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Complex Peptidyl Nucleoside Antibiotics: Efficient Syntheses of the Glycosyl Nucleoside Amino Acid Cores

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Employing an amino acid chiral template strategy, the present research describes a general and highly efficient protocol for the rapid construction of enantiopure furanosyl and pyranosyl nucleoside amino acid cores as present in various complex peptidyl nucleoside antibiotics. Starting from easily available D-serine, the strategy and the approach involve rapid and efficient stereoselective synthesis of five- or six-membered lactone amino alcohols, followed by incorporation of the required functionalities of the target molecules on these strategically functionalized chiral templates.

The complex peptidyl nucleoside antibiotics are secondary microbial metabolites with impressive antifungal activity against various human pathogenic fungi.[1] In a novel mode of action, many of these compounds act by strong and selective inhibition of chitin synthase, the enzyme responsible for the biosynthesis of chitin, an essential component of the fungal cell wall.[2] Because the chitin biosynthetic pathway is absent in humans and other vertebrates, inhibition of chitin biosynthesis is considered to be of immense therapeutic potential for combating various opportunistic fungal infections.[3] By virtue of their potent and selective chitin synthase inhibitory action, the peptidyl nucleoside antibiotics represent extremely promising leads for the development of novel, nontoxic antifungal therapeutics.[4] Representative structures of some complex peptidyl nucleoside antibiotics are shown in Figure 1. Among these compounds, the polyoxins and the nikkomycins are the best-known and most effective inhibitors of chitin synthase. The structurally more complex ezomycins, amipurimycin, and miharamycins also exhibit a broad range of antifungal activity, although the modes of action of these compounds are yet to be determined.[1]

Typically, these unique natural products consist of three distinct structural components: (i) nucleobase, (ii) a central carbohydrate framework, and (iii) peptidyl region. Interestingly, a recurring theme in these compounds is the attachment of an α-amino acid (amino alcohol in the ezomycins) functionality at the C4′ or C5′ position of the nucleoside component. A major structural difference in these groups of compounds, however, is the presence of a furanosyl nucleosidic core in the polyoxins, nikkomycins, and ezomycins, while the amipurimycin and miharamycin families of compounds consists of a pyranosyl nucleoside core. Extensive efforts are being directed toward synthesis and structure−activity relationship (SAR) studies of these peptidyl nucleosides toward their pharmacophore elucidation, improvement of inhibitory potencies, and enhancement of antifungal properties.[5]

Among the various complex peptidyl nucleosides, total syntheses of several polyoxins and nikkomycins have been reported in the literature; however, the total syntheses of the ezomycin, amipurimycin, and miharamycin families of compounds have not yet been accomplished.[5] Traditionally, a common strategy for the synthesis of the central glycosyl amino acid core of the peptidyl nucleosides has involved utilization of readily available carbohydrate starting materials.[6] However, a

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(6) For representative examples, see: (a) Kuzuhara, H.; Ohrui, H.; Emoto, S. *Tetrahedron Lett.* **1973**, *14*, 5055−5058. (b) Dondoni, A.; Franco, S.; Junquera, F.; Merchan, F. M.; Merino, P.; Tejero, T. *J. Org. Chem.* **1997**, *62*, 2, 5497−5507. (c) Kato, K.; Chen, C. Y.; Akita, H.

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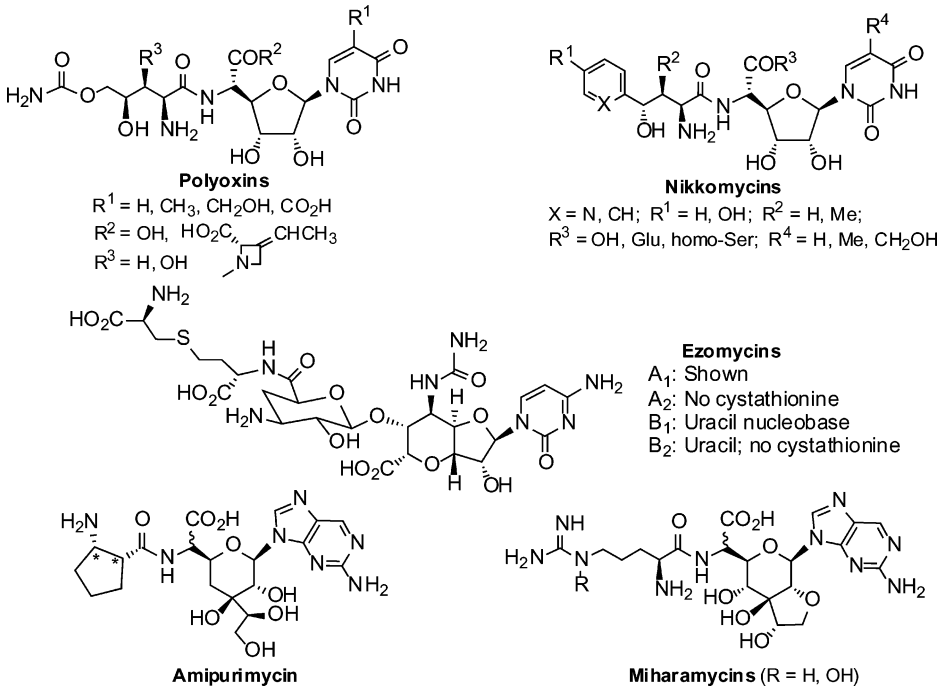


FIGURE 1. Representative examples of complex peptidyl nucleoside antibiotics.

disadvantage inherent in the carbohydrate approach has been the often extensive protection−deprotection sequences necessitated by the presence of multiple hydroxy groups, and the requirement of additional reaction steps to incorporate the α-amino acid functionality as present in the target products. Therefore, development of alternative strategies, involving asymmetric synthesis of the above glycosyl amino acid core, starting from a more simple non-carbohydrate synthon remains an attractive proposition. In one such pioneering effort, Garner and co-workers have utilized serine as a starting material to develop a novel synthetic route to the polyoxins.[7] Similarly, employing a hetero Diels−Alder cycloaddition involving a serine-derived homochiral oxazolidine aldehyde (Garner's aldehyde[8]), the same research group has also developed an efficient route to the branched carbohydrate amino acid fragment of amipurimycin.[9] Besides circumventing the shortcomings of the carbohydrate approach, the amino acid-based strategy affords greater flexibility toward various structural modifications and also allows more control over creation of new stereocenters, essential tools for pharmacophore modification and further structure−activity relationship studies.

In view of the above observations, and in continuation of our efforts toward amino acid chiral template-assisted stereoselective synthesis of bioactive molecules,[10] we have initiated a research program exploring new and more efficient methods for the synthesis and SAR studies of various complex peptidyl nucleoside antibiotics. Details of our preliminary studies, culminating in the development of a versatile route to the glycosyl amino acid nucleoside cores of the peptidyl nucleoside antibiotics, are described herein.

Results and Discussion

A common structural feature of the peptidyl nucleosides is the presence of a furanosyl or a pyranosyl α-amino acid nucleoside subunit. Our retrosynthetic plan therefore envisages a unified synthetic strategy based upon initial stereocontrolled formation of a pivotal furanosyl amino acid precursor **1** (for the polyoxin, nikkomycin, and ezomycin series), or the corresponding pyranosyl analogue **2** (for amipurimycin and miharamycins), followed by construction of the remaining structural adornments on these strategically functionalized chiral templates (Figure 2). Further disconnection reveals the 1,2-

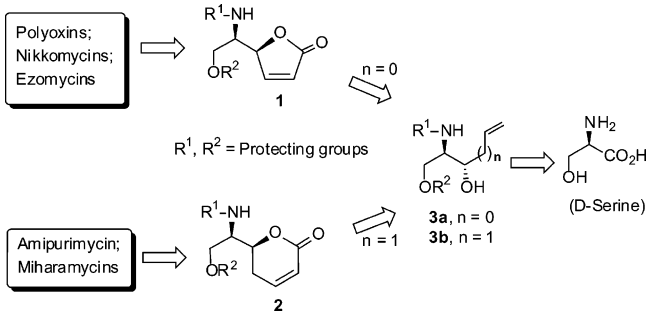


FIGURE 2. Retrosynthetic analysis and strategy.

Synthesis **1998**, 1527−1533. (d) Chen, A.; Thomas, E. J.; Wilson, P. D. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3305−3310. (e) Kutterer, K. M. K.; Just, G. *Heterocycles* **1999**, *51*, 1409−1420. (f) Ghosh, A. K.; Wang, Y. *J. Org. Chem.* **1999**, *64*, 2789−2795. (g) Gonda, J.; Martinkova, M.; Walko, M.; Zavacka, E.; Budesinsky, M.; Cisarova, I. *Tetrahedron Lett.* **2001**, *42*, 4401−4404.

(7) Garner, P.; Park, J. M. *J. Org. Chem.* **1990**, *55*, 3772−3787.

(8) Garner, P. *Tetrahedron Lett.* **1984**, *25*, 5855−5858.

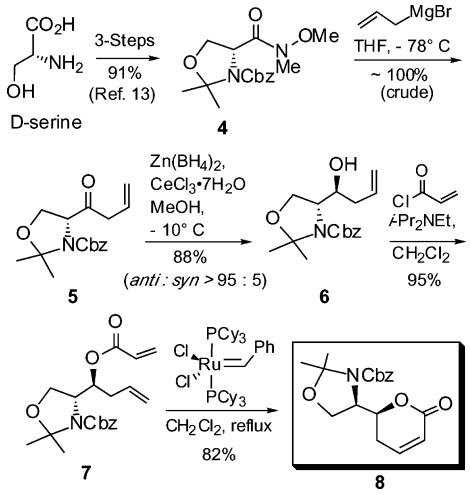
(9) Garner, P.; Yoo, J. K.; Sarabu, R.; Kennedy, V. O.; Youngs, W. J. *Tetrahedron* **1998**, *55*, 9303−9316.

(10) For some recent studies, see: (a) Khalaf, J. K.; Datta, A. *J. Org. Chem.* **2004**, *69*, 387−390. (b) Stauffer, C. S.; Datta, A. *Tetrahedron* **2002**, *58*, 9765−9767. (c) Ravi Kumar, J. S.; Roy, S.; Datta, A. *Tetrahedron* **2001**, *57*, 1169−1173. (d) Veeresa, G.; Datta, A. *J. Org. Chem.* **2000**, *65*, 7609−7611 and references therein.

anti-amino alcohol **3** as a convenient building block for the pivotal lactones **1** or **2**. Finally, easily available enantiopure D-serine, containing an amine and two potentially orthogonal (masked) carbonyl functionalities, represents the ideal platform for launching our proposed synthetic endeavor.

As precedented in the literature, addition of vinyl- or allyl-Grignard reagents to Garner's aldehyde results in the corresponding allylic- or homoallylic alcohol adducts **3a** or **3b**, respectively, with moderate *anti*-selectivity.[11] Although methods have been developed, wherein use of chiral reagents or chiral allyl substrates resulted in improved selectivity in the formation of the homoallylic alcohol **3b**, these methods usually require the multistep synthesis of the corresponding chiral catalysts/substrates and their subsequent use in stoichiometric quantities.[12] Moreover, these methods are not amenable toward the synthesis of the allylic alcohol adduct **3a**. We therefore decided to investigate an alternative approach toward more efficient formation of both the allylic and the homoallylic *anti*-1,2-amino alcohol adducts required for our proposed synthesis.

SCHEME 1

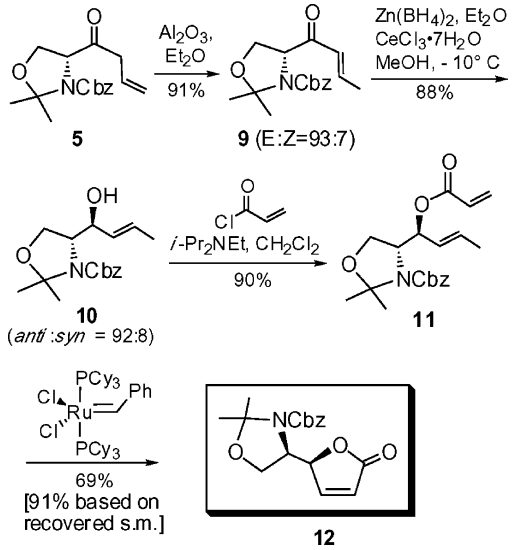


We have recently reported an efficient method for the stereoselective synthesis of *anti*-1,2-amino alcohol **6** (Scheme 1).[10a] The method involves initial conversion of D-serine to the corresponding *N*,*O*-acetonide protected Weinreb amide **4** in good overall yield (Scheme 1).[13] Reaction of the amide **4** with allylmagnesium bromide cleanly results in the corresponding allyl ketone **5** in quantitative yield. However, it was observed that prolonged storage or attempted column chromatographic purification of **5** resulted in partial isomerization of the terminal olefin to the corresponding α,β-unsaturated ketone derivative. Subsequently, instead of purification, the crude ketone was directly subjected to the next reaction. Accordingly, neighboring -*N*Cbz group-assisted chelation-controlled reduction of the ketone **5** with zinc-borohydride in the presence of $CeCl_3 \cdot 7H_2O$[14] provided the required 1,2-*anti*-amino alcohol derivative **6** with excellent stereocontrol (*anti*:*syn* > 95:5) and high overall yield.[10a]

As per our retrosynthetic strategy (Figure 2), utilization of **6** toward formation of the desired chiral amino lactone derivative **8** constitutes the first step in our present research goal. Thus, reaction of **6** with acryloyl chloride under standard conditions resulted in the corresponding acrylate **7** in near quantitative yield. Subjecting **7** to ring closure under Grubbs' olefin metathesis protocol[15] cleanly resulted in the lactone **8** (Scheme 1) in high yield.

The next target in our synthetic scheme entailed development of a similar route toward the five-membered amino lactone **1**. Unfortunately, unlike the formation of the allylic ketone **5** (Scheme 1), direct conversion of the Weinreb amide **4** to the corresponding vinyl ketone (via addition of vinylmagnesium bromide) was found to be problematic. Lability of the product vinylic ketone (a good Michael acceptor) toward adventitious nucleophiles during reaction workup, purification, and subsequent reactions of this intermediate precluded its further use. In an innovative solution to this problem, however, we found an efficient protocol, whereupon the allylic ketone **5** itself could be utilized for our intended synthesis. As mentioned earlier (vide supra), the allylic ketone **5** was found to be prone to double bond isomerization. Taking advantage of this observation, treatment of **5** with neutral alumina at rt resulted in its clean conversion to the corresponding double bond isomerized α,β-unsaturated ketone **9** (*E*:*Z* = 93:7) in high yield (Scheme 2). Gratifyingly, the chelation-controlled reduction of the ketone **9** with zinc

SCHEME 2



(11) For addition of vinylmagnesium bromide, see: (a) Tamamura, H.; Yamashita, M.; Nakajima, Y.; Sakano, K.; Otaka, A.; Ohno, H.; Ibuka, T.; Fujii, N. *J. Chem. Soc., Perkin Trans. I* **1999**, 2983−2996. (b) Ojima, I.; Vidal, E. S. *J. Org. Chem.* **1998**, *63*, 7999−8003 and references therein. For addition of allylmagnesium bromide, see: (c) Jackson, M. D.; Gould, S. J.; Zabriskie, T. M. *J. Org. Chem.* **2002**, *67*, 2934−2941.

(12) (a) Pattenden, G.; Plowright, A. T. *Tetrahedron Lett.* **2000**, *41*, 983−986. (b) Roush, W. R.; Hunt, J. A. *J. Org. Chem.* **1995**, *60*, 798−806. (c) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321−2336.

(13) Collier, P. N.; Campbell, A. D.; Patel, I.; Raynham, T. M.; Taylor, R. J. K. *J. Org. Chem.* **2002**, *67*, 1802.

(14) Campbell, J. E.; Englund, E. E.; Burke, S. D. *Org. Lett.* **2002**, *4*, 2273.

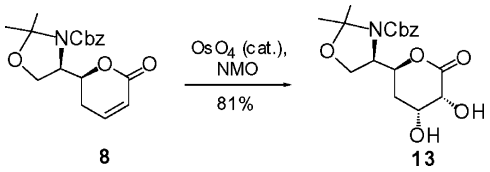
(15) For a similar lactonization approach, see: Ghosh, A. K.; Cappielo, J.; Shin, D. *Tetrahedron Lett.* **1998**, *39*, 4651−4654.

borohydride proceeded smoothly to form the allylic alcohol derivative **10** with high *anti*-selectivity (*anti*:*syn* = 92:8). Thus, the above strategy resulted in an efficient pathway in which the same ketone intermediate **5** could be easily manipulated to afford either the homoallylic or the allylic *anti*-1,2-amino alcohol adducts **6** and **10**, respectively. Following the same sequence of reactions as in Scheme 1, the amino alcohol **10** was subsequently converted to the desired amino butenolide **12** (Scheme 2) in good overall yield.

Following the concise and efficient pathways described in the above schemes, we could readily synthesize gram quantities of **8** and **12** in consistently good overall yields. As is evident, these strategically functionalized intermediates already incorporate the desired amine functionality as present in the various peptidyl nucleosides of our interest. Moreover, the protected terminal primary hydroxy group in the above intermediates represents a convenient precursor for carboxylic acid or aldehyde functional groups. The ring olefinic bond allows for a one-step introduction of the required diol functionality and also provides an easy handle for carrying out future structural modifications (epoxidation, nucleophilic/electrophilic addition, deoxygenation, halogenation, hydrogenation, etc.) at these sites. Similarly, the lactone carbonyl can be utilized toward desired introduction of nucleobases. Importantly, the chirality of the starting amino acid can be easily utilized to control and "grow" asymmetry [16] in the subsequent reactions, thereby providing access to various natural and nonnatural stereoisomeric products.

Successful attainment of our preliminary synthetic goals (Figure 2) created the opportunity to further explore the transformation of the pivotal lactones **8** and **12** to more highly functionalized furanosyl and pyranosyl nucleoside amino acid structural framework. Accordingly, when the chiral aminopyrone **8** was subjected to osmium tetroxide-assisted dihydroxylation, it underwent a highly stereoselective oxidation (>95%) to form the corresponding diol **13** (Scheme 3).

SCHEME 3



The structure and assigned stereochemistry of the diol **13** was confirmed by X-ray crystallographic studies (Figure 3). The stereochemical outcome of the above dihydroxylation can be attributed to the selective osmylation of **8** from the less hindered α-face.

Reduction of the lactone to the corresponding lactol and acetylation of the three hydroxy groups uneventfully afforded the triacetate derivative **14** (Scheme 4). Toward incorporation of the C-5 amino acid functionality, the *N*,*O*-acetonide linkage was cleaved, unmasking the amino alcohol **15**. Subsequent oxidation of the primary hydroxy group to carboxylic acid and esterification of the crude

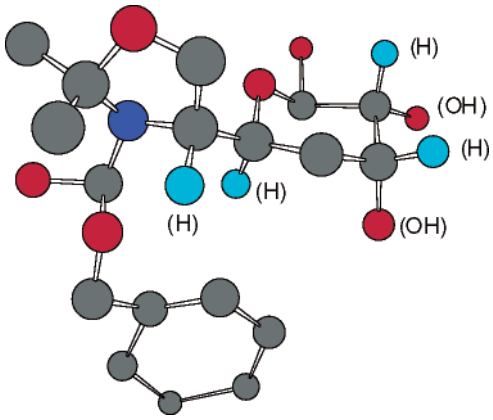
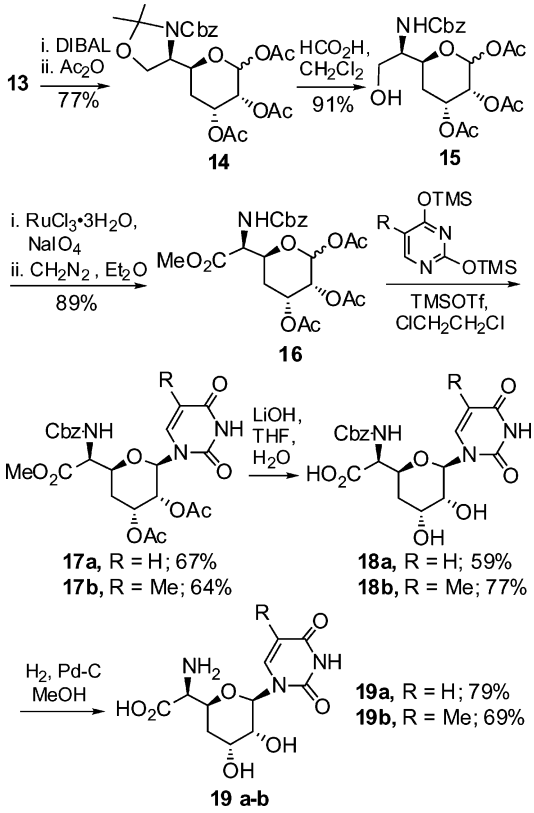


FIGURE 3. Ball-and-stick model of diol **13** (adapted from the X-ray crystal structure).

SCHEME 4

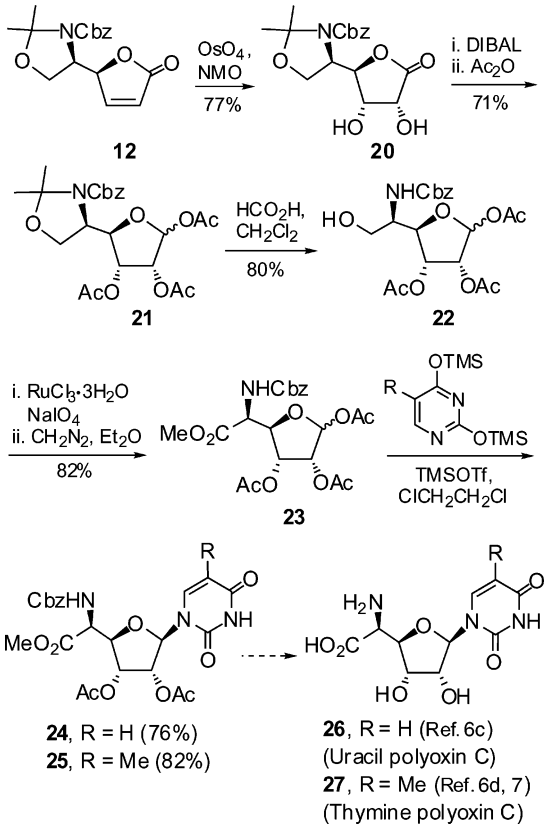


acid with diazomethane provided the *N*-Cbz-protected amino acid ester **16** in good overall yield. Coupling of **16** with bis-silylated uracil in the presence of trimethylsilyltriflate (Vorbrüggen's protocol)[17] resulted in the pyranosyl nucleoside **17a** as the only product. Chemical shift and coupling constant of H-1′ ($J_{1',2'}$ = 9.7 Hz) confirmed the product to be the β-anomer. Similarly, reaction of **16** with bis-silylated thymine following the same reaction conditions afforded the corresponding pyranosyl thymine nucleoside **17b** in 64% yield. The stereoselectivity in the above nucleobase incorporation reactions can be rationalized by invoking neighboring C2′-acetoxy group-assisted stabilization of the oxonium

(16) Hanessian, S. *Total Synthesis of Natural Products: The "Chiron" Approach*; Pergamon Press: Oxford, 1983.

(17) For a review, see: Vorbrüggen, H.; Ruh-Polenz, C. *Org. React.* **2000**, *55*, 1−654.

SCHEME 5



ion intermediate (anchimeric assistance) and consequent blocking of the α-face, followed by approach of the nucleobase from the *β*-face, resulting in the observed stereochemistry. Finally, in a two-step sequence, hydrolytic cleavage of the ester functionalities to form **18a** and **18b**, respectively, followed by hydrogenolytic removal of the amine protecting group culminated in a concise route to the desired pyranosyl nucleoside amino acid derivatives **19a**,**b**. The above reaction scheme clearly demonstrates the potential utility of lactone **8** in the rapid construction of the right-hand side nucleoside structural framework of various pyranosyl peptidyl nucleoside antibiotics (e.g., amipurimycin, miharamycins, etc.) and modified analogues thereof.

In further studies, elaboration of the amino butenolide **12** to the furanosyl nucleoside amino acid was next undertaken. It is worth mentioning that Garner and coworkers have also utilized a similar amino lactone in their synthetic studies on polyoxins.[7] Following the same sequence of reactions as described in Schemes 3 and 4 above, dihydroxylation of the lactone double bond afforded the corresponding diol **20** (Scheme 5) as the only product.[7] Partial reduction of the lactone to lactol and subsequent peracetylation provided the triacetate **21** in good overall yield. Hydrolysis of the acetonide to form **22**, its oxidation to the corresponding carboxylic acid, and subsequent esterification resulted in the amino acid ester derivative **23**. Coupling of this suitably protected glycosyl donor with bis-silylated uracil and bis-silylated thymine, respectively, afforded the corresponding nucleosides **24** and **25** in good yields. The spectral and analytical data of both of these products were in good agreement with those reported in the literature,[6c,d,7] thereby confirming the assigned structures and stereochemical integrity.

As deprotection of **24** and **25** to form uracil polyoxin C (**26**) and thymine polyoxin C (**27**) have already been reported in the literature,[6c,d,8] the reaction sequence depicted in Scheme 5 represents formal total synthetic routes to the above nucleosidic components as present in various polyoxin and nikkomycin family of complex peptidyl nucleoside antibiotics. In terms of brevity and overall yield, the present method compares well with the earlier reported syntheses of the above nucleoside fragments.[5,6] From an SAR investigation viewpoint too, the versatility of the key lactone intermediate **12** toward easy structural modifications and consequent possible access to a variety of modified nucleoside analogues is expected to be an added advantage of the present route.

In conclusion, utilizing a serine chiral template, the strategy and the approach described herein demonstrates a general protocol toward efficient construction of both the five- and the six-membered glycosyl α-amino acid components of the peptidyl nucleoside antibiotics. It is expected that ongoing research involving logical extension of the present studies will provide access to some as yet unattained targets in peptidyl nucleoside antibiotics research and have a positive contribution toward realizing the high therapeutic potential of this unique class of bioactive natural products.

Experimental Procedure

(4*R*)-4-[(1′*S*)-1-Acryloyloxy-but-3-enyl)-3-*N*-benzyloxycarbonyl-2,2-dimethyl-1,3-oxazolidine (7). To an ice-cooled solution of the homoallylic alcohol **6**[10a] (7.98 g, 26.1 mmol) in anhydrous CH_2Cl_2 (120 mL) was added *N*,*N*-diisopropylethylamine (13.6 mL, 78.3 mmol), followed by dropwise addition of acryloyl chloride (5.3 mL, 65.4 mmol) with stirring. The reaction was allowed to come to rt and was stirred for 1 h. After the reaction was quenched with ice-water, the organic layer was separated, dried with Na_2SO_4, and concentrated under vacuum. The residual oil was purified by flash chromatography (hexanes/EtOAc = 7:3) to obtain the acrylate **7** as a thick yellow oil (8.9 g, 95%): $[\alpha]^{25}_D$ −29.2 (*c* 1, CH_2Cl_2); IR (NaCl) 1726, 1700, 1634 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$; mixture of rotamers) *δ* 1.44−1.55, (4s, 6H), 2.21−2.37 (m, 2H), 3.96−4.14 (m, 3H), 4.97−5.19 (m, 4H), 5.45−5.86 (m, 3H), 6.13 (m, 1H), 6.44 (d, *J* = 17.3 Hz, 1H), 7.38 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$; mixture of rotamers) 23.5, 24.9, 26.2, 27.2, 36.7, 58.9, 60.1, 63.6, 63.9, 67.5, 67.7, 72.0, 72.5, 94.6, 95.1, 118.5, 128.4, 128.5, 128.6, 128.7, 128.9, 131.8, 133.2, 133.5, 136.5, 152.7, 153.6, 165.9; HRMS calcd. for $C_{20}H_{26}NO_5$ *m/z* $(M + H)^+$, 360.1811; found, 360.1812.

(6*S*)-6-[(4*R*)-3-*N*-Benzyloxycarbonyl-2,2-dimethyl-1,3-oxazolidin-4-yl]-5,6-dihydro-pyran-2-one (8). To the acrylate **7** (5.68 g, 15.8 mmol) dissolved in anhydrous CH_2Cl_2 (900 mL) was added a CH_2Cl_2 solution (10 mL) of bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride [Grubbs' 1st generation catalyst] (0.65 g, 5 mol %), and the resulting solution was refluxed for 12 h. A second portion of the catalyst (0.65 g, 5 mol %) was then added to the reaction mixture, and refluxing continued for another 12 h. After the solution was cooled to rt, DMSO (0.1 mL), activated charcoal powder (10 g), and silica gel (25 g) were added to the reaction mixture and stirred for 12 h. The solids were filtered off, the residue was washed thoroughly with chloroform, and the combined filtrate was concentrated under vacuum. The residual oily liquid was purified by flash chromatography (EtOAc/hexanes = 2:3) to afford the lactone **8** as a viscous yellow oil (4.29 g, 82%): $[\alpha]^{25}_D$ 29.1 (*c* 1.05, CH_2Cl_2); IR (NaCl) 1736, 1700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$; mixture of rotamers) *δ* 1.50−1.61

(4s, 6H), 2.26−2.57 (m, 2H), 3.95 (m, 1H), 4.15−4.46 (4m, 3H), 5.08−5.21 (m, 2H), 5.95 and 6.03 (2d, J = 9.4 Hz, 1H), 6.65 and 6.91 (2br s, 1H), 7.37 (s, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$; mixture of rotamers) δ 23.2, 24.7, 26.9, 27.2, 27.5, 28.1, 59.1, 60.0, 64.8, 65.6, 67.6, 68.0, 94.9, 95.0, 121.9, 128.5, 128.7, 129.0, 136.1, 145.6, 145.9, 152.9, 154.3, 163.6, 163.8; HRMS calcd. for $C_{18}H_{22}NO_5$ *m/z* $(M + H)^+$, 332.1498; found, 332.1506.

1-[(4*R*)-3-*N*-Benzyloxycarbonyl-2,2-dimethyl-1,3-oxazolidin-4-yl]-but-2-ene-1-one (9). To a solution of the ketone **5**[10a] (12 g, 39.6 mmol) in diethyl ether (250 mL) at rt was added neutral alumina (25 g), and the mixture was stirred for 3 h. The alumina was filtered off and washed thoroughly with EtOAc (3 × 50 mL). The combined filtrate was concentrated, and the residue was purified by flash chromatography (EtOAc/hexanes = 1:6 to 1:3) to afford the *trans*-α,β-unsaturated ketone **9** as a colorless oil (10.92 g, 91%): $[\alpha]^{25}_D$ 44.9 (*c* 1.02, $CHCl_3$); IR (NaCl) 1710, 1634 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$; mixture of rotamers) δ 1.53 and 1.59 (2s, 3H), 1.67 and 1.75 (2s, 3H), 1.88 and 1.93 (2d, J = 6.6 Hz, 3H), 3.99 (m, 1H), 4.21 (m, 1H), 4.63 and 4.78 (2dd, J = 3.1 & 7.5 Hz, 1H), 5.07 and 5.19 (2q, J = 5.9 Hz, 2H), 6.23−6.31 (2d, J = 15.6 Hz, 1H), 6.90−7.04 (m, 1H), 7.38 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$; mixture of rotamers) δ 18.4, 18.5, 23.9, 25.0, 25.1, 25.9, 63.5, 63.9, 65.5, 66.0, 66.7, 67.4, 94.7, 95.4, 126.8, 127.6, 127.7, 127.8, 127.9, 128.0, 128.3, 128.4, 136.0, 136.1, 145.0, 145.1, 151.9, 152.8, 194.9, 195.5; FABMS calcd. for $C_{17}H_{22}NO_4$ *m/z* $(M + H)^+$, 304.16; found, 304.2.

(1*S*)-1-[(4*R*)-3-*N*-Benzyloxycarbonyl-2,2-dimethyl-1,3-oxazolidin-4-yl]-but-2-en-1-ol (10). To a solution of the ketone **9** (9.2 g, 30.3 mmol) in MeOH (150 mL) was added $CeCl_3 \cdot 7H_2O$ (3.72 g, 10 mmol) in one portion, and the resulting solution was cooled to −10 °C (ice-salt bath) with continuous stirring. A solution of $Zn(BH_4)_2$ (0.189 M in Et_2O, 300 mL, 55 mmol) was then added dropwise to the reaction mixture (1.5 h), and stirring continued at the same temperature for another 1 h. The reaction was quenched by slow addition of saturated aqueous $NaHCO_3$ (60 mL), allowed to attain rt, and then filtered through a sintered glass funnel. The residual solid was washed thoroughly with EtOAc, the organic layer was separated from the filtrate, and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic extract was washed with brine, dried (Na_2SO_4), and concentrated under vacuum. The residue was purified by flash chromatography (hexane/EtOAc = 4:1 to 3:1) to afford the amino alcohol **10** as a colorless oil (8.15 g, 88%, *anti*/*syn* = 92:8): $[\alpha]^{25}_D$ 21.33 (*c* 1.05, $CHCl_3$); IR (NaCl) 3458, 1701 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, mixture of rotamers) δ 1.39−1.58 (m, 9H), 3.74−4.10 (m, 4H), 4.98−5.10 (m, 3H), 5.30−5.59 (m, 2H), 7.39 (s, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers) δ 18.1, 23.3, 25.1, 26.6, 61.4, 62.9, 64.8, 65.2, 67.2, 68.0, 73.4, 73.9, 95.1, 128.4, 128.6, 129.0, 129.9, 130.9, 136.3, 136.6, 152.9, 154.9; FABMS calcd. for $C_{17}H_{24}NO_4$ *m/z* $(M + H)^+$, 306.16; found, 306.3. HPLC: CHIRALCEL OD-H, *i*-PrOH/hexanes = 5/95, 1.0 mL/min, 254 nm, t_R major isomer (*anti*) = 23.05 min (92%), t_R minor isomer (*syn*) = 26.24 min (8%).

(4*R*)-4-[(1′*S*)-1-Acryloyloxy-but-2-enyl)-3-*N*-benzyloxycarbonyl-2,2-dimethyl-1,3-oxazolidine (11). Starting from allylic alcohol **10** (15.0 g, 49.2 mmol), the experimental procedure as described for preparation of **7** was followed. The product thus obtained was purified by flash chromatography (hexanes/EtOAc = 9:1) to obtain acrylate **11** as a thick yellow oil (15.9 g, 90%): $[\alpha]^{25}_D$ 7.2 (*c* 1.0, $CHCl_3$); IR (NaCl) 1726, 1707 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$; mixture of rotamers) δ 1.41−1.59 (4s, 6H), 1.67 (m, 3H), 3.97−4.19 (m, 3H), 5.10 and 5.19 (2d, J = 12.2 Hz, 2H), 5.31−5.47 (m, 1H), 5.67−5.87 (m, 3H), 6.14 (m, 1H), 6.47 (d, J = 17.3 Hz, 1H), 7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$; mixture of rotamers) δ 17.7, 23.1, 24.5, 25.9, 26.8, 59.3, 60.2, 63.6, 64.0, 66.9, 67.1, 73.5, 73.8, 94.2, 94.8, 126.0, 127.9, 128.0, 128.3, 128.4, 130.6, 130.7, 131.0, 131.2, 136.2, 152.3, 153.1, 165.0; FABMS calcd. for $C_{20}H_{26}NO_5$ *m/z* $(M + H)^+$, 360.17; found, 360.2.

(5*S*)-5-[(4*R*)-3-*N*-Benzyloxycarbonyl-2,2-dimethyl-1,3-oxazolidin-4-yl]-2,5-dihydro-furan-2-one (12). Starting from acrylate **11** (2.3 g, 6.4 mmol), the same experimental procedure as described for preparation of **8** was followed. The crude product was purified by flash chromatography (EtOAc/hexanes = 3:7) to afford some unreacted starting material (0.48 g) followed by the lactone **12** as a viscous yellow oil (1.37 g, 69% [91% based on recovered starting material]): $[\alpha]^{25}_D$ −7.3 (*c* 1.0, $CHCl_3$); IR (NaCl) 1792, 1757, 1700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$; mixture of rotamers) δ 1.45, 1.50, 1.58 and 1.62 (4s, 6H), 3.89−4.14 (m, 3H), 4.94−5.22 (m, 3H), 5.90 and 6.14 (2d, J = 4.5 Hz, 1H), 7.24 and 7.49 (2 brd, J = 5.2 Hz,1H), 7.36 (s, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$; mixture of rotamers) δ 23.1, 24.7, 27.3, 28.0, 59.7, 60.2, 65.1, 66.0, 67.7, 68.2, 82.6, 95.1, 95.6, 121.6, 128.5, 128.8, 129.1, 135.9, 136.0, 152.4, 153.8, 155.5, 155.8, 172.6, 172.9; HRMS calcd. for $C_{17}H_{20}NO_5$ *m/z* $(M + H)^+$, 318.1341; found, 318.1336.

Dihydroxylation of 8 to the Diol 13. Lactone **8** (4.47 g, 13.5 mmol) was dissolved in acetone/water (40 mL, 4:1), and to this was added NMO (4.04 g, 33.7 mmol), followed by OsO_4 (5% in toluene, 3.5 mL, 2 mol %). The resulting solution was stirred at rt for 2 h. After completion of the reaction (TLC monitoring), 10% aqueous $NaHSO_3$ (10 mL) was added to the reaction mixture and stirred for 30 min. The precipitate was filtered off and washed with EtOAc (3 × 20 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated under vacuum. Flash column chromatography (EtOAc/hexanes = 7:3 to 100% EtOAc) afforded the diol **13** as a white crystalline solid (3.46 g, 81%): mp = 172−173 °C; $[\alpha]^{25}_D$ 78.8 (*c* 1.02, MeOH); IR (NaCl) 3446, 1741, 1695 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6; mixture of rotamers) δ 1.42 and 1.52 (2 br s, 6H), 1.81−1.85 (br s, 2H), 3.93−4.11 (m, 5H), 4.78 (br s, 1H), 5.12 (s, 2H), 5.43 (s, 1H), 5.61 (s, 1H), 7.38 (s, 5H); ^{13}C NMR (100.6 MHz, DMSO-d_6, mixture of rotamers) δ 23.7, 25.3, 26.5, 27.4, 32.9, 59.9, 60.8, 63.7, 64.3, 66.8, 67.2, 67.4, 71.2, 75.5, 76.3, 94.4, 94.8, 128.5, 128.7, 129.3, 137.2, 137.3, 152.5, 153.3, 173.8; HRMS calcd. for $C_{18}H_{24}NO_7$ *m/z* $(M + H)^+$, 366.1553; found, 366.1565.

Conversion of Diol 13 to the Triacetate 14. (Step 1): The diol **13** (1.22 g, 3.34 mmol) was dissolved in anhydrous CH_2Cl_2 (40 mL) and cooled to −78 °C. To this stirring solution was added DIBAL-H (1 M in toluene, 11.0 mL, 11.0 mmol) dropwise. The reaction was stirred at −78 °C for 1.5 h and then quenched by careful addition of MeOH (1.0 mL). The reaction mixture was brought to rt, diluted with EtOAc (50 mL), and saturated aqueous sodium potassium tartrate (50 mL) was added to it. The resulting mixture was stirred until two clear layers were seen. The two layers were separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated, and the crude lactol (1.06 g) was carried onto the next step without further purification.

(Step 2): The lactol (1.06 g, 2.89 mmol) from the above reaction was dissolved in anhydrous CH_2Cl_2 (20 mL) and cooled to 0 °C (ice-bath), and to this solution was added anhydrous pyridine (0.7 mL, 8.7 mmol), DMAP (25 mg, catalytic), followed by Ac_2O (2.75 mL, 28.9 mmol). The reaction mixture was stirred at rt for 2 h and then quenched with the addition of an ice-cooled water mixture (15 mL). The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (1 × 20 mL) and brine (1 × 20 mL), dried with Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography (EtOAc/hexanes = 2:3) to obtain the triacetate **14** as a viscous semisolid (1.27 g, 77% over two steps): IR (NaCl) 1746, 1700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, anomeric mixture) δ 1.26−1.66 (4s, 6H) 1.69−1.87 (m, 2H), 2.02−2.12 (4s, 9H), 3.86−4.11 (m, 4H), 4.72−5.04 (m, 1H), 5.12 (br s, 2H), 5.43 and 5.55 (2s, 1H), 5.93−6.16 (m, 1H), 7.37 (s, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$, anomeric mixture) δ 21.0, 21.1, 21.2, 21.3, 23.3, 24.8, 27.2, 27.6, 27.9, 32.1, 32.7, 32.8, 59.5, 60.4, 65.1, 65.7, 67.4,

67.6, 67.9, 69.8, 69.9, 72.1, 77.6, 89.6, 90.8, 94.5, 95.1, 128.5, 128.7, 128.8, 129.0, 136.2, 152.7, 154.0, 169.5, 169.7, 170.0, 170.1, 170.3; HRMS calcd. for $C_{24}H_{32}NO_{10}$ *m/z* $(M + H)^+$, 494.2026; found, 494.2007.

Conversion of Triacetate 14 to the Amino Alcohol 15. The triacetate **14** (1.4 g, 2.83 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL) and cooled to 0 °C, followed by addition of 96% formic acid (7 mL). The reaction was stirred at 0 °C for 2 h, after which the excess solvent was removed under high vacuum. The residue was dissolved in CH_2Cl_2 (20 mL) and washed with saturated aqueous $NaHCO_3$ (1 × 10 mL). The organic layer was dried (Na_2SO_4) and concentrated under vacuum, and the residue was purified by flash chromatography (EtOAc/hexanes = 2:3 to 4:1) to afford the amino alcohol **15** as a low-melting semisolid (1.16 g, 91%): IR (NaCl) 3370, 1751, 1715 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, anomeric mixture) δ 1.96−2.12 (m, 11H), 2.61 (s, exchangeable with D_2O, 1H), 3.58−3.82 (m, 2H), 3.87−4.35 (m, 2H), 4.84−5.10 (2m, 1H), 5.11 (br s, 2H), 5.44−5.56 (2m, 2H), 5.86 and 6.17 (2d, J = 8.7 & 3.8 Hz, 1H), 7.38 (s, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, anomeric mixture) δ 20.4, 20.5, 20.6, 20.7, 20.8, 20.9, 31.4, 32.2, 54.4, 54.5, 61.1, 61.3, 61.5, 65.3, 66.4, 66.9, 67.0, 67.2, 69.2, 71.8, 89.2, 90.8, 127.9, 128.0, 128.1, 128.2, 128.4, 128.5, 136.1, 156.1, 156.2, 169.4, 169.6, 169.7, 169.8, 170.0, 171.6; HRMS calcd. for $C_{21}H_{28}NO_{10}$ *m/z* $(M + H)^+$, 454.1913; found, 454.2035.

Conversion of Alcohol 15 to Methyl Ester 16. (Step 1): To a mixture of $CH_3CN-CCl_4-H_2O$ (12 mL; 1:1:10) was added $NaIO_4$ (0.85 g, 3.9 mmol) and $RuCl_3 \cdot 3H_2O$ (0.036 g, 0.14 mmol) sequentially. The mixture was stirred at rt for 45 min and then added into a solution of the alcohol **15** (0.96 g, 2.12 mmol) in CH_3CN (4 mL), followed by addition of a second portion of $NaIO_4$ (0.42 g, 1.9 mmol). The resulting mixture was stirred at rt for 30 min, filtered through Celite, and the Celite layer was washed with EtOAc (3 × 20 mL). The combined filtrate was washed once with water, and the aqueous layer was re-extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under vacuum. The crude acid (∼1 g) thus obtained was carried to the next step without further purification.

(Step 2): [**CAUTION**: Diazomethane is an explosive and a highly toxic gas. Explosions may occur if the substance is dry and undiluted. All operations involving diazomethane should be carried out in an efficient fumehood following appropriate precaution.] To an ice-cooled biphasic solution of KOH (8 g) in H_2O (20 mL) and ether (30 mL) was added *N*-methyl-*N*′-nitro-*N*-nitrosoguanindine (MNNG, 2 g) in one lot. The organic layer turned bright yellow. The ethereal layer was decanted into an ice-cooled Erlenmeyer flask containing KOH pellets. The aqueous layer was washed with ether (3 × 25 mL), and the ethereal layers were combined. The diazomethane (CH_2N_2) thus prepared was added to a stirred solution of the crude acid (1 g in 10 mL of ether) as obtained from step 1 and was stirred for 30 min. Excess CH_2N_2 was removed by bubbling nitrogen into the reaction mixture for 15 min, followed by removal of solvent under vacuum to yield the crude product. Purification by flash chromatography (EtOAc/hexanes = 2:3) yielded the methyl ester **16** as a low-melting solid (0.91 g, 89% over two steps): IR (NaCl) 1746 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, anomeric mixture) δ 1.96−2.17 (m, 11H), 3.79 (s, 3H), 4.24 (d, J = 11.9 Hz, 1H), 4.44 (m, 1H), 4.80 (dd, J = 3.0 & 8.5 Hz, 0.8H), 5.23 (t, J = 3.7, 0.2H), 5.14 (s, 2H), 5.55−5.64 (m, 2H), 5.93 and 6.18 (2d, J = 8.5 & 3.9 Hz, 1H), 7.38 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, anomeric mixture) δ 20.4, 20.5, 20.8, 31.1, 31.5, 52.5, 52.6, 56.3, 65.3, 66.6, 67.1, 67.2, 69.1, 73.0, 89.0, 90.2, 128.1, 128.2, 128.4, 135.9, 155.6, 169.0, 169.1, 169.3, 169.5, 169.6, 169.7; FAB+ calcd. for $C_{22}H_{28}NO_{11}$ *m/z* $(M + H)^+$, 482.45; found, 482.3.

Conversion of 16 to 17a. To a solution of the triacetate **16** (0.96 g, 2.0 mmol) in anhydrous 1,2-dichloroethane (5 mL) was added sequentially a solution of bis(trimethylsilyl)uracil (2.56 g, 10 mmol) in 1,2-dichloroethane (5 mL) and freshly distilled TMSOTf (2.17 mL, 12.0 mmol). The reaction was allowed to stir at rt for 5 h and then quenched by addition of saturated aqueous $NaHCO_3$ (10 mL). The precipitated solid was removed by filtration and washed with $CHCl_3$ (3 × 5 mL). The organic layer was separated from the filtrate, and the aqueous layer was extracted with $CHCl_3$ (3 × 10 mL). The combined organic extracts were washed once with brine, dried (Na_2SO_4), concentrated under vacuum, and the residue was purified by flash chromatography (EtOAc/hexanes = 3:2 to 100%) to give the pyranosyl uracil nucleoside **17a** as a white solid (0.67 g, 67%): mp = 103−105 °C; $[\alpha]^{25}_D$ 18.1 (*c* 0.27, $CHCl_3$); IR (NaCl) 3262, 1741, 1701, 1695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.98 (s, 3H), 2.02−2.09 (m, 1H), 2.21 (s, 3H), 2.20−2.27 (m, 1H), 3.81 (s, 3H), 4.35 (br d, J = 12.2 Hz, 1H), 4.51 (br d, J = 8.9 Hz, 1H), 4.90 (br d, J = 9.6 Hz, 1H), 5.14 (s, 2H), 5.58 (s, 1H), 5.74 (d, J = 8.1 Hz, 1H), 5.95 (d, J = 8.9 Hz, 1H), 6.10 (d, J = 9.7 Hz, 1H), 7.14 (d, J = 8.7 Hz, 1H), 7.38 (m, 5H), 8.93 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 20.9, 21.4, 32.1, 53.2, 56.9, 67.3, 67.8, 68.7, 75.2, 78.7, 104.1, 128.5, 128.7, 128.9, 129.6, 136.2, 139.1, 150.6, 156.1, 162.7, 169.4, 170.1, 170.2; HRMS calcd. for $C_{24}H_{28}N_3O_{11}$ *m/z* $(M + H)^+$, 534.1724; found, 534.1698.

Conversion of 16 to 17b. To a solution of triacetate **16** (0.096 g, 0.2 mmol) in anhydrous $(CH_2Cl)_2$ (2 mL) was added bis(trimethylsilyl)thymine (0.13 g, 0.5 mmol), followed by freshly distilled TMSOTf (0.22 mL, 1.0 mmol). The reaction was stirred at rt for 5 h, and then saturated aqueous $NaHCO_3$ (2 mL) was added. The two layers were separated, and the aqueous layer was extracted with $CHCl_3$ (3 × 5 mL). The combined organic layers were washed with brine (1 × 10 mL), dried (Na_2SO_4), concentrated under vacuum, and the residue was purified by flash chromatography (EtOAc/hexanes = 4:1) to yield the pyranosyl thymine nucleoside **17b** as a white solid (0.070 g, 64%): mp = 108−111 °C; $[\alpha]^{25}_D$ 23.0 (*c* 0.2, $CHCl_3$); IR (NaCl) 3257, 1746, 1690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.88 (s, 3H), 1.94 (s, 3H), 1.99−2.16 (m, 1H), 2.19 (s, 3H), 2.20−2.32 (m, 1H), 3.82 (s, 3H), 4.35 (d, J = 11.7 Hz, 1H), 4.51 (d, J = 7.4 Hz, 1H), 4.90 (br s, 1H), 5.13 (s, 2H), 5.58 (s, 1H), 6.10 (d, J = 9.7 Hz, 1H), 6.16 (d, J = 8.6 Hz, 1H), 6.99 (br s, 1H), 7.35 (s, 5H), 9.2 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 12.7, 12.9, 20.9, 21.4, 32.2, 51.3, 53.2, 57.0, 67.3, 67.7, 68.7, 75.0, 78.5, 112.5, 128.3, 128.4, 128.6, 128.8, 128.9, 129.5, 134.6, 135.8, 136.3, 140.1, 150.9, 156.2, 163.5, 169.6, 170.1, 170.2; HRMS calcd. for $C_{25}H_{30}N_3O_{11}$ *m/z* $(M + H)^+$, 548.1880; found, 548.1893.

Conversion of 17a to 18a. To an ice-cooled solution of **17a** (0.096 g, 0.18 mmol) in THF/H_2O (6 mL, 5:1) was added LiOH·H_2O (0.026 g, 0.63 mmol), and the solution stirred at the same temperature for 2 h. The reaction mixture was diluted with H_2O (5 mL) and then extracted with CH_2Cl_2 (1 × 10 mL). The aqueous layer was cooled to 0 °C, and EtOAc (10 mL) was added to it and acidified to pH = 2−3 with 1 M HCl. The two layers were separated, and the aqueous layer was extracted thoroughly with EtOAc (5 ×10 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under vacuum, and the residue was purified by flash chromatography ($CHCl_3$/MeOH = 3:2 to 100% MeOH, with 0.01% AcOH) to yield **18a** as a white solid (0.046 g, 59%): mp = decomposes >175 °C; $[\alpha]^{25}_D$ 16.4 (*c* 0.25, MeOH); IR (Teflon film) 3354, 1695 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 1.81−1.89 (m, 1H), 1.95−2.15 (m, 1H), 3.61 (d, J = 7.7 Hz, 1H), 4.22 (s, 1H), 4.28 (s, 1H), 4.45 (d, J = 11.8 Hz, 1H), 5.12 (m, 2H), 6.65 (d, J = 8.0 Hz, 1H), 5.92 (d, J = 9.3 Hz, 1H), 7.36 (m, 5H), 7.57 (d, J = 7.8 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 32.7, 59.0, 66.0, 67.4, 69.3, 73.4, 80.4, 101.6, 127.3, 127.4, 127.9, 136.9, 141.3, 151.4, 156.7, 164.6, 174.7; FAB+ calcd. for $C_{19}H_{22}N_3O_9$ *m/z* $(M + H)^+$, 436.13; found, 436.1.

Conversion of 17b to 18b. Starting with **17b** (0.059 g, 0.1 mmol), the experimental procedure for **18a** was followed. The crude product was purified by flash chromatography ($CHCl_3$/MeOH = 7:3 to 100% MeOH) to afford **18b** as a white solid (0.035 g, 77%): mp = decomposes >200 °C; $[\alpha]^{25}_D$ −3.08 (*c* 0.26, MeOH); IR (Teflon film) 3380, 1695 cm^{-1}; ^1H NMR (400 MHz,

CD_3OD) δ 1.86 (s, 3H), 1.90−2.12 (m, 1H), 3.61−3.67 (m, 1H), 4.23 (br s, 2H), 4.42 (d, J = 9.4 Hz, 1H), 5.08 (s, 2H), 5.91 (d, J = 9.1 Hz, 1H), 7.34 (s, 5H), 7.47 (s, 1H); ^{13}C NMR (100.6 MHz, CD_3OD) δ 11.4, 33.4, 59.5, 66.5, 67.9, 69.6, 75.1, 80.8, 110.7, 127.8, 127.9, 128.0, 128.4, 137.2, 137.5, 152.1, 157.2, 165.3, 175.4; FAB+ calcd. for $C_{20}H_{24}N_3O_9$ *m/z* $(M + H)^+$, 450.14; found, 450.2.

Conversion of 18a to 19a. To a solution of **18a** (0.028 g, 0.064 mmol) in anhydrous MeOH (3 mL) was added 10% palladium on activated carbon (0.1 g), and the mixture was stirred under an H_2 atmosphere for 3 h. The reaction mixture was filtered through Celite and charcoal, and the residue was washed with MeOH. The combined filtrate was concentrated to yield **19a** as a white solid (0.015 g, 79%): mp = decomposes >190 °C; $[\alpha]^{25}_D$ −21.33 (*c* 0.3, MeOH); IR (Teflon film) 3380, 1685 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 1.85−2.13 (m, 2H), 3.73−3.79 (m, 2H), 4.27 (br s, 1H), 4.59 (d, J = 12.3 Hz, 1H), 5.75 (d, J = 8.0 Hz, 1H), 5.95 (d, J = 9.5 Hz, 1H), 7.77 (d, J = 8.1 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 32.4, 57.4, 67.6, 69.1, 71.6, 81.3, 102.1, 142.1, 151.9, 164.9, 179.2; HRMS calcd. for $C_{11}H_{16}N_3O_7$ *m/z* $(M + H)^+$, 302.0988; found, 302.0997.

Conversion of 18b to 19b. Starting from **18b** (0.023 g, 0.05 mmol), the experimental procedure as in **19a** was followed to afford **19b** as a white solid (0.011 g, 69%): mp = decomposes >175 °C; $[\alpha]^{25}_D$ −14.9 (*c* 0.55, MeOH); IR (Teflon film) 3365, 1695, 1664 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 1.76−1.85 (m, 1H), 1.90 (s, 3H), 1.92−2.06 (m, 1H), 3.54 (dd, J = 3.5, 10.8 Hz, 1H), 3.66−3.72 (m, 1H), 4.17−4.24 (m, 2H), 4.41 (br s, 1H), 5.95 (dd, J = 9.4 & 15.8 Hz, 1H), 7.64 (d, J = 15.2 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 10.8, 31.2, 32.2, 58.5, 62.3, 67.5, 67.6, 69.2, 69.4, 73.8, 74.4, 80.4, 82.2, 110.1, 137.3, 151.7, 165.0, 176.1, 176.8; ESI+ calcd. for $C_{12}H_{18}N_3O_7$ *m/z* $(M + H)^+$, 316.11; found, 316.1.

Conversion of 12 to the Diol 20. Lactone **12** (1.35 g, 4.2 mmol) was dissolved in acetone/water (15 mL, 2:1), and to this was added citric acid (0.61 g, 3.1 mmol), followed by $K_2OsO_2(OH)_4$ (6.0 mg, 0.017 mmol). To this stirring mixture was added NMO (0.54 g, 4.67 mmol), and stirring continued at rt for 16 h. Saturated aqueous Na_2SO_3 (1 mL) and EtOAc (15 mL) were then added to the reaction mixture and stirred for 15 min. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under vacuum, and the residue was purified by flash chromatography (EtOAc/hexanes = 3:2) to obtain diol **20** as a white solid (1.14 g, 77%): mp = 147−149 °C; $[\alpha]^{25}_D$ 2.89 (*c* 0.65, $CHCl_3$); IR (NaCl) 3420, 3248, 1796, 1658 cm^{-1}; ^{1}H (500 MHz, DMSO-d_6, mixture of rotamers) δ 1.45 and 1.52 (2s, 6H), 3.85 (d, J = 9.4 Hz, 1H), 3.94 (dd, J = 4.3 & 9.3 Hz, 1H), 4.04−4.20 (m, 3H), 4.32 and 4.49 (2 brs, 1H), 5.04−5.16 (m, 2H), 5.54 (s, 1H), 5.76−5.84 (m, 1H), 7.34−7.40 (m, 5H); ^{13}C NMR (125 MHz, DMSO-d_6, mixture of rotamers) δ 22.9, 24.3, 27.0, 27.9, 55.2, 56.6, 57.2, 65.2, 65.4, 66.8, 67.2, 68.4, 68.5, 68.8, 84.2, 94.2, 94.4, 128.3, 128.4, 128.9, 136.5, 152.2, 153.6, 175.8, 175.4; HRMS calcd. for $C_{17}H_{22}NO_7$ *m/z* $(M + H)^+$, 352.1396; found, 352.1384.

Conversion of 20 to the Triacetate 21. Starting with diol **20** (0.7 g, 2 mmol), the same experimental procedure as in **14** was followed. The crude product was purified by flash chromatography (EtOAc/hexanes = 7:3) to obtain triacetate **21** as a thick oil (0.681 g, 71% over two steps): IR (NaCl) 1752, 1709 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, anomeric mixture) δ 1.48, 1.56, 1.61 and 1.64 (4s, 6H), 1.87, 1.94, 2.03, 2.11, 2.12 and 2.14 (6s, 9H), 3.92−4.10 (m, 2H), 4.17−4.36 (m, 2H), 4.93−5.42 (m, 3H), 5.63−5.45 (m, 1H), 6.09 and 6.14 (2s, 1H), 7.34−7.47 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, anomeric mixture) 20.6, 20.9, 21.1, 21.5, 23.4, 24.9, 26.8, 27.5, 30.1, 59.3, 60.0, 65.3, 66.2, 67.7, 67.8, 71.8, 72.4, 74.7, 75.0, 80.4, 80.6, 94.6, 95.1, 98.1, 98.2, 128.5, 128.7, 128.9, 129.0, 129.1, 136.3, 136.4, 152.5, 154.0, 169.2, 169.5, 169.7, 169.8, 169.9, 170.0; HRMS calcd. for $C_{23}H_{30}NO_{10}$ *m/z* $(M + H)^+$, 480.1870; found, 480.1879.

Conversion of 21 to 22. Starting with triacetate **21** (0.228 g, 0.48 mmol), the experimental procedure as in **15** was followed. The crude product was purified by flash chromatography (EtOAc/hexanes = 3:7) to afford alcohol **22** as a thick oil (0.167 g, 80%): ^{1}H NMR (400 MHz, $CDCl_3$, anomeric mixture) δ 2.09, 2.12, 2.13 and 2.14 (4s, 9H), 2.23 (br s, 1H), 3.77 (br s, 1H), 3.88 (br s, 2H), 4.34 (m, 1 H), 5.13 (d, J = 8.5 Hz, 2H), 5.21−5.53 (4m, 3H), 6.15 (s, 0.4H), 6.41 (d, J = 4.3 Hz, 0.6H), 7.37 (br s, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, anomeric mixture) δ 20.2, 20.3, 20.4, 20.5, 20.9, 21.0, 53.4, 54.1, 61.2, 61.5, 67.0, 69.7, 70.2, 71.5, 74.1, 80.5, 83.3, 93.5, 98.0, 128.1, 128.2, 128.3, 128.4, 128.5, 136.0, 156.1, 168.0, 169.2, 169.3, 169.4, 169.5, 170.2; FAB+ calcd. for $C_{20}H_{26}NO_{10}$ *m/z* $(M + H)^+$, 440.16; found, 440.1.

Conversion of 22 to 23. Starting with alcohol **22** (0.333 g, 0.76 mmol), the experimental procedure as in **16** was followed. The crude product was purified by flash chromatography (EtOAc/hexanes = 3:7) to obtain methyl ester **23** as a semisolid (0.291 g, 82% over two steps): IR (NaCl) 1745 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, anomeric mixture) δ 1.99, 2.0 and 2.07 (3s, 9H), 3.71 (br s, 3H), 4.46−4.48 (m, 1H), 4.67−4.70 (m, 1H), 5.08 (s, 2H), 5.28 (d, J = 4.6 Hz, 1H), 5.52−5.55 (m, 1H), 5.79 (d, J = 8.6 Hz, 1H), 6.08 (s, 0.75H), 6.34 (d, J = 4.4 Hz, 0.25H), 7.32 (s, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$, anomeric mixture) δ 20.7, 20.8, 20.9, 21.0, 21.3, 21.4, 53.0, 53.4, 55.6, 55.8, 67.7, 69.9, 70.0, 70.6, 74.3, 77.6, 81.8, 85.3, 94.1, 98.2, 128.5, 128.7, 128.8, 128.9, 136.3, 156.1, 169.1, 169.3, 169.5, 169.7, 169.8, 169.9, 170.0, 170.5; HRMS calcd. for $C_{21}H_{26}NO_{11}$ *m/z* $(M + H)^+$, 468.1506; found, 468.1498.

Conversion of 23 to 24. Starting with the triacetate **23** (0.894 g, 1.9 mmol) and bis(trimethylsilyl)uracil (2.56 g, 10 mmol), the same procedure as in **17a** was followed. The product was purified by flash chromatorgraphy (MeOH/$CHCl_3$ = 1:49) to provide the uracil nucleoside **24** as a white solid (0.749 g, 76%): mp = 80−82 °C (lit.[6c] mp. 78−80 °C); $[\alpha]^{25}_D$ 18.7 (*c* 1, $CHCl_3$) [lit.[6c] $[\alpha]_D$ +16 (*c* 1.043, $CHCl_3$]; IR (NaCl) 1745, 1709, 1687 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.10 (s, 6H), 3.80 (s, 3H), 4.42 (br s, 1H), 4.85 (br s, 1H), 5.15 (AB_q, J = 7.8 & 16.2 Hz, 2H), 5.27 (t, J = 5.9 Hz, 1H), 5.50 (t, J = 5.7 Hz, 1H), 5.67 (d, J = 6.4 Hz, 1H), 5.75 (br s, 1H), 5.92 (d, J = 5.5 Hz, 1H), 7.21 (d, J = 8.2 Hz, 1H), 7.38 (s, 5H), 8.09 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 53.4, 55.3, 67.8, 69.9, 72.7, 82.2, 88.3, 103.9, 128.5, 128.8, 129.0, 136.2, 140.2, 150.6, 163.0, 169.7, 170.0, 170.1; HRMS calcd. for $C_{23}H_{26}N_3O_{11}$ *m/z* $(M + H)^+$, 520.1567; found, 520.1571.

Conversion of 23 to 25. Starting with the triacetate **23** (0.317 g, 0.68 mmol) and bis(trimethylsilyl)thymine (0.65 g, 2.5 mmol), the same procedure as in **17b** was followed. The crude product was purified by flash chromatography (MeOH/$CHCl_3$ = 1:49) to yield thymine nucleoside **25** as a white solid (0.297 g, 82%): mp = 74−77 °C (lit. mp.[7] 80−82 °C); $[\alpha]^{25}_D$ 21.0 (*c* 0.5, $CHCl_3$) [lit.[7] $[\alpha]_D$ +19.8 (*c* 0.56, $CHCl_3$]; IR (NaCl) 1753, 1718, 1702 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.90 (s, 3H), 2.10 (s, 6H), 3.82 (s, 3H), 4.41 (br t, J = 4.4 Hz, 1H), 4.85 (br s, 1H), 5.16 (dd, J = 5.7 & 11.9 Hz, 2H), 5.31 (t, J = 5.6 Hz, 1H), 5.54 (t, J = 5.9 Hz, 1H), 5.95 (d, J = 5.5 Hz, 2H), 7.07 (s, 1H), 7.33 (s, 5H), 9.18 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.9, 20.8, 53.4, 55.5, 67.8, 70.1, 72.7, 82.2, 88.0, 112.4, 128.5, 128.7, 128.8, 128.9, 136.0, 136.3, 151.0, 156.5, 164.1, 169.7, 170.0, 170.1; HRMS calcd. for $C_{24}H_{28}N_3O_{11}$ *m/z* $(M + H)^+$, 534.1724; found, 534.1714.

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Supporting Information Available: General experimental methods and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. Crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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