Glycosyl α-Amino Acids via Stereocontrolled Buildup of a Penaldic Acid Equivalent. A Novel Synthetic Approach to the Nucleosidic Component of the Polyoxins and Related Substances

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A novel approach to glycosyl α-amino acids is exemplified by the stereocontrolled and asymmetric synthesis of thymine polyoxin C (**4**) from the known (serine-derived) penaldic acid equivalent **5**. The overall synthetic strategy involves four distinct phases: (1) diastereoselective addition of a 3-carbon nucleophile (lithio ethyl propiolate) to the protected serinal derivative (**5** → **54**), (2) stereocontrolled elaboration of the 5-amino-5-deoxyallofuranose moiety via cis-hydroxylation of a 4-substituted butenolide (**54** → **63**), (3) release of the latent α-amino acid moiety in a suitably protected form (**63** → **69**), and (4) stereo- and regioselective nucleoside formation using Vorbrüggen's glycosylation methodology followed by deprotection (**69** → **4**). A similar route employing lithiopropiolaldehyde dimethyl acetal as the 3-carbon nucleophile led to the formation of stereoisomeric 5-amino-5-deoxymannofuranuronic acid nucleosides (cf. **42** and **46**) along with the novel acyclic 1-methoxy-D-*allo*-hexouronate nucleosides **52**/**53**.

Introduction

As part of a program to develop an asymmetric approach to complex peptidyl nucleoside antibiotics[1] such as polyoxin J (**1**)[2] and amipurimycin (**2**),[3] we envisaged a unified synthetic strategy based upon the stereocontrolled assembly of their glycosyl α-amino acid nucleoside subunits. This unusual structural feature (cf. II, Figure 1) takes the form of a furanosylpyrimidine in the polyoxin series, whereas a highly unusual branched pyranosylpurine distinguishes the amipurimycin skeleton. Even though various synthetic approaches to the furanosyl α-amino acid system have been reported over the years,[4] we felt none of them would be satisfactory in terms of both stereocontrol and generality. For example, while the basic polyoxin nucleoside skeleton can be obtained in relatively short order via (nonselective) Strecker addition to uridine-5′-aldehyde followed by separation of the resulting diastereomers and hydrolysis,[4e] this protocol cannot be applied to more complex targets such as amipurimycin since the corresponding sugar aldehyde would not be readily accessible.

In this context, a particularly attractive strategy for the asymmetric synthesis of such systems involves the stereocontrolled buildup of a serine-derived "penaldic acid equivalent" (i.e. I → II),[5] followed by assembly of the glycosyl nucleoside portion of the target. Herein we present details of a study which has culminated in a stereocontrolled and asymmetric synthesis of thymine polyoxin C (**4**) from D-serine by means of this "penaldic acid equivalent" strategy.[6] Our target **4** had been obtained along with 5-*O*-carbamoylpolyoxamic acid (**3**)[5b] after acidic hydrolysis of polyoxin J (**1**) and is representative of the α-aminouronic acid residues found in the polyoxin, neopolyoxin, and nikkomycin families of antibiotics—all of which are isolated from *Streptomyces* broths.[1] Since both **4** and its corresponding uracil derivative have been the targets of numerous previous syntheses, the comparative utility of our approach to this and structurally similar glycosyl α-amino acid nucleosides can be readily evaluated.

Results and Discussion

We began with the serine-derived oxazolidine aldehyde **5**, a chiral, nonracemic synthon developed in this laboratory[7] that has already been shown by us and others to be a very useful homochiral building block.[5,6,8] In order to access the 5-amino-5-deoxyallofuranose system embodied in the polyoxins, it would be necessary to append a three-carbon unit to **5** taking into consideration both stereochemical requirements and ease of subsequent furanose/nucleoside formation (Scheme I).

Addition of the lithio derivative of propiolaldehyde dimethyl acetal[9] to aldehyde **5** proceeded with good (8:1)

(1) Two reviews dealing with various aspects of nucleoside antibiotic chemistry have recently been published: (a) Structure, Biological Activity, and Biosynthesis: Isono, K. *J. Antibiotics* **1988**, *41*, 1711. (b) Garner, P. Synthetic Approaches to Complex Nucleoside Antibiotics. In *Studies in Natural Products Chemistry, Vol. 1. Stereoselective Synthesis, Part A*; Atta-Ur-Rahman, E.; Elsevier: Amsterdam, 1988; pp 397-434.

(2) (a) Isono, K.; Asahi, K.; Suzuki, S. *J. Am. Chem. Soc.* **1969**, *91*, 7490. (b) For a comprehensive review of the polyoxins, see: Isono, K.; Suzuki, S. *Heterocycles* **1979**, *13*, 333.

(3) Goto, T.; Toya, Y.; Ohgi, T.; Kondto, T. *Tetrahedron Lett.* **1982**, 1271.

(4) From carbohydrate templates: (a) Naka, T.; Hashizume, T.; Nishimura, M. *Tetrahedron Lett.* **1971**, 95. (b) Ohrui, H.; Kuzuhara, H.; Emoto, S. *Ibid.* **1971**, 4267. (c) Tabusa, F.; Yamada, T.; Suzuki, K.; Mukaiyama, T. *Chem. Lett.* **1984**, 405. (d) Mukaiyama, T.; Suzuki, K.; Yamada, T.; Tabusa, F. *Tetrahedron* **1990**, *46*, 265. Using Strecker methodology: (e) Damodaran, N. P.; Jones, G. H.; Moffatt, J. G. *J. Am. Chem. Soc.* **1971**, *93*, 3812. (f) Robins, M. J.; Parker, J. M. R. *Can. J. Chem.* **1983**, *61*, 312, 317. (g) Boehm, J. C.; Kingsbury, W. D. *J. Org. Chem.* **1986**, *51*, 2307. (h) Fiandor, J.; Garcia-Lõpez, M.-T.; De las Heras, F. G.; Méndez-Castrillõn, P. P. *Synthesis* **1987**, 978. Via the Ugi 4-component condensation: (i) Joullié, M. M.; Wang, P. C.; Semple, J. E. *J. Am. Chem. Soc.* **1980**, *102*, 887. (j) Semple, J. E.; Wang, P. C.; Lysenko, Z.; Joullié, M. M. *Ibid.* **1980**, *102*, 7505. (k) Tsuchida, K.; Mizuno, Y.; Ikeda, K. *Nucleic Acids Symp. Series* **1980**, *8*, s49. By reduction of α-oximinoesters: (l) Masamune, T.; Ono, M. *Chem. Lett.* **1975**, 625. By hydrogenation of α,β-unsaturated α-amino acids: (m) Bischofberger, K.; Hall, R. H.; Jordaan, A. *J. Chem. Soc. Chem. Commun.* **1975**, 806. Via nitrone cycloaddition: (n) Vasella, A.; Voeffray, R. *Helv. Chim. Acta* **1982**, *65*, 1134.

(5) We have already shown that this strategy may be used for the asymmetric synthesis of acyclic hydroxyaminoacids. (a) Garner, P. *Tetrahedron Lett.* **1984**, 5855. (b) Garner, P.; Park, J. M. *J. Org. Chem.* **1988**, *53*, 2979.

(6) Preliminary communication: Garner, P.; Park, J. M. *Tetrahedron Lett.* **1989**, 5065.

(7) (a) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361. (b) Garner, P.; Park, J. M. Submitted to *Organic Syntheses*.

(8) Other synthetic applications of **4** and its antipode include the following. The sphingosine bases: (a) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A. *J. Chem. Soc., Chem. Commun.* **1988**, 10. (b) Herold, P. *Helv. Chim. Acta* **1988**, *71*, 354. (c) Nimkar, S.; Menaldino, D.; Merrill, A. H.; Liotta, D. *Tetrahedron Lett.* **1988**, 3037. (d) Garner, P.; Park, J. M.; Malecki, E. *J. Org. Chem.* **1988**, *53*, 4395. (e) Radunz, H.-E.; Devant, R. M.; Eiermann, V. *Justus Liebigs Ann. Chem.* **1988**, 1103. An aminosugar constituent of calicheamicin: (f) Kahne, D.; Yang, D.; Lee, M. D. *Tetrahedron Lett.* **1990**, 21.

0022-3263/90/1955-3772$02.50/0

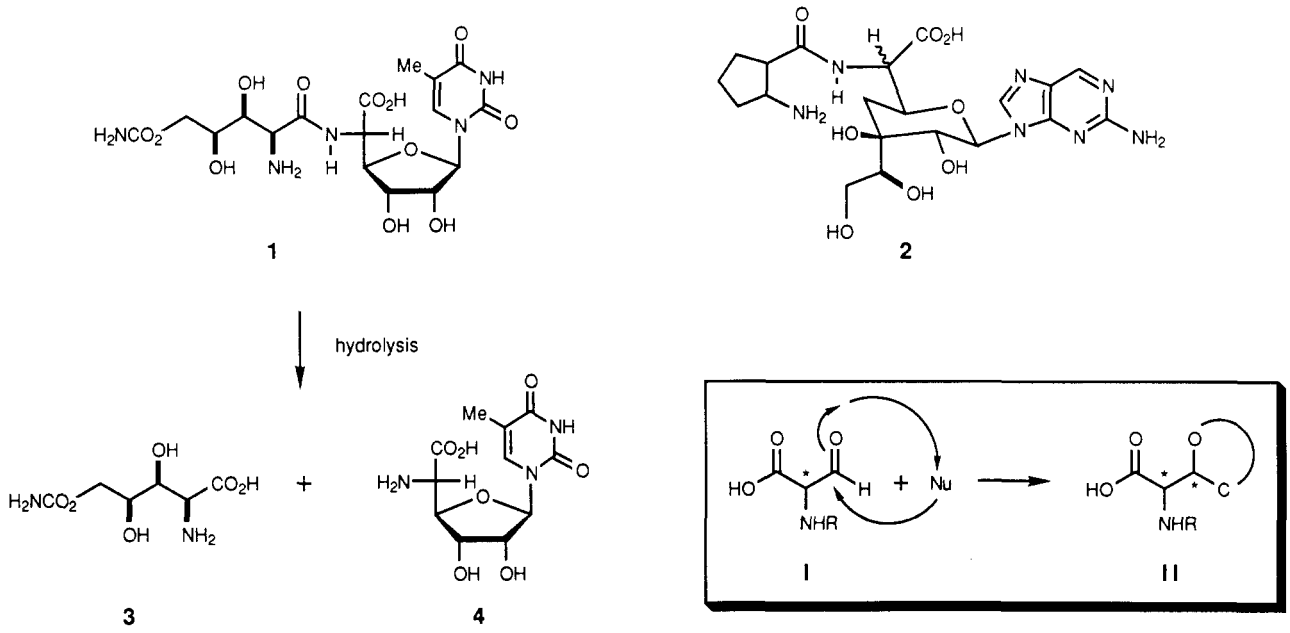
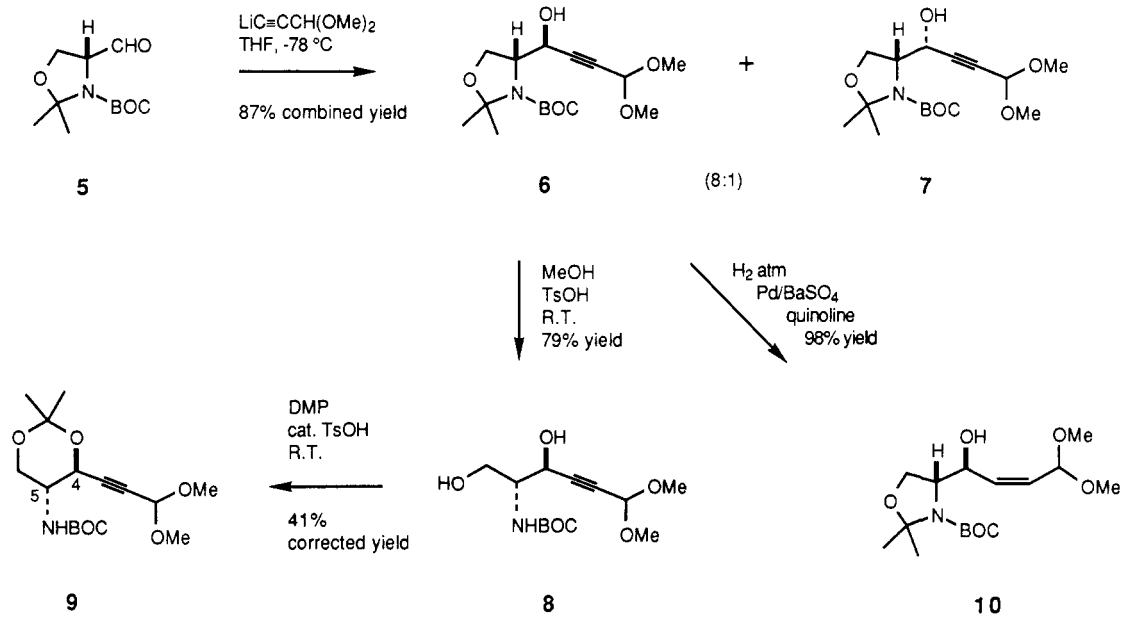


Figure 1.

Scheme I



diastereoselectivity to give **6** as the major adduct in 75% yield after flash chromatography. Evidence supporting the stereochemical assignment was obtained by converting **6** to the conformationally well-defined dioxolane **9** and examining its ^1H NMR spectrum. The observed 8-Hz vicinal coupling constant between H-4 and H-5 indicated their trans-diaxial disposition in **9** (chair conformation) and thus confirmed the erythro stereochemistry of **6**. Erythro-selective nucleophilic additions to **5** are typically observed when nonchelating conditions are employed and can be ascribed to a Felkin–Anh–Houk transition-state model.[10]

Semihydrogenation of the propargylic alcohol **6** proceeded cleanly using $Pd/BaSO_4$ + quinoline as a Lindlar-type catalyst[11] to afford the *Z*-allylic alcohol **10** in 98% yield after flash chromatography[12] (Scheme II).

Pyridinium *p*-toluenesulfonate (PPTS)[13] promoted cyclization of **10** led to a (42:58) mixture of "anomeric" dihydrofurans **11** and **12** in 97% combined yield after chromatography. The use of TsOH instead of PPTS re-

(9) Prepared in two steps (37% overall distilled yield on a 5-mol scale) from acrolein by a route analogous to that reported for propiolaldehyde diethyl acetal: Le Coq, A.; Gorgues, A. In *Organic Syntheses*; Coates, R. M., E.; Wiley: New York, 1979; Vol. 59, pp 10–15. However, we found it more convenient and economical to use KOH as the base for the double dehydrohalogenation step rather than the 300 mol % of $Bu_4N^+HSO_4^-$ reported in the *Organic Syntheses* procedure. Cf.: Sheehan, J. C.; Robinson, C. A. *J. Am. Chem. Soc.* **1949**, *71*, 1436.

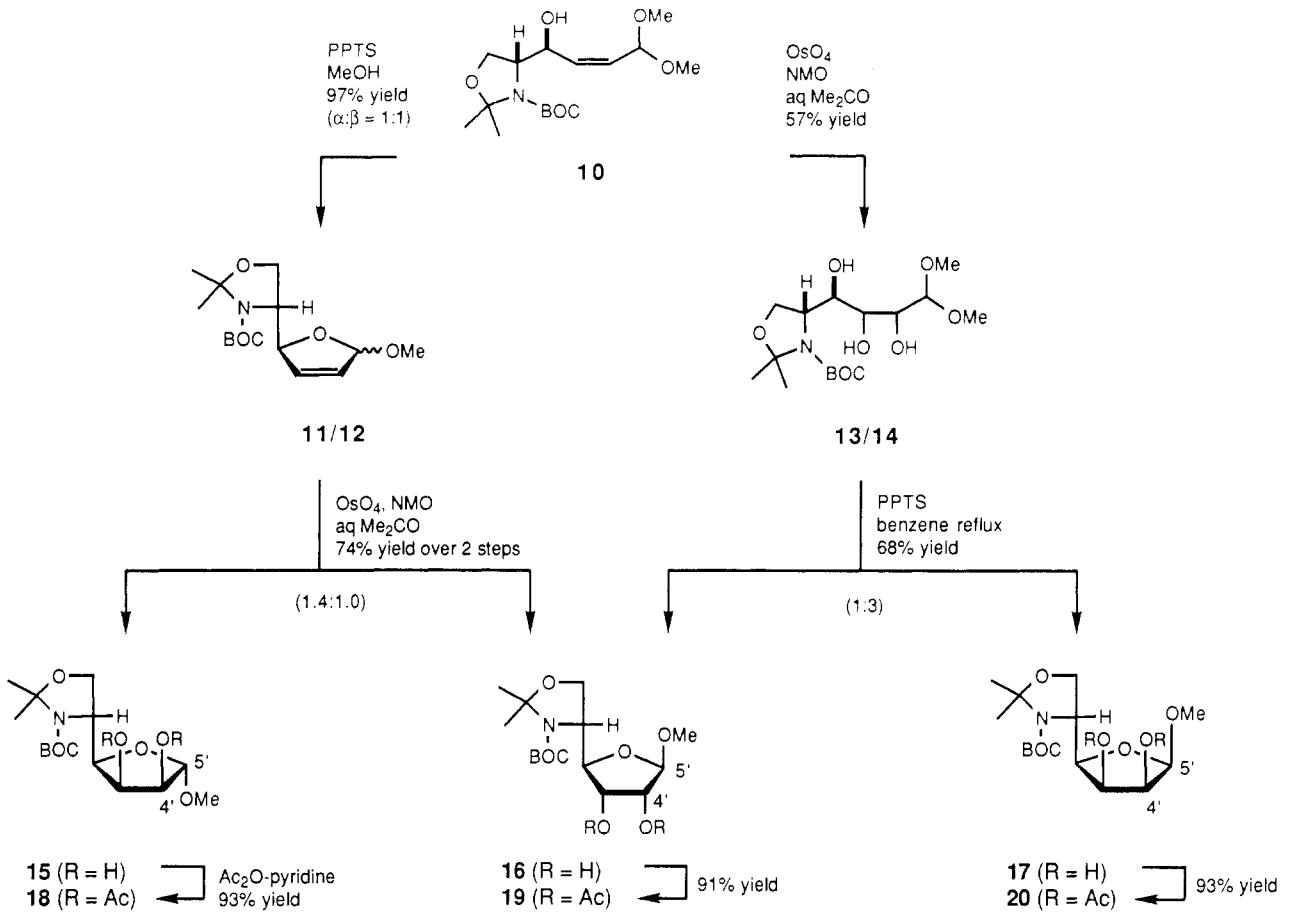
(10) (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (b) Anh, N. T.; Eisenstein, O. *Nouv. J. Chem.* **1977**, *1*, 61. (c) Review: Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145. (d) See also: Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 908.

(11) Cram, D. J.; Allinger, N. L. *J. Am. Chem. Soc.* **1956**, *78*, 2518.

(12) Chemical evidence for the *Z*-olefin geometry in **10** was gleaned at this stage from an attempted high temperature ^{13}C NMR experiment wherein it was observed that prolonged heating of a C_6D_6 solution of **10** at 60 °C for a period of 4–5 h resulted in spontaneous cyclization to the dihydrofurans **11** and **12**. Cf.: Seyfath, H. E. *Chem. Ber.* **1968**, *101*, 619.

(13) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.

Scheme II



sulted in both premature oxazolidine methanolysis and elimination to give furan containing products as judged by ^{1}H NMR spectroscopy. The mixture of **11** and **12** was not resolved into its components but submitted directly to osmium tetraoxide mediated cis-hydroxylation.[14] Two isomeric diols, eventually shown to have structures **15** and **16**, were isolated from this reaction in 32 and 44% yield, respectively (corresponding to the starting ratio of **11** to **12**), after chromatographic separation, but, as it turned out, only one of them (**16**, mp 120–121 °C) possessed the required allo configuration (vide infra).

On the other hand, subjection of **10** directly to these same osmylation conditions resulted in the formation of what appeared to be a single triol as judged by TLC analysis. Because of the nondescript nature of its ^{1}H NMR spectrum, this material was not characterized further at this stage, but cyclized directly by heating it in the presence of PPTS. Two isomeric furanose products were obtained in 17 and 51% yield after flash chromatography, and they were identified as the previously isolated β-methyl allofuranoside **16** (mp 120–122 °C) and a new compound, mp 72–78 °C, subsequently identified as the β-methyl mannofuranoside **17**. Since **17** could only have come from a triol **14** having the mannose configuration, it was concluded that osmylation of **10** must have occurred predominantly from the *re* face of the olefin and that, in this case at least, Kishi's empirical rule[15] did not hold. It should be noted that the stereochemistry of furanoses **15**, **16**, and **17** could not be unambiguously deduced at this stage but had to await subsequent correlations to be described later.[16,17] In preparation for subsequent events these diols were each converted to their corresponding diacetates **18**–**20** in high yield by the action of acetic anhydride in pyridine (Scheme III).

The next stage of our plan called for "unmasking" of the latent α-amino acid functionality embodied in the oxazolidine ring system of **18**–**20** (thus realizing the penaldic acid equivalency of **5**). The sequence began with TsOH-catalyzed methanolysis of the 2,2-dimethyloxazolidine moiety to afford the N-protected amino alcohols **21**–**23** in moderate to good yield based on (recovered) unreacted starting material. Compounds **21**–**23** were then oxidized to their corresponding carboxylic acids **24**–**26** using a catalytic amount of $RuO_2 \cdot H_2O$ in the presence of excess $NaIO_4$ as a carrier oxidant.[18] Without purification, the crude carboxylic acids so obtained were esterified with diazomethane to give **27**–**29** in good overall yield after flash chromatography. Removal of the BOC protecting groups was accomplished with trifluoroacetic acid, and the am-

(14) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.

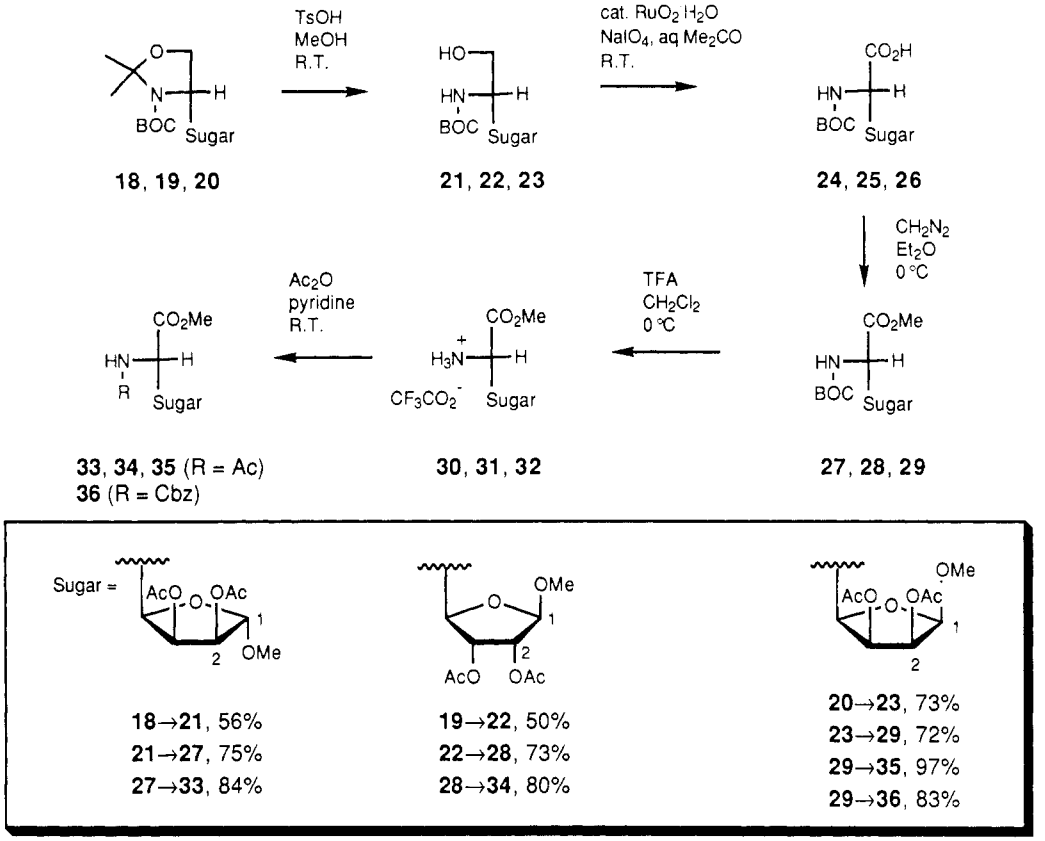
(15) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247 and references cited therein.

(16) In fact, we had initially misassigned compounds **16** and **17**, believing them to be anomeric allofuranosides, see ref 1b.

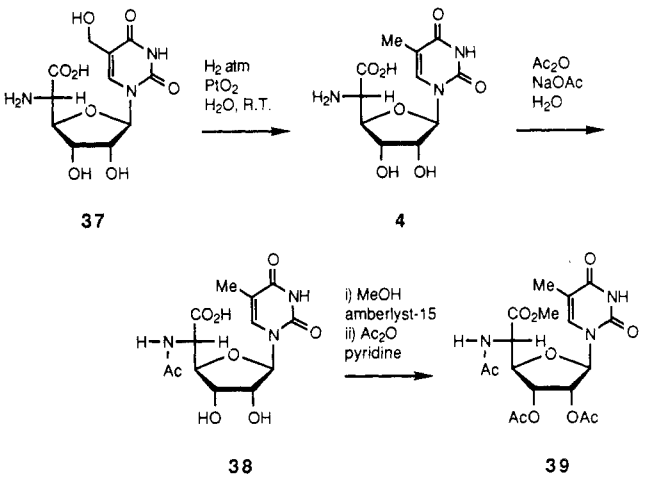
(17) The ^{13}C chemical shift of the anomeric carbons in these compounds was, however, indicative of the spacial relationship between the substituents at C-4′ and C-5′ with the respective anomeric carbons of **15** and **16** (both 4′,5′-trans disubstituted) resonating 7.8 and 5.6 ppm downfield of the anomeric carbon in **17** (4′,5′-cis disubstituted). Cf.: Ritchie, R. G. S.; Cyr, N.; Korsch, B.; Koch, H. J.; Perlin, A. S. *Can. J. Chem.* **1975**, *53*, 1424. For a review of the use of carbon-13 NMR spectroscopy for structural characterization of monosaccharides, see: Bock, K.; Pedersen, C. *Adv. Carbohydr. Chem. Biochem.* **1983**, *41*, 27.

(18) We did not experience any difficulty with this oxidation, performed here in aqueous acetone, due to the formation of (inactive) lower valent ruthenium carboxylates. Compare: Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

Scheme III



monium salts **30–32** were treated directly with Ac_2O in pyridine to give the *N*-acetyl amino esters **33–35** in high yield. The amine corresponding to **32** was also converted to its *N*-Cbz derivative **36** in 83% yield by the action of benzyl chloroformate.



Our attention now focused the remaining problems of nucleoside introduction and stereochemical correlation with authentic samples of thymine polyoxin C (**4**), its known *N*-acetate **38**,[2a] and the fully protected derivative **39**.[19] The well-established glycosylation methodology of Vorbrüggen[20] was chosen for introduction of the pyrimidine moiety since it had already been successfully applied to the polyoxin problem in a similar context.[4b-d] First, anomeric "activation" was accomplished by exposure of either **33** or **35** to a modification of Hudson's "transforming mixture", which resulted in facile acetolysis with the formation of a single tetraacetate **40**[21] (Scheme IV). Kuzuhara's reported nucleosidation conditions,[4b] i.e. $SnCl_4$-catalyzed coupling of **40** with 2,4-bis(trimethylsiloxy)-5-methylpyridine (**41**)[22] in dichloroethane at room temperature, produced a (3:1) mixture of N^1- and N^3-nucleosides **42** and **43** (not shown) in 60% combined yield. The regiochemistry of these nucleosides was easily ascertained from their ^1H NMR spectra since only the N^3-substituted pyrimidine exhibited coupling between H-6 and N^1-H. The 1′,2′-trans stereochemistry of **42** was deduced from a series of NOE difference experiments that resulted in enhancements of H-1′, H-3′ (overlapping signals), and H-2′ upon irradiation of the H-6 signal and a reciprocal enhancement of H-6 upon irradiation of H-2′. We later found that performing the coupling at 95 °C with trimethylsilyl triflate (TMSOTf)[4c,d] catalysis led to a superior result with the N^1-nucleoside **42** being produced in 79% isolated yield. None of the N^3-regioisomer could be detected.

Saponification of **42** resulted in the formation of a compound **44** whose TLC and NMR data did not match that of *N*-acetylthymine polyoxin C **38**. In a similar manner, the *N*-Cbz derivative **45** was converted to the N^1-nucleoside **46**, again using the Vorbrüggen protocol.[23] Compound **46** was completely deprotected by sequential saponification and hydrogenolysis to give the free aminouronic acid nucleoside **49**, which also did not match our

(19) Prepared by mild esterification of **38** using amberlyst-15 as an acid catalyst (Petrini, M.; Ballini, R.; Marcantoni, E.; Rosini, G. *Synth. Commun.* **1988**, *18*, 847) followed by standard O-acetylation (Ac_2O + pyridine).

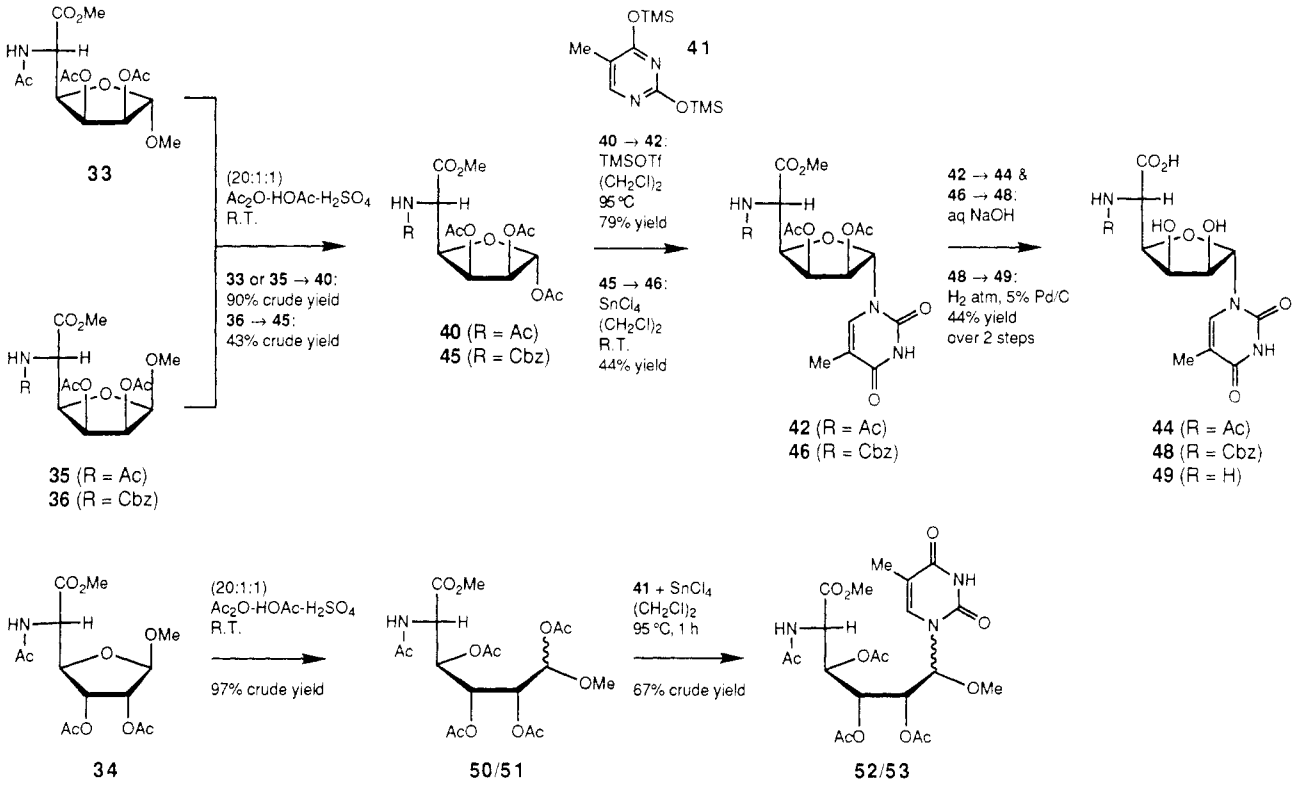
(20) (a) $SnCl_4$ catalysis: Niedballa, H.; Vorbrüggen, U. *J. Org. Chem.* **1974**, *39*, 3654. (b) TMSOTf catalysis: Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234.

(21) Hann, R. M.; Hudson, C. S. *J. Am. Chem. Soc.* **1934**, *56*, 2465.

(22) Nishimura, T.; Iwa, I. *Chem. Pharm. Bull.* **1964**, *12*, 352.

(23) Preliminary indication that the benzyloxycarbonyl group would survive these acidic nucleosidation conditions was available to us. See: Paulsen, H.; Brieden, M.; Benz, G. *Justus Leibigs Ann. Chem.* **1987**, 565.

Scheme IV



sample of naturally derived thymine polyoxin C (**4**). Taken together, these results led us to conclude that the remaining glycoside **34** must, in fact, possess the allo stereochemistry as required for the polyoxins. However, when **34** was subjected to the Hudson acetolysis conditions and the crude product mixture submitted directly to the nucleosidation conditions described above, there was obtained not the expected product (see structure **39**) but a (1:1) mixture of diastereomeric acyclic nucleosides **52** and **53** in 62% combined yield (at 64% conversion of starting material). These unusual acyclic nucleoside products[24] were separately characterized by both ^{1}H NMR spectroscopy (signals due to N^1-substituted thymine, acetal OMe, and 3 × OAc) and high-resolution FAB mass spectrometry (molecular formula = $C_{21}H_{29}N_{30}O_{12}$). Obviously, they arise from the aberrant acetolysis products **50** and **51**, which are themselves the result of an unexpected endocyclic mode of glycosyl cleavage during the acetolysis.[25]

This phase of our study thus revealed two rather serious obstacles to our synthetic plan: (1) lack of allo-selectivity during the cis-hydroxylation of either **10** or **11**/**12** and (2) undesired endocyclic cleavage of **34** upon attempted glycosyl activation. In a sense, both of these problems could be traced back to our choice of the dimethyl acetal as a glycosyl C-1 surrogate: In the case of the osmylations, the nonselective formation of mixed acetals **11** and **12** and the apparent subversion of allylic alcohol direction by the dimethyl acetal function during osmylation of **10** were responsible for the overall lack of cis-hydroxylation selectivity. The electronic properties of the methoxyl group are also believed to exacerbate the endocyclic cleavage of methyl glycosides (versus the corresponding anomeric acetates) (cf. **34** → **50**/**51**).[25] With these thoughts in mind, we turned to a modified route that was designed to circumvent these problems altogether.

Addition of ethyl lithiopropiolate[26] to **5** in tetrahydrofuran + hexamethylphosphoric triamide (HMPA) at −78 °C proceeded with excellent (13:1) erythro selectivity to give **54** in 75% yield after flash chromatography (Scheme V). The initial assignment of erythro stereochemistry to **54** was based strictly on extrapolation (cf. **5** → **6**), but it was later proven beyond doubt by correlation with thymine polyoxin C (**4**) itself. The use of HMPA as a cosolvent for nucleophilic additions to **5** seems to increase the erythro selectivity by sequestering lithium and precluding possible chelation.[8b] At this point we sought to demonstrate the configurational integrity of **5** during this addition reaction by measuring the enantiomeric excess associated with product **54**. This was readily accomplished by condensing **54** with (−)-(*S*)- and (+)-(*R*)-methyl(trifluoromethyl)phenylacetic acid (MTPA) to give the diastereomeric Mosher esters **59** and **60**, respectively.[27] Careful ^{1}H and ^{19}F NMR analyses of these compounds indicated less than 2% cross contamination or >96% ee. This level of enantiomeric purity is to be expected since the preparation of **5** itself produces material with an enantiomeric excess of about 95%.[7a]

The next sequence of events was concerned with the known transformation of a γ-hydroxypropiolate into a

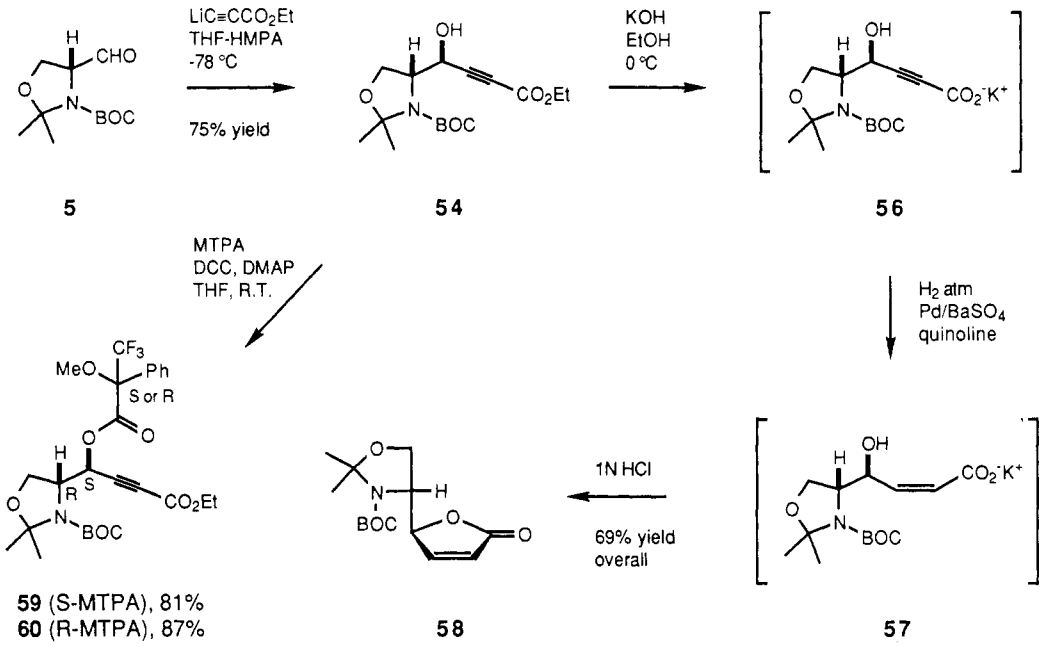
(24) Acyclic nucleosides such as this are not unknown. See for example: Wolfrom, M. L.; Foster, A. B.; McWain, P.; Bebenburg, W. v.; Thompson, A. *J. Org. Chem.* **1961**, *26*, 3095.

(25) The question of just what factors govern endocyclic versus exocyclic glycosyl cleavage in sugars is of general interest, but a detailed understanding of the problem remains somewhat elusive. (Cf.: Cossé-Barbi, A.; Watson, D. G.; Dubois, J. E. *Tetrahedron Lett.* **1989**, 163. Dubois, J. E.; Cossé-Barbi, A.; Watson, D. G. *Ibid.* **1989**, 167.) In the case at hand, we theorize that a combination of conformational and stereoelectronic factors must work together to make the endocyclic cleavage mode more favorable for the methyl β-allofuranoside **34**. It would be interesting to compare the reactivity of the corresponding α-anomer of **34** (not shown) though this diastereomer is unavailable to us by the routes described here.

(26) Midland, M. M.; Tramontano, A.; Cable, J. R. *J. Org. Chem.* **1980**, *45*, 28.

(27) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

Scheme V



butenolide,[28] but began with the saponification of **54**. The resulting propiolate salt **56** was then dissolved in water and subjected to Lindlar semihydrogenation to produce a (*Z*)-hydroxycrotonate **57** which, upon acidic workup, spontaneously lactonized to afford the butenolide **58** in 69% overall yield after flash chromatography. This rather unorthodox protocol was arrived at after it was found that attempted semihydrogenation of the **54** (or its corresponding free acid)[28a] resulted in an unacceptable amount of overreduction. Conversion of the ester substituent to a negatively charged carboxylate apparently makes the substrate behave like an electron-rich alkyne, which are known to be more resistant to such overreduction (cf. **6** → **10**).

The butenolide **58** now underwent a very selective OsO_4-mediated cis-hydroxylation using trimethylamine *N*-oxide as the carrier oxidant.[29] This reaction afforded a single diol **61**, which was isolated in 58% yield after flash chromatography along with 12% of unreacted **58** (Scheme VI). It was anticipated that osmylation of this 4-substituted butenolide would occur preferentially from the less hindered α-face of **58**,[30] a prediction initially supported by the ^1H NMR spectrum of **61** which showed $^3J_{2',3'} = 0$ Hz, a value consistent with a 90° angle between H-2′ and H-3′. (This is possible only when these protons are trans to each other.) The allo stereochemical assignment was later confirmed by correlation of **61** with thymine polyoxin C (**4**). At this point, lactone to lactol reduction was accomplished with diisobutylaluminum hydride (DIBAL), and the resulting crude triol mixture was peracetylated to give a (4:1) mixture of anomeric acetates **63** in 80% combined yield after flash chromatography. The major component was identified as the β-anomer based on ^1H NMR similarities between it and the previously synthesized methyl glycoside **19**.

Acetolysis of **63** (at 40% conversion) afforded the *N*-BOC amino alcohol **64**, which was isolated in 77% yield after flash chromatographic separation from unreacted **63**. Though of no consequence to our synthetic plan, both **64** and recovered **63** were found to be further enriched in their β-anomers. The key element of this sequence was the absence of the undesired endocyclic cleavage that had been observed during Hudson acetolysis of methyl allofuranoside **34** (vide supra). Ruthenium tetroxide catalyzed oxidation of **64** followed by esterification the crude acid **65** with diazomethane produced the *N*-BOC methyl ester **66** in 68% overall yield. As with the methyl glycoside series, the BOC moiety was quantitatively removed by the action of trifluoroacetic acid and the resulting amine salt **67** was converted to both its corresponding *N*-acetyl derivative **68** and *N*-Cbz derivative **69** in 69% and 82% overall yield, respectively.

Trimethylsilyl triflate (TMSOTf) catalyzed coupling[20b] of **68** and bis-silylated thymine **41** resulted in the formation of an N^1-nucleoside in 23% isolated yield that was identical with the authentic polyoxin C derivative **39**. However, the major product of this reaction was found not to be a nucleoside at all, but the bicyclic 1,5-anhydro derivative **70**, which was isolated in 55% yield[31] (Scheme VII). The structure of this compound was supported by its measured mass, lack of an N–H stretch in the IR spectrum, a simplified ^1H NMR spectrum in which the signals for H-1, H-4, and H-5 appeares as singlets, and a ^{13}C chemical shift for C-1 that was consistent with the O–C–N substitution pattern. On the other hand, the *N*-Cbz derivative **69** was found to produce the protected N^1-nucleoside **71** in 75% isolated yield after flash chromatography—competitive intramolecular attack by nitrogen not being a problem in this case. Compound **71** was transformed to thymine polyoxin C (**4**) by the standard deprotection sequence (via **73**). Synthetic **4** was shown to be identical in all respects with the authentic sample which we had prepared from

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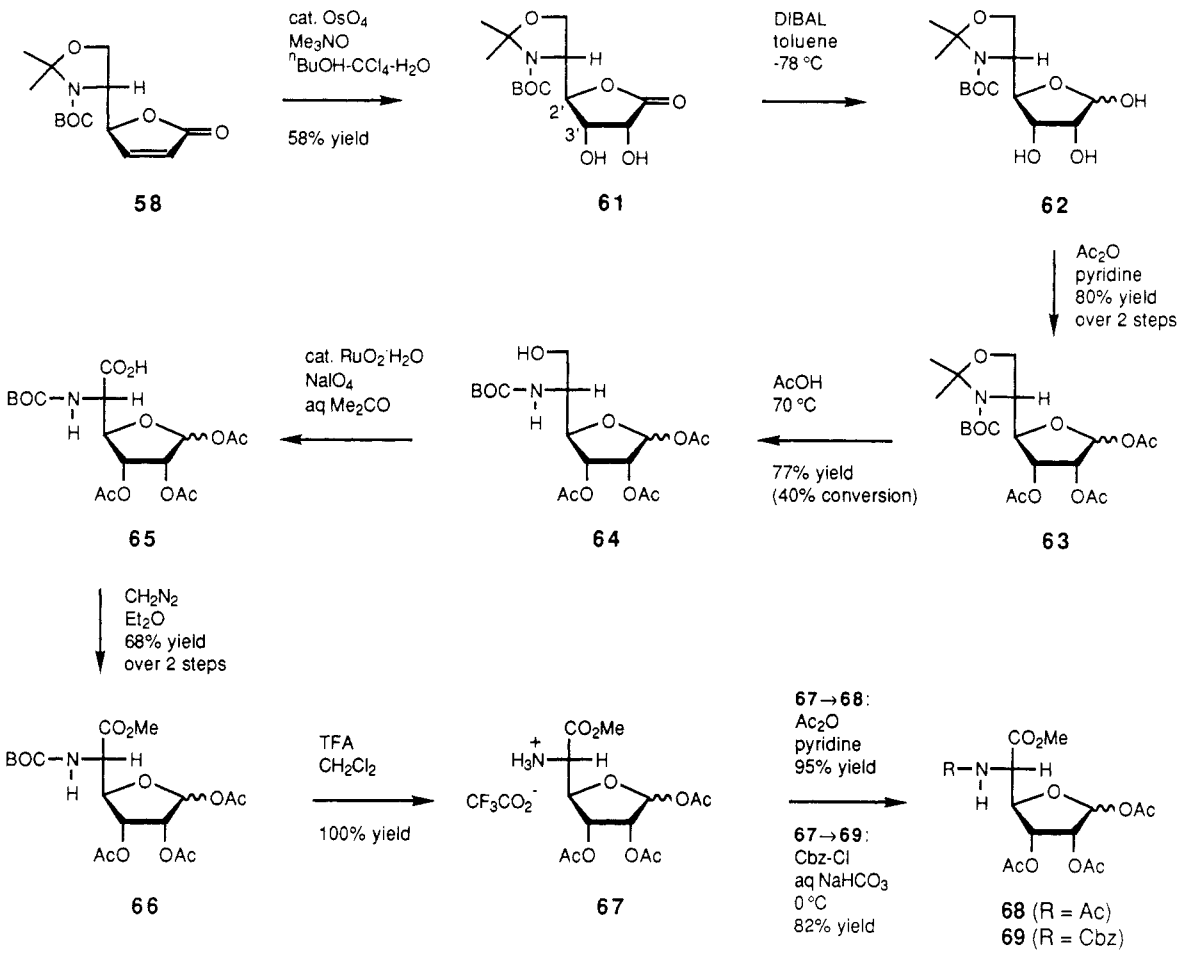
(29) We thank Professor Frank Hauser (SUNY/Albany) for alerting us to the advantages of substituting trimethylamine-N-oxide as the carrier oxidant in this reaction. Cf. Ray, R.; Matteson, D. S. *Tetrahedron Lett.* **1980**, 449. Hauser, F. M.; Rhee, R. P.; Ellenberger, S. R. *J. Org. Chem.* **1984**, *49*, 2236.

(30) (a) Stork, G.; Kahn, M. *Tetrahedron Lett.* **1983**, 3951. (b) Lukes, R.; Moll, M.; Zobăcovă, A.; Jary, J. *Collect. Czech. Commun.* **1962**, *27*, 500.

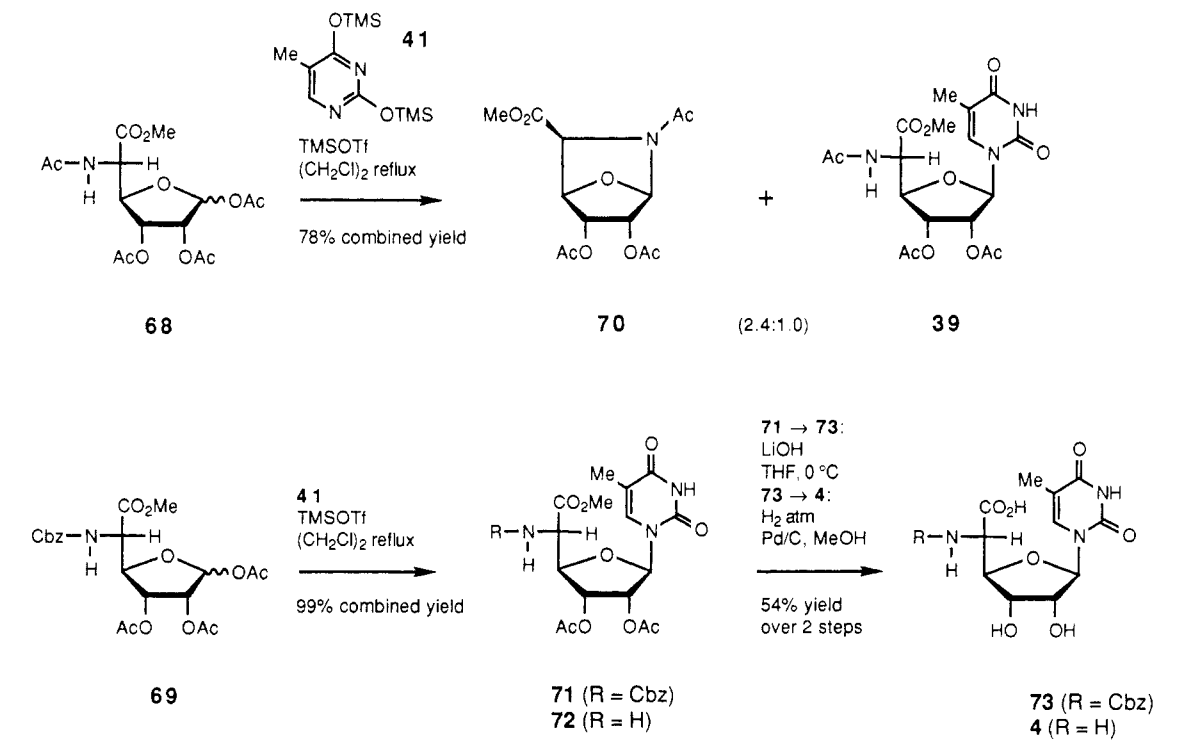
(31) A similar problem was encountered by Rosenthal and Cliff during their work on the synthesis of polyoxin analogues having the *N*-trifluoroacetamido glycine methyl ester moiety appended to C-3, see: Rosenthal, A.; Cliff, B. *Carbohydr. Res.* **1980**, *79*, 63.

Scheme VI



58 61 62 63 64 65 66 67

Scheme VII



68 70 39 69

37, thus corroborating the structure of synthetic **39** and confirming all stereochemical and regiochemical assignments in this series. A small amount of N-deprotected nucleoside **72** was also isolated from this reaction as well, but no N^3-nucleosides could be detected.

Conclusion

Thymine polyoxin C (**4**) was prepared in 5% overall

yield via a 15-step sequence starting from the serine-derived penaldic acid equivalent **5**. The overall synthetic strategy involved four distinct phases: (1) diastereoselective addition of a 3-carbon nucleophile (ethyl lithiopropiolate) to the protected serinal derivative (**5** → **54**), (2) stereocontrolled elaboration of the 5-amino-5-deoxyallofuranose moiety via cis-hydroxylation of a 4-substituted butenolide (**54** → **63**), (3) release of the latent α-amino acid moiety in a suitably protected form (**63** → **69**), and (4) stereo- and regioselective nucleoside formation using Vorbrüggen's glycosylation methodology followed by deprotection (**69** → **4**). This asymmetric synthesis of **4** from the penaldic acid equivalent **5** illustrates the viability and efficacy of our general approach to glycosyl α-amino acids and sets the stage for the application of this strategy to more complex peptidyl nucleoside targets such as amipurimycin (**2**).

Experimental Section

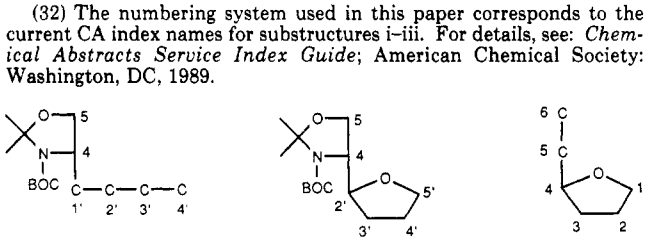
TLC analysis was performed on Merck silica gel 60 F-254 plates and visualized with UV illumination and charring with (A) 0.3% ninhydrin in (97:3) *n*-BuOH–AcOH or (B) 5% anisaldehyde in (95:5:1) EtOH–AcOH–H_2SO_4. Melting points and boiling points are uncorrected. Mass spectral data (EI unless stated otherwise) are reported for $m/e \geq 100$. Combustion analyses were performed on TLC homogeneous and in some cases recrystallized samples. ^1H NMR spectra were recorded at 200 or 400 MHz, ^{13}C NMR at 50.4 MHz, and ^{19}F NMR at 188 MHz in the indicated solvent at room temperature unless otherwise indicated. The ^1H signal assignments[32] were based on selective homonuclear decoupling experiments and the ^{13}C assignments were based on both APT (attached proton test)[33] experiments and proton-coupling data, with the APT results being indicated as "+" or "–" depending on the phase of the signal. Tetrahydrofuran (THF) and toluene were each distilled from sodium-benzophenone ketyl under nitrogen in a recycling still. Dichloromethane (CH_2Cl_2) and 1,2-dichloroethane $(CH_2Cl)_2$ were distilled from P_2O_5 and stored over 4-Å molecular sieves. Pyridine, hexamethyldisilazane (HMDS), and hexamethylphosphoric triamide (HMPA) were distilled from CaH_2 (the latter under reduced pressure) and stored over 4-Å molecular sieves. Tin tetrachloride, trimethylsilyl chloride (TMSCl), and trimethylsilyl triflate (TMSOTf) were distilled under nitrogen just prior to use. Diazomethane solutions (approximately 0.6 M) were prepared from *N*-nitroso-*N*-methylurea according to the procedure of Arndt.[34]

1,1-Dimethylethyl [*S*-(*R,*S**)]-4-(1-Hydroxy-4,4-dimethoxy-2-butynyl)-2,2-dimethyl-3-oxazolidinecarboxylate (6).** To a stirred −78 °C solution of propiolaldehyde dimethyl acetal (13.0 g, 0.130 mol)[9] in dry THF (225 mL) was added slowly *n*-BuLi (2.3 M in hexanes, 47 mL, 0.11 mol) under N_2 atmosphere. The slightly yellow suspension was stirred for 1 h at −78 °C, and then to this solution was added slowly a −78 °C solution of **5** (13.5 g, 0.0591 mol) in dry THF (75 mL) over 15 min. After stirring for 2 h at −78 °C, the TLC in 4:1 hexanes–EtOAc showed the formation of product, R_f 0.11, at the expense of starting aldehyde, R_f 0.30 (char B). The resulting solution was slowly poured into ice-cold 1 M NaH_2PO_4 (2 L, pH 7) with swirling. The mixture was extracted into Et_2O (3 × 1 L), washed with brine (1 L), dried over $MgSO_4$, filtered, and concentrated in vacuo to give a pale yellow oil (19.5 g). The ^1H NMR spectrum showed an 8:1 mixture of **6** and **7** by comparison of their respective H-1′ signals (vide infra). Flash chromatography on silica gel, eluting with 12:1 hexanes–EtOAc gave the pure erythro product **6** (14.5 g, 75%) followed by threo product **7** (2.38 g, 12%). For **6**: $[\alpha]_D$ +52.0° (*c* 1.2, $CHCl_3$); IR (neat) 3450, 1700 cm^{-1}; ^1H NMR (200 MHz, C_6D_6, 60 °C) δ 0.92 (br s, 1 H, OH), 1.39 (s, 9 H, $C(CH_3)_3$), 1.46, 1.71 (2 s, 2 × 3 H, $C(CH_3)_2$), 3.22 (s, 6 H, 2 OCH_3), 3.69 (m, 2 H, H-5a and 5b), 3.98 (br s, 1 H, H-4), 4.61 (br s, 1 H, H-1′), 5.13 (d, J = 1.2 Hz, 1 H, H-4′); ^{13}C NMR (C_6D_6, 60 °C) δ 26.1 (q, –, $C(CH_3)_2$), 28.2 (q, –, $C(CH_3)_3$), 52.1 (q, –, OCH_3), 60.1 (s, +, $C(CH_3)_3$), 63.2 (d, –, C-5), 64.3 (d, –, C-1′), 65.2 (t, +, C-5), 81.0 (s, +, C-2′ or C-3′), 84.9 (s, +, C-3′ or C-2′), 93.5 (d, –, C-4′), 95.1 (s, +, C-2), 154.5 (s, +, NCO_2); MS (% relative intensity, *m/e*) 298.1575 (1.6, M − CH_3O, 298.1654 calcd for $C_{15}H_{24}NO_5$), 242 (21.0), 200 (23.4), 144 (47.7), 101 (12.8), 100 (100). For **7**: ^1H NMR (200 MHz, C_6D_6, 60 °C) δ 1.35 (s, 9 H, $C(CH_3)_3$), 1.42, 1.68 (2 s, 3 H, $C(CH_3)_2$), 3.19 (s, 6 H, 2 OCH_3), 3.72 (dd + br s, J = 9.8 and 6.9 Hz, 2 H, H-5a and OH), 4.02 (br s, 1 H, H-4), 4.09 (d, J = 8.2 Hz, 1 H, H-5b), 4.81 (br s, 1 H, H-1′), 5.13 (d, J = 1.2 Hz, 1 H, H-4′); MS (% relative intensity, *m/e*) 330.1931 (0.1, M + 1, 330.1917 calcd for $C_{16}H_{28}NO_6$), 242 (21.6), 200 (26.6), 143 (45.8), 101 (12.2), 100 (100.0).

1,1-Dimethylethyl (4*S*-*trans*)-[4-(3,3-Dimethoxy-1-propynyl)-2,2-dimethyl-1,3-dioxan-5-yl]carbamate (9). A solution of **6** (580 mg, 1.76 mmol) and $TsOH \cdot H_2O$ (54 mg, 0.29 mmol) in MeOH (15 mL) was stirred at room temperature for 7.5 h at which time the TLC in 1:1 hexanes–EtOAc showed the formation of product, R_f 0.16, at the expense of starting material, R_f 0.60 (char A). The reaction mixture was poured into half-saturated $NaHCO_3$ solution (80 mL) and extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give an amber oil (509 mg). Flash chromatography on silica gel, eluting with 1:1 hexanes–EtOAc, gave pure **8** (400 mg, 79%) yield as a slightly yellow oil which was submitted directly to the next step. A solution of **8** (50 mg, 0.173 mmol) and $TsOH \cdot H_2O$ (2.5 mg) in 2,2-dimethoxypropane (2 mL) was stirred at room temperature for 1 h, at which time the TLC in 1:1 hexanes–EtOAc showed the formation of product **9**, R_f 0.76, along with reformed **6**, R_f 0.67, at the expense of starting diol **8**, R_f 0.16 (char A). The reaction mixture was partitioned between saturated $NaHCO_3$ (30 mL) and EtOAc (2 × 50 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give an amber oil (54 mg). Flash chromatography on silica gel, eluting with 4:1 hexanes–EtOAc, gave pure **9** (15.9 mg) along with recovered **8** and **6** (16 mg each). **9**: ^1H NMR (200 MHz, C_6D_6 + D_2O, 60 °C) δ 1.21 (s, 3 H, 0.5 $C(CH_3)_2$), 1.41 (s, 9 H, $C(CH_3)_3$), 1.46 (s, 3 H, 0.5 $C(CH_3)_2$), 3.19, 3.20 (2 s, 2 × 3 H, $CH(OCH_3)_2$), 3.40 (dd, J = 11.2 and 7.2 Hz, 1 H, H-6a), 3.75 (m, 1 H, H-5), 3.89 (dd, J = 11.5 and 4.3 Hz, 1 H, H-6b), 4.53 (br d, J = 7.2 Hz, 1 H, H-4, when $CH(OCH_3)_2$ was irradiated, the measured coupling constant was 7.7 Hz), 5.08 (d, J = 1.3 Hz, $CH(OCH_3)_2$).

1,1-Dimethylethyl [*S*-[(*R,*S**-(*Z*)]]-4-(1-Hydroxy-4,4-dimethoxy-2-butenyl)-2,2-dimethyl-3-oxazolidinecarboxylate (10).** To a solution of **6** (8.38 g, 25.5 mmol) in dry benzene (180 mL) were added synthetic quinoline (1.05 mL, 1.5 g, 8.9 mmol) and reduced 5% Pd/$BaSO_4$ (2.68 g, 134 mg of Pd, 1.26 mmol). The black suspension was stirred under an H_2 atmosphere for a period of 2 h at room temperature at which time the TLC in 1:1 hexanes–EtOAc showed the formation of product, R_f 0.59, at the expense of the starting material, R_f 0.67 (char B). Therefore, the catalyst was filtered off through Celite, washing with benzene, and the yellow filtrate (350 mL) was concentrated in vacuo to give a dark brown oil (9.1 g) containing a residual amount of quinoline. Flash chromatography on silica gel, eluting with 4:1 hexanes–EtOAc, gave pure **10** (8.29 g, 98%) as a colorless oil: $[\alpha]_D$ +34.2° (*c* 0.86, $CHCl_3$); IR ($CHCl_3$) 3350, 1690 cm^{-1}; ^1H NMR (200 MHz, C_6D_6, 60 °C) δ 0.89 (br s, 1 H, OH, exchanged with D_2O), 1.39 (s, 9 H, $C(CH_3)_3$), 1.46, 1.65 (2 s, 2 × 3 H, $C(CH_3)_2$), 3.18, 3.20

(32) The numbering system used in this paper corresponds to the current CA index names for substructures i–iii. For details, see: *Chemical Abstracts Service Index Guide*; American Chemical Society: Washington, DC, 1989.



(33) For more information about the "attached proton test" (APT), see: *XL-Series NMR Spectrometer System. Advanced Operation*; Publication No. 87-146-006, Rev. A383; Varian Instrument Division: Palo Alto, CA, 1983; pp 2–29. Le Cocq, C.; Lallemand, J.-Y. *J. Chem. Soc., Chem. Commun.* **1981**, 150.

(34) Arndt, F. In *Organic Syntheses*; Blatt, A. H., E.; Wiley: New York, 1943; Collect. Vol. 2, pp 165–167, Note 3.

(2 s, 2 × 3 H, OCH_3), 3.67 (dd, J = 9.1 and 6.7 Hz, 1 H, H-5a), 3.96 (d, J = 9.3 Hz, 1 H, H-5b), 4.01 (br s, 1 H, H-4), 4.79 (br s, 1 H, H-1'), 5.29 (d, J = 4.1 Hz, 1 H, H-4'), 5.69 (m, 2 H, H-2' and H-3'); MS (% relative intensity, m/e) 300.1869 (0.3, M − OCH_3, 300.1811 calcd for $C_{15}H_{26}NO_5$), 212 (32.7), 201 (15.5), 200 (63.1), 144 (44.0), 101 (12.8), 100 (100.0).

1,1-Dimethylethyl [2*S*-[2α(*R),5α]]-4-(2,5-Dihydro-5-methoxy-2-furanyl)-2,2-dimethyl-3-oxazolidinecarboxylate (11) and 1,1-Dimethylethyl [2*S*-[2α(*R**),5β]]-4-(2,5-Dihydro-5-methoxy-2-furanyl)-2,2-dimethyl-3-oxazolidinecarboxylate (12).** To a solution of **10** (4.20 g, 12.7 mmol) in methanol (180 mL) was added solid PPTS (326 mg, 1.30 mmol). The clear solution was stirred at room temperature for 2.5 h, at which time the TLC in 2:1 hexanes–EtOAc showed the formation of product R_f 0.64, at the expense of the starting material, R_f 0.38 (char B). The reaction was poured into a half-saturated $NaHCO_3$ solution (500 mL), extracted with CH_2Cl_2 (500 mL), and washed with brine (500 mL). Each aqueous layer was re-extracted with CH_2Cl_2 (2 × 500 mL), and all organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo to obtain an amber oil (4.2 g). ^1H NMR of crude product showed a 1:1 mixture of α- and β-anomers (vide infra). Flash chromatography on silica gel, eluting with 4:1 hexanes–EtOAc gave **11/12** (3.70 g, 97%), as a colorless oil: $[\alpha]_D$ −12.2° (*c* 0.96, $CHCl_3$); IR (neat) 3080, 1700, 1685, 1620 cm^{-1}; ^1H NMR (200 MHz, C_6D_6, 60 °C) δ 1.39, 1.41 (2 s, 9 H, $C(CH_3)_3$), 1.53 (s, 3 H, 0.5 $C(CH_3)_2$), 1.68, 1.73 (2 s, 3 H, 0.5 $C(CH_3)_2$), 3.20, 3.30 (2 s, 3 H, OCH_3), 3.65 (dd, J = 8.9 and 6.0 Hz, 1 H, H-5a), 3.80 (br s, 1 H, H-4), 4.02 (d, J = 8.8 Hz, 0.5 H, H-5b), 4.21 (d, J = 8.9 Hz, 0.5 H, H-5b), 5.07 (br s, 1 H, H-2'), 5.54 (m 1 H, H-4'), 5.58 (s, 0.5 H, H-5'), 5.71 (d, J = 4.4 Hz, 0.5 H, H-3'), 5.92 (d, J = 6.4 Hz, 0.5 H, H-5'), 6.04 (d, J = 5.9 Hz, 0.5 H, H-3'); ^{13}C NMR (C_6D_6, 60 °C) δ 24.8 (q, –, $C(CH_3)_2$), 28.4 (q, –, $C(CH_3)_3$), 53.4, 54.7 (q, –, OCH_3, α and β), 61.1, 61.3 (d, –, C-4, α and β), 65.0 (t, +, C-5), 79.7 (s, +, $C(CH_3)_3$), 85.8 (d, –, C-2'), 94.3 (s, +, C-2), 109.5, 109.8 (d, –, C-5', α and β), 126.9, 127.2 (d, –, C-3' or C-4', α and β), 133.7, 134.5 (d, –, C-4' or C-3', α and β), 155.5 (s, +, NCO_2).

1,1-Dimethylethyl [2*R*-[2α(*R),3α,4α,5β]]-4-(3,4-Dihydroxytetrahydro-5-methoxy-2-furanyl)-2,2-dimethyl-3-oxazolidinecarboxylate (15) and 1,1-Dimethylethyl [2*R*-[2α(*R**),3β,4β,5α]]-4-(3,4-Dihydroxytetrahydro-5-methoxy-2-furanyl)-2,2-dimethyl-3-oxazolidinecarboxylate (16).** To a solution of **11/12** (3.65 g, 12.2 mmol) in acetone (80 mL) was added a stock solution of OsO_4 + NMO in water (90 mL, 0.008 M in OsO_4, 1.20 M in NMO). The yellow solution was stirred at room temperature for 12 h when the TLC in 1:1 hexane–EtOAc showed the formation of two products, R_f 0.40 and R_f 0.16, at the expense of the starting material, R_f 0.67 (char A). The reaction mixture was poured into saturated Na_2SO_3 solution (500 mL) and extracted with EtOAc (500 mL). The organic layer was washed with pH 4 buffer solution (500 mL) and brine (500 mL). Each aqueous layer was re-extracted with EtOAc (2 × 500 mL), and all organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a slightly yellow solid (3.91 g). Flash chromatography on silica gel, eluting with 1:1 hexanes–EtOAc gave α-methyl mannofuranoside **15** (R_f 0.40, 1.8 g, 44%) as a colorless oil and β-methyl allofuranoside **16** (R_f 0.16, 1.3 g, 32%) as a white solid (mp 120–121 °C). For **15**: $[\alpha]_D$ +97.8° (*c* 1.13, $CHCl_3$); IR (neat) 3400, 1670 cm^{-1}; ^1H NMR (200 MHz, C_6D_6, 60 °C) δ 1.25 (s, 9 H, $C(CH_3)_3$), 1.28, 1.39 (2 s, 2 × 3 H, $C(CH_3)_2$), 3.23 (s, 3 H, OCH_3), 3.40 (d, J = 9.5 Hz, 1 H, OH), 3.63 (dd, J = 9.1 and 5.4 Hz, 1 H), 3.95 (br s, 2 H), 4.17 (dd, J = 9.9 and 5.5 Hz, 1 H), 4.24 (d, J = 9.2 Hz, 1 H), 4.34 (m, 1 H), 5.03 (d, J = 3.42 Hz, 1 H, H-5'), 6.03 (br s, 1 H, OH); ^{13}C NMR (C_6D_6, 60 °C): δ 27.7 (q, –, $C(CH_3)_2$), 28.2 (q, –, $C(CH_3)_3$), 55.6 (q, –, OCH_3), 60.0 (d, –, C-4), 65.3 (t, +, C-5), 70.9 (d, –, C-3'), 79.0 (d, –, C-4'), 80.7 (d, –, C-2'), 81.6 (s, +, $C(CH_3)_3$), 94.2 (s, +, C-2), 110.7 (d, –, C-5'), 154.4 (s, +, NCO_2); MS (% relative intenstiy, m/e) 318.1565 (11.8, M − CH_3, 318.1552 calcd for $C_{14}H_{24}NO_7$), 218 (14.3), 204 (11.0), 200 (37.7), 186 (13.6), 116 (38.4), 101 (12.8), 100 (100). For **16**: $[\alpha]_D$ −55° (*c* 1.47, $CHCl_3$); IR (KBr) 3460, 1660 cm^{-1}; ^1H NMR (200 MHz C_6D_6, 60 °C) δ 1.36 (s, 9 H, $C(CH_3)_3$), 1.46, 1.62 (2 s, 2 × 3 H, $C(CH_3)_2$), 2.31 (br s, 1 H, OH, exchanged with D_2O), 3.10 (s, 3 H, OCH_3), 3.67 (dd, J = 8.9 and 5.8 Hz, 1 H), 3.95 (t, J = 6.0 Hz, 1 H), 4.0 (br d, J = 4.4 Hz, 1 H), 4.18 (q + br s, J = 7.1 Hz, 2 H), 4.44 (br s, 1 H), 4.77 (s, 1 H, H-5'); ^{13}C NMR (C_6D_6, 60 °C) δ 27.3 (q, –, $C(CH_3)_2$), 28.4 (q, –, $C(CH_3)_3$), 54.9 (q, –, OCH_3), 60.7 (d, –, C-4), 65.2 (t, +, C-5), 74.4 (d, –, C-3'), 76.5 (d, –, C-4'), 80.4 (s, +, $C(CH_3)_3$), 83.6 (d, –, C-2'), 94.4 (s, +, C-2), 108.5 (d, –, C-5'), 153.4 (s, +, NCO_2). Anal. Calcd for $C_{15}H_{27}NO_7$: C, 54.04; H, 8.16; N, 4.20. Found: C, 53.88; H, 8.17; N, 4.27.

1,1-Dimethylethyl [2*R*-[2α(*R),3β,4β,5α]]-4-(3,4-Dihydroxytetrahydro-5-methoxy-2-furanyl)-2,2-dimethyl-3-oxazolidinecarboxylate (16) and 1,1-Dimethylethyl [2*R*-[2α(*R**),3α,4α,5α]]-4-(3,4-Dihydroxytetrahydro-5-methoxy-2-furanyl)-2,2-dimethyl-3-oxazolidinecarboxylate (17).** To a solution of **10** (8.29 g, 25.1 mmol) in acetone (140 mL) was added the stock solution of OsO_4 + NMO (140 mL, 0.003 M in OsO_4, 1.20 M in NMO). The brown solution was stirred for 24 h at room temperature. The TLC in EtOAc showed the formation of product, R_f 0.38, at the expense of the starting material, R_f 0.78 (char A). The reaction was poured into saturated Na_2SO_3 solution (1 L) and stirred for 30 min at room temperature. After the acetone was removed by rotary evaporation, the reaction mixture was extracted with EtOAc (1 L), and then the organic layer was washed with 0.5 N HCl (1 L) and brine (1 L). The aqueous layers were each re-extracted with EtOAc (2 × 1 L), respectively, and the combined organics were dried with $MgSO_4$, filtered, and concentrated in vacuo to give an amber oil (5.87 g). Flash chromatography on silica gel, eluting with 4:1 hexanes–EtOAc, gave the (inseparable) triol mixture **13/14** (5.24 g, 57%) as a white solid. This material was submitted directly to the following cyclization conditions: To a solution of **13/14** (4.62 g, 12.7 mmol) in benzene (1.4 L) was added PPTS (340 mg, 1.33 mmol). The clear solution was refluxed for 1 h, at which time the TLC in EtOAc showed the disappearance of the starting triols, R_f 0.50, and the formation of two products, $R_{f\,\text{minor}}$ 0.79 and $R_{f\,\text{major}}$ 0.59 (char A). The reaction was cooled to room temperature and poured into a half-saturated $NaHCO_3$ solution (1 L). The mixture was extracted with C_6H_6 and washed with brine (1 L). Each aqueous layer was re-extracted with EtOAc (2 × 1 L), and the combined organic layers were processed as above to give a yellow gum (3.39 g). Flash chromatography on silica gel, eluting with 5:1 hexanes–EtOAc, gave **16** (0.70 g, 17% yield) as a white solid, mp 120–122 °C, which was identical with one of the products from the cyclic route, followed by the α-methyl mannofuranoside **17** (2.14 g, 51% yield) as a white solid (mp 72–78 °C). For **17**: $[\alpha]_D$ −65° (*c* 1.21, $CHCl_3$); IR (KBr) 3450, 1675 cm^{-1}; ^1H NMR (200 MHz, C_6D_6, 60 °C) δ 1.29 (s, 9 H, $C(CH_3)_3$), 1.35, 1.51 (2 s, 2 × 3 H, $C(CH_3)_2$), 3.21 (s, 3 H, OCH_3), 3.67 (dd, J = 9.0 and 5.7 Hz), 3.78 (br s, 1 H), 3.93 (br s, 2 H), 4.25 (t, J = 5.8 Hz, 1 H), 4.34 (dd, J = 9.0 and 1.2 Hz, 1 H), 4.60 (d, J = 4.98 Hz, 1 H, H-5'), 5.27 (br s, 2 H, 2 OH); ^{13}C NMR (C_6D_6, 60 °C) δ 27.7 (q, –, $C(CH_3)_2$), 28.0 (q, –, $C(CH_3)_3$), 55.8 (q, –, OCH_3), 57.0 (d, –, C-4), 65.0 (t, +, C-5), 69.9 (d, –, C-3'), 74.2 (d, –, C-4'), 80.8 (d, –, C-2'), 81.1 (s, +, $C(CH_3)_3$), 94.1 (s, +, C-2), 102.9 (d, –, C-5'), 151.6 (s, +, NCO_2); MS (% relative intensity, m/e) 334.1868 (1.3, M + 1, 334.1866 calcd for $C_{15}H_{28}NO_7$), 318 (28.0), 246 (15.3), 228 (14.9), 218 (32.6), 203 (14.6), 200 (96.5), 186 (61.0), 146 (10.0), 144 (100.0), 143 (11.0), 116 (39.1), 100 (19.2).

General Procedure for Acetylation. To a 0.21 M solution of dihydroxyfuranose in 1:1 Ac_2O–pyridine was added 0.02 equiv of DMAP. The homogeneous solution was stirred at room temperature for 24 h, at which time the TLC in 1:1 hexanes–EtOAc indicated the disappearence of starting material and the clean formation of product (char A). The reaction was diluted with EtOAc (200 mL), and organic layer was washed with 1 N HCl (100 mL), saturated $NaHCO_3$ solution (100 mL), and brine (100 mL). The aqueous layers were each re-extracted with EtOAc (2 × 200 mL), respectively, and all organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo to give an amber oil. Each product was chromatographed on silica gel, eluting with 1:1 hexanes–EtOAc to obtain the pure diacetate (90–93% yield).

1,1-Dimethylethyl [2*R*-[2α(*R),3α,4α,5β]]-4-[3,4-Bis(acetyloxy)tetrahydro-5-methoxy-2-furanyl]-2,2-dimethyl-3-oxazolidinecarboxylate (18).** The starting material **15** (44.1 mg, 0.132 mmol, R_f 0.39) gave **18** (51.1 mg, 93% yield, R_f 0.53) as a white solid: mp 114–115 °C; $[\alpha]_D$ +80.4° (*c* 0.99, $CHCl_3$); IR ($CHCl_3$) 1750, 1700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 55 °C) δ 1.44 (s, 9 H, $C(CH_3)_3$), 1.48, 1.56 (2 s, 2 × 3 H, $C(CH_3)_2$), 2.01, 2.06 (2 s, 2 × 3 H, $OCOCH_3$), 3.36 (s, 3 H, OCH_3), 3.92 (dd, J = 8.8 and 6.2 Hz, 1 H, H-5a), 4.23 (d + br s, J = 10.0 Hz, 2 H, H-5b

and H-4), 4.45 (t, J = 3.6 Hz, 1 H, H-2′), 4.99 (d, J = 2.9 Hz, 1 H, H-5′), 5.22 (dd, J = 5.1 and 2.9 Hz, 1 H, H-4′), 5.40 (t, J = 4.6 Hz, 1 H, H-3′); MS (% relative intensity, m/e) 417.1975 (0.1, M^+, 417.1999 calcd for $C_{19}H_{31}NO_9$), 302 (63.2), 200 (28.9), 126 (25.9), 100 (100.0).

1,1-Dimethylethyl [2*R*-[2α(*R),3β,4β,5α]]-4-[3,4-Bis(acetyloxy)tetrahydro-5-methoxy-2-furanyl]-2,2-dimethyl-3-oxazolidinecarboxylate (19).** The starting material **16** (487 mg, 1.46 mmol, R_f 0.23) gave **19** (553 mg, 91% yield, R_f 0.74), as a colorless oil: $[\alpha]_D$ 0°, $[\alpha]_{578}$ −3.1° (c 1.00, $CHCl_3$); IR ($CHCl_3$) 1750, 1690 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 55 °C) δ 1.45 (s, 9 H, $C(CH_3)_3$), 1.48, 1.55 (2 s, 2 × 3 H, $C(CH_3)_2$), 1.97, 2.05 (2 s, 2 × 3 H, $OCOCH_3$), 3.35 (s, 3 H, OCH_3), 3.91 (dd, J = 8.6 and 5.6 Hz, 1 H, H-5a), 4.04 (d + br s, J = 8.7 Hz, 2 H, H-5b + H-4), 4.25 (t, J = 6.0 Hz, 1 H, H-2′), 4.83 (s, 1 H, H-5′), 5.25 (d, J = 4.8 Hz, 1 H, H-4′), 5.45 (t, J = 5.8 Hz, 1 H, H-3′); ^{13}C NMR (C_6D_6, 60 °C) δ 19.6 (q, −, $OCOCH_3$), 26.9 (q, −, $C(CH_3)_2$), 27.9 (q, −, $C(CH_3)_3$), 54.7 (q, −, OCH_3), 59.4 (d, −, C-4), 64.7 (t, +, C-5), 72.9 (d, −, C-3′), 75.5 (d, −, C-4′), 79.9 (s, +, $C(CH_3)_3$), 81.1 (d, −, C-2′), 94.1 (s, +, C-2), 106.4 (d, −, C-5′), 151.6 (s, +, NCO_2), 168.6 (s, +, $OCOCH_3$); MS (% relative intensity, m/e) 402.1675 (2.1, M − CH_3, 402.1764 calcd for $C_{18}H_{28}NO_9$), 200 (16.1), 168 (14.0), 144 (26.1), 126 (26.9), 115 (34.0), 100 (100).

1,1-Dimethylethyl [2*R*-[2α(*R),3α,4α,5α]]-4-[3,4-Bis(acetyloxy)tetrahydro-5-methoxy-2-furanyl]-2,2-dimethyl-3-oxazolidinecarboxylate (20).** The starting material **17** (1.40 g, 4.21 mmol, R_f 0.15) gave **20** (1.62 g, 93% yield, R_f 0.61) as a colorless oil: $[\alpha]_D$ −28.7° (c 0.90, $CHCl_3$); IR ($CHCl_3$) 1750, 1690 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 55 °C) δ 1.46 (s, 9 H, $C(CH_3)_3$), 1.48, 1.58 (2 s, 2 × 3 H, $C(CH_3)_2$), 2.05, 2.07 (2 s, 2 × 3 H, CO_2CH_3), 3.45 (s, 3 H, OCH_3), 3.93 (dd, J = 8.6 and 6.8 Hz, 1 H, H-5a), 3.99 (br s, 1 H, H-4), 4.37 (dd, J = 8.7 and 1.9 Hz, 1 H, H-5b), 4.64 (dd, J = 5.0 and 2.0 Hz, 1 H, H-2′), 5.01 (br s, 2 H, H-2′ + H-5′), 5.52 (m, 1 H, H-3′); ^{13}C NMR (C_6D_6, 60 °C) δ 19.6 (q, −, $OCOCH_3$), 26.6 (q, −, $C(CH_3)_2$), 28.0 (q, −, $C(CH_3)_3$), 55.3 (q, −, OCH_3), 57.2 (d, −, C-4), 64.1 (t, +, C-5), 69.8 (d, −, C-3′), 72.0 (d, −, C-4′), 79.0 (s, +, $C(CH_3)_3$), 79.4 (d, −, C-2′), 93.3 (s, +, C-2), 100.9 (d, −, C-5′), 151.8 (s, +, NCO_2), 168.7 (s, +, $OCOCH_3$); MS (% relative intensity, m/e) 419.2149 (0.7, M + 2, 419.2155 calcd for $C_{19}H_{33}NO_9$), 362 (11.1), 330 (24.8), 318 (11.2), 303 (13.8), 302 (67.2), 270 (24.4), 200 (55.2), 168 (11.7), 158 (14.0), 143 (66.2), 140 (15.9), 127 (10.8), 126 (69.7), 108 (13.8), 101 (27.8), 100 (100.0).

General Procedure for Oxazolidine Methanolysis. To a 0.038 M solution of each oxazolidine (**18**, **19**, or **20**) in MeOH was added 0.16 equiv of $TsOH·H_2O$. The homogeneous solution was stirred at room temperature for 12 h at which time the TLC showed the partial formation of product along with the starting material (char A). With substrates **19** and **20** it was noted that prolonged reaction times resulted in the cleavage of the BOC group as indicated by increasing amounts of ninhydrin active material at the TLC origin. The reaction was poured into a saturated $NaHCO_3$ solution (80 mL), and the resulting mixture was extracted with EtOAc (3 × 250 mL). The combined organics were washed with brine (80 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude product. Flash chromatography on silica gel, eluting with 1:1 hexanes–EtOAc, gave the pure product along with the recovered starting material.

Methyl 5-Deoxy-5-[[(1,1-dimethylethoxy)carbonyl]amino]-α-D-mannofuranoside, 2,3-Diacetate (21). The starting material **18** (315 mg, 0.755 mmol, R_f 0.72) gave **21** (159 mg, 56% yield after 100% conversion of starting material) as a colorless oil, R_f 0.37, in 2:1 EtOAc–hexanes: $[\alpha]_D$ +69.9° (c 1.64, $CHCl_3$); IR (neat) 3450, 1750, 1710 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.38 (s, 9 H, $C(CH_3)_3$), 2.03, 2.09 (2 s, 2 × 3 H, $OCOCH_3$), 3.38 (s, 3 H, OCH_3), 3.71 (dd, J = 11.2 and 3.2 Hz, 1 H, H-6a), 3.93 (dd, J = 11.3 and 3.4 Hz, 1 H, H-6b), 4.04 (m, 1 H, H-5), 4.27 (dd, J = 8.6 and 3.9 Hz, 1 H, H-4), 4.99 (d, J = 3.5 Hz, 1 H, H-1), 5.18 (dd, J = 5.0 and 3.3 Hz, 1 H, H-3), 5.51 (t, J = 3.9 Hz, 1 H, H-2); MS (% relative intensity, m/e) 346.1513 (3.9, M − OCH_3, 346.1502 calcd for $C_{15}H_{24}NO_8$), 290, 230 (12.6), 217 (15.4), 188 (13.8), 186 (11.0), 159 (10.8), 158 (34.4), 141 (15.8), 129 (16.1), 127 (15.6), 126 (100.0), 116 (18.4), 115 (66.1), 112 (17.7), 104 (19.8), 103 (12.4), 102 (23.3), 100 (13.5).

Methyl 5-Deoxy-5-[[(1,1-dimethylethoxy)carbonyl]amino]-β-D-allofuranoside, 2,3-Diacetate (22). The starting material **19** (244 mg, 0.585 mmol, R_f 0.74) gave **22** (84.6 mg, 50% yield after 77% conversion of starting material, as a white solid, R_f 0.21 in 1:1 EtOAc–hexanes: $[\alpha]_D$ −17.3° (c 0.99, $CHCl_3$); IR ($CHCl_3$) 3450, 1750, 1710 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.43 (s, 9 H, $C(CH_3)_3$), 2.03, 2.09 (2 s, 2 × 3 H, $OCOCH_3$), 2.57 (br s, 1 H, OH), 3.39 (s, 3 H, OCH_3), 3.78 (m, 3 H, H-6a, H-6b, and H-5), 4.25 (t, J = 6.5 Hz, 1 H, H-4), 4.88 (s, 1 H, H-1), 5.12 (d, J = 6.5 Hz, 1 H, NH), 5.23 (d, J = 5.2 Hz, 1 H, H-2), 5.43 (dd, J = 7.0 and 4.9 Hz, 1 H, H-3).

Methyl 5-Deoxy-5-[[(1,1-dimethylethoxy)carbonyl]amino]-β-D-mannofuranoside, 2,3-Diacetate (23). The starting material **20** (640 mg, 1.54 mmol, R_f 0.50) gave **23** (332 mg, 73% yield after 78% conversion of starting material) as a white solid, mp 50–53 °C, R_f 0.16 in 1:1 EtOAc–hexanes: $[\alpha]_D$ −84° (c 1.17, $CHCl_3$); IR ($CHCl_3$) 3440, 1740, 1710 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$ + D_2O) δ 1.38 (s, 9 H, $C(CH_3)_3$), 2.06, 2.12 (2 s, 2 × 3 H, $OCOCH_3$), 3.37 (s, 3 H, OCH_3), 3.69 (dd, J = 12.3 and 3.0 Hz, 1 H, H-6a), 3.90 (dd, J = 11.1 and 3.0 Hz, 1 H, H-6b), 4.03 (br s, 1 H, H-5), 4.19 (dd, J = 9.0 and 4.6 Hz, 1 H, H-4), 5.02 (br s, 2 H, H-1 and H-2), 5.60 (t, J = 4.5 Hz, 1 H, H-3); ^{13}C NMR (C_6D_6) δ 19.8, 20.7 (2 q, −, 2 $OCOCH_3$), 28.1 (q, −, $C(CH_3)_3$), 51.1 (d, −, C-5), 55.5 (q, −, OCH_3), 62.2 (t, +, C-6), 68.9 (d, −, C-3), 72.2 (d, −, C-2), 76.6 (d, −, C-4), 78.9 (s, +, $C(CH_3)_3$), 101.2 (d, −, C-1), 155.2 (s, +, NCO_2), 169.5 (s, +, $OCOCH_3$), 169.8 (s, +, $OCOCH_3$). Anal. Calcd for $C_{16}H_{27}NO_9$: C, 50.92; H, 7.21; N, 3.71. Found: C, 50.97; H, 7.40; N, 3.80.

General Procedure for Alcohol Oxidation. To a 0.038 M solution of *N*-BOC amino alcohol (**21**, **22**, or **23**) in 60% aqueous acetone was added 10 equiv of solid $NaIO_4$ followed by 0.08 equiv of $RuO_2·H_2O$. The greenish suspension was stirred for 24 h at room temperature at which time the TLC in EtOAc showed the disappearance of starting alcohol and the formation of acid at the origin (char A). ^{i}PrOH (6 mL) was added to the reaction mixture, and it was stirred for an additional 30 min to consume excess oxidant. The resulting suspension was filtered through Celite to remove the catalyst and $NaIO_2$, and the yellow filtrate was concentrated in vacuo to give a brown foam. The brown foam was dissolved in Et_2O (10 mL) at 0 °C and treated directly with diazomethane solution (5 mL) at which point the TLC in 1:1 EtOAc–hexanes or in EtOAc showed the clean transformation of acid to an ester (char A). Excess diazomethane was quenched by dropwise addition of HOAc. The mixture was diluted with Et_2O (50 mL) and then washed with saturated $NaHCO_3$ solution (20 mL) and brine (20 mL). The resulting saturated $NaHCO_3$ layer and brine layer were re-extracted with Et_2O (2 × 20 mL), respectively, and the organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a brown foam. Flash chromatography on silica gel, eluting with 1:1 hexanes–EtOAc, gave the pure *N*-BOC amino ester (72–75% yield).

Methyl [Methyl 5-deoxy-5-[[(1,1-dimethylethoxy)carbonyl]amino]-α-D-mannofuranosid]uronate, 2,3-Diacetate (27). The starting material **21** (150 mg, 0.399 mmol) gave **27** (121 mg, 75% yield) as a colorless oil, R_f 0.48 in 1:1 EtOAc–hexanes: $[\alpha]_D$ +83.7° (c 1.17, $CHCl_3$); IR (neat) 3350, 1750, 1715 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.43 (s, 9 H, $C(CH_3)_3$), 2.04, 2.11 (2 s, 2 × 3 H, $OCOCH_3$), 3.34 (s, 3 H, OCH_3), 3.71 (s, 3 H, CO_2CH_3), 4.66 (t, J = 6.2 Hz, 1 H, H-4), 4.81 (dd, J = 9.8 and 6.3 Hz, 1 H, H-5), 4.96 (d, J = 1.2 Hz, 1 H, H-1), 5.07 (br s, 1 H, NH), 5.12 (dd, J = 5.43 and 1.4 Hz, 1 H, H-2), 5.64 (t, J = 5.9 Hz, 1 H, H-3); MS (% relative intensity, m/e) 406.1722 (0.1, M + 1, 406.1713 calcd for $C_{17}H_{28}NO_{10}$, 217 (80.4), 126 (19.3), 116 (17.3), 115 (100.0).

Methyl [Methyl 5-deoxy-5-[[(1,1-dimethylethoxy)carbonyl]amino]-β-D-allofuranosid]uronate, 2,3-Diacetate (28). The starting material **22** (58 mg, 0.15 mmol) gave **8** (46 mg, 73% yield) as a colorless oil, R_f 0.39 in EtOAc: IR ($CHCl_3$) 3400, 1750, 1710 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.42 (s, 9 H, $C(CH_3)_3$), 2.01, 2.08 (2 s, 2 × 3 H, $OCOCH_3$), 3.32 (s, 3 H, OCH_3), 3.74 (s, 3 H, CO_2CH_3), 4.40 (dd, J = 7.9 and 4.1 Hz, 1 H, H-4), 4.56 (dd, J = 8.3 and 4.2 Hz, 1 H, H-5), 4.81 (s, 1 H, H-1), 5.18 (d, J = 4.8 Hz, 1 H, H-2), 5.42 (d, J = 8.3 Hz, 1 H, NH), 5.53 (dd, J = 7.8 and 4.8 Hz, 1 H, H-3); MS (% relative intensity, m/e) 406.1708 (0.1, M + 1, 406.1713 calcd for $C_{17}H_{28}NO_{10}$), 217 (86.2), 157 (30.8), 126 (14.5), 116 (11.1), 115 (100.0).

Methyl [Methyl 5-deoxy-5-[[(1,1-dimethylethoxy)carbonyl]amino]-β-D-mannofuranosid]uronate, 2,3-Diacetate (29). The starting material **23** (440 mg, 1.17 mmol) gave **29** (340 mg, 72% yield) as a white solid, mp 42–45 °C, R_f 0.39 in 1:1

EtOAc–hexanes: $[\alpha]_D$ −42.5° (*c* 1.17, $CHCl_3$); IR ($CHCl_3$) 3450, 1750, 1710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 9 H, $C(CH_3)_3$), 2.07, 2.13 (2 s, 2 × 3 H, $OCOCH_3$), 3.42 (s, 3 H, OCH_3), 3.67 (s, 3 H, CO_2CH_3), 4.69 (dd, *J* = 8.3 and 4.2 Hz, 1 H, H-5), 4.84 (t, *J* = 5.0 Hz, 1 H, H-4), 4.98 (t, *J* = 5.2 Hz, 1 H, H-2), 5.04 (d, *J* = 4.58 Hz, 1 H, H-1), 5.32 (d, *J* = 8.7 Hz, 1 H, NH), 5.66 (t, *J* = 5.8 Hz, 1 H, H-3); ^{13}C NMR (C_6D_6) δ 19.8, 20.1 (2 q, –, $OCOCH_3$), 28.0 (q, –, $C(CH_3)_3$), 51.5 (q, –, OCH_3), 53.5 (q, –, CO_2CH_3), 55.4 (d, –, C-5), 68.7 (d, –, C-4), 7.13 (d, –, C-3), 77.7 (d, –, C-2), 79.2 (s, +), 101.3 (d, –, C-1), 155.0 (s, +, NCO_2), 168.9, 169.2 (2 s, +, $OCOCH_3$), 170.6 (s, +, CO_2CH_3). Anal. Calcd for $C_{17}H_{27}NO_{10}$: C, 50.35; H, 6.72; N, 3.46. Found: C, 50.43; H, 6.77; N, 3.52.

General Procedure for N-Acetylation. To a 0.12 M solution of *N*-BOC methyl ester in CH_2Cl_2 was added 10 equiv of TFA. The slightly yellow solution was stirred for 1 h at room temperature at which time the TLC in 1:1 hexanes–EtOAc showed the disappearance of starting alcohol and the formation of amine at the origin (char A). The solvent was evaporated in vacuuo to give a yellow liquid. This crude amine salt was treated with 1:1 Ac_2O–pyridine (0.18 M in amine salt), and the homogeneous solution was stirred at room temperature for 2 h. The TLC in EtOAc showed the clean formation of product, at the expense of the starting amine (char A). All solvents were removed in vacuo to give an amber oil, which was chromatographed on silica gel, eluting with 2:1 hexanes–EtOAc to give the pure *N*-acetyl amino ester (ca. 93% yield).

Methyl [Methyl 5-(acetylamino)-5-deoxy-α-D-mannofuranosid]uronate, 2,3-Diacetate (33). The starting material **27** (55.5 mg, 0.137 mmol) gave **33** (40.0 mg, 84% yield, R_f 0.60) as a colorless oil: ^1H NMR (200 MHz, $CDCl_3$) δ 2.02, 2.05, 2.06 (3 s, 3 × 3 H, 2 $OCOCH_3$, $NCOCH_3$), 3.34 (s, 3 H, OCH_3), 3.71 (s, 3 H, CO_2CH_3), 4.63 (t, *J* = 6.4 Hz, 1 H, H-4), 4.96 (d, *J* = 1.6 Hz, 1 H, H-1), 5.15 (m, 2 H, H-2 and H-5), 5.62 (t, *J* = 5.7 Hz, 1 H, H-3), 5.95 (d, *J* = 9.4 Hz, 1 H, NH); MS (% relative intensity *m/e*) 348.1332 (3.4, M + 1, 348.1294 calcd for $C_{14}H_{22}NO_9$), 316 (10.9), 218 (12.7), 217 (100.0), 186 (15.6), 157 (35.9), 154 (17.9).

Methyl [Methyl 5-(acetylamino)-5-deoxy-β-D-allofuranosid]uronate, 2,3-Diacetate (34). The starting material **28** (220 mg, 0.543 mmol) gave **34** (150 mg, 80% yield, R_f 0.49) as a colorless oil: ^1H NMR (200 MHz, $CDCl_3$) δ 2.02, 2.04, 2.08 (3 s, 3 × 3 H, 2 $OCOCH_3$, $NCOCH_3$), 3.32 (s, 3 H, OCH_3), 3.75 (s, 3 H, CO_2CH_3), 4.42 (dd, *J* = 8.0 and 3.6 Hz, 1 H, H-4), 4.81 (s, 1 H, H-1), 4.87 (dd, *J* = 8.0 and 4.8 Hz, 1 H, H-5), 5.18 (d, *J* = 4.8 Hz, 1 H, H-2), 5.56 (dd, *J* = 8.0 and 4.6 Hz, 1 H, H-3), 6.35 (d, *J* = 7.8 Hz, 1 H, NH); MS (% relative intensity, *m/e*) 316.1039 (2.7, M – OCH_3, 316.1032 calcd for $C_{13}H_{18}NO_8$), 217 (42.1), 157 (12.9), 115 (100.0).

Methyl [Methyl 5-(acetylamino)-5-deoxy-β-D-mannofuranosid]uronate, 2,3-Diacetate (35). The starting material **29** (291 mg, 0.721 mmol) gave **35** (242 mg, 97% yield, R_f 0.30) as a colorless oil: $[\alpha]_D$ −55.0° (*c* 1.47, $CHCl_3$); IR ($CHCl_3$) 3450, 1750, 1685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.06, 2.09, 2.14 (3 s, 3 × 3 H, 2 $OCOCH_3$ and $NCOCH_3$), 3.43 (s, 3 H, OCH_3), 3.70 (s, 3 H, CO_2CH_3), 4.74 (t, *J* = 6.4 Hz, 1 H, H-4), 4.98 (t, *J* = 5.4 Hz, 1 H, H-2), 5.04 (d, *J* = 4.8 Hz, 1 H, H-1), 5.14 (dd, *J* = 8.9 and 7.2 Hz, 1 H, H-5), 5.67 (t, *J* = 5.8 Hz, 1 H, H-3), 6.28 (d, *J* = 8.8 Hz, 1 H, NH); ^{13}C NMR (C_6D_6) δ 19.6, 20.2, 22.4 (3 q, –, 2 $OCOCH_3$ and $NCOCH_3$), 51.6 (q, –, OCH_3), 52.1 (d, –, C-5), 55.3 (q, –, CO_2CH_3), 68.6 (d, –, C-4), 71.4 (d, –, C-3), 77.6 (d, –, C-2), 101.4 (d, –, C-1), 169.0 (s, +, NCO_2), 169.3 (s, +, 2 $OCOCH_3$), 170.5 (s, +, CO_2CH_3); MS (% relative intensity, *m/e*) 348.1292 (1.3, M + 1, calcd for $C_{14}H_{22}NO_9$ 348.1294), 217 (90.0), 186 (14.1), 157 (31.0), 154 (15.0), 131 (14.5), 126 (26.5), 115 (100.0).

Methyl [Methyl 5-deoxy-5-[[(phenylmethoxy)carbonyl]amino]-α-D-mannofuranosid]uronate, 2,3-Diacetate (36). To a 0 °C solution of **32** (301 mg) in dioxane (11 ml) was added 7% $NaHCO_3$ solution (3 mL) followed by benzyl chloroformate (0.15 mL, 1.00 mmol). The resulting suspension was stirred for 10 min at room temperature, at which time the TLC in 1:1 hexanes–EtOAc showed the clean formation of **36**, R_f 0.25, at the expense of starting amine at the origin (char A). The reaction mixture was diluted with tap water (100 mL) and extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give a colorless oil (359 mg). Flash chromatography on silica gel, eluting with 1:1 hexanes–Et_2O, gave the pure *N*-Cbz amino ester **36** (228 mg, 83% yield over two steps) as a colorless oil: $[\alpha]_D$ −43.2° (*c* 0.87 $CHCl_3$); IR ($CHCl_3$) 3340, 1750, 1725 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.05, 2.08 (2 s, 2 × 3 H, 2 $OCOCH_3$), 3.28 (s, 3 H, OCH_3), 3.69 (s, 3 H, CO_2CH_3), 4.76 (t, *J* = 6.5 Hz, 1 H, H-4), 4.87–4.98 (m, 2 H, H-2 and H-5), 5.02 (d, *J* = 4.6 Hz, 1 H, H-1), 5.07 (d, *J* = 12.1 Hz, 1 H, CH_2Ph), 5.16 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 5.61 (d, *J* = 7.3 Hz, 1 H, NH), 5.66 (t, *J* = 5.8 Hz, 1 H, H-3), 7.33 (s, 5 H, C_6H_5).

5-Amino-1,5-dideoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1(2*H*)-pyrimidinyl)-β-D-allofuranuronic Acid (Thymine Polyoxin C) (4). To a solution of authentic polyoxin C (**37**) (14.5 mg, 0.0460 mmol) in H_2O (1.5 mL) was added PtO_2 (2.9 mg). The brown suspension was stirred under hydrogen for 1.5 h, at which time the suspension turned black and the TLC in 2:1:1 *n*-BuOH–H_2O–AcOH showed the formation of product, R_f 0.37, at the expense of staring material, R_f 0.31 (char A). The catalyst was filtered off through a pad of Celite + activated carbon, and the filtrate (15 mL) was concentrated in vacuo to give thymine polyoxin C (**4**) as a white solid (12.3 mg, 89% crude yield): mp 190–194 °C (shr 170 °C); ^1H NMR (400 MHz, D_2O + DCl, pD = 0.70, 2 mg/0.4 mL) δ 1.72 (s, 3 H, 5-CH_3), 4.20 (dd, *J* = 6.8 and 2.4 Hz, 1 H, H-4′), 4.27 (t, *J* = 5.0 Hz, 1 H, H-3′), 4.40 (d, *J* = 2.5 Hz, 1 H, H-5′), 4.53 (t, *J* = 6.7 Hz, 1 H, H-2′), 5.60 (d, *J* = 3.7 Hz, 1 H, H-1′), 7.17 (s, 1 H, H-6); HRMS (FAB/glycerol matrix) *m/e* 302.0999, M + 1, 302.0988 calcd for $C_{11}H_{16}N_3O_7$.

5-(Acetylamino)-1,5-dideoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1(2*H*)-pyrimidinyl)-β-D-allofuranuronic Acid (*N*-Acetylthymine Polyoxin C) (38). To a solution of **4** (5.8 mg, 0.016 mmol) in water (0.9 mL) was added 0.15 M NaOAc solution (0.23 mL, 0.035 mmol) and Ac_2O (0.025 mL). The clear solution (pH = 4) was stirred at room temperature for 4 h when the TLC in 2:1:1 *n*-BuOH–H_2O–AcOH showed the formation of product, R_f 0.52, at the expense of starting material, R_f 0.45 (char A). The mixture was extracted with EtOAc (6 × 3 mL), the aqueous layer containing the product was acidified to pH = 1 with 0.1 N HCl, and the water was removed in vacuo to give crude **38** as a white solid (7.8 mg) which contained NaCl. The NMR sample (5.2 mg) was treated with D_2O (1.0 mL), and the HDO + excess D_2O were evaporated prior to taking the ^1H NMR spectrum: ^1H NMR (400 MHz, DMSO-d_6, 5.2 mg/1 mL) δ 1.76 (s, 3 H, 5-CH_3), 1.87 (s, 3 H, $NCOCH_3$), 4.04 (m, 3 H, H-2′, H-3′, and H-4′), 4.14 (d, *J* = 2.7 Hz, 1 H, H-5′), 5.76 (d, *J* = 6.5 Hz, 1 H, H-1′), 7.45 (br s, 1 H, H-6).

Methyl 5-(Acetylamino)-1,5-dideoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1(2*H*)-pyrimidinyl)-β-D-allofuranuronate, 2,3-Diacetate (39). To a solution of **38** (0.9 mg) containing sodium chloride in MeOH (2 mL) was added Amberlyst-15 (5 mg). The yellow suspension was stirred at room temperature for 2 days at which time the TLC in 2:1:1 *n*-BuOH–H_2O–AcOH showed the formation of a product, R_f 0.75, at the expense of starting material, R_f 0.55 (char A). The catalyst was removed by filtration through Celite, eluting with MeOH, and the filtrate (10 mL) was concentrated in vacuo to give a product (1.5 mg). A solution of this ester (1.5 mg) in CH_2Cl_2 (0.5 mL) was treated with pyridine (0.05 mL) and Ac_2O (0.05 mL). The resulting clear solution was stirred at room temperature for 2 h at which time the TLC in 13:1 $CHCl_3$–MeOH showed the formation of product, R_f 0.24, and the disappearance of starting material at the origin. All volatiles were evaporated in vacuo to give **39** (1.3 mg): ^1H NMR (200 MHz, $CDCl_3$) δ 1.92 (d, *J* = 1.1 Hz, 3 H, 5-CH_3), 2.04, 2.07, 2.09 (3 s, 3 × 3 H, 2 $OCOCH_3$ and $NCOCH_3$), 3.80 (s, 3 H, CO_2CH_3), 4.36 (t, *J* = 4.6 Hz, 1 H, H-4′), 4.98 (dd, *J* = 7.5 and 3.8 Hz, 1 H, H-5′), 5.28 (t, *J* = 5.7 Hz, 1 H, H-3′), 5.53 (t, *J* = 5.8 Hz, 1 H, H-2′), 5.81 (d, *J* = 5.5 Hz, 1 H, H-1′), 6.20 (d, *J* = 7.6 Hz, 1 H, NH), 7.03 (d, *J* = 1.1 Hz, 1 H, H-6), 8.00 (br s, 1 H, N^3H); HRMS (FAB/glycerol matrix) *m/e* 442.1455, M + 1, 442.1462 calcd for $C_{18}H_{24}N_3O_{10}$.

General Procedure for Modified Hudson Acetolysis. A cold 0.007 M solution of *N*-acetyl amino ester in 20:1:1 Ac_2O–AcOH–H_2SO_4 was stirred between −25 and −20 °C for 1.5 h when a sample was withdrawn and quenched with MeOH to consume excess Ac_2O prior to TLC analysis. The TLC in EtOAc showed the disappearance of starting material and the formation of product (char A). Cold MeOH was slowly added to the reaction over a period of 0.5 h, and then the resulting solution was carefully

added in 10 portions to an ice-cold saturated $NaHCO_3$ solution. The product was extracted with CH_2Cl_2 (3 × 500 mL), and the combined organics were washed with brine (500 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give the crude anomeric acetates as yellow foams.

Methyl 5-(Acetylamino)-5-deoxy-α-D-mannofuranuronate, 1,2,3-Triacetate (40). The α-mannofuranoside **33** (40.0 mg, 0.115 mmol, R_f 0.90) gave **40** (41.9 mg, 97% crude yield) as a red solid which was recrystallized from 5:1 EtOAc–hexanes to give a white solid: mp 77–79 °C; $[\alpha]_D$ +111.6° (*c* 1.26, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 2.00, 2.06, 2.07, 2.09 (4 s, 4 × 3 H, 3 $OCOCH_3$ and $NCOCH_3$), 3.71 (s, 3 H, CO_2CH_3), 4.71 (t, *J* = 6.3 Hz, 1 H, H-4), 5.13 (dd, *J* = 9.4 and 7.0 Hz, 1 H, H-5), 5.31 (dd, *J* = 5.4 and 2.7 Hz, 1 H, H-2), 5.65 (t, *J* = 5.6 Hz, 1 H, H-3), 5.99 (d, *J* = 9.4 Hz, 1 H, NH), 6.22 (d, *J* = 2.0 Hz, 1 H, H-1). An identical tetraacetate (79.3 mg, 91% yield, R_f 0.45) was obtained from the β-mannofuranoside **35** (80 mg, 0.231 mmol, R_f 0.30).

2,4-Bis(trimethylsiloxy)-5-methylpyrimidine (41). To a dried flask containing a solid thymine (2.5 g, 0.020 mol) under an Ar atmosphere was added sequentially distilled dichloroethane (130 mL), distilled HMDS (30 mL, 0.143 mol), and distilled TMSCl (6.0 mL, 0.047 mmol). The stirred white suspension was refluxed at 120 °C (bath temperature) for 1 h, at which time the suspension had been replaced by a homogeneous solution. All solvents were removed by simple distillation under an Ar atmosphere. Vacuum distillation of the residue gave a colorless oil (4.5 g, 84% yield, bp 78–80 °C/0.5 mm). During this distillation, cold water was not circulated through the condenser since the product tended to solidify: ^1H NMR (200 MHz, $CDCl_3$) δ 0.34, 0.36 (2 s, 2 × 9 H), 2.00 (s, 3 H, 5-CH_3), 8.01 (s, 1 H, H-6).

Methyl 5-(Acetylamino)-1,5-dideoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1(2*H*)-pyrimidinyl)-β-D-mannofuranuronate, 2,3-Diacetate (42). To a solution of **40** (32 mg, 0.086 mmol) in dry dichloroethane (3.5 mL) were added sequentially bis-silylated thymine **41** (94 mg, 0.35 mmol) and TMSOTf (0.10 mL, 0.134 g, 0.637 mmol) under an Ar atmosphere. The yellow solution was refluxed at 95 °C for 30 min when the TLC in 9:1 $CHCl_3$–MeOH showed the formation of a UV-active product, R_f 0.52, at the expense of starting material **40** at R_f 0.56. The reaction was cooled to room temperature, diluted with CH_2Cl_2 (30 mL), and then washed with saturated $NaHCO_3$ solution (20 mL) and brine (20 mL). The resulting two aqueous layers were each reextracted with CH_2Cl_2 (2 × 30 mL), respectively, and all organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo to give a slightly yellow foam (42 mg). Flash chromatography on silica gel, eluting with 15:1 $CHCl_3$–MeOH, gave pure **42** (30 mg, 79% yield) as a white foam: $[\alpha]_D$ +70.1° (*c* 0.84, $CHCl_3$); IR ($CHCl_3$) 3380, 1750, 1680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.90 (s, 3 H, 5-CH_3), 1.99, 2.18 (2 s, 9 H, 2 $OCOCH_3$, $NCOCH_3$), 3.76 (s, 3 H, CO_2CH_3), 4.92 (dd, *J* = 9.1 and 3.4 Hz, 1 H, H-4′), 5.10 (t, *J* = 9.4 Hz, 1 H, H-5′), 5.73 (m, 2 H, H-1′ and H-3′), 5.86 (dd, *J* = 6.6 and 4.9 Hz, 1 H, H-2′), 6.50 (d, *J* = 9.5 Hz, 1 H, NH), 6.98 (d, *J* = 1.2 Hz, 1 H, H-6), 8.7 (br s, 1 H, N^3H); ^{13}C NMR (acetone-d_6) δ 10.6 (q, –, 5-CH_3), 18.6, 18.9, 20.9 (3 q, –, 2 $OCOCH_3$ and $NCOCH_3$), 50.0 (d, –, C-5′), 50.8 (q, –, CO_2CH_3), 69.6 (d, –, C-4′), 72.1 (d, –, C-3′), 78.9 (d, –, C-2′), 88.4 (d, –, C-1′), 108.0 (d, –, C-5), 136 (s, +, C-6), 151.4 (s, +, C-2), 164.4 (s, +, C-4), 168.3, 169.5 (s, +, $OCOCH_3$), 176.1 (s, +, CO_2CH_3); HRMS (FAB/glycerol matrix): *m/e* 442.1468, M, 442.1462 calcd for $C_{18}H_{23}N_3O_{10}$. For comparison, a sample of the regioisomeric N^3-nucleoside **43** was obtained from the corresponding $SnCl_4$-catalyzed reaction (see text): ^1H NMR (400 MHz, $CDCl_3$) δ 1.86 (s, 3 H, 5-CH_3), 2.00, 2.01, 2.15 (3 s, 3 × 3 H, 2 $OCOCH_3$, $NCOCH_3$), 3.72 (s, 3 H, CO_2CH_3), 5.12 (m, 2 H, H-4′ and H-5′), 5.80 (dd, *J* = 5.3 and 2.9 Hz, 1 H, H-3′), 6.17 (t, *J* = 5.5 Hz, 1 H, H-2′), 6.65 (d, *J* = 6.7 Hz, 1 H, H-1′), 6.75 (br s, 1 H, NH), 6.96 (d, *J* = 5.3 Hz, 1 H, H-6), 8.92 (d, *J* = 4.8 Hz, 1 H, N^1H); HRMS (FAB/glycerol matrix) *m/e* 442.1460, M, 442.1462 calcd for $C_{18}H_{23}N_3O_{10}$.

5-(Acetylamino)-1,5-dideoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1(2*H*)-pyrimidinyl)-α-D-mannofuranuronic Acid (44). To a flask containing **42** (22 mg, 0.050 mmol) was added cold 0.1 N NaOH solution (1.5 mL, 0.15 mmol) at 0 °C. The slightly yellow solution was stirred at 0 °C for 3 h, at which time the TLC in 2:1:1 *n*-BuOH–H_2O–AcOH showed the formation of product, R_f 0.48 (authentic *N*-acetyl thymine polyoxin C (**38**), R_f 0.52), at the expense of the starting material, R_f 0.84 (char A). The basic mixture was extracted with EtOAc (6 × 10 mL), and the aqueous layer was acidified to pH = 1 with 0.1 N HCl. The water was removed in vacuo to give crude **44** as a yellow solid (15.9 mg) that contained NaCl. The NMR sample (2.5 mg) was treated with D_2O (0.5 mL), and then HDO and excess D_2O was removed in vacuo prior to taking the ^1H NMR spectrum: ^1H NMR (400 MHz, DMSO-d_6, 2.5 mg/0.5 mL) δ 1.76 (s, 3 H, 5-CH_3), 1.85 (s, 3 H, $NCOCH_3$), 4.04 (br s, 1 H), 4.32 (br s, 1 H), 4.35 (t, *J* = 6.8 Hz, 1 H, H-2′), 4.53 (dd, *J* = 6.5 and 3.1 Hz, 1 H, H-3′), 5.76 (d, *J* = 7.78 Hz, 1 H, H-1′), 7.62 (s, 1 H, H-6).

Methyl 1,5-Dideoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1-(2*H*)-pyrimidinyl)-5-[[(phenylmethoxy)carbonyl]amino]-α-D-mannofuranuronate, 2,3-Diacetate (46) and Methyl 1,5-Dideoxy-3-(3,4-dihydro-5-methyl-2,4-dioxo-1(2*H*)-pyrimidinyl)-5-[[(phenylmethoxy)carbonyl]amino]-α-D-mannofuranuronate, 2,3-Diacetate (47). To a cold (–25 °C) solution of **36** (91 mg, 0.21 mmol) in CH_2Cl_2 (5 mL) was added 20:1:1 Ac_2O–AcOH–H_2SO_4 (0.5 mL). The clear solution was stirred between –25 and –20 °C for 1 h when a sample was withdrawn and treated with MeOH to quench the excess Ac_2O. The TLC in (1:1) hexanes–EtOAc showed the clean conversion of starting material, R_f 0.33 to product, R_f 0.43 (char A). Cold MeOH (1 mL) was slowly added to the reaction mixture over 0.5 h, and then it was diluted with CH_2Cl_2 (50 mL), and the solution was carefully added to an ice-cold saturated $NaHCO_3$ solution (50 mL) with swirling. The product was extracted into CH_2Cl_2 (3 × 50 mL), which was then washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give a red oil (41.7 mg, 43% crude yield). For **45**: ^1H NMR (200 MHz, $CDCl_3$, room temperature) δ 1.95, 2.01, 2.06 (3 s, 3 × 3 H, 3 $OCOCH_3$), 3.71 (s, 3 H, CO_2CH_3), 4.83–4.95 (m, 2 H, H-4 and H-5), 5.08 (d, *J* = 12.2 Hz, CH_2Ph), 5.20 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 5.23 (dd, *J* = 5.53 and 1.24 Hz, 1 H, H-2), 5.34 (d, *J* = 9.1 Hz, 1 H, NH), 5.69 (t, *J* = 6.0 Hz, 1 H, H-3), 6.20 (s, 1 H, H-1), 7.35 (s, 5 H, C_6H_5). This crude product was submitted to the nucleoside reaction without further purification. To a solution of **45** (40 mg, 0.086 mmol) in dry $(CH_2Cl)_2$ (2 mL) was added sequentially bis-silylated thymine **41** (81 mg, 0.30 mmol) and $SnCl_4$ (0.07 mL, 156 mg, 0.598 mmol) under an Ar atmosphere. The slightly yellow solution was stirred at room temperature for 30 min when the TLC in EtOAc showed the formation of **46**, R_f 0.80, and **47**, R_f 0.63, respectively, at the expense of starting **45**, R_f 0.88 (char A). The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with saturated $NaHCO_3$ solution (30 mL) and brine (30 mL). These resulting two aqueous layers were re-extracted with CH_2Cl_2 (2 × 50 mL), and all organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo to give a dark brown oil (38.6 mg, ^1H NMR of crude product showed a (4:1) mixture of N^1 and N^3 nucleosides). Flash chromatography on silica gel, eluting with 2:1 hexanes–EtOAc, gave pure **46** (20.2 mg, 44% yield) and **47** (4.8 mg, 11% yield). For **46**: ^1H NMR (200 MHz, $CDCl_3$) δ 1.89 (s, 3 H, 5-CH_3), 2.01, 2.09 (2 s, 2 × 3 H, 2 $OCOCH_3$), 3.72 (s, 3 H, CO_2CH_3), 4.84 (t, *J* = 8.8 Hz, 1 H, H-5′), 4.97 (dd, *J* = 7.8 and 4.1 Hz, 1 H, H-4′), 5.08 (d, *J* = 12.2 Hz, 1 H, CH_2Ph), 5.12 (d, *J* = 11.9 Hz, 1 H, CH_2Ph), 5.53 (d, *J* = 9.6 Hz, NH), 5.66–5.70 (m, 2 H, H-1′ and H-2′), 5.74 (t, *J* = 4.4 Hz, 1 H, H-3′), 6.90 (s, 1 H, H-6), 7.33 (s, 5 H, C_6H_5), 8.77 (s, 1 H, N^3H); HRMS (FAB/glycerol matrix) *m/e* 534.1723, M + 1, 534.1724 calcd for $C_{24}H_{28}N_3O_{11}$. For **47**: ^1H NMR (200 MHz, $CDCl_3$) δ 1.86 (s, 3 H, 5-CH_3), 1.93, 2.09 (s, 2 × 3 H, 2 $OCOCH_3$), 3.69 (s, 3 H, CO_2CH_3), 4.87 (t, *J* = 9.1 Hz, 1 H, H-5′), 5.03 (m, 1 H, H-4′), 5.10 (apparent d, *J* = 6.0 Hz, 2 H, CH_2Ph), 5.52 (d, *J* = 9.9 Hz, 1 H, NH), 5.80 (t, *J* = 5.3 Hz, 1 H, H-3′), 5.97 (t, *J* = 5.3 Hz, 1 H, H-2′), 6.54 (d, *J* = 4.6 Hz, 1 H, H-1′), 6.85 (s, 1 H, H-6), 7.34 (s, 5 H, C_6H_5), 8.28 (s, 1 H, N^1H); HRMS (FAB/glycerol matrix) *m/e* 534.1731, M + 1, 534.1724 calcd for $C_{24}H_{28}N_3O_{11}$.

5-Amino-1,5-dideoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1-(2*H*)-pyrimidinyl)-α-D-mannofuranuronic Acid (49). To a flask containing **46** (9.0 mg, 0.017 mmol) was added 0.1 N NaOH solution (0.5 mL, 0.05 mmol) at 0 °C. The yellow solution was stirred at 0 °C for 2 h at which time the TLC in EtOAc showed the disappearence of starting material, R_f 0.69, and the formation of **48** at the origin (char A). The basic mixture was extracted with EtOAc (2 × 3 mL), and aqueous layer containing product was acidified to pH = 1 with 0.1 N HCl. The product was extracted

with EtOAc (3 × 3 mL), the combined wet organic layer was filtered through short Na_2SO_4 column, and the filtrate was concentrated in vacuo to give crude *N*-Cbz nucleoside **48** (4.4 mg, 60% crude yield). To a solution of **48** (4.4 mg, 0.010 mmol) in MeOH (0.5 mL) was added 5% Pd/C (4 mg). The black suspension was stirred under H_2 atm for 1.5 h at which time the TLC in 5:4:1 $CHCl_3$–MeOH–H_2O showed the formation of **49**, R_f 0.29, at the expense of starting material, R_f 0.57 (char A). The TLC in 2:1:1 *n*-BuOH–MeOH–H_2O showed the product to have the same R_f value as authentic thymine polyoxin C (**4**), R_f 0.32 (char A). The catalyst was removed by filtration through a Celite + carbon pad, eluting with 1:1 MeOH–H_2O, and the filtrate (10 mL) was concentrated in vacuo to give **49** as a yellow solid (2 mg). Chromatography on sephadex G25 SF, eluting with 1:1 MeOH–H_2O gave pure **49** (1.3 mg, 44% yield) as a white solid: ^{1}H NMR (400 MHz, D_2O + DCl, pD 1–2, room temperature) δ 1.81 (s, 3 H, 5-CH_3), 4.37 (d, J = 5.7 Hz, 1 H, H-5′), 4.44 (t, J = 3.6 Hz, 1 H, H-4′), 4.53 (dd, J = 7.2 and 4.4 Hz, 1 H, H-2′), 4.95 (dd, J = 5.4 and 3.6 Hz, 1 H, H-3′), 5.88 (d, J = 7.2 Hz, 1 H, H-1′), 7.48 (s, 1 H, 6-H) [this ^{1}H NMR spectrum did not match that of an authentic sample of thymine polyoxin C (**4**)]; HRMS (FAB/glycerol matrix) m/e 302.0984, M + 1, 302.0988 calcd for $C_{11}H_{16}N_3O_7$.

Methyl 5-(Acetylamino)-1,5-dideoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1(2*H*)-pyrimidinyl)-1(*RS*)-methoxy-D-*allo*-hexouronate, 2,3,4-Triacetate (52 and 53). Application of the modified Hudson acetolysis conditions to **34** (35 mg, 0.10 mmol, R_f 0.43) gave what turned out to be the acyclic pentaacetates **50**/**51** as a chromatographically homogeneous red oil (37 mg, 97% yield, R_f 0.50) which was directly submitted to the nucleosidation without characterization: To a solution of crude **50**/**51** (54.9 mg, 0.118 mmol) in dry $(CH_2Cl)_2$ (2.5 mL) was added sequentially bis-silylated thymine **41** (98.6 mg, 0.364 mmol) and $SnCl_4$ (0.07 mL, 0.599 mmol) under an Ar atmosphere. The slightly yellow solution was refluxed at 95 °C for 1 h when the TLC in 13:1 $CHCl_3$–MeOH showed the formation of two product, R_f 0.32 and R_f 0.26, along with the starting material R_f 0.36 (char A). The reaction was cooled to room temperature, diluted with CH_2Cl_2 (70 mL), and washed with saturated $NaHCO_3$ solution (30 mL) and then brine (30 mL). The resulting aqueous layers were each re-extracted with CH_2Cl_2 (2 × 70 mL), respectively, and all the organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo to give a yellow oil (47.4 mg, 67% crude yield, ^{1}H NMR of crude product showed a 1:1 mixture of diastereomers **52**/**53**). Flash chromatography on silica gel, eluting with 30:1 $CHCl_3$–MeOH, gave starting material (19.6 mg) and two new products, **52** (12.3 mg, R_f 0.32) and **53** (11.5 mg, R_f 0.26). For **52**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.91 (s, 3 H, 5-CH_3), 1.96, 2.05, 2.07, 2.16 (4 s, 4 × 3 H, 3 $OCOCH_3$ and $NCOCH_3$), 3.37 (s, 3 H, OCH_3), 3.79 (s, 3 H, CO_2CH_3), 5.15 (d, J = 8.6 Hz, 2 H, H-4′ and H-5′), 5.49 (br s, 2 H, H-2′ and H-3′), 5.87 (d, J = 8.7 Hz, 1 H, H-1′), 6.17 (d, J = 8.7 Hz, 1 H, NH), 7.02 (s, 1 H, H-6), 8.08 (br s, 1 H, N^3H); HRMS (FAB/glycerol matrix) m/e 516.1822, M + 1, 516.1829 calcd for $C_{21}H_{30}N_3O_{12}$. For **53**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.95 (s, 3 H, 5-CH_3), 2.01, 2.06, 2.08, 2.10 (4 s, 4 × 3 H, 3 $OCOCH_3$ and $NCOCH_3$), 3.31 (s, 3 H, OCH_3), 3.74 (s, 3 H, CO_2CH_3), 5.00 (dd, J = 8.3 and 3.7 Hz, 1 H, H-5′), 5.30 (m, 3 H, H-2′, H-3′, and H-4′), 5.63 (d, J = 5.0 Hz, 1 H, H-1′), 6.24 (d, J = 8.2 Hz, 1 H), 7.04 (br s, 1 H, H-6), 8.30 (br s, 1 H, N^3H); HRMS (FAB/glycerol matrix) m/e 516.1834, M + 1, 516.1829 calcd for $C_{21}H_{30}N_3O_{12}$.

1,1-Dimethylethyl [*S*-(*R,*S**)]-4-(4-Ethoxy-1-hydroxy-4-oxo-2-butynyl)-2,2-dimethyl-3-oxazolidinecarboxylate (54).** To a stirred −78 °C solution of ethyl propiolate (3.1 mL, 3.00 g, 30.6 mmol) in dry THF (170 mL) was added slowly *n*-BuLi (2.3 M in hexane, 12.8 mL, 29.3 mmol) under an Ar atmosphere. The resulting solution was stirred at −78 °C for a period of 1 h. Then, dry HMPA (6.8 mL, 7.00 g, 39.1 mmol) was added to the above solution, and, after 10 min stirring at −78 °C, a cold −78 °C solution of **5** (4.74 g, 20.7 mmol) in dry THF (17 mL) was added via cannula using positive Ar pressure. The resulting solution was stirred at −78 °C for 1 h at which time the TLC in 2:1 hexanes–EtOAc showed the clean formation of products, $R_{f\,\text{erythro}}$ 0.55 and $R_{f\,\text{threo}}$ 0.50 (char B), at the expense of starting aldehyde, R_f 0.65. The reaction mixture was poured into an ice-cold 1 M NaH_2PO_4 solution (500 mL, pH 6) and extracted with Et_2O (3 × 300 mL). The combined organic layers were washed with brine (500 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give an amber oil (7.03 g, ^{1}H NMR of crude product indicated 13:1 mixture of erythro and threo products). Flash chromatography on silica gel, eluting with 3:1 hexanes–EtOAc, gave pure **54** (4.96 g, 75% yield after purification) as a colorless oil: $[\alpha]_D$ +46.8° (*c* 2.53, $CHCl_3$); IR (neat) 3420, 2230, 1710, 1670 cm^{-1}; ^{1}H NMR (200 MHz, C_6D_6, 60 °C) δ 0.88 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 1.36 (s, 9 H, $C(CH_3)_3$), 1.40, 1.67 (2 s, 2 × 3 H, $C(CH_3)_2$), 3.56 (br t, J = 7.0 Hz, 2 H, H-5a and H-5b), 3.88 (q + br s, J = 6.8 Hz, 3 H, CH_2CH_3 and H-4), 4.43 (br s, 1 H, H-1′), 5.44 (br s, 1 H, OH); ^{13}C NMR (C_6D_6, 60 °C) δ 13.8 (q, −, CH_2CH_3), 26.2 (q, −, $C(CH_3)_2$), 28.3 (q, −, $C(CH_3)_3$), 61.7 (t, +, CH_2CH_3), 62.6 (d, −, C-4), 64.1 (d, −, C-1′), 65.1 (t, −, C-5), 78.0 (s, +, $C(CH_3)_3$), 81.2 (s, +, C-3′), 86.2 (s, +, C-2′), 95.2 (s, +, C-2), 153.2 (s, +, NCO_2), 164.4 (s, +, CO_2Et); MS (% relative intensity, m/e) 254.1031 (4.4, M − CO_2Et, 254.1392 calcd for $C_{13}H_{20}NO_4$), 212 (12.0), 144 (20.2), 128 (34.2), 100 (100). For the threo product **55**: ^{1}H NMR (200 MHz, C_6D_6, 60 °C) δ 0.88 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 1.32 (s, 9 H, $C(CH_3)_3$), 1.33 (br s, 1 H, OH), 1.42, 1.66 (2 s, 2 × 3 H, $C(CH_3)_2$), 3.62 (dd, J = 9.8 and 6.4 Hz, 1 H, H-5a), 3.88 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 3.95 (dd + br s, J = 7.8 and 1.8 Hz, H-5b and H-4), 4.72 (dd, J = 6.9 and 4.3 Hz, H-1′).

1,1-Dimethylethyl [*S*-[(*R,*S**),4*R*]]-1-[α-Methoxy-α-(trifluoromethyl)-α-phenylacetyl]-4-(4,4-dimethoxy-2-butynyl)-2,2-dimethyl-3-oxazolidinecarboxylate (59) and 1,1-Dimethylethyl [*S*-[(*R**,*R**),4*R*]]-1-[α-Methoxy-α-(trifluoromethyl)-α-phenylacetyl]-4-(4,4-dimethoxy-2-butynyl)-2,2-dimethyl-3-oxazolidinecarboxylate (60).** To a solution of **54** (32.8 mg, 0.100 mmol) in distilled CH_2Cl_2 under an Ar atmosphere was added to stock solution of DCC (0.35 M in CH_2Cl_2, 0.35 mL, 0.12 mmol) and a stock solution of DMAP (0.097 M in CH_2Cl_2, 0.1 mL, 0.001 mmol). To this yellow solution was added a stock solution of (*R*)-MTPA (0.171 M in CH_2Cl_2, 0.8 mL, 0.137 mmol), and the resulting suspension was stirred at room temperature for 12 h at which time the TLC in 2:1 hexanes–EtOAc showed the formation of product, R_f 0.67, at the expense of starting alcohol R_f 0.46. The suspension was filtered through a cotton plug, and the clear filtrate was concentrated in vacuo to give the crude product (63.5 mg). Flash chromatography on silica gel, eluting with 6:1 hexanes–EtOAc gave pure **59** (39.6 mg, 81% yield): $[\alpha]_D$ +17.7° (*c* 2.46, $CHCl_3$); IR (neat) 2240, 1760, 1710, 1700, 1690 cm^{-1}; ^{1}H NMR (200 MHz, C_6D_6, 60 °C) δ 0.84 (t, J = 7.2 Hz, CH_2CH_3), 1.39 (s, 12 H, 0.5 $C(CH_3)_2$ and $C(CH_3)_3$), 1.59 (s, 3 H, 0.5 $C(CH_3)_2$), 3.42 (s, 3 H, OCH_3), 3.63 (dd, J = 9.5 Hz and 7.1 Hz, H-5a), 3.84 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 3.92 (dd + br s, J = 9.4 and 2.7 Hz, H-5b and H-4, respectively), 6.38 (br s, 1 H, H-1′), 7.10 (m, 3 H, Ph), 7.68 (d, J = 6.9 Hz, 2 H, Ph); ^{19}F NMR (C_6D_6, 60 °C) δ 5.08. An essentially identical procedure was performed with (*R*)-MTPA to give **60** (47.3 mg, 87% yield): $[\alpha]_D$ +60.7° (*c* 2.68, $CHCl_3$); IR (neat) 2240, 1760, 1710, 1690 cm^{-1}; ^{1}H NMR (200 MHz, C_6D_6, 60 °C) δ 0.84 (t, J = 7.2 Hz, CH_2CH_3), 1.29, 1.35 (2 s, 2 × 3 H, $C(CH_3)_2$), 1.39 (s, 9 H, $C(CH_3)_3$), 3.53 (s, 3 H, OCH_3), 3.60 (dd, J = 9.4 Hz and 6.7 Hz, H-5a), 3.84 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 3.91 (dd, J = 9.4 and 2.7 Hz, H-5b), 3.98 (br s, 1 H, H-4), 6.30 (br s, 1 H, H-1′), 7.09 (m, 3 H, Ph), 7.67 (d, J = 6.9 Hz, 2 H, Ph); ^{19}F NMR (C_6D_6, 60 °C) δ 5.60.

1,1-Dimethylethyl [*S*-(*R,*S**)]-4-(2,5-Dihydro-5-oxo-2-furanyl)-2,2-dimethyl-3-oxazolidinecarboxylate (58).** A solution of **54** (1.06 g, 3.23 mmol) in EtOH (8.0 mL) was cooled to 0 °C, and to this cold solution was added dropwise a 5% KOH solution (11.0 mL, 9.79 mmol). The resulting brown solution was stirred at 0 °C for 10 min and then at room temperature for 50 min when the TLC in 2:1 hexanes–EtOAc showed the disappearance of starting ester, R_f 0.65 (char B), and the formation of a new product at the origin. The ethyl alcohol was removed on a rotary evaporator, and then quinoline (0.1 mL, 0.8 mmol), water (30 mL), and reduced 5% Pd/$BaSO_4$ (160 mg, 0.075 mmol) were added to the basic (pH 12) aqueous solution. The black suspension was stirred under H_2 atmospheric pressure for 5 h when a sample was withdrawn and treated with 1:1 H_2O–AcOH to induce lactonization prior to the TLC analysis. The TLC in 1:1 MeOH–EtOAc + 1 drop of HOAc showed the clean formation of unsaturated lactone, R_f 0.92, at the expense of starting alkyne, R_f 0.70 (char B). The catalyst was filtered off through a Celite pad eluting with water (50 mL) and Et_2O (50 mL). The resulting

two-phase mixture was extracted with Et_2O (2 × 50 mL) to remove the neutral byproducts and then acidified to pH 1–2 with cold 1 N HCl and extracted with CH_2Cl_2 (5 × 100 mL). The extracts were washed with brine (100 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo to give an amber oil (713 mg). The ^1H NMR of this material showed a 4:1 ratio of butenolide to reduced acid. When the amber oil was kept under vacuum (0.5 Torr) over 12 h at room temperature, it spontaneously cyclized to the desired butenolide which was then chromatographed on silica gel, eluting with 1:1 hexanes–EtOAc to afford pure **58** (633 mg, 69% yield) as a colorless oil: $[\alpha]_D$ −41.3° (*c* 1.19, $CHCl_3$); IR (neat) 3100, 1760, 1695, 1600 cm^{-1}; ^1H NMR (200 MHz, C_6D_6, 60 °C) δ 1.32 (s, 9 H, $C(CH_3)_3$), 1.37, 1.53 (2 s, 2 × 3 H, $C(CH_3)_2$), 3.41 (dd, *J* = 9.34 and 5.56 Hz, 1 H, H-5a), 3.52 (br s, 1 H, H-4), 3.70 (d, *J* = 9.3 Hz, 1 H, H-5b), 4.80 (br s, 1 H, H-1′) 5.59 (dd, *J* = 5.76 and 1.92 Hz, 1 H, H-3′), 6.80 (dd, *J* = 5.77 and 1.47 Hz, 1 H, H-2′); ^{13}C NMR (C_6D_6, 60 °C) δ 27.4 (q, –, $C(CH_3)_2$), 28.3 (q, –, $C(CH_3)_3$), 59.8 (d, –, C-4), 64.8 (t, +, C-5), 80.6 (s, +, $C(CH_3)_3$), 82.4 (d, –, C-1′), 94.6 (s, +, C-2), 121.3 (d, –, C-3′), 154.6 (d, –, C-2′), 156.7 (s, +, NCO_2), 171.4 (s, +, CO_2); MS (% relative intensity, *m/e*) 227.0805 (0.6, M − $H_2C{=}C(CH_3)_2$, 227.0794 calcd for $C_{10}H_{13}NO_5$), 210 (11.9), 200 (12.4), 168 (22.0), 144 (20.0), 100 (100.0).

1,1-Dimethylethyl [2*R*-[2α(*R),3β,4β]]-2,2-Dimethyl-4-(tetrahydro-3,4-dihydroxy-5-oxo-2-furanyl)-3-oxazolidinecarboxylate (61).** To a solution of **58** (4.21 g, 14.8 mmol) in Me_2CO (100 mL) + H_2O (40 mL) was added trimethyl *N*-oxide (3.24 g, 29.2 mmol) and OsO_4 solution (8 × 10^{-3} M in 3:1 *t*-BuOH–CCl_4, 36 mL, 0.29 mmol). The homogeneous solution was stirred at room temperature for 22 h when the TLC in 2:1 EtOAc–hexanes showed the formation of diol, R_f 0.27 (char A), along with residual starting **58**, R_f 0.55. To this was added 10% $NaHSO_3$ solution (40 mL), and the resulting solution was stirred for 30 min to decompose excess oxidant. After removing the Me_2CO on the rotary evaporator, the aqueous mixture was extracted with EtOAc (6 × 150 mL), washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give a slightly dark foam (2.96 g). Flash chromatography on silica gel, eluting with 2:1 hexanes–EtOAc first gave unreacted **58** (250 mg) followed by pure **61** (2.15 g, 49% yield based on recovered starting material) as a white foam: $[\alpha]_D$ +31.8° (*c* 0.87, $CHCl_3$); IR ($CHCl_3$) 3550, 1790, 1695, 1675 cm^{-1}; ^1H NMR (400 MHz, C_6D_6, 60 °C, 4.4 mg in 0.4 mL of C_6D_6) δ 1.30 (s, 9 H, $C(CH_3)_3$), 1.33, 1.45 (2 s, 2 × 3 H, $C(CH_3)_2$), 2.20, 2.28 (2 br s, 2 × 1 H, 2 OH, exchanged with D_2O), 3.40 (dd, *J* = 9.4 and 5.3 Hz, 1 H, H-5a), 3.48 (dd, *J* = 9.1 and 5.4 Hz, 1 H, H-4), 3.67 (d, *J* = 9.5 Hz, 1 H, H-5b), 4.27 (d, *J* = 9.5 Hz, 1 H, H-2′), 4.35 (br s, 2 H, H-3′ and H-4′); ^{13}C NMR (C_6D_6, 60 °C) δ 27.8 (q, –, $C(CH_3)_2$), 28.4 (q, –, $C(CH_3)_3$), 57.7 (d, –, C-4), 65.6 (t, +, C-5), 69.4 (d, –, C-4′ or C-3′), 69.8 (d, –, C-3′ or C-4′), 81.3 (s, +, $C(CH_3)_3$), 84.9 (d, –, C-2′), 94.8 (s, +, C-2), 153.2 (s, +, NCO_2), 175.5 (s, +, CO_2); MS (% relative intensity, *m/e*) 302.1246 (8.7, M − CH_3, 302.1240 calcd for $C_{13}H_{20}NO_7$), 244 (11.9), 203 (12.7), 202 (100), 144 (12.5), 100 (55.7).

1,1-Dimethylethyl [2*R*-[2α(*R),3β,4β,5α]]-2,2-Dimethyl-4-[3,4,5-tris(acetyloxy)tetrahydro-2-furanyl]-3-oxazolidinecarboxylate (63).** To a stirred −78 °C solution of **61** (2.0 g, 6.3 mmol) in dry CH_2Cl_2 (14 mL, −78 °C) was added DIBAL (1.5 M in toluene, 14 mL, 21 mmol) over a 15-min period under an Ar atmosphere. After stirring for 1 h at −78 °C, the TLC in EtOAc showed the formation of lactol **62**, R_f 0.40, at the expense of starting lactone, R_f 0.74 (char A). Cold MeOH (7.7 mL) was slowly added to this solution at −78 °C, and this was poured into ice-cold 1 N HCl (300 mL). The resulting mixture was extracted with EtOAc (3 × 300 mL), washed with brine (200 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give a slightly yellow foam (1.40 g). Flash chromatography on silica gel, eluting with EtOAc, gave some **61** (211.3 mg) followed by **62** (1.15 g, 64% yield based on recovered the starting material), as a white foam. This lactol (1.14 g, 3.60 mmol) was dissolved in pyridine (3.0 mL) + Ac_2O (3.0 mL), and the slightly yellow solution was stirred for 5 h at room temperature when the TLC in 1:1 hexanes–EtOAc showed the complete formation of triacetate **63**, R_f 0.62, at the expense of **62**, R_f 0.09 (char A). The solvent was removed in vacuo to give an amber oil (1.57 g). Flash chromatography on silica gel, eluting with 1:1 hexanes–EtOAc, gave **63** (1.53 g, 96% yield, ^1H NMR of product showed a 4:1 ratio of β- and α-anomers) as a colorless oil: $[\alpha]_D$ −1.82° (*c* 0.88, $CHCl_3$); IR ($CHCl_3$) 1750, 1690 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 55 °C) δ 1.49 (s, 9 H, $C(CH_3)_3$), 1.50, 1.51 (2 s, 2 × 3 H, $C(CH_3)_2$), 2.02 (s, 0.75 × 3 H), 2.04 (s, 0.25 × 3 H), 2.08 (s, 0.75 × 3 H), 2.09 (s, 0.25 × 3 H), 2.10 (s, 3 H), 3.92 (dd, *J* = 9.2 and 5.2 Hz, 1 H, H-5a), 4.04 (d, *J* = 8.3 Hz, 1 H, H-5b), 4.05 (br s, 1 H, H-4), 4.28 (t, *J* = 7.5 Hz, 1 H, H-2′), 5.29 (dd, *J* = 6.6 and 4.5 Hz, 0.25 H, H-4′α), 5.42 (d, *J* = 4.8 Hz, 0.75 H, H-4′β), 5.62 (m, 1 H, H-3′), 6.14 (s, 0.75 H, H-5′β), 6.38 (d, *J* = 4.8 Hz, 0.25 H, H-5′α); ^{13}C NMR (C_6D_6, 60 °C) δ 19.8, 20.0, 20.4 (q, –, 3 $OCOCH_3$), 27.4, 27.6 (q, –, $C(CH_3)_2$), 28.4 (q, –, $C(CH_3)_3$) 58.9, 59.9 (d, –, C-4 α and β), 65.5 (t, +, C-5), 70.5, 72.7 (d, –, C-3′ α and β), 70.5, 75.5 (D, –, C-4′), 80.6 (s, +, $C(CH_3)_3$), 82.1, 84.2 (d, –, C-2′ α and β), 94.5 (s, +, C-2), 94.0, 98.8 (d, –, C-5′ α and β), 152.3 (s, +, NCO_2), 168.9 (s, +, $OCOCH_3$); MS (% relative intensity, *m/e*) 430.1712 (2.8, M − CH_3, 430.1713 calcd for $C_{19}H_{28}NO_{10}$), 200 (17.0), 168 (18.5), 144 (22.9), 143 (10.7), 100 (100).

5-Deoxy-5-[[(1,1-dimethylethoxy)carbonyl]amino]-β-D-allofuranose, 1,2,3-Triacetate (64). A solution of **63** (1.56 g, 3.52 mmol) in 70% HOAc (100 mL) was heated to 45 °C and stirred for 4 h at this temperature. The TLC in 1:1 hexanes–EtOAc showed the partial formation of *N*-BOC amino alcohol **64**, R_f 0.24 (char A), along with the starting material, R_f 0.60. Prolonged reaction times resulted in cleavage of the BOC group as indicated by increasing amounts of ninhydrin active material at the base line. The reaction was cooled to room temperature at this point and carefully poured into cold saturated $NaHCO_3$ solution (200 mL). The resulting mixture was extracted with EtOAc (3 × 200 mL), washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give a white foam (769.5 mg). Flash chromatography on silica gel, eluting with 1:1 hexanes–EtOAc, gave unreacted **63** (0.791 g) followed by **64** (0.504 g, 71% yield based on recovered starting material; ^1H NMR of product showed 7:1 ratio of β- and α-anomers) as a colorless oil: $[\alpha]_D$ −9.5° (*c* 0.96, $CHCl_3$); IR ($CHCl_3$) 3400, 1750, 1700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.32 (s, 9 H, $C(CH_3)_3$), 1.93, 1.99, 2.00 (3 s, 3 × 3 H, 3 $OCOCH_3$), 2.07 (br s, 1 H, OH, exchanged with D_2O), 3.65 (m, 3 H, H-5, H-6a, and H-6b), 4.16 (t, *J* = 6.9 Hz, 1 H, H-4), 4.96 (br d, *J* = 7.3 Hz, 1 H, NH, slowly exchanged with D_2O), 5.10 (dd, *J* = 6.6 and 4.6 Hz, 0.12 H, H-2α), 5.23 (d, *J* = 4.8 Hz, 0.88 H, H-2β), 5.32 (dd, *J* = 6.6 and 5.3 Hz, 0.12 H, H-3α), 5.38 (dd, *J* = 6.7 and 5.3 Hz, 0.88 H, H-3β), 6.02 (s, 0.88 H, H-1β), 6.29 (d, *J* = 4.5 Hz, 0.12 H, H-1α); ^{13}C NMR (C_6D_6, for β-anomer) δ 19.6, 19.8, 20.1 (q, –, 3 $OCOCH_3$), 28.5 (q, –, $C(CH_3)_3$), 54.4 (d, –, C-5), 61.3 (t, +, C-6), 72.4 (d, –, C-3 or C-4), 74.8 (d, –, C-4 or C-3), 79.2 (s, +, $C(CH_3)_3$), 80.6 (d, –, C-2), 98.4 (D, –, C-1), 155.7 (s, +, NCO_2), 168.9 (s, +, $OCOCH_3$); MS (% relative intensity, *m/e*) 374.1421 (6.3, M − OCH_3, 374.1451 calcd for $C_{16}H_{24}NO_9$), 272 (21.1), 258 (12.2), 230 (13.7), 214 (25.9), 202 (16.7), 187 (15.2), 186 (16.6), 170 (18.8), 160 (27.9), 158 (17.7), 154 (13.9), 146 (26.8), 144 (13.8), 143 (56.0), 142 (12.6), 128 (15.6), 126 (100), 116 (21.9), 115 (59.1), 102 (96.6).

Methyl 5-Deoxy-5-[[(1,1-dimethylethoxy)carbonyl]amino]-β-D-allofuranuronate, 1,2,3-Triacetate (66). To a solution of **64** (460 mg, 1.14 mmol) in Me_2CO (20 mL) and H_2O (10 mL) was added solid $NaIO_4$ (4.84 g, 22.6 mmol) followed by $RuO_2{\cdot}H_2O$ (33 mg, 0.25 mmol). The greenish suspension was stirred for 24 h at room temperature at which time the TLC in EtOAc showed the disappearance of starting alcohol at R_f 0.30 and the formation of a polar product at the origin (char A). ^iPrOH (10 mL) was added to the reaction mixture, and it was stirred for an additional 30 min to consume excess oxidant. The resulting suspension was filtered through Celite to remove the catalyst + $NaIO_2$, and the yellow filtrate was concentrated in vacuo to give crude **65** as a brown foam (600 mg). This material was dissolved in Et_2O (20 mL) and treated with diazomethane solution (10 mL) until the TLC in 1:1 hexanes–EtOAc showed the clean transformation of the acid to a less polar spot at R_f 0.57 (char A). Excess diazomethane was quenched by dropwise addition of HOAc, and the mixture was diluted with Et_2O (50 mL) and then washed with saturated $NaHCO_3$ solution (20 mL) and brine (20 mL). The resulting three aqueous layers were re-extracted with Et_2O (2 × 50 mL), and the organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a slightly yellow foam (390 mg). Flash chromatography on silica gel, eluting with 2:1 EtOAc–hexanes gave pure **66** (340 mg, 69% yield over two steps, ^1H NMR of the product showed 7:1 ratio of β- and α-anomers),

as a white foam: $[\alpha]_D$ +16.1° (*c* 0.84, $CHCl_3$); IR ($CHCl_3$) 3350, 1750, 1710 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.42 (s, 9 H, $C(CH_3)_3$), 2.03, 2.08, 2.09 (3 s, 3 × 3 H, 3 $OCOCH_3$), 3.74 (s, 3 H, CO_2CH_3), 4.41 (dd, *J* = 7.5 and 4.8 Hz, 1 H, H-4), 4.57 (dd, *J* = 8.7 and 4.8 Hz, 1 H, H-5), 5.30 (d, *J* = 5.0 Hz, 1 H, H-2), 5.37 (d, *J* = 7.5 Hz, 1 H, NH), 5.53 (t, *J* = 6.2 Hz, 1 H, H-3), 6.1 (s, 0.88 H, H-1β), 6.38 (d, *J* = 4.5 Hz, 0.12 H, H-1α); ^{13}C NMR (C_6D_6) δ 19.5, 20.1 (q, –, 3 $OCOCH_3$), 27.9 (q, –, $C(CH_3)_3$), 51.6 (q, –, CO_2CH_3), 55.5 (d, –, C-5), 70.9 (d, –, C-3 or C-4), 74.2 (d, –, C-4 or C-3), 79.7 (s, +, $C(CH_3)_3$), 81.9 (d, –, C-2), 98.0 (d, –, C-1), 155.0 (s, +, NCO_2), 168.6, 168.8 169.4 (s, +, 3 $OCOCH_3$); MS (% relative intensity, *m/e*) 318.0852 (5.0, M – OAc – $H_2C{=}C(CH_3)_2$, 318.0825 calcd for $C_{12}H_{16}NO_9$), 246 (10.7), 245 (84.2), 203 (32.4), 197 (24.2), 155 (12.8), 144 (100), 133 (54.1), 126 (10.9).

Methyl 5-(Acetylamino)-5-deoxy-β-D-allofuranuronate, 1,2,3-Triacetate (68). A solution of **66** (77 mg, 0.18 mmol) in CH_2Cl_2 (3 mL) and TFA (0.3 mL) was stirred for 1 h at room temperature. The TLC in EtOAc showed clean formation of **67**, R_f 0.20 (char A), at the expense of starting material at R_f 0.89. The solvent was evaporated in vacuo to give an amber oil, which was dissolved in pyridine (0.1 mL) and Ac_2O (0.1 mL). The resulting solution was stirred for 1 h at room temperature at which time the TLC in EtOAc showed the clean formation of **68**, R_f 0.56, at the expense of starting amine, R_f 0.14 (char A). The solvents were removed in vacuo to give an amber oil (125 mg). Flash chromatography on silica gel, eluting with 1:1 EtOAc–hexanes, gave some recovered **66** (10 mg) followed by pure **68** (55 mg, 95% yield based on recovered **66**, ^1H NMR of this product showed a 7:1 ratio of β- and α-anomers, see below), as a white foam: $[\alpha]_D$ +33.8° (*c* 0.83, $CHCl_3$); IR ($CHCl_3$) 3350, 1750, 1675 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.93, 1.97, 2.00, 2.10 (4 s, 4 × 3 H, 3 $OCOCH_3$, $NCOCH_3$), 3.66 (s, 3 H, CO_2CH_3), 4.33 (dd, *J* = 7.4 and 4.2 Hz, 1 H, H-4), 4.81 (dd, *J* = 8.4 and 4.3 Hz, 1 H, H-5), 5.20 (d, *J* = 4.9 Hz, 1 H, H-2), 5.46 (dd, *J* = 7.4 and 5.0 Hz, 1 H, H-3), 5.98 (s, 0.88 H, H-1β), 6.24 (d, *J* = 4.5 Hz, 0.12 H, H-1α), 6.48 (d, *J* = 8.5 Hz, 1 H, NH); ^{13}C NMR (C_6D_6) δ 19.6, 19.8, 20.1, 21.9 (q, –, 3 $OCOCH_3$, $NCOCH_3$), 51.7 (q, –, CO_2CH_3), 53.7 (d, –, C-5), 70.7 (d, –, C-3 or C-4), 74.3 (d, –, C-4 or C-3), 82.1 (d, –, C-2), 98.0 (d, –, C-1), 168.1, 168.7, 169.0, 169.2 (s, +, $OCOCH_3$, $NCOCH_3$, CO_2CH_3).

Methyl 5-(Acetylamino)-1,5-dideoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1(2*H*)-pyrimidinyl)-β-D-allofuranuronate, 2,3-Diacetate (Synthetic 39). To a solution of **68** (31 mg, 0.084 mmol) in dry $(CH_2Cl)_2$ (3 mL) was added sequentially bis-silylated thymine **41** (78 mg, 0.289 mmol) and TMSOTf (0.10 mL, 0.118 g, 0.531 mmol) under an Ar atmosphere. The yellow solution was refluxed at 95 °C for 30 min when the TLC in 13:1 $CHCl_3$–MeOH showed the formation of a product at R_f 0.29 (which matched an authentic sample of **39**) and a UV-inactive product at R_f 0.45, at the expense of starting material at R_f 0.36 (char A). The reaction was cooled to room temperature, diluted with CH_2Cl_2 (30 mL), and then washed with saturated $NaHCO_3$ solution (20 mL) and brine (20 mL). The resulting two aqueous layers were re-extracted with CH_2Cl_2 (2 × 30 mL), and all organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo to give a slightly yellow foam (33 mg). Flash chromatography on silica gel, eluting with 30:1 $CHCl_3$–MeOH resulted in the isolation of a compound identified as **70** (14.6 mg, 55.3% yield) followed by pure **39** (8.6 mg, 23% yield), both as white foams. For synthetic **39**: $[\alpha]_D$ +35.6° (*c* 0.83, $CHCl_3$); IR ($CHCl_3$) 3380, 1740, 1685 cm^{-1}. The ^1H NMR and HRMS spectra were identical with those obtained for an authentic sample of **39** (vide supra). For the bicyclic compound **70**: $[\alpha]_D$ –57.7° (*c* 1.16, $CHCl_3$); IR ($CHCl_3$): 1750, 1670 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.10, 2.18 (2 s, 6 H and 3 H, 2 $OCOCH_3$, $NCOCH_3$), 3.80 (s, 3 H, CO_2CH_3), 4.37 (d, *J* = 4.7, 1 H), 4.92 (d, *J* = 4.6 Hz, 1 H), 5.14 (s, 2 H), 5.63 (s, 1 H, H-1); ^{13}C NMR (C_6D_6) δ 19.5, 21.0 ($OCOCH_3$, $NCOCH_3$), 52.0, 58.7, 71.7, 75.2, 80.9, 89.4 (C-1), 168.9; MS (% relative intensity, *m/e*) 316.1029 (12.2, M^+ + 1, 316.1032 calcd for $C_{13}H_{18}NO_8$), 272 (30.1), 256 (41.4), 228 (52.3), 214 (73.4), 186 (79.1), 182 (43.6), 172 (89.9), 171 (56.0), 157 (95.5), 154 (37.3), 144 (63.4), 142 (49.9), 140 (31.6), 126 (100), and 115 (76.1).

Synthetic *N*-Acetylthymine Polyoxin C (38). To a solution of synthetic **39** (3.6 mg, 0.0082 mmol) in 1:1 H_2O–THF (5 mL) in an ice bath was added a stock solution of $LiOH{\cdot}H_2O$ (0.27 M, 0.1 mL, 0.027 mmol). The slightly yellow solution was stirred at 0 °C for 1 h when the TLC in 2:1:1 *n*-BuOH–H_2O–HOAc showed the formation of a product at R_f 0.52 at the expense of starting material. The reaction mixture was acidified with 0.1 N HCl to a pH of 1–2, and then all solvents were removed in vacuo to give a white solid containing LiCl (7.0 mg). The ^1H NMR spectrum of this sample matched that of authentic *N*-acetylthymine polyoxin C (**38**) contaminated with NaCl (vide supra).

Methyl 5-Deoxy-5-[[(phenylmethoxy)carbonyl]amino]-β-D-allofuranuronate, 1,2,3-Triacetate (69). A solution of **65** (340 mg, 0.790 mmol) in CH_2Cl_2 (20 mL) and TFA (2 mL) was stirred for 1 h at room temperature. The TLC in EtOAc showed clean formation of **67**, R_f 0.16 (char A), at the expense of starting **66** at R_f 0.90. The solvent was evaporated in vacuo to give an amber oil (540 mg), which was dissolved in dioxane (15 ml) and cooled to 0 °C. To this solution was added 7% $NaHCO_3$ solution (5 mL) followed benzyl chloroformate (0.25 mL, 2.79 mmol), and the resulting suspension was stirred for 50 min at room temperature at which time the TLC in EtOAc showed the clean formation of **69**, R_f 0.93, at the expense of starting amine, R_f 0.16 (char A). The reaction mixture was diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give a white foam (410 mg). Flash chromatography on silica gel, eluting with 2:1 EtOAc–hexanes, gave pure **69** (310 7g, 84% yield over two steps, ^1H NMR of this product showed a 7:1 ratio of β- and α-anomers, see below), as a white foam: $[\alpha]_D$ +16.8° (*c* 0.62, $CHCl_3$); IR ($CHCl_3$) 3420, 1750, 1720, 1715 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.01 (s, 6 H, 2 $OCOCH_3$), 2.10 (s, 3 H, $OCOCH_3$), 3.75 (s, 3 H, CO_2CH_3), 4.45 (dd, *J* = 7.6 and 4.4 Hz, 1 H, H-4), 4.67 (dd, *J* = 8.7 and 4.3 Hz, 1 H, H-5), 5.11 (s, 2 H, CH_2Ph), 5.28 (d, *J* = 4.7 Hz, 1 H, H-2), 5.54 (m, 2 H, H-3 and NH), 6.08 (s, 0.88 H, H-1β), 6.36 (d, *J* = 4.3 Hz, 0.12 H, H-1α), 7.33 (s, 5 H, C_6H_5); ^{13}C NMR (C_6D_6) 25.2, 24.6, 24.7 (q, –, 3 $OCOCH_3$), 56.9 (q, –, CO_2CH_3), 61.1 (d, –, C-5), 71.4 (t, +, CH_2Ph), 76.0 (d, –, C-3), 79.0 (d, –, C-2), 86.2 (d, –, C-4), 103.1 (d, –, C-1), 133.0, 122.5 (d, –, Ph), 142.1 (d, –, Ph), 162.2 (s, +, $OCOCH_3$, NCO_2), 174 (s, +, CO_2CH_3); MS (% relative intensity, *m/e*) 407.1223 (2.6, M – HOAc, calcd for $C_{19}H_{21}NO_9$ 407.1216), 245 (68.9), 203 (19.5), 197 (12.9), 162 (16.9), 155 (15.0), 143 (100), 127 (10.4).

Methyl 1,5-Dideoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1-(2*H*)-pyrimidinyl)-5-[[(phenylmethoxy)carbonyl]amino]-β-D-allofuranuronate, 2,3-Diacetate (71) and Methyl 5-Amino-1,5-dideoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1-(2*H*)-pyrimidinyl)-β-D-allofuranuronate, 2,3-Diacetate (72). To a solution of **69** (299 mg, 0.640 mmol) in dry $(CH_2Cl)_2$ (27 mL) was added sequentially bis-silylated thymine **41** (583 mg, 2.15 mmol) and TMSOTf (0.76 mL, 0.871 g, 3.92 mmol) under an Ar atmosphere. The slightly yellow solution was refluxed at 100 °C for 30 min when the TLC in 13:1 $CHCl_3$–MeOH showed the formation of two UV-active products, R_f 0.58 (*N*-Cbz nucleoside **71**) and R_f 0.49 (N-deprotected nucleoside **72**), at the expense of starting material at R_f 0.64. The reaction was cooled to room temperature, diluted with CH_2Cl_2 (200 mL), and then washed with saturated $NaHCO_3$ solution (150 mL) and brine (100 mL). The resulting two aqueous layers were re-extracted with CH_2Cl_2 (2 × 100 mL), respectively, and all organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo to give a slightly yellow foam (320 mg). Flash chromatography on silica gel, eluting with 30:1 $CHCl_3$–MeOH, gave pure **71** (272 mg, mp 80–82 °C, 85% yield) along with **72** (34.6 mg, 14% yield), as white foams. For **71**: $[\alpha]_D$ +19.8° (*c* 0.56, $CHCl_3$); IR ($CHCl_3$) 3380, 1750, 1715, 1690 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.87 (d, *J* = 0.7 Hz, 3 H, 5-CH_3), 2.06 (s, 6 H, 2 $OCOCH_3$), 3.78 (s, 3 H, CO_2CH_3), 4.37 (dd, *J* = 4.7 and 3.5 Hz, 1 H, H-4′), 4.81 (dd, *J* = 8.5 and 3.7 Hz, 1 H, H-5′), 5.11 (s, 2 H, CH_2Ph), 5.24 (t, *J* = 6.0 Hz, 1 H, H-2′), 5.50 (t, *J* = 5.9 Hz, 1 H, H-3′), 5.79 (d, *J* = 8.1 Hz, 1 H, NH), 5.92 (d, *J* = 5.6 Hz, 1 H, H-1′), 7.03 (d, *J* = 0.6 Hz, 1 H, H-6), 7.32 (br s, 5 H, C_6H_5), 8.55 (br s, 1 H, N^3H, exchanged with D_2O); ^{13}C NMR (acetone-d_6) δ 10.8 (q, –, 5-CH_3), 18.7 (q, –, $OCOCH_3$), 51.2 (q, –, CO_2CH_3), 54.5 (d, –, C-5′), 65.5 (t, +, CH_2Ph), 69.0 (d, –, C-3′ or C-4′), 71.3 (d, –, C-4′ or C-3′), 80.2 (d, –, C-2′), 87.6 (d, –, C-1′), 110 (s, +, C-5), 126.9, 127.1, 127.5 (d, –, Ph), 135.8 (d, –, C-6), 136.0 (s, +, Ph), 149.0 (s, +, C-2), 155.4 (s, +, NCO_2), 162.5 (s, +, C-4), 168.3, 168.4 (s, +, $OCOCH_3$), 168.5 (s, +, CO_2CH_3); MS (FAB/glycerol, *m/e*) 534.1715, M + 1,

534.1724 calcd for $C_{24}H_{28}N_3O_{11}$. For **72**: IR ($CHCl_3$) 3380, 3020, 1740, 1690 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.78 (s, 3 H, 5-CH_3), 2.00, 2.07 (2 s, 2 × 3 H, $OCOCH_3$), 3.63 (s, 3 H, CO_2CH_3), 3.74 (d, J = 5.0 Hz, 1 H, H-5′), 4.18 (t, J = 4.12 Hz, 1 H, H-4′), 5.37 (dd, J = 5.89 and 3.24 Hz, 1 H, H-3′), 5.44 (t, J = 6.3 Hz, 1 H, H-2′), 5.95 (d, J = 6.3 Hz, 1 H, H-1′), 7.83 (s, 1 H, H-6); ^{13}C NMR (acetone-d_6) δ 11.0 (q, –, 5-CH_3), 18.6, 18.9 (q, –, $OCOCH_3$), 50.9 (q, –, CO_2CH_3), 63.2 (d, –, C-5′), 70.2 (d, –, C-3′ or C-4′), 71.4 (d, –, C-4′ or C-2′), 82.8 (d, –, C-2′), 84.2 (d, –, C-1′), 109.8 (s, +, C-5), 134.3 (d, –, C-6), 149.8 (s, +, C-2), 162.2 (s, +, C-4), 167.7, 168.3 (s, +, 2 $OCOCH_3$), 170.9 (s, +, CO_2CH_3); HRMS (FAB/glycerol) m/e 400.1346, M + 1, 400.1356 calcd for $C_{16}H_{22}N_3O_9$.

5-Amino-1,5-dideoxy-1-(3,4-dihydro-5-methyl-2,4-dioxo-1(2*H*)-pyrimidinyl)-β-D-allofuranuronic Acid (Synthetic Thymine Polyoxin C) (4). To a 0 °C solution of **71** (88.7 mg, 0.166 mmol) in THF (8 mL) and H_2O (1.5 mL) was added solid $LiOH·H_2O$ (24 mg, 0.57 mmol). The resulting yellow solution was stirred at 0 °C for 1 h at which time the TLC in 5:4:1 $CHCl_3$–MeOH–H_2O showed the formation of **73**, R_f 0.59, at the expense of starting material, R_f 0.96 (char A). The reaction was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL) to remove any nonacidic material, and the resulting basic solution was cooled to 0 °C and acidified to pH = 2–3 with 1 N HCl. This mixture was extracted with EtOAc (6 × 20 mL), and all organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo to give **73** a yellow solid (49 mg). To a solution of this material (42.1 mg, 0.10 mmol) in MeOH (4.5 mL) was added 5% Pd/C (33 mg). The black suspension was stirred under H_2 atm for 4 h when the TLC in 5:4:1 $CHCl_3$–MeOH–H_2O showed the formation of thymine polyoxin C (**4**), R_f 0.21 (char A), at the expense of starting material at R_f 0.51. The reaction mixture was filtered through a pad of Celite + activated carbon eluting with hot H_2O (3 × 10 mL), and the filtrate was concentrated in vacuo to give synthetic **4** as a yellow solid (20.8 mg, 54% yield): mp 182–185 °C, (shr 145 °C) [authentic **4**: mp 190–194 °C (shr at 170 °C), lit.[1a] mp 240–244 °C, lit.[4b] mp 242–244 °C]; $[\alpha]_D$ +8.0° (c 0.37, H_2O) [lit.[1a] $[\alpha]_D$ +8.7° (c 0.208, H_2O), lit.[4b] $[\alpha]_D$ +8.2° (c 0.7, H_2O)]; ^1H NMR (400 MHz, D_2O + DCl, pD = 0.68) δ 1.72 (s, 3 H, 5-CH_3), 4.20 (dd, J = 6.9 and 2.6 Hz, 1 H, H-4′), 4.27 (dd, J = 6.1 and 4.0 Hz, 1 H, H-2′), 4.40 (d, J = 2.6 Hz, 1 H, H-5′), 4.53 (t, J = 6.5 Hz, 1 H, H-3′), 5.60 (d, J = 3.9 Hz, 1 H, H-1′), 7.17 (s, 1 H, H-6). This ^1H NMR spectrum was identical with one obtained with authentically derived thymine polyoxin C (vide supra). ^{13}C NMR (2:1 D_2O–DMSO-d_6) δ 11.8 (q, –, 5-CH_3), 55.7 (d, –, C-5′), 69.8 (d, –, C-3′), 72.6 (d, –, C-4′), 83.1 (d, –, C-2′), 89.2 (d, –, C-1′), 111.2 (s, +, C-5), 138.0 (d, –, C-6), 151.7 (s, +, C-2), 165.4 (s, +, C-4), 169.3 (s, +, CO_2H); HRMS (FAB/glycerol) m/e 302.0999, M + 1, 302.0988 calcd for $C_{11}H_{16}N_3O_7$.

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Synthesis of Cyclopentanobenz[*a*]anthracene Compounds Related to Carcinogenic Benz[*a*]anthracene and Cholanthrene Hydrocarbons

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Syntheses of benz[*e*]aceanthrylene (**4a**), 8-methylbenz[*e*]aceanthrylene (**4b**), and their 1,2-dihydro derivatives (**3a,b**), as well as 6-methylbenz[*j*]aceanthrylene (**5a**) and its 1,2-dihydro derivative (**2b**) from benz[*a*]anthracene-7,12-dione are described. Compounds **2b**, **3b**, **4b**, and **5b**, all of which contain a methyl group in nonbenzo bay region position, are predicted to be relatively potent carcinogens.

Methyl substitution in the 7- or 12-positions of benz[*a*]anthracene (BA) markedly enhances its carcinogenic activity,[1-5] and fusion of a cyclopentano ring in this same molecular region has a similar effect. Thus, while 7-methyl-BA (**1b**), 12-methyl-BA (**1c**), 7,12-dimethyl-BA (**1d**), cholanthrene[6] (**2a**), 6-methylcholanthrene (**2b**), 3-methylcholanthrene (**2c**), and 3,6-dimethylcholanthrene (**2d**) are relatively potent tumorigens, the parent hydrocarbon (**1a**) exhibits only weak borderline activity.[1,2]

In order to probe these structure–activity relationships further, we have undertaken the synthesis of several benz[*a*]anthracene derivatives that combine these structural features, i.e. a methyl group and a fused cyclopentano ring in the meso region. We now report the synthesis of 1,2-dihydrobenz[*e*]aceanthrylene (**3a**), 8-methyl-1,2-dihydrobenz[*e*]aceanthrylene (**3b**), **2b**, and the related fully unsaturated hydrocarbons benz[*e*]aceanthrylene (**4a**), 8-methylbenz[*e*]aceanthrylene (**4b**), and 6-methylbenz[*j*]aceanthrylene (**5b**). On the basis of current concepts concerning the mechanisms of metabolic activation and cancer induction by polycyclic hydrocarbons,[2,7] all of these hydrocarbons may be predicted to exhibit mutagenic and/or tumorigenic activity. In particular, compounds **2b**,

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