containing the amide function, such as the phosphodiester mimic, have been extensively studied for potential nucleic acid-based therapeutic applications.[10,17] Among them, the C3′-CH_2-CO-NH-C5′ internucleoside amide linkage present in dimers **C** and **D** (Figure 1) seems to be one of the most promising achiral nonionic phosphate linkage mimic candidates of chemically modified nucleosides developed so far. It is worth noting that in both deoxyribo- and ribo-oligonucleotides with the C3′-CH_2-NH-CO-C5′ internucleoside amide linkage, one of the other four possible structural isomers of amide dimers between the C3′ of the upper base and the C5′ of the lower base displayed very similar binding affinities compared to the C3′-CH_2-CO-NH-C5′ internucleoside amide linkage present in dimers **C** and **D** (see Figure 1).

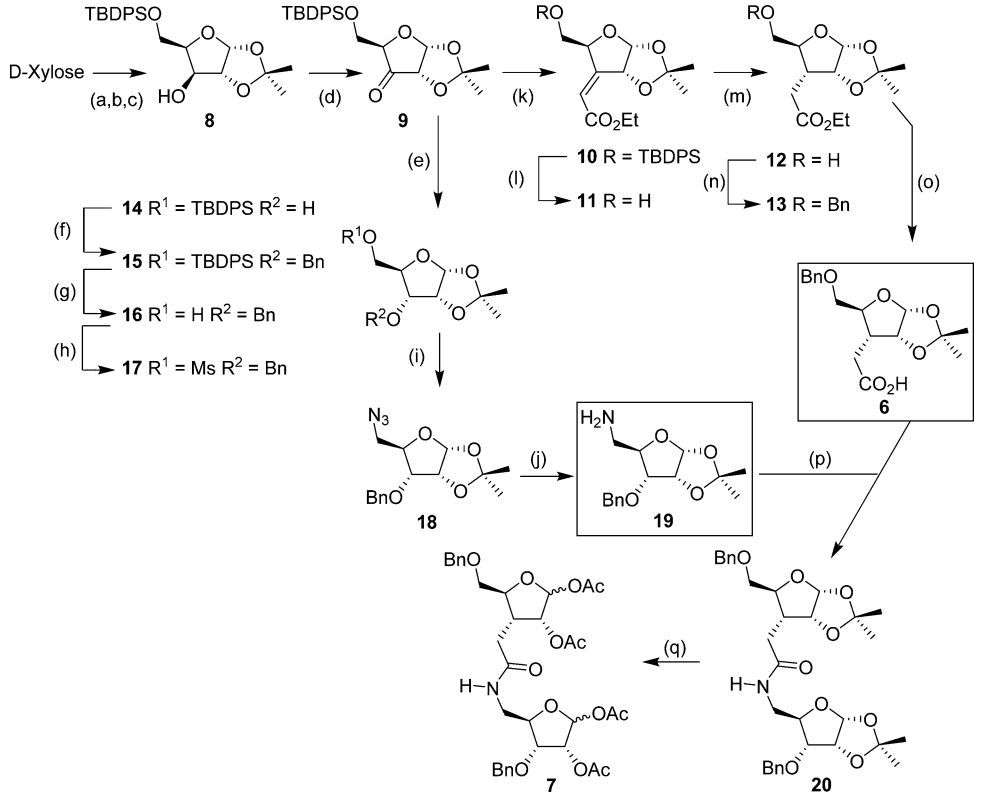
In general, the amide-linked deoxyribonucleoside dimers, such as in **C** (see Figure 1), have been obtained from the commercially available natural nucleosides. In this way, the carboxylic acid monomers were efficiently synthesized by free-radical allylation at C3′ with total α-diastereoselectivity from 5′-*O*-protected 2′-deoxynucleoside precursors.[18] This key step was followed by successive oxidation reactions to provide the desired acid monomer. This is in sharp contrast to the synthesis of amide-linked ribonucleoside dimers **D**, for which the reaction applied to 2′,5′-di-*O*-protected ribonucleoside intermediates led to the desired products contaminated by the other diastereoisomer arising from free-radical allylation at C3′ on the β-face. Consequently, in this series, the synthesis of these required carboxylic acid monomers has been largely reported from sugars, mainly D-xylose or D-glucose.[19] As previously mentioned, this sugar route to prepare the required carboxylic acid monomers of amide-linked ribonucleoside dimers **D** turned out to be more efficient: from a protected α-D-*erythro*-pentofuranos-3-ulose intermediate, a sequence of the Wittig–Horner reaction followed by diastereoselective hydrogenation provided the desired glycosyl precursor, which was then involved in an *N*-glycosylation to introduce the desired nucleobase. At the final stage, these amine and carboxylic acid monomers are assembled using well established peptide coupling chemistry and, after protecting group manipulation, their protected phosphoramidite dimeric blocks are incorporated into the desired amide-linked RNA strands according to standard solid-phase oligomerization on RNA synthesizers. To be complete, it should be noted that an original approach concerning the synthesis of RNA sequences containing up to three consecutive internal amide linkages such as in **D** has been published by Rozners and co-workers.[20] From the 5′-*N*-MMT (4-methoxytrityl) aminouridine-3′-phosphoramidite monomer, these authors used a combination of standard solid-support automated phosphoramidite chemistry and manual addition of 5′-amino-3′-carboxymethyluridine derivative and 5′-*O*-MMT 3′-carboxymethyluridine monomers, as their activated carboxylic ester derivatives formed separately under conventional peptide coupling conditions.

2. RESULTS AND DISCUSSION

As part of our interest in the synthesis of modified nucleosides, we initiated a new program for the efficient and general preparation of amide-linked ribonucleoside dimers **D**, with the aim of avoiding the fastidious preparation of each of the four monomeric building block amine and carboxylic acid nucleoside precursors required to access any given base sequence. To reach this goal, our retrosynthetic analysis of these protected amide-linked ribonucleoside dimers **D**, delineated in Scheme 1, relied on an original sequential introduction of a nucleobase sequence from a common two-furanoside amide-linked scaffold **4**. It should be highlighted that the late-stage stereocontrolled implantation of nucleobases avoids the tedious manipulations of various sensitive protected nucleoside derivatives, which greatly facilitates both the synthesis and the purification. The crucial issue of this strategy was the stability of the isopropylidene protecting group in the 1,2 positions of the upper furanose in **4**, under the Vorbrüggen *N*-glycosylation[21] conditions required to introduce the first nucleobase. Then, it was also expected that further transformations, including acetolysis and a second Vorbrüggen *N*-glycosylation, should be compatible with the various chemical functionalities on this advanced intermediate **3**. The successful implementation of this strategy would provide amide-linked ribonucleoside dimers **1** with all possible combinations of nucleobases from a common scaffold **4**.

DOI: 10.1021/acs.joc.6b01822
J. Org. Chem. 2016, 81, 10742−10758

Scheme 2[a]



[a]Conditions: (a) H_2SO_4, $CuSO_4$, acetone, rt, 40 h; (b) HCl, MeOH, 40 °C, 2 h, quant. for two steps; (c) TBDPSCl, imidazole, DMF, rt, 48 h, 70%; (d) BAIB, TEMPO, DCM (0.6 M), rt, 40 h, quant. (e) $NaBH_4$, EtOH/water (9:1), rt, 16 h, 95%, dr >95:5; (f) NaH, BnBr, THF, rt, 16 h, 92%; (g) TBAF, THF, 4 °C, 3 h then rt, 16 h, 80%; (h) MsCl, pyridine, rt, 3 h, quant.; (i) NaN_3, DMF, 90 °C, 3 h, 95%; (j) H_2 (atm. press.), Pd/C (5 wt.%), EtOH, rt, 4 h, 94%; (k) $Ph_3P{=}CHCO_2Et$, DCM, rt, 24 h, 95%, dr >95:5; (l) TBAF, THF, 4 °C, 3 h, then rt, 2 h, 92%; (m) H_2 (atm. press.), Pd/C (5 wt.%), EtOH, rt, 24 h, quant.; (n) NaH, BnBr, DMF, rt, 20 h, 84%; (o) LiOH, dioxane/water (1:1), rt, 22 h, quant.; (p) TBTU, HOBt, Et_3N, CH_3CN, 5 °C, 30 min, then **19**, Et_3N, 5 °C to rt, 16 h, quant.; (q) Ac_2O, CSA (0.05 equiv), AcOH, 85 °C, 1 h, then CSA (0.05 equiv), 85 °C, 3 h, 39%.

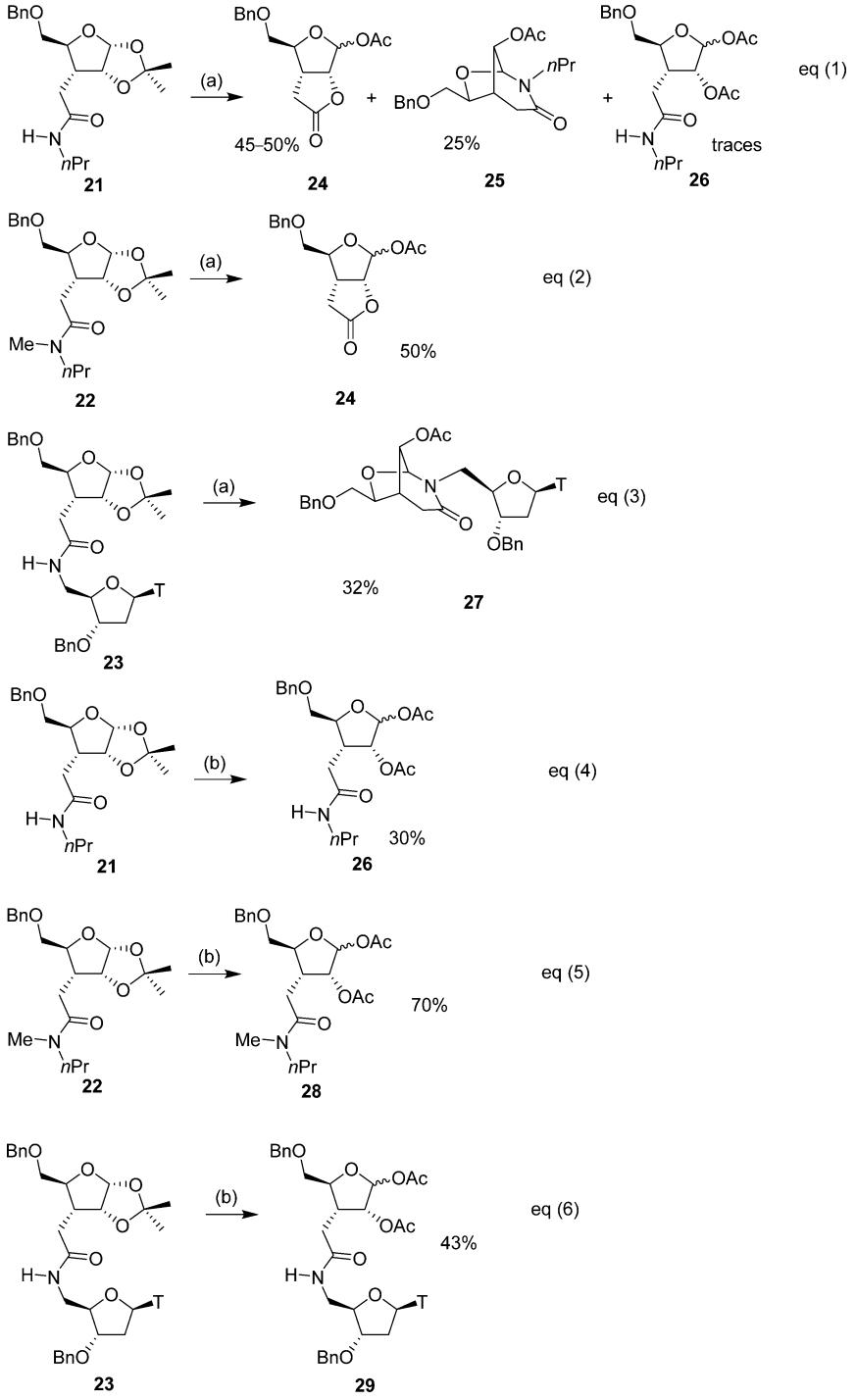
As a prelude to this approach, a straightforward synthesis of the amide-linked ribonucleoside homodimers such as **1** (Base[1] = Base[2]) was investigated using a similar strategy from a tetraacetate scaffold **7** in which a one-pot double Vorbrüggen transglycosylation with a suitable single type of base provided the desired homodimer, as outlined in Scheme 5.[22] It should be pointed out that the convergent synthesis of the common scaffold **4** and its related tetraacetate analogue **7**, as outlined in Schemes 4 and 2 respectively, is based on the same building blocks that are readily available from D-xylose.

The first common glycosyl donor **7** was prepared as depicted in Scheme 2. The synthesis of both amine **19** and acid **6** monomers started from the known TBDPS-protected 3-ulose **9** derivative, which was readily obtained according to a known procedure from D-xylose by a four-step sequence along with an optimized scalable oxidation step. Our synthesis commenced with acetalization of D-xylose,[23] followed by selective cleavage of the 3′,5′-acetal as described by Bozo and co-workers[24] and finally selective protection of the resulting primary alcohol function with TBDPSCl[25] to furnish the secondary alcohol **8** in 70% overall yield. The latter was oxidized into its corresponding ketone **9** in quantitative yield with a TEMPO/BAIB[26] system under mild conditions. It should be pointed out that this oxidation procedure was more efficient on a large scale (up to 10 g) than conventional methods such as CrO_3/pyridine/Ac_2O, PCC, or Swern oxidation.

At this juncture, having in hand this common ketone **9**, we turned our attention toward the synthesis of the carboxylic acid synthon **6**. In accordance with our plan, the 5-*O*-TBDPS-1,2-*O*-isopropylidene-*α*-D-erythro-pentofuranos-3-ulose derivative **9** was treated with [(ethoxycarbonyl)-methylene]-triphenylphosphorane in DCM to provide stereoselectively the (*Z*)-*α*,*β*-unsaturated ester **10** in 95% yield. Although of no consequence to the synthesis, the *Z* geometry of the ester was confirmed from the ^1H and ^{13}C NMR spectra, which were in agreement with the reported data.[27] At this point, we envisaged that diastereoselective reduction of the double bond could be carried out directly from the fully protected intermediate **10** to provide the desired 3*α* diastereoisomer.[28] All attempts to reduce this *α*,*β*-unsaturated ester **10**, either by hydrogenation or with $NaBH_4$, led to a diastereomeric mixture. At this point, prompted by Robins's reports,[19c] the silyl group of **10** was cleaved with tetrabutylammonium fluoride (TBAF) and the corresponding primary alcohol **11** was engaged in the reduction step. Classic catalytic hydrogenation of **11** under atmospheric pressure in the presence of 5% palladium on charcoal in EtOH at room temperature afforded the saturated ester **12** in quantitative crude yield as the sole diastereoisomer according to ^1H and ^{13}C NMR analyses. This result suggested that the alcohol function at C5 in intermediate **11** is able to bind to the heterogeneous catalyst surface to exert stereochemical control of hydrogen addition to the olefin with a high level of

DOI: 10.1021/acs.joc.6b01822
J. Org. Chem. 2016, 81, 10742−10758

Scheme 3[a]

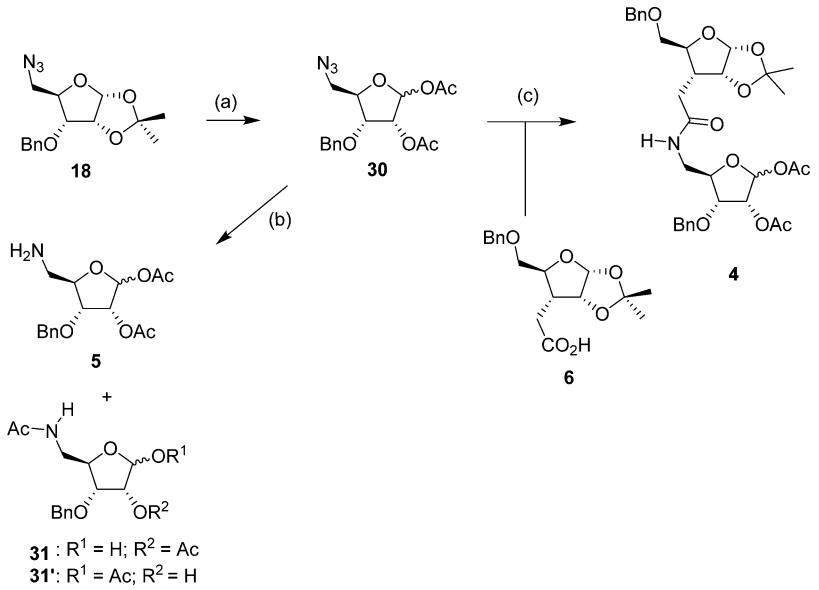


[a]Conditions: (a) AcOH aq (or TFA aq), 90 °C, 6−24 h then Ac_2O, pyridine, rt, 20 h; (b) Ac_2O, CSA (0.1−0.2 equiv), AcOH, 80 °C, 40 min to 4 h.

diastereoselectivity. We also anticipated that upon switching the protecting group from silyl- to benzyl-ether would remedy the partial cleavage of the 5-*O*-TBDPS group under the acidic conditions of the acetolysis reaction (vide infra) as observed in our preliminary investigations. Finally, benzylation of the primary alcohol **12** under classic conditions furnished the expected benzylether **13** in 84% yield, which upon treatment with LiOH led quantitatively to the key acid synthon **6**. With the synthesis of the acid **6** secured in nine steps from D-xylose with an excellent overall yield of 50%, we began to focus our attention on the synthesis of the amine monomer **19**. Preparation of the amine **19** began with a diastereoselective reduction of the key ketone intermediate **9** and subsequent benzylation of the resulting alcohol function at C3 in **14**, followed by fluoride-mediated cleavage of the silylether. Finally, activation of the liberated alcohol as a mesylate led to compound **17** in 50% overall yield.[29] Nucleophilic displacement of the 5-*O*-mesylate group of **17** with sodium azide gave the desired azido derivative **18**, which was then reduced to provide the corresponding amine monomer **19** in 90% overall

DOI: 10.1021/acs.joc.6b01822
J. Org. Chem. 2016, 81, 10742−10758

Scheme 4[a]



[a]Conditions: (a) Ac_2O, CSA (0.05 equiv), AcOH, 85 °C, 1 h, then CSA (0.05 equiv), 85 °C, 1 h, 87% (α:β = 15/85); (b) H_2 (atm. press.), Pd/C (5 wt.%), THF, 3 h, total conversion; (c) Me_3P then **6**, DIC, HOBt, THF, rt, 4 h, 65%.

yield for this two-step sequence. It is noteworthy that the palladium on a charcoal source had no influence on the chemoselectivity of this catalytic hydrogenation reaction, which was run at various scales with no problem. This key amine monomer **19** was synthesized in six steps from the intermediate ketone **9** and in ten steps from D-xylose with a very good yield of 45%. With the synthesis of both amine **19** and acid **6** monomers secured, the stage was then set for the coupling reaction to give the first amide-linked glycosyl donor **7**. The targeted amide-linked pentose dimer **20** was isolated in near quantitative yield upon treatment of acid **6** with amine **19** monomers with a coupling reagent cocktail of 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), 1-hydroxybenzotriazole (HOBt) and Et_3N in DCM.[30] Next, conversion of both 1,2-*O*-isopropylidene protection groups of compound **20** into its corresponding peracetylated glycosyl donor proved to be problematic to provide our amide-linked dimer **7**. Most of the common protocols to perform this latter transformation involve acidic cleavage (AcOH, TFA, H_2SO_4) of the acetonide followed by acetylation of the resulting 1,2-diol with Ac_2O in a one-pot or sequential reaction.[31] From dimer **20**, extensive optimization of this crucial transformation in our plan, with regard to the acid component (AcOH,[32] TFA,[33] H_2SO_4[34]), revealed that a one-pot two-step sequence with camphorsulfonic acid (CSA)[35] in a mixture of AcOH and Ac_2O was the most efficient in our hands. Obviously, acid additives significantly influenced the reaction. However, after silica gel column chromatography purification, the yields of this acetolysis reaction leading to the tetraacetylated dimer **7** were modest (39%) (vide infra). This tetraacetylated dimer **7** was finally obtained in 17 steps from D-xylose and with an 18% overall yield.

In addition to our acetolysis optimization, suspecting that the pendant amide moiety at C3 in dimer **20** could interfere[36] with the course of this transformation, we explored this process with model substrates **21** and **22**, as well as a more advanced model **23**. Our more relevant findings are presented in Scheme 3.

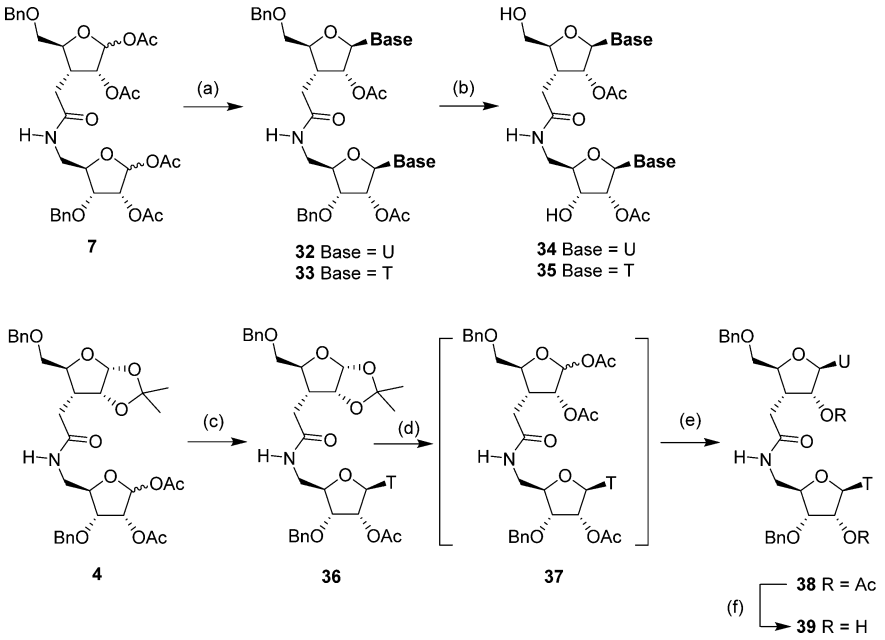
Acetonide deprotection of the amide **21** with aqueous AcOH followed by acetylation with Ac_2O in pyridine resulted in a mixture of the lactone **24**[19c,37] in 45−50% yield, as well as a bridged heterobicyclic lactam **25**, arising from an intramolecular *N*-glycosidation with the nitrogen atom of the amide function, in 25% yield (Scheme 3, eq 1). To avoid the possibility of intramolecular amide cyclization at the anomeric position, the *N*-methyl derivative **22** was subjected to a standard two-step acetolysis. Only the lactone **24** was isolated in 50% yield after purification (Scheme 3, eq 2). Under the same acetolysis conditions, the more advanced model **23** led only to the formation of the lactam **27** in 32% yield (Scheme 3, eq 3). The formation of the bridged heterobicyclic lactams **25** and **27** resulted from the intramolecular nucleophilic attack of the N−H of the amide parents **21** and **23** on the furanose oxocarbenium ion formed by acid-promoted cleavage of the acetonide moiety and subsequent elimination of water. The structures of **24**−**25** and **27** were assigned by extensive NMR study (see Supporting Information for details).

In the second set of experiments on these model substrates **21**−**23**, a one-pot two-step acetolysis in the presence of CSA afforded the desired 1,2-di-*O*-acetate adducts **26** and **28**−**29** (Scheme 3, eq 4−6) as an anomeric mixture in moderate to good yields after purification. As will be seen, we later found that substantial decomposition of these 1,2-di-*O*-acetate derivatives occurred during silica gel column chromatography purification.

With an efficient preparation of our first glycosyl dimer **7** in hand, we next turned our efforts to the production of the second key dimer **4** as depicted in Scheme 4. On the basis of our previous experience, as discussed above, our optimized conditions of acetolysis were applied to the azido intermediate **18** to yield the corresponding 1,2-di-*O*-acetate compound **30**. Analysis of the ^1H NMR spectrum of this latter crude reaction mixture clearly indicated that the only product of this transformation was the required azidodiacetate **30** (>95% crude yield, >95% purity). Surprisingly, silica gel chromatography purification afforded only a modest 50% yield of the

DOI: 10.1021/acs.joc.6b01822
J. Org. Chem. 2016, 81, 10742−10758

Scheme 5[a]



[a]Conditions: (a) base, BSA, CH_3CN, 60 °C, 1 h, then TMSOTf, CH_3CN, reflux, 2 h, 62% for thymine, 56% for uracil; (b) H_2 (atm. press.), Pd/C (30 wt %), EtOH, 24 h, 93% for **34**, 71% for **35**; (c) thymine, BSA, CH_3CN, 60 °C, 1 h, then TMSOTf, CH_3CN, rt, 24 h, 89%; (d) Ac_2O, CSA (0.05 equiv), AcOH, 85 °C, 1 h, then CSA (0.05 equiv), 85 °C, 3 h; (e) uracil, BSA, CH_3CN, 60 °C, 1 h, then TMSOTf, CH_3CN, rt, 26 h, 83%, for 2 steps. (f) K_2CO_3, MeOH, rt, 4 h, quant.

desired pure compound **30**. To avoid loss of product during silica gel purification, the organic layer was washed around ten times during the workup with an aqueous saturated solution of $NaHCO_3$ to provide the azidodiacetate **30** in 87% crude yield, which was directly used without further purification. With this azidodiacetate **30** in hand, we explored its reduction under hydrogenation conditions (1 atm. H_2, 5% palladium on charcoal, THF, rt) into the corresponding amine **5** required for the amide coupling reaction to provide the dimeric amide framework **4**. Unfortunately, under these conditions, a mixture of products whose structures were tentatively assigned as amine **5** (M = 323) and acetamides **31** or **31′** (M = 323) arising from the migration of acetate[38] was obtained.[39] Attempts to reduce the azide **30** using the Staudinger reaction led to the formation of the corresponding unusually stable iminophosphorane intermediate, which clearly could not be hydrolyzed into the amine **5**. However, to circumvent the acetate migration, we ultimately found that the most efficient route to the amide-linked dimer **4** was the three-component Staudinger−Vilarrasa ligation from the carboxylic acid **6** and azide **30**.[40] A first experiment employing a catalytic variant[41] of this Staudinger−Vilarrasa coupling reaction with PySeSePy as activator afforded the targeted dimer **4** in a modest yield of 37%. In accordance with the work of Strazewski,[40] reaction between the azide **30** and trimethylphosphine provided the corresponding aza-ylide intermediate, which was then treated by addition of the corresponding activated ester of the parent acid **6** formed in situ by exposure to DIC and HOBt in THF at room temperature. Under these optimized conditions, the amide-linked dimer **4** was isolated in 65% yield after purification on silica gel chromatography. Thus, synthesis of the second glycosyl dimer **4** was achieved in 16 steps with an overall yield of 30% from D-xylose.

Then, we proceeded to evaluate our plan for a one-pot and sequential introduction of the nucleobases as outlined in Scheme 5. In the first instance, we examined the preparation of ribonucleosidic homodimers from the amide-linked sugar dimer precursor **7**.

To this end, the tetraacetate glycosyl donor **7** was submitted to a double one-pot Vorbrüggen *N*-glycosylation with uridine. According to standard Vorbrüggen *N*-glycosylation protocols,[21] the glycosyl donor **7** was reacted with bis(trimethylsilyl)uracil, formed in situ by silylation of uracil with bis(trimethylsilyl)-acetamide (BSA), and trimethylsilyltriflate (TMSOTf) as a promoter, in freshly distilled acetonitrile at 60 °C, to give stereoselectively the *β*-configured protected homodimer UU-**32** in 56% yield after purification. Importantly, the anchimeric assistance of the 2-*O*-acetyl group in this Vorbrüggen type coupling prevented the formation of an anomeric mixture and led to the exclusive formation of the amide-backbone uracil protected ribodinucleoside **32** as the *β*-anomer. The same transformation using thymine resulted in essentially identical efficiency with a 62% yield of the homodimer TT-**33**. To finish, cleavage of the benzyl protecting groups in UU-**32** and TT-**33** under classic hydrogenolysis conditions proceeded smoothly to furnish the target homodimers UU-**34** and TT-**35** in 93% and 71% yields, respectively. It should be noted that no cleavage by ethanolysis or migration of the acetyl group at C3′ in both nucleosides, due to the slightly acidic nature of the palladium on charcoal catalyst, was observed during this transformation. Following the successful synthesis of the homodimers UU-**34** and TT-**35**, our efforts were focused on our ultimate goal, which was the preparation of a heterodimer to validate our strategy. At this point, the Vorbrüggen *N*-glycosylation with thymine, using the previous conditions, was performed on the glycosyl donor **4** to furnish the intermediate **36** in an excellent yield of 89% after purification. Then, this latter glycosyl donor

DOI: 10.1021/acs.joc.6b01822
J. Org. Chem. 2016, 81, 10742−10758

36 was subjected to previously optimized acetolysis conditions and the resulting triacetate intermediate **37** was directly engaged without further purification in the last Vorbrüggen *N*-glycosylation step with uracil to afford stereoselectively the desired heterodimer UT-**38** in 83% overall yield, after silica gel chromatography. Cleavage of the acetate groups in dimer **38** by classic methanolysis furnished the benzyl protected dimer **39** in quantitative yield. It should be pointed out that orthogonal deprotection of dimers **32**, **33** and **38** afforded efficiently the corresponding partially protected dimers **34**, **35** and **39** in good yields.

3. CONCLUSION

To the best of our knowledge, the work reported here is the first example of the synthesis of nucleosidic heterodimers with an internucleoside amide linkage, such as dimers **D**, via the sequential introduction of pyrimidine bases using two stereocontrolled *N*-glycosidation reactions on a two-furanoside platform precursor **4**. From D-xylose, homodimers UU-**34** and TT-**35** were obtained in 18 steps with excellent overall yields of more than 10%, while the heterodimer route led to UT-**39** in 19 steps with an overall yield of around 10%.

The present preliminary investigation demonstrates the feasibility of our original strategy to introduce all four natural nucleobases into both top and bottom sugars of the dimer platform **4**, potentially leading to the 16 possible combinations. The extension of this strategy to the preparation of dimers bearing various or original bases other than thymine and uracil is underway.

4. EXPERIMENTAL SECTION

General Information. All solvents were reagent grade. Solvent used for chromatography (dichloromethane, ethyl acetate and petroleum ether) were distilled on a rotavapor. Acetonitrile was freshly distilled from calcium hydride under argon.

Purifications were performed with flash column chromatography on silica gel or with flash chromatography instrument. TLC was performed on silica gel 60 F 254 analytical plates, compounds were detected by UV (λ = 254 nm).

^{1}H and ^{13}C NMR spectra were recorded with 300 MHz spectrometer fitted with a 5 mm i.d. BBO probe carefully tuned to the recording frequency of 300.13 MHz (for ^{1}H) and 75.47 MHz (for ^{13}C), the temperature of the probe was set at room temperature (around 293−294 K), on the spectrometer fitted with a 5 mm i.d. BBFO+ probe carefully tuned to the recording frequency of 400.13 MHz (for ^{1}H) and 100.61 MHz (for ^{13}C), the temperature of the probe was set at 303 K, on the 500 MHz spectrometer fitted with a 5 mm i.d. ^{13}C/^{1}H cryoprobe carefully tuned to the recording frequency of 500.13 MHz (for ^{1}H) and 125.76 MHz (for ^{13}C), the temperature of the probe was set at 303 K. The spectra are referenced to the solvent in which they were run (7.26 ppm for ^{1}H $CDCl_3$ and 77.16 ppm for ^{13}C $CDCl_3$, 2.50 ppm for ^{1}H DMSO-d_6 and 39.52 ppm for ^{13}C DMSO-d_6, 3.31 ppm for ^{1}H CD_3OD and 49.00 ppm for ^{13}C, 7.16 ppm for ^{1}H C_6D_6 and 128.06 ppm for ^{13}C C_6D_6). Chemical shifts (δ) are given in parts per million (ppm), and coupling constants (J) are given in Hz. Multiplicity of signals is indicated as following: s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet), brs (broad singlet), dd (doublet of doublet), dt (doublet of triplet). All assignments were confirmed with the aid of two-dimensional experiments both homonuclear ^{1}H−^{1}H (COSY) and heteronuclear ^{1}H−^{13}C (HSQC and HMBC) correlation spectroscopy, standard pulse programs were used. In case of dimer, we used the symbol A for the upper unit and B for the lower unit.

Low resolution mass spectrometry (MS) were recorded on a quadripolar spectrometer (coupled with a TracUltra GC apparatus) for Chemical Ionization (CI), on a TOF spectrometer for ElectroSpray Ionization (ESI).

High resolution mass spectrometry (HRMS) were recorded on an electro-magnetic spectrometer (for CI), on a TOF spectrometer (for ESI+ and MALDI+).

Optical rotation data were obtained on a polarimeter, in a 100 mm cell, under Na lamp radiation at 20 °C.

*1,2-O-Isopropylidene-3-deoxy-3-(1,2-O-acetyl-3-O-benzyl-5-deoxy-5-acetamido-β-ribosyl)-5-O-benzyl-α-D-ribofuranose (**4**).* Acid **6** (1.3 equiv, 0.74 mmol, 239 mg) and HOBt.H_2O (1.3 equiv, 0.74 mmol, 100 mg) were coevaporated with toluene and then diluted with THF (7 mL), cooled down to 0 °C under N_2 for 10 min. DIC (1.25 equiv, 0.7 mmol, 88 mg) was added and the reaction mixture was stirred at 0 °C for 15 min and then 10 min at room temperature. A 1 M solution of trimethylphosphine in THF (2 equiv, 1.14 mmol, 1.14 mL) was added to azide **30** (1 equiv, 0.57 mmol, 200 mg) in THF (7 mL) and the reaction mixture was stirred at room temperature for 5 min. The acid mixture was added to the iminophosphorane solution and stirred for 4 h at room temperature. The mixture was concentrated under reduced pressure, diluted with toluene (20 mL) and washed with water (2 × 20 mL) to eliminate urea. The organic layer was dried over Na_2SO_4, filtered, concentrated under reduced pressure. The crude was purified by flash column chromatography (DCM/*i*-PrOH: 99.5/0.5 to 95/5) to give **4** as a beige sticky oil (225 mg, 0.36 mmol, 65%). TLC (DCM/*i*-PrOH:95/5): R_f = 0.40. ^{1}H NMR (400 MHz, $CDCl_3$) of two anomers α/β in a 20/80 ratio δ (ppm) = 7.36−7.28 (m, 10H, H_{ar}), 6.30 (d, $J_{1B,2B}$ = 4.5 Hz, 0.2H, $H_{1B\alpha}$), 6.11 (s, 0.8H, $H_{1B\beta}$), 5.89 (m, 1H, NH_{amide}), 5.80 (d, J = 3.9 Hz, 1H, H_{1A}), 5.27 (d, $J_{2B,3B}$ = 4.4 Hz, 1H, $H_{2B\beta}$), 5.07 (dd, $J_{2B,3B}$ = 6.5 Hz and $J_{1B,2B}$ = 4.5 Hz, 1H, $H_{2B\alpha}$), 4.69 (t, J = 3.7 Hz, 1H, H_{2A}), 4.59 (d, J_{gem} = 11.1 Hz, 1H, C$\underline{H}_2$Ph$_{Aa}$), 4.58−4.56 (m, 2H, C$\underline{H}_2$Ph$_B$), 4.46 (d, J_{gem} = 11.1 Hz, 1H, C$\underline{H}_2$Ph$_{Ab}$), 4.15−4.10 (m, 1H, H_{4B}), 4.01 (d, $J_{2B,3B}$ = 4.4 Hz, 1H, H_{3B}), 3.96−3.91 (m, 1H, H_{4A}), 3.65−3.41 (m, 4H, H_{5A} and H_{5B}), 2.45−2.37 (m, 2H, H_{3A} and C$\underline{H}$H′CO), 2.31−2.24 (m, 1H, CH$\underline{H}$′CO), 2.12 (s, 3H, Me_{Ac}), 2.08 (s, 3H, Me_{Ac}), 1.49 (s, 3H, $Me_{acetonide}$), 1.31 (s, 3H, $Me_{acetonide}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 171.2 (CO_{amide}), 169.8 (CO_{Ac}), 168.9 (CO_{Ac}), 138.0 ($C_{IV(ar)}$), 137.2 ($C_{IV(ar)}$), 128.6 (C_{ar}), 128.5 (C_{ar}), 128.1 (C_{ar}), 127.8 (C_{ar}), 111.5 ($C_{IV(acetonide)}$), 105.0 (C_{1A}), 98.6 ($C_{1B\beta}$), 94.3 ($C_{1B\alpha}$) 81.2 (C_{2A}), 80.9 (C_{4B}), 80.1 (C_{4A}), 77.8 (C_{3B}), 73.6 ($\underline{C}H_2$Ph), 73.6 ($C_{2B\beta}$), 73.6 ($\underline{C}H_2$Ph), 70.9 ($C_{2B\alpha}$), 70.0 (C_{5A}), 42.4 (C_{3A}), 41.4 (C_{5B}), 32.0 ($\underline{C}H_2$CO), 26.8 ($Me_{acetonide}$), 26.4 ($Me_{acetonide}$), 21.1 (Me_{Ac}), 20.7 (Me_{Ac}). MS (CI$^+$) m/z = 628.4 Da $[MH]^+$, 570.3 Da $[MH\text{-acetone}]^+$. HRMS (MALDI$^+$: DHB, PEG 600) calcd for $C_{33}H_{41}N_1O_{11}Na$ = 650.2572 Da, found 650.2577 Da.

*1,2-O-Isopropylidene-3-deoxy-3-C-carboxymethyl-5-O-benzyl-α-D-ribofuranose (**6**).* To a solution of **13** (1 equiv, 1.86 mmol, 650 mg) in a 1:1 mixture dioxane/water (40 mL) was added LiOH (20 equiv, 37.2 mmol, 1.56 g). The mixture was stirred at room temperature for 48 h, then diluted with DCM (40 mL) and acidified with HCl 2N (16.8 mL) until pH = 2. The aqueous layer was extracted with DCM (3 × 20 mL), the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the desired compound as a brown oil (600 mg, 1.86 mmol, quantitative). TLC (DCM): R_f = 0.09. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.38−7.33 (m, 5H, H_{ar}), 5.85 (d, $J_{1,2}$ = 3.8 Hz, 1H, H_1), 4.80 (t, $J_{1,2}$ = $J_{2,3}$ = 3.8 Hz, 1H, H_2), 4.61 (d, J_{gem} = 12.2 Hz, 1H, C$\underline{H}_2$Ph), 4.53 (d, J_{gem} = 12.2 Hz, 1H, C$\underline{H}_2$Ph), 3.94 (dt, $J_{3,4}$ = 10.1 Hz and $J_{4,5a}$ = $J_{4,5b}$ = 4.2 Hz, 1H, H_4), 3.66 (dd, J_{gem} = 10.8 Hz and $J_{4,5a}$ = 3.8 Hz, 1H, H_{5a}), 3.56 (dd, J_{gem} = 10.8 Hz and $J_{4,5b}$ = 4.2 Hz, 1H, H_{5b}), 2.71 (dd, J_{gem} = 17.8 Hz and $J_{3,Ha}$ = 10.8 Hz, 1H, H_a (CH_2CO)), 2.47−2.36 (m, 2H, H_b (CH_2CO) and H_3), 1.49 (s, 3H, $Me_{acetonide}$), 1.32 (s, 3H, $Me_{acetonide}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 177.2 (CO), 138.0 ($C_{IV(ar)}$), 128.6 (C_{ar}), 127.9 (C_{ar}), 111.8 ($C_{IV(acetonide)}$), 105.0 (C_1), 81.0 (C_2), 79.6 (C_4), 73.7 ($\underline{C}H_2$Ph), 69.4 (C_5), 41.6 (C_3), 29.6 ($\underline{C}H_2CO_2H$), 26.8 ($Me_{acetonide}$), 26.5 ($Me_{acetonide}$). MS (ESI$^+$) m/z = 345.1 Da $[MNa]^+$. HRMS (ESI$^+$) calcd for $C_{17}H_{22}O_6Na$ = 345.1314 Da, found = 345.1314 Da. $[\alpha]_D^{20}$ = +33.3 ($CHCl_3$, c = 1 g/100 mL).

*1,2-O-Acetyl-3-deoxy-3-(1,2-O-acetyl-3-O-benzyl-5-deoxy-5-acetamido-β-D-ribosyl)-5-O-benzyl-β-D-ribofuranose (**7**).* To a solution of **20** (1 equiv, 0.41 mmol, 240 mg) in acetic acid (18 mL) was added

DOI: 10.1021/acs.joc.6b01822
J. Org. Chem. 2016, 81, 10742−10758

acetic anhydride (80 equiv, 32.8 mmol, 3 mL), camphor sulfonic acid (0.05 equiv, 0.02 mmol, 4.7 mg). The mixture was stirred for 4 h at 80−85 °C, then another portion of camphor sulfonic acid (5% weight, 0.02 mmol, 4.7 mg) was added and stirring was pursued for 1 h. The reaction mixture was diluted with DCM (15 mL), washed with water (3 × 20 mL) and a saturated aqueous solution of $NaHCO_3$ (3 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, concentrated under reduced pressure and coevaporated with toluene (20 mL) then Et_2O (20 mL). The crude was purified by flash column chromatography (Et_2O/Petroleum Ether: 90/10) to give the desired compound as a single diastereoisomer as a beige oil (110 mg, 0.16 mmol, 39%). TLC (Et_2O): R_f = 0.18. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.35−7.30 (m, 10H, H_{ar}), 6.10 (s, 1H, H_1), 6.07 (s, 1H, H_1), 5.78 (t, $J_{NH,5B}$ = 5.7 Hz, 1H, NH_{amide}), 5.29−5.27 (m, 2H, H_2), 4.60−4.54 (m, 4H, 2C$\underline{H}_2$Ph), 4.13−4.08 (m, 2H, H_4), 3.97 (dd, J = 8.1 Hz and J = 4.4 Hz, 1H, H_{3B}), 3.67−3.58 (m, 3H, $2H_{5A}$ and H_{5B}), 3.32−3.26 (m, 1H, H_{5B}), 2.96−2.88 (m, 1H, H_{3A}), 2.37−2.31 (m, 2H, CH_2CO), 2.09 (s, 3H, Me_{Ac}), 2.07 (s, 6H, Me_{Ac}), 1.95 (s, 3H, Me_{Ac}). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 170.4 (CO_{amide}), 169.88 (CO_{Ac}), 169.84 (CO_{Ac}), 169.5 (CO_{Ac}), 169.1 (CO_{Ac}), 138.1 ($C_{IV(ar)}$), 137.2 ($C_{IV(ar)}$), 128.7 (C_{ar}), 128.6 (C_{ar}), 128.6 (C_{ar}), 128.5 (C_{ar}), 128.4 (C_{ar}), 128.2 (C_{ar}), 128.1 (C_{ar}), 127.8 (C_{ar}), 127.8 (C_{ar}), 127.7 (C_{ar}), 98.8 (C_1), 98.7 (C_1), 83.6 (C_{4A}), 80.8 (C_{4B}), 78.2 (C_{3B}), 77.9 (C_{2A}), 73.62 ($\underline{C}H_2$Ph), 73.58 (C_{2B}), 73.5 ($\underline{C}H_2$Ph), 71.9 (C_{5A}), 42.2 (C_{5B}), 39.0 (C_{3A}), 32.4 ($\underline{C}H_2CO$), 21.2 ($2Me_{Ac}$), 20.8 ($2Me_{Ac}$). MS (MALDI$^+$: DHB) m/z = 694.2 Da $[MNa]^+$. HRMS (MALDI$^+$: DHB, PEG 600) calcd for $C_{34}H_{41}N_1O_{13}Na$ = 694.2470 Da, found 694.2450 Da. $[\alpha]_D^{20}$ = +8.7 ($CHCl_3$, c = 1.5 g/100 mL).

*1,2-O-Isopropylidene-5-O-tert-butyldiphenylsilyl-α-D-xylofuranose (**8**).* The precursor of **8**, the 1,2-*O*-isopropylidene-α-D-xylofuranose, was obtained as followed. To 350 mL of reagent acetone were added successively: sulfuric acid concentrated (2 mL), copper sulfate (1.88 equiv, 250 mmol, 40 g) and xylose (1 equiv, 133 mmol, 20 g). The reaction was stirred at room temperature for 48 h. The mixture was filtered, NH_4OHconc. (25%, 6.4 mL) was added, the mixture was filtered, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was diluted with methanol (150 mL) and HCl 0.1 N (44 mL) was added. The reaction was stirred at 40 °C for 2 h and quenched with $NaHCO_3$ (6.3 g until neutral pH). The mixture was filtered and concentrated under reduced pressure. The residue was coevaporated with EtOH/toluene, was diluted with DCM, dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the desired 1,2-*O*-isopropylidene-α-D-xylofuranose (25.3 g, 133 mmol, quantitative). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 5.96 (d, $J_{1,2}$ = 3.6 Hz, 1H, H_1), 4.51 (d, $J_{1,2}$ = 3.6 Hz, 1H, H_2), 3.34 (br, 1H, H_3), 4.15 (q, $J_{4,5a}$ = $J_{4,5b}$ = $J_{4,3}$ = 3.2 Hz, 1H, H_4), 4.08 (d, $J_{5a,5b}$ = 12.2 Hz, 1H, H_{5a}), 3.50 (d, $J_{5a,5b}$ = 12.2 Hz, 1H, H_{5b}), 1.47 (s, 3 H, $Me_{acetonide}$), 1.31 (s, 3 H, $Me_{acetonide}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 112.1 (C_{IV}), 105.6 (C_1), 85.8 (C_2), 83.8 (C_4), 79.00 (C_3), 66.3 (C_5), 27.00 ($Me_{acetonide}$), 26.3 ($Me_{acetonide}$). MS (CI$^+$) m/z = 208 Da $[MNH_4]^+$, 191 Da $[MH]^+$. MS (ESI$^+$) m/z = 213.1 Da $[MNa]^+$. HRMS (ESI$^+$) calcd for $C_8H_{14}O_5Na$ = 213.0739 Da, found = 213.0739 Da.

To a cooled solution of 1,2-*O*-isopropylidene-α-D-xylofuranose (1 equiv, 36.8 mmol, 7g) and imidazole (2.2 equiv, 81 mmol, 5.5 g) in DMF (70 mL) was added *tert*-butyldiphenylsilyl chloride (1 equiv, 36.8 mmol, 9.5 mL). After stirring at room temperature for 48 h, the reaction was quenched with Et_2O (70 mL) and water (70 mL). The aqueous layer was extracted with Et_2O (3 × 70 mL) and the combined organic layers were washed with brine (5 × 70 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was poured into pentane, after 1 h at −18 °C the colorless solid was filtered to obtain the desired compound (11.3 g, 25 mmol, 70%). Spectroscopic data of this compound **8** were consistent with those reported in the literature.[25] mp 91−92 °C. TLC (DCM): R_f = 0.35. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.73−7.66 (m, 4H, H_{ar}), 7.48−7.37 (m, 6H, H_{ar}), 6.02 (d, $J_{1,2}$ = 3.7 Hz, 1H, H_1), 4.55 (d, $J_{1,2}$ = 3.7 Hz, 1H, H_2), 4.38 (d, $J_{3,4}$ = 2.0 Hz, 1H, H_4), 4.14−4.10 (m, 3H, H_3, H_{5a}, H_{5b}), 4.07 (d, $J_{OH,3}$ = 3.3 Hz, 1H, OH), 1.47 (s, 3H, $Me_{acetonide}$), 1.33 (s, 3H, $Me_{acetonide}$), 1.05 (s, 9 H, Me_{tBu}). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 135.8 (C_{ar}), 135.6 (C_{ar}), 132.6 ($C_{IV(ar)}$), 132.0 ($C_{IV(ar)}$), 130.2 (C_{ar}), 128.1 (C_{ar}), 111.7 ($C_{IV(acetonide)}$), 105.1 (C_1), 85.6 (C_2), 78.5 (C_3), 77.1 (C_4), 63.0 (C_5), 26.9 ($Me_{acetonide}$), 26.8 (Me_{tBu}), 26.3 ($Me_{acetonide}$), 19.2 ($C_{IV(tBu)}$). MS (ESI$^+$) m/z = 451.2 Da $[MNa]^+$. HRMS (ESI$^+$) calcd for $C_{24}H_{32}O_5SiNa$ = 451.1917 Da, found = 451.1923 Da.

*1,2-O-Isopropylidene-3-deoxy-3-keto-5-O-tert-butyldiphenylsilyl-α-D-xylofuranose (**9**).* To a solution of 1,2-*O*-isopropylidene-5-*O*-*tert*-butyldiphenylsilyl-α-D-xylofuranose **8** (1 equiv, 23.3 mmol, 10 g) in DCM (40 mL) were added BAIB (1.1 equiv, 25.6 mmol, 8.3 g) and TEMPO (0.1 equiv, 2.3 mmol, 350 mg). After 36 h, the mixture was diluted with DCM (20 mL), quenched with $Na_2S_2O_3$ (20 mL) and extracted with DCM (4 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (Petroleum Ether/Et_2O, 1/0 to 4/1) to obtain the desired compound as a beige oil (10 g, 23.4 mmol, quantitative). Spectroscopic data of this compound **9** were consistent with those reported in the literature.[25] TLC (DCM): R_f = 0.35. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.69−7.66 (m, 2H, H_{ar}), 7.62−7.59 (m, 2H, H_{ar}), 7.43−7.39 (m, 6H, H_{ar}), 6.26 (d, $J_{1,2}$ = 4.5 Hz, 1H, H_1), 4.43 (dd, $J_{1,2}$ = 4.5 Hz and $J_{2,4}$ = 1.0 Hz, 1H, H_2), 4.40−4.35 (m, 1H, H_4), 3.92 (dd, J_{gem} = 11 Hz and $J_{4,5a}$ = 1.8 Hz, 1 H, H_{5a}), 3.85 (dd, J_{gem} = 11 Hz and $J_{4,5b}$ = 2.0 Hz, 2H, H_{5b}), 1.48 (s, 3H, $Me_{acetonide}$), 1.47 (s, 3H, $Me_{acetonide}$), 1.00 (s, 9 H, Me_{tBu}). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 211.1 (CO), 135.7 (C_{ar}), 135.6 (C_{ar}), 132.5 ($C_{IV(ar)}$), 132.3 ($C_{IV(ar)}$), 130.1 (C_{ar}), 130.1 (C_{ar}), 128.0 (C_{ar}), 114.4 ($C_{IV(acetonide)}$), 103.9 (C_1), 81.7 (C_4), 77.3 (C_2), 64.6 (C_5), 27.9 ($Me_{acetonide}$), 27.4 ($Me_{acetonide}$), 26.8 (Me_{tBu}), 19.2 ($C_{IV(tBu)}$). MS (CI$^+$) m/z = 444.0 Da $[MNH_4]^+$, MS (ESI$^+$) m/z = 481.2 Da [M +MeOH+Na]$^+$. HRMS (ESI$^+$) calcd for $C_{25}H_{34}O_6SiNa$ = 481.2022 Da, found = 481.2028 Da. $[\alpha]_D^{20}$ = +76.9 ($CHCl_3$, c = 1.7 g/100 mL).

*1,2-O-Isopropylidene-3-deoxy-3-C-(Z)-ethoxycarbonylmethylene-5-O-tert-butyldiphenylsilyl-α-D-xylofuranose (**10**).* To a solution of **9** (1 equiv, 10.5 mmol, 4.5 g) in DCM (30 mL) was added (carbethoxymethylene) triphenylphosphorane (1.15 equiv, 12.07 mmol, 4.2 g). After stirring under argon at room temperature for 30 min the mixture became pink. After stirring for 24 h the mixture was concentrated and the residue was diluted with Et_2O (100 mL) and stirred for 30 min. Triphenylphosphine oxide was filtered, the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (DCM) to obtain the desired compound as a yellow oil (5.0 g, 10 mmol, 95%). TLC (DCM): R_f = 0.64. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.67−7.61 (m, 4H, H_{ar}), 7.44−7.37 (m, 6H, H_{ar}), 5.99 (d, $J_{1,2}$ = 4.1 Hz, 1H, H_1), 5.97 (t, $J_{CH,2}$ = $J_{CH,4}$ = 1.7 Hz, 1H, CH═C), 5.71 (dt, $J_{1,2}$ = 4.1 Hz and $J_{2,4}$ = $J_{CH,2}$ = 1.7 Hz, 1H, H_2), 4.90 (tt, $J_{4,5a}$ = $J_{4,5b}$ = 3.5, $J_{4,2}$ = $J_{4,CH}$ = 1.7, 1 H, H_4), 4.27 (q, J = 7.1 Hz, 1H, C$\underline{H}_2$CH$_3$), 4.26 (q, J = 7.1 Hz, 1H, C$\underline{H}_2$CH$_3$), 3.86 (dd, J_{gem} = 10.9 Hz and $J_{4,5a}$ = 3.8 Hz, 1 H, H_{5a}), 3.71 (dd, J_{gem} = 10.9 Hz and $J_{4,5b}$ = 3.2 Hz, 1H, H_{5b}), 1.49 (s, 3H, $Me_{acetonide}$), 1.45 (s, 3H, $Me_{acetonide}$), 1.33 (t, J = 7.1 Hz, 3H, $CH_2C\underline{H}_3$), 1.03 (s, 9H, tBu). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 165.1 (CO), 156.8 (C_3), 135.74 ($C_{ar(o)}$), 135.70 ($C_{ar(o)}$), 132.9 (C_{IV}), 130.0 ($C_{ar(m)}$), 129.8 ($C_{ar(m)}$), 127.9 ($C_{ar(p)}$), 116.9 ($\underline{C}HCO_2Et$), 113.1 ($C_{IV(acetonide)}$), 105.8 (C_1), 81.5 (C_4), 79.1 (C_2), 66.2 (C_5), 60.8 ($\underline{C}H_2CH_3$), 27.7 ($Me_{acetonide}$), 27.4 ($Me_{acetonide}$), 26.9 (Me_{tBu}), 19.3 ($C_{IV(tBu)}$), 14.3 ($CH_2\underline{C}H_3$). MS (ESI$^+$) m/z = 519.2 Da $[MNa]^+$. HRMS (ESI$^+$) calcd for $C_{28}H_{36}O_6SiNa$ = 519.2178 Da, found = 519.2179 Da. $[\alpha]_D^{20}$ = +47 ($CHCl_3$, c = 1 g/100 mL).

*1,2-O-Isopropylidene-3-deoxy-3-C-ethoxycarbonylmethylene-α-D-xylofuranose (**11**).* To a solution of **10** (1 equiv, 12.9 mmol, 6.4 g) in THF (100 mL) at 0 °C was added TBAF (1.2 equiv, 15.5 mmol, 1 M solution in THF). The brown reaction mixture was stirred under argon at 4 °C for 3 h. The cold bath was removed and the reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (100 mL), extracted with DCM (3 × 80 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (DCM/Petroleum Ether: 9/1 then DCM/MeOH: 100/0 to 96/4) to give the desired compound as a yellow oil (3.06 g, 11.86 mmol, 92%). Spectroscopic data of this compound were

DOI: 10.1021/acs.joc.6b01822
J. Org. Chem. 2016, 81, 10742−10758

consistent with those reported in the literature.[27] TLC (DCM/MeOH:99/1): R_f = 0.18. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 5.92 (d, $J_{1,2}$ = 4.2 Hz, 1H, H_1), 5.90 (t, $J_{CH,2}$ = $J_{CH,4}$ = 1.8 Hz, 1H, CH=C), 5.75−5.68 (m, 1H, H_2), 4.92−4.86 (m, 1H, H_4), 4.23 (q, J = 7.1 Hz, 2H, $C\underline{H}_2CH_3$), 3.92 (dd, J_{gem} = 12.2 Hz and $J_{4,5a}$ = 3.3 Hz, 1H, H_{5a}), 3.72 (dd, J_{gem} = 12.2 Hz and $J_{4,5b}$ = 4.3 Hz, 1H, H_{5b}), 1.50 (s, 3H, $Me_{acetonide}$), 1.42 (s, 3H, $Me_{acetonide}$), 1.30 (t, J = 7.1 Hz, 3H, $CH_2C\underline{H}_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 164.9 (CO), 154.6 (C_3), 116.9 ($\underline{C}HCO_2Et$), 113.0 ($C_{IV(acetonide)}$), 105.0 (C_1), 80.5 (C_4), 78.5 (C_2), 63.1 (C_5), 61.0 ($\underline{C}H_2CH_3$), 27.5 ($Me_{acetonide}$), 27.2 ($Me_{acetonide}$), 14.3 ($CH_2\underline{C}H_3$). MS (ESI$^+$) m/z = 281.1 Da $[MNH_4]^+$. HRMS (ESI$^+$) calcd for $C_{12}H_{18}O_6Na$ = 281.1001 Da, found = 281.1005 Da.

*1,2-O-Isopropylidene-3-deoxy-3-C-[(ethoxycarbonyl)methyl]-α-D-ribofuranose (**12**).* To a solution of **11** (8.5 mmol, 2.2 g) in EtOH (35 mL) was added 10% Pd/C (5% weigth, 110 mg). The reaction was stirred under an atmosphere of hydrogen (1 bar) at room temperature for 24 h. The mixture was filtered and concentrated under reduced pressure to give **12** as a single product (2.2 g, 8.5 mmol, quantitative). Spectroscopic data of this compound were consistent with those reported in the literature.[28b] TLC (DCM/Et_2O:9/1): R_f = 0.40. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 5.82 (d, $J_{1,2}$ = 3.9 Hz, 1H, H_1), 4.78 (t, $J_{1,2}$ = $J_{2,3}$ = 3.9 Hz, 1H, H_2), 4.16 (q, J = 7.1 Hz, 2H, $C\underline{H}_2CH_3$), 3.89−3.85 (m, 2H, H_4 and H_{5a}), 3.56 (dd, J_{gem} = 13.2 Hz and $J_{4,5b}$ = 4.2 Hz, 1H, H_{5b}), 2.70 (dd, J_{gem} = 16.3 Hz and J = 7.9 Hz, 1H, CH_2CO), 2.49−2.34 (m, 2H, CH_2CO, H_3), 1.98 (brs, 1H, OH), 1.49 (s, 3H, $Me_{acetonide}$), 1.32 (s, 3H, $Me_{acetonide}$), 1.27 (t, J = 7.1 Hz, 3H, $CH_2C\underline{H}_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 172.5 (CO), 111.9 ($C_{IV(acetonide)}$), 104.9 (C_1), 81.8 (C_2), 81.5 (C_4), 61.5 (C_5), 61.0 ($\underline{C}H_2CH_3$), 39.8 (C_3), 30.0 ($\underline{C}H_2CO_2Et$), 26.8 ($Me_{acetonide}$), 26.4 ($Me_{acetonide}$), 14.3 ($CH_2\underline{C}H_3$). MS (ESI$^+$) m/z = 283.1 $[MNa]^+$. HRMS (ESI$^+$) calcd for $C_{12}H_{20}O_6Na$ = 283.1158 Da, found = 283.1160 Da. $[\alpha]_D^{20}$ = +59.4 ($CHCl_3$, c = 1 g/100 mL).

*1,2-O-Isopropylidene-3-deoxy-3-C-[(ethoxycarbonyl)methyl]-5-O-benzyl-α-D-ribofuranose (**13**).* To a solution of **12** (1 equiv, 3.8 mmol, 1 g) in dry DMF (30 mL) at 0 °C was added slowly NaH (1.2 equiv, 4.61 mmol, 185 mg of a 60% suspension in oil). The mixture was stirred under argon at 5 °C for 10 min and then was added BnBr (1.5 equiv, 5.8 mmol, 0.70 mL). The cold bath was removed and the reaction mixture was stirred at room temperature until completion (TLC monitoring) and then cooled to 0 °C. The reaction mixture was quenched with NH_4Cl (30 mL) and extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine (5 × 30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (DCM/Petroleum Ether: 9/1 to 9/0) to give the desired compound as a yellow oil (1.1 g, 3.14 mmol, 84%). TLC (DCM/Et_2O:9/1): R_f = 0.31. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.37−7.28 (m, 5H, H_{ar}), 5.84 (d, $J_{1,2}$ = 3.9 Hz, 1H, H_1), 4.78 (dd, $J_{1,2}$ = 3.9 Hz and $J_{2,3}$ = 3.9 Hz, 1H, H_2), 4.60 (d, J_{gem} = 12.2 Hz, 1H, $C\underline{H}_2Ph$), 4.53 (d, J_{gem} = 12.2 Hz, 1H, $C\underline{H}_2Ph$), 4.13 (q, J = 7.1 Hz, 2H, $C\underline{H}_2CH_3$), 3.97−3.92 (m, 1H, H_4), 3.65 (dd, J_{gem} = 10.8 Hz and $J_{4,5a}$ = 3.5 Hz, 1H, H_{5a}), 3.53 (dd, J_{gem} = 10.8 Hz and $J_{4,5b}$ = 4.4 Hz, 1H, H_{5b}), 2.64 (dd, J_{gem} = 15.9 Hz and ^3J = 9.4 Hz, 1H, CH_2CO), 2.44−2.31 (m, 2H, CH_2CO, H_3), 1.49 (s, 3H, $Me_{acetonide}$), 1.31 (s, 3H, $Me_{acetonide}$), 1.26 (t, J = 7.1 Hz, 3H, $CH_2C\underline{H}_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 172.2 (CO), 138.1 ($C_{IV(ar)}$), 128.7 (C_{ar}), 128.5 (C_{ar}), 127.8 (C_{ar}), 127.1 (C_{ar}), 111.7 ($C_{IV(acetonide)}$), 105.0 (C_1), 81.2 (C_2), 79.8 (C_4), 73.6 ($\underline{C}H_2Ph$), 69.5 (C_5), 60.7 ($\underline{C}H_2CH_3$), 41.7 (C_3), 29.9 ($\underline{C}H_2CO_2Et$), 26.8 ($Me_{acetonide}$), 26.5 ($Me_{acetonide}$), 14.3 ($CH_2\underline{C}H_3$). MS (ESI$^+$) m/z = 373.1 Da $[MNa]^+$. HRMS (ESI+) calcd for $C_{19}H_{26}O_6Na$ = 373.1627 Da, found = 373.1631 Da. $[\alpha]_D^{20}$ = +31.6 ($CHCl_3$, c = 1 g/100 mL).

*1,2-O-Isopropylidene-5-O-tert-butyldiphenylsilyl-α-D-ribofuranose (**14**).* To a solution of **9** (1 equiv, 2.2 mmol, 950 mg) in a mixture of EtOH/water 9/1 (13.5 mL/1.5 mL) at 0 °C was added $NaBH_4$ (3.6 equiv, 8.3 mmol, 317 mg) portion-wise. The reaction mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure, diluted in mixture DCM/NH_4Cl (25 mL/25 mL) and stirred for 30 min. The aqueous layer was extracted with DCM (25 mL), the combined organic layers were washed with NH_4Cl, water and brine, then dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the desired compound as a pink oil (900 mg, 2.1 mmol, 95%). Except for the H-3 and H-4 attribution, spectroscopic data of this compound were consistent with those reported in the literature.[42] TLC (DCM/PE:9/1): R_f = 0.40. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.71−7.67 (m, 4H, H_{ar}), 7.41−7.37 (m, 6H, H_{ar}), 5.85 (d, $J_{1,2}$ = 3.9 Hz, 1H, H_1), 4.61 (dd, $J_{2,3}$ = 5.0 Hz and $J_{1,2}$ = 3.9 Hz, 1H, H_2), 4.14 (dd, $J_{3,4}$ = 8.1 Hz and $J_{2,3}$ = 5.0 Hz, 1H, H_3), 3.98−3.93 (m, 1H, H_{5a}), 3.88−3.82 (m, 2H, H_{5b} and H_4), 2.30 (brs, 1H, OH), 1.56 (s, 3H, $Me_{acetonide}$), 1.38 (s, 3H, $Me_{acetonide}$), 1.05 (s, 9H, Me_{tBu}). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 135.8 (C_{ar}), 135.7 (C_{ar}), 133.5 ($C_{IV(ar)}$), 133.3 ($C_{IV(ar)}$), 129.8 (C_{ar}), 127.8 (C_{ar}), 112.7 ($C_{IV(acetonide)}$), 104.3 (C_1), 81.4 (C_2), 78.9 (C_3), 71.4 (C_4), 62.5 (C_5), 26.9 ($Me_{acetonide}$), 26.9 (Me_{tBu}), 26.8 ($Me_{acetonide}$), 19.4 ($C_{IV(tBu)}$). MS (ESI$^+$) m/z = 451.2 Da $[MNa]^+$. HRMS (ESI$^+$) calcd for $C_{24}H_{32}O_5SiNa$ = 451.1911 Da, found = 451.1904 Da. $[\alpha]_D^{20}$ = +28.2 ($CHCl_3$, c = 1 g/100 mL).

*1,2-O-Isopropylidene-3-O-benzyl-5-O-tert-butyldiphenylsilyl-α-D-ribofuranose (**15**).* To a solution of **14** (1 equiv, 2.1 mmol, 900 mg) in dry THF (30 mL) at 4 °C was added NaH (1.2 equiv, 2.52 mmol, 101 mg of a 60% suspension in oil) under argon and portion-wise. Benzyl bromide (1 equiv, 2.1 mmol, 900 mL) was then added slowly. The reaction mixture was stirred overnight at room temperature. The mixture was diluted with Et_2O, washed with NH_4Cl, water and brine then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (Petroleum Ether/AcOEt: 9/1) to give the desired compound as a colorless oil (1 g, 1.93 mmol, 92%). TLC (PE/AcOEt: 9/1): R_f = 0.21. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.68−7.65 (m, 4H, $H_{ar(Ph)}$), 7.43−7.30 (m, 11H, $H_{ar(Ph,\ Bn)}$), 5.77 (d, $J_{1,2}$ = 3.6 Hz, 1H, H_1), 4.78 (d, J_{gem} = 12.1 Hz, 1H, $C\underline{H}H'Ph$), 4.60 (d, J_{gem} = 12.1 Hz, 1H, $CH\underline{H}'Ph$), 4.61 (t, $J_{1,2}$ = $J_{2,3}$ = 4.0 Hz, 1H, H_2), 4.14 (dt, $J_{3,4}$ = 8.8 Hz and $J_{4,5}$ = 2.3 Hz, 1H, H_4), 4.06 (dd, $J_{3,4}$ = 8.8 Hz and $J_{2,3}$ = 4.1 Hz, 1H, H_3), 3.98 (dd, J_{gem} = 11.8 Hz and $J_{4,5a}$ = 1.6 Hz, 1H, H_{5a}), 3.80 (dd, J_{gem} = 11.8 Hz and $J_{4,5b}$ = 2.7 Hz, 1H, H_{5b}), 1.60 (s, 3H, $Me_{acetonide}$), 1.38 (s, 3H, $Me_{acetonide}$), 1.01 (s, 9H, Me_{tBu}). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 137.9 ($C_{IV(Bn)}$), 135.8 (C_{ar}), 135.7 (C_{ar}), 133.7 ($C_{IV(ar)}$), 133.3 ($C_{IV(ar)}$), 129.77−127.77 (C_{ar}), 113.0 ($C_{IV(acetonide)}$), 104.3 (C_1), 79.7 (C_4), 77.8 (C_2), 76.8 (C_3), 72.4 ($\underline{C}H_2Ph$), 61.9 (C_5), 27.1 ($Me_{acetonide}$), 26.9 (Me_{tBu}), 26.7 ($Me_{acetonide}$), 19.5 ($C_{IV(tBu)}$). MS (CI$^+$) m/z = 536.2 Da $[MNH_4]^+$; (ESI$^+$) m/z = 541.2 Da $[MNa]^+$. HRMS (ESI$^+$) calcd for $C_{31}H_{38}O_5SiNa$ = 541.2386 Da, found = 541.2390 Da. $[\alpha]_D^{20}$ = +8.9 ($CHCl_3$, c = 1 g/100 mL).

*1,2-O-Isopropylidene-3-O-benzyl-α-D-ribofuranose (**16**).* To a solution of **15** (1 equiv, 1.6 mmol, 800 mg) in THF (20 mL) at 0 °C was added TBAF (1.1 equiv, 1.8 mmol, 1.8 mL of a 1 M solution in THF). The yellow reaction mixture was stirred at 4 °C for 3 h, then at room temperature overnight. The reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (15 mL), extracted with DCM (3 × 15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (DCM/MeOH: 98/2 to 97/3) to give the desired compound as an orange oil (360 mg, 1.28 mmol, 80%). TLC (DCM/MeOH:98/2): R_f = 0.35. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.38−7.30 (m, 5H, H_{ar}), 5.72 (d, $J_{1,2}$ = 3.6 Hz, 1H, H_1), 4.77 (d, J_{gem} = 11.9 Hz, 1H, $C\underline{H}H'Ph$), 4.59 (d, J_{gem} = 11.9 Hz, 1H, $CH\underline{H}'Ph$), 4.57 (dd, $J_{2,3}$ = 4.3 Hz and $J_{1,2}$ = 3.6 Hz, 1H, H_2), 4.11 (dt, $J_{3,4}$ = 9.1 Hz and $J_{4,5a}$ = $J_{4,5b}$ = 2.7 Hz, 1H, H_4), 3.91 (dd, J_{gem} = 12.5 Hz and $J_{4,5a}$ = 2.4 Hz, 1H, H_{5a}), 3.84 (dd, $J_{3,4}$ = 9.1 Hz and $J_{2,3}$ = 4.3 Hz, 1H, H_3), 3.64 (dd, J_{gem} = 12.5 Hz and $J_{4,5b}$ = 3.0 Hz, 1H, H_{5b}), 1.73 (brs, 1H, OH), 1.60 (s, 3H, $Me_{acetonide}$), 1.36 (s, 3H, $Me_{acetonide}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 137.7 ($C_{IV(ar)}$), 128.6 (C_{ar}), 128.2 ($C_{ar(p)}$), 128.1 (C_{ar}), 113.2 ($C_{IV(acetonide)}$), 104.2 (C_1), 78.9 (C_4), 77.7 (C_2), 76.7 (C_3), 72.5 ($\underline{C}H_2Ph$), 60.7 (C_5), 27.0 ($Me_{acetonide}$), 26.6 ($Me_{acetonide}$). MS (ESI$^+$) m/z = 303.1 Da $[MNa]^+$, 583.2 Da $[2MNa]^+$. HRMS (ESI$^+$) calcd for $C_{15}H_{20}O_5Na$ = 303.1208 Da, found 303.1210 Da. $[\alpha]_D^{20}$ = +54 ($CHCl_3$, c = 1 g/100 mL).

*1,2-O-Isopropylidene-3-O-benzyl-5-O-mesyl-α-D-ribofuranose (**17**).* To a solution of **16** (1 equiv, 4.5 mmol, 1.27 g) in pyridine (18 mL) at 0 °C was added dropwise mesyl chloride (2 equiv, 9 mmol, 0.7 mL). The mixture was stirred overnight under argon. The reaction

DOI: 10.1021/acs.joc.6b01822
J. Org. Chem. 2016, 81, 10742−10758

mixture was quenched with water (2 mL), concentrated under reduced pressure and coevaporated with toluene (20 mL). The residue was diluted with DCM (30 mL), washed with a saturated aqueous solution of $NaHCO_3$ (3 × 20 mL), brine (1 × 20 mL) then dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the desired compound as a brown oil (1.64 g, 4.5 mmol, quantitative). TLC (PE/AcOEt: 9/1): R_f = 0.25. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.38−7.33 (m, 5 H, H_{ar}), 5.73 (d, $J_{1,2}$ = 3.6 Hz, 1H, H_1), 4.77 (d, J_{gem} = 11.8 Hz, 1H, C<u>H</u>H′Ph), 4.58 (d, J_{gem} = 11.8 Hz, 1H, CH<u>H</u>′Ph), 4.57 (t, $J_{1,2}$ = $J_{2,3}$ = 4.0 Hz, 1H, H_2), 4.48−4.43 (m, 1H, H_{5a}), 4.27 (dd, J_{gem} = 13.3 Hz and $J_{4,5b}$ = 4.0 Hz, 1 H, H_{5b}), 4.24 (ddd, $J_{3,4}$ = 9.0 Hz, $J_{4,5b}$ = 4.0 Hz and $J_{4,5a}$ = 1.8 Hz, 1H, H_4), 3.76 (dd, $J_{3,4}$ = 9.0 Hz and $J_{2,3}$ = 4.0 Hz, 1H, H_3), 2.98 (s, 3H, $MeSO_2$), 1.59 (s, 3H, $Me_{acetonide}$), 1.37 (s, 3H, $Me_{acetonide}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 137.2 ($C_{IV(ar)}$), 128.8 (C_{ar}), 128.4 (C_{ar}), 128.3 (C_{ar}), 113.5 ($C_{IV(acetonide)}$), 104.3 (C_1), 77.4 (C_2), 77.0 (C_3), 76.4 (C_4), 72.6 ($\underline{C}H_2Ph$), 67.8 (C_5), 37.7 ($MeSO_2$), 26.9 ($Me_{acetonide}$), 26.6 ($Me_{acetonide}$). MS (ESI$^+$) m/z = 381.1 Da [MNa]$^+$. HRMS (ESI$^+$) calcd for $C_{16}H_{22}O_7S_1Na$ = 381.0978 Da, found 381.0977 Da. $[\alpha]_D^{20}$ = +8.1 ($CHCl_3$, c = 1 g/100 mL).

*1,2-O-Isopropylidene-3-O-benzyl-5-azido-α-D-ribofuranose (**18**).* To a solution of **17** (1 equiv, 3.2 mmol, 1.16 g) in DMF (30 mL) was added sodium azide (1.5 equiv, 4.8 mmol, 312 mg) at 0 °C. The reaction mixture was stirred 3 h at 90 °C. The mixture was quenched with water (30 mL), extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine, then dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the desired compound as a yellow oil (940 mg, 3.07 mmol, 95%). TLC (DCM/PE: 7/3): R_f = 0.54. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.38−7.32 (m, 5H, H_{ar}), 5.75 (d, $J_{1,2}$ = 3.6 Hz, 1H, H_1), 4.77 (d, J_{gem} = 11.9 Hz, 1H, C<u>H</u>H′Ph), 4.58 (t, $J_{2,3}$ = $J_{1,2}$ = 3.9 Hz, 1H, H_2), 4.55 (d, J_{gem} = 11.9 Hz, 1H, CH<u>H</u>′Ph), 4.22−4.16 (m, 1H, H_4), 3.77 (dd, $J_{3,4}$ = 8.9 Hz and $J_{2,3}$ = 4.2 Hz, 1H, H_3), 3.66 (dd, J_{gem} = 13.5 Hz and $J_{4,5a}$ = 2.6 Hz, 1H, H_{5a}), 3.24 (dd, J_{gem} = 13.5 Hz and $J_{4,5b}$ = 3.9 Hz, 1H, H_{5b}), 1.59 (s, 3H, $Me_{acetonide}$), 1.36 (s, 3H, $Me_{acetonide}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 137.4 ($C_{IV(ar)}$), 128.7 (C_{ar}), 128.4 ($C_{ar(p)}$), 128.2 (C_{ar}), 113.4 ($C_{IV(acetonide)}$), 104.2 (C_1), 77.9 (C_3), 77.5 (C_4), 77.4 (C_2), 72.5 ($\underline{C}H_2Ph$), 50.6 (C_5), 26.9 ($Me_{acetonide}$), 26.6 ($Me_{acetonide}$). MS (ESI$^+$) m/z = 328.1 Da [MNa]$^+$. HRMS (ESI$^+$) calcd for $C_{15}H_{19}N_3O_4Na$ = 328.1268 Da, found 328.1264 Da. $[\alpha]_D^{20}$ = +158.3 ($CHCl_3$, c = 1 g/100 mL).

*1,2-O-Isopropylidene-3-O-benzyl-5-amino-α-D-ribofuranose (**19**).* The compound **18** (1.1 mmol, 340 mg) was hydrogenated in the presence of 10% Pd/C (5% weigth, 17 mg) in EtOH (5 mL) under a hydrogen atmosphere. After stirring at room temperature for 4 h, the TLC analysis (DCM) showed disappearance of the starting material. The mixture was filtered and concentrated under reduced pressure to give the desired compound as a light brown oil (290 mg, 1.04 mmol, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.35−7.28 (m, 5H, H_{ar}), 5.72 (d, $J_{1,2}$ = 3.7 Hz, 1H, H_1), 4.80 (d, J_{gem} = 12.0 Hz, 1H, C<u>H</u>H′Ph), 4.60 (t, $J_{1,2}$ = $J_{2,3}$ = 4.1 Hz, 1H, H_2), 4.54 (d, J_{gem} = 12.0 Hz, 1H, CH<u>H</u>′Ph), 4.05 (ddd, $J_{3,4}$ = 9.0 Hz, $J_{4,5b}$ = 5.4 Hz and $J_{4,5a}$ = 3.2 Hz, 1H, H_4), 3.64 (dd, $J_{3,4}$ = 9.0 Hz and $J_{2,3}$ = 4.3 Hz, 1H, H_3), 3.04 (dd, J_{gem} = 13.8 Hz and $J_{4,5a}$ = 3.4 Hz, 1H, H_{5a}), 2.73 (dd, J_{gem} = 13.8 Hz and $J_{4,5b}$ = 5.4 Hz, 1H, H_{5b}), 1.60 (s, 3H, $Me_{acetonide}$), 1.36 (s, 3H, $Me_{acetonide}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 137.7 ($C_{IV(ar)}$), 128.6 (C_{ar}), 128.5 (C_{ar}), 128.14 (C_{ar}), 128.06 (C_{ar}), 128.0 (C_{ar}), 113.0 ($C_{IV(acetonide)}$), 104.1 (C_1), 79.5 (C_3), 78.2 (C_4), 77.5 (C_2), 72.1 ($\underline{C}H_2Ph$), 42.5 (C_5), 26.8 ($Me_{acetonide}$), 26.6 ($Me_{acetonide}$). MS (ESI$^+$) m/z = 280.2 Da [MH]$^+$. HRMS (ESI$^+$) calcd for $C_{15}H_{22}N_1O_4$ = 280.1549 Da, found 280.1546 Da. $[\alpha]_D^{20}$ = +53.8 ($CHCl_3$, c = 1 g/100 mL).

*1,2-O-Isopropylidene-3-(1,2-O-isopropylidene-3-O-benzyl-5-deoxy-5-acetamido-α-D-ribosyl)-5-O-benzyl-α-D-ribofuranose (**20**).* To a solution of **6** (1 equiv, 1.5 mmol, 483 mg) in DCM (18 mL) at 0 °C was added TBTU (1.4 equiv, 2.1 mmol, 690 mg), HOBt.H_2O (0.5 equiv, 0.75 mmol, 100 mg) and triethylamine (1.1 equiv, 1.65 mmol, 230 μL). The mixture was stirred under argon for 30 min at 5 °C. The amine **19** was then added (1 equiv, 1.5 mmol, 419 mg) followed by triethylamine (1.1 equiv, 1.65 mmol, 230 μL), and the reaction mixture was stirred overnight at room temperature. The reaction mixture was quenched with water (35 mL), extracted with DCM (3 × 35 mL) and the combined organic layers were washed with brine (2 × 30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was diluted with toluene and washed with water (3 × 30 mL) to eliminate urea. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (DCM to DCM/MeOH: 99/1) to give the desired compound as a beige sticky oil (880 mg, 1.5 mmol, quantitative). TLC (DCM/MeOH: 98/2): R_f = 0.21. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.41−7.29 (m, 10H, H_{ar}), 5.83 (dd, $J_{NH,5Ba}$ = 5.6 Hz and $J_{NH,5Bb}$ = 4.3 Hz, 1H, NH_{amide}), 5.74 (d, $J_{1A,2A}$ = 3.8 Hz, 1H, H_{1A}), 5.67 (d, $J_{1B,2B}$ = 3.7 Hz, 1H, H_{1B}), 4.78 (d, J_{gem} = 12.3 Hz, 1H, C<u>H</u>H′Ph_B), 4.60 (d, J_{gem} = 12.3 Hz, 1H, CH<u>H</u>′Ph_B), 4.59 (d, J_{gem} = 12.3 Hz, 1H, C<u>H</u>H′Ph_A), 4.54 (d, J_{gem} = 12.3 Hz, 1H, CH<u>H</u>′Ph_A), 4.50 (t, $J_{1B,2B}$ = $J_{2B,3B}$ = 3.9 Hz, 1H, H_{2B}), 4.36 (t, $J_{1A,2A}$ = $J_{2A,3A}$ = 3.8 Hz, 1H, H_{2A}), 4.16−4.10 (m, 1H, H_{4B}), 3.93−3.88 (m, 1H, H_{4A}), 3.70−3.61 (m, 2H, H_{5Aa} and H_{5Ba}), 3.55−3.45 (m, 3H, H_{5Ab}, H_{5Bb} and H_{3B}), 2.42−2.23 (m, 2H, H_{3A}, C<u>H</u>H′CO), 2.26−2.20 (m, 1H, CH<u>H</u>′CO), 1.59 (s, 3H, $Me_{acetonide}$), 1.46 (s, 3H, $Me_{acetonide}$), 1.36 (s, 3H, $Me_{acetonide}$), 1.23 (s, 3H, $Me_{acetonide}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 171.1 (CO_{amide}), 138.1 ($C_{IV(ar)}$), 137.6 ($C_{IV(ar)}$), 128.7 (C_{ar}), 128.6 (C_{ar}), 128.2 (C_{ar}), 128.1 (C_{ar}), 127.9 (C_{ar}),127.9 (C_{ar}), 113.4 ($C_{IV(acetonide)}$), 111.6 ($C_{IV(acetonide)}$), 105.2 (C_{1A}), 104.2 (C_{1B}), 81.2 (C_{2A}), 80.3 (C_{4A}), 78.5 (C_{3B}), 77.7 (C_{2B}), 77.4 (C_{4B}), 73.7 ($\underline{C}H_2Ph_A$), 72.4 ($\underline{C}H_2Ph_B$), 70.0 (C_{5A}), 42.7 (C_{3A}), 39.7 (C_{5B}), 32.5 ($\underline{C}H_2CO$), 26.91 ($Me_{acetonide}$), 26.88 ($Me_{acetonide}$), 26.63 ($Me_{acetonide}$), 26.61 ($Me_{acetonide}$). MS (CI$^+$) m/z = 584.4 Da [MH]$^+$, 601.4 Da [MNH_4]$^+$. HRMS (MALDI$^+$: DHB, PEG 600) calcd for $C_{32}H_{41}N_1O_9Na$ = 606.2674 Da, found 606.2662 Da. $[\alpha]_D^{20}$ = +25 ($CHCl_3$, c = 1 g/100 mL).

*1,2-O-Isopropylidene-3-deoxy-3-propylacetamido-5-O-benzyl-α-D-ribofuranose (**21**).* To a cooled solution (0 °C) of **6** (1 equiv, 1.86 mmol, 600 mg) in DCM (30 mL) was added TBTU (1.4 equiv, 2.6 mmol, 840 mg), HOBt.H_2O (0.5 equiv, 0.9 mmol, 126 mg) and triethylamine (1.1 equiv, 2 mmol, 285 μL). The mixture was stirred for 30 min at 5 °C. Then was added propylamine (1.5 equiv, 2.8 mmol, 230 μL) and triethylamine (1.1 equiv, 1.24 mmol, 285 μL), the mixture was stirred overnight at room temperature. The reaction was quenched with water (40 mL), extracted with DCM (3 × 40 mL) and the combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (2 × 40 mL) and brine (2 × 40 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. If necessary, the crude was diluted with toluene and washed with water (3 × 40 mL) to eliminate urea. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the desired compound as a yellow oil (570 mg, 1.578 mmol, 74%). TLC (DCM): R_f = 0.84. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.33−7.32 (m, 5H, H_{ar}), 5.83 (d, $J_{1,2}$ = 3.7 Hz, 1H, H_1), 5.71 (brs, 1H, NH_{amide}), 4.69 (d, $J_{1,2}$ = 3.7 Hz, 1H, H_2), 4.56 (s, 2H, $C\underline{H}_2Ph$), 3.95 (ddd, $J_{3,4}$ = 8.9 Hz and $J_{4,5a}$ = $J_{4,5b}$ = 4.4 Hz, 1H, H_4), 3.64 (dd, J_{gem} = 10.7 Hz and $J_{4,5a}$ = 3.5 Hz, 1H, H_{5a}), 3.53 (dd, J_{gem} = 10.7 Hz and $J_{4,5b}$ = 4.8 Hz, 1H, H_{5b}), 3.25 (dq, J_{gem} = 18.0 Hz and $J_{Ha(C\underline{H}2NH),Ha(C\underline{H}2CH3)}$ = $J_{Ha(C\underline{H}2NH),Hb(C\underline{H}2CH3)}$ = $J_{Ha(C\underline{H}2NH),NH}$ = $J_{Ha(C\underline{H}2NH),NH}$ = 6.6 Hz, 1H, $H_{a(C\underline{H}2NH)}$), 3.14 (dq, J_{gem} = 18.0 Hz and $J_{Hb(C\underline{H}2NH),Ha(C\underline{H}2CH3)}$ = $J_{Hb(C\underline{H}2NH),Hb(C\underline{H}2CH3)}$ = $J_{Hb(C\underline{H}2NH),NH}$ = $J_{Hb(C\underline{H}2NH),NH}$ = 6.6 Hz, 1H, $H_{b(C\underline{H}2NH)}$), 2.44−2.37 (m, 2H, $H_{a(C\underline{H}2CO)}$ and H_3), 2.28−2.18 (m, 1H, $H_{b(C\underline{H}2CO)}$), 1.50 (q, $J_{CH2,CH3}$ = 7.4 Hz, 2H, $C\underline{H}_2CH_3$), 1.50 (s, 3H, $Me_{acetonide}$), 1.31 (s, 3H, $Me_{acetonide}$), 0.91 (t, $J_{CH2,CH3}$ = 7.4 Hz, 3H, $CH_2C\underline{H}_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 170.1 (CO_{amide}), 137.0 ($C_{IV(ar)}$), 128.9 (C_{ar}), 127.5 (C_{ar}), 126.9 (C_{ar}), 126.8 (C_{ar}), 110.7 ($C_{IV(acetonide)}$), 104.0 (C_1), 80.3 (C_2), 79.3 (C_4), 72.7 ($\underline{C}H_2Ph$), 69.0 (C_5), 41.8 (C_3), 40.4 (NH-$\underline{C}H_2$), 31.6 ($\underline{C}H_2CO$), 25.8 ($Me_{acetonide}$), 25.5 ($Me_{acetonide}$), 21.9 ($\underline{C}H_2CH_3$), 10.4 ($CH_2\underline{C}H_3$). MS (ESI$^+$) m/z = 386.2 Da [MNa]$^+$. HRMS (ESI$^+$) calcd for $C_{20}H_{29}N_1O_5Na$ = 386.1943 Da, found = 386.1945 Da.

*1,2-O-Isopropylidene-3-deoxy-3-propyl-N-methyl-acetamido-5-O-benzyl-α-D-ribofuranose (**22**).* To a cooled solution of **6** (1 equiv, 1.55 mmol, 500 mg) in DCM (30 mL) was added TBTU (1.4 equiv, 2.17 mmol, 600 mg), HOBt.H_2O (0.5 equiv, 0.78 mmol, 90 mg) and triethylamine (1.1 equiv, 1.7 mmol, 200 μL). The mixture was stirred

DOI: 10.1021/acs.joc.6b01822
J. Org. Chem. 2016, 81, 10742−10758

for 30 min about 5 °C. Then was added methylpropylamine (1.5 equiv, 2.32 mmol, 210 μL) and triethylamine (1.1 equiv, 1.7 mmol, 200 μL), the mixture was stirred overnight at room temperature. The reaction was quenched with water (30 mL), extracted with DCM (3 × 30 mL) and the combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (2 × 40 mL) and brine (2 × 30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (DCM/Et_2O, 99/1) to obtain the desired compound as a colorles oil (375 mg, 1 mmol, 65%). TLC (DCM/Et_2O: 9/1): R_f = 0.34. ^{1}H NMR (400 MHz, $CDCl_3$) of two rotamers in 1/1 ratio δ (ppm) = 7.37−7.29 (m, 5H, H_{ar}), 5.82 (d, $J_{1,2}$ = 3.8 Hz, 0.5H, H_1), 5.81 (d, $J_{1,2}$ = 3.8 Hz, 0.5H, H_1), 4.83 (t, $J_{1,2}$ = $J_{2,3}$ = 4.2 Hz, 1H, H_2), 4.56−4.55 (m, 2H, $C\underline{H}_2$Ph), 4.02−3.96 (m, 1H, H_4), 3.65−3.56 (m, 2H, H_5), 3.41−3.16 (m, 2H, $C\underline{H}_2$NMe), 2.92 (s, 1.5H, NMe), 2.90 (s, 1.5H, NMe), 2.70−2.59 (m, 2H, $H_{a(C\underline{H}2CO)}$, H_3), 2.34 (dd, J_{gem} = 15.9 Hz and $J_{CH2,H3}$ = 3.5 Hz, 0.5H, $H_{b(C\underline{H}2CO)}$), 2.29 (dd, J_{gem} = 15.9 Hz and $J_{CH2,H3}$ = 3.5 Hz, 0.5H, $H_{b(C\underline{H}2CO)}$), 1.60−1.49 (m, 2H, $C\underline{H}_2CH_3$), 1.48 (s, 1.5H, $Me_{acetonide}$), 1.47 (s, 1.5H, $Me_{acetonide}$), 1.29 (s, 3H, $Me_{acetonide}$), 0.88 (t, $J_{CH2,CH3}$ = 7.4 Hz, 1.5H, $CH_2C\underline{H}_3$), 0.87 (t, $J_{CH2,CH3}$ = 7.4 Hz, 1.5H, $CH_2C\underline{H}_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 170.99 (CO_{amide}), 170.98 (CO_{amide}), 138.3 ($C_{IV(ar)}$), 138.2 ($C_{IV(ar)}$), 128.6 (C_{ar}), 128.5 (C_{ar}), 128.5 (C_{ar}), 127.9 (C_{ar}), 127.8 (C_{ar}), 127.7 (C_{ar}), 127.1 (C_{ar}), 111.4 ($C_{IV(acetonide)}$), 111.4 ($C_{IV(acetonide)}$), 105.2 (C_1), 105.1 (C_1), 81.5 (C_2), 80.0 (C_4), 79.9 (C_4), 73.7 ($\underline{C}H_2$Ph), 73.6 ($\underline{C}H_2$Ph), 70.7 (C_5), 70.5 (C_5), 51.6 ($\underline{C}H_2$NMe), 49.6 ($\underline{C}H_2$NMe), 42.9 (C_3), 42.7 (C_3), 35.4 ($\underline{C}H_2$CO), 33.5 ($\underline{C}H_2$CO), 29.0 (NMe), 28.5 (NMe), 26.88 ($Me_{acetonide}$), 26.86 ($Me_{acetonide}$), 26.48 ($Me_{acetonide}$), 26.46 ($Me_{acetonide}$), 21.5 ($\underline{C}H_2CH_3$), 20.7 ($\underline{C}H_2CH_3$), 11.3 ($CH_2\underline{C}H_3$), 11.2 ($CH_2\underline{C}H_3$). MS (ESI$^+$) m/z = 400.2 Da [MNa]$^+$, 777.4 Da [2MNa]$^+$. HRMS (ESI$^+$) calcd for $C_{21}H_{31}N_1O_5Na$ = 400.2094 Da, found = 400.2103 Da. $[\alpha]_D^{20}$ = +13.6 ($CHCl_3$, c = 1 g/100 mL).

5′-O-Trityl-thymidine. To a solution of thymidine (1 equiv, 20 mmol, 4.8 g) in dry pyridine (25 mL) at 80 °C were added trityl chloride (1.2 equiv, 24.4 mmol, 6.8 g) and DMAP (0.025 equiv, 0.5 mmol, 60 mg) under argon. The mixture was stirred overnight at 80 °C, then cooled to room temperature. The reaction mixture was poured into iced-cooled water (1 L) and filtered. The solid was freeze-dried to obtain the desired compound as a colorless solid (7.2 g, 14.86 mmol, 74%). mp = 125 °C. TLC (DCM/MeOH: 94/6): R_f = 0.61. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 10.08 (s, 1H, NH_T), 7.35−7.23 (m, 16H, H_{ar}, H_6), 6.48 (dd, $J_{1′,2′b}$ = 7.4 Hz and $J_{1′,2′a}$ = 6.1 Hz, 1H, $H_{1′}$), 4.64 (dt, $J_{2′b,3′}$ = 6.2 Hz and $J_{2′a,3′}$ = $J_{3′,4′}$ = 3.0, 1H, $H_{3′}$), 4.14 (q, $J_{3′,4′}$ = $J_{4′,5′a}$ = $J_{4′,5′b}$ = 3.0 Hz, 1H, $H_{4′}$), 3.50 (dd, J_{gem} = 10.6 Hz and $J_{4′,5′a}$ = 3.0 Hz, 1H, $H_{5′a}$), 3.40 (dd, J_{gem} = 10.7 Hz and $J_{4′,5′b}$ = 3.3 Hz, 1H, $H_{5′b}$), 2.50 (ddd, J_{gem} = 13.6 Hz, $J_{1′,2′a}$ = 6.1 Hz and $J_{2′a,3′}$ = 3.2 Hz, 1H, $H_{2′a}$), 2.34 (ddd, J_{gem} = 13.8 Hz, $J_{1′,2′b}$ = 7.4 Hz and $J_{2′b,3′}$ = 6.5 Hz, 1H, $H_{2′b}$), 1.50 (d, $J_{6,Me(T)}$ = 0.9 Hz, 3H, Me_T). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 164.4 (C_4), 149.3 (C_2), 143.4 ($C_{IV(ar)}$), 136.2 (C_6), 128.6−127.3 (C_{ar}), 111.0 (C_5), 87.3 ($C_{3′}$), 86.3 ($C_{1′}$), 84.8 ($C_{4′}$), 63.8 ($C_{5′}$), 41.0 ($C_{2′}$), 11.8 (Me_T). MS (ESI$^+$) m/z = 507.2 Da [MNa]$^+$, 991.4 Da [2MNa]$^+$. HRMS (ESI$^+$) calcd for $C_{29}H_{28}N_2O_5Na$ = 507.1890 Da, found = 507.1897 Da.

*1,2-O-Isopropylidene-3-deoxy-3-(2′-deoxy-3′-O-benzyl-5′-deoxy-5′-acetamido-thymidinyl)-5-O-benzyl-α-D-ribofuranose (**23**).* The compound **23** was obtained by peptide coupling from carboxylic acid **6** and the 3′-*O*-benzyl-5′-amino-thymidine obtained as followed. To a solution of 5′-*O*-trityl-thymidine (1 equiv, 2.67 mmol, 1.3 g) in a 2:1 mixture of benzene/dioxane (15 mL) were added KOH (10 equiv, 26.7 mmol, 1.5 g) and benzyl chloride (1.5 equiv, 4 mmol, 0.46 mL) under argon. The mixture was stirred at reflux for 3 h then quickly filtered. It was diluted with DCM (20 mL), washed with HCl 0.5 N water (2 × 20 mL) and the aqueous layer was extracted with DCM (20 mL). The combined organic layers were washed with water (2 × 20 mL) and brine (2 × 20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude of the desired 3′-*O*-benzyl-5′-*O*-trityl-thymidine was used in the next step without further purification. TLC (DCM/MeOH: 97/3): R_f = 0.60. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.04 (brs, 1H, NH_T), 7.57 (d, J = 1.2 Hz, 1H, H_6), 7.39−7.27 (m, 20H, H_{ar}), 6.37 (dd, $J_{1,2b}$ = 7.9 Hz and $J_{1,2a}$ = 5.8 Hz, 1H, $H_{1′}$), 4.54 (d, J_{gem} = 11.9 Hz, 1H, C$\underline{H}$H′Ph), 4.45 (d, J_{gem} = 11.9, 1H, CH$\underline{H}$′Ph), 4.31 (ddd, $J_{2′b,3′}$ = 6.1 Hz, $J_{3′,4′}$ = 2.8 Hz and $J_{2′a,3′}$ = 2.5 Hz, 1H, $H_{3′}$), 4.18 (q, $J_{3′,4′}$ = $J_{4′,5′a}$ = $J_{4′,5′b}$ = 2.8 Hz, 1H, $H_{4′}$), 3.46 (dd, J_{gem} = 10.6 Hz and $J_{4′,5′a}$ = 2.8 Hz, 1H, $H_{5′a}$), 3.31 (dd, J_{gem} = 10.6 Hz and $J_{4′,5′b}$ = 3.1 Hz, 1H, $H_{5′b}$), 2.54 (ddd, J_{gem} = 13.6 Hz, $J_{1′,2′a}$ = 5.7 Hz and $J_{2′a,3′}$ = 2.5 Hz, 1H, $H_{2′a}$), 2.20 (ddd, J_{gem} = 13.6 Hz, $J_{1′,2′b}$ = 7.9 Hz and $J_{2′b,3′}$ = 6.1 Hz, 1H, $H_{2′b}$), 1.45 (d, $J_{6,Me(T)}$ = 1.1 Hz, 3H, Me_T). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 163.7 (C_4), 150.1 (C_2), 143.5 ($C_{IV(ar)}$), 137.5 (C_6), 135.7 ($C_{IV(ar)}$), 128.8−127.4 (C_{ar}), 111.3 (C_5), 85.1 ($C_{1′}$), 84.2 ($C_{4′}$), 78.8 ($C_{3′}$), 71.5 ($\underline{C}H_2$Ph), 64.0 ($C_{5′}$), 38.2 ($C_{2′}$), 12.0 (Me_T). MS (ESI$^+$) m/z = 597.2 Da [MNa]$^+$. HRMS (ESI$^+$) calcd for $C_{36}H_{34}O_5N_2Na$ = 597.2360 Da, found = 597.2363 Da.

A solution of this 3′-*O*-benzyl-5′-*O*-trityl-thymidine in acetic acid 80% (15 mL) was refluxed for 20 min. The mixture was coevaporated with water (2 × 10 mL), diluted with DCM and washed with a saturated aqueous solution of $NaHCO_3$ until pH = 9. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the desired 3′-*O*-benzyl-thymidine (400 mg, 1.2 mmol, 45% for two steps). TLC (DCM/MeOH: 97/3): R_f = 0.37. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.48 (brs, 1H, NH_T), 7.39−7.29 (m, 6H, H_6, H_{ar}), 6.12 (dd, $J_{1′,2′}$ = 7.3 Hz and $J_{1′,2′}$ = 6.1 Hz, 1H, $H_{1′}$), 4.58 (d, J_{gem} = 11.7 Hz, 1H, C$\underline{H}$H′Ph), 4.52 (d, J_{gem} = 11.7 Hz, 1H, CH$\underline{H}$′Ph), 4.29 (dt, $J_{2′a,3′}$ = 6.2 Hz and $J_{2′b,3′}$ = $J_{3′,4′}$ = 3.1 Hz, 1H, $H_{3′}$), 4.17 (q, J = 2.9 Hz, 1H, $H_{4′}$), 3.93 (dd, J_{gem} = 11.8 Hz and $J_{4′,5′a}$ = 2.7 Hz, 1H, $H_{5′a}$), 3.75 (dd, J_{gem} = 11.8 Hz and $J_{4′,5′b}$ = 2.9 Hz, 1H, $H_{5′b}$), 2.41−2.35 (m, 1H, $H_{2′}$), 1.91 (d, $J_{6,Me(T)}$ = 1.1 Hz, 3H, Me_T). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 163.7 (C_4), 150.4 (C_2), 137.1 (C_6), 137.7 ($C_{IV(ar)}$), 128.7 (C_{ar}), 128.2 (C_{ar}), 127.8 (C_{ar}), 111.2 (C_5), 87.6 ($C_{1′}$), 85.3 ($C_{4′}$), 78.8 ($C_{3′}$), 71.8 ($\underline{C}H_2$Ph), 63.0 ($C_{5′}$), 37.3 ($C_{2′}$), 12.6 (Me_T). MS (ESI$^+$) m/z = 355.1 Da [MNa]$^+$. HRMS (ESI$^+$) calcd for $C_{17}H_{20}N_2O_5Na$ = 355.1270 Da, found = 355.1273 Da. Spectroscopic data of this compound were consistent with those reported in the literature.[43]

To a cooled solution (0 °C) of 3′-*O*-benzyl-thymidine (1 equiv, 3 mmol, 1 g) in pyridine (12 mL) was added dropwise methanesulfonyl chloride (2 equiv, 6 mmol, 465 μL). The cold bath was removed and the mixture was stirred at room temperature under argon for 3 h. The reaction mixture was quenched with water (2 mL) then coevaporated with toluene (2 × 5 mL). The residue was diluted with DCM (20 mL), washed successively with a saturated aqueous solution of $NaHCO_3$ (2 × 15 mL) and brine (2 × 15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the desired 3′-*O*-benzyl-5′-*O*-mesyl-thymidine as a brown oil (1.2 g, 2.9 mmol, 96%). TLC (DCM/MeOH: 97/3): R_f = 0.48. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.80 (brs, 1H, NH_T), 7.38−7.32 (m, 6H, H_{ar} and H_6), 6.30 (dd, $J_{1′,2′b}$ = 7.5 Hz and $J_{1′,2′a}$ = 6.3 Hz, 1H, $H_{1′}$), 4.60 (d, J_{gem} = 11.7 Hz, 1H, C$\underline{H}$H′Ph), 4.51 (d, J_{gem} = 11.7 Hz, 1H, CH$\underline{H}$′Ph), 4.46 (dd, J_{gem} = 11.2 Hz and $J_{4′,5′a}$ = 2.7 Hz, 1H, $H_{5′a}$), 4.35 (dd, J_{gem} = 11.2 Hz and $J_{4′,5′b}$ = 3.2 Hz, 1H, $H_{5′b}$), 4.28−4.23 (m, 2H, $H_{3′}$, $H_{4′}$), 3.04 (s, 3H, $MeSO_2$), 2.49 (ddd, J_{gem} = 13.8 Hz, $J_{1′,2′a}$ = 6.3 Hz and $J_{2′a,3′}$ = 2.9 Hz, 1H, $H_{2′a}$), 2.13 (ddd, J_{gem} = 13.8 Hz, $J_{1′,2′b}$ = 7.5 Hz and $J_{2′b,3′}$ = 6.1 Hz, 1H, $H_{2′b}$), 1.94 (d, $J_{6,Me(T)}$ = 1.1 Hz, 3H, Me_T). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 163.9 (C_4), 150.6 (C_2), 137.7 ($C_{IV(ar)}$), 136.6 (C_6), 129.7 ($C_{ar(o)}$), 128.9 ($C_{ar(m)}$), 128.5 ($C_{ar(p)}$), 111.2 (C_5), 86.2 ($C_{4′}$), 85.8 ($C_{1′}$), 78.4 ($C_{3′}$), 72.0 ($\underline{C}H_2$Ph), 66.5 ($C_{5′}$), 37.4 ($MeSO_2$), 36.7 ($C_{2′}$), 12.3 (Me_T). MS (ESI$^+$) m/z = 411.1 Da [MH]$^+$, 821.2 Da [2MH]$^+$. HRMS (ESI$^+$) calcd for $C_{18}H_{23}N_2O_7S_1$ = 411.1221 Da, found = 411.1221 Da.

To a solution of 3′-*O*-benzyl-5′-*O*-mesyl-thymidine (1 equiv, 3 mmol, 1.2 g) in DMF (25 mL) was added sodium azide (1.5 equiv, 4.5 mmol, 293 mg). The mixture was stirred for 2 h at 85 °C, then cooled to room temperature and quenched with brine (30 mL). The aqueous layer was extracted with Et_2O (2 × 30 mL) and the combined organic layers were washed with brine (5 × 30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the desired 3′-*O*-benzyl-5′-azido-thymidine as a colorless oil (1 g, 2.8 mmol, 93%). TLC (DCM/Et_2O: 7/3): R_f = 0.55. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.40 (brs, 1H, NH_T), 7.40−7.30 (m, 6H, H_{ar} and H_6), 6.27 (dd, $J_{1′,2′b}$ = 7.5 Hz and $J_{1′,2′a}$ = 6.2 Hz, 1H, $H_{1′}$), 4.59 (d, J_{gem} = 11.7

DOI: 10.1021/acs.joc.6b01822
J. Org. Chem. 2016, 81, 10742−10758

Hz, 1H, CHH′Ph), 4.49 (d, J_{gem} = 11.7 Hz, 1H, CHH′Ph), 4.17−4.13 (m, 2H, $H_{3'}$ and $H_{4'}$), 3.70 (dd, J_{gem} = 13.1 Hz and $J_{4',5'a}$ = 3.1 Hz, 1 H, $H_{5'a}$), 3.49 (dd, J_{gem} = 13.1 Hz and $J_{4',5'b}$ = 3.2 Hz, 1H, $H_{5'b}$), 2.47 (ddd, J_{gem} = 13.8 Hz, $J_{1',2'a}$ = 6.2 Hz and $J_{2'a,3'}$ = 2.7 Hz, 1H, $H_{2'a}$), 2.16−2.07 (m, 1H, $H_{2'b}$), 1.94 (d, $J_{6,Me(T)}$ = 1.1 Hz, 3H, Me_T). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 163.8 (C_4), 150.4 (C_2), 137.0 (C_6), 135.4 ($C_{IV(ar)}$), 132.3 (C_{ar}), 132.1 (C_{ar}), 128.7 (C_{ar}), 128.6 (C_{ar}), 111.0 (C_5), 85.5 ($C_{1'}$ and $C_{4'}$), 79.1 ($C_{3'}$), 71.6 (CH_2Ph), 62.7 ($C_{5'}$), 37.6 ($C_{2'}$), 12.6 (Me_T). MS (ESI$^+$) m/z = 358.1 Da $[MH]^+$, 715.2 Da $[2MH]^+$. HRMS (ESI$^+$) calcd for $C_{17}H_{20}N_5O_4$ = 358.1510 Da, found = 358.1515 Da.

To a solution of 3′-*O*-benzyl-5′-azido-thymidine (6.8 mmol, 2.3 g) in EtOH (25 mL) was added 10% Pd/C (5% weight, 115 mg). The reaction was stirred under hydrogen atmosphere (1 bar) at room temperature for 3 h. The mixture was filtered and concentrated under reduced pressure to give the desired precursor 3′-*O*-benzyl-5′-amino-thymidine as a colorless powder (2.25 g, 6.8 mmol, quantitative). mp = 96−97 °C. TLC (alumin, DCM/MeOH: 94/6): R_f = 0.48. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.01 (s, 1H, NH_T), 7.39−7.30 (m, 6H, H_{ar}, H_6), 6.23 (t, $J_{1',2'}$ = 6.9 Hz, 1H, $H_{1'}$), 4.58 (d, J_{gem} = 11.8 Hz, 1H, CHH′Ph), 4.51 (d, J_{gem} = 11.8 Hz, 1H, CHH′Ph), 4.14−4.09 (m, 1H, $H_{3'}$), 4.04−4.00 (m, 1H, $H_{4'}$), 3.04 (dd, J_{gem} = 13.6 Hz and $J_{4',5'a}$ = 4.1 Hz, 1H, $H_{5'a}$), 2.90 (dd, J_{gem} = 13.6 Hz and $J_{4',5'b}$ = 5.4 Hz, 1H, $H_{5'b}$), 2.45 (ddd, J_{gem} = 13.7 Hz, $J_{1',2'a}$ = 6.3 Hz and $J_{2'a,3'}$ = 3.3 Hz, 1H, $H_{2'a}$), 2.13 (dt, J_{gem} = 13.9 Hz and $J_{1',2'b}$ = $J_{2'b,3'}$ = 7.1 Hz, 1H, $H_{2'b}$), 1.92 (brs, 3 H, Me_T). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 164.0 (C_4), 150.5 (C_2), 137.6 ($C_{IV(ar)}$), 135.9 (C_6), 128.7 (C_{ar}), 128.1 ($C_{ar(p)}$), 127.8 (C_{ar}), 111.3 (C_5), 85.3 ($C_{1'}$ and $C_{4'}$), 78.8 ($C_{3'}$), 71.8 (CH_2Ph), 43.9 ($C_{5'}$), 37.6 ($C_{2'}$), 12.7 (Me_T). MS (MALDI$^+$: DHB) m/z = 332.2 Da $[MH]^+$. HRMS (MALDI$^+$: DHB, PEG 200) calcd for $C_{17}H_{22}N_3O_4$ = 332.1605 Da, found 332.1601 Da.

To a cooled solution of **6** (1 equiv, 1.76 mmol, 570 mg) in DCM (12 mL) was added TBTU (1.4 equiv, 2.4 mmol, 791 mg), HOBt.H_2O (0.5 equiv, 0.88 mmol, 119 mg) and triethylamine (1.1 equiv, 1.93 mmol, 263 μL). The mixture was stirred for 30 min at 5 °C then was added a solution of 3′-*O*-benzyl-5′-amino-thymidine (1 equiv, 1.76 mmol, 590 mg) in DCM (10 mL) and triethylamine (1.1 equiv, 1.93 mmol, 263 μL). The mixture was stirred at room temperature overnight. The reaction was quenched with water (50 mL), extracted with DCM (3 × 50 mL) and the combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (2 × 50 mL) and brine (2 × 50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. If necessary, the crude was diluted with toluene and washed with water (3 × 50 mL) to eliminate urea. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the desired compound **23** as a beige amorphous solid (1 g, 1.57 mmol, 89%). TLC (Et_2O/*i*-PrOH: 98/2): R_f = 0.34. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.06 (brs, 1H, NH_T), 7.38−7.30 (m, 10H, H_{ar}), 7.09 (d, $J_{6B,Me(T)}$ = 1.2 Hz, 1H, H_{6B}), 6.50−6.44 (m, 1H, NH_{amide}), 5.94 (dd, $J_{1'B,2'B}$ = 7.9 Hz and $J_{1'B,2'B}$ = 6.4 Hz, 1H, $H_{1'B}$), 5.82 (d, $J_{1A,2A}$ = 3.7 Hz, 1H, H_{1A}), 4.69 (t, ^3J = 4.1 Hz, 1H, H_{2A}), 4.57 (AB syst., J = 11.8 Hz) 2H, CH_2Ph), 4.51 (AB syst., J = 11.0 Hz, 2H, CH_2Ph), 4.14−4.11 (m, 1H, $H_{4'B}$), 4.08−4.05 (m, 1H, $H_{3'B}$), 3.98−3.94 (m, 1H, H_{4A}), 3.70−3.63 (m, 2H, H_{5A}, $H_{5'B}$), 3.55 (dd, J_{gem} = 10.9 Hz and $J_{4A,5A}$ = 4.7 Hz, 1H, H_{5A}), 3.43 (dt, J_{gem} = 14.2 Hz and $J_{4'B,5'B}$ = $J_{NH,5'B}$ = 4.2 Hz, 1H, $H_{5'B}$), 2.51−2.28 (m, 5H, $H_{2'B}$, H_{3A}, CH_2CO), 1.93 (d, $J_{6B,Me(T)}$ = 1.2 Hz, 3H, Me_T), 1.48 (s, 3H, $Me_{acetonide}$), 1.28 (s, 3H, $Me_{acetonide}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 171.7 (CO_{amide}), 163.2 (C_{4B}), 150.1 (C_{2B}), 138.1 ($C_{IV(ar)}$), 137.5 (C_{6B}), 137.4 ($C_{IV(ar)}$), 128.7 (C_{ar}), 128.6 (C_{ar}), 128.3 (C_{ar}), 127.9 (C_{ar}), 127.8 (C_{ar}), 111.6 (C_{5B}), 111.5 ($C_{IV(acetonide)}$), 105.1 (C_{1A}), 88.8 ($C_{1'B}$), 83.6 ($C_{4'B}$), 81.3 (C_{2A}), 80.2 (C_{4A}), 79.6 ($C_{3'B}$), 73.7 (CH_2Ph), 72.0 (CH_2Ph), 69.9 (C_{5A}), 42.5 (C_{3A}), 41.7 ($C_{5'B}$), 36.4 ($C_{2'B}$), 32.1 (CH_2CO), 26.9 ($Me_{acetonide}$), 26.6 ($Me_{acetonide}$), 12.6 (Me_T). MS (ESI$^+$) m/z = 658.3 Da $[M+MeOH+Na]^+$. HRMS (ESI$^+$) calcd for $C_{34}H_{41}N_3O_9Na$ = 658.2740 Da, found = 658.2747 Da.

Attempt to Acetolysis of 21 (Formation of Byproducts 24 and 25). A solution of **21** (1 equiv, 0.72 mmol, 260 mg) in acetic acid/water (4 mL/1 mL) was stirred for 6 h at 90 °C and then coevaporated with pyridine. The crude was diluted with pyridine and acetic anhydride (17 equiv, 12.6 mmol, 1.1 mL) was added. The mixture was stirred for 20 h at room temperature, and then iced water was added. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were washed with water (2 × 15 mL) and HCl 0.2 N (15 mL), then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (DCM/Et_2O, 95/5 to 85/5) to obtain compound **24** as a single isomer (80 mg, 0.26 mmol, 45%) and **25** (52 mg, 0.15 mmol, 26%).

*(3aR,4S,6aR)-4-((Benzyloxy)methyl)-2-oxohexahydrofuro[3,4-b]-furan-6-yl acetate (**24**).* TLC (DCM/Et_2O: 8/2): R_f = 0.82. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.37−7.30 (m, 5H, H_{ar}), 5.33 (s, 1H, H_1), 4.90 (d, $J_{2,3}$ = 6.3 Hz, 1H, H_2), 4.56 (s, 2H, CH_2Ph), 4.24−4.20 (m, 1H, H_4), 3.63 (dd, J_{gem} = 9.9 Hz and $J_{4,5a}$ = 5.2 Hz, 1 H, H_{5a}), 3.50 (dd, J_{gem} = 9.9 Hz and $J_{4,5b}$ = 6.7 Hz, 1H, H_{5b}), 3.16−3.11 (m, 1H, H_3), 2.84 (dd, J_{gem} = 18.2 Hz and $J_{Ha(CH2CO),3}$ = 9.1 Hz, 1H, Ha_{CH2CO}), 2.52 (dd, J_{gem} = 18.2 Hz and $J_{Hb(CH2CO),3}$ = 2.1 Hz, 1H, Hb_{CH2CO}), 2.00 (s, 3H, Me_{Ac}). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 174.9 (CO), 169.1 (CO_{Ac}), 137.8 ($C_{IV(ar)}$), 128.7 (C_{ar}), 128.1 (C_{ar}), 127.8 (C_{ar}), 99.9 (C_1), 87.4 (C_4), 86.9 (C_2), 73.7 (CH_2Ph), 72.0 (C_5), 40.1 (C_3), 34.0 (CH_2CO), 21.2 (Me_{Ac}). MS (CI$^+$) m/z = 324.1 Da $[MNH_4]^+$; (CI$^-$) m/z = 340.9 Da $[M+Cl]^-$, (MALDI$^+$: DHB) m/z = 307.2 Da $[MH]^+$. HRMS (MALDI$^+$: DHB, PEG 200) calcd for $C_{16}H_{19}O_6$ = 307.1178 Da, found 307.1176 Da.

*(1S,5R,6S,8R)-6-((Benzyloxy)methyl)-3-oxo-2-propyl-7-oxa-2-azabicyclo[3.2.1]octan-8-yl acetate (**25**).* TLC (DCM/Et_2O: 8/2): R_f = 0.57. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.25−7.38 (m, 5H, H_{ar}), 5.17 (dd, $J_{1,2}$ = 4.3 Hz and $J_{1,3}$ = 0.7 Hz, 1H, H_1), 5.10 (t, $J_{2,3}$ = 4.8 Hz and $J_{1,2}$ = 4.3 Hz, 1H, H_2), 4.58 (d, J_{gem} = 12.1 Hz, 1H, CH_2Ph), 4.52 (d, J_{gem} = 12.1 Hz, 1H, CH_2Ph), 4.12 (t, $J_{4,5a}$ = $J_{4,5b}$ = 4.5 Hz, 1H, H_4), 3.54 (dd, J_{gem} = 10.4 Hz and $J_{4,5a}$ = 4.8 Hz, 1H, H_{5a}), 3.50 (dd, J_{gem} = 10.4 Hz and $J_{4,5b}$ = 4.3 Hz, 1H, H_{5b}), 3.47−3.43 (m, 1H, CH_2N), 3.26−3.16 (m, 1H, CH_2N), 2.81 (dd, J_{gem} = 17.8 Hz and $J_{Ha(CH2CO),3}$ = 4.5 Hz, 1H, $H_{a(CH2CO)}$), 2.70−2.63 (m, 1H, H_3), 2.39 (dd, J_{gem} = 17.8 Hz and $J_{Hb(CH2CO),3}$ = 1.5 Hz, 1H, $H_{b(CH2CO)}$), 2.07 (s, 3H, Me_{Ac}), 1.57−1.43 (m, 2H, $CH_{2(Pr)}$), 0.87 (t, $J_{CH2,CH3}$ = 7.4 Hz, 3H, Me_{Pr}). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 170.4 (CO_{amide}), 169.1 (CO_{Ac}), 137.8 ($C_{IV(ar)}$), 128.6 (C_{ar}), 128.0 (C_{ar}), 127.8 (C_{ar}), 85.4 (C_1), 81.8 (C_4), 73.8 (CH_2Ph), 71.3 (C_5), 70.2 (C_2), 48.0 (CH_2N), 36.4 (CH_2CO), 36.1 (C_3), 22.0 ($CH_{2(Pr)}$), 20.8 (Me_{Ac}), 11.3 (Me_{Pr}). MS (CI$^+$) m/z = 348.1 Da $[MH]^+$; (CI$^-$) m/z = 382.1 Da $[M+Cl]^-$, (MALDI$^+$: DHB) m/z = 348.2 Da $[MH]^+$, 370.2 $[MNa]^+$. HRMS (MALDI$^+$: DHB, PEG 200) calcd for $C_{19}H_{26}N_1O_5$ = 348.1805 Da, found 348.1802 Da.

*1,2-O-Acetyl-3-deoxy-3-propylacetamido-5-O-benzyl-β-D-ribofuranose (**26**).* To a solution of **21** (1 equiv, 0.41 mmol, 150 mg) in acetic acid (3 mL) was added acetic anhydride (40 equiv, 16.4 mmol, 1.5 mL), camphor sulfonic acid (0.1 equiv, 0.04 mmol, 9 mg). The latter mixture was stirred for 20 min at 80 °C, a second portion of camphor sulfonic acid (0.1 equiv, 0.04 mmol, 9 mg) was added and stirring was pursued for 20 min. The mixture was concentrated under reduced pressure, diluted with DCM (15 mL) and washed with water (2 × 20 mL) and a saturated aqueous solution of $NaHCO_3$ (2 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, concentrated under reduced pressure. The crude was purified by flash column chromatography (DCM/Et_2O, 90/10) to obtain the desired compound as a single isomer as an orange oil (50 mg, 0.12 mmol, 30%). TLC (DCM/Et_2O: 9/1): R_f = 0.27. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.34−7.27 (m, 5H, H_{ar}), 6.07 (s, 1H, H_1), 5.58 (brs, 1H, NH), 5.26 (d, $J_{2,3}$ = 4.7 Hz, 1H, H_2), 4.56 (s, 2H, CH_2Ph), 4.12 (dt, $J_{3,4}$ = 9.5 Hz and $J_{4,5a}$ = $J_{4,5b}$ = 4.8 Hz, 1H, H_4), 3.63−3.58 (m, 2H, H_5), 3.22−3.10 (m, 2H, CH_2NH), 2.94−2.87 (m, 1H, H_3), 2.37−2.29 (m, 2H, CH_2CO), 2.09 (s, 3H, Me_{Ac}), 1.95 (s, 3H, Me_{Ac}), 1.47 (q, $J_{CH2,CH3}$ = 7.3 Hz, 2H, CH_2CH_3), 0.89 (t, $J_{CH2,CH3}$ = 7.3 Hz, 3H, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 170.3 (CO_{amide}), 170.0 (CO_{Ac}), 169.5 (CO_{Ac}), 138.2 ($C_{IV(ar)}$), 128.5 (C_{ar}), 127.8 (C_{ar}), 127.78 (C_{ar}), 98.8 (C_1), 83.7 (C_4), 78.1 (C_2), 73.5 (CH_2Ph), 71.9 (C_5), 41.5 (CH_2NH), 39.0 (C_3), 32.7 (CH_2CO), 22.9 (CH_2CH_3), 21.2 (Me_{Ac}), 20.8 (Me_{Ac}), 11.4 (CH_2CH_3). MS (CI$^+$) m/z = 408.2 Da $[MH]^+$, 348.1 Da [MH-AcOH]$^+$; (MALDI$^+$: DHB) m/z = 430.2 Da

DOI: 10.1021/acs.joc.6b01822
J. Org. Chem. 2016, 81, 10742−10758

$[MNa]^+$, 348.2 Da $[MH\text{-}AcOH]^+$. HRMS (MALDI$^+$: DHB, PEG 400) calcd for $C_{21}H_{29}N_1O_7Na$ = 430.1836 Da, found 430.1837 Da.

*2-O-Acetyl-1,3-deoxy-3-(2′-deoxy-3′-O-benzyl-5′-deoxy-5′-cycloacetamido-thymidinyl)-5-O-benzyl-α-D-ribofuranose (**27**).* A solution of acetonide **23** (1 equiv, 0.31 mmol, 200 mg) in trifluoroacetic acid/water (2.4 mL/0.6 mL) was stirred for 24 h at room temperature. The reaction mixture was diluted with DCM then washed successively with water and a saturated aqueous solution of $NaHCO_3$, and dried over Na_2SO_4. The crude was coevaporated with pyridine, diluted in pyridine (5 mL). Acetic anhydride (20 equiv, 6.3 mmol, 0.8 mL) was added to the solution and the reaction mixture was stirred for 20 h at room temperature. The reaction mixture was diluted with DCM (10 mL), washed with water and HCl 1N (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (DCM/Et_2O, 6/4 to 0/10) to give compound **27** as a beige oil (65 mg, 0.10 mmol, 32%). TLC (DCM/Et_2O: 6/4): R_f = 0.21. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.88 (s, 1H, NH_T), 7.43 (d, $J_{6B,Me(T)}$ = 1.0 Hz, 1H, H_{6B}), 7.37−7.30 (m, 10H, H_{ar}), 6.23 (dd, $J_{1'B,2'Bb}$ = 8.1 Hz and $J_{1'B,2'Ba}$ = 5.6 Hz, 1H, $H_{1'B}$), 5.36 (d, $J_{1A,2A}$ = 4.1 Hz, 1H, H_{1A}), 5.07 (t, ^3J = 4.8 Hz, 1H, H_{2A}), 4.47−4.59 (m, 4H, 2×C$\underline{H}_2$Ph), 4.14−4.10 (m, 1H, $H_{4'B}$), 4.01−3.96 (m, 2H, $H_{3'B}$ and H_{4A}), 3.82 (dd, J_{gem} = 14.2 Hz and $J_{4'B,5'Ba}$ = 8.8 Hz, 1H, $H_{5'Ba}$), 3.51−3.49 (m, 2H, H_{5A}), 3.41 (dd, J_{gem} = 14.2 Hz and $J_{4'B,5'Bb}$ = 3.4 Hz, 1H, $H_{5'Bb}$), 2.83 (dd, J_{gem} = 17.9 Hz and $J_{CH2CO,3A}$ = 4.2 Hz, 1H, C$\underline{H}$H′CO), 2.69−2.67 (m, 1H, H_{3A}), 2.47 (ddd, J_{gem} = 13.8 Hz, $J_{1'B,2'Ba}$ = 5.6 Hz and $J_{2'Ba,3'B}$ = 2.5 Hz, 1H, $H_{2'Ba}$), 2.41 (d, J_{gem} = 17.9 Hz, 1H, CH$\underline{H}$′CO), 1.99 (s, 3H, Me_{Ac}), 1.95 (d, $J_{6B,Me(T)}$ = 1.0 Hz, 3H, Me_T). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 170.6 (CO_{Ac}), 169.8 (CO_{amide}), 163.9 (C_{4B}), 150.3 (C_{2B}), 137.7 ($C_{IV(ar)}$), 137.4 ($C_{IV(ar)}$), 135.8 (C_{6B}), 128.7 (C_{ar}), 127.8 (C_{ar}), 127.8 (C_{ar}), 111.3 (C_{5B}), 85.6 ($C_{1'B}$), 84.6 (C_{1A}), 81.8 (C_{4A}), 81.7 ($C_{4'B}$), 79.6 ($C_{3'B}$), 73.7 ($\underline{C}H_2$Ph), 71.6 ($\underline{C}H_2$Ph), 71.1 (C_{5A}), 70.1 (C_{2A}), 47.1 ($C_{5'B}$), 37.1 ($C_{2'B}$), 36.4 ($\underline{C}H_2$CO), 36.0 (C_{3A}), 20.7 (Me_{Ac}), 12.4 (Me_T). MS (MALDI$^+$: DHB): 642.3 $[MNa]^+$, 620.3 $[MH\text{-}H_2O]^+$. HRMS (MALDI$^+$: DHB, PEG 600) calcd for $C_{33}H_{37}N_3O_9Na$ = 642.2427, found 642.2411.

*1,2-O-Acetyl-3-deoxy-3-propyl-N-methyl-acetamido-5-O-benzyl-D-ribofuranose (**28**).* To a solution of **22** (1 equiv, 0.45 mmol, 170 mg) in acetic acid (3 mL) was added acetic anhydride (40 equiv, 18 mmol, 1.7 mL), camphor sulfonic acid (0.02 equiv, 0.009 mmol, 2 mg). The mixture was stirred for 90 min at 80 °C, then three portions of camphor sulfonic acid (0.05 equiv, 0.02 mmol, 5 mg each portion) were added every hour. After stirring for 4 h, the mixture was concentrated under reduced pressure, diluted with DCM (15 mL) and washed with water (2 × 20 mL) and a saturated aqueous solution of $NaHCO_3$ (2 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, concentrated under reduced pressure. The crude was purified by flash column chromatography (eluent: DCM/Et_2O, 95/5, v/v) to obtain the desired compound as a colorless oil (82 mg, 0.19 mmol, 75% from 0.26 mmol remaining in the mixture after GC samples). TLC (DCM/Et_2O: 8/2): R_f = 0.46. ^{1}H NMR (300 MHz, $CDCl_3$) mixture of two anomers in a 85:15 ratio δ (ppm) = 7.35−7.31 (m, 5H, H_{ar}), 6.42 (dd, $J_{1,2}$ = 4.3 Hz and $J_{1,3}$ = 1.0 Hz, 0.15H, $H_{1\alpha}$), 6.09 (s, 0.85H, $H_{1\beta}$), 5.41 (dd, $J_{2,3}$ = 8.4 Hz and $J_{1,2}$ = 4.4 Hz, 0.15H, $H_{2\alpha}$), 5.33 (d, $J_{2,3}$ = 4.7 Hz, 0.85H, $H_{2\beta}$), 4.58−4.57 (m, 0.3H, C$\underline{H}_2$Ph$_\alpha$), 4.56−4.54 (m, 1.7H, C$\underline{H}_2$Ph$_\beta$), 4.23−4.20 (m, 0.15H, $H_{4\alpha}$), 4.19−4.12 (m, 0.85H, $H_{4\beta}$), 3.66−3.58 (m, 2H, H_5), 3.32−3.15 (m, 2H, C$\underline{H}_2$NMe), 3.00−2.94 (m, 1H, H_3), 2.57−2.46 (m, 2H, CH_2CO), 2.09 (s, 0.9H, $Me_{Ac\alpha}$), 2.08 (s, 2.1H, $Me_{Ac\beta}$), 2.07 (s, 0.9H, $Me_{Ac\beta}$), 2.06 (s, 2.1H, $Me_{Ac\alpha}$), 1.57−1.47 (m, 2H, C$\underline{H}_2$CH$_3$), 0.90−0.84 (m, 3H, CH$_2$C$\underline{H}_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 170.2 (CO_{amide}), 169.8 (CO_{Ac}), 169.6 (CO_{Ac}), 138.2 ($C_{IV(ar)}$), 128.5 (C_{ar}), 127.7 (C_{ar}), 98.8 (C_1), 83.4 ($C_{4\beta}$), 83.2 ($C_{4\alpha}$), 78.1 ($C_{2\beta}$), 77.4 ($C_{2\alpha}$), 73.5 ($\underline{C}H_2$Ph), 72.4 (C_5), 72.3 (C_5), 51.4 ($\underline{C}H_2$NMe), 49.6 ($\underline{C}H_2$NMe), 39.3 (C_3), 39.0 (C_3), 29.5 ($\underline{C}H_2$CO), 28.9 (CH_2CO), 21.6 ($\underline{C}H_2$CH$_3$), 21.3 (NMe), 20.9 (Me_{Ac}), 20.6 ($\underline{C}H_2$CH$_3$), 11.3 (CH$_2\underline{C}$H$_3$), 11.2 (CH$_2\underline{C}$H$_3$). MS (CI$^+$) m/z = 422.3 $[MNH_3]^+$, 462.2 $[MNH_3\text{−}AcOH]^+$; (ESI$^+$) m/z = 444.2 Da $[MNa]^+$. HRMS (ESI$^+$) calcd for $C_{22}H_{31}N_1O_7Na$ = 444.1998 Da, found = 444.2002 Da.

*1,2-O-Acetyl-3-deoxy-3-(2′-deoxy-3′-O-benzyl-5′-deoxy-5′-acetamido-thymidinyl)-5-O-benzyl-β-D-ribofuranose (**29**).* To a solution of **23** (1 equiv, 0.28 mmol, 180 mg) in acetic acid (4 mL) were added acetic anhydride (40 equiv, 11.2 mmol, 1.1 mL) and camphor sulfonic acid (0.05 equiv, 0.01 mmol, 3.2 mg). The mixture was stirred for 1 h at 90 °C and another portion of camphor sulfonic acid (0.05 equiv, 0.01 mmol, 3.2 mg) was added. The mixture was stirred for 1 h then concentrated under reduced pressure, diluted with DCM (15 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (3 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (DCM/*i*PrOH, 96/4) to give **29** as a light brown solid (85 mg, 0.12 mmol, 43%). The compound **29** was isolated as a single isomer. mp = 75−76 °C. TLC (Et_2O/*i*-PrOH: 98/2): R_f = 0.10. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.29 (brs, 1H, NH_T), 7.35−7.30 (m, 10H, H_{ar}), 7.05 (d, $J_{6B,Me(T)}$ = 0.9 Hz, 1H, H_{6B}), 6.58−6.55 (m, 1H, NH_{amide}), 6.07 (s, 1H, H_{1A}), 5.80 (t, $J_{1'B,2'B}$ = 7.1 Hz, 1H, $H_{1'B}$), 5.26 (d, $J_{2A,3A}$ = 4.7 Hz, 1H, H_{2A}), 4.57 (AB syst., J = 12.2 Hz, 2H, C$\underline{H}_2$Ph), 4.52 (AB syst., J = 11.6 Hz, 2H, C$\underline{H}_2$Ph), 4.16−4.09 (m, 3H, H_{4A}, $H_{3'B}$ and $H_{4'B}$), 3.69−3.63 (m, 1H, $H_{5'B}$), 3.62−3.61 (m, 2H, H_{5A}), 3.44−3.37 (m, 1H, $H_{5'B}$), 2.98−2.92 (m, 1H, H_{3A}), 2.54−2.45 (m, 1H, $H_{2'B}$), 2.39−2.37 (m, 2H, CH_2CO), 2.36−2.30 (m, 1H, $H_{2'B}$), 2.08 (s, 3H, Me_{Ac}), 1.96 (s, 3H, Me_{Ac}), 1.93 (d, $J_{6B,Me(T)}$ = 0.9 Hz, 3H, Me_T). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 171.0 (CO_{amide}), 170.0 (CO_{Ac}), 169.5 (CO_{Ac}), 163.3 (C_{4B}), 150.3 (C_{2B}), 138.3 (C_{6B}), 138.2 ($C_{IV(ar)}$), 137.5 ($C_{IV(ar)}$), 128.74−127.74 (C_{ar}), 111.5 (C_{5B}), 99.0 (C_{1A}), 90.0 ($C_{1'B}$), 83.6 (C_4 or $C_{4'}$), 83.4 (C_4 or $C_{4'}$), 79.5 ($C_{3'B}$), 77.7 (C_{2A}), 73.5 ($\underline{C}H_2$Ph), 72.2 ($\underline{C}H_2$Ph), 71.7 (C_{5A}), 41.7 ($C_{5'B}$), 39.0 (C_{3A}), 36.4 ($C_{2'B}$), 32.2 ($\underline{C}H_2$CO), 21.2 (Me_{Ac}), 20.9 (Me_{Ac}), 12.4 (Me_T). MS (CI$^+$) m/z = 680.4 Da $[MH]^+$, 620.4 Da $[MH\text{-}AcOH]^+$; (MALDI$^+$: DHB): 702.3 $[MNa]^+$. HRMS (MALDI$^+$: DHB, PEG 600) calcd for $C_{35}H_{41}N_3O_{11}Na$ = 702.2633, found 702.2610.

*1,2-O-Acetyl-3-O-benzyl-5-deoxy-5-azido-D-ribofuranose (**30**).* To a solution of **18** (1 equiv, 2.95 mmol, 900 mg) in acetic acid (33 mL) was added acetic anhydride (40 equiv, 118 mmol, 11 mL), camphor sulfonic acid (0.05 equiv, 0.15 mmol, 34 mg). The reaction mixture was stirred for 1 h at 80 °C and a second portion of camphor sulfonic acid (0.05 equiv, 0.15 mmol, 34 mg) was then added. The reaction mixture was stirred at 80 °C for an additional 1 h, then diluted with DCM (40 mL), washed with water (2 × 50 mL) and a saturated aqueous solution of $NaHCO_3$ (5 × 50 mL). The organic layer was dried over Na_2SO_4, filtered, concentrated under reduced pressure. The crude was coevaporated three times with toluene to obtain the desired compound as a beige oil (900 mg, 2.58 mmol, 87%). TLC (DCM/EP: 7/3): R_f = 0.37. ^{1}H NMR (400 MHz, $CDCl_3$) of two anomers α/β in 15/85 ratio δ (ppm) = 7.36−7.28 (m, 5H, H_{ar}), 6.39 (d, $J_{1,2}$ = 4.5 Hz, 0.15H, $H_{1\alpha}$), 6.15 (s, 0.85H, $H_{1\beta}$), 5.32 (d, $J_{2,3}$ = 4.2 Hz, 0.85H, $H_{2\beta}$), 5.15 (dd, $J_{2,3}$ = 6.5 Hz and $J_{1,2}$ = 4.5 Hz, 0.15H, $H_{2\alpha}$), 4.63 (d, J_{gem} = 11.3 Hz, 1H, C$\underline{H}_2$Ph), 4.46 (d, J_{gem} = 11.3 Hz, 1H, C$\underline{H}_2$Ph), 4.29−4.26 (m, 0.15H, $H_{4\alpha}$), 4.27 (dd, $J_{3,4}$ = 8.1 Hz and $J_{2,3}$ = 4.2 Hz, 0.85H, $H_{3\beta}$), 4.21 (dt, $J_{3,4}$ = 8.1 Hz and $J_{4,5a}$ = $J_{4,5b}$ = 3.2 Hz, 0.85H, $H_{4\beta}$), 4.02 (dd, $J_{2,3}$ = 6.5 Hz and $J_{3,4}$ = 5.0 Hz, 0.15H, $H_{3\alpha}$), 3.63 (dd, J_{gem} = 13.7 Hz and $J_{4,5a}$ = 3.0 Hz, 0.85H, $H_{5a\beta}$), 3.44 (dd, J_{gem} = 13.3 Hz and $J_{4,5a}$ = 3.6 Hz, 0.15H, $H_{5a\alpha}$), 3.15 (dd, J_{gem} = 13.7 Hz and $J_{4,5b}$ = 3.5 Hz, 0.85H, $H_{5b\beta}$), 3.12 (dd, J_{gem} = 13.3 Hz and $J_{4,5b}$ = 4.2 Hz, 0.15H, $H_{5b\alpha}$), 2.13 (s, 2.55H, $Me_{Ac\beta}$), 2.11 (s, 0.45H, $Me_{Ac\alpha}$), 2.09 (s, 2.55H, $Me_{Ac\beta}$), 2.07 (s, 0.45H, $Me_{Ac\alpha}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 170.2 ($C_{Ac\alpha}$), 170.0 ($C_{Ac\alpha}$), 169.8 ($C_{Ac\beta}$), 169.1 ($C_{Ac\beta}$), 137.2 ($C_{IV(ar)}$), 128.6 (C_{ar}), 128.3 (C_{ar}), 128.3 (C_{ar}), 128.1 (C_{ar}), 98.4 ($C_{1\beta}$), 94.6 ($C_{1\alpha}$), 81.5 ($C_{4\alpha}$), 80.9 ($C_{4\beta}$), 76.6 ($C_{3\beta}$), 75.8 ($C_{3\alpha}$), 73.6 ($C_{2\beta}$), 73.5 ($\underline{C}H_2$Ph), 71.0 ($C_{2\alpha}$), 51.7 ($C_{5\alpha}$), 51.1 ($C_{5\beta}$), 21.1 ($Me_{Ac\beta}$), 21.0 ($Me_{Ac\alpha}$), 20.8 ($Me_{Ac\beta}$), 20.6 ($Me_{Ac\alpha}$). MS (ESI$^+$) m/z = 372.1 $[MNa]^+$, 290.1 $[MH\text{-}AcOH]^+$, 721.2 $[2MNa]^+$. HRMS (ESI$^+$) calcd for $C_{16}H_{19}N_3O_6Na$ = 372.1166, found 372.1179.

*2′-O-Acetyl-3′-deoxy-3′-(2′-O-acetyl-3′O-benzyl-5′-deoxy-5′-acetamido-β-uridyl)-5′-O-benzyl-β-uridine (**32**).* To a solution of uracil (3 equiv, 0.45 mmol, 51 mg) in freshly distilled acetonitrile (4 mL) were added **7** (1 equiv, 0.15 mmol, 100 mg) under argon then BSA (12 equiv, 1.8 mmol, 440 μL). The reaction mixture was stirred for 1 h at 60 °C, then cooled to 5 °C before adding TMSOTf (4 equiv,

DOI: 10.1021/acs.joc.6b01822
J. Org. Chem. 2016, 81, 10742−10758

0.6 mmol, 108 μL). The reaction was stirred for 2 h at reflux then diluted with DCM (10 mL) and cooled to 5 °C before adding a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with DCM (2 × 10 mL) and the combined organic layers were washed with brine (2 × 10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (DCM/MeOH: 99/1 to 95/5 for the first chromatography; and DCM/*i*-PrOH:, 96/4, for the second) to give the desired compound as a beige oil (65 mg, 0.084 mmol, 56%). TLC (DCM/*i*-PrOH: 95/5): R_f = 0.58. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.94 (brs, 1H, NH_U), 9.43 (brs, 1H, NH_U), 7.85 (d, $J_{5A,6A}$ = 8.1 Hz, 1H, H_{6A}), 7.32−7.29 (m, 10H, H_{ar}), 7.14 (d, $J_{5B,6B}$ = 8.0 Hz, 1H, H_{6B}), 6.71 (dd, $J_{NH,5'aB}$ = 6.8 Hz and $J_{NH,5'bB}$ = 3.2 Hz, 1H, NH_{amide}), 5.96 (d, $J_{1'A,2'A}$ = 2.2 Hz, 1H, $H_{1'A}$), 5.70 (dd, $J_{5B,6B}$ = 8.0 Hz and $J_{5B,NH(U)}$ = 1.9 Hz, 1H, H_{5B}), 5.54 (dd, $J_{2'A,3'A}$ = 5.8 Hz and $J_{1'A,2'A}$ = 2.2 Hz, 1H, $H_{2'A}$), 5.45 (dd, $J_{2'B,3'B}$ = 6.5 Hz and $J_{1'B,2'B}$ = 3.1 Hz, 1H, $H_{2'B}$), 5.36 (dd, $J_{5A,6A}$ = 8.1 Hz and $J_{5A,NH(U)}$ = 2.0 Hz, 1H, H_{5A}), 5.26 (d, $J_{1'B,2'B}$ = 3.1 Hz, 1H, $H_{1'B}$), 4.60−4.47 (m, 4H, 2×C$\underline{H_2}$Ph), 4.35 (t, $J_{2'B,3'B}$ = $J_{3'B,4'B}$ = 6.5 Hz, 1H, $H_{3'B}$), 4.15−4.08 (m, 2H, $H_{4'A}$ and $H_{4'B}$), 3.89 (dd, J_{gem} = 11.0 Hz and $J_{4'A,5'Aa}$ = 2.2 Hz, 1H, $H_{5'Aa}$), 3.76 (ddd, J_{gem} = 14.5 Hz, $J_{NH(amide),5'Ba}$ = 6.8 Hz and $J_{4'A,5'Ba}$ = 3.2 Hz, 1H, $H_{5'Ba}$), 3.65 (dd, J_{gem} = 11.0 Hz and $J_{4'A,5'Ab}$ = 2.4 Hz, 1H, $H_{5'Ab}$), 3.45 (dt, J_{gem} = 14.5 Hz and $J_{4',5'Bb}$ = $J_{5'Bb,NH}$ = 3.2 Hz, 1H, $H_{5'Bb}$), 3.07−3.00 (m, 1H, $H_{3'A}$), 2.40 (dd, J_{gem} = 15.4 Hz and $J_{H3'A,Ha(CH2CO)}$ = 7.6 Hz, 1H, $H_{a(CH2CO)}$), 2.22 (dd, J_{gem} = 15.4 Hz and $J_{H3'A,Hb(CH2CO)}$ = 6.3 Hz, 1H, $H_{b(CH2CO)}$), 2.13 (s, 3H, Me_{Ac}), 2.06 (s, 3H, Me_{Ac}). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 170.9 (CO_{amide}), 170.4 ($CO_{Ac(B)}$), 170.2 ($CO_{Ac(A)}$), 163.6 (C_{4B}), 163.3 (C_{4A}), 151.0 (C_{2A}), 150.5 (C_{2B}), 143.8 (C_{6B}), 140.4 (C_{6A}), 137.5 ($C_{IV(ar)}$), 137.4 ($C_{IV(ar)}$), 128.7 (C_{ar}), 128.6 (C_{ar}), 128.4 (C_{ar}), 128.1 (C_{ar}), 102.9 (C_{5B}), 102.5 (C_{5A}), 95.6 ($C_{1'B}$), 89.1 ($C_{1'A}$), 83.7 ($C_{4'A}$), 81.2 ($C_{4'B}$), 77.4 ($C_{2'A}$), 76.1 ($C_{3'B}$), 74.1 ($\underline{C}H_2$Ph), 73.9 ($\underline{C}H_2$Ph), 73.8 ($C_{2'B}$), 69.1 ($C_{5'A}$), 39.7 ($C_{5'B}$), 37.8 ($C_{3'A}$), 32.2 ($\underline{C}H_2$CO), 20.9 ($Me_{Ac(A)}$), 20.8 ($Me_{Ac(B)}$). MS (ESI$^+$) m/z = 798.3 Da $[MNa]^+$. HRMS (ESI$^+$) calcd for $C_{38}H_{41}N_5O_{13}Na$ = 798.2599 Da, found 798.2582 Da. $[\alpha]_D^{20}$ = +11.6 ($CHCl_3$, c = 0.203 g/100 mL).

*2′-O-Acetyl-3′-deoxy-3′-(2′-O-acetyl-3′O-benzyl-5′-deoxy-5′-acetamido-β-ribothymidinyl)-5′-O-benzyl-β-ribothymidine (**33**).* To a solution of thymine (3 equiv, 0.45 mmol, 56 mg) in freshly distilled acetonitrile (4 mL) were added **7** (1 equiv, 0.15 mmol, 100 mg) under argon then BSA (12 equiv, 1.8 mmol, 440 μL). The reaction mixture was stirred for 1 h at 60 °C, then cooled to 5 °C before adding TMSOTf (4 equiv, 0.6 mmol, 108 μL). The reaction mixture was stirred for 2 h at reflux then diluted with DCM (10 mL) and cooled to 5 °C before adding a saturated aqueous solution of $NaHCO_3$ (10 mL). The aqueous layer was extracted with DCM (2 × 15 mL) and the combined organic layers were washed with brine (2 × 15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (DCM/MeOH: 99/1 to 95/5 for the first chromatography; and DCM/*i*-PrOH: 96/4, for the second) to give the desired compound as a beige sticky oil (75 mg, 0.093 mmol, 62%). TLC (DCM/*i*-PrOH: 95/5): R_f = 0.35. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.65 (brs, 1H, NH_T), 9.06 (brs, 1H, NH_T), 7.57 (d, $J_{6A,Me(T)}$ = 0.9 Hz, 1H, H_{6A}), 7.36−7.28 (m, 10H, H_{ar}), 6.94 (d, $J_{6B,Me(T)}$ = 0.8 Hz, 1H, H_{6B}), 6.71 (dd, $J_{NH,5'aB}$ = 6.9 Hz and $J_{NH,5'bB}$ = 2.7 Hz, 1H, NH_{amide}), 6.00 (d, $J_{1'A,2'A}$ = 2.6 Hz, 1H, $H_{1'A}$), 5.56 (dd, $J_{2'A,3'A}$ = 6.1 Hz and $J_{1'A,2'A}$ = 2.6 Hz, 1H, $H_{2'A}$), 5.48 (dd, $J_{2'B,3'B}$ = 6.3 Hz and $J_{1'B,2'B}$ = 2.9 Hz, 1H, $H_{2'B}$), 5.18 (d, $J_{1'B,2'B}$ = 2.9 Hz, 1H, $H_{1'B}$), 4.62−4.53 (m, 4H, 2×C$\underline{H_2}$Ph), 4.42 (t, $J_{2'B,3'B}$ = $J_{3'B,4'B}$ = 7.2 Hz, 1H, $H_{3'B}$), 4.12−4.11 (m, 1H, $H_{4'A}$), 4.10−4.09 (m, 1H, $H_{4'B}$), 3.88 (dd, J_{gem} = 11.1 Hz and $J_{4'A,5'Aa}$ = 2.0 Hz, 1H, $H_{5'Aa}$), 3.79 (ddd, J_{gem} = 14.5 Hz, $J_{NH(amide),5'Ba}$ = 6.9 Hz and $J_{4'A,5'Ba}$ = 2.8 Hz, 1H, $H_{5'Ba}$), 3.63 (dd, J_{gem} = 11.1 Hz and $J_{4'A,5'Ab}$ = 2.6 Hz, 1H, $H_{5'Ab}$), 3.40 (dt, J_{gem} = 14.5 Hz and $J_{4',5'Bb}$ = $J_{5'Bb,NH}$ = 2.7 Hz, 1H, $H_{5'Bb}$), 3.15−3.05 (m, 1H, $H_{3'A}$), 2.40 (dd, J_{gem} = 15.4 Hz and $J_{H3'A,Ha(CH2CO)}$ = 8.0 Hz, 1H, $H_{a(CH2CO)}$), 2.22 (dd, J_{gem} = 15.4 Hz and $J_{H3'A,Hb(CH2CO)}$ = 6.0 Hz, 1H, $H_{b(CH2CO)}$), 2.16 (s, 3H, $Me_{Ac(A)}$), 2.06 (s, 3H, $Me_{Ac(B)}$), 1.91 (d, $J_{6B,Me(T)}$ = 0.8 Hz, 3H, $Me_{T(B)}$), 1.57 (d, $J_{6A,Me(T)}$ = 0.8 Hz, 3H, $Me_{T(A)}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 170.82 (CO_{amide}), 170.4 ($CO_{Ac(B)}$), 170.2 ($CO_{Ac(A)}$), 164.1 (C_{4B}), 163.5 (C_{4A}), 151.2 (C_{2A}), 150.7 (C_{2B}), 139.9 (C_{6B}), 137.6 ($C_{IV(ar)}$), 137.5 ($C_{IV(ar)}$), 135.9 (C_{6A}), 128.7 (C_{ar}), 128.6 (C_{ar}), 128.4 (C_{ar}), 127.9 (C_{ar}), 111.6 (C_{5B}), 111.6 (C_{5A}), 96.2 ($C_{1'B}$), 89.1 ($C_{1'A}$), 83.4 ($C_{4'A}$), 81.2 ($C_{4'B}$), 77.6 ($C_{2'A}$), 76.1 ($C_{3'B}$), 74.2 ($\underline{C}H_2$Ph), 74.0 ($C_{2'B}$), 73.9 ($\underline{C}H_2$Ph), 69.3 ($C_{5'A}$), 39.7 ($C_{5'B}$), 38.0 ($C_{3'A}$), 32.2 ($\underline{C}H_2$CO), 21.0 ($Me_{Ac(A)}$), 20.9 ($Me_{Ac(B)}$), 12.4 ($Me_{T(B)}$), 12.2 ($Me_{T(A)}$). MS (ESI$^+$) m/z = 826.3 Da $[MNa]^+$, 804.3 Da $[MH]^+$. HRMS (ESI$^+$) calcd for $C_{40}H_{45}N_5O_{13}Na$ = 826.2906 Da, found = 826.2884 Da., calcd $C_{40}H_{46}N_5O_{13}$ = 804.3087 Da, found 804.3065 Da. $[\alpha]_D^{20}$ = −28 ($CHCl_3$, c = 0.1 g/100 mL).

*2′-O-Acetyl-3′-deoxy-3′-(2′-O-acetyl-5′-deoxy-5′-acetamido-β-uridyl)-β-uridine (**34**).* The compound **32** (0.058 mmol, 45 mg) was hydrogenated in the presence of 10% Pd/C (30% weight, 14 mg) in EtOH (5 mL) under an atmosphere of hydrogen. After stirring at room temperature for 24 h, the mixture was filtered, washed with EtOH and concentrated under reduced pressure to give the desired compound as a colorless amorphous solid (32 mg, 0.054 mmol, 93%). TLC (DCM/*i*-PrOH: 95/5): R_f = 0.3. ^{1}H NMR (300 MHz, MeOD) δ (ppm) = 8.03 (d, $J_{5A,6A}$ = 8.0 Hz, 1H, H_{6A}), 7.66 (d, $J_{5B,6B}$ = 8.1 Hz, 1H, H_{6B}), 5.80 (d, $J_{1'B,2'B}$ = 4.6 Hz, 1H, $H_{1'B}$), 5.76 (d, $J_{1'A,2'A}$ = 1.5 Hz, 1H, $H_{1'A}$), 5.72−5.67 (m, 2H, H_{5B} and H_{5A}), 5.42 (dd, $J_{2'A,3'A}$ = 6.1 Hz and $J_{1'A,2'A}$ = 1.5 Hz, 1H, $H_{2'A}$), 5.28 (dd, $J_{2'B,3'B}$ = 6.0 Hz and $J_{1'B,2'B}$ = 4.6 Hz, 1H, $H_{2'B}$), 4.30 (dd, $J_{2'B,3'B}$ = $J_{3'B,4'B}$ = 6.0 Hz, 1H, $H_{3'B}$), 3.98−3.92 (m, 3H, $H_{4'A}$, $H_{4'B}$ and $H_{5'Aa}$), 3.70 (dd, J_{gem} = 12.5 Hz and $J_{4'A,5'Ab}$ = 2.9 Hz, 1H, $H_{5'Ab}$), 3.45−3.56 (m, 2H, $H_{5'B}$), 2.96−2.90 (m, 1H, $H_{3'A}$), 2.44−2.39 (m, 2H, CH_2CO), 2.11 (s, 6H, 2xMe_{Ac}). ^{13}C NMR (75 MHz, MeOD) δ (ppm) = 173.7 (CO_{amide}), 171.8 ($CO_{Ac(B)}$), 171.5 ($CO_{Ac(A)}$), 166.2 (C_{4B}), 166.0 (C_{4A}), 152.1 (C_{2A}), 152.0 (C_{2B}), 143.9 (C_{6B}), 142.7 (C_{6A}), 103.1 (C_{5B}), 102.5 (C_{5A}), 91.5 ($C_{1'A}$), 91.1 ($C_{1'B}$), 86.0 ($C_{4'A}$), 83.9 ($C_{4'B}$), 79.2 ($C_{2'A}$), 76.1 ($C_{2'B}$), 70.9 ($C_{3'B}$), 61.6 ($C_{5'A}$), 41.8 ($C_{5'B}$), 38.3 ($C_{3'A}$), 32.2 ($\underline{C}H_2$CO), 20.7 ($Me_{Ac(A)}$), 20.6 ($Me_{Ac(B)}$). MS (ESI$^+$) m/z = 618.2 Da $[MNa]^+$. HRMS (ESI$^+$) calcd for $C_{24}H_{29}N_5O_{13}Na$ = 618.1654 Da, found 618.1647 Da.

*2′-O-Acetyl-3′-deoxy-3′-(2′-O-acetyl-5′-deoxy-5′-acetamido-β-ribothymidinyl)-β-ribothymidine (**35**).* The compound **33** (0.05 mmol, 40 mg) was hydrogenated in the presence of 10% Pd/C (30% weight, 12 mg) in EtOH (5 mL) under an atmosphere of hydrogen. After stirring at room temperature for 24 h, the mixture was filtered, washed with EtOH and concentrated under reduced pressure to give the desired compound as a colorless amorphous solid (22 mg, 0.035 mmol, 71%). TLC (DCM/*i*-PrOH: 95/5): R_f = 0.2 ^{1}H NMR (400 MHz, MeOD) δ (ppm) = 7.82 (d, $J_{Me(T),6A}$ = 1.1 Hz, 1H, H_{6A}), 7.47 (d, $J_{Me(T),6B}$ = 1.1 Hz, 1H, H_{6B}), 5.79 (d, $J_{1'B,2'B}$ = 4.9 Hz, 1H, $H_{1'B}$), 5.77 (d, $J_{1'A,2'A}$ = 1.9 Hz, 1H, $H_{1'A}$), 5.37 (dd, $J_{2'A,3'A}$ = 6.3 Hz and $J_{1'A,2'A}$ = 1.9 Hz, 1H, $H_{2'A}$), 5.27 (dd, $J_{2'B,3'B}$ = 5.9 Hz and $J_{1'B,2'B}$ = 4.9 Hz, 0.8H, $H_{2'B(R1)}$), 5.05 (dd, $J_{2'B,3'B}$ = 5.9 Hz and $J_{1'B,2'B}$ = 4.2 Hz, 0.2 H, $H_{2'B(R2)}$), 4.51 (t, $J_{2'B,3'B}$ = $J_{3'B,4'B}$ = 5.9 Hz, 0.2H, $H_{3'B(R2)}$), 4.30 (t, $J_{2'B,3'B}$ = $J_{3'B,4'B}$ = 5.9 Hz, 0.8H, $H_{3'B(R1)}$), 3.97−3.94 (m, 2H, $H_{4'A}$, $H_{4'B}$), 3.92 (dd, J_{gem} = 12.5 Hz and $J_{4'A,5'Aa}$ = 2.2 Hz, 1H, $H_{5'Aa}$), 3.71 (dd, J_{gem} = 12.5, $J_{4'A,5'Ab}$ = 2.9 Hz, 1H, $H_{5'Ab}$), 3.63−3.57 (m, 1H, $H_{5'Ba}$), 3.47 (dd, J_{gem} = 14.3 Hz and $J_{4'B,5'Bb}$ = 3.7 Hz, 1H, $H_{5'Bb}$), 3.01−2.94 (m, 1H, $H_{3'A}$), 2.50−2.36 (m, 2H, CH_2CO), 2.11 (s, 3H, Me_{Ac}), 2.09 (s, 3H, Me_{Ac}), 1.88 (brs, 6H, Me_T). ^{13}C NMR (100 MHz, MeOD) δ (ppm) = 173.7 (CO_{amide}), 171.8 ($CO_{Ac(B)}$), 171.5 ($CO_{Ac(A)}$), 166.4 (C_{4B}), 166.3 (C_{4A}), 152.4 (C_{2A}), 152.1 (C_{2B}), 139.4 (C_{6B}), 138.4 (C_{6A}), 112.0 (C_{5B}), 111.4 (C_{5A}), 91.3 ($C_{1'A}$), 90.9 ($C_{1'B}$), 85.9 ($C_{4'A}$), 83.9 ($C_{4'B}$), 79.2 ($C_{2'A}$), 76.0 ($C_{2'B}$), 71.0 ($C_{3'B}$), 61.7 ($C_{5'A}$), 42.0 ($C_{5'B}$), 38.4 ($C_{3'A}$), 32.5 ($\underline{C}H_2$CO), 20.6 (Me_{Ac}), 20.5 (Me_{Ac}), 12.4 (Me_T), 12.2 (Me_T). MS (ESI$^+$) m/z = 624.2 Da $[MH]^+$, 646.2 Da $[MNa]^+$, 1247.4 Da $[2MH]^+$, 1269.4 Da $[2MNa]^+$. HRMS (ESI$^+$) calcd for $C_{26}H_{34}N_5O_{13}$ = 624.2147 Da, found 624.2143 Da.

*1,2-O-Isopropylidene-3-deoxy-3-(2′-O-acetyl-3′-O-benzyl-5′-deoxy-5′-acetamido-β-ribothymidinyl)-5-O-benzyl-α-D-ribofuranose (**36**).* To a solution of thymine (3 equiv, 1.01 mmol, 126 mg) in freshly distilled acetonitrile (8 mL) were added **4** (1 equiv, 0.29 mmol, 180 mg) then BSA (6 equiv, 1.74 mmol, 495 μL) under argon. The reaction mixture was stirred for 1 h at 60 °C, then cooled to 5 °C before adding TMSOTf (2 equiv, 1.35 mmol, 243 μL). The reaction was stirred for 2 h at reflux then diluted with DCM (25 mL) and cooled to 5 °C before adding a saturated aqueous solution of $NaHCO_3$

DOI: 10.1021/acs.joc.6b01822
J. Org. Chem. 2016, 81, 10742−10758

(25 mL). The aqueous layer was extracted with DCM (2 × 25 mL) and the combined organic layers were washed with water (to eliminate thymine) and brine (2 × 25 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography (Petroleum Ether/AcOEt: 1/1 to 0/1) to give the desired compound as a colorless sticky foam (180 mg, 0.26 mmol, 89%). TLC (AcOEt/PE: 7/3): R_f = 0.37 ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.54 (brs, 1H, NH_T), 7.35−7.30 (m, 10H, H_{ar}), 6.97 (d, $J_{6B,Me(T)}$ = 1.1 Hz, 1H, H_{6B}), 6.23 (m, 1H, NH_{amide}), 5.82 (d, $J_{1A,2A}$ = 3.7 Hz, 1H, H_{1A}), 5.46 (dd, $J_{2'B,3'B}$ = 6.2 Hz and $J_{2'B,1'B}$ = 3.5 Hz, 1H, $H_{2'B}$), 5.40 (d, $J_{1'B,2'B}$ = 3.5 Hz, 1H, $H_{1'B}$), 4.75 (t, $J_{2A,1A}$ = $J_{2A,3A}$ = 4.0 Hz, 1 H, H_{2A}), 4.58−4.56 (AB syst., J_{gem} = 12.1 Hz, 2H, C$\underline{H}_2$Ph), 4.54−4.52 (AB syst., J_{gem} = 11.1 Hz, 2 H, C$\underline{H}_2$Ph), 4.26 (t, $J_{3'B,2'B}$ = $J_{3'B,4'B}$ = 6.7 Hz, 1H, $H_{3'B}$), 4.10−4.06 (m, 1H, $H_{4'B}$), 3.98−3.94 (m, 1H, H_{4A}), 3.69−3.65 (m, 1H, $H_{5'Ba}$), 3.64−3.62 (m, 1H, H_{5Aa}), 3.56 (dd, J_{gem} = 10.9 Hz and $J_{5Ab,4A}$ = 4.7 Hz, 1H, H_{5Ab}), 3.51−3.45 (m, 1H, $H_{5'Bb}$), 2.51 (dd, J_{gem} = 14.3 Hz and $J_{Ha(C\underline{H}2CO),3A}$ = 9.9 Hz, 1H, $H_{a(CH2CO)}$), 2.46−2.39 (m, 1H, H_{3A}), 2.26 (dd, J_{gem} = 14.3 Hz and $J_{3A,Hb(CH2CO)}$ = 3.9 Hz, 1H, $H_{b(CH2CO)}$), 2.10 (s, 3H, Me_{Ac}), 1.92 (d, $J_{Me(T),6B}$ = 1.1 Hz, 3H, Me_T), 1.50 (s, 3H, $Me_{acetonide}$), 1.30 (s, 3H, $Me_{acetonide}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 170.7 (CO_{amide}), 169.2 (CO_{Ac}), 162.4 (C_{4B}), 149.1 (C_{2B}), 137.6 (C_{6B}), 137.2 ($C_{IV(ar)}$), 136.3 ($C_{IV(ar)}$), 127.7 (C_{ar}), 127.7 (C_{ar}), 127.6 (C_{ar}), 127.5 (C_{ar}), 127.5 (C_{ar}), 127.4 (C_{ar}), 127.3 (C_{ar}), 127.3 (C_{ar}), 126.9 (C_{ar}), 126.8 (C_{ar}), 110.70 ($C_{IV(acetonide)}$), 110.56 (C_{5B}), 104.13 (C_{1A}), 92.89 ($C_{1'B}$), 80.42 (C_{2A}), 80.3 ($C_{4'B}$), 79.3 (C_{4A}), 75.5 ($C_{3'B}$), 73.0 (C$\underline{H}_2$Ph), 72.8 ($C_{2'B}$), 72.7 (C$\underline{H}_2$Ph), 68.9 (C_{5A}), 41.4 ($C_{3'A}$), 39.3 ($C_{5'B}$), 30.9 (C$\underline{H}_2$CO), 25.9 ($Me_{acetonide}$), 25.6 ($Me_{acetonide}$), 19.9 (Me_{Ac}), 11.5 (Me_T). MS (ESI$^+$) m/z = 694.3 Da $[MH]^+$, 636.3 Da [MH-acetone]$^+$. HRMS (ESI$^+$) calcd for $C_{36}H_{44}N_3O_{11}$ = 694.2976 Da, found = 694.2967 Da. $[\alpha]_D^{20}$ = +11.3 ($CHCl_3$, c = 1 g/100 mL).

To a solution of **36** (1 equiv, 0.24 mmol, 170 mg) in acetic acid (15 mL) was added acetic anhydride (40 equiv, 9.6 mmol, 960 μL), camphor sulfonic acid (0.05 equiv, 0.01 mmol, 3 mg). The mixture was stirred for 1 h at 80 °C and a second portion of camphor sulfonic acid (0.05 equiv, 0.01 mmol, 3 mg) was then added. The reaction mixture was stirred for an additional 1 h, then diluted with DCM (15 mL), washed with water (2 × 15 mL) and a saturated aqueous solution of $NaHCO_3$ (5 × 10 mL). The organic layer was dried over Na_2SO_4, filtered, concentrated under reduced pressure. The crude was coevaporated three times with toluene and then directly engaged in Vorbrüggen coupling reaction.

*2′-O-Acetyl-3′-deoxy-3′-(2′-O-acetyl-3′O-benzyl-5′-deoxy-5′-acetamido-β-ribothymidinyl)-5′-O-benzyl-β-uridine (**38**).* The compound **38** was obtained by Vorbrüggen coupling between uracil and 1,2-*O*-acetyl-3-deoxy-3-(2′-*O*-acetyl-3′-*O*-benzyl-5′-deoxy-5′-acetamido-β-ribothymidinyl)-5-*O*-benzyl-α-D-ribofuranose (**37**) obtained as followed. To a solution of **36** (1 equiv, 0.24 mmol, 170 mg) in acetic acid (15 mL) was added acetic anhydride (40 equiv, 9.6 mmol, 960 μL), camphor sulfonic acid (0.05 equiv, 0.01 mmol, 3 mg). The mixture was stirred for 1 h at 80 °C and a second portion of camphor sulfonic acid (0.05 equiv, 0.01 mmol, 3 mg) was then added. The reaction mixture was stirred for an additional 1 h, then diluted with DCM (15 mL), washed with water (2 × 15 mL) and a saturated aqueous solution of $NaHCO_3$ (5 × 10 mL). The organic layer was dried over Na_2SO_4, filtered, concentrated under reduced pressure. The crude was coevaporated three times with toluene and then directly engaged in Vorbrüggen coupling reaction.

To a solution of uracil (1.5 equiv, 0.36 mmol, 41 mg) in freshly distilled acetonitrile (12 mL) under argon were added **37** (1 equiv, 0.24 mmol if quantitative reaction) then BSA (6 equiv, 1.4 mmol, 355 μL). The mixture was stirred for 1 h at 60 °C, then cooled to 5 °C before adding TMSOTf (1.5 equiv, 0.36 mmol, 65 μL). The reaction mixture was stirred for 26 h at room temperature then diluted with DCM (15 mL) and cooled to 5 °C before adding a saturated aqueous solution of $NaHCO_3$ (15 mL). The aqueous layer was extracted with DCM (2 × 15 mL) and the combined organic layers were washed with brine (2 × 15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography instrument (Petroleum ether/AcOEt: 3/7 to 0/10) to give the desired compound as a colorless foam (157 mg, 0.2 mmol, 83% for two steps). TLC (AcOEt/PE: 7/3): R_f = 0.2. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 10.00 (brs, 1H, NH_U), 9.51 (brs, 1H, NH_T), 7.83 (d, $J_{5A,6A}$ = 8.1 Hz, 1H, H_{6A}), 7.33−7.29 (m, 10H, H_{ar}), 6.95 (brs, 1H, H_{6B}), 6.78−6.77 (m, 1H, NH_{amide}), 5.98 (d, $J_{1'A,2'A}$ = 2.1 Hz, 1H, $H_{1'A}$), 5.53 (dd, $J_{2'A,3'A}$ = 5.9 Hz and $J_{1'A,2'A}$ = 2.1 Hz, 1H, $H_{2'A}$), 5.47 (dd, $J_{2'B,3'B}$ = 6.2 Hz and $J_{1'B,2'B}$ = 3.0 Hz, 1H, $H_{2'B}$), 5.38 (d, $J_{5A,6A}$ = 8.1 Hz, 1H, H_{5A}), 5.22 (d, $J_{1'B,2'B}$ = 2.9 Hz, 1H, $H_{1'B}$), 4.60−4.49 (m, 4H, 2×C$\underline{H}_2$Ph), 4.40 (t, $J_{2'B,3'B}$ = $J_{3'B,4'B}$ = 6.8 Hz, 1H, $H_{3'B}$), 4.14−4.09 (m, 2H, $H_{4'A}$, $H_{4'B}$), 3.88 (dd, J_{gem} = 11.0 Hz and $J_{4'A,5'Aa}$ = 2.1 Hz, 1H, $H_{5'Aa}$), 3.80−3.74 (m, 1H, $H_{5'B}$), 3.65 (dd, J_{gem} = 11.0 Hz and $J_{4'A,5'Ab}$ = 2.1 Hz, 1H, $H_{5'Ab}$), 3.45−3.41 (m, 1H, $H_{5'B}$), 3.15−3.05 (m, 1H, $H_{3'A}$), 2.42 (dd, J_{gem} = 15.4 Hz and $J_{H3'A,Ha(CH2CO)}$ = 7.6 Hz, 1H, $H_{a(CH2CO)}$), 2.23 (dd, J_{gem} = 15.4 Hz and $J_{H3'A,Hb(CH2CO)}$ = 6.1 Hz, 1H, $H_{b(CH2CO)}$), 2.15 (s, 3H, $Me_{Ac(A)}$), 2.07 (s, 3H, $Me_{Ac(B)}$), 1.88 (d, $J_{6B,Me(T)}$ = 0.8, 3H, $Me_{T(B)}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 170.8 (CO_{amide}), 170.4 ($CO_{Ac(B)}$), 170.1 ($CO_{Ac(A)}$), 164.4 (C_{4B}), 163.2 (C_{4A}), 151.1 (C_{2A}), 150.7 (C_{2B}), 140.4 (C_{6A}), 139.8 (C_{6B}), 137.5 ($C_{IV(ar)}$), 137.5 ($C_{IV(ar)}$), 128.7 (C_{ar}), 128.6 (C_{ar}), 128.4 (C_{ar}), 128.3 (C_{ar}), 128.2 (C_{ar}), 128.1 (C_{ar}), 111.5 (C_{5B}), 102.7 (C_{5A}), 95.8 ($C_{1'B}$), 89.1 ($C_{1'A}$), 83.6 ($C_{4'A}$), 81.2 ($C_{4'B}$), 77.8 ($C_{2'A}$), 76.1 ($C_{3'B}$), 74.1 (C$\underline{H}_2$Ph), 74.0 ($C_{2'B}$), 73.9 (C$\underline{H}_2$Ph), 69.1 ($C_{5'A}$), 39.8 ($C_{5'B}$), 37.8 ($C_{3'A}$), 32.1 (C$\underline{H}_2$CO), 20.93 (Me_{Ac}), 20.85 (Me_{Ac}), 12.3 ($Me_{T(B)}$). MS (ESI$^+$) m/z = 812.3 Da $[MNa]^+$, 790.3 Da $[MH]^+$. HRMS (ESI$^+$) calcd for $C_{39}H_{43}N_5O_{13}Na$ = 812.2755 Da, found = 812.2754 Da. $[\alpha]_D^{20}$ = −1.8 ($CHCl_3$, c = 0.5 g/100 mL).

*3′-Deoxy-3′-(5′-deoxy-5′-acetamido-β-ribothymidinyl)-β-uridine (**39**).* To a solution of **38** (40 mg, 0.05 mmol) in MeOH, was added K_2CO_3 (1.5 equiv, 0.07, 10 mg). The mixture was stirred at room temperature for 4 h and concentrated under reduced pressure to obtain the desired compound as a colorless foam (35 mg, 0.05 mmol, quant). TLC (DCM/*i*-PrOH: 95/5): R_f = 0.25. ^{1}H NMR (500 MHz, MeOD) δ (ppm) = 8.17 (d, $J_{5A,6A}$ = 8.1 Hz, 1H, H_{6A}), 7.44 (d, $J_{6B,Me(T)}$ = 1.1 Hz, 1H, H_{6B}), 7.41−7.27 (m, 10H, H_{ar}), 5.78 (d, $J_{1'B,2'B}$ = 5.2 Hz, 1H, $H_{1'B}$), 5.70 (s, 1H, $H_{1'A}$), 5.17 (d, $J_{5A,6A}$ = 8.1 Hz, 1H, H_{5A}), 4.73 (d, J_{gem} = 11.6 Hz, 1H, C$\underline{H}_2$Ph), 4.59 (d, J_{gem} = 11.6 Hz, 1H, C$\underline{H}_2$Ph), 4.60−4.57 (AB syst. J_{gem} = 11.2, 2 H, C$\underline{H}_2$Ph), 4.36 (t, $J_{2'B,3'B}$ = $J_{1'B,2'B}$ = 5.2 Hz, 1H, $H_{2'B}$), 4.21 (d, $J_{2'A,3'A}$ = 5.0 Hz, 1H, $H_{2'A}$),, 4.15−4.10 (m, 2H, $H_{4'A}$, $H_{4'B}$), 3.97 (dd, J_{gem} = 11.3 Hz and $J_{4'A,5'Aa}$ = 2.2 Hz, 1H, $H_{5'Aa}$), 3.92 (t, $J_{2'B,3'B}$ = $J_{3'B,4'B}$ = 5.2 Hz, 1H, $H_{3'B}$), 3.66 (dd, J_{gem} = 11.3 Hz and $J_{4'A,5'Ab}$ = 2.2 Hz, 1H, $H_{5'Ab}$), 3.56 (dd, J_{gem} = 14.3 Hz and $J_{4'B,5'Ba}$ = 6.3 Hz, 1H, $H_{5'B}$), 3.40 (dd, J_{gem} = 14.3 Hz and $J_{4'B,5'Bb}$ = 4.2 Hz, 1H, $H_{5'B}$), 2.70−2.64 (m, 1H, $H_{3'A}$), 2.54 (dd, J_{gem} = 14.9 Hz and $J_{H3'A,Ha(CH2CO)}$ = 8.8 Hz, 1H, $H_{a(CH2CO)}$), 2.25 (dd, J_{gem} = 14.9 Hz and $J_{H3'A,Hb(CH2CO)}$ = 5.7 Hz, 1H, $H_{b(CH2CO)}$), 1.88 (d, $J_{6B,Me(T)}$ = 1.1 Hz, 3H, $Me_{T(B)}$). ^{13}C NMR (125 MHz, MeOD) δ (ppm) = 174.4 (CO_{amide}), 166.4 (C_{4A}), 166.3 (C_{4B}), 152.6 (C_{2A}), 152.2 (C_{2B}), 142.4 (C_{6A}), 139.30 ($C_{IV(ar)}$), 139.28 ($C_{IV(ar)}$), 138.9 (C_{6B}), 129.5 (C_{ar}), 129.4 (C_{ar}), 129.3 (C_{ar}), 129.1 (C_{ar}), 129.0 (C_{ar}), 128.9 (C_{ar}), 111.9 (C_{5A}), 101.3 (C_{5B}), 93.4 ($C_{1'A}$), 92.6 ($C_{1'B}$), 85.2 ($C_{4'A}$), 82.2 ($C_{4'B}$), 79.2 ($C_{3'B}$), 78.0 ($C_{2'A}$), 74.6 ($C_{2'B}$), 73.7 (C$\underline{H}_2$Ph), 73.6 (C$\underline{H}_2$Ph), 69.4 ($C_{5'A}$), 42.0 ($C_{5'B}$), 38.9 ($C_{3'A}$), 32.1 (C$\underline{H}_2$CO), 12.3 ($Me_{T(B)}$). MS (ESI$^+$) m/z = 728.3 Da $[MNa]^+$. HRMS (ESI$^+$) calcd for $C_{35}H_{39}N_5O_{11}Na$ = 728.2544 Da, found = 728.2531 Da. $[\alpha]_D^{20}$ = +2.4 (MeOH, c = 1.1 g/100 mL).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01822.

NMR elucidation of structure for compounds **24**, **25** and **27**; NMR spectra for compounds **4**, **6**−**23**, **26**, **28**−**30**, **32**−**36**, **38**−**39** (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: monique.mathe@univ-nantes.fr.
*E-mail: jacques.lebreton@univ-nantes.fr.

DOI: 10.1021/acs.joc.6b01822
J. Org. Chem. 2016, 81, 10742−10758

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors are deeply indebted to the Ministère de l'Enseignement Supérieur et de la Recherche, the Centre National de la Recherche Scientifique (CNRS) and the Université de Nantes for their support. This project was funded by a grant from the "Association Française contre les Myopathies".

■ REFERENCES

(1) Zamecnik, P. C.; Stephenson, M. L. *Proc. Natl. Acad. Sci. U. S. A.* **1978**, *75*, 280−284.
(2) For recent reviews, see: (a) Deleavey, G. F.; Damha, M. *Chem. Biol.* **2012**, *19*, 937−954. (b) Shum, K.-T.; Rossi, J. J. *Adv. Genet.* **2015**, *89*, 153−177.
(3) Suryawanshi, J. A. S. *J. Med. Genet. Genomics* **2011**, *3*, 109−114.
(4) (a) Tonelli, R.; Mclntyre, A.; Cameri, C.; Walters, Z. S.; Di Leo, K.; Selfe, J.; Purgato, S.; Missiaglia, E.; Tortori, A.; Renshaw, J.; Astolfi, A.; Taylor, K. R.; Serravalle, S.; Bishop, R.; Nanni, C.; Valentijn, L. J.; Faccini, A.; Leuschner, I.; Formica, S.; Reis-Filho, J. S.; Ambrosini, V.; Thway, K.; Franzoni, M.; Summersgill, B.; Marchelli, R.; Hrelia, P.; Cantelli-Forti, G.; Fanti, S.; Corradini, R.; Pession, A.; Shipley, J. *Clin. Cancer Res.* **2012**, *18*, 796−807. (b) Gagnon, K. T.; Watts, J. K.; Pendergraff, H. M.; Montaillier, C.; Thai, D.; Potier, P.; Corey, D. R. *J. Am. Chem. Soc.* **2011**, *133*, 8404−8407.
(5) (a) Esau, C. C.; Monia, B. P. *Adv. Drug Delivery Rev.* **2007**, *59*, 101−114. (b) Matsuda, S.; Keiser, K.; Nair, J. K.; Charisse, K.; Manoharan, R. M.; Kretschmer, P.; Peng, C. G.; Kel'in, A. V.; Kandasamy, P.; Willoughby, J. L. S.; Liebow, A.; Querbes, W.; Yucius, K.; Nguyen, T.; Stuart Milstein, S.; Maier, M. A.; Rajeev, K. G.; Manoharan, M. *ACS Chem. Biol.* **2015**, *10*, 1181−1187 and cited literature.
(6) (a) Mulamba, G. B.; Hu, A.; Azad, R. F.; Anderson, K. P.; Coen, D. M. *Antimicrob. Agents Chemother.* **1998**, *42*, 971−973.
(7) (a) Sinha, G. *Nat. Biotechnol.* **2013**, *31*, 179−180. (b) For a recent review, see: Sharma, V. K.; Sharma, R. K.; Singh, S. K. *MedChemComm* **2014**, *5*, 1454−1471.
(8) (a) Reyes-Darias, J.; Sanchez-Luque, F. J.; Morales, J. C.; Pérez-Rentero, S.; Eritja, R.; Berzal-Herranz, A. *ChemBioChem* **2015**, *16*, 584−591. (b) Agarwala, A.; Jones, P.; Nambi, V. *Curr. Atheroscler. Rep.* **2015**, *17*, 467−475 and cited literature.
(9) For a recent review in this field, see: Lächelt, U.; Wagner, E. *Chem. Rev.* **2015**, *115*, 11043−11078.
(10) For recent contributions in this field, see: (a) Banerjee, A.; Bagmare, S.; Varada, M.; Kumar, V. A. *Bioconjugate Chem.* **2015**, *26*, 1737−1742. (b) Sunkari, Y. K.; Pal, C.; Reddy, T. J.; Chakraborty, T. K. *Tetrahedron* **2014**, *70*, 5455−5462.
(11) De Mesmaeker, A.; Lebreton, J.; Waldner, A.; Cook, P. D. International Patent WO 92/20,823, 1992.
(12) (a) De Mesmaeker, A.; Waldner, A.; Lebreton, J.; Hoffmann, P.; Fritsch, V.; Wolf, R. M.; Freier, S. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 226−229. (b) Lebreton, J.; Waldner, A.; Lesueur, C.; De Mesmaeker, A. *Synlett* **1994**, *1994*, 137−140. (c) Fonne-Pfister, R.; Beaudegnies, R.; Chekatt, H.; Jung, P. M. J.; Murphy-Kessabi, F.; De Mesmaeker, A.; Wendeborn, S. *J. Am. Chem. Soc.* **2005**, *127*, 6027−6038.
(13) De Mesmaeker, A.; Lebreton, J.; Jouanno, C.; Fritsch, V.; Wolf, R. M.; Wendeborn, S. *Synlett* **1997**, *1997*, 1287−1290.
(14) (a) Lebreton, J.; De Mesmaeker, A.; Waldner, A.; Fritsch, V.; Wolf, R. M.; Freier, S. M. *Tetrahedron Lett.* **1993**, *34*, 6383−6386. (b) Lebreton, J.; Waldner, A.; Fritsch, V.; Wolf, R. M.; De Mesmaeker, A. *Tetrahedron Lett.* **1994**, *35*, 5225−5228. (c) De Mesmaeker, A.; Lebreton, J.; Waldner, A.; Fritsch, V.; Wolf, R. M. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 873−878. (d) De Mesmaeker, A.; Lebreton, J.; Waldner, A.; Fritsch, V.; Wolf, R. M.; Freier, S. M. *Synlett* **1994**, *1993*, 733−736.
(15) (a) Rozners, E.; Katkevica, D.; Bizdena, E.; Strömberg, R. *J. Am. Chem. Soc.* **2003**, *125*, 12125−12136. (b) Selvam, C.; Thomas, S.; Abbott, J.; Kennedy, S. D.; Rozners, E. *Angew. Chem., Int. Ed.* **2011**, *50*, 2068−2070. (c) Mutisya, D.; Selvam, C.; Lunstad, B. D.; Pallan, P. S.; Haas, A.; Leake, D.; Egli, M.; Rozners, E. *Nucleic Acids Res.* **2014**, *42*, 6542−6551.
(16) (a) Iwase, R.; Toyama, T.; Nishimori, K. *Nucleosides, Nucleotides Nucleic Acids* **2007**, *26*, 1451−1454. (b) Iwase, R.; Kurokawa, R.; Ueno, J. *Nucleic Acids Symp. Ser.* **2009**, *53*, 119−120.
(17) For selected recent contributions on this topic, see: (a) Jabgunde, A. M.; Yeole, S. D.; Sanap, S. P.; Gadre, S. R.; Dhavale, D. D. *Synthesis* **2012**, *44*, 2277−2286. (b) Bagmare, S.; Gunjal, A. D.; Kumar, A. V. *Tetrahedron* **2015**, *71*, 2442−2449.
(18) Sanghvi, Y. S.; Bharadwaj, R.; Debart, F.; De Mesmaeker, A. *Synthesis* **1994**, *1994*, 1163−1166.
(19) For selected recent preparations of monomeric building block amines and carboxylic acids, see: (a) Peterson, M. A.; Nilsson, B. L.; Sarker, S.; Doboszewski, B.; Zhang, W.; Robins, M. J. *J. Org. Chem.* **1999**, *64*, 8183−8192. (b) Lu, D.-M.; Min, J.-M.; Zhang, L.-H. *Carbohydr. Res.* **1999**, *317*, 193−197. (c) Robins, M. J.; Doboszewski, B.; Timoshchuk, V. A.; Peterson, M. A. *J. Org. Chem.* **2000**, *65*, 2939−2945. (d) Kochetkova, S. V.; Varizhuk, A. M.; Kolganova, N. A.; Timofeev, E. N.; Florent'ev, V. L. *Russ. J. Bioorg. Chem.* **2009**, *35*, 68−74. (e) Xu, Q.; Katkevica, D.; Rozners, E. *J. Org. Chem.* **2006**, *71*, 5906−5913.
(20) Tanui, P.; Kennedy, S. D.; Lunstad, B. D.; Haas, A.; Leake, D.; Rozners, E. *Org. Biomol. Chem.* **2014**, *12*, 1207−1210.
(21) (a) Bennua-Skalmowski, B.; Krolikiewicz, K.; Vorbrüggen, H. *Tetrahedron Lett.* **1995**, *36*, 7845−7848. (b) Niedballa, U.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 461−462. For recent references, see: (c) Das, S. N.; Chowdhury, A.; Tripathi, N.; Jana, P. K.; Mandal, S. B. *J. Org. Chem.* **2015**, *80*, 1136−1148. (d) Plevová, K.; Briestenská, K.; Colobert, F.; Mistríková, J.; Milata, V.; Leroux, F. R. *Tetrahedron Lett.* **2015**, *56*, 5112−5115.
(22) For examples of one-pot polynucleoside base insertion under Vorbrüggen conditions, see: (a) Sengupta, J.; Mukhopadhyay, R.; Bhattacharjya, A. *J. Org. Chem.* **2007**, *72*, 4621−4625. (b) Sengupta, J.; Bhattacharjya, A. *J. Org. Chem.* **2008**, *73*, 6860−6863. (c) Das, N. S.; Rana, R.; Chatterjee, S.; Kumar, G. S.; Mandal, B. S. *J. Org. Chem.* **2014**, *79*, 9958−9969.
(23) Baker, B. R.; Schaub, R. E. *J. Am. Chem. Soc.* **1955**, *77*, 5900−5905.
(24) Bozó, É.; Boros, S.; Kuszmann, J.; Gács-Baitz, E.; Párkányi, L. *Carbohydr. Res.* **1998**, *308*, 297−310.
(25) Kim, J.; Weledji, Y. N.; Greenberg, M. M. *J. Org. Chem.* **2004**, *69*, 6100−6104.
(26) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974−6977.
(27) Xavier, N. M.; Rauter, A. P. *Org. Lett.* **2007**, *9*, 3339−3341.
(28) For successful diastereoselective hydrogenation reactions on related structures, see: (a) Rosenthal, A.; Nuyen, L. *J. Org. Chem.* **1969**, *34*, 1029−1034. (b) Xie, M.; Berges, D. A.; Robins, M. J. *J. Org. Chem.* **1996**, *61*, 5178−5179. (c) Yang, E. G.; Sekar, K.; Lear, M. J. *Tetrahedron Lett.* **2013**, *54*, 4406−4408.
(29) Knijnenburg, A. D.; Tuin, A. W.; Spalburg, E.; de Neeling, A. J.; Mars-Groenendijk, R. H.; Noort, D.; Otero, J. M.; Llamas-Saiz, A. L.; van Raaij, M. J.; van der Marel, G. A.; Overkleeft, H. S.; Overhand, M. *Chem. - Eur. J.* **2011**, *17*, 3995−4004.
(30) Dunetz, J. R.; Magano, J.; Weisenburger, G. A. *Org. Process Res. Dev.* **2016**, *20*, 140−177 and cited literature.
(31) For investigations of acetolysis conditions on related substrates, see: Tanui, P.; Kullberg, M.; Song, N.; Chivate, Y.; Rozners, E. *Tetrahedron* **2010**, *66*, 4961−4964.
(32) Gaster, J.; Marx, A. *Chem. - Eur. J.* **2005**, *11*, 1861−1870.
(33) Hrdlicka, P. J.; Andersen, N. K.; Jepsen, J. S.; Hansen, F. G.; Haselmann, K. F.; Nielsen, C.; Wengel, J. *Bioorg. Med. Chem.* **2005**, *13*, 2597−2621.
(34) Rangam, G.; Rudinger, N. Z.; Müller, H. M.; Marx, A. *Synthesis* **2005**, 1467−1472.

DOI: 10.1021/acs.joc.6b01822
J. Org. Chem. 2016, 81, 10742−10758

(35) Prhavc, M.; Bhat, B.; Just, G.; Dan Cook, P.; Manoharan, M. *Nucleosides, Nucleotides Nucleic Acids* **2001**, *20*, 995−997.
(36) For some examples concerning this point, see: (a) Lavallée, J.-F.; Just, G. *Tetrahedron Lett.* **1991**, *32*, 3469−3471. (b) Liu, Z.; Li, D.; Yin, B.; Zhang, J. *Tetrahedron Lett.* **2010**, *51*, 240−243. (c) Kim, K. S.; Suk, D.-H. *Trends Glycosci. Glycotechnol.* **2011**, *23*, 53−66.
(37) For examples of lactone formation on similar structures, see: Lourens, G. J.; Koekemoer, J. M. *Tetrahedron Lett.* **1975**, *16*, 3719−3722.
(38) For examples of azide reduction-acetate migration, see: (a) von Itzstein, M.; Wu, W.-Y.; Jin, B. *Carbohydr. Res.* **1994**, *259*, 301−305. (b) Albler, C.; Hollaus, R.; Kählig, H.; Schmid, W. *Beilstein J. Org. Chem.* **2014**, *10*, 2230−2234.
(39) Note: the structures **5**, **31** (or **31′**) are consistent with HRMS (calcd for $C_{16}H_{21}N_1O_6$ = 323.1363 Da, found = 323.1365 Da) and the fact that the ratio between **5** and **31** (or **31′**) evolved during evaporation, suggesting that an acetate migration was taking place intra- or intermolecularly.
(40) (a) Garcia, J.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1984**, *25*, 4841−4844. (b) Chapuis, H.; Strazewski, P. *Tetrahedron* **2006**, *62*, 12108−12115. (c) Krishnakumar, K. S.; Strazewski, P. *Synlett* **2010**, *2010*, 1055−1058.
(41) Burés, J.; Martın, M.; Urpı, F.; Vilarrasa, J. *J. Org. Chem.* **2009**, *74*, 2203−2206.
(42) van Straten, N. C. R.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron* **1997**, *53*, 6509−6522.
(43) Griffin, B. E.; Todd, A. *J. Chem. Soc.* **1958**, 1389−1393.

DOI: 10.1021/acs.joc.6b01822
J. Org. Chem. 2016, 81, 10742−10758