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Synthetic Studies on Ezomycins: Stereoselective Route to a Thymine Octosyl Nucleoside Derivative

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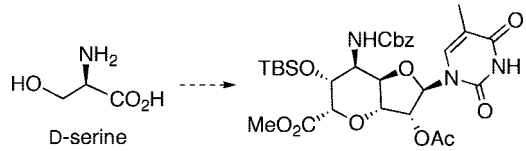

The ezomycins are *Streptomyces*-derived antifungal natural products, belonging to the complex peptidyl nucleoside family of antibiotics. Employing D-serine as a chiral platform, we report herein a novel synthetic route to the bicyclic octosyl nucleoside core of the ezomycins. A key step in the sequence involved a stereoselective 6-exo-*trig* oxymercuration−oxidation of a strategic δ-hydroxy alkene derivative, toward construction of the trans-fused furopyran ring system as present in the target products. In contrast to the known carbohydrate-based synthetic routes to the above furopyranyl fragment, the present amino acid chiral template approach is expected to offer a more flexible pathway toward potential SAR-targeted structural/stereochemical modifications of this central bicyclic nucleoside component of the ezomycins.

Introduction

The ezomycins (Figure 1) are *Streptomyces*-derived antifungal natural products, belonging to the complex peptidyl nucleoside superfamily of antibiotics.[1] Isolated and identified during the 1970s, the ezomycins are active against phytopathogenic fungi such as *Sclerotinia* and *Botrytis*.[2] The antifungal mechanism of action of the ezomycins has however not yet been ascertained. The structure and stereochemistry of the ezomycins were determined by extensive spectroscopic and chemical degradation studies.[2,3] A common structural feature of the various ezomycins is the bicyclic nucleoside disaccharide core, comprising a novel trans-fused furopyranyl nucleoside-containing disaccharide (Figure 1). As evident, the two structurally distinct constituents of the above ezomycin nucleoside disaccharide core are ezoaminuroic acid and the octosyl nucleoside segment. The ezoaminuroic acid as present in ezomycins is the first example of a naturally occurring 3-amino-3-deoxyhexuronic acid, whereas, the structurally rigid octosyl nucleoside component of the ezomycins is made up of a furanoid ring trans-fused to a pyranoid ring, forming the 3,7-anhydrooctose moiety. While the ezomycins A_1 and A_2 contain cytosine as the nucleobase, in ezomycins B_1 and B_2 the nucleobase is of the pseudouridine (γ-uracil) type.

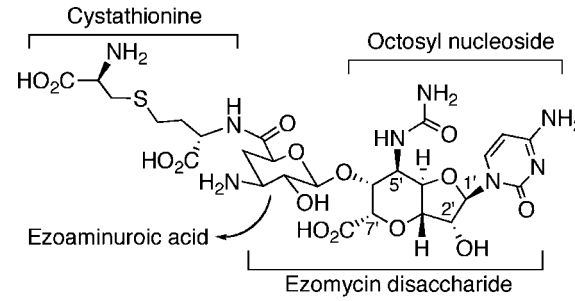

FIGURE 1. Structures of representative ezomycins.

In addition to the ezomycins, differently substituted, but otherwise structurally similar bicyclic 3,7-anhydrooctose nucleo-

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(1) For reviews on complex peptidyl nucleoside antibiotics, see: (a) Garner, P. Synthetic approaches to complex nucleoside antibiotics. In *Studies in Natural Products Chemistry.* Atta-ur-Rahman. Ed.; Stereoselective synthesis (Part A); Elsevier: Amsterdam, 1988;, Vol. *1*, 397−435. (b) Isono, K. *Pharmacol. Ther.* **1991**, *52*, 269–286. (c) Knapp, S. *Chem. Rev.* **1995**, *95*, 1859–1876. (d) Zhang, D.; Miller, M. J. *Curr. Pharm. Design* **1999**, *5*, 73–99, and references therein.

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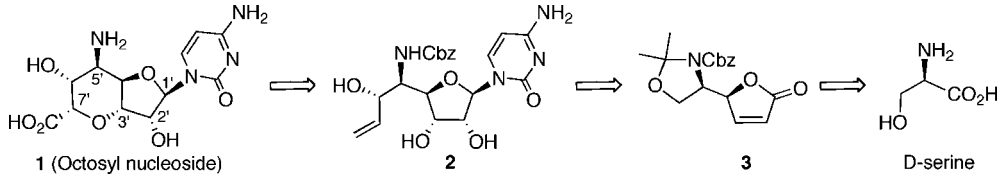

FIGURE 2. Retrosynthetic strategy and approach.

side motifs are also found in nucleoside antibiotics, such as the octosyl acids and malayamycin A.[4] Interestingly, in biological studies, the L-cystathionine side-chain-containing ezomycins A_1 and B_1 were found to display antifungal activity, whereas those lacking this pseudopeptide (e.g., ezomycins A_2 and B_2) were devoid of activity.[2] Although a few syntheses of the ezomycin structural fragments have been reported,[1a–c,4c,5] the total synthesis or detailed structure−activity relationship (SAR) studies of these natural products are yet to be accomplished.

The antifungal activity, challenging structural features, an as yet undetermined mechanism of action, and limited synthetic or medicinal chemical studies, render the ezomycins as attractive targets for further exploration. As part of an ongoing research investigating the antifungal peptide nucleoside antibiotics,[6,7] we report herein the preliminary results of our synthetic studies directed at the octosyl nucleoside core of the ezomycins.

Results and Discussion

In the literature reported syntheses of the octosyl nucleoside core, various carbohydrate starting materials have been employed as chiral synthons to construct the bicyclic furopyranyl structural framework.[1a–c,4c,5] In a strategic deviation from the above approaches, our plan for the present synthesis involves de novo construction of the target bicyclic nucleoside component, starting from a structurally simpler and more flexible chiral amino acid building block. In recent studies, we have utilized serine as a versatile chiral precursor in the stereoselective synthesis of the glycosyl nucleoside amino acid cores of various peptidyl nucleoside antibiotics.[6] In continuation of the above approach, our synthetic strategy for the construction of the octosyl nucleoside core envisages utilization of the D-serine-derived enantiopure aminobutenolide **3** as an appropriate chiral template toward initial formation of the C-4′ carbon chain extended furanosyl nucleoside derivative **2** (Figure 2). A subsequent stereoselective 6-exo-*trig* cyclization involving the strategically located terminal olefin and the C-3′ oxygen functionality of **2** ultimately leads to the desired *trans*-furopyranyl bicyclic nucleoside **1**. For the sake of convenience, we decided to pursue the present study employing the structurally simpler and commercially available bis-TMS-thymine as the nucleobase donor.

In accordance with the above strategy, and employing a recently developed protocol from our laboratory,[6a] readily available D-serine was converted to the corresponding strategically functionalized aminobutenolide **3** (Scheme 1) in good overall yield (53%, eight steps from D-serine). Subsequent potassium osmate catalyzed dihydroxylation of **3** under reported conditions resulted in the known diol **4** with high stereocontrol.[6a] Partial reduction of the lactone, followed by treatment of the resulting lactol with an excess of acetic anhydride provided the triacetate derivative **5** (anomeric mixture) in good overall yield. The nucleobase introduction was performed by reacting **5** with bis-silylated thymine in the presence of TMSOTf, resulting in a highly stereoselective formation of the nucleoside derivative **6**.[6a,8] Interestingly, the acidic reaction conditions employed during the nucleobase incorporation also led to clean cleavage of the *N*,*O*-acetonide protection, thereby eliminating the need of an otherwise necessary additional reaction step.[8,9] Aiming for a two-carbon elongation at the C-4′ side chain, in a two-step sequence, Dess−Martin periodinane oxidation of the alcohol **6** to the corresponding aldehyde and its subsequent reaction with a stabilized Wittig reagent yielded the *E*-α,*β*-unsaturated ester **7** in good overall yield.

Toward stereoselective installation of the desired C-6′ hydroxy functionality, conversion of the side chain acryloyl moiety to the corresponding allylic alcohol and its subsequent epoxidation were next investigated. Accordingly, DIBAL-mediated reduction of the ester **7** resulted in the corresponding allylic alcohol **8** in good yield. It is noteworthy that, under the reaction conditions employed, the acetate functionalities of **7** were found to be unaffected, and only the carbomethoxy functionality underwent reduction to the corresponding alcohol.[10] Having obtained the desired allylic alcohol intermediate **8**, its stereoselective conversion to the corresponding epoxy alcohol was initiated. Unfortunately, when subjected to the Sharpless asymmetric epoxidation (SAE),[11] in the presence of either of the chiral ligands, (+)-DET or (−)-DET, the allylic alcohol **8** failed to undergo any desired epoxidation, instead the starting material was recovered unchanged. The surprising failure in the above SAE of **8** forced us to consider an alternative epoxidation of the olefin. Accordingly, when subjected to reaction with *m*-CPBA, the olefin **8** did indeed react to form the corresponding

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(6) For some recent studies, see:(a) Bhaket, P.; Stauffer, C. S.; Datta, A. *J. Org. Chem.* **2004**, *69*, 8594–8601. (b) Stauffer, C. S.; Bhaket, P.; Fothergill, A. W.; Rinaldi, M. G.; Datta, A. *J. Org. Chem.* **2007**, *72*, 9991–9997. (c) Stauffer, C. S.; Datta, A. *J. Org. Chem.* **2008**, *73*, 4166–4174.

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(10) For an example of a similar selective reduction with DIBAL, see: Roush, W. R.; Coffey, D. S.; Madar, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 11331–11332.

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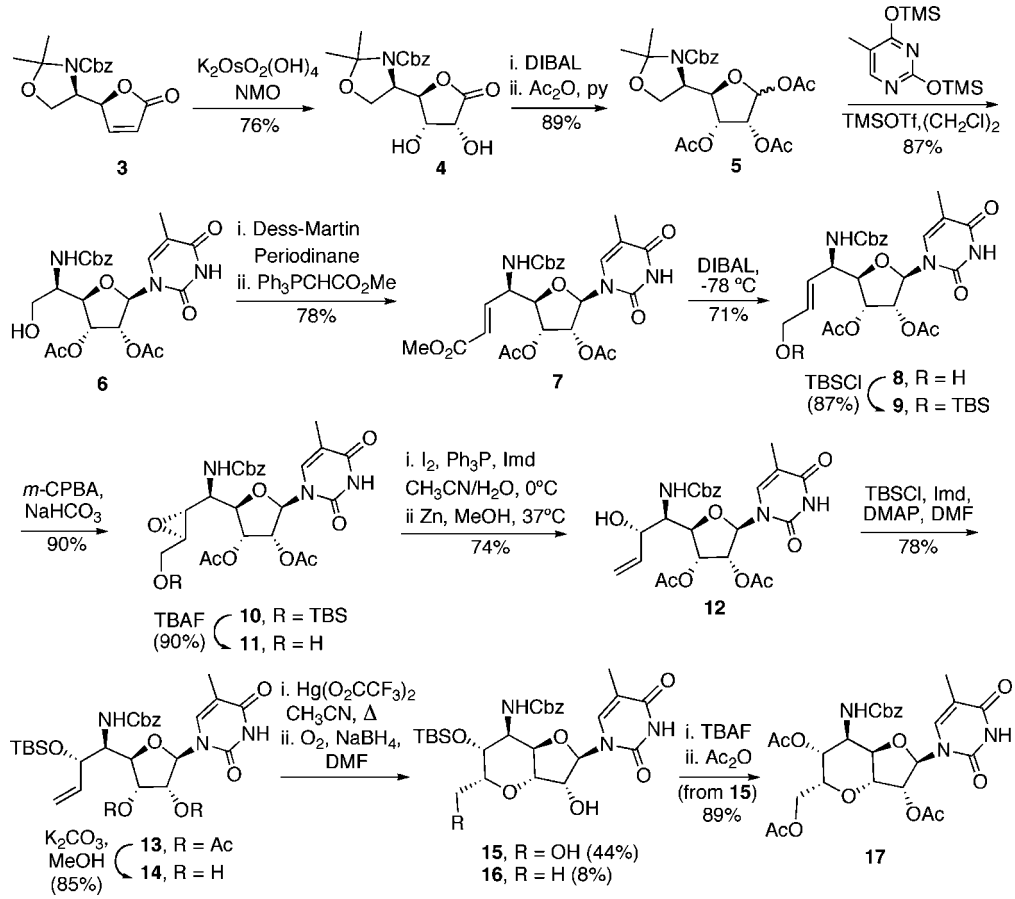
SCHEME 1



epoxide, albeit with poor stereoselectivity (~1:1 mixture of diastereoisomers by ^{1}H NMR). The unsatisfactory selectivity in the above epoxidation prompted us to investigate prior protection of the primary hydroxyl group of **8** and study the subsequent effect on *m*-CPBA epoxidation. Gratifyingly, protection of the alcohol **8** to the corresponding TBS-ether derivative **9** followed by its reaction with *m*-CPBA, resulted in the stereoselective formation of the epoxide **10** along with minor quantities of the other diastereoisomer (major/minor = 5:1 by ^{1}H NMR).[12] The tentatively assigned stereochemistry of the epoxide **10** was based on the assumption that the bulky carbamoyl substituent adjacent to the olefin would direct the epoxidizing reagent to approach from the less hindered α-face.[12] True to our expectation, the above stereochemical assignment was subsequently proven to be correct on the basis of extensive NMR analysis of a downstream product obtained from **10** (compound **17**, vide infra). At this stage, several attempts to construct the trans-fused bicyclic furopyran framework via acetate deprotection and subsequent 6-endo addition of the resulting C-3′ hydroxyl group to the C-7′ of the epoxide **10** were however not successful. Following an alternative strategy, the silyl ether protection of **10** was then removed to form the corresponding epoxy alcohol derivative **11**. In a two-step sequence, **11** was then transformed to the corresponding secondary allylic alcohol derivative **12** by initial conversion of the primary hydroxyl group to iodo, followed by reductive elimination in the presence of Zn, resulting in clean formation of the rearranged product.[13] The above sequence helped install the secondary hydroxyl bearing the desired chiral center at C-6′, and also provided the terminal olefin functionality as a strategic handle toward construction of the desired furopyran bicyclic skeleton. Subsequent protection of the free secondary hydroxy group of **12** as its TBS−ether derivative **13** followed by removal of the acetate protection afforded the diol **14** in high yield. Toward performing the desired bicyclic ring formation, an intramolecular 6-exo-*trig* cyclization was next investigated. Gratifyingly, when **14** was subjected to an oxymercuration−oxidation protocol by initial reaction with mercuric trifluoroacetate in refluxing acetonitrile, followed by treatment of the resulting alkylmercury intermediate with $NaBH_4$ amid continuous bubbling of oxygen,[14] the corresponding bicyclic furopyranyl nucleoside **15** was isolated as the major product, along with minor quantities of the corresponding C-7′ methyl analogue **16**.

With an aim to simplify the ^{1}H NMR spectrum for structural assignment, sequential silyl deprotection and acetylation of **15** provided the triacetate derivative **17** (Scheme 1). At this stage, extensive NMR analysis of **17** unambiguously confirmed the bicyclic structure and the assigned stereochemistry of this trans-fused furopyranyl nucleoside. Thus, in an HMBC experiment, the observed three-bonds connectivity between H-7′ and C-3′ confirmed the furopyran bicyclic ring formation. Similarly, strong NOE correlations between H-3′/H-7′ and H-6′/H-7′

(12) For examples of m-CPBA epoxidation of acyclic chiral allylic amides and stereoelectivities thereof, see: Roush, W. R.; Straub, J. A.; Brown, R. J. *J. Org. Chem.* **1987**, *52*, 5127–5136.

(13) For an example of a similar functional group transformation, see: Yadav, J. S.; Srihari, P. *Tetrahedron: Asymmetry* **2004**, *15*, 81–89, and references therein.

(14) For similar examples of intramolecular oxymercuration−oxidation protocol, see:(a) Hill, C. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 1269–1278. (b) Khalaf, J. K.; Datta, A. *J. Org. Chem.* **2004**, *69*, 387–390.

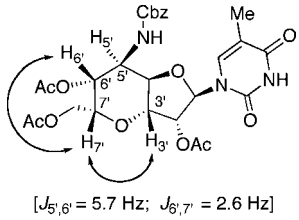


FIGURE 3. Diagnostic NOE correlations and coupling constants of compound **17**.

indicated a cis-relationship between these protons, thereby confirming the assigned stereochemistry at the C-6′ and C-7′ chiral centers (Figure 3). Additionally, the observed coupling constant between H-5′ and H-6′ (J = 5.7 Hz) substantiated the assigned trans-relationship between these two protons.

The observed stereoselectivity in the above intramolecular oxymercuration (**14** → **15**) is probably attributable to the sterically more favorable chairlike transition state **II** (Figure 4) leading to the stereoselective formation of the desired trans-fused furopyran bicyclic derivative **15**.

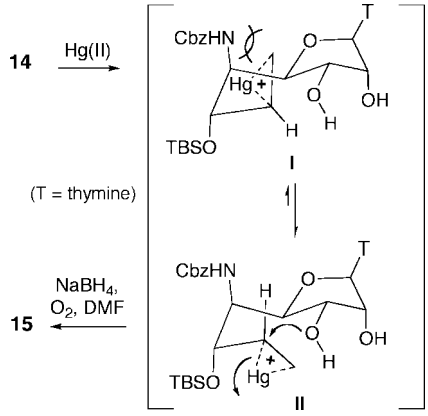


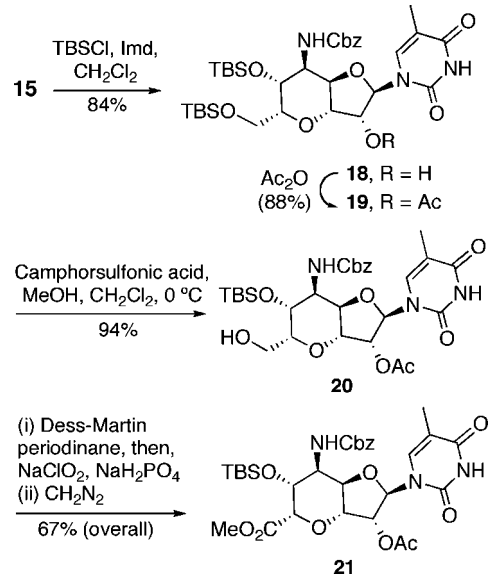
FIGURE 4. Probable mechanistic pathway leading to the stereoselective formation of compound **15**.

Toward formation of the 7′-carboxylic acid substituent, exhaustive oxidation of the C-7′ hydroxymethylene functionality of **15** was next undertaken. Initial attempts at one-step, selective oxidation of the primary hydroxy group in presence of the free C-2′ secondary hydroxy,[5f] were however not successful. Subsequently, following a selective protection−deprotection protocol, silyl protection of the primary hydroxy group of **15** to form the di-TBS-derivative **18**, followed by acetyl protection of the secondary 2′-hydroxy group resulted in the corresponding fully protected bicyclic nucleoside **19** (Scheme 2). Selective deprotection[15] of the primary hydroxyl to unmask the monohydroxy compound **20** and oxidation of the hydroxy group to carboxylic acid and its subsequent esterification furnished the fully protected thymine octosyl nucleoside derivative **21** in good overall yield.

The assigned structure and stereochemical integrity of **21** was ascertained by high-resolution NMR studies. Similar to the earlier observations as in compound **17**, strong NOE interactions were observed between H-3′/H-7′ and H-6′/H-7′. Additionally, conformity of the NMR data of **21** with structurally similar octosyl nucleosides reported in the literature, reconfirmed the assigned structure and stereochemistry of **21** and its precursors.

(15) Nelson, T. D.; Crouch, R. D. *Synthesis* **1996**, 1031–1069.

SCHEME 2



In summary, employing D-serine as a chiral building block, a novel synthetic route to an appropriately functionalized octosyl nucleoside derivative of the ezomycins has been developed. The present approach represents the first instance wherein the octosyl nucleoside component has been constructed starting from a noncarbohydrate precursor. An advantage of this de novo approach is expected to be increased flexibility in terms of potential SAR modifications at the carbohydrate core as well as in the creation of non-natural stereocenter containing derivatives. In future studies, extension of the present route toward incorporation of cytosine nucleobase, and completion of the total synthesis via glycosidic attachment of ezoaminuroic acid at C-6′ will be pursued.

Experimental Section

(2*R*,3*R*,4*R*,5*R*)-2-((*R*)-1-(Benzyloxycarbonylamino)-2-hydroxyethyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3,4-diyl diethanoate (6). To a stirring, room temperature solution of the triacetate **5**[6a] (2.30 g, 4.80 mmol) in anhydrous CH_2Cl_2 (65 mL) under N_2 atmosphere, freshly prepared bis-silylated thymine (3.25 g, 12.0 mmol) was added, and the resulting suspension stirred for 5 min. Freshly distilled TMSOTf (4.34 mL, 24.0 mmol) was then added to the reaction mixture, resulting in a clear solution. After stirring at ambient temperature for 2 h, the reaction was quenched with a saturated solution of $NaHCO_3$ (10 mL). The two layers were separated, and the aqueous layer was further extracted with $CHCl_3$ (3 × 10 mL). The combined organic layer was then dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford the crude product. Purification by flash chromatography (hexane/EtOAc = 2:3 to 1:5) afforded the amino alcohol **6** as a white foamy solid (2.11 g, 87%): mp = 98−100 °C; $[\alpha]_D = -1.20$ (*c* 1.00, $CHCl_3$). IR (NaCl) 3308, 1749, 1697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.91 (s, 3H), 2.09 (s, 3H), 2.10 (s, 3H), 2.94 (br s, 1H exchangeable with D_2O), 3.78−3.81 (m, 1H), 3.91−3.93 (m, 1H), 4.03−4.08 (m, 1H), 4.26 (t, J = 5.1 Hz, 1H), 5.14 (br s, 2H), 5.42 (t, J = 5.8 Hz, 1H), 5.55 (t, J = 5.6 Hz, 1H), 5.78 (br d, J = 7.9 Hz, 2H), 7.10 (br s, 1H), 7.28−7.37 (m, 5H), 9.10 (br s, 1H exchangeable with D_2O). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 12.4, 20.4, 20.5, 53.4, 61.7, 67.2, 70.8, 72.5, 82.0, 88.9, 112.0, 128.0, 128.3, 128.6, 136.1, 136.4, 150.4, 163.1, 169.8, 170.1. HRMS (ES+) calcd for $C_{23}H_{27}N_3O_{10}$ *m/z* $(M + H)^+$, 506.1775; found, 506.1753.

(2*R*,3*R*,4*R*,5*R*)-2-((*R*,*E*)-1-(Benzyloxycarbonylamino)-4-methoxy-4-oxobut-2-enyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3,4-diyl diethanoate (7). Step 1. Dess−Martin periodinane (15% in CH_2Cl_2 solution, 5.75 mL, 2.04 mmol) was added dropwise to an ice-cooled solution of the amino alcohol **6** (0.856 g, 1.69 mmol) dissolved in CH_2Cl_2 (33 mL), and the reaction mixture was stirred at 0 °C for another 30 min. The reaction was then allowed to attain room temperature, and the stirring continued for another 2 h. The reaction was quenched by the addition of a solution of 10 mL of saturated aqueous $NaHCO_3$ containing 1.5 g of $Na_2S_2O_3$. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4, and removal of solvent under vacuum resulted in a colorless oily residue, which was used directly for the subsequent reaction.

Step 2. The crude aldehyde obtained from the above reaction was dissolved in anhydrous CH_2Cl_2 (32 mL) and cooled to 0 °C. The Wittig reagent (0.68 g, 2.03 mmol) was then added to the reaction mixture and stirred for 2 h. Removal of solvent under vacuum and purification of the residue by flash chromatography ($CHCl_3$/MeOH = 99:1 to 95:5) yielded the *E*-ester **7** as a white foamy solid (0.891 g, 78% over two steps): mp = 102 − 104 °C; $[\alpha]_D = -0.66$ (*c* 0.80, $CHCl_3$). IR (NaCl) 3306, 1751, 1697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.92 (s, 3H), 2.07 (s, 3H), 2.12 (s, 3H), 3.77 (s, 3H), 4.24 (t, *J* = 5.4 Hz, 1H), 4.81 (br s, 1H), 5.13 (s, 2H), 5.34−5.42 (m, 2H), 5.64 (d, *J* = 8.7 Hz, 1H), 5.78 (d, *J* = 4.2 Hz, 1H), 6.13 (d, *J* = 15.7 Hz, 1H), 6.90 − 6.96 (m, 2H), 7.36 (br s, 5H), 8.84 (s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 12.8, 20.7, 20.8, 52.3, 53.4, 67.6, 69.9, 73.1, 82.3, 89.8, 112.5, 123.8, 128.4, 128.6, 128.9, 129.4, 136.4, 136.7, 142.7, 151.0, 156.5, 164.2, 166.5, 170.0, 170.1. HRMS (ES+) calcd for $C_{26}H_{29}N_3O_{11}$ *m*/*z* (M + Na)$^+$, 582.1700; found, 582.1710.

(2*R*,3*R*,4*R*,5*R*)-2-(5-Methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-5-((*R*,*E*)-10,10,11,11-tetramethyl-3-oxo-1-phenyl-2,9-dioxa-4-aza-10-siladodec-6-en-5-(yl)-tetrahydrofuran-3,4-diyl diethanoate (8). The ester **7** (1.86 g, 3.33 mmol) was dissolved in anhydrous THF (80 mL) and cooled to −78 °C. To this stirring solution, DIBAL-H (1 M in toluene, 18.3 mL, 5.5 mmol) was added dropwise, and the reaction was stirred for 2 h at the same temperature. The reaction was quenched by careful addition of MeOH (3 mL) and then allowed to attain room temperature, followed by dilution with EtOAc (30 mL) and saturated aqueous sodium potassium tartrate (30 mL). The resulting mixture was stirred until two clear layers were seen. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extract was dried over anhydrous Na_2SO_4 and concentrated under vacuum to give the crude product. Purification by column chromatography (hexane/EtOAc = 9:1) afforded the allyl alcohol **8** as a white foamy solid (1.15 g, 71% based on recovered starting material 0.18 g): mp = 100 − 102 °C; $[\alpha]_D$ = 2.70 (*c* 1.00, $CHCl_3$). IR (NaCl) 3308, 1751, 1697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.92 (s, 3H), 2.10 (s, 6H), 2.45 (br s, 1H exchangeable with D_2O), 4.19 − 4.24 (2 br s, 3H), 4.58 (br s, 1H), 5.12 (s, 2H), 5.40 (d, *J* = 3.2 Hz, 2H), 5.52 (br d, *J* = 7.9 Hz, 1H), 5.72−5.78 (m, 2H), 5.99 (br d, *J* = 15.4 Hz, 1H), 7.05 (s, 1H), 7.35 (br s, 5H), 9.24 (s, 1H exchangeable with D_2O). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 12.3, 20.4, 20.5, 53.5, 53.6, 62.0, 67.1, 69.7, 72.6, 82.9, 89.8, 112.0, 124.6, 128.1, 128.2, 128.6, 134.2, 136.2, 136.8, 150.3, 155.9, 163.4, 169.7, 169.9. HRMS (ES+) calcd for $C_{25}H_{29}N_3O_{10}$ *m*/*z* (M + Na)$^+$, 554.1751; found, 554.1729.

(2*R*,3*R*,4*R*,5*R*)-2-(5-Methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-5-((*R*,*E*)-10,10,11,11-tetramethyl-3-oxo-1-phenyl-2,9-dioxa-4-aza-10-siladodec-6-en-5-yl)-tetrahydrofuran-3,4-diyl diethanoate (9). The allylic alcohol **8** (1.19 g, 2.23 mmol) was dissolved in anhydrous CH_2Cl_2 (50 mL), followed by sequential addition of imidazole (0.61 g, 8.92 mmol), DMAP (25 mg, catalytic), and TBSCl (1.10 g, 6.69 mmol). The reaction mixture was allowed to stir at room temperature for 3 h and then quenched with ice-cooled water (10 mL). The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum to give the crude product. Purification by column chromatography (hexane/EtOAc = 2:3) afforded the TBS compound **9** as a white foamy solid (1.26 g, 87%): mp = 92−94 °C; $[\alpha]_D = 2.95$ (*c* 1.11, $CHCl_3$). IR (NaCl) 3306, 1751, 1697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.91 (s, 9H), 1.91 (s, 3H), 2.09 (s, 6H), 4.18−4.22 (m, 3H), 4.63 (br s, 1H), 5.14 (br s, 2H), 5.25 (t, *J* = 5.9 Hz, 1H), 5.32−5.37 (m, 2H), 5.72 (dd, *J* = 6.3 and 15.4 Hz, 1H), 5.91 (br d, *J* = 15.4 Hz, 1H), 5.99 (d, *J* = 5.4 Hz, 1H), 7.05 (s, 1H), 7.36 (br s, 5H), 8.99 (s, 1H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ −5.3, 12.6, 18.4, 20.3, 20.4, 25.9, 53.5, 62.6, 67.1, 69.6, 72.3, 82.9, 87.1, 112.1, 123.2, 128.1, 128.2, 128.6, 134.3, 135.1, 136.2, 150.2, 155.8, 163.1, 169.5. HRMS (ES+) calcd for $C_{31}H_{43}N_3O_{10}Si$ *m*/*z* (M + Na)$^+$, 668.2615; found, 668.2511.

(2*R*,3*R*,4*R*,5*R*)-2-((*R*)-(Benzyloxycarbonylamino)((2*R*,3*R*)-3-((*tert*-butyldimethylsilyloxy)methyl)oxiran-2-yl)methyl)-5-(5-methyl-2,4-dioxo-3,4-dihydro-pyrimidin-1-(2*H*)-yl)tetrahydrofuran-3,4-diyl diethanoate (10). *m*-CPBA (0.856 g, 3.72 mmol) and $NaHCO_3$ (0.470 g, 5.58 mmol) were added to a solution of the TBS compound **9** (1.20 g, 1.86 mmol) dissolved in anhydrous CH_2Cl_2 (45 mL). The reaction mixture was stirred at room temperature overnight and then concentrated under vacuum to give the crude product. Purification by column chromatography (hexane/EtOAc = 2:3 to 3:2) afforded the epoxide **10** as a white foamy solid (1.10 g, 90%): mp = 92−94 °C; $[\alpha]_D = 2.33$ (*c* 1.30, $CHCl_3$). IR (NaCl) 3304, 1751, 1697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, diastereomeric mixtures 1:5) δ 0.07 (s, 6H), 0.89 (s, 9H), 1.93 (s, 3H), 2.08 (s, 3H), 2.10 (s, 3H), 3.02 (br s, 1H), 3.24 (s, 1H), 3.67 (dd, *J* = 4.5 and 12.2 Hz, 1H), 3.94 (br d, *J* = 11.0 Hz, 1H), 4.20−4.25 (m, 1H), 4.40−4.44 (m, 1H), 5.12 (s, 2H), 5.16 (br d, *J* = 9.7 Hz, 1H), 5.37 (t, *J* = 5.8 Hz, 5/6H), 5.41 (t, *J* = 5.8 Hz, 1/6H), 5.48 (t, *J* = 5.8 Hz, 1H), 5.55 (t, *J* = 5.8 Hz, 1/6H), 5.93 (d, *J* = 5.2 Hz, 5/6H), 5.97 (d, *J* = 5.2 Hz, 1/6H), 7.15 (s, 5/6H), 7.21 (s, 1/6H), 7.36 (br s, 5H), 8.82 (s, 5/6H exchangeable with D_2O), 8.86 (s, 1/6H). ^{13}C NMR (125.8 MHz, $CDCl_3$, diastereomeric mixtures) δ −5.4, 12.5, 12.4, 18.3, 20.3, 20.4, 25.8, 50.2, 52.8, 53.4, 55.3, 62.1, 62.2, 67.4, 70.0, 72.4, 81.7, 82.1, 87.8, 88.3, 112.0, 112.2, 128.1, 128.2, 128.3, 128.6, 130.2, 133.3, 135.7, 135.9, 150.2, 150.4, 156.3, 163.3, 163.4, 169.4, 169.5, 169.6. HRMS (ES+) calcd for $C_{31}H_{43}N_3O_{11}Si$ *m*/*z* (M + Na)$^+$, 684.2565; found, 684.2583.

(2*R*,3*R*,4*R*,5*R*)-2-((*R*)-(Benzyloxycarbonylamino)((2*R*,3*R*)-3-(hydroxymethyl)oxiran-2-yl)methyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetra-hydro-furan-3,4-diyl diethanoate (11). To an ice-cooled solution of the epoxide **10** (1.12 g, 1.74 mmol), in anhydrous THF (25 mL) was added TBAF (1 M in THF, 3.65 mL, 3.65 mmol) dropwise. The reaction mixture was stirred at 0 °C for 1.5 h and then quenched by water (5 mL); the two layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum to give the crude product. Purification by column chromatography (hexane/EtOAc = 1:5) afforded the epoxy alcohol as a white foamy solid **11** (0.855 g, 90%): mp = 108−110 °C; $[\alpha]_D = 1.82$ (*c* 1.10, $CHCl_3$). IR (NaCl) 3306, 1751, 1697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.89 (s, 3H), 2.07 (s, 3H), 2.09 (s, 3H), 2.93 (br s, 1H exchangeable with D_2O), 3.12 (d, *J* = 2.1 Hz, 1H), 3.38 (br s, 1H), 3.77 (br d, *J* = 12.6 Hz, 1H), 3.87 (br d, *J* = 12.2 Hz, 1H), 4.26 (d, *J* = 5.7 Hz, 2H), 5.11 (s, 2H), 5.48 − 5.51 (m, 1H), 5.56−5.63 (m, 2H), 5.68−5.76 (m, 1H), 7.09 (s, 1H), 7.34 (br s, 5H), 9.38 (s, 1H exchangeable with D_2O). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 12.3, 20.3, 20.4, 51.0, 53.2, 56.1, 60.3, 67.3, 69.9, 72.8, 81.8, 90.5, 111.9, 128.1, 128.3, 128.6, 136.1, 137.1, 150.4, 156.4, 163.6, 169.7, 169.8. HRMS (ES+) calcd for $C_{25}H_{29}N_3O_{11}$ *m*/*z* (M + Na)$^+$, 570.1702; found, 570.1700.

(2*R*,3*R*,4*R*,5*R*)-2-((1*R*,2*S*)-1-(Benzyloxycarbonylamino)-2-hydroxybut-3-enyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1-(2*H*)-yl)tetrahydrofuran-3,4-diyl diethanoate (12). Step 1. The epoxy alcohol **11** (0.820 g, 1.50 mmol) was dissolved in a mixture

of Et_2O/CH_3CN (3:1, 11 mL) and cooled to 0 °C. To this stirring solution, imidazole (0.286 g, 4.20 mmol), triphenylphosphine (0.866 g, 3.30 mmol) and iodine (0.838 g, 3.30 mmol) were added sequentially. After stirring at 0 °C for 20 min, the reaction mixture was diluted with EtOAc (10 mL) and 5% aqueous HCl (5 mL). The two layers were separated, and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum to give the crude iodo derivative, which was taken to the next step without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 (s, 3H), 2.06 (s, 3H), 2.10 (s, 3H), 3.14−3.19 (m, 4H), 4.17 (t, J = 5.7 Hz, 1H), 4.37 (t, J = 7.2 Hz, 1H), 5.04 (d, J = 8.9 Hz, 1H), 5.11 (s, 2H), 5.40 (t, J = 5.6 Hz, 1H), 5.48 (t, J = 5.9 Hz, 1H), 5.85 (d, J = 4.6 Hz, 1H), 7.13 (s, 1H), 7.35 (s, 5H), 8.27 (s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 3.7, 12.9, 14.6, 20.8, 20.9, 23.1, 32.0, 51.0, 55.6, 60.2, 67.8, 70.5, 72.8, 82.0, 89.3, 112.4, 128.6, 128.8, 129.0, 136.2, 136.6, 150.7, 156.6, 163.9, 170.0, 170.1.

Step 2. The crude iodo compound obtained from the above reaction was dissolved in anhydrous MeOH (85 mL). To this stirring solution, AcOH (15 mL) and Zn (3.9 g, 60 mmol) were added, and the reaction was heated to 37 °C. After stirring at the same temperature overnight, solvent was removed under vacuum and the residue was diluted with EtOAc (50 mL) and filtered. The filtrate was washed sequentially with saturated aqueous solution of $NaHCO_3$ and saturated solution of $Na_2S_2O_3$. The organic layer was dried over Na_2SO_4 and concentrated under vacuum to give the crude product. Purification by column chromatography ($CHCl_3$/MeOH = 99:1 to 95:5) afforded the allylic alcohol **12** as a white foamy solid (0.590 g, 74% over two steps): mp = 90−92 °C; $[\alpha]_D$ = −2.13 (*c* 1.00, $CHCl_3$). IR (NaCl) 3308, 1751, 1695 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90 (s, 3H), 2.09 (s, 6H), 3.00 (br s, 1H exchangeable with D_2O), 4.00 (t, J = 7.6 Hz, 1H), 4.24−4.29 (m, 1H), 4.55 (br s, 1H), 5.14 (br s, 2H), 5.23 (d, J = 10.4 Hz, 1H), 5.36 − 5.40 (m, 2H), 5.50−5.53 (m, 1H), 5.59 (d, J = 8.9 Hz, 1H), 5.84−5.92 (m, 1H), 5.95 (d, J = 5.6 Hz, 1H), 7.14 (s, 1H), 7.35 (br s, 5H), 8.94 (br s, 1H exchangeable with D_2O). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 12.4, 20.4, 20.5, 56.1, 67.3, 70.2, 71.3, 72.3, 82.2, 87.5, 112.1, 116.8, 117.8, 127.9, 128.2, 128.3, 128.6, 135.8, 136.2, 136.8, 150.5, 157.1, 163.4, 169.8, 170.1. HRMS (ES+) calcd for $C_{25}H_{29}N_3O_{10}$ *m/z* (M + Na)$^+$, 554.1751; found, 554.1719.

(2*R*,3*R*,4*R*,5*R*)-2-(5-Methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-5-((5*S*,6*S*)-8,8,9,9-tetramethyl-3-oxo-1-phenyl-6-vinyl-2,7-dioxa-4-aza-8-siladecan-5-yl)tetra-hydrofuran-3,4-diyl diethanoate (13). The allylic alcohol **12** (0.550 g, 1.036 mmol) was dissolved in anhydrous DMF (20 mL), and to this solution were added sequentially imidazole (0.353 g, 5.18 mmol), DMAP (25 mg, catalytic), and TBSCl (0.624 g, 4.14 mmol). The reaction mixture was allowed to stir at room temperature overnight. The solvent was concentrated under high vacuum, and the resulting residue was dissolved in CH_2Cl_2 (20 mL) and poured into 10 mL of H_2O. The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated to give the crude product. Purification by column chromatography (hexane/EtOAc = 1:1) afforded the TBS-protected product **13** as a white solid (0.521 g, 78%): mp = 140−142 °C; $[\alpha]_D$ = −2.63 (*c* 1.00, $CHCl_3$). IR (NaCl) 3219, 1753, 1697 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.10 (s, 3H), 0.93 (s, 9H), 1.99 (s, 3H), 2.05 (s, 3H), 2.08 (s, 3H), 3.87 (t, J = 9.4 Hz, 1H), 4.02−4.05 (m, 1H), 4.47 (d, J = 5.4 Hz, 1H), 5.10−5.30 (m, 5H), 5.42 (t, J = 6.2 Hz, 1H), 5.46−5.49 (m, 1H), 5.78−5.87 (m, 1H), 6.06 (d, J = 6.1 Hz, 1H), 7.09 (s, 1H), 7.33−7.41 (m, 5H), 8.30 (br s, 1H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ −5.1, −4.4, 12.6, 18.2, 20.4, 25.9, 57.4, 67.3, 71.2, 71.4, 71.9, 80.2, 86.7, 112.3, 116.9, 128.0, 128.2, 128.3, 128.6, 134.9, 136.1, 137.4, 150.1, 156.8, 163.0, 169.2, 169.4. HRMS (ES+) calcd for $C_{31}H_{43}N_3O_{10}Si$ *m/z* (M + Na)$^+$, 668.2616; found, 668.2601.

Benzyl (1*S*,2*S*)-2-(*tert*-butyldimethylsilyloxy)-1-((2*R*,3*S*,4*R*,5*R*)-3,4-dihydroxy-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-2-yl)but-3-enyl-carbamate (14). Powdered K_2CO_3 (0.131 g, 0.95 mmol) was added to an ice-cooled solution of the diacetate **13** (0.480 g, 0.74 mmol) dissolved in anhydrous MeOH (25 mL). After stirring the reaction mixture at 0 °C for 3.5 h, solvent was removed under vacuum to give the crude product. Purification by column chromatography (hexane/EtOAc = 1:9) afforded the diol as a white foamy solid **14** (0.353 g, 85%): mp = 88−90 °C; $[\alpha]_D$ = −6.09 (*c* 1.20, $CHCl_3$). IR (NaCl) 3431, 1697 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.09 (s, 3H), 0.92 (s, 9H), 1.92 (s, 3H), 3.68 (br s, 1H exchangeable with D_2O), 3.79 (t, J = 9.4 Hz, 1H), 3.97 (br d, J = 9.3 Hz, 1H), 4.34 (br s, 2H), 4.49 (d, J = 5.3 Hz, 1H), 4.72 (br s, 1H exchangeable with D_2O), 5.12−5.37 (m, 5H), 5.79−5.87 (m, 2H), 7.16 (s, 1H), 7.28−7.36 (m, 5H), 9.84 (br s, 1H exchangeable with D_2O). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ −5.1, −4.3, 12.5, 18.2, 25.8, 25.9, 57.5, 67.2, 71.3, 71.6, 73.8, 82.7, 90.8, 111.5, 116.5, 128.0, 128.2, 128.6, 136.2, 136.3, 137.9, 151.0, 157.2, 164.0. HRMS (ES+) calcd for $C_{27}H_{39}N_3O_8Si$ *m/z* (M + Na)$^+$, 584.2404; found, 584.2422.

Benzyl (2*R*,3*R*,3a*S*,5*R*,6*R*,7*S*,7a*R*)-6-(*tert*-butyldimethylsilyloxy)-3-hydroxy-5-(hydroxymethyl)-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)hexa-hydro-2*H*-furo[3,2-b]pyran-7-ylcarbamate (15) and Benzyl (2*R*,3*R*,3a*S*,5*R*,6*R*,7*S*,7a*R*)-6-(*tert*-butyldimethylsilyloxy)-3-hydroxy-5-methyl-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)hexahydro-2*H*-furo [3,2-b]pyran-7-ylcarbamate (16). Step 1. To a stirred solution of the diol **14** (0.938 g, 1.67 mmol) in CH_3CN (100 mL), mercuric(II) trifluoroacetate (0.912 g, 5.28 mmol) was added, and the mixture was refluxed overnight. The reaction was cooled to room temperature and diluted by the addition of EtOAc (50 mL) and brine (50 mL). The resulting biphasic mixture was stirred at room temperature for 3 h. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organic extract was dried over anhydrous Na_2SO_4, and solvent was removed in vacuo to give a white foamy solid which was used as such for the subsequent reaction.

Step 2. To a well-stirred solution of $NaBH_4$ (0.20 g, 5.29 mmol) in DMF (9 mL) at room temperature, oxygen (O_2) gas was bubbled for 1 h. To this mixture was added dropwise over 2 h, a DMF solution (9 mL) of the crude mercuric compound (0.828 g) obtained from the earlier step, with continuous bubbling of O_2. After being stirred for a further 8 h, the reaction mixture was filtered through celite, the residue was washed thoroughly with EtOAc (4 × 20 mL), and the filtrate was concentrated under vacuum. Purification of the crude residue by flash chromatography (hexane/MeOH/EtOAc = 18:2:80) yielded the bicyclic diol **15** and minor quantities of the corresponding methylated product **16**.

15 (major product). Obtained as a white foamy solid (0.501 g, 52%): mp = 156−158 °C; $[\alpha]_D$ = −3.12 (*c* 0.96, $CHCl_3$). IR (NaCl) 3339, 1697 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD) δ 0.09 (s, 3H), 0.20 (s, 3H), 0.91 (s, 9H), 1.69 (s, 3H), 3.26 − 3.28 (m, 2H), 3.57−3.71 (m, 3H), 3.81−3.85 (m, 2H), 4.20 (d, J = 5.1 Hz, 1H), 4.33−4.35 (br m, 1H), 4.24 (br s, 1H), 5.04−5.14 (m, 2H), 5.63 (s, 1H), 7.25−7.36 (m, 6H). ^{13}C NMR (125.8 MHz, CD_3OD) δ −5.1, −4.3, 12.7, 19.0, 26.4, 54.7, 62.9, 68.2, 71.9, 74.0, 74.7, 74.8, 80.2, 95.0, 111.5, 129.4, 129.7, 138.1, 138.4, 152.2, 158.7, 166.5. HRMS (ES+) calcd for $C_{27}H_{39}N_3O_9Si$ *m/z* (M + Na)$^+$, 600.2353; found, 600.2346.

16 (minor product). Obtained as a white foamy solid (0.065 g, 7%): mp = 120−124 °C; $[\alpha]_D$ = 1.90 (*c* 1.0, $CHCl_3$). IR (NaCl) 3339, 1701 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.13 (s, 3H), 0.27 (s, 3H), 0.95 (s, 9H), 1.22 (d, J = 5.9 Hz, 3H), 1.85 (s, 3H), 2.93 (br s, 1H exchangeable with D_2O), 3.90 (br s, 1H), 4.01 (d, J = 6.2 Hz 1H), 4.25−4.28 (m, 2H), 4.48 (d, J = 3.8 Hz, 1H), 5.09−5.19 (m, 3H), 5.62 (br s, 1H), 7.00 (s, 1H), 7.32 (m, 5H), 9.34 (br s, 1H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ −5.0, −4.6, 12.2, 14.1, 16.7, 18.0, 22.7, 25.8, 29.4, 29.7, 53.8, 55.4, 66.9, 70.9, 72.4, 73.0, 73.2, 74.4, 98.6, 111.2, 127.7, 128.2, 128.4, 128.5, 128.7,

136.1, 139.7, 150.1, 156.5, 163.5. HRMS (ES+) calcd for $C_{27}H_{39}N_3O_8Si$ *m/z* (M + Na)$^+$, 584.2404; found, 584.2408.

(2*R*,3*R*,3a*R*,5*R*,6*R*,7*S*,7a*R*)-7-(Benzyloxycarbonylamino)-5-(ethanoyloxymethyl)-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)hexahydro-2*H*-furo[3,2-b]-pyran-3,6-diyl diethanoate (17). Step 1. To a stirred, ice-cooled solution of the diol **15** (0.042 g, 0.07 mmol) in anhydrous THF (3 mL), was added TBAF (1 M in THF, 0.1 mL, 0.1 mmol). The reaction mixture was stirred at the same temperature for 1.5 h, followed by quenching of the reaction by addition of H_2O (0.5 mL). The two layers were separated and the aqueous layer was extracted with EtOAc (3 × 1 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum to give the crude triol, which was used as such for the subsequent reaction.

Step 2. The triol from the above reaction was dissolved in anhydrous CH_2Cl_2 (2 mL), followed by sequential addition of anhydrous pyridine (0.018 mL, 0.222 mmol), DMAP (10 mg, catalytic), and Ac_2O (0.021 mL, 0.222 mmol). After stirring at room temperature for 2 h, the reaction was quenched by addition of ice-cooled water (0.5 mL). The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 1 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, and concentrated under vacuum to give the crude product. Purification by column chromatography (hexane/EtOAc = 2:3) afforded the triacetate **17** as a white foamy solid (0.036 g, 89% over two steps): mp = 150−152 °C; $[\alpha]_D$ 1.13 (*c* 0.80, $CHCl_3$). IR (NaCl) 3329, 1747, 1697 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.88 (s, 3H), 2.08 (s, 3H), 2.17 (s, 3H), 2.23 (s, 3H), 4.10−4.30 (m, 4H), 4.35 (br s, 1H), 4.58 (br s, 1H), 5.10−5.18 (m, 3H), 5.35−5.37 (m, 1H), 5.43 (br s, 1H), 5.88 (br s, 1H), 6.89 (s, 1H), 7.31 (s, 5H), 9.11 (s, 1H). ^{13}C NMR (201.2 MHz, $CDCl_3$) δ 12.3, 20.8, 20.9, 51.4, 62.3, 67.1, 68.2, 71.5, 73.9, 74.1, 74.9, 97.4, 111.6, 128.2, 128.3, 128.5, 136.1, 139.5, 150.3, 156.4, 163.5, 169.0, 170.7, 170.9. HRMS (ES+) calcd for $C_{27}H_{31}N_3O_{12}$ *m/z* (M + H)$^+$, 590.1986; found, 590.1982.

Benzyl (2*R*,3*R*,3a*S*,5*R*,6*R*,7*S*,7a*R*)-6-(*tert*-butyldimethylsilyloxy)-5-((*tert*-butyl-dimethylsilyloxy)methyl)-3-hydroxy-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)hexahydro-2*H*-furo[3,2-b]pyran-7-ylcarbamate (18). To a room temperature solution of the diol **15** (0.362 g, 0.63 mmol) in anhydrous CH_2Cl_2 (15 mL), was added sequentially imidazole (0.13 g, 1.9 mmol), 4-DMAP (5 mg, catalytic), and TBSCl (0.12 g, 1.8 mmol). After stirring for 3 h, the reaction was quenched by the addition of water (10 mL). The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extract was dried over anhydrous Na_2SO_4 and concentrated under vacuum to give the crude product. Purification by column chromatography (hexane/EtOAc = 2:3) afforded the primary TBS protected product **18** as a white foamy solid (0.366 g, 84%): mp = 120−122 °C; $[\alpha]_D$ = −0.70 (*c* 1.00, $CHCl_3$). IR (NaCl) 3336, 1701 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.13 (br s, 3H), 0.27 (br s, 3H), 0.91 (2s, 18H), 1.89 (s, 3H), 2.67 (s, 1H exchangeable with D_2O), 3.74 (br s, 2H), 3.88 (t, *J* = 5.6 Hz, 1H), 4.17−4.33 (m, 4H), 4.53 (d, *J* = 4.2 Hz, 1H), 5.13 (s, 2H), 5.22 (br s, 1H), 5.48 (br s, 1H), 7.03 (s, 1H), 7.35 (br s, 5H), 8.74 (br s, 1H exchangeable with D_2O). ^{13}C NMR (201.2 MHz, $CDCl_3$) δ −5.1, −4.3, 12.4, 18.1, 18.6, 26.0, 26.1, 53.8, 62.8, 67.1, 68.6, 72.4, 73.2, 73.6, 79.3, 98.4, 111.4, 128.4, 128.8, 139.6, 150.2, 156.6, 163.7. HRMS (ES+) calcd for $C_{33}H_{53}N_3O_9Si_2$ *m/z* (M + Na)$^+$, 714.3218; found, 714.3223.

(2*R*,3*R*,3a*R*,5*R*,6*R*,7*S*,7a*R*)-7-(Benzyloxycarbonylamino)-6-(*tert*-butyldimethyl-silyloxy)-5-((*tert*-butyldimethylsilyloxy)methyl)-2-(5-methyl-2,4-dioxo-3,4-dihydro-pyrimidin-1(2*H*)-yl)hexahydro-2*H*-furo[3,2-b]pyran-3-yl ethanoate (19). To a solution of the di-TBS alcohol **18** (0.230 g, 0.333 mmol) in anhydrous CH_2Cl_2 (10 mL) was added sequentially, anhydrous pyridine (0.067 mL, 0.717 mmol), DMAP (10 mg, catalytic), and Ac_2O (0.064 mL, 0.792 mmol). After stirring at room temperature for 2 h, the reaction was quenched by the addition of ice-cooled water (2 mL). The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, and concentrated under vacuum to give the crude product. Purification by column chromatography afforded the acetate **19** as a white foamy solid (0.215 g, 88%): mp = 120−122 °C; $[\alpha]_D$ = 0.9 (*c* 0.64, $CHCl_3$). IR (NaCl) 3306, 1699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.15 (br s, 3H), 0.27 (br s, 3H), 0.90 and 0.95 (2s, 18H), 1.90 (s, 3H), 2.17 (s, 3H), 3.73 (br s, 2H), 3.80 (t, *J* = 6.2 Hz, 1H), 4.22−4.35 (m, 4H), 5.13−5.19 (m, 3H), 5.36 (d, *J* = 5.5 Hz, 1H), 5.55 (br s, 1H), 6.94 (s, 1H), 7.35 (s, 5H), 8.58 (br s, 1H). ^{13}C NMR (201.2 MHz, $CDCl_3$) δ −5.1, −5.0, −4.9, −4.4, 12.5, 18.2, 18.6, 21.0, 25.8, 26.0, 26.1, 53.5, 62.2, 67.0, 68.0, 71.9, 74.1, 80.0, 96.5, 111.6, 128.3, 128.4, 128.7, 136.4, 139.4, 150.0, 156.6, 163.5, 170.9. HRMS (ES+) calcd for $C_{35}H_{55}N_3O_{10}Si_2$ *m/z* (M + Na)$^+$, 756.3324; found, 756.3342.

(2*R*,3*R*,3a*R*,5*R*,6*R*,7*S*,7a*R*)-7-(Benzyloxycarbonylamino)-6-(*tert*-butyldimethyl silyloxy)-5-(hydroxymethyl)-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl-hexahydro-2*H*-furo[3,2-b]pyran-3-yl ethanoate (20). The di-TBS derivative **19** (0.200 g, 0.273 mmol) was dissolved in a mixture of CH_2Cl_2/MeOH (1:1, 12 mL) and cooled to 0 °C. To the stirring solution was added camphor sulfonic acid (0.031 g, 0.133 mmol) and the mixture was stirred at the same temperature for 3 h. Removal of solvent under reduced pressure and purification of the crude residue by column chromatography afforded the monohydroxy product **20** as a white foamy solid (0.159 g, 94%): mp = 140−142 °C; $[\alpha]_D$ = 2.70 (*c* 0.60, $CHCl_3$). IR (NaCl) 3263, 1697 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.13 (br s, 3H), 0.27 (br s, 3H), 0.94 (s, 9H), 1.89 (s, 3H), 2.17 (s, 3H), 2.30 (s, 1H exchangeable with D_2O), 3.60 (br s, 1H), 3.83−3.95 (m, 2H), 4.10 (br s, 1H), 4.20−4.28 (m, 2H), 4.43 (br s, 1H), 5.07−5.13 (m, 2H), 5.16 (br d, *J* = 5.2 Hz, 1H), 5.44 (br d, *J* = 4.4 Hz, 1H), 5.81 (br s, 1H), 6.94 (s, 1H), 7.34 (s, 5H), 9.06 (br s, 1H exchangeable with D_2O). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ −5.2, −4.6, 12.3, 17.8, 20.8, 25.6, 25.7, 29.7, 53.4, 62.9, 66.8, 68.8, 69.1, 71.6, 73.3, 73.7, 79.0, 96.4, 111.4, 128.1, 128.2, 128.5, 136.1, 139.3, 150.1, 156.5, 163.4, 170.8. HRMS (ES+) calcd for $C_{29}H_{41}N_3O_{10}Si$ *m/z* (M + Na)$^+$, 642.2459; found, 642.2453.

(2*R*,3*R*,3a*R*,5*S*,6*R*,7*S*,7a*R*)-Methyl-7-(benzyloxycarbonylamino)-6-(*tert*-butyldimethylsilyloxy)-3-(ethanoyloxy)-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)hexahydro-2*H*-furo[3,2-b]pyran-5-carboxylate (21). Step 1. Dess−Martin periodinane (15% in CH_2Cl_2 solution, 0.86 mL, 0.302 mmol) was added to an ice-cooled solution of the alcohol **20** (0.146 g, 0.232 mmol) in CH_2Cl_2 (10 mL), and the reaction mixture was stirred at 0 °C for 30 min. The reaction was then allowed to attain room temperature and stirring continued for another 2 h. The reaction was quenched by the addition of a solution of 6 mL of saturated $NaHCO_3$ containing 0.3 g of $Na_2S_2O_3$. The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extract was washed sequentially with 5.0 mL each of saturated aqueous $NaHCO_3$, H_2O, and brine. Drying over anhydrous Na_2SO_4 and removal of solvent under vacuum resulted in a colorless oily residue, which was used directly for the subsequent reaction.

Step 2. The crude aldehyde (0.12 g) as obtained above was dissolved in *tert*-butanol (16.5 mL) followed by addition of a solution of 2-methyl-2-butene (1.20 mL, 11.1 mmol). To the resulting mixture at room temperature was added dropwise a solution of $NaClO_2$ (0.205 g, 2.27 mmol) and NaH_2PO_4 (0.212 g, 1.76 mmol) in H_2O (4 mL). The reaction mixture was stirred at room temperature for 30 min, partitioned with 2 mL of H_2O, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 6 mL). The combined organic extract was dried over anhydrous Na_2SO_4 and solvent was removed in vacuum to give the acid derivative as a colorless viscous oil, which was used as such for the subsequent esterification.

Step 3. [CAUTION: Diazomethane (CH_2N_2) is an explosive and a highly toxic gas. Explosions may occur if the substance is dried and undiluted. All operations involving diazomethane should be carried out in an efficient fume hood, following appropriate

precautions]. To a biphasic solution of KOH (0.500 g) in H_2O (1 mL) and ether (1.0 mL) at 0 °C was added *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (MNNG, 50% in H_2O, 0.5 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 × 5 mL), and the ethereal layers were combined. The CH_2N_2 thus prepared was added to a stirred solution of the crude acid (0.11 g in 2 mL of ether) obtained from step 2, and 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. Purification by flash chromatography (hexane/EtOAc 7:3) yielded the protected octosyl nucleoside derivative **21** as a white solid (0.101 g, 67% over three steps): mp = 142−144 °C; $[\alpha]_D$ 2.83 (*c* 0.40, $CHCl_3$). IR (NaCl) 3329, 1697 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.08 (br s, 3H), 0.25 (br s, 3H), 0.89 (s, 9H), 1.89 (s, 3H), 2.22 (s, 3H), 3.77 (s, 3H), 4.24 (br s, 1H), 4.31 (br d, J = 10 Hz, 1H), 4.54 (s, 1H), 4.55−4.58 (m, 2H), 4.99−5.13 (m, 2H), 5.16−5.19 (m, 1H), 5.30 (d, J = 6.0 Hz, 1H), 5.78 (br d, J = 5.2 Hz, 1H), 6.89 (s, 1H), 7.32 (s, 5H), 8.87 and 8.96 (2s, 1H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ −5.4, −4.4, 12.3, 17.8, 21.0, 25.4, 25.6, 52.3, 53.6, 67.0, 69.9, 71.2, 73.4, 74.1, 78.2, 97.7, 111.5, 111.6, 128.2, 128.5, 128.7, 136.0, 139.7, 150.2, 150.3, 156.7, 163.2, 163.3, 168.4, 171.4. HRMS (ES+) calcd for $C_{30}H_{41}N_3O_{11}Si$ *m*/*z* $(M + Na)^+$, 670.2408; found, 670.2398. HPLC: Agilent, Zorbax SB-C18 5.0 μm, 10%−95% CH_3CN/H_2O, 0.5 mL/min, 225 nm, retention time = 14.19 min.

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Supporting Information Available: General experimental details and copies of NMR spectra (^1H and ^{13}C) of all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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