JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

# Stereoselective Synthesis of Uridine-Derived Nucleosyl Amino Acids

Anatol P. Spork,[‡] Daniel Wiegmann,[‡] Markus Granitzka,[†] Dietmar Stalke,[†] and Christian Ducho*[,‡,§]

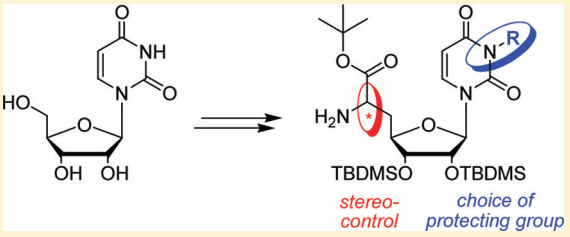
[‡]Department of Chemistry, Institute of Organic and Biomolecular Chemistry, Georg-August-University Göttingen, Tammannstr. 2, 37 077 Göttingen, Germany

[†]Department of Chemistry, Institute of Inorganic Chemistry, Georg-August-University Göttingen, Tammannstr. 4, 37 077 Göttingen, Germany

[§]Department of Chemistry, University of Paderborn, Warburger Strasse 100, 33 098 Paderborn, Germany

Supporting Information

**ABSTRACT:** Novel hybrid structures of 5′-deoxyuridine and glycine were conceived and synthesized. Such nucleosyl amino acids (NAAs) represent simplified analogues of the core structure of muraymycin nucleoside antibiotics, making them useful synthetic building blocks for structure−activity relationship (SAR) studies. The key step of the developed synthetic route was the efficient and highly diastereoselective asymmetric hydrogenation of didehydro amino acid precursors toward protected NAAs. It was anticipated that the synthesis of unprotected muraymycin derivatives via this route would require a suitable intermediate protecting group at the N-3 of the uracil base. After initial attempts using PMB- and BOM-N-3 protection, both of which resulted in problematic deprotection steps, an N-3 protecting group-free route was envisaged. In spite of the pronounced acidity of the uracil-3-NH, this route worked equally efficient and with identical stereoselectivities as the initial strategies involving N-3 protection. The obtained NAA building blocks were employed for the synthesis of truncated 5′-deoxymuraymycin analogues.




## INTRODUCTION

The chemical modification of naturally occurring nucleoside and nucleotide structures is an important field in nucleic acid and medicinal chemistry. For instance, nucleoside analogues are known to be potential antiviral and anticancer agents.[1] Modified oligonucleotides are important tools for biomedical research[2] as well as DNA-based nanotechnology.[3] Within such areas of research, mixing structural principles of nucleic acids and peptides is an important issue. The most striking example of this approach might be the design of peptide nucleic acids (PNA), nucleic acid analogues with an artificial peptidic backbone.[4] Furthermore, amide internucleotide linkages have been introduced into oligonucleotides,[5] and DNA-peptide or -protein conjugates have gained widespread attention.[6]

Amino acid−nucleoside hybrid structures can also be found in natural products. Nucleoside antibiotics are microbially produced secondary metabolites often bearing unusual nucleoside moieties.[7] Most of these naturally occurring nucleoside derivatives inhibit the bacterial membrane protein translocase I (MraY), a key enzyme in the intracellular part of peptidoglycan formation.[8] With respect to the emerging resistances of bacterial strains toward established antibiotics,[9] MraY is discussed as a potential new drug target.[10] Representative examples of the complex structures found in nucleoside antibiotics are given by the muraymycins[11] and caprazamycins[12] (e.g., muraymycin A1 **1** and caprazamycin A **2**, Figure 1). Both of those *Streptomyces*-produced classes of natural products share a common nucleoside core structure of type **3**. The most remarkable aspect about structure **3** is the C−C linkage of the 5′-carbon atom of the uridine moiety to the $\alpha$-carbon atom of a glycine unit (C-6′). Thus, **3** might be considered a hybrid of an amino acid with a nucleoside, making it a relevant structural motif for several applications (vide supra). Synthetic access to protected versions of **3** include the aldol-type reaction of a glycine-derived enolate with a uridine-5′-aldehyde,[13] Sharpless aminohydroxylation,[14] and diasteroselective epoxide formation using sulfur ylide chemistry, followed by double-inversion opening of the epoxide.[15] However, the stereocontrolled construction of both stereocenters at C-5′ and C-6′ of $\beta$-hydroxy amino acid **3** is not trivial.

Several analogues of both the muraymycins[13,16] and the caprazamycins[17] have already been prepared and tested for their antibiotic potencies. Remarkably, muraymycin analogues derived from the 5′-epimer of **3** (not displayed) were also proven to be biologically active. Thus, truncated synthetic muraymycin analogues **4a−e** with the unnatural (5′*R*)-configuration showed reasonable antibacterial activities (Figure 1). Derivatives lacking the synthetic protecting groups still present in **4a−e** were surprisingly found to be nearly inactive. Astonishingly, the congeners of this series of analogues with natural product-like (5′*S*)-configuration (not displayed) did not feature any significant biological potency.[13]

**Received:** September 19, 2011
**Published:** November 7, 2011

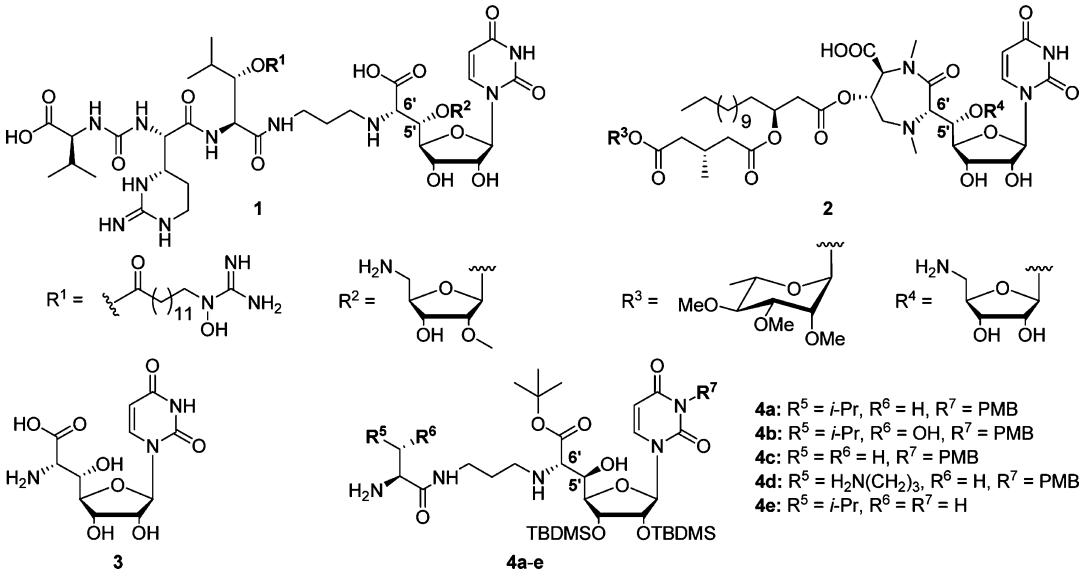



**Figure 1.** The nucleoside antibiotics muraymycin A1 **1** and caprazamycin A **2**, their common uridine-derived core structure **3** and bioactive synthetic muraymycin analogues **4a**-**e**.

Besides these results, the aminoribosyl unit of the muraymycins has been found not to be essential for antibacterial activity as proven by a bioactive nonaminoribosylated derivative (muraymycin A5, not displayed).[11] This has led to the design of 5′-deoxy analogues of **3**, i.e., compounds of type **5** (with (6′*S*)-configuration as in the natural products **1** and **2**) and of type **6** (displaying unnatural (6′*R*)-configuration, Figure 2). Uridine-derived nucleosyl amino acids (NAAs) **5** and

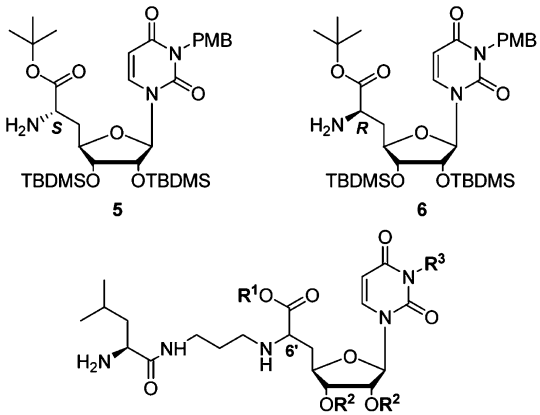



**Figure 2.** Uridine-derived nucleosyl amino acid (NAA) building blocks **5** and **6** and the corresponding muraymycin analogues **7** and **8**.

**6** represent truncated analogues of the nucleoside moieties found in nucleoside antibiotics such as **1** and **2**, lacking the 5′-hydroxy group as the site for aminoribosylation. Compounds derived from NAA structures **5** and **6** therefore represent interesting candidates with improved chemical tractability for structure−activity relationship (SAR) studies. They might be valuable additions to the existing SAR results for truncated muraymycin analogues **4** (vide supra), particularly with respect to the role of the 5′-substituent and to the stereochemistry at the 6′-position.

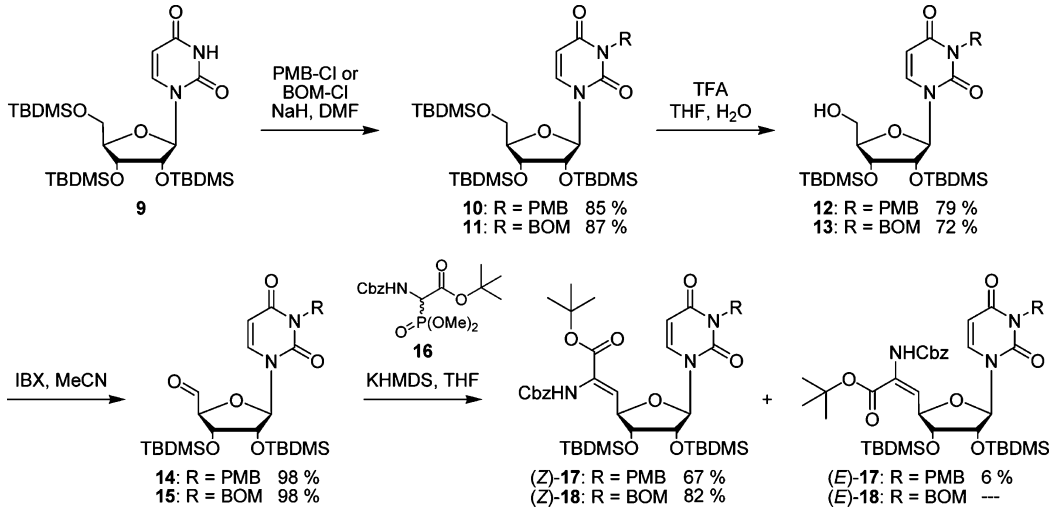
We have recently described the concise stereoselective synthesis of unprecedented uridine-derived NAAs **5** and **6** in communication format.[18] They could be used as building blocks for the preparation of truncated muraymycin derivatives **7a** and **8a**, which represent analogues of the established muraymycin-based synthetic antibiotics **4**. However, it would also be desirable to obtain partially or globally deprotected muraymycin derivatives such as **7b** and **8b** (as analogues of **4e**) or **7c** and **8c**, respectively, for SAR studies (Figure 2). From a synthetic point of view, the choice of the N-3 protecting group at the uracil base might be crucial in order to achieve this goal. In this work, we therefore present a more detailed study on the synthesis of uridine-derived NAAs with a particular focus on different strategies for uracil protection.

## RESULTS AND DISCUSSION

The principle synthetic route toward NAA structures of type **5** and **6** involved the oxidation of protected uridine derivatives to the respective 5′-aldehydes, the Wittig−Horner transformation of the aldehydes into didehydro amino acids, and finally, the stereoselective hydrogenation of those key intermediates to furnish protected NAAs.[18] In order to obtain the hydrogenation precursors, protecting groups had to be installed first. Trisilylated uridine **9**[19] (which can easily be obtained from uridine in quantitative yield) was N-3-alkylated (products **10**[15a] and **11**, yields 85% and 87%) and then selectively 5′-O-desilylated[20] to yield **12**[15a] and **13** in yields of 79% and 72%, respectively (Scheme 1). Because of the acidity of the uracil NH, *p*-methoxybenzyl (PMB, for **10** and **12**) or benzyloxymethyl (BOM, for **11** and **13**) protection of the uracil-N-3 position was anticipated to be necessary in order to allow the subsequent Wittig−Horner reaction to proceed efficiently. There is precedent though for Wittig reactions using basic nonstabilized ylides and Wittig−Horner transformations employing basic deprotonated phosphonates with N-3-unprotected uridine derivatives.[21] However, yields for such processes were either not disclosed[21a] or moderate at best.[21b]


dx.doi.org/10.1021/jo201935w | J. Org. Chem. 2011, 76, 10083−10098

**Scheme 1. Synthesis of Didehydro Amino Acids 17 and 18**

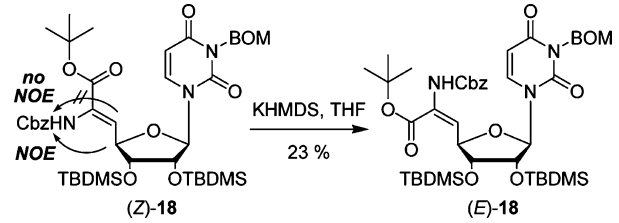



Alcohols **12** and **13** were oxidized with IBX to give protected uridine 5′-aldehydes **14** and **15** as Wittig–Horner substrates in 98% yield each (Scheme 1). Though they showed limited stability, freshly prepared aldehydes **14** and **15** could easily be used for the subsequent Wittig–Horner transformations with amino acid phosphonate **16**[22] under basic conditions. This reaction furnished uridine-derived didehydro amino acids (*Z*)-**17**[18] and (*Z*)-**18** in isolated yields of 67% and 82%, respectively. As expected,[23] the Wittig–Horner reactions displayed pronounced (*Z*)-stereoselectivity. In the case of **17**, the corresponding (*E*)-isomer (*E*)-**17** was obtained as a byproduct only (6% isolated yield after column chromatography),[18] while for **18**, the (*E*)-congener (*E*)-**18** was not found at all. We have previously described that similar transformations can also be carried out using the *N*-Boc-protected amino acid phosphonate. However, the acidic Boc deprotection at a later stage of the synthetic route was problematic,[18] and consequently, this approach is not described in further detail here.

It is known that homogeneous asymmetric hydrogenation reactions occur more rapidly and with significantly better stereoselectivities for (*Z*)-didehydro amino acids than for the (*E*)-isomers.[24] It was therefore essential to prove unambiguously that the main products obtained from the Wittig–Horner reactions were indeed (*Z*)-configured, though this was strongly suggested by numerous precedent. In order to determine the stereochemical configuration of the didehydro amino acids using established NMR criteria,[25] both the (*Z*)- and the (*E*)-isomers of **17** as well as **18** were required. However, in contrast to (*E*)-**17**, the BOM-protected congener (*E*)-**18** could not be obtained as a byproduct from the Wittig–Horner reaction and thus had to be prepared separately. Treatment of (*Z*)-**18** with potassium hexamethyldisilazide (KHMDS) led to partial isomerization of the olefinic double bond, most likely resulting from deprotonation of the amino acid $\alpha$-NH providing an azaallyl anion. After chromatographic separation from remaining (*Z*)-**18**, (*E*)-**18** could be isolated in 23% yield (Scheme 2).

With both (*E*)-isomers in hand, application of the aforementioned empirical NMR criteria for configurational assignment of the double bond was attempted. It had been reported by Mazurkiewicz et al. that both the $\beta$-CH as well as the $\alpha$-NH of (*E*)-didehydro amino acids was further downfield-shifted than the corresponding signals of the respective (*Z*)-isomers in $^1$H NMR spectra recorded in deuterated chloroform

**Scheme 2. Synthesis of (*E*)-18 and Relevant $^1$H NMR NOEs of (*Z*)-18**




($\delta_{\beta\text{-CH}}(E) > \delta_{\beta\text{-CH}}(Z)$ and $\delta_{\alpha\text{-NH}}(E) > \delta_{\alpha\text{-NH}}(Z)$, respectively).[25] This was found to be true for the $\beta$-CH, but the rule was violated for the $\alpha$-NH signals of both **17** and **18**. However, the configuration of (*Z*)-**17** had been verified by a $^1$H–$^1$H NOESY NMR (2D) experiment before.[18] $^1$H NOE NMR (1D) studies now clearly proved the proposed configuration of (*Z*)-**18** to be correct. For (*Z*)-**18**, no transfer of nuclear spin polarization by a nuclear Overhauser effect (NOE) from the $\beta$-CH to the $\alpha$-NH was found. In contrast, an NOE-derived signal proving a polarization transfer from the nucleoside H-4′ to the amino acid $\alpha$-NH was observed (Scheme 2, also see the Supporting Information).

With both precursor compounds (*Z*)-**17** and (*Z*)-**18** in hand, asymmetric hydrogenation providing the desired NAA structures was performed. The chiral homogeneous catalysts (+)-1,2-bis-((2*S*,5*S*)-2,5-dimethylphospholano)benzene-(cyclooctadiene)rhodium(I) tetrafluoroborate ((*S*,*S*)-Me-DUPHOS-Rh) **19** and (−)-1,2-bis-((2*R*,5*R*)-2,5-dimethylphospholano)benzene(cyclooctadiene)rhodium(I) tetrafluoroborate ((*R*,*R*)-Me-DUPHOS-Rh) **20**[26] have been shown to be highly useful for such transformations, particularly when *N*-urethane-protected didehydro amino acids were employed.[27] As briefly reported in our previous communication,[18] hydrogenation of (*Z*)-**17** in the presence of **19** gave NAA (*S*)-**21** in excellent diastereoselectivity (dr > 98:2 as determined by $^1$H NMR), while catalyst **20** furnished NAA (*R*)-**21** with similar selectivity. Primary reaction products **21** could easily be deprotected by subsequent hydrogenolysis under heterogeneous catalysis (palladium on charcoal) in a one-pot fashion to provide NAAs (*S*)-**22** and (*R*)-**22** in overall yields of 86% and 80%, respectively (Scheme 3). The assignment of the stereochemical configuration at C-6′ was


dx.doi.org/10.1021/jo201935w | J. Org. Chem. 2011, 76, 10083–10098

**Scheme 3. Synthesis of Nucleosyl Amino Acids (*S*)-22 and (*R*)-22 as Well as (*S*)-23 and (*R*)-23**

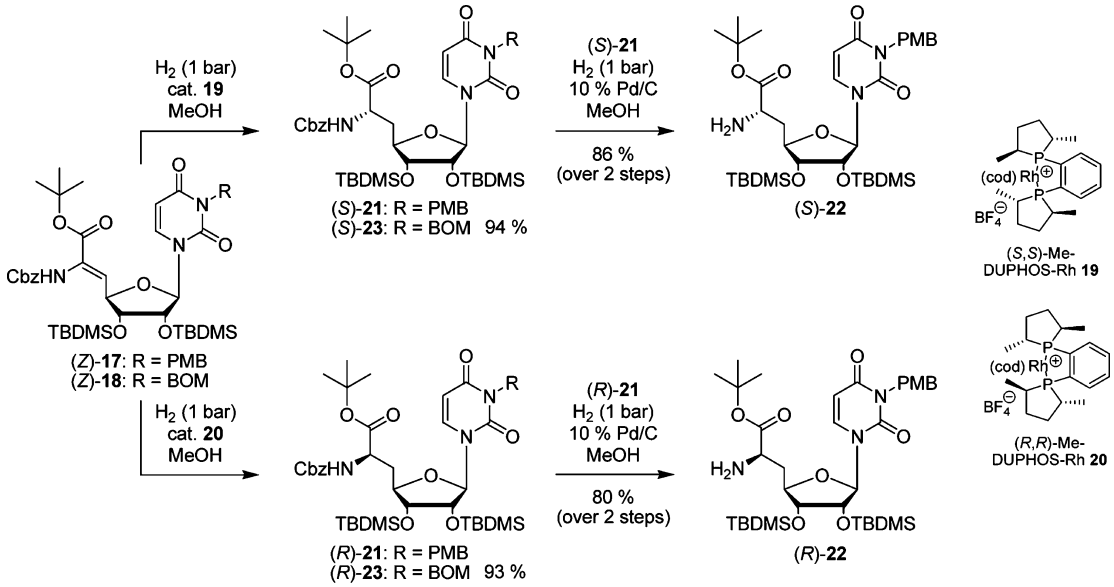
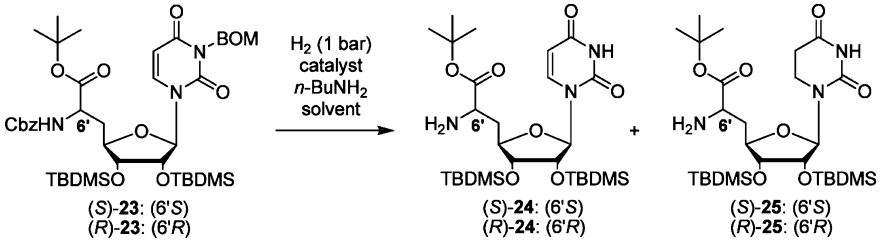



**Table 1. Hydrogenolytic Deprotection of (*S*)-23 and (*R*)-23**




| entry | isomer | scale/mg[a] | catalyst | solvent | time/h | amount 25[b]/% | yield 24[c]/% |
|---|---|---|---|---|---|---|---|
| 1 | 6′*S* | 30 | 10% Pd/C | MeOH | 20 | ∼80 | [d] |
| 2 | 6′*S* | 20 | Pd black | MeOH | 6 | ∼5 | [d] |
| 3 | 6′*S* | 50 | Pd black | MeOH | 120 | ∼5 | [d] |
| 4 | 6′*S* | 40 | Pd black | MeOH | 2.5 | <5 | 92 |
| 5 | 6′*S* | 790 | Pd black | MeOH | 8.5 | ∼30 | [d] |
| 6 | 6′*R* | 30 | Pd black | MeOH | 12 | 5−10 | [d] |
| 7 | 6′*R* | 50 | Pd black | MeOH | 96 | ∼20 | [d] |
| 8 | 6′*R* | 30 | Pd black | EtOAc | 18 | ∼90 | [d] |
| 9 | 6′*R* | 40 | Pd black | MeOH | 2.5 | <5 | 96 |
| 10 | 6′*R* | 30 | Pearlman[e] | MeOH | 2 | ∼90 | [d] |
| 11 | 6′*R* | 30 | Lindlar | MeOH | 96 | ∼70 | [d] |

[a]Amount of starting material. [b]Amount of undesired byproduct **25** detected in the crude reaction product by $^1$H NMR. [c]Isolated yield of desired product **24**. [d]**24** could not be isolated as **24** and **25** were chromatographically inseparable. [e]Pearlman's catalyst = 20% $Pd(OH)_2/C$.

based on literature precedent clearly indicating that **19** would always provide L-amino acids while **20** leads to the respective D-isomers.[26,27] It could be ruled out that this catalyst-provided stereoinduction was overruled by substrate-controlled selectivity for the hydrogenation of (*Z*)-**17** as the reaction was of catalyst-controlled nature.[18] The asymmetric hydrogenation step worked equally well with BOM-protected congener (*Z*)-**18**, thus giving rise to the synthesis of NAAs (*S*)-**23** and (*R*)-**23** in yields of 94% and 93%, respectively, and again with excellent diastereoselectivities (dr > 98: 2 each as determined by $^1$H NMR, Scheme 3).

The envisaged preparation of NAAs and derived muraymycin analogues lacking a uracil-N-3 protecting group (vide supra) would require either (i) the selective cleavage of the PMB group from (*S*)-**22** and (*R*)-**22** or subsequent reaction products, respectively, or (ii) the concomitant hydrogenolytic removal of both the Cbz and the BOM group from (*S*)-**23** and (*R*)-**23**. We have previously reported that (*S*)-**22** and (*R*)-**22** can readily be converted into muraymycin analogues **7a** and **8a**.[18] The most obvious strategy would be to remove the PMB group from these compounds at a late stage to obtain **7b** and **8b** (also see Figure 2). To our surprise, any attempt to efficiently cleave the PMB group from **7a** or **8a** under oxidative conditions was not successful in spite of literature precedent for its use for uracil-N-3 protection.[13,28] No reaction was observed when DDQ was employed. In contrast, treatment with CAN led to tedious product mixtures, most likely due to the pronounced acidic nature of aqueous solutions of CAN. When buffered CAN solutions were used in order to overcome this problem, no reaction was observed. As a result of the hurdles


dx.doi.org/10.1021/jo201935w | J. Org. Chem. 2011, 76, 10083−10098

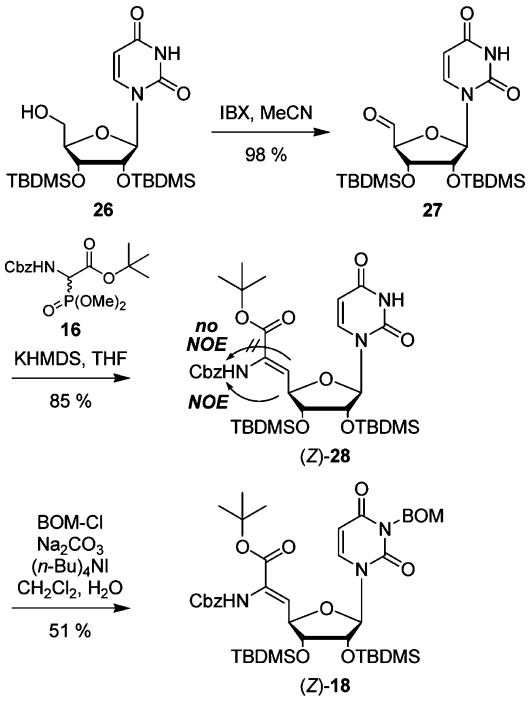
encountered for the PMB removal, it was decided to focus on the BOM-based strategy, i.e., the selective hydrogenolytic deprotection of NAAs (*S*)-**23** and (*R*)-**23**.

For the concomitant hydrogenolysis of the Cbz and the BOM group from (*S*)-**23** and (*R*)-**23**, different conditions were investigated (Table 1). On the basis of literature precedent,[14a] it was anticipated that the formaldehyde liberated upon cleavage of the BOM group might react with the 6′-amino group. Thus, the *N*-methylated product would be furnished under the reductive conditions of hydrogenolysis reactions. In order to overcome this limitation, an excess of *n*-butylamine was added to the reaction mixture to capture the formaldehyde, giving *n*-butylmethylamine as a sufficiently volatile byproduct. Experiments for similar hydrogenolytic BOM cleavage reactions using the according thymidine derivatives in the absence of *n*-butylamine indeed proved that the 6′-*N*-methylated product was formed to a major extent, thus confirming the need to add the amine as a formaldehyde scavenger (reaction not shown). However, when 10% palladium on charcoal was used as a standard catalyst for the hydrogenolytic deprotection of (*S*)-**23**, not only the desired product (*S*)-**24** was obtained, but ca. 80% formation of undesired byproduct (*S*)-**25** resulting from unwanted reduction of the uracil-C5−C6 double bond was observed (Table 1, entry 1). As (*S*)-**25** could not be separated from (*S*)-**24** by column chromatography, it was essential to minimize the unwanted overreduction leading to byproduct formation to a level significantly below 5%. In a first series of experiments, palladium black was used as hydrogenation catalyst instead of palladium on support material. Thus, the amount of (*S*)-**25** was limited to ca. 5% (Table 1, entry 2), but it was difficult to drive the reaction to completion under these conditions. The reaction time could be prolonged to several days without increased overreduction (entry 3), but quantitative conversions were still not feasible this way. The strategy to compensate for the apparent limited reactivity of the catalyst, which might have been the result of partial poisoning due to the presence of excess *n*-butylamine, was then to add significantly larger amounts of the catalyst. Using an excess of palladium black, high conversion was achieved in a short reaction time, and byproduct formation was reduced to a minimum. Hence, the deprotected NAA (*S*)-**24** was isolated in 92% yield (entry 4). Unfortunately, this transformation was not robust toward upscale. When the amount of starting material was raised ca. 20-fold, byproduct (*S*)-**25** was formed in 30% again (entry 5). Overall, the practical applicability of the deprotection reaction was therefore limited by two drawbacks: first, the costs of high amounts of palladium black needed for selective hydrogenolysis, and second, the reaction being tied to small scales in the range of ca. 30−50 mg starting material.

Similar observations were made for the hydrogenolytic deprotection of (*R*)-**23** providing NAA (*R*)-**24**. The tendency to display formation of byproduct (*R*)-**25** resulting from overreduction was even slightly more pronounced (Table 1, entries 6 and 7 vs entries 2 and 3). An attempt to replace methanol as solvent with ethyl acetate, speculating for milder hydrogenation conditions in this solvent, gave a surprisingly high amount of (*R*)-**25** (ca. 90%, Table 1, entry 8). However, the previously successful strategy (vide supra) could also be applied for this diastereomer. An excess of palladium black led to high conversion in a short reaction time and minimal byproduct formation. The deprotected NAA (*R*)-**24** was thus isolated in 96% yield, but again on a small scale only (40 mg (*R*)-**23** as starting material, entry 9). Two other palladium catalysts were also tested for the deprotection of (*R*)-**23**. Using Pearlman's catalyst (20% palladium hydroxide on charcoal), it was anticipated that reaction times might be reduced to such an extent that overreduction might be avoided. In contrast, (*R*)-**25** was furnished in ca. 90% in this reaction (entry 10). Even with the usually mild and selective poisoned Lindlar catalyst, ca. 70% formation of (*R*)-**25** was observed (entry 11). It was therefore decided not to continue any attempts to further optimize the hydrogenolysis reaction.

Due to the practical limitations of concomitant Cbz and BOM cleavage from (*S*)-**23** and (*R*)-**23** (vide supra), alternative strategies were sought. It was obvious from the straightforward deprotection of the Cbz group in (*S*)-**21** and (*R*)-**21** (see Scheme 3) that problems were caused by the BOM group. However, only few protecting groups for the uracil-N-3 are established. It would therefore be an attractive option to perform the synthesis of NAAs (*S*)-**24** and (*R*)-**24** without protection of the uracil-N-3 position. It was anticipated though that a Wittig−Horner transformation of a uridine derivative lacking nucleobase protection should be hindered in terms of yield and/or stereoselectivity due to the acidity of the uracil-3-NH (vide supra). However, after selectively silylated uridine **26**[20] (obtained by 5′-O-deprotection of **9** in 93% yield) had been oxidized to the corresponding 5′-aldehyde **27** with IBX in 98% yield,[15,29] aldehyde **27** could be reacted with phosphonate **16** in the presence of base to furnish didehydro amino acid (*Z*)-**28** with a yield of 85% (Scheme 4). This surprisingly efficient

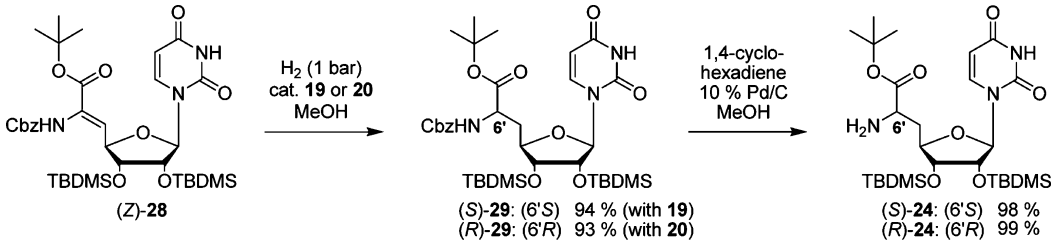
**Scheme 4. Synthesis of (*Z*)-28 and Proof of the Stereochemical Assignment**




Wittig−Horner reaction did not provide any (*E*)-isomer at all. Even without the (*E*)-isomer as a reference compound, the assignment of the double-bond configuration of (*Z*)-**28** was supported by similar $^1$H NOE NMR experimental results as observed for (*Z*)-**18**. Furthermore, when (*Z*)-**28** was reacted with benzyloxymethyl chloride in the presence of base, material identical to (*Z*)-**18** (as proven by rigorous NMR analysis) could


dx.doi.org/10.1021/jo201935w | J. Org. Chem. 2011, 76, 10083−10098

**Scheme 5. Synthesis of Nucleosyl Amino Acids (*S*)-24 and (*R*)-24**

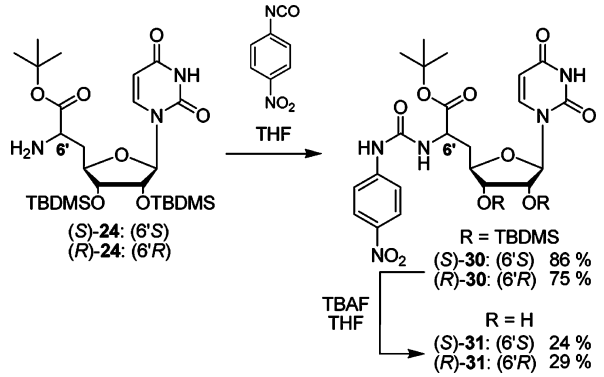



be isolated in 51% yield (Scheme 4). This alkylation of (*Z*)-**28** proceeded without isomerization of the double bond. This was demonstrated by treatment of (*Z*)-**28** with all reagents used for the transformation into (*Z*)-**18** except of benzyloxymethyl chloride, which led to the reisolation of (*Z*)-**28** in nearly quantitative yield (reaction not shown).

With key intermediate (*Z*)-**28** obtained by the Wittig–Horner reaction in hand, asymmetric hydrogenation was performed (Scheme 5). Similar to the transformations carried out with uracil-N-3 protected precursors (*Z*)-**17** and (*Z*)-**18** (vide supra), high diastereoselectivities (dr > 98:2 as determined by $^1$H NMR) were obtained with chiral catalysts **19** and **20**, furnishing nucleosyl amino acids (*S*)-**29** and (*R*)-**29** in excellent yields of 94% and 93%, respectively. The subsequent hydrogenolytic Cbz cleavage was hindered by the pronounced tendency of both diastereomers of **29** to undergo unwanted hydrogenation of the uracil-C5–C6 double bond. However, under transfer hydrogenation conditions using 1,4-cyclohexadiene as hydrogen source, this undesired side reaction was avoided, and target nucleosyl amino acids (*S*)-**24** and (*R*)-**24** were isolated in nearly quantitative yields (Scheme 5).

Though the stereochemical assignment of all nucleosyl amino acids synthesized in this study was clearly supported by literature precedent regarding rhodium(I) catalysts **19** and **20**,[18,26,27] further proof by X-ray crystallography was desired. The growth of single crystals of nucleosyl amino acid derivatives was limited by their low crystallization tendency though. In the course of our synthetic studies on the native nucleoside core structure of muraymycin antibiotics, we have already noticed that N-3-unprotected analogues of this type of compounds appear to crystallize more easily,[15b] and consequently, both diastereomers of **24** were suitable candidates for single crystal growth. In order to further support crystal formation, the 6′-amino group of (*S*)-**24** and (*R*)-**24** was transformed into a *p*-nitrophenylurea moiety[13] to provide (*S*)-**30** and (*R*)-**30** in yields of 86% and 75%, respectively (Scheme 6). Unfortunately, neither diastereomer of **30** gave suitable crystals. However, after both (*S*)-**30** and (*R*)-**30** had been desilylated to (*S*)-**31** and (*R*)-**31** (24% and 29% yield, respectively, reactions not optimized), single crystals of (*R*)-**31** suitable for X-ray diffraction could be obtained.[30] Although the absolute structure determination based on the Flack-x parameter[30g] refinement was bound to fail, the consideration of the inherent stereochemical configuration of the ribose moiety enabled the relative assignment of the stereogenic center at the 6′-position of (*R*)-**31** ((*R*) as postulated, structure displayed in the Supporting Information). Crystal structure analysis thus demonstrated that the proposed stereochemical assignment of (*R*)-**24** and therefore also diastereomer (*S*)-**24** (as well as their respective precursors (*R*)-**29** and (*S*)-**29**) had indeed been correct.

**Scheme 6. Synthesis of Nucleosyl Amino Acids (*S*)-31 and (*R*)-31**

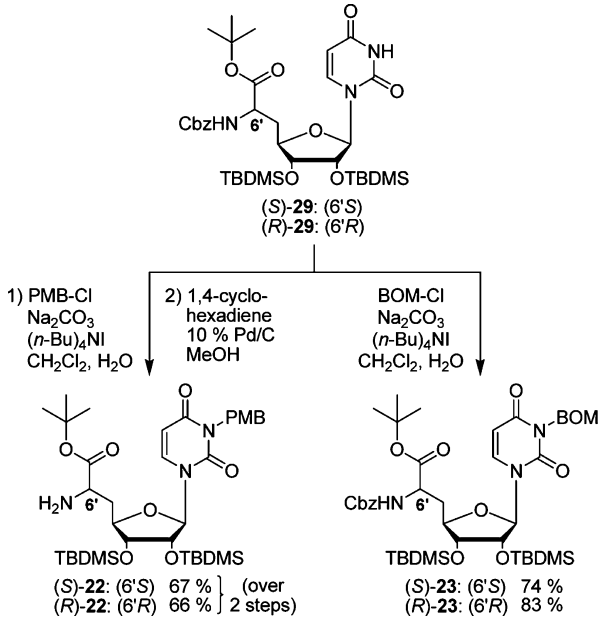



Further transformations of **29** into NAAs **22** and **23** demonstrated that this stereochemical assignment was valid throughout regardless of the protecting group pattern of the didehydro amino acid precursor. When both (*S*)-**29** and (*R*)-**29** were alkylated at the uracil-N-3 with *p*-methoxybenzyl chloride under mildly basic conditions and subsequently selectively deprotected by hydrogenolysis, (*S*)-**22** and (*R*)-**22** were obtained in yields of 67% and 66%, respectively, over two steps. Similar transformations of (*S*)-**29** and (*R*)-**29** using benzyloxymethyl chloride as alkylating agent and leaving out the Cbz cleavage step gave (*S*)-**23** and (*R*)-**23** in yields of 74% and 83%, respectively (Scheme 7). The identity of the thus obtained compounds with the material furnished from asymmetric hydrogenation of PMB- or BOM-protected precursors (*Z*)-**17** and (*Z*)-**18** (vide supra) was proven by rigorous NMR analyses and HPLC coinjections.

Based on the efficient synthesis of N-3-unprotected nucleosyl amino acids **24**, the preparation of novel muraymycin analogues **7b,c** and **8b,c** was feasible (Scheme 8). In principle, two routes can be employed to install the truncated muraymycin side chain: (i) reductive amination with a building block already containing the terminal amino acid moiety and the aminopropyl linker or (ii) reductive amination with an N-3-protected 3-aminopropanal derivative, thus allowing the introduction of different amino acid or peptide motifs by standard coupling procedures following selective deprotection. In contrast to our previous report,[18] we have opted for the latter strategy with respect to its convergent nature, thus potentially enabling synthetic access to a variety of diverse muraymycin analogues with different peptide structures. Consequently, both (*S*)-**24** and (*R*)-**24** were reacted with aldehyde **32** in reductive amination transformations, leading to the isolation of key intermediates (*S*)-**33** and (*R*)-**33** in 91% and 85% yield, respectively. Selective hydrogenolytic removal of the Cbz group under transfer hydrogenation conditions, followed by peptide coupling with *N*-Cbz-leucine, furnished (*S*)-**34** and (*R*)-**34** in


dx.doi.org/10.1021/jo201935w | J. Org. Chem. 2011, 76, 10083–10098

**Scheme 7. Transformations of Nucleosyl Amino Acids 29 into 22 and 23**




70% and 75% yield, respectively, over two steps. Cbz deprotection by hydrogenolysis then provided novel N-3-unprotected target structures **7b** and **8b** in nearly quantitative yields. Finally, global acidic deprotection with TFA in water led to target compounds **7c** and **8c** in the form of the corresponding bis-TFA salts in yields of 80% and 83%, respectively (Scheme 8).

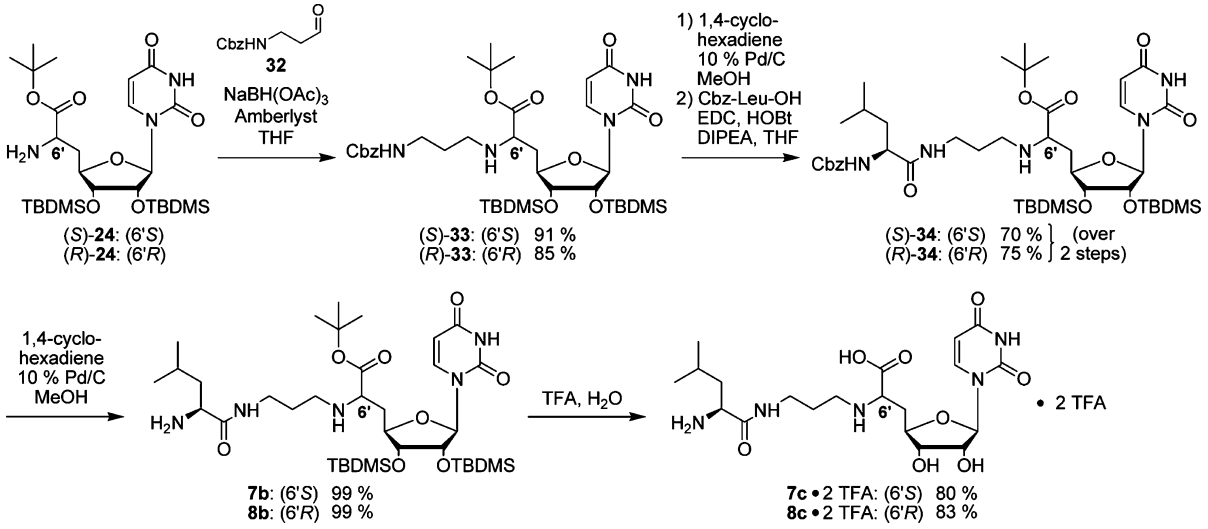
The target muraymycin analogues **7c** and **8c** as well as previously reported compounds **7a** and **8a**[18] were subjected to a preliminary screen for antibacterial activity using agarose plate techniques and a variety of different bacterial strains. No significant activity could be detected so far.

## CONCLUSION

In summary, we have accomplished the concise and efficient synthesis of uridine-derived nucleosyl amino acids (NAAs) as formal hybrids of nucleoside and amino acid structures. The design of these compounds had been inspired by the core structure of naturally occurring muraymycin nucleoside antibiotics. Employing a highly stereoselective asymmetric hydrogenation of didehydro amino acid precursors, synthetic access to protected NAA building blocks such as (*S*)-**24** and (*R*)-**24** was achieved with perfect stereocontrol and overall yields of 71% each in just six steps from uridine. However, the protecting group strategy regarding the uracil-N-3 played an essential role. Although N-3-alkylated muraymycin derivatives can display antibacterial activity,[13] it was desired to establish a synthetic route suitable for the synthesis of N-3-unprotected NAAs as building blocks for novel muraymycin analogues. As both PMB- and BOM-protection of the uracil moiety gave unsatisfactory results regarding deprotection, an approach completely avoiding N-3 protection proved to be optimal. This highlights that transformations of uridine derivatives requiring basic conditions, such as the Wittig–Horner reaction used for the synthesis of the didehydro amino acid precursors, can be performed efficiently with good yields and stereoselectivities without protection of the reasonably acidic uracil-3-NH. Based on these results, it appears recommendable to try reactions of uridine or thymidine derivatives without nucleobase protection first, even if the NH acidity is anticipated to represent a hurdle for the envisaged transformation.

The N-3-unprotected NAA building blocks (*S*)-**24** and (*R*)-**24** were employed for the synthesis of novel 5′-deoxy analogues of the muraymycin antibiotics. Target compounds **7b,c** and **8b,c** were obtained in overall yields of 50–63% over three or four steps from (*S*)-**24** and (*R*)-**24**, respectively. A preliminary biological screening of some selected compounds indicated no potent antibiotic to be among the synthesized muraymycin analogues. This lack of activity does not necessarily indicate poor biological potential though as it might be owed to the polarity, e.g., of **7c** and **8c**, which might limit cellular uptake. In future work, the novel 5′-deoxy muraymycin analogues will therefore also be investigated in an MraY enzyme assay[31] to evaluate their binding potency to the biological target MraY itself. If strong MraY binders are identified, their cellular uptake will potentially be enhanced by the application of prodrug methodology.

**Scheme 8. Synthesis of Target Muraymycin Analogues 7b,c and 8b,c**





dx.doi.org/10.1021/jo201935w | J. Org. Chem. 2011, 76, 10083–10098

## EXPERIMENTAL SECTION

**General Methods.** Compounds **9**,[19] **16**,[22] and **26**[20] were prepared according to established procedures. Reactions involving oxygen and/or moisture sensitive reagents were carried out under an atmosphere of argon using anhydrous solvents. Anhydrous solvents were obtained in the following manner: THF was dried over sodium/benzophenone and distilled, MeOH was dried over activated molecular sieves (3 Å) and degassed, MeCN was dried over $P_2O_5$ and distilled, and DMF was dried over activated molecular sieves (4 Å) and degassed. All other solvents were of technical quality and distilled prior to use, and deionized water was used throughout. Column chromatography was carried out on silica gel 60 (0.040−0.063 mm, 230−400 mesh ASTM) under flash conditions. TLC was performed on aluminum plates precoated with silica gel 60 $F_{254}$. Visualization of the spots was carried out using UV light (254 nm) and/or staining under heating ($H_2SO_4$ staining solution: 4 g of vanillin, 25 mL of concd $H_2SO_4$, 80 mL of AcOH, and 680 mL of MeOH; $KMnO_4$ staining solution: 1 g of $KMnO_4$, 6 g of $K_2CO_3$, and 1.5 mL of 1.25 M NaOH solution, all dissolved in 100 mL of $H_2O$; ninhydrin staining solution: 0.3 g of ninhydrin, 3 mL of AcOH, and 100 mL of 1-butanol). Analytical HPLC was performed on a standard system with a diode array UV detector and equipped with a LiChroCart column (4 × 125 mm) containing reversed-phase silica gel Purospher RP18e (5 μm). Method I: eluent A water (0.1% TFA), eluent B MeCN; 0−15 min gradient of B (3−30%), 15−20 min 100% B, 20−22 min gradient of B (100−3%), 22−30 min 3% B; flow 1.0 mL/min. Method II: eluent A water (0.1% TFA), eluent B MeCN; 0−18 min gradient of B (84−95%), 18−24 min 100% B, 24−30 min 84% B; flow 1.0 mL/min. Method III: eluent A water (0.1% TFA), eluent B MeCN; 0−15 min gradient of B (60−100%), 15−20 min 100% B, 20−30 min 60% B; flow 1.0 mL/min. Preparative HPLC was carried out on a standard system with a UV/vis detector (detection at 260 nm) and equipped with a column (10 × 250 mm) containing reversed-phase silica gel Nucleodur 100−5 C18ec (5 μm). Eluent A water (0.1% TFA), eluent B 80:20 MeCN−water (0.1% TFA); 0−20 min gradient of B (5−10%), 20−30 min 100% B, 30−35 min 5% B; flow 3.0 mL/min. $^1$H NMR spectra were recorded at 300 or 600 MHz. $^{13}$C NMR spectra were recorded at 75, 76, or 126 MHz and were $^1$H-decoupled. $^{19}$F NMR spectra were recorded at 283 MHz and were $^1$H-decoupled. All spectra were measured at room temperature except of samples in DMSO-$d_6$ and $D_2O$ (standard 35 °C). All NMR spectra were referenced internally to solvent reference frequencies wherever possible. Chemical shifts ($\delta$) are quoted in ppm, and coupling constants ($J$) are reported in Hz. Assignment of signals was carried out using $^1$H,$^1$H−COSY, HSQC, and HMBC spectra. Infrared spectroscopy (IR) was either performed on a spectrometer equipped with an ATR unit or on a machine lacking the ATR unit, with solids being measured as KBr pills. Peaks are given as wavenumbers ($\nu$) in cm$^{-1}$. UV/vis spectroscopy: wavelengths of maximum absorption ($\lambda_{max}$) are reported in nm with the corresponding logarithmic molar extinction coefficient (log ($\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$)) given in parentheses. Melting points (mp) are not corrected. Optical rotations were recorded with a Na source using a 10 cm cell (concentrations in g/100 mL).

**General Procedure A (Oxidation of 5′-O-Unprotected Uridine Derivatives).** To a solution of the 5′-O-unprotected uridine derivative in MeCN was added IBX, and the reaction mixture was heated to 80 °C for 45 min. After cooling to 0 °C, the insoluble material was filtered off and washed with EtOAc (3×). The filtrate was evaporated to dryness under reduced pressure. The resultant products were sufficiently pure (>95% as judged by $^1$H NMR) without further purification. With respect to the poor stability of the uridine 5′-aldehydes, they were prepared freshly and directly used for subsequent Wittig−Horner transformations. For the same reason, characterization of the aldehydes was limited to $^1$H NMR and MS.

**General Procedure B (Wittig−Horner Reaction of Uridine 5′-Aldehydes).** To a solution of KHMDS in THF was added a solution of the phosphonate in THF at −78 °C. After 15 min, a solution of the protected uridine 5′-aldehyde in THF was added dropwise at −78 °C. The reaction mixture was stirred for 17 h and slowly warmed to rt during this period. The reaction was quenched by addition of MeOH at 10 °C. After the addition of EtOAc, the organic layer was washed with half-saturated NaCl solution (1×), dried over $Na_2SO_4$, and evaporated under reduced pressure. The resultant crude product was purified by column chromatography.

**General Procedure C (Asymmetric Hydrogenation of Didehydro Amino Acids).** Under strictly anaerobic conditions, the respective Me-DUPHOS-Rh catalyst was added to a solution of the (*Z*)-didehydro amino acid in MeOH. The reaction mixture was stirred under an atmosphere of $H_2$ (1 bar) at rt for the listed time. The solvent was evaporated under reduced pressure and the resultant crude product was purified by column chromatography.

**General Procedure D (Hydrogenolytic Deprotection Using Transfer Conditions).** To a solution of the protected compound in MeOH, 10% Pd/C, and 1,4-cyclohexadiene were added, and the reaction mixture was stirred at rt for 3 h. After filtration through a syringe filter and rinsing of the filter with MeOH (3×), the filtrate was evaporated under reduced pressure. The resultant products were sufficiently pure (>97% as judged by $^1$H NMR) without further purification.

**General Procedure E (N-3 Alkylation of Uridine Derivatives under Mild Conditions).** To a solution of the uridine derivative in $CH_2Cl_2$, tetra-*n*-butylammonium iodide (TBAI), the alkylating agent (*p*-methoxybenzyl chloride or benzyloxymethyl chloride), and aqueous $Na_2CO_3$ solution were added and stirred at rt for the listed time with TLC control. The reaction mixture was diluted with $CH_2Cl_2$ or EtOAc. The organic layer was washed with sat $NaHCO_3$ solution (1×), dried over $Na_2SO_4$, and evaporated under reduced pressure. The resultant crude product was purified by column chromatography.

**N-Unprotected (6′*S*)-Configured Muraymycin Analogue (7b).** General procedure D with *N*-Cbz-protected muraymycin analogue (*S*)-**34** (150 mg, 0.168 mmol), 1,4-cyclohexadiene (159 μL, 1.68 mmol), 10% Pd/C (25 mg, 23 μmol), and MeOH (5 mL) to give **7b** as a colorless solid (126 mg, 99%): $^1$H NMR (600 MHz, $CD_3OD$) $\delta$ 0.09 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.12 (s, 3H, $SiCH_3$), 0.13 (s, 3H, $SiCH_3$), 0.91 (s, 9H, $SiC(CH_3)_3$), 0.92 (d, $J$ = 6.7 Hz, 3H, Leu-5-H$_a$), 0.93 (s, 9H, $SiC(CH_3)_3$), 0.95 (d, $J$ = 6.5 Hz, 3H, Leu-5-H$_b$), 1.37 (ddd, $J$ = 13.5, 7.9, 6.6 Hz, 1H, Leu-3-H$_a$), 1.49 (s, 9H, $OC(CH_3)_3$), 1.52 (ddd, $J$ = 13.5, 7.7, 6.4 Hz, 1H, Leu-3-H$_b$), 1.65−1.73 (m, 3H, propylene-2-H, Leu-4-H), 1.90 (ddd, $J$ = 13.9, 11.1, 4.6 Hz, 1H, 5′-H$_a$), 2.04 (ddd, $J$ = 13.9, 9.4, 2.8 Hz, 1H, 5′-H$_b$), 2.53 (ddd, $J$ = 11.6, 7.4, 6.5 Hz, 1H, propylene-1-H$_a$), 2.64 (ddd, $J$ = 11.6, 7.2, 6.9 Hz, 1H, propylene-1-H$_b$), 3.20−3.36 (m, 4H, 6′-H, propylene-3-H, Leu-2-H), 3.90 (dd, $J$ = 4.7, 4.5 Hz, 1H, 3′-H), 4.06 (ddd, $J$ = 11.1, 4.7, 2.8 Hz, 1H, 4′-H), 4.33 (dd, $J$ = 4.5, 4.4 Hz, 1H, 2′-H), 5.75 (d, $J$ = 8.0 Hz, 1H, 5-H), 5.78 (d, $J$ = 4.4 Hz, 1H, 1′-H), 7.66 (d, $J$ = 8.0 Hz, 1H, 6-H); $^{13}$C NMR (126 MHz, $CD_3OD$) $\delta$ −4.5, −4.4, −4.4, −4.0, 18.9, 18.9, 22.6, 23.4, 25.9, 26.4, 26.5, 28.5, 30.4, 38.1, 38.1, 45.7, 46.1, 54.7, 60.7, 75.9, 76.6, 82.6, 82.8, 91.9, 103.0, 142.8, 152.2, 166.1, 174.9, 178.1; MS (ESI$^+$) $m/z$ 756.5 (M + H$^+$); HRMS (ESI$^+$) $m/z$ calcd for $C_{36}H_{70}N_5O_8Si_2$ 756.4757 (M + H$^+$), found 756.4766 (M + H$^+$); IR (ATR) $\nu$ 1687, 1253, 1153, 1118, 1066, 867, 836, 812, 775; UV (MeOH) $\lambda_{max}$ (log $\varepsilon$) 259 (4.25); mp 68 °C; $[\alpha]^{20}_D$ +25.9 (*c* 1.0, MeOH).

**Fully Deprotected (6′*S*)-Configured Muraymycin Analogue (7c·2TFA).** A solution of N-unprotected (6′*S*)-configured muraymycin analogue **7b** (33 mg, 44 μmol) in 80% aqueous TFA (6.6 mL) was stirred at rt for 24 h. The reaction mixture was diluted with water (20 mL), and the solvent was evaporated under reduced pressure. The resultant crude product was purified by preparative HPLC to give **7c·2TFA** as a colorless solid (24 mg, 80%): $^1$H NMR (600 MHz, $D_2O$) $\delta$ 1.06 (d, $J$ = 6.7 Hz, 3H, Leu-5-H$_a$), 1.07 (d, $J$ = 6.8 Hz, 3H, Leu-5-H$_b$), 1.75 (dqq, $J$ = 7.1, 6.8, 6.7 Hz, 1H, Leu-4-H), 1.83 (dd, $J$ = 7.4, 7.1 Hz, 2H, Leu-3-H), 2.06 (dddd, $J$ = 7.6, 7.4, 7.0, 7.0 Hz, 2H, propylene-2-H), 2.42 (ddd, $J$ = 15.0, 10.4, 6.2 Hz, 1H, 5′-H$_a$), 2.59 (ddd, $J$ = 15.0, 6.6, 2.8 Hz, 1H, 5′-H$_b$), 3.22 (ddd, $J$ = 12.6, 7.4, 7.4 Hz, 1H, propylene-1-H$_a$), 3.26 (ddd, $J$ = 12.6, 7.6, 7.6 Hz, 1H, propylene-1-H$_b$), 3.42 (ddd, $J$ = 14.1, 7.0, 7.0 Hz, 1H, propylene-3-H$_a$), 3.48 (ddd, $J$ = 14.1, 7.0, 7.0 Hz, 1H, propylene-3-H$_b$), 4.07 (dd, $J$ = 7.4, 7.4 Hz, 1H, Leu-2-H), 4.11 (dd, $J$ = 6.6, 6.1 Hz, 1H, 6′-H), 4.21 (dd, $J$ = 6.4, 5.9 Hz, 1H, 3′-H), 4.28 (ddd, $J$ = 10.4, 6.4, 2.8 Hz, 1H, 4′-H), 4.55


dx.doi.org/10.1021/jo201935w | J. Org. Chem. 2011, 76, 10083−10098

(dd, $J$ = 5.9, 3.8 Hz, 1H, 2′-H), 5.87 (d, $J$ = 3.8 Hz, 1H, 1′-H), 6.01 (d, $J$ = 8.1 Hz, 1H, 5-H), 7.76 (d, $J$ = 8.1 Hz, 1H, 6-H); $^{13}$C NMR (126 MHz, $D_2O$) $\delta$ 23.7, 24.2, 26.6, 28.1, 35.3, 38.9, 42.5, 47.0, 54.6, 61.9, 75.2, 75.5, 82.4, 94.5, 104.9, 119.0 (q, $^1J_{CF}$ = 291.6 Hz, $F_3\underline{C}COO$), 145.4, 154.0, 165.5 (q, $^2J_{CF}$ = 35.2 Hz, $F_3C\underline{C}OO$), 168.7, 173.3, 174.1; $^{19}$F NMR (283 MHz, $D_2O$) $\delta$ −75.4; MS (ESI$^+$) $m/z$ 472.3 (M − (2 TFA)+H$^+$); HRMS (ESI$^+$) $m/z$ calcd for $C_{20}H_{34}N_5O_8$ 472.2402 (M − (2 TFA) + H$^+$), found 472.2405 (M − (2 TFA) + H$^+$); IR (ATR) $\nu$ 1665, 1184, 1130, 1060, 835, 798, 720, 551, 519; UV ($H_2O$) $\lambda_{max}$ (log $\varepsilon$) 260 (3.94); mp 69 °C; analytical HPLC $t_R$ 6.5 min (method I); preparative HPLC $t_R$ 15.3 min; $[\alpha]^{20}_D$ +29.2 ($c$ 0.77, $H_2O$).

**N-Unprotected (6′*R*)-Configured Muraymycin Analogue (8b).** General Procedure D with *N*-Cbz-protected muraymycin analogue (*R*)-**34** (135 mg, 0.152 mmol), 1,4-cyclohexadiene (144 μL, 1.52 mmol), 10% Pd/C (25 mg, 23 μmol), and MeOH (4.5 mL) to give **8b** as a colorless solid (114 mg, 99%): $^1$H NMR (600 MHz, $CD_3OD$) $\delta$ 0.08 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.12 (s, 3H, $SiCH_3$), 0.14 (s, 3H, $SiCH_3$), 0.90 (s, 9H, $SiC(CH_3)_3$), 0.92 (d, $J$ = 6.6 Hz, 3H, Leu-5-H$_a$), 0.94 (s, 9H, $SiC(CH_3)_3$), 0.95 (d, $J$ = 6.2 Hz, 3H, Leu-5-H$_b$), 1.37 (ddd, $J$ = 13.5, 8.0, 6.6 Hz, 1H, Leu-3-H$_a$), 1.47 (s, 9H, $OC(CH_3)_3$), 1.52 (ddd, $J$ = 13.5, 7.6, 6.4 Hz, 1H, Leu-3-H$_b$), 1.63−1.73 (m, 3H, propylene-2-H, Leu-4-H), 1.93−2.01 (m, 2H, 5′-H), 2.48 (ddd, $J$ = 11.6, 7.6, 6.5 Hz, 1H, propylene-1-H$_a$), 2.66 (ddd, $J$ = 11.6, 7.3, 6.7 Hz, 1H, propylene-1-H$_b$), 3.20−3.31 (m, 4H, 6′-H, propylene-3-H, Leu-2-H), 3.93 (dd, $J$ = 4.5, 4.3 Hz, 1H, 3′-H), 4.16 (ddd, $J$ = 9.8, 4.3, 4.1 Hz, 1H, 4′-H), 4.31 (dd, $J$ = 4.9, 4.5 Hz, 1H, 2′-H), 5.74 (d, $J$ = 8.1 Hz, 1H, 5-H), 5.82 (d, $J$ = 4.9 Hz, 1H, 1′-H), 7.65 (d, $J$ = 8.1 Hz, 1H, 6-H); $^{13}$C NMR (126 MHz, $CD_3OD$) $\delta$ −4.4, −4.4, −4.4, −4.0, 18.9, 19.0, 22.6, 23.4, 25.9, 26.4, 26.5, 28.4, 30.6, 37.7, 38.2, 45.7, 46.2, 54.7, 61.1, 75.8, 76.7, 82.7, 83.0, 91.4, 103.0, 142.7, 152.3, 166.1, 175.3, 178.1; MS (ESI$^+$) $m/z$ 756.5 (M + H$^+$); HRMS (ESI$^+$) $m/z$ calcd for $C_{36}H_{70}N_5O_8Si_2$ 756.4757 (M + H$^+$), found 756.4756 (M + H$^+$); IR (ATR) $\nu$ 1692, 1252, 1151, 1085, 1063, 866, 835, 812, 775; UV (MeOH) $\lambda_{max}$ (log $\varepsilon$) 260 (4.25); mp 72 °C; $[\alpha]^{20}_D$ +27.1 ($c$ 1.0, MeOH).

**Fully Deprotected (6′*R*)-Configured Muraymycin Analogue (8c·2TFA).** A solution of N-unprotected (6′*R*)-configured muraymycin analogue **8b** (36 mg, 48 μmol) in 80% aqueous TFA (7.2 mL) was stirred at rt for 24 h. The reaction mixture was diluted with water (20 mL) and the solvent was evaporated under reduced pressure. The resultant crude product was purified by preparative HPLC to give **8c·2TFA** as a colorless solid (28 mg, 83%): $^1$H NMR (600 MHz, $D_2O$) $\delta$ 1.06 (d, $J$ = 6.6 Hz, 3H, Leu-5-H$_a$), 1.08 (d, $J$ = 6.7 Hz, 3H, Leu-5-H$_b$), 1.76 (dqq, $J$ = 7.2, 6.7, 6.6 Hz, 1H, Leu-4-H), 1.84 (dd, $J$ = 7.4, 7.2 Hz, 2H, Leu-3-H), 2.03 (dddd, $J$ = 8.3, 7.5, 7.0, 6.8 Hz, 2H, propylene-2-H), 2.48 (ddd, $J$ = 15.6, 11.1, 4.7 Hz, 1H, 5′-H$_a$), 2.60 (ddd, $J$ = 15.6, 5.6, 2.8 Hz, 1H, 5′-H$_b$), 3.19 (ddd, $J$ = 12.6, 8.3, 7.5 Hz, 1H, propylene-1-H$_a$), 3.24 (ddd, $J$ = 12.6, 8.3, 7.5 Hz, 1H, propylene-1-H$_b$), 3.39 (ddd, $J$ = 14.0, 7.0, 7.0 Hz, 1H, propylene-3-H$_a$), 3.45 (ddd, $J$ = 14.0, 6.8, 6.8 Hz, 1H, propylene-3-H$_b$), 4.08 (dd, $J$ = 7.4, 7.4 Hz, 1H, Leu-2-H), 4.12 (dd, $J$ = 5.6, 4.7 Hz, 1H, 6′-H), 4.16 (ddd, $J$ = 11.1, 6.6, 2.8 Hz, 1H, 4′-H), 4.24 (dd, $J$ = 6.6, 6.1 Hz, 1H, 3′-H), 4.56 (dd, $J$ = 6.1, 3.7 Hz, 1H, 2′-H), 5.85 (d, $J$ = 3.7 Hz, 1H, 1′-H), 6.01 (d, $J$ = 8.0 Hz, 1H, 5-H), 7.78 (d, $J$ = 8.0 Hz, 1H, 6-H); $^{13}$C NMR (126 MHz, $D_2O$) $\delta$ 23.7, 24.2, 26.5, 28.1, 34.5, 39.0, 42.5, 47.3, 54.6, 62.4, 75.0, 75.4, 82.1, 94.9, 105.0, 119.0 (q, $^1J_{CF}$ = 292.1 Hz, $F_3\underline{C}COO$), 145.8, 154.1, 165.46 (q, $^2J_{CF}$ = 35.2 Hz, $F_3C\underline{C}OO$), 168.7, 173.3, 174.1; $^{19}$F NMR (283 MHz, $D_2O$) $\delta$ −75.4; MS (ESI$^+$) $m/z$ 472.3 (M − (2 TFA)+H$^+$); HRMS (ESI$^+$) $m/z$ calcd for $C_{20}H_{34}N_5O_8$ 472.2402 (M − (2 TFA)+H$^+$), found 472.2396 (M − (2 TFA)+H$^+$); IR (ATR) $\nu$ 1665, 1182, 1130, 1054, 834, 798, 767, 720, 551; UV ($H_2O$) $\lambda_{max}$ (log $\varepsilon$) 261 (3.77); mp 68 °C; analytical HPLC $t_R$ 6.2 min (method I); preparative HPLC $t_R$ 14.9 min; $[\alpha]^{20}_D$ +22.3 ($c$ 0.61, $H_2O$).

**2′,3′,5′-Tris(*O*-*tert*-butyldimethylsilyl)-3-(*N*-(*p*-methoxybenzyl))uridine (10).** To a suspension of NaH (60% dispersion in mineral oil, 97 mg, 2.4 mmol) in DMF (3 mL) was slowly added a solution of trisilylated uridine **9**[19] (950 mg, 1.62 mmol) in DMF (5 mL) at 0 °C and the mixture stirred at 0 °C for 15 min. *p*-Methoxybenzyl chloride (0.44 mL, 3.2 mmol) was added dropwise, and the reaction mixture was stirred at rt for 11 h. Water (5 mL) and EtOAc (150 mL) were added. The organic layer was washed with satd $NaHCO_3$ solution (3 × 50 mL), dried over $Na_2SO_4$, and evaporated under reduced pressure. The resultant crude product was purified by column chromatography (4:1 petroleum ether−$Et_2O$) to give **10** as a colorless oil (972 mg, 85%): $^1$H NMR (300 MHz, $C_6D_6$) $\delta$ −0.03 (s, 3H, $SiCH_3$), −0.03 (s, 3H, $SiCH_3$), 0.01 (s, 3H, $SiCH_3$), 0.04 (s, 3H, $SiCH_3$), 0.18 (s, 3H, $SiCH_3$), 0.24 (s, 3H, $SiCH_3$), 0.86 (s, 9H, $SiC(CH_3)_3$), 0.93 (s, 9H, $SiC(CH_3)_3$), 1.01 (s, 9H, $SiC(CH_3)_3$), 3.25 (s, 3H, $OCH_3$), 3.52 (dd, $J$ = 11.8, 1.6 Hz, 1H, 5′-H$_a$), 3.76 (dd, $J$ = 11.8, 2.1 Hz, 1H, 5′-H$_b$), 4.08 (ddd, $J$ = 6.0, 2.1, 1.6 Hz, 1H, 4′-H), 4.13 (dd, $J$ = 6.0, 3.9 Hz, 1H, 3′-H), 4.22 (dd, $J$ = 3.9, 3.2 Hz, 1H, 2′-H), 5.04 (d, $J$ = 13.4 Hz, 1H, PMB-$CH_2$-H$_a$), 5.15 (d, $J$ = 13.4 Hz, 1H, PMB-$CH_2$-H$_b$), 5.77 (d, $J$ = 8.1 Hz, 1H, 5-H), 6.07 (d, $J$ = 3.2 Hz, 1H, 1′-H), 6.72 (d, $J$ = 8.8 Hz, 2H, PMB-3-H, PMB-5-H), 7.70 (d, $J$ = 8.8 Hz, 2H, PMB-2-H, PMB-6-H), 7.88 (d, $J$ = 8.1 Hz, 1H, 6-H); $^{13}$C NMR (126 MHz, $C_6D_6$) $\delta$ −5.5, −5.2, −4.7, −4.5, −4.0, −3.9, 18.4, 18.4, 18.7, 26.2, 26.2, 26.3, 43.7, 54.7, 61.8, 70.9, 76.8, 84.2, 90.3, 101.8, 114.0, 129.9, 131.5, 137.8, 151.5, 159.6, 162.1; MS (ESI$^+$) $m/z$ 729.4 (M + Na$^+$); HRMS (ESI$^+$) $m/z$ calcd for $C_{35}H_{62}N_2NaO_7Si_3$ 729.3757 (M + Na$^+$), found 729.3776 (M + Na$^+$); IR (ATR) $\nu$ 1665, 1247, 1132, 1105, 1068, 831, 808, 773, 748; UV (MeCN) $\lambda_{max}$ (log $\varepsilon$) 223 (4.14), 263 (3.97); TLC $R_f$ 0.38 (7:3 petroleum ether−$Et_2O$); $[\alpha]^{20}_D$ +26.5 ($c$ 1.1, $CHCl_3$).

**2′,3′,5′-Tris(*O*-*tert*-butyldimethylsilyl)-3-(*N*-benzyloxymethyl)uridine (11).** To a suspension of NaH (60% dispersion in mineral oil, 960 mg, 24.0 mmol) in DMF (60 mL) was slowly added a solution of trisilylated uridine **9**[19] (9.42 g, 16.0 mmol) in DMF (30 mL) at 0 °C. Benzyloxymethyl chloride (2.67 mL, 3.01 g, 19.2 mmol) was added dropwise, and the reaction mixture was stirred at 0 °C for 5 h. $Et_2O$ (600 mL) and satd $NaHCO_3$ solution (100 mL) were added. The organic layer was washed with water (4 × 250 mL), satd $NaHCO_3$ solution (1 × 250 mL), and brine (1 × 250 mL), dried over $Na_2SO_4$, and evaporated under reduced pressure. The resultant crude product was purified by column chromatography (19:1 petroleum ether−EtOAc) to give **11** as a colorless oil (9.84 g, 87%): $^1$H NMR (300 MHz, $C_6D_6$) $\delta$ −0.03 (s, 3H, $SiCH_3$), −0.02 (s, 3H, $SiCH_3$), 0.03 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$), 0.21 (s, 3H, $SiCH_3$), 0.33 (s, 3H, $SiCH_3$), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.94 (s, 9H, $SiC(CH_3)_3$), 1.04 (s, 9H, $SiC(CH_3)_3$), 3.54 (dd, $J$ = 11.8, 1.3 Hz, 1H, 5′-H$_a$), 3.79 (dd, $J$ = 11.8, 2.2 Hz, 1H, 5′-H$_b$), 4.08−4.17 (m, 2H, 3′-H, 4′-H), 4.25 (dd, $J$ = 3.6, 2.9 Hz, 1H, 2′-H), 4.67 (d, $J$ = 13.2 Hz, 1H, BOM-$CH_2$-H$_a$), 4.72 (d, $J$ = 13.2 Hz, 1H, BOM-$CH_2$-H$_b$), 5.45 (d, $J$ = 16.4 Hz, 1H, $NCH_2O$-H$_a$), 5.48 (d, $J$ = 16.4 Hz, 1H, $NCH_2O$-H$_b$), 5.73 (d, $J$ = 8.2 Hz, 1H, 5-H), 5.99 (d, $J$ = 2.9 Hz, 1H, 1′-H), 7.03−7.15 (m, 3 H, BOM-3-H, BOM-4-H, BOM-5-H), 7.36 (d, $J$ = 6.8 Hz, 2H, BOM-2-H, BOM-6-H), 7.92 (d, $J$ = 8.2 Hz, 1H, 6-H); $^{13}$C NMR (76 MHz, $C_6D_6$) $\delta$ −5.7, −5.4, −4.9, −4.8, −4.0, −4.0, 18.2, 18.3, 18.5, 26.0, 26.1, 26.1, 61.4, 70.4, 70.5, 72.3, 76.7, 83.9, 90.6, 101.5, 127.5, 127.9, 128.2, 138.6, 139.0, 151.2, 162.2; MS (ESI$^+$) $m/z$ 729.4 (M + Na$^+$); HRMS (ESI$^+$) $m/z$ calcd for $C_{35}H_{62}N_2NaO_7Si_3$ 729.3757 (M + Na$^+$), found 729.3755 (M + Na$^+$); IR (ATR) $\nu$ 1667, 1253, 1129, 1100, 1067, 832, 808, 775, 734; UV (MeCN) $\lambda_{max}$ (log $\varepsilon$) 264 (3.97); TLC $R_f$ 0.48 (4:1 petroleum ether−EtOAc); $[\alpha]^{20}_D$ +26.4 ($c$ 0.9, $CHCl_3$).

**3′,5′-Bis(*O*-*tert*-butyldimethylsilyl)-3-(*N*-(*p*-methoxybenzyl))-uridine (12).** To a solution of uridine derivative **10** (9.63 g, 13.6 mmol) in THF (100 mL) was added dropwise a 1:1 TFA−water mixture (50 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 8 h and adjusted to pH 9 by the addition of satd $NaHCO_3$ solution (400 mL) and solid $Na_2CO_3$, and EtOAc (600 mL) was added. The organic layer was washed with satd $NaHCO_3$ solution (2 × 200 mL), and the combined aqueous solutions were extracted with EtOAc (1 × 100 mL). The combined organics were dried over $Na_2SO_4$ and evaporated under reduced pressure. The resultant crude product was purified by column chromatography (9:1 $CH_2Cl_2$−EtOAc) to give **12** as a colorless solid (6.36 g, 79%): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ −0.02 (s, 3H, $SiCH_3$), 0.00 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$), 0.81 (s, 9H, $SiC(CH_3)_3$), 0.90 (s, 9H, $SiC(CH_3)_3$), 3.40 (dd, $J$ = 8.2, 2.7 Hz, 1H, OH), 3.70 (ddd, $J$ = 12.3, 8.2, 2.4 Hz, 1H, 5′-H$_a$), 3.77 (s, 3H, $OCH_3$), 3.91 (ddd, $J$ = 12.3, 2.7, 2.4 Hz, 1H,


dx.doi.org/10.1021/jo201935w | J. Org. Chem. 2011, 76, 10083−10098

5′-$H_b$), 4.06 (ddd, $J$ = 2.4, 2.4, 2.4 Hz, 1H, 4′-H), 4.16 (dd, $J$ = 4.7, 2.4 Hz, 1H, 3′-H), 4.57 (dd, $J$ = 6.1, 4.7 Hz, 1H, 2′-H), 4.99 (d, $J$ = 13.5 Hz, 1H, PMB-$CH_2$-$H_a$), 5.05 (d, $J$ = 13.5 Hz, 1H, PMB-$CH_2$-$H_b$), 5.45 (d, $J$ = 6.1 Hz, 1H, 1′-H), 5.76 (d, $J$ = 8.1 Hz, 1H, 5-H), 6.81 (d, $J$ = 8.7 Hz, 2H, PMB-3-H, PMB-5-H), 7.44 (d, $J$ = 8.7 Hz, 2H, PMB-2-H, PMB-6-H), 7.46 (d, $J$ = 8.1 Hz, 1H, 6-H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ −5.1, −4.8, −4.7, −4.5, 17.9, 18.0, 25.7, 25.8, 43.6, 55.2, 62.0, 72.2, 73.1, 86.7, 94.8, 102.0, 113.6, 128.8, 131.0, 141.1, 151.0, 159.1, 162.5; MS (ESI$^+$) $m/z$ 615.7 (M + $Na^+$); HRMS (ESI$^+$) $m/z$ calcd for $C_{29}H_{49}N_2O_7Si_2$ 593.3073 (M + $H^+$), found 593.3073 (M + $H^+$); IR (KBr) $\nu$ 2931, 1666, 1514, 1461, 1250, 1097, 837, 776, 582; UV (MeCN) $\lambda_{max}$ (log $\varepsilon$) 194 (4.72), 222 (4.17), 263 (4.00); mp 69 °C; TLC $R_f$ 0.57 (1:1 $CH_2Cl_2$−EtOAc); $[\alpha]^{20}_D$ +32.6 ($c$ 1.2, $CHCl_3$).

**3′,5′-Bis(*O*-*tert*-butyldimethylsilyl)-3-(*N*-benzyloxymethyl)-uridine (13).** To a solution of uridine derivative **11** (3.53 g, 4.99 mmol) in THF (50 mL) was added dropwise a 1:1 TFA−water mixture (25 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 7 h and then adjusted to pH 9 by the addition of satd $NaHCO_3$ solution (400 mL) and solid $Na_2CO_3$, and EtOAc (600 mL) was added. The organic layer was washed with satd $NaHCO_3$ solution (1 × 200 mL) and brine (1 × 200 mL), dried over $Na_2SO_4$, and evaporated under reduced pressure. The resultant crude product was purified by column chromatography (9:1 $CH_2Cl_2$−EtOAc) to give **13** as a colorless solid (2.13 g, 72%): $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ −0.02 (s, 3H, $SiCH_3$), 0.03 (s, 3H, $SiCH_3$), 0.09 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.82 (s, 9H, $SiC(CH_3)_3$), 0.88 (s, 9H, $SiC(CH_3)_3$), 3.58 (ddd, $J$ = 12.0, 4.4, 3.0 Hz, 1H, 5′-$H_a$), 3.70 (ddd, $J$ = 12.0, 4.6, 3.4 Hz, 1H, 5′-$H_b$), 3.92 (ddd, $J$ = 3.4, 3.2, 3.0 Hz, 1H, 4′-H), 4.15 (dd, $J$ = 4.3, 3.2 Hz, 1H, 3′-H), 4.27 (dd, $J$ = 5.4, 4.3 Hz, 1H, 2′-H), 4.58 (s, 2H, BOM-$CH_2$), 5.24 (dd, $J$ = 4.6, 4.4 Hz, 1H, OH), 5.33 (s, 2H, $NCH_2O$), 5.85 (d, $J$ = 8.3 Hz, 1H, 5-H), 5.85 (d, $J$ = 5.4 Hz, 1H, 1′-H), 7.22−7.36 (m, 5H, Aryl-H), 8.03 (d, $J$ = 8.3 Hz, 1H, 6-H); $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ −5.0, −4.9, −4.9, −4.6, 17.5, 17.7, 25.5, 25.6, 60.1, 69.8, 70.9, 71.5, 74.6, 85.3, 87.8, 101.1, 127.0, 127.2, 127.9, 137.8, 139.5, 150.7, 161.6; MS (ESI$^+$) $m/z$ 615.3 (M + $Na^+$); HRMS (ESI$^+$) $m/z$ calcd for $C_{29}H_{48}N_2NaO_7Si_2$ 615.2892 (M + $Na^+$), found 615.2891 (M + $Na^+$); IR (ATR) $\nu$ 1715, 1666, 1151, 1100, 1084, 1054, 876, 830, 771; UV (MeCN) $\lambda_{max}$ (log $\varepsilon$) 206 (4.22), 264 (3.98); mp 105 °C; TLC $R_f$ 0.40 (4:1 $CH_2Cl_2$-EtOAc); $[\alpha]^{20}_D$ −15.3 ($c$ 1.0, $CHCl_3$).

**3′,5′-Bis(*O*-*tert*-butyldimethylsilyl)-3-(*N*-(*p*-methoxybenzyl))-uridine-5′-aldehyde (14).** General procedure A with uridine derivative **12** (100 mg, 0.170 mmol), IBX (118 mg, 0.420 mmol), and MeCN (3 mL) to give **14** as a colorless solid (98 mg, 98%): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ −0.19 (s, 3H, $SiCH_3$), −0.06 (s, 3H, $SiCH_3$), 0.09 (s, 6H, $SiCH_3$), 0.78 (s, 9H, $SiC(CH_3)_3$), 0.90 (s, 9H, $SiC(CH_3)_3$), 3.75 (s, 3H, $OCH_3$), 4.20−4.49 (m, 3H, 2′-H, 3′-H, 4′-H), 4.99−5.03 (m, 2H, PMB-$CH_2$), 5.75 (d, $J$ = 6.0 Hz, 1H, 1′-H), 5.81 (d, $J$ = 8.1 Hz, 1H, 5-H), 6.79 (d, $J$ = 8.8 Hz, 2H, PMB-3-H, PMB-5-H), 7.41 (d, $J$ = 8.8 Hz, 2H, PMB-2-H, PMB-6-H), 7.52 (d, $J$ = 8.1 Hz, 1H, 6-H), 9.79 (s, 1H, 5′-H); MS (ESI$^+$) $m/z$ 645.3 (M + MeOH + $Na^+$); HRMS (ESI$^+$) $m/z$ calcd for $C_{30}H_{50}N_2NaO_8Si_2$ 645.2998 (M + MeOH + $Na^+$), found 645.3004 (M + MeOH + $Na^+$).

**3′,5′-Bis(*O*-*tert*-butyldimethylsilyl)-3-(*N*-benzyloxymethyl)-uridine-5′-aldehyde (15).** General procedure A with uridine derivative **13** (4.11 g, 6.93 mmol), IBX (4.85 g, 17.3 mmol), and MeCN (60 mL) to give **15** as a colorless solid (4.01 g, 98%): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ −0.03 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.84 (s, 9H, $SiC(CH_3)_3$), 0.91 (s, 9H, $SiC(CH_3)_3$), 4.21 (dd, $J$ = 4.1, 3.3 Hz, 1H, 3′-H), 4.32 (dd, $J$ = 5.6, 4.1 Hz, 1H, 2′-H), 4.52 (d, $J$ = 3.3 Hz, 1H, 4′-H), 4.66 (s, 2H, BOM-$CH_2$), 5.43 (d, $J$ = 14.0 Hz, 1H, $NCH_2O$-$H_a$), 5.48 (d, $J$ = 14.0 Hz, 1H, $NCH_2O$-$H_b$), 5.72 (d, $J$ = 5.6 Hz, 1H, 1′-H), 5.81 (d, $J$ = 8.1 Hz, 1H, 5-H), 7.25−7.35 (m, 5H, Aryl-H), 7.60 (d, $J$ = 8.1 Hz, 1H, 6-H), 9.82 (s, 1H, 5′-H); MS (ESI$^+$) $m/z$ 613.3 (M + $Na^+$); HRMS (ESI$^+$) $m/z$ calcd for $C_{29}H_{46}N_2NaO_7Si_2$ 613.2736 (M + $Na^+$), found 613.2729 (M + $Na^+$).

**3-(*N*-PMB)-Protected Didehydro Nucleosyl Amino Acid (17).** General procedure B with aldehyde **14** (1.99 g, 3.37 mmol), phosphonate **16**[22] (1.21 g, 3.24 mmol), KHMDS (0.5 M in toluene, 6.48 mL, 3.24 mmol), and THF (12 mL (**14**), 25 mL (**16**), 20 mL (KHMDS)). Purification by column chromatography (4:1 petroleum ether−EtOAc) gave (*Z*)-**17** as a colorless solid (1.82 g, 67%) and (*E*)-**17** as a colorless solid (159 mg, 6%). (*Z*)-**17**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ −0.01 (s, 3H, $SiCH_3$), 0.01 (s, 3H, $SiCH_3$), 0.04 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$), 0.83 (s, 9H, $SiC(CH_3)_3$), 0.86 (s, 9H, $SiC(CH_3)_3$), 1.46 (s, 9H, $OC(CH_3)_3$), 3.75 (s, 3H, $OCH_3$), 3.91 (dd, $J$ = 5.5, 4.1 Hz, 1H, 3′-H), 4.28 (dd, $J$ = 4.1, 3.9 Hz, 1H, 2′-H), 4.82 (dd, $J$ = 7.4, 5.5 Hz, 1H, 4′-H), 4.97 (d, $J$ = 13.5 Hz, 1H, PMB-$CH_2$-$H_a$), 5.04 (d, $J$ = 13.5 Hz, 1H, PMB-$CH_2$-$H_b$), 5.11 (s, 2H, Cbz-$CH_2$), 5.62 (d, $J$ = 3.9 Hz, 1H, 1′-H), 5.74 (d, $J$ = 8.1 Hz, 1H, 5-H), 6.28 (d, $J$ = 7.4 Hz, 1H, 5′-H), 6.70 (s, 1H, NH), 6.79 (d, $J$ = 8.8 Hz, 2H, PMB-3-H, PMB-5-H), 7.15 (d, $J$ = 8.1 Hz, 1H, 6-H), 7.28−7.35 (m, 5H, Cbz-aryl-H), 7.41 (d, $J$ = 8.8 Hz, 2H, PMB-2-H, PMB-6-H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ −4.7, −4.5, −4.3, 18.1, 18.2, 25.8, 25.9, 27.9, 43.5, 55.3, 67.5, 74.6, 76.2, 79.6, 82.6, 92.9, 102.1, 113.6, 124.8, 128.1, 128.2, 128.4, 128.9, 130.7, 130.8, 135.7, 138.2, 150.5, 153.5, 159.0, 162.3, 162.7; MS (ESI$^+$) $m/z$ 860.4 (M + $Na^+$); HRMS (ESI$^+$) $m/z$ calcd for $C_{43}H_{63}N_3NaO_{10}Si_2$ 860.3944 (M + $Na^+$), found 860.3952 (M + $Na^+$); IR (KBr) $\nu$ 2957, 1715, 1666, 1514, 1456, 1251, 1157, 1055, 839; UV (MeCN) $\lambda_{max}$ (log $\varepsilon$) 225 (4.31), 257 (4.14); mp 72 °C; TLC $R_f$ 0.42 (7:3 petroleum ether−EtOAc); $[\alpha]^{20}_D$ +39.1 ($c$ 1.1, $CHCl_3$). (*E*)-**17**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ −0.25 (s, 3H, $SiCH_3$), −0.05 (s, 3H, $SiCH_3$), 0.04 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.77 (s, 9H, $SiC(CH_3)_3$), 0.93 (s, 9H, $SiC(CH_3)_3$), 1.46 (s, 9H, $OC(CH_3)_3$), 3.75 (s, 3H, $OCH_3$), 4.44 (dd, $J$ = 3.2, 2.5 Hz, 1H, 3′-H), 4.51 (dd, $J$ = 6.9, 3.2 Hz, 1H, 2′-H), 4.98 (d, $J$ = 13.9 Hz, 1H, PMB-$CH_2$-$H_a$), 4.99 (dd, $J$ = 8.6, 2.5 Hz, 1H, 4′-H), 5.04 (d, $J$ = 13.9 Hz, 1H, PMB-$CH_2$-$H_b$), 5.09 (d, $J$ = 12.2 Hz, 1H, Cbz-$CH_2$-$H_a$), 5.18 (d, $J$ = 12.2 Hz, 1H, Cbz-$CH_2$-$H_b$), 5.76 (d, $J$ = 6.9 Hz, 1H, 1′-H), 5.77 (d, $J$ = 8.0 Hz, 1H, 5-H), 6.43 (d, $J$ = 8.6 Hz, 1H, 5′-H), 6.68 (s, 1H, NH), 6.78 (d, $J$ = 8.7 Hz, 2H, PMB-3-H, PMB-5-H), 7.09 (d, $J$ = 8.0 Hz, 1H, 6-H), 7.30−7.36 (m, 5H, Cbz-aryl-H), 7.37 (d, $J$ = 8.7 Hz, 2H, PMB-2-H, PMB-6-H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ −5.1, −4.2, 18.0, 18.2, 25.9, 26.0, 28.0, 43.6, 55.3, 67.5, 74.5, 75.4, 79.1, 82.8, 92.6, 102.2, 113.6, 126.0, 127.9, 128.0, 128.2, 128.5, 128.8, 130.4, 135.8, 139.6, 150.6, 154.1, 158.9, 162.5, 163.0; MS (ESI$^+$) $m/z$ 860.5 (M + $Na^+$); HRMS (ESI$^+$) $m/z$ calcd for $C_{43}H_{63}N_3NaO_{10}Si_2$ 860.3944 (M + $Na^+$), found 860.3948 (M + $Na^+$); IR (KBr) $\nu$ 2959, 2935, 1673, 1391, 1339, 1251, 1161, 1051, 839; UV (MeCN) $\lambda_{max}$ (log $\varepsilon$) 224 (4.28), 257 (4.09); mp 69 °C; TLC $R_f$ 0.35 (7:3 petroleum ether−EtOAc); $[\alpha]^{20}_D$ −21.9 ($c$ 1.1, $CHCl_3$).

**3-(*N*-BOM)-Protected Didehydro Nucleosyl Amino Acid (18).** *Synthesis of (Z)-18 from 15.* General procedure B with aldehyde **15** (500 mg, 0.846 mmol), phosphonate **16**[22] (265 mg, 0.710 mmol), KHMDS (0.5 M in toluene, 1.42 mL, 0.710 mmol), and THF (4.2 mL (**15**), 5.0 mL (**16**), 6.7 mL (KHMDS)). Purification by column chromatography (4:1 petroleum ether−EtOAc) gave (*Z*)-**18** as a colorless solid (483 mg, 82%) while (*E*)-**18** could not be isolated. (*Z*)-**18**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.06 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$), 0.11 (s, 3H, $SiCH_3$), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.88 (s, 9H, $SiC(CH_3)_3$), 1.46 (s, 9H, $OC(CH_3)_3$), 3.92 (dd, $J$ = 6.5, 3.8 Hz, 1H, 3′-H), 4.28 (dd, $J$ = 3.8, 3.2 Hz, 1H, 2′-H), 4.67 (s, 2H, BOM-$CH_2$), 4.86 (dd, $J$ = 7.6, 6.5 Hz, 1H, 4′-H), 5.12 (s, 2H, Cbz-$CH_2$), 5.42 (d, $J$ = 12.2 Hz, 1H, $NCH_2O$-$H_a$), 5.46 (d, $J$ = 12.2 Hz, 1H, $NCH_2O$-$H_b$), 5.58 (d, $J$ = 3.2 Hz, 1H, 1′-H), 5.74 (d, $J$ = 8.2 Hz, 1H, 5-H), 6.24 (d, $J$ = 7.6 Hz, 1H, 5′-H), 6.74 (s, 1H, NH), 7.20 (d, $J$ = 8.2 Hz, 1H, 6-H), 7.26−7.37 (m, 10H, BOM-aryl-H, Cbz-aryl-H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ −4.7, −4.7, −4.3, −4.3, 18.1, 18.2, 25.9, 25.9, 27.9, 67.5, 70.2, 72.2, 74.7, 76.1, 79.2, 82.6, 93.2, 101.9, 124.4, 127.6, 128.1, 128.2, 128.2, 128.4, 131.2, 135.7, 137.8, 138.8, 150.5, 153.4, 162.4, 162.6; MS (ESI$^+$) $m/z$ 860.4 (M + $Na^+$); HRMS (ESI$^+$) $m/z$ calcd for $C_{43}H_{63}N_3NaO_{10}Si_2$ 860.3944 (M + $Na^+$), found 860.3950 (M + $Na^+$); IR (ATR) $\nu$ 1663, 1254, 1221, 1151, 1054, 836, 775, 734, 696; UV (MeCN) $\lambda_{max}$ (log $\varepsilon$) 205 (4.46), 258 (4.12); mp 43 °C; TLC $R_f$ 0.52 (7:3 petroleum ether−EtOAc); $[\alpha]^{20}_D$ +50.1 ($c$ 1.0, $CHCl_3$).

*Synthesis of (Z)-18 from (Z)-28.* General procedure E with didehydro nucleosyl amino acid (*Z*)-**28** (20 mg, 28 μmol), benzyloxymethyl chloride (0.42 M solution in $CH_2Cl_2$, 0.10 mL, 42 μmol), TBAI (0.5 mg, 1 μmol), $Na_2CO_3$ (0.82 M solution in water,

0.13 mL, 0.11 mmol), $CH_2Cl_2$ (1.0 mL), and a reaction time of 18 h. Purification by column chromatography (17:3 petroleum ether−EtOAc) gave (*Z*)-**28** as a colorless solid (12 mg, 51%). Analytical data were identical to those given above.

*Synthesis of (E)-**18**.* To a solution of didehydro nucleosyl amino acid (*Z*)-**18** (100 mg, 0.120 mmol) in THF (5 mL) was added dropwise KHMDS (0.5 M in toluene, 72 μL, 36 μmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 2 h. Water (2 mL) and EtOAc (100 mL) were added. The organic layer was washed with half-saturated NaCl solution (1 × 150 mL), dried over $Na_2SO_4$, and evaporated under reduced pressure. The resultant crude product was purified by column chromatography (4:1 petroleum ether−EtOAc) to give (*E*)-**18** as a colorless solid (23 mg, 23%): $^1$H NMR (600 MHz, $CDCl_3$) δ −0.08 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$), 0.11 (s, 3H, $SiCH_3$), 0.84 (s, 9H, $SiC(CH_3)_3$), 0.93 (s, 9H, $SiC(CH_3)_3$), 1.46 (s, 9H, $OC(CH_3)_3$), 4.45−4.50 (m, 1H, 3′-H), 4.62 (d, *J* = 12.1 Hz, 1H, BOM-$CH_2$-$H_a$), 4.65 (d, *J* = 12.1 Hz, 1H, BOM-$CH_2$-$H_b$), 4.68 (dd, *J* = 6.6, 3.5 Hz, 1H, 2′-H), 5.06 (dd, *J* = 8.8, 2.7 Hz, 1H, 4′-H), 5.11 (d, *J* = 12.2 Hz, 1H, Cbz-$CH_2$-$H_a$), 5.16 (d, *J* = 12.2 Hz, 1H, Cbz-$CH_2$-$H_b$), 5.42 (d, *J* = 9.9 Hz, 1H, $NCH_2O$-$H_a$), 5.48 (d, 1H, *J* = 9.9 Hz, $NCH_2O$-$H_b$), 5.66 (d, *J* = 6.6 Hz, 1H, 1′-H), 5.76 (d, *J* = 8.1 Hz, 1H, 5-H), 6.45 (d, *J* = 8.8 Hz, 1H, 5′-H), 6.69 (s, 1H, NH), 7.13 (d, *J* = 8.1 Hz, 1H, 6-H), 7.23−7.37 (m, 10H, BOM-aryl-H, Cbz-aryl-H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ −5.0, −4.3, −4.2, −4.2, 18.0, 18.2, 25.9, 26.0, 28.0, 67.6, 70.1, 72.0, 74.5, 75.0, 79.2, 82.8, 93.9, 101.9, 126.0, 127.5, 127.6, 128.0, 128.2, 128.2, 128.5, 135.7, 137.7, 140.9, 140.9, 150.6, 154.2, 162.6, 163.1; MS (ESI$^+$) *m*/*z* 860.4 (M + $Na^+$); HRMS (ESI$^+$) *m*/*z* calcd for $C_{43}H_{63}N_3NaO_{10}Si_2$ 860.3944 (M + $Na^+$), found 860.3968 (M + $Na^+$); IR (ATR) ν 1714, 1666, 1251, 1152, 1050, 838, 775, 735, 697; UV (MeCN) $\lambda_{max}$ (log ε) 259 (4.05); mp 47 °C; TLC $R_f$ 0.38 (7:3 petroleum ether−EtOAc); $[\alpha]^{20}_D$ −24.0 (*c* 0.7, $CHCl_3$).

**3-(*N*-PMB)-Protected Nucleosyl Amino Acid ((*S*)-22).** *Synthesis of (S)-**22** from (Z)-**17**.* General procedure C with didehydro nucleosyl amino acid (*Z*)-**17** (1.00 g, 1.19 mmol), (*S*,*S*)-Me-DUPHOS-Rh (12 mg, 20 μmol), and MeOH (25 mL) and a reaction time of 3 d. In contrast to the general procedure, the reaction mixture was not evaporated under reduced pressure, but 10% Pd/C (136 mg, 0.128 mmol) was added and stirring under an $H_2$ atmosphere (1 bar) was continued for 5 h. The reaction mixture was then filtered through a pad of Celite, the Celite washed with hot MeOH (100 mL), and the filtrate evaporated under reduced pressure. The resultant crude product was purified by column chromatography (40:40:19:1 petroleum ether−$CH_2Cl_2$−EtOAc−$NEt_3$) to give (*S*)-**22** as a colorless solid (723 mg, 86%): $^1$H NMR (300 MHz, $CD_3OD$) δ −0.01 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.12 (s, 3H, $SiCH_3$), 0.85 (s, 9H, $SiC(CH_3)_3$), 0.93 (s, 9H, $SiC(CH_3)_3$), 1.47 (s, 9H, $OC(CH_3)_3$), 1.86 (ddd, *J* = 14.1, 11.3, 5.3 Hz, 1H, 5′-$H_a$), 2.13 (ddd, *J* = 14.1, 8.0, 2.5 Hz, 1H, 5′-$H_b$), 3.55 (dd, *J* = 8.0, 5.3 Hz, 1H, 6′-H), 3.75 (s, 3H, $OCH_3$), 3.85 (dd, *J* = 5.0, 5.0 Hz, 1H, 3′-H), 4.14 (ddd, *J* = 11.3, 5.0, 2.5 Hz, 1H, 4′-H), 4.27 (dd, *J* = 5.0, 4.2 Hz, 1H, 2′-H), 4.96 (d, *J* = 13.7 Hz, 1H, PMB-$CH_2$-$H_a$), 5.06 (d, *J* = 13.7 Hz, 1H, PMB-$CH_2$-$H_b$), 5.80 (d, *J* = 4.2 Hz, 1H, 1′-H), 5.84 (d, *J* = 8.1 Hz, 1H, 5-H), 6.82 (d, *J* = 8.8 Hz, 2H, PMB-3-H, PMB-5-H), 7.35 (d, *J* = 8.8 Hz, 2H, PMB-2-H, PMB-6-H), 7.64 (d, *J* = 8.1 Hz, 1H, 6-H); $^{13}$C NMR (75 MHz, $CD_3OD$) δ −4.5, −4.5, −4.3, −4.0, 18.8, 19.0, 26.4, 26.5, 28.3, 39.1, 44.5, 53.6, 55.7, 76.0, 76.6, 82.8, 83.0, 92.7, 102.5, 114.7, 130.3, 131.4, 140.8, 152.2, 160.7, 164.7, 174.6; MS (ESI$^+$) *m*/*z* 706.2 (M + $H^+$); HRMS (ESI$^+$) *m*/*z* calcd for $C_{35}H_{60}N_3O_8Si_2$ 706.3913 (M + $H^+$), found 706.3915 (M + $H^+$); IR (KBr) ν 2931, 1670, 1513, 1456, 1391, 1250, 1159, 839, 777; UV (MeCN) $\lambda_{max}$ (log ε) 194 (4.72), 223 (4.16), 263 (3.99); mp 69 °C; TLC $R_f$ 0.17 (40:40:19:1 petroleum ether−$CH_2Cl_2$−EtOAc−$NEt_3$); analytical HPLC $t_R$ 10.6 min (Method III); $[\alpha]^{20}_D$ +44.6 (*c* 1.2, MeOH).

*Synthesis of (S)-**22** from (S)-**29**.* General procedure E with nucleosyl amino acid (*S*)-**29** (42 mg, 58 μmol), *p*-methoxybenzyl chloride (0.44 M solution in $CH_2Cl_2$, 0.25 mL, 0.11 mmol), TBAI (1 mg, 3 μmol), $Na_2CO_3$ (0.82 M solution in water, 0.28 mL, 0.23 mmol), and $CH_2Cl_2$ (2 mL) and a reaction time of 30 h. In contrast to the general procedure, more *p*-methoxybenzyl chloride (0.44 M solution in $CH_2Cl_2$, 0.25 mL, 0.11 mmol) and $Na_2CO_3$ (0.82 M solution in water, 0.28 mL, 0.23 mmol) were added after 15 h. Purification by double column chromatography (1) 17:3 petroleum ether−EtOAc, (2) 9:1 $CH_2Cl_2$−$Et_2O$) furnished the 3-alkylated derivative as a colorless solid (35 mg). This was then deprotected by application of general procedure D with the Cbz-protected 3-alkylated nucleosyl amino acid (10 mg, 12 μmol), 1,4-cyclohexadiene (11 μL, 0.12 mmol), 10% Pd/C (5 mg, 5 μmol), and MeOH (3 mL) to give (*S*)-**22** as a colorless solid (7.9 mg, 67% over two steps from (*S*)-**29**). Analytical data were identical to those given above.

**3-(*N*-PMB)-Protected Nucleosyl Amino Acid ((*R*)-22).** *Synthesis of (R)-**22** from (Z)-**17**.* General procedure C with didehydro nucleosyl amino acid (*Z*)-**17** (1.00 g, 1.19 mmol), (*R*,*R*)-Me-DUPHOS-Rh (24 mg, 40 μmol), and MeOH (25 mL) and a reaction time of 14 d. In contrast to the general procedure, the reaction mixture was not evaporated under reduced pressure, but 10% Pd/C (120 mg, 0.113 mmol) was added and stirring under an $H_2$ atmosphere (1 bar) was continued for 5 h. The reaction mixture was then filtered through a pad of Celite, the Celite washed with hot MeOH (100 mL), and the filtrate evaporated under reduced pressure. The resultant crude product was purified by column chromatography (40:40:19:1 petroleum ether−$CH_2Cl_2$−EtOAc−$NEt_3$) to give (*R*)-**22** as a colorless solid (675 mg, 80%): $^1$H NMR (300 MHz, $CD_3OD$) δ −0.02 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.13 (s, 3H, $SiCH_3$), 0.84 (s, 9H, $SiC(CH_3)_3$), 0.94 (s, 9H, $SiC(CH_3)_3$), 1.48 (s, 9H, $OC(CH_3)_3$), 2.07 (dd, *J* = 6.8, 5.7 Hz, 2H, 5′-H), 3.65 (dd, *J* = 5.7, 5.7 Hz, 1H, 6′-H), 3.75 (s, 3H, $OCH_3$), 3.89 (dd, *J* = 4.5, 4.5 Hz, 1H, 3′-H), 4.13 (dd, *J* = 6.8, 4.5 Hz, 1H, 4′-H), 4.32 (dd, *J* = 4.5, 4.5 Hz, 1H, 2′-H), 4.97 (d, *J* = 13.7 Hz, 1H, PMB-$CH_2$-$H_a$), 5.05 (d, *J* = 13.7 Hz, 1H, PMB-$CH_2$-$H_b$), 5.77 (d, *J* = 4.5 Hz, 1H, 1′-H), 5.83 (d, *J* = 8.1 Hz, 1H, 5-H), 6.82 (d, *J* = 8.8 Hz, 2H, PMB-3-H, PMB-5-H), 7.35 (d, *J* = 8.8 Hz, 2H, PMB-2-H, PMB-6-H), 7.61 (d, *J* = 8.1 Hz, 1H, 6-H); $^{13}$C NMR (75 MHz, $CD_3OD$) δ −4.5, −4.5, −4.3, −4.0, 18.8, 19.0, 26.4, 26.5, 28.3, 37.4, 44.5, 53.8, 55.7, 75.5, 76.6, 82.6, 83.1, 93.0, 102.4, 114.7, 130.3, 131.4, 141.0, 152.2, 160.7, 164.7, 174.3; MS (ESI$^+$) *m*/*z* 706.3 (M + $H^+$); HRMS (ESI$^+$) *m*/*z* calcd for $C_{35}H_{60}N_3O_8Si_2$ 706.3913 (M + $H^+$), found 706.3909 (M + $H^+$); IR (KBr) ν 2931, 1670, 1514, 1456, 1391, 1250, 1160, 839, 777; UV (MeCN) $\lambda_{max}$ (log ε) 223 (4.14), 263 (3.96); mp 52 °C; TLC $R_f$ 0.17 (40:40:19:1 petroleum ether−$CH_2Cl_2$−EtOAc−$NEt_3$); Analytical HPLC $t_R$ 10.9 min (method III); $[\alpha]^{20}_D$ +30.1 (*c* 0.9, MeOH).

*Synthesis of (R)-**22** from (R)-**29**.* General procedure E with nucleosyl amino acid (*R*)-**29** (42 mg, 58 μmol), *p*-methoxybenzyl chloride (0.44 M solution in $CH_2Cl_2$, 0.25 mL, 0.11 mmol), TBAI (1 mg, 3 μmol), $Na_2CO_3$ (0.82 M solution in water, 0.28 mL, 0.23 mmol), and $CH_2Cl_2$ (2 mL) and a reaction time of 30 h. In contrast to the general procedure, more *p*-methoxybenzyl chloride (0.44 M solution in $CH_2Cl_2$, 0.25 mL, 0.11 mmol) and $Na_2CO_3$ (0.82 M solution in water, 0.28 mL, 0.23 mmol) were added after 15 h. Purification by double column chromatography ((1) 17:3 petroleum ether−EtOAc, (2) 9:1 $CH_2Cl_2$−$Et_2O$) furnished the 3-alkylated derivative as a colorless solid (34 mg). This was then deprotected by application of general procedure D with the Cbz-protected 3-alkylated nucleosyl amino acid (10 mg, 12 μmol), 1,4-cyclohexadiene (11 μL, 0.12 mmol), 10% Pd/C (5 mg, 5 μmol), and MeOH (3 mL) to give (*R*)-**22** as a colorless solid (8.0 mg, 66% over two steps from (*R*)-**29**). Analytical data were identical to those given above.

**3-(*N*-BOM)-Protected Nucleosyl Amino Acid ((*S*)-23).** *Synthesis of (S)-**23** from (Z)-**18**.* General procedure C with didehydro nucleosyl amino acid (*Z*)-**18** (730 mg, 0.871 mmol), (*S*,*S*)-Me-DUPHOS-Rh (8.0 mg, 10 μmol), and MeOH (20 mL) and a reaction time of 4 d. Purification by column chromatography (4:1 petroleum ether−EtOAc) gave (*S*)-**23** as a colorless solid (690 mg, 94%): $^1$H NMR (600 MHz, $C_6D_6$) δ −0.02 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$), 0.13 (s, 3H, $SiCH_3$), 0.13 (s, 3H, $SiCH_3$), 0.93 (s, 9H, $SiC(CH_3)_3$), 0.98 (s, 9H, $SiC(CH_3)_3$), 1.32 (s, 9H, $OC(CH_3)_3$), 2.09 (ddd, *J* = 15.1, 10.9, 4.8 Hz, 1H, 5′-$H_a$), 2.23 (ddd, *J* = 15.1, 7.4, 2.5 Hz, 1H, 5′-$H_b$), 3.72 (dd, *J* = 5.3, 4.1 Hz, 1H, 3′-H), 4.37 (dd, *J* = 4.1, 3.8 Hz, 1H, 2′-H), 4.42 (ddd, *J* = 10.9, 5.3, 2.5 Hz, 1H, 4′-H), 4.61 (ddd, *J* = 7.4, 6.5, 4.8 Hz, 1H, 6′-H), 4.66 (d, *J* = 14.3 Hz, 1H, BOM-$CH_2$-$H_a$), 4.68 (d, *J*


dx.doi.org/10.1021/jo201935w | J. Org. Chem. 2011, 76, 10083−10098

= 14.3 Hz, 1H, BOM-$CH_2$-$H_b$), 5.00 (s, 2H, Cbz-$CH_2$), 5.42 (d, $J$ = 18.2 Hz, 1H, $NCH_2O$-$H_a$), 5.44 (d, $J$ = 18.2 Hz, 1H, $NCH_2O$-$H_b$), 5.64 (d, $J$ = 6.5 Hz, 1H, NH), 5.70 (d, $J$ = 8.2 Hz, 1H, 5-H), 5.72 (d, $J$ = 3.8 Hz, 1H, 1′-H), 7.03−7.20 (m, 8H, BOM-3-H, BOM-4-H, BOM-5-H, Cbz-aryl-H) 7.32 (d, $J$ = 8.2 Hz, 1H, 6-H), 7.34 (d, $J$ = 7.6 Hz, 2H, BOM-2-H, BOM-6-H); $^{13}$C NMR (126 MHz, $C_6D_6$) $\delta$ −4.6, −4.5, −4.1, −3.9, 18.4, 18.4, 26.1, 26.2, 28.0, 36.9, 52.8, 67.1, 70.5, 72.3, 75.3, 76.0, 81.0, 82.3, 92.9, 102.1, 127.6, 127.7, 128.4, 128.5, 128.6, 136.9, 138.9, 139.2, 151.2, 155.8, 162.1, 170.8; MS (ESI$^+$) $m/z$ 862.4 (M + $Na^+$); HRMS (ESI$^+$) $m/z$ calcd for $C_{43}H_{65}N_3NaO_{10}Si_2$ 862.4101 (M + $Na^+$), found 862.4103 (M + $Na^+$); IR (ATR) $\nu$ 1713, 1665, 1252, 1153, 1058, 837, 775, 734, 696; UV (MeCN) $\lambda_{max}$ (log $\varepsilon$) 205 (4.45), 264 (4.01); mp 38 °C; TLC $R_f$ 0.27 (7:3 petroleum ether−EtOAc); analytical HPLC $t_R$ 15.1 min (method II); $[\alpha]^{20}_D$ +51.3 ($c$ 1.0, $CHCl_3$).

*Synthesis of (S)-**23** from (S)-**29**.* General procedure E with nucleosyl amino acid (*S*)-**29** (21 mg, 29 μmol), benzyloxymethyl chloride (0.44 M solution in $CH_2Cl_2$, 0.10 mL, 44 μmol), TBAI (0.5 mg, 1 μmol), $Na_2CO_3$ (0.82 M solution in water, 0.14 mL, 0.12 mmol), and $CH_2Cl_2$ (1.0 mL) and a reaction time of 23 h. Purification by column chromatography (17:3 petroleum ether−EtOAc) gave (*S*)-**23** as a colorless solid (18 mg, 74%). Analytical data were identical to those given above.

**3-(*N*-BOM)-Protected Nucleosyl Amino Acid ((*R*)-23).** *Synthesis of (R)-**23** from (Z)-**18**.* General procedure C with didehydro nucleosyl amino acid (*Z*)-**18** (730 mg, 0.871 mmol), (*R,R*)-Me-DUPHOS-Rh (8.0 mg, 10 μmol), and MeOH (20 mL) and a reaction time of 7 d. In contrast to the general procedure, more (*R,R*)-Me-DUPHOS-Rh (8.0 mg, 10 μmol) was added after 5 d. Purification by column chromatography (4:1 petroleum ether−EtOAc) gave (*R*)-**23** as a colorless solid (680 mg, 93%): $^1$H NMR (600 MHz, $C_6D_6$) $\delta$ −0.04 (s, 3H, $SiCH_3$), −0.01 (s, 3H, $SiCH_3$), 0.11 (s, 3H, $SiCH_3$), 0.20 (s, 3H, $SiCH_3$), 0.92 (s, 9H, $SiC(CH_3)_3$), 0.96 (s, 9H, $SiC(CH_3)_3$), 1.36 (s, 9H, $OC(CH_3)_3$), 1.91 (ddd, $J$ = 14.7, 11.6, 3.9 Hz, 1H, 5′-$H_a$), 2.23 (ddd, $J$ = 14.7, 5.0, 4.0 Hz, 1H, 5′-$H_b$), 3.72 (dd, $J$ = 6.1, 4.3 Hz, 1H, 3′-H), 4.25−4.30 (m, 2H, 2′-H, 4′-H), 4.64 (d, $J$ = 18.4 Hz, 1H, BOM-$CH_2$-$H_a$), 4.66 (d, $J$ = 18.4 Hz, 1H, BOM-$CH_2$-$H_b$), 4.73 (ddd, $J$ = 8.5, 5.0, 3.9 Hz, 1H, 6′-H), 4.97 (d, $J$ = 12.3 Hz, 1H, Cbz-$CH_2$-$H_a$), 5.14 (d, $J$ = 12.3 Hz, 1H, Cbz-$CH_2$-$H_b$), 5.34 (d, $J$ = 2.0 Hz, 1H, 1′-H), 5.36 (d, $J$ = 15.6 Hz, 1H, $NCH_2O$-$H_a$), 5.38 (d, $J$ = 15.6 Hz, 1H, $NCH_2O$-$H_b$), 5.39 (d, $J$ = 8.2 Hz, 1H, 5-H), 5.91 (d, $J$ = 8.5 Hz, 1H, NH), 6.65 (d, $J$ = 8.2 Hz, 1H, 6-H), 7.00−7.22 (m, 8H, BOM-3-H, BOM-4-H, BOM-5-H, Cbz-aryl-H), 7.33 (d, $J$ = 7.6 Hz, 2H, BOM-2-H, BOM-6-H); $^{13}$C NMR (126 MHz, $C_6D_6$) $\delta$ −4.7, −4.7, −3.9, −3.9, 18.3, 18.3, 26.2, 26.2, 28.1, 34.8, 53.6, 67.0, 70.4, 72.4, 74.7, 75.7, 81.0, 82.0, 93.7, 101.9, 127.6, 127.7, 128.3, 128.4, 128.5, 128.6, 137.0, 138.9, 138.2, 150.9, 156.2, 161.9, 170.4; MS (ESI$^+$) $m/z$ 862.4 (M + $Na^+$); HRMS (ESI$^+$) $m/z$ calcd for $C_{43}H_{65}N_3NaO_{10}Si_2$ 862.4101 (M + $Na^+$), found 862.4098 (M + $Na^+$); IR (ATR) $\nu$ 1714, 1665, 1151, 1061, 865, 837, 775, 735, 696; UV (MeCN) $\lambda_{max}$ (log $\varepsilon$) 205 (4.40), 263 (3.96); mp 41 °C; TLC $R_f$ 0.38 (7:3 petroleum ether-EtOAc); Analytical HPLC $t_R$ 14.7 min (method II); $[\alpha]^{20}_D$ +50.7 ($c$ 1.2, $CHCl_3$).

*Synthesis of (R)-**23** from (R)-**29**.* General procedure E with nucleosyl amino acid (*R*)-**29** (21 mg, 29 μmol), benzyloxymethyl chloride (0.44 M solution in $CH_2Cl_2$, 0.10 mL, 44 μmol), TBAI (0.5 mg, 1 μmol), $Na_2CO_3$ (0.82 M solution in water, 0.14 mL, 0.12 mmol), and $CH_2Cl_2$ (1.0 mL) and a reaction time of 23 h. Purification by column chromatography (17:3 petroleum ether−EtOAc) gave (*R*)-**23** as a colorless solid (20 mg, 83%). Analytical data were identical to those given above.

**3-Unprotected Nucleosyl Amino Acid ((*S*)-24).** General procedure D with Cbz-protected nucleosyl amino acid (*S*)-**29** (150 mg, 0.208 mmol), 1,4-cyclohexadiene (197 μL, 2.08 mmol), 10% Pd/C (20 mg, 19 μmol), and MeOH (4 mL) to give (*S*)-**24** as a colorless solid (119 mg, 98%): $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 0.09 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.11 (s, 3H, $SiCH_3$), 0.13 (s, 3H, $SiCH_3$), 0.90 (s, 9H, $SiC(CH_3)_3$), 0.93 (s, 9H, $SiC(CH_3)_3$), 1.47 (s, 9H, $OC(CH_3)_3$), 1.84 (ddd, $J$ = 14.0, 11.2, 5.1 Hz, 1H, 5′-$H_a$), 2.11 (ddd, $J$ = 14.0, 8.2, 2.6 Hz, 1H, 5′-$H_b$), 3.51 (dd, $J$ = 8.2, 5.1 Hz, 1H, 6′-H), 3.88 (dd, $J$ = 5.0, 4.5 Hz, 1H, 3′-H), 4.12 (ddd, $J$ = 11.2, 5.0, 2.6 Hz, 1H, 4′-H), 4.30 (dd, $J$ = 4.5, 4.2 Hz, 1H, 2′-H), 5.73 (d, $J$ = 8.1 Hz, 1H, 5-H), 5.76 (d, $J$ = 4.2 Hz, 1H, 1′-H), 7.65 (d, $J$ = 8.1 Hz, 1H, 6-H); $^{13}$C NMR (126 MHz, $CD_3OD$) $\delta$ −4.5, −4.4, −4.4, −4.0, 18.9, 18.9, 26.4, 26.5, 28.3, 39.5, 53.8, 76.0, 76.6, 82.6, 82.9, 92.0, 103.0, 142.6, 152.3, 166.3, 175.2; MS (ESI$^+$) $m/z$ 586.4 (M + $H^+$); HRMS (ESI$^+$) $m/z$ calcd for $C_{27}H_{52}N_3O_7Si_2$ 586.3338 (M + $H^+$), found 586.3337 (M + $H^+$); IR (ATR) $\nu$ 1687, 1252, 1153, 1056, 867, 835, 812, 774, 735; UV (MeOH) $\lambda_{max}$ (log $\varepsilon$) 207 (3.96), 262 (4.00); mp 48 °C; TLC $R_f$ 0.27 (19:1 $CH_2Cl_2$−MeOH); $[\alpha]^{20}_D$ +42.6 ($c$ 1.1, MeOH).

**3-Unprotected Nucleosyl Amino Acid ((*R*)-24).** General procedure D with Cbz-protected nucleosyl amino acid (*R*)-**29** (150 mg, 0.208 mmol), 1,4-cyclohexadiene (197 μL, 2.08 mmol), 10% Pd/C (20 mg, 19 μmol), and MeOH (4 mL) to give (*R*)-**24** as a colorless solid (120 mg, 99%): $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 0.10 (s, 3H, $SiCH_3$), 0.11 (s, 3H, $SiCH_3$), 0.12 (s, 3H, $SiCH_3$), 0.14 (s, 3H, $SiCH_3$), 0.90 (s, 9H, $SiC(CH_3)_3$), 0.95 (s, 9H, $SiC(CH_3)_3$), 1.48 (s, 9H, $OC(CH_3)_3$), 1.99−2.06 (m, 2H, 5′-H), 3.53 (dd, $J$ = 6.0, 5.6 Hz, 1H, 6′-H), 3.90 (dd, $J$ = 5.1, 4.4 Hz, 1H, 3′-H), 4.14 (ddd, $J$ = 8.3, 5.3, 5.1 Hz, 1H, 4′-H), 4.30 (dd, $J$ = 4.4, 4.2 Hz, 1H, 2′-H), 5.73 (d, $J$ = 8.1 Hz, 1H, 5-H), 5.78 (d, $J$ = 4.2 Hz, 1H, 1′-H), 7.64 (d, $J$ = 8.1 Hz, 1H, 6-H); $^{13}$C NMR (126 MHz, $CD_3OD$) $\delta$ −4.5, −4.5, −4.3, −4.0, 18.9, 18.9, 26.4, 26.5, 28.3, 38.3, 54.1, 75.8, 76.7, 82.5, 82.6, 91.9, 102.9, 142.4, 152.4, 166.4, 175.7; MS (ESI$^+$) $m/z$ 586.3 (M + $H^+$); HRMS (ESI$^+$) $m/z$ calcd for $C_{27}H_{52}N_3O_7Si_2$ 586.3338 (M + $H^+$), found 586.3334 (M + $H^+$); IR (ATR) $\nu$ 1687, 1252, 1153, 1087, 1053, 866, 835, 812, 775; UV (MeOH) $\lambda_{max}$ (log $\varepsilon$) 207 (3.94), 262 (3.99); mp 54 °C; TLC $R_f$ 0.27 (19:1 $CH_2Cl_2$−MeOH); $[\alpha]^{20}_D$ +25.1 ($c$ 0.9, MeOH).

**3′,5′-Bis(*O-tert*-butyldimethylsilyl)uridine-5′-aldehyde (27).** General procedure A with uridine derivative **26**[20] (2.30 g, 4.87 mmol), IBX (3.41 g, 12.2 mmol), and MeCN (46 mL) to give **27** as a colorless solid (2.25 g, 98%): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ −0.01 (s, 3H, $SiCH_3$), 0.03 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.85 (s, 9H, $SiC(CH_3)_3$), 0.91 (s, 9H, $SiC(CH_3)_3$), 4.22 (dd, $J$ = 4.0, 3.3 Hz, 1H, 3′-H), 4.30 (dd, $J$ = 5.6, 4.0 Hz, 1H, 2′-H), 4.53 (d, $J$ = 3.3 Hz, 1H, 4′-H), 5.72 (d, $J$ = 5.6 Hz, 1H, 1′-H), 5.78 (d, $J$ = 8.1 Hz, 1H, 5-H), 7.66 (d, $J$ = 8.1 Hz, 1H, 6-H), 8.54 (s, 1H, NH), 9.80 (s, 1H, 5′-H); MS (ESI$^+$) $m/z$ 493.2 (M + $Na^+$); HRMS (ESI$^+$) $m/z$ calcd for $C_{21}H_{38}N_2NaO_6Si_2$ 493.2161 (M + $Na^+$), found 493.2160 (M + $Na^+$).

**3-Unprotected Didehydro Nucleosyl Amino Acid ((*Z*)-28).** General procedure B with aldehyde **27** (2.93 g, 6.22 mmol), phosphonate **16**[22] (1.86 g, 4.98 mmol), KHMDS (0.5 M in toluene, 9.96 mL, 4.98 mmol), and THF (30 mL (**27**), 25 mL (**16**), 25 mL (KHMDS)). Purification by column chromatography (3:1 petroleum ether−EtOAc) gave (*Z*)-**28** as a colorless solid (3.03 g, 85%) while the (*E*)-isomer could not be isolated: $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 0.07 (s, 3H, $SiCH_3$), 0.09 (s, 3H, $SiCH_3$), 0.09 (s, 3H, $SiCH_3$), 0.12 (s, 3H, $SiCH_3$), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.90 (s, 9H, $SiC(CH_3)_3$), 1.48 (s, 9H, $OC(CH_3)_3$), 3.95 (dd, $J$ = 6.3, 3.8 Hz, 1H, 3′-H), 4.34 (dd, $J$ = 3.8, 3.3 Hz, 1H, 2′-H), 4.88 (dd, $J$ = 7.7, 6.3 Hz, 1H, 4′-H), 5.14 (s, 2H, Cbz-$CH_2$), 5.58 (d, $J$ = 3.3 Hz, 1H, 1′-H), 5.73 (d, $J$ = 8.1 Hz, 1H, 5-H), 6.26 (d, $J$ = 7.7 Hz, 1H, 5′-H), 6.75 (s, 1H, 6′-NH), 7.27 (d, $J$ = 8.1 Hz, 1H, 6-H), 7.30−7.39 (m, 5H, Cbz-aryl-H), 8.56 (s, 1H, 3-NH); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ −4.9, −4.8, −4.5, −4.4, 18.0, 18.1, 25.8, 25.8, 27.8, 67.5, 74.7, 76.1, 79.1, 82.6, 92.8, 102.3, 124.6, 128.1, 128.3, 128.5, 131.3, 135.8, 140.4, 149.8, 162.7, 163.1; MS (ESI$^+$) $m/z$ 740.3 (M + $Na^+$); HRMS (ESI$^+$) $m/z$ calcd for $C_{35}H_{55}N_3NaO_9Si_2$ 740.3369 (M + $Na^+$), found 740.3379 (M + $Na^+$); IR (ATR) $\nu$ 1686, 1254, 1222, 1152, 1051, 833, 814, 776, 735; UV (MeCN) $\lambda_{max}$ (log $\varepsilon$) 255 (4.20); mp 65 °C; TLC $R_f$ 0.29 (3:2 petroleum ether−EtOAc); $[\alpha]^{20}_D$ +47.9 ($c$ 1.0, $CHCl_3$).

**3-Unprotected Nucleosyl Amino Acid ((*S*)-29).** General procedure C with didehydro nucleosyl amino acid (*Z*)-**28** (1.26 g, 1.75 mmol), (*S,S*)-Me-DUPHOS-Rh (12 mg, 20 μmol), and MeOH (30 mL) and a reaction time of 6 d. In contrast to the General Procedure, more (*S,S*)-Me-DUPHOS-Rh (9.0 mg, 15 μmol) was added after 5 d. Purification by column chromatography (7:3 petroleum ether−EtOAc) gave (*S*)-**29** as a colorless solid (1.19 g, 94%): $^1$H NMR (300 MHz, $C_6D_6$) $\delta$ 0.01 (s, 3H, $SiCH_3$), 0.05 (s, 3H,

$SiCH_3$), 0.16 (s, 3H, $SiCH_3$), 0.20 (s, 3H, $SiCH_3$), 0.95 (s, 9H, $SiC(CH_3)_3$), 1.00 (s, 9H, $SiC(CH_3)_3$), 1.33 (s, 9H, $OC(CH_3)_3$), 2.14 (ddd, $J$ = 14.1, 10.7, 5.2 Hz, 1H, 5′-$H_a$), 2.28 (ddd, $J$ = 14.1, 7.1, 2.6 Hz, 1H, 5′-$H_b$), 3.76 (dd, $J$ = 5.3, 4.6 Hz, 1H, 3′-H), 4.38−4.46 (m, 2H, 2′-H, 4′-H), 4.61 (ddd, $J$ = 7.1, 6.3, 5.2 Hz, 1H, 6′-H), 5.02 (s, 2H, Cbz-$CH_2$), 5.60 (d, $J$ = 8.0 Hz, 1H, 5-H), 5.61 (s, 1H, 1′-H), 5.76 (d, $J$ = 6.3 Hz, 1H, 6′-NH), 7.05−7.28 (m, 6H, 6-H, Cbz-aryl-H) 9.60 (s, 1H, 3-NH); $^{13}$C NMR (126 MHz, $C_6D_6$) $\delta$ −4.8, −4.7, −4.3, −4.1, 18.2, 18.2, 26.0, 26.1, 27.8, 36.5, 52.8, 67.0, 75.0, 75.9, 80.9, 82.2, 92.8, 102.4, 128.3, 128.4, 128.6, 137.0, 140.8, 150.6, 155.9, 163.0, 171.0; MS (ESI$^+$) $m/z$ 742.3 (M + $Na^+$); HRMS (ESI$^+$) $m/z$ calcd for $C_{35}H_{57}N_3NaO_9Si_2$ 742.3526 (M + $Na^+$), found 742.3527 (M + $Na^+$); IR (ATR) $\nu$ 1683, 1252, 1153, 866, 836, 775, 735, 697; UV (MeCN) $\lambda_{max}$ (log $\varepsilon$) 206 (4.20), 261 (3.99); mp 70 °C; TLC $R_f$ 0.23 (3:2 petroleum ether−EtOAc); $[\alpha]^{20}_D$ +54.9 ($c$ 1.0, $CHCl_3$).

**3-Unprotected Nucleosyl Amino Acid ((*R*)-29).** General procedure C with didehydro nucleosyl amino acid (*Z*)-**28** (270 mg, 0.376 mmol), (*R*,*R*)-Me-DUPHOS-Rh (9.0 mg, 15 μmol), MeOH (20 mL) and a reaction time of 14 d. In contrast to the general procedure, more (*R*,*R*)-Me-DUPHOS-Rh (6.0 mg, 9.9 μmol) was added both after 7 and 11 d. Purification by column chromatography (7:3 petroleum ether−EtOAc) gave (*R*)-**29** as a colorless solid (253 mg, 93%): $^1$H NMR (300 MHz, $C_6D_6$) $\delta$ 0.03 (s, 3H, $SiCH_3$), 0.04 (s, 3H, $SiCH_3$), 0.18 (s, 3H, $SiCH_3$), 0.24 (s, 3H, $SiCH_3$), 0.95 (s, 9H, $SiC(CH_3)_3$), 1.00 (s, 9H, $SiC(CH_3)_3$), 1.39 (s, 9H, $OC(CH_3)_3$), 2.04 (ddd, $J$ = 13.8, 10.9, 4.2 Hz, 1H, 5′-$H_a$), 2.30 (ddd, $J$ = 13.8, 4.6, 2.4 Hz, 1H, 5′-$H_b$), 3.74 (dd, $J$ = 6.6, 3.9 Hz, 1H, 3′-H), 4.29 (ddd, $J$ = 10.9, 6.6, 2.4 Hz, 1H, 4′-H), 4.39 (dd, $J$ = 3.9, 2.4 Hz, 1H, 2′-H), 4.75 (ddd, $J$ = 8.6, 4.6, 4.2 Hz, 1H, 6′-H), 5.01 (d, $J$ = 12.3 Hz, 1H, Cbz-$CH_2$-$H_a$), 5.16 (d, $J$ = 12.3 Hz, 1H, Cbz-$CH_2$-$H_b$), 5.31 (d, $J$ = 2.4 Hz, 1H, 1′-H), 5.39 (d, $J$ = 8.2 Hz, 1H, 5-H), 6.03 (d, $J$ = 8.6 Hz, 1H, 6′-NH), 6.70 (d, $J$ = 8.2 Hz, 1H, 6-H), 7.04−7.27 (m, 5H, Cbz-aryl-H) 10.34 (s, 1H, 3-NH); $^{13}$C NMR (126 MHz, $C_6D_6$) $\delta$ −4.8, −4.8, −4.1, −4.1, 18.2, 18.2, 26.0, 26.0, 27.9, 34.6, 53.6, 66.9, 74.5, 75.5, 80.9, 81.9, 93.6, 102.3, 128.3, 128.5, 128.6, 137.1, 140.0, 150.6, 156.3, 163.4, 170.7; MS (ESI$^+$) $m/z$ 742.3 (M + $Na^+$); HRMS (ESI$^+$) $m/z$ calcd for $C_{35}H_{57}N_3NaO_9Si_2$ 742.3526 (M + $Na^+$), found 742.3527 (M + $Na^+$); IR (ATR) $\nu$ 1685, 1252, 1154, 1064, 866, 836, 813, 775, 736; UV (MeCN) $\lambda_{max}$ (log $\varepsilon$) 206 (4.19), 261 (3.98); mp 63 °C; TLC $R_f$ 0.24 (3:2 petroleum ether−EtOAc); $[\alpha]^{20}_D$ +44.1 ($c$ 1.1, $CHCl_3$).

**Silylated Nucleosyl Amino Acid Urea Derivative ((*S*)-30).** To a solution of nucleosyl amino acid (*S*)-**24** (70 mg, 0.12 mmol) in THF (6 mL), 4-nitrophenyl isocyanate (23 mg, 0.14 mmol) was added and the reaction mixture was stirred at rt for 20 h. The solvent was evaporated under reduced pressure. The resultant crude product was purified by column chromatography (petroleum ether−EtOAc gradient (25−30%)) to give (*S*)-**30** as a colorless solid (77 mg, 86%): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.05 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.86 (s, 9H, $SiC(CH_3)_3$), 0.87 (s, 9H, $SiC(CH_3)_3$), 1.46 (s, 9H, $OC(CH_3)_3$), 2.03−2.18 (m, 1H, 5′-$H_a$), 2.21−2.31 (m, 1H, 5′-$H_b$), 3.77 (dd, $J$ = 4.5, 4.4 Hz, 1H, 3′-H), 4.21−4.28 (m, 1H, 4′-H), 4.30 (dd, $J$ = 4.4, 4.2 Hz, 1H, 2′-H), 4.57 (ddd, $J$ = 6.6, 6.1, 6.0 Hz, 1H, 6′-H), 5.64 (d, $J$ = 4.2 Hz, 1H, 1′-H), 5.83 (d, $J$ = 8.0 Hz, 1H, 5-H), 6.49 (d, $J$ = 6.6 Hz, 1H, 6′-NH), 7.54 (d, $J$ = 9.2 Hz, 2H, urea-aryl-2-H, urea-aryl-6-H), 7.56 (d, $J$ = 8.0 Hz, 1H, 6-H), 8.03 (s, 1H, urea-aryl-NH), 8.11 (d, $J$ = 9.2 Hz, 2H, urea-aryl-3-H, urea-aryl-5-H), 9.93 (s, 1H, 3-NH); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ −4.8, −4.8, −4.7, −4.3, 17.9, 18.0, 25.7, 25.7, 27.9, 35.8, 52.0, 74.0, 75.2, 82.0, 83.0, 92.2, 102.4, 117.6, 125.2, 141.9, 141.9, 141.9, 150.5, 154.0, 163.8, 171.8; MS (ESI$^+$) $m/z$ 772.4 (M + $Na^+$); HRMS (ESI$^+$) $m/z$ calcd for $C_{34}H_{55}N_5NaO_{10}Si_2$ 772.3380 (M + $Na^+$), found 772.3377 (M + $Na^+$); IR (ATR) $\nu$ 1681, 1329, 1252, 1155, 1110, 867, 835, 776, 751; UV (MeCN) $\lambda_{max}$ (log $\varepsilon$) 262 (3.99), 332 (4.16); mp 102 °C; TLC $R_f$ 0.05 (7:3 petroleum ether−EtOAc); $[\alpha]^{20}_D$ +53.6 ($c$ 1.1, $CHCl_3$).

**Silylated Nucleosyl Amino Acid Urea Derivative ((*R*)-30).** To a solution of nucleosyl amino acid (*R*)-**24** (66 mg, 0.11 mmol) in THF (6 mL), 4-nitrophenyl isocyanate (21 mg, 0.13 mmol) was added and the reaction mixture was stirred at rt for 20 h. The solvent was evaporated under reduced pressure. The resultant crude product was purified by column chromatography (petroleum ether−EtOAc gradient (25−30%)) to give (*R*)-**30** as a colorless solid (62 mg, 75%): $^1$H NMR (300 MHz, $CDCl_3$, 55 °C) $\delta$ 0.05 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.09 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.92 (s, 9H, $SiC(CH_3)_3$), 1.49 (s, 9H, $OC(CH_3)_3$), 2.07 (ddd, $J$ = 14.4, 11.4 Hz, $J$ = 3.8 Hz, 1H, 5′-$H_a$), 2.39 (ddd, $J$ = 14.4, 5.5, 2.5 Hz, 1H, 5′-$H_b$), 3.77 (dd, $J$ = 4.8, 4.6 Hz, 1H, 3′-H), 4.17 (ddd, $J$ = 11.4, 4.8, 2.5 Hz, 1H, 4′-H), 4.32 (dd, $J$ = 4.6, 4.2 Hz, 1H, 2′-H), 4.73 (ddd, $J$ = 8.2, 5.5, 3.8 Hz, 1H, 6′-H), 5.48 (d, $J$ = 4.2 Hz, 1H, 1′-H), 5.66 (d, $J$ = 8.1 Hz, 1H, 5-H), 6.49 (d, $J$ = 8.2 Hz, 1H, 6′-NH), 7.25 (d, $J$ = 8.1 Hz, 1H, 6-H), 7.54 (d, $J$ = 9.2 Hz, 2H, urea-aryl-2-H, urea-aryl-6-H), 8.03 (s, 1H, urea-aryl-NH), 8.09 (d, $J$ = 9.2 Hz, 2H, urea-aryl-3-H, urea-aryl-5-H), 9.70 (s, 1H, 3-NH); $^{13}$C NMR (126 MHz, $CDCl_3$, 50 °C) $\delta$ −4.7, −4.7, −4.6, −4.2, 17.9, 18.1, 25.8, 25.9, 28.1, 34.8, 51.9, 73.7, 75.3, 81.8, 82.8, 93.1, 102.2, 117.8, 125.1, 141.6, 142.2, 142.2, 150.1, 154.3, 163.8, 170.8; MS (ESI$^+$) $m/z$ 772.4 (M + $Na^+$); HRMS (ESI$^+$) $m/z$ calcd for $C_{34}H_{55}N_5NaO_{10}Si_2$ 772.3380 (M + $Na^+$), found 772.3377 (M + $Na^+$); IR (ATR) $\nu$ 1682, 1329, 1253, 1154, 1110, 865, 836, 776, 751; UV (MeCN) $\lambda_{max}$ (log $\varepsilon$) 261 (3.99), 332 (4.16); mp 92 °C; TLC $R_f$ 0.06 (7:3 petroleum ether−EtOAc); $[\alpha]^{20}_D$ +11.1 ($c$ 1.0, $CHCl_3$).

**Desilylated Nucleosyl Amino Acid Urea Derivative ((*S*)-31).** To a solution of nucleosyl amino acid urea derivative (*S*)-**30** (61 mg, 81 μmol) in THF (4 mL) was added TBAF trihydrate (101 mg, 0.320 mmol) at 10 °C. The reaction mixture was stirred at rt for 3 h, and then petroleum ether (1 mL) was added. The resultant mixture was directly applied on a silica gel column and purified twice by column chromatography ((1) 1:4 petroleum ether−THF, (2) $CH_2Cl_2$−MeOH gradient (5−10%)) to give (*S*)-**31** as a colorless solid (10 mg, 24%): $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 1.46 (s, 9H, $OC(CH_3)_3$), 2.16 (ddd, $J$ = 14.4, 9.3, 5.9 Hz, 1H, 5′-$H_a$), 2.34 (ddd, $J$ = 14.4, 6.0, 3.3 Hz, 1H, 5′-$H_b$), 3.95 (dd, $J$ = 6.7, 5.7 Hz, 1H, 3′-H), 4.03 (ddd, $J$ = 9.3, 6.7, 3.3 Hz, 1H, 4′-H), 4.19 (dd, $J$ = 5.7, 3.4 Hz, 1H, 2′-H), 4.73 (dd, $J$ = 6.0, 5.9 Hz, 1H, 6′-H), 5.72 (d, $J$ = 8.0 Hz, 1H, 5-H), 5.75 (d, $J$ = 3.4 Hz, 1H, 1′-H), 7.59 (d, $J$ = 9.3 Hz, 2H, urea-aryl-2-H, urea-aryl-6-H), 7.64 (d, $J$ = 8.0 Hz, 1H, 6-H), 8.15 (d, $J$ = 9.3 Hz, 2H, urea-aryl-3-H, urea-aryl-5-H); $^{13}$C NMR (126 MHz, $CD_3OD$) $\delta$ 28.2, 36.5, 52.8, 74.8, 74.8, 81.2, 83.3, 92.8, 102.9, 118.6, 126.0, 143.3, 147.5, 152.1, 156.3, 166.1, 172.6; MS (ESI$^-$) $m/z$ 520.2 (M − $H^-$); HRMS (ESI$^-$) $m/z$ calcd for $C_{22}H_{26}N_5O_{10}$ 520.1685 (M − $H^-$), found 520.1683 (M − $H^-$); IR (ATR) $\nu$ 1678, 1335, 1111, 1093, 1055, 851, 566, 548, 526; UV (MeOH) $\lambda_{max}$ (log $\varepsilon$) 202 (4.40), 263 (4.08), 327 (4.13); mp 215 °C; TLC $R_f$ 0.13 (92:8 $CH_2Cl_2$−MeOH); $[\alpha]^{20}_D$ +60.9 ($c$ 0.35, MeOH).

**Desilylated Nucleosyl Amino Acid Urea Derivative ((*R*)-31).** To a solution of nucleosyl amino acid urea derivative (*R*)-**30** (52 mg, 69 μmol) in THF (4 mL) was added TBAF trihydrate (88 mg, 0.28 mmol) at 10 °C. The reaction mixture was stirred at rt for 3.5 h, and then petroleum ether (1 mL) was added. The resultant mixture was directly applied on a silica gel column and purified twice by column chromatography ((1) 1:4 petroleum ether−THF, (2) $CH_2Cl_2$−MeOH gradient (5−10%)) to give (*R*)-**31** as a colorless solid (10 mg, 29%): $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 1.49 (s, 9H, $OC(CH_3)_3$), 2.18−2.19 (m, 2H, 5′-H), 3.92−4.03 (m, 2H, 3′-H, 4′-H), 4.22 (dd, $J$ = 5.1, 3.8 Hz, 1H, 2′-H), 4.49 (dd, $J$ = 6.2, 5.7 Hz, 1H, 6′-H), 5.65 (d, $J$ = 8.0 Hz, 1H, 5-H), 5.78 (d, $J$ = 3.8 Hz, 1H, 1′-H), 7.55−7.60 (m, 3H, 6-H, urea-aryl-2-H, urea-aryl-6-H), 8.14 (d, $J$ = 9.1 Hz, 2H, urea-aryl-3-H, urea-aryl-5-H); $^{13}$C NMR (126 MHz, $CD_3OD$) $\delta$ 28.3, 36.1, 53.0, 74.7, 74.7, 81.6, 83.3, 92.8, 103.0, 118.6, 126.0, 142.9, 143.2, 147.5, 152.2, 156.6, 166.0, 172.9; MS (ESI$^+$) $m/z$ 544.2 (M + $Na^+$); HRMS (ESI$^+$) $m/z$ calcd for $C_{22}H_{27}N_5NaO_{10}$ 544.1650 (M + $Na^+$), found 544.1641 (M + $Na^+$); IR (ATR) $\nu$ 1668, 1503, 1327, 1221, 1149, 1108, 1032, 750, 551; UV (MeOH) $\lambda_{max}$ (log $\varepsilon$) 202 (4.41), 263 (4.01), 328 (4.16); mp 218 °C; TLC $R_f$ 0.11 (92:8 $CH_2Cl_2$−MeOH); $[\alpha]^{20}_D$ +33.2 ($c$ 0.90, MeOH).

**6′-*N*-Alkylated Nucleosyl Amino Acid ((*S*)-33).** To a solution of 3-unprotected nucleosyl amino acid (*S*)-**24** (66 mg, 0.11 mmol) in THF (3.5 mL) were added anhydrous molecular sieves (4 Å), and the mixture was stirred at rt for 5 min. Aldehyde **32** (23 mg, 0.11 mmol) was then added and the reaction mixture was stirred at rt for 20 h with


dx.doi.org/10.1021/jo201935w | J. Org. Chem. 2011, 76, 10083−10098

MeCN (1 mL) being added after 15 h. Subsequently, Amberlyst-15™ (4.9 mg, 23 μmol), sodium triacetoxyborohydride (47 mg, 0.22 mmol) and THF (2 mL) were added and stirring at rt was continued for further 18 h. The unsoluble material was then filtered off and washed with EtOAc (3 × 10 mL). The filtrate was washed with satd $Na_2CO_3$ solution (1 × 50 mL) and the aqueous layer was extracted with EtOAc (1 × 30 mL). The combined organics were dried over $Na_2SO_4$ and evaporated under reduced pressure. The resultant crude product was purified by column chromatography (98:2 $CH_2Cl_2$–MeOH) to give (*S*)-**33** as a colorless solid (78 mg, 91%): $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 0.00 (s, 3H, $SiCH_3$), 0.03 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.09 (s, 3H, $SiCH_3$), 0.83 (s, 9H, $SiC(CH_3)_3$), 0.88 (s, 9H, $SiC(CH_3)_3$), 1.40 (s, 9H, $OC(CH_3)_3$), 1.52 (dddd, $J$ = 7.0, 6.9, 6.7, 6.7 Hz, 2H, propylene-2-H), 1.85–1.97 (m, 3H, 5′-H, 6′-NH), 2.39 (ddd, $J$ = 11.5, 7.0, 7.0 Hz, 1H, propylene-1-H$_a$), 2.52 (ddd, $J$ = 11.5, 6.9, 6.9 Hz, 1H, propylene-1-H$_b$), 3.03 (ddd, $J$ = 6.7, 6.7, 5.6 Hz, 2H, propylene-3-H), 3.12 (dd, $J$ = 7.7, 6.1 Hz, 1H, 6′-H), 3.88 (ddd, $J$ = 8.5, 4.4, 4.3 Hz, 1H, 4′-H), 3.91 (dd, $J$ = 4.5, 4.3 Hz, 1H, 3′-H), 4.33 (dd, $J$ = 4.9, 4.2 Hz, 1H, 2′-H), 5.00 (s, 2H, Cbz-$CH_2$), 5.67 (d, $J$ = 8.1 Hz, 1H, 5-H), 5.71 (d, $J$ = 4.9 Hz, 1H, 1′-H), 7.15 (dd, $J$ = 5.6, 5.6 Hz, 1H, Cbz-NH), 7.30–7.37 (m, 5H, Cbz-aryl-H), 7.60 (d, $J$ = 8.1 Hz, 1H, 6-H), 11.32 (s, 1H, 3-NH); $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ −5.0, −5.0, −4.9, −4.6, 17.5, 17.6, 25.5, 25.6, 27.6, 29.9, 36.3, 38.4, 44.6, 59.1, 65.0, 73.5, 74.5, 80.2, 80.9, 88.5, 102.0, 127.6, 127.6, 128.2, 137.2, 140.9, 150.5, 156.0, 162.9, 173.3; MS (ESI$^+$) $m/z$ 777.5 (M + H$^+$); HRMS (ESI$^+$) $m/z$ calcd for $C_{38}H_{65}N_4O_9Si_2$ 777.4285 (M + H$^+$), found 777.4298 (M + H$^+$); IR (ATR) $\nu$ 1686, 1251, 1151, 1065, 866, 835, 812, 774, 695; UV (MeOH) $\lambda_{max}$ (log $\varepsilon$) 207 (4.21), 263 (3.99); mp 57 °C; TLC $R_f$ 0.07 (96:4 $CH_2Cl_2$–MeOH); $[\alpha]^{20}_D$ +26.5 (*c* 0.84, MeOH).

**6′-N-Alkylated Nucleosyl Amino Acid ((*R*)-33).** To a solution of 3-unprotected nucleosyl amino acid (*R*)-**24** (74 mg, 0.13 mmol) in THF (4 mL) were added anhydrous molecular sieves (4 Å), and the mixture was stirred at rt for 5 min. Aldehyde **32** (27 mg, 0.13 mmol) was then added, and the reaction mixture was stirred at rt for 20 h with MeCN (1 mL) being added after 15 h. Subsequently, Amberlyst-15 (5.7 mg, 27 μmol), sodium triacetoxyborohydride (55 mg, 0.26 mmol), and THF (2 mL) were added and stirring at rt was continued for further 18 h. The unsoluble material was then filtered off and washed with EtOAc (3 × 10 mL). The filtrate was washed with satd $Na_2CO_3$ solution (1 × 50 mL), and the aqueous layer was extracted with EtOAc (1 × 30 mL). The combined organics were dried over $Na_2SO_4$ and evaporated under reduced pressure. The resultant crude product was purified by column chromatography (98:2 $CH_2Cl_2$–MeOH) to give (*R*)-**33** as a colorless solid (83 mg, 85%): $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ −0.02 (s, 3H, $SiCH_3$), 0.04 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.09 (s, 3H, $SiCH_3$), 0.83 (s, 9H, $SiC(CH_3)_3$), 0.89 (s, 9H, $SiC(CH_3)_3$), 1.41 (s, 9H, $OC(CH_3)_3$), 1.47–1.54 (m, 2H, propylene-2-H), 1.78 (ddd, $J$ = 13.8, 8.5, 4.2 Hz, 1H, 5′-H$_a$), 1.83 (s, 1H, 6′-NH), 1.88 (ddd, $J$ = 13.8, 8.7, 4.6 Hz, 1H, 5′-H$_b$), 2.34 (ddd, $J$ = 11.3, 7.1, 7.0 Hz, 1H, propylene-1-H$_a$), 2.54 (ddd, $J$ = 11.3, 7.1, 6.8 Hz, 1H, propylene-1-H$_b$), 3.02 (ddd, $J$ = 6.6, 6.5, 5.7 Hz, 2H, propylene-3-H), 3.08 (dd, $J$ = 8.7, 4.2 Hz, 1H, 6′-H), 3.99–4.04 (m, 2H, 3′-H, 4′-H), 4.34 (dd, $J$ = 5.8, 4.4 Hz, 1H, 2′-H), 5.00 (s, 2H, Cbz-$CH_2$), 5.66 (d, $J$ = 8.1 Hz, 1H, 5-H), 5.76 (d, $J$ = 5.8 Hz, 1H, 1′-H), 7.14 (dd, $J$ = 5.7, 5.7 Hz, 1H, Cbz-NH), 7.28–7.38 (m, 5H, Cbz-aryl-H), 7.59 (d, $J$ = 8.1 Hz, 1H, 6-H), 11.32 (s, 1H, 3-NH); $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ −5.1, −4.9, −4.8, −4.7, 17.4, 17.6, 25.5, 25.6, 27.6, 30.0, 36.3, 38.4, 44.5, 59.0, 65.0, 73.4, 74.9, 80.2, 81.7, 88.0, 102.0, 127.6, 127.6, 128.2, 137.2, 140.8, 150.6, 156.0, 162.8, 173.7; MS (ESI$^+$) $m/z$ 777.5 (M + H$^+$); HRMS (ESI$^+$) $m/z$ calcd for $C_{38}H_{65}N_4O_9Si_2$ 777.4285 (M + H$^+$), found 777.4291 (M + H$^+$); IR (ATR) $\nu$ 1687, 1251, 1149, 1086, 1063, 866, 835, 812, 774; UV (MeOH) $\lambda_{max}$ (log $\varepsilon$) 256 (4.28), 305 (3.98); mp 59 °C; TLC $R_f$ 0.09 (96:4 $CH_2Cl_2$–MeOH); $[\alpha]^{20}_D$ +15.6 (*c* 0.67, MeOH).

***N*-Cbz-Protected Muraymycin Analogue ((*S*)-34).** General procedure D with 6′-N-alkylated nucleosyl amino acid (*S*)-**33** (60 mg, 77 μmol), 1,4-cyclohexadiene (73 μL, 0.77 mmol), 10% Pd/C (10 mg, 9.4 μmol), and MeOH (4 mL) to give the N-deprotected derivative as a colorless solid (48 mg). Some of this material (36 mg, 56 μmol) was then dissolved in THF (4 mL). To a solution of *N*-Cbz-L-leucine (13 mg, 50 μmol) in THF (2 mL) were added HOBt (6.8 mg, 50 μmol), EDC hydrochloride (9.6 mg, 50 μmol), and DIPEA (8.7 μL, 50 μmol). The resultant suspension was stirred at rt for 45 min and then added to the aforementioned solution of the amine at 0 °C. The reaction mixture was stirred at 0 °C for 10 h and at rt for 6 h. It was then diluted with EtOAc (50 mL) and washed with satd $Na_2CO_3$ solution (1 × 50 mL). The organic layer was dried over $Na_2SO_4$ and evaporated under reduced pressure. The resultant crude product was purified by column chromatography (97.5:2.5 $CH_2Cl_2$–MeOH) to give (*S*)-**34** as a colorless solid (32 mg, 70% over two steps from (*S*)-**33**): $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ −0.00 (s, 3H, $SiCH_3$), 0.03 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.09 (s, 3H, $SiCH_3$), 0.83 (s, 9H, $SiC(CH_3)_3$), 0.84 (d, $J$ = 6.9 Hz, 3H, Leu-5-H$_a$), 0.86 (d, $J$ = 6.6 Hz, 3H, Leu-5-H$_b$), 0.88 (s, 9H, $SiC(CH_3)_3$), 1.35 (s, 9H, $OC(CH_3)_3$), 1.40–1.53 (m, 4H, propylene-2-H, Leu-3-H), 1.55–1.62 (m, 1H, Leu-4-H), 1.86–1.90 (m, 2H, 5′-H), 2.35–2.41 (m, 1H, propylene-1-H$_a$), 2.48–2.53 (m, 1H, propylene-1-H$_b$), 3.00–3.06 (m, 1H, propylene-3-H$_a$), 3.08–3.14 (m, 2H, 6′-H, propylene-3-H$_b$), 3.87–3.91 (m, 2H, 3′-H, 4′-H), 3.95–4.00 (m, 1H, Leu-2-H), 4.33 (dd, $J$ = 4.9, 4.6 Hz, 1H, 2′-H), 5.00 (d, $J$ = 12.6 Hz, 1H, Cbz-$CH_2$-H$_a$), 5.03 (d, $J$ = 12.6 Hz, 1H, Cbz-$CH_2$–H$_b$), 5.67 (d, $J$ = 8.1 Hz, 1H, 5-H), 5.70 (d, $J$ = 4.9 Hz, 1H, 1′-H), 7.24 (d, $J$ = 8.2 Hz, 1H, Leu-NH), 7.28–7.38 (m, 5H, Cbz-aryl-H), 7.60 (d, $J$ = 8.1 Hz, 1H, 6-H), 7.79 (dd, $J$ = 5.6, 5.5 Hz, 1H, propylene-NH), 11.31 (s, 1H, 3-NH); $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ −5.0, −5.0, −4.9, −4.6, 17.5, 17.6, 21.5, 22.8, 24.1, 25.5, 25.6, 27.6, 29.6, 36.3, 36.6, 40.9, 44.6, 53.1, 59.1, 65.2, 73.5, 73.5, 80.2, 80.8, 88.5, 102.0, 127.5, 127.6, 128.2, 137.0, 140.9, 152.2, 155.8, 162.9, 171.9, 173.3; MS (ESI$^+$) $m/z$ 890.5 (M + H$^+$); HRMS (ESI$^+$) $m/z$ calcd for $C_{44}H_{76}N_5O_{10}Si_2$ 890.5125 (M + H$^+$), found 890.5124 (M + H$^+$); IR (ATR) $\nu$ 1686, 1251, 1153, 1043, 867, 835, 813, 775, 696; UV (MeOH) $\lambda_{max}$ (log $\varepsilon$) 204 (4.34), 262 (4.01), 318 (2.62); mp 71 °C; TLC $R_f$ 0.24 (19:1 $CH_2Cl_2$–MeOH); analytical HPLC $t_R$ 9.9 min (method III); $[\alpha]^{20}_D$ +14.8 (*c* 1.1, MeOH).

***N*-Cbz-Protected Muraymycin Analogue ((*R*)-34).** General procedure D with 6′-N-alkylated nucleosyl amino acid (*R*)-**33** (63 mg, 81 μmol), 1,4-cyclohexadiene (77 μL, 0.81 mmol), 10% Pd/C (10 mg, 9.4 μmol) and MeOH (4 mL) to give the N-deprotected derivative as a colorless solid (51 mg). Some of this material (41 mg, 64 μmol) was then dissolved in THF (4 mL). To a solution of *N*-Cbz-L-leucine (15 mg, 58 μmol) in THF (2.3 mL), HOBt (7.8 mg, 58 μmol), EDC hydrochloride (11 mg, 58 μmol) and DIPEA (10 μL, 58 μmol) were added. The resultant suspension was stirred at rt for 45 min and then added to the aforementioned solution of the amine at 0 °C. The reaction mixture was stirred at 0 °C for 10 h and at rt for 6 h. It was then diluted with EtOAc (50 mL) and washed with satd $Na_2CO_3$ solution (1 × 50 mL). The organic layer was dried over $Na_2SO_4$ and evaporated under reduced pressure. The resultant crude product was purified by column chromatography (97.5:2.5 $CH_2Cl_2$–MeOH) to give (*R*)-**34** as a colorless solid (39 mg, 75% over two steps from (*R*)-**33**): $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ −0.02 (s, 3H, $SiCH_3$), 0.03 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.09 (s, 3H, $SiCH_3$), 0.83 (s, 9H, $SiC(CH_3)_3$), 0.84 (d, $J$ = 6.9 Hz, 3H, Leu-5-H$_a$), 0.86 (d, $J$ = 6.7 Hz, 3H, Leu-5-H$_b$), 0.88 (s, 9H, $SiC(CH_3)_3$), 1.37–1.52 (m, 4H, propylene-2-H, Leu-3-H), 1.41 (s, 9H, $OC(CH_3)_3$), 1.55–1.62 (m, 1H, Leu-4-H), 1.77 (ddd, $J$ = 14.0, 8.6, 4.0 Hz, 1H, 5′-H$_a$), 1.88 (ddd, $J$ = 14.0, 9.4, 4.6 Hz, 1H, 5′-H$_b$), 2.30–2.35 (m, 1H, propylene-1-H$_a$), 2.51–2.55 (m, 1H, propylene-1-H$_b$), 2.99–3.13 (m, 3H, 6′-H, propylene-3-H), 3.95–4.05 (m, 3H, Leu-2-H, 3′-H, 4′-H), 4.34 (dd, $J$ = 5.8, 4.4 Hz, 1H, 2′-H), 5.00 (d, $J$ = 12.7 Hz, 1H, Cbz-$CH_2$-H$_a$), 5.03 (d, $J$ = 12.7 Hz, 1H, Cbz-$CH_2$-H$_b$), 5.66 (d, $J$ = 8.1 Hz, 1H, 5-H), 5.76 (d, $J$ = 5.8 Hz, 1H, 1′-H), 7.23 (d, $J$ = 8.3 Hz, 1H, Leu-NH), 7.28–7.37 (m, 5H, Cbz-aryl-H), 7.59 (d, $J$ = 8.1 Hz, 1H, 6-H), 7.78 (dd, $J$ = 5.6, 5.6 Hz, 1H, propylene-NH), 11.31 (s, 1H, 3-NH); $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ −5.1, −4.9, −4.8, −4.7, 17.4, 17.6, 21.5, 22.8, 24.1, 25.5, 25.6, 27.6, 29.8, 36.4, 36.6, 41.0, 44.7, 53.1, 59.0, 65.2, 73.4, 74.9, 80.2, 81.7, 88.0, 102.0, 127.5, 127.6, 128.2, 137.0, 140.8, 150.6, 155.7, 162.8, 171.9, 173.7; MS (ESI$^+$) $m/z$ 890.5 (M + H$^+$); HRMS (ESI$^+$) $m/z$ calcd for $C_{44}H_{76}N_5O_{10}Si_2$ 890.5125 (M +


dx.doi.org/10.1021/jo201935w | J. Org. Chem. 2011, 76, 10083–10098

$H^+$), found 890.5122 (M + $H^+$); IR (ATR) $\nu$ 1686, 1551, 1151, 1049, 866, 836, 812, 775, 696; UV (MeOH) $\lambda_{max}$ (log $\varepsilon$) 204 (4.32), 263 (4.01); mp 69 °C; TLC $R_f$ 0.27 (19:1 $CH_2Cl_2$–MeOH); Analytical HPLC $t_R$ 10.5 min (method III); $[\alpha]^{20}_D$ +15.9 (*c* 1.0, MeOH).

**Optimization of the Hydrogenolytic Deprotection of (*S*)-23 and (*R*)-23.** Hydrogenolysis reactions described in Table 1 were carried out as follows. To a solution of (*S*)-**23** or (*R*)-**23** in the listed solvent (0.125 mL/mg starting material) was added the listed catalyst. The reaction mixture was stirred under an atmosphere of $H_2$ (1 bar, balloon) at rt for the listed time. After filtration through a syringe filter and rinsing of the filter with MeOH (3×), the solvent of the filtrate was removed under reduced pressure. The resultant products were analyzed by $^1$H NMR spectroscopy.

**X-ray Structure Determination of (*R*)-31.** A single crystal was selected from the Schlenk flask under argon atmosphere and covered with perfluorinated polyether oil on a microscope slide, which was cooled with a nitrogen gas flow using the X-TEMP 2.[30a,b] An appropriate crystal was selected using a polarize microscope, mounted on the tip of a MiTeGen MicroMount, fixed to a goniometer head and shock-cooled by the crystal cooling device. The data of (*R*)-**31** were collected on a Bruker SMART APEXII Quazar diffractometer with D8 goniometer (100 K, Mo K$\alpha$ radiation, $\lambda$ = 71.073 pm; mirror optics).[30c] The data were integrated with SAINT,[30d] and an empirical absorption correction (SADABS) was applied.[30e] The structure was solved by direct methods (SHELXS) and refined on $F^2$ using the full-matrix least-squares methods of SHELXL.[30f] All non-hydrogen atoms were refined with anisotropic displacement parameters. The hydrogen atoms at the nitrogen and oxygen atoms are refined freely using distance restraints, all carbon bonded hydrogen atoms bonded to $sp^2$ ($sp^3$) carbon atoms were assigned ideal positions and refined using a riding model with $U_{iso}$ constrained to 1.2 (1.5) times the $U_{eq}$ value of the parent carbon atom. The crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Centre and are available under no. 840892. Copies of the data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

## ■ ASSOCIATED CONTENT

### Supporting Information

$^1$H, $^{13}$C, and $^{19}$F NMR spectra of all new compounds (including details of the $^1$H NOE NMR experiments) and data on the X-ray crystal structure of (*R*)-**31** including a full-page size thermal ellipsoid and packing plot. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

### Corresponding Author

*E-mail: christian.ducho@uni-paderborn.de.

## ■ ACKNOWLEDGMENTS

We thank the Deutsche Forschungsgemeinschaft (DFG, SFB 803 "Functionality controlled by organization in and between membranes") and the Fonds der Chemischen Industrie (FCI, Sachkostenzuschuss) for financial support. We are also grateful for support from the Danish National Research Foundation (DNRF) funded Center of Materials Crystallography (CMC) (D.S., M.G.). Technical support by Friederike Lizzy is gratefully acknowledged.

## ■ DEDICATION

Dedicated to Professor Joachim Thiem on the occasion of his 70th birthday.

## ■ REFERENCES

(1) (a) De Clercq, E. *J. Med. Chem.* **2010**, *53*, 1438–1450. (b) De Clercq, E. *Biochem. Pharmacol.* **2011**, *82*, 99–109. (c) Miura, S.; Izuta, S. *Curr. Drug Targets* **2004**, *5*, 191–195. (d) Bonate, P. L.; Arthaud, L.; Cantrell, W. R.; Stephenson, K.; Secrist, J. A.; Weitman, S. *Nat. Rev. Drug Discovery* **2006**, *5*, 855–863.

(2) (a) Wagner, R. W. *Nature* **1994**, *372*, 333–335. (b) Xodo, L. E.; Cogoi, S.; Rapozzi, V. *Curr. Pharm. Des.* **2004**, *10*, 805–819. (c) Arenz, C. *Angew. Chem.* **2006**, *118*, 5170–5172; *Angew. Chem., Int. Ed.* **2006**, *45*, 5048–5050. (d) De Mesmaeker, A.; Häner, R.; Martin, P.; Moser, H. E. *Acc. Chem. Res.* **1995**, *28*, 366–374. (e) Cobb, A. J. A. *Org. Biomol. Chem.* **2007**, *5*, 3260–3275.

(3) (a) Rothemund, P. W. K. *Nature* **2006**, *440*, 297–302. (b) Feldkamp, U.; Niemeyer, C. M. *Angew. Chem.* **2006**, *118*, 1888–1910; *Angew. Chem., Int. Ed.* **2006**, *45*, 1856–1876. (c) Gramlich, P. M. E.; Wirges, C. T.; Manetto, A.; Carell, T. *Angew. Chem.* **2008**, *120*, 8478–8487; *Angew. Chem., Int. Ed.* **2008**, *47*, 8350–8358.

(4) (a) Nielsen, P. E.; Egholm, M.; Berg, R. H.; Buchardt, O. *Science* **1991**, *254*, 1497–1500. (b) Zhilina, Z. V.; Ziemba, A. J.; Ebbinghaus, S. W. *Curr. Top. Med. Chem.* **2005**, *5*, 1119–1131. (c) Karkare, S.; Bhatnagar, D. *Appl. Microbiol. Biotechnol.* **2006**, *71*, 575–586.

(5) (a) Lebreton, J.; De Mesmaeker, A.; Waldner, A.; Fritsch, V.; Wolf, R. M.; Freier, S. M. *Tetrahedron Lett.* **1993**, *34*, 6383–6386. (b) De Mesmaeker, A.; Waldner, A.; Lebreton, J.; Hoffmann, P.; Fritsch, V.; Wolf, R. M.; Freier, S. M. *Synlett* **1993**, 733–736. (c) De Mesmaeker, A.; Waldner, A.; Lebreton, J.; Hoffmann, P.; Fritsch, V.; Wolf, R. M.; Freier, S. M. *Angew. Chem.* **1994**, *106*, 237–240; *Angew. Chem., Int. Ed.* **1994**, *33*, 226–229. (d) Lebreton, J.; Waldner, A.; Fritsch, V.; Wolf, R. M.; De Mesmaeker, A. *Tetrahedron Lett.* **1994**, *35*, 5225–5228. (e) Rozners, E.; Katkevica, D.; Bizdena, E.; Stromberg, R. *J. Am. Chem. Soc.* **2003**, *125*, 12125–12136. (f) Selvam, C.; Thomas, S.; Abbott, J.; Kennedy, S. D.; Rozners, E. *Angew. Chem.* **2011**, *123*, 2116–2118; *Angew. Chem., Int. Ed.* **2011**, *50*, 2068–2070.

(6) (a) Dai, N.; Guo, J.; Teo, Y. N.; Kool, E. T. *Angew. Chem.* **2011**, *123*, 5211–5215; *Angew. Chem., Int. Ed.* **2011**, *50*, 5105–5109. (b) Niemeyer, C. M. *Angew. Chem.* **2010**, *122*, 1220–1238; *Angew. Chem., Int. Ed.* **2010**, *49*, 1200–1216.

(7) (a) Kimura, K.-I.; Bugg, T. D. H. *Nat. Prod. Rep.* **2003**, *20*, 252–273. (b) Winn, M.; Goss, R. J. M.; Kimura, K.-I.; Bugg, T. D. H. *Nat. Prod. Rep.* **2010**, *27*, 279–304.

(8) (a) Struve, W. G.; Neuhaus, F. C. *Biochem. Biophys. Res. Commun.* **1965**, *18*, 6–12. (b) Struve, W. G.; Sinha, R. K.; Neuhaus, F. C.; Prime, M. S. *Biochemistry* **1966**, *5*, 82–93. (c) Heydanek, M. G.; Struve, W. G.; Neuhaus, F. C. *Biochemistry* **1969**, *8*, 1214–1221. (d) Ikeda, M.; Wachi, M.; Jung, H. K.; Ishino, F.; Matsuhashi, M. *J. Bacteriol.* **1991**, *173*, 1021–1025. (e) Boyle, D. S.; Donachie, W. D. *J. Bacteriol.* **1998**, *180*, 6429–6432.

(9) (a) Taubes, G. *Science* **2008**, *321*, 356–361. (b) Cooper, M. A.; Shlaes, D. *Nature* **2011**, *472*, 32.

(10) (a) Dini, C. *Curr. Top. Med. Chem.* **2005**, *5*, 1221–1236. (b) Bugg, T. D. H.; Lloyd, A. J.; Roper, D. I. *Infect. Disorders Drug Targets* **2006**, *6*, 85–106.

(11) McDonald, L. A.; Barbieri, L. R.; Carter, G. T.; Lenoy, E.; Lotvin, J.; Petersen, P. J.; Siegel, M. M.; Singh, G.; Williamson, R. T. *J. Am. Chem. Soc.* **2002**, *124*, 10260–10261.

(12) Igarashi, M.; Nakagawa, N.; Doi, S.; Hattori, N.; Naganawa, H.; Hamada, M. *J. Antibiot.* **2003**, *56*, 580–583.

(13) Yamashita, A.; Norton, E.; Petersen, P. J.; Rasmussen, B. A.; Singh, G.; Yang, Y.; Mansour, T. S.; Ho, D. M. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3345–3350.

(14) (a) Hirano, S.; Ichikawa, S.; Matsuda, A. *Angew. Chem.* **2005**, *117*, 1888–1890; *Angew. Chem., Int. Ed.* **2005**, *44*, 1854–1856. (b) Hirano, S.; Ichikawa, S.; Matsuda, A. *J. Org. Chem.* **2007**, *72*, 9936–9946. (c) Tanino, T.; Ichikawa, S.; Shiro, M.; Matsuda, A. *J. Org. Chem.* **2010**, *75*, 1366–1377.

(15) (a) Spork, A. P.; Koppermann, S.; Ducho, C. *Synlett* **2009**, 2503–2507. (b) Spork, A. P.; Koppermann, S.; Dittrich, B.; Herbst-Irmer, R.; Ducho, C. *Tetrahedron: Asymmetry* **2010**, *21*, 763–766.

(16) (a) Lin, Y.-I.; Li, Z.; Francisco, G. D.; McDonald, L. A.; Davis, R. A.; Singh, G.; Yang, Y.; Mansour, T. S. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2341–2344. (b) Tanino, T.; Ichikawa, S.; Al-Dabbagh, B.;

Bouhss, A.; Oyama, H.; Matsuda, A. *ACS Med. Chem. Lett.* **2010**, *1*, 258−262.
(17) (a) Hirano, S.; Ichikawa, S.; Matsuda, A. *J. Org. Chem.* **2008**, *73*, 569−577. (b) Hirano, S.; Ichikawa, S.; Matsuda, A. *Bioorg. Med. Chem.* **2008**, *16*, 428−436. (c) Hirano, S.; Ichikawa, S.; Matsuda, A. *Bioorg. Med. Chem.* **2008**, *16*, 5123−5133. (d) Ii, K.; Ichikawa, S.; Al-Dabbagh, B.; Bouhss, A.; Matsuda, A. *J. Med. Chem.* **2010**, *53*, 3793−3813.
(18) Spork, A. P.; Ducho, C. *Org. Biomol. Chem.* **2010**, *8*, 2323−2326.
(19) Hisamatsu, Y.; Hasada, K.; Amano, F.; Tsubota, Y.; Wasada-Tsutsui, Y.; Shirai, N.; Ikeda, S.; Odashima, K. *Chem.—Eur. J.* **2006**, *12*, 7733−7741.
(20) Zhu, X.-F.; Williams, H. J.; Scott, A. I. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2305−2306.
(21) (a) Smith, D. B.; Martin, J. A.; Klumpp, K.; Baker, S. J.; Blomgren, P. A.; Devos, R.; Granycome, C.; Hang, J.; Hobbs, C. J.; Jiang, W.-R.; Laxton, C.; Le Pogam, S.; Leveque, V.; Ma, H.; Maile, G.; Merrett, J. H.; Pichota, A.; Sarma, K.; Smith, M.; Swallow, S.; Symons, J.; Vesey, D.; Najera, I.; Cammack, N. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2570−2576. (b) Nencka, R.; Sinnaeve, D.; Karalic, I.; Martins, J. C.; Van Calenbergh, S. *Org. Biomol. Chem.* **2010**, *8*, 5234−5246.
(22) (a) Schmidt, U.; Lieberknecht, A.; Schanbacher, U.; Beuttler, T.; Wild, J. *Angew. Chem.* **1982**, *94*, 797−798; *Angew. Chem., Int. Ed.* **1982**, *21*, 776−777. (b) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1984**, 53−60. (c) Schmidt, U.; Wild, J. *Liebigs Ann. Chem.* **1985**, 1882−1894. (d) Hamzavi, R.; Dolle, F.; Tavitian, B.; Dahl, O.; Nielsen, P. E. *Bioconjugate Chem.* **2003**, *14*, 941−954.
(23) Schmidt, U.; Griesser, H.; Leitenberger, V.; Lieberknecht, A.; Mangold, R.; Meyer, R.; Riedl, B. *Synthesis* **1992**, 487−490.
(24) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Wienkauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946−5952.
(25) Mazurkiewicz, R.; Kuźnik, A.; Grymel, M.; Kuźnik, N. *Magn. Reson. Chem.* **2005**, *43*, 36−40.
(26) Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518−8519.
(27) (a) Masquelin, T.; Broger, E.; Müller, K.; Schmid, R.; Obrecht, D. *Helv. Chim. Acta* **1994**, *77*, 1395−1411. (b) Ducho, C.; Hamed, R. B.; Batchelar, E. T.; Sorensen, J. L.; Odell, B.; Schofield, C. J. *Org. Biomol. Chem.* **2009**, *7*, 2770−2779.
(28) Gentle, C. A.; Harrison, S. A.; Inukai, M.; Bugg, T. D. H. *J. Chem. Soc., Perkin Trans 1* **1999**, 1287−1294.
(29) (a) Sarabia, F.; Martín-Ortiz, L. *Tetrahedron* **2005**, *61*, 11850−11865. (b) More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001−3003.
(30) (a) Kottke, T.; Stalke, D. *J. Appl. Crystallogr.* **1993**, *26*, 615−619. (b) Stalke, D. *Chem. Soc. Rev.* **1998**, *27*, 171−178. (c) Schulz, T.; Meindl, K.; Leusser, D.; Stern, D.; Graf, J.; Michaelsen, C.; Ruf, M.; Sheldrick, G. M.; Stalke, D. *J. Appl. Crystallogr.* **2009**, *42*, 885−891. (d) SAINT v7.68A in Bruker APEX v2011.9, Bruker AXS Inst. Inc., Madison, 2008. (e) Sheldrick, G. M. SADABS 2008/2, Göttingen, 2008. (f) Sheldrick, G. M. *Acta Crystallogr., Sect. A* **2008**, *64*, 112−122. (g) Flack, H. D. *Acta Crystallogr., Sect. A* **1983**, *39*, 876−881.
(31) (a) Bouhss, A.; Crouvoisier, M.; Blanot, D.; Mengin-Lecreulx, D. *J. Biol. Chem.* **2004**, *279*, 29974−29980. (b) Stachyra, T.; Dini, C.; Ferrari, P.; Bouhss, A.; van Heijernoort, J.; Mengin-Lecreulx, D.; Blanot, D.; Biton, J.; Le Beller, D. *Antimicrob. Agents Chemother.* **2004**, *48*, 897−902.