Fully Synthetic Stereoselective Routes to the Differentially Protected Subunits of the Tunicamycins

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Abstract: Total syntheses of the two subunits corresponding to tunicamycins have been achieved. One of the key steps involves a cyclocondensation reaction of 7-carbon aldehydo nucleoside with activated diene **8** under catalysis with stannic chloride (see **7** + **8** → **9a,b**). Stereospecific Fitzsimmons cycloadditions of dibenzyl azodicarboxylate to galactal **12** and glucal **22** simplified construction of the amino pyranose systems.

The tunicamycins, isolated from a variety of fermentation sources,[1,2] comprise a family of closely related nucleosides with a novel structural pattern. The most distinguishing feature is the backbone sugar of 11 carbon atoms. This undecose, which is termed "tunicamine", has not been successfully retrieved by degradation of a tunicamycin. Its 11 carbon atoms are deployed to form a furanose ring and a pyranose ring separated by a substituted "ethano" spacer. The furano moiety is of the D-ribo configuration and the pyrano substructure can be seen as belonging to the D-2-deoxy-2-acetamidogalactose series. The nucleoside-like attachment of the uracil base is to the ribose ring. The substructure in which the tunicamine and uracil subunits are attached is called a "tunicaminyluracil". In the tunicamycins an additional carbohydrate residue, i.e., a D-2-deoxy-2-acetamidoglucose unit is joined to the anomeric carbon of the galactosamine system, through a novel β,α-trehalose linkage. The acyl groups of the nitrogens of the galactosamine and glucosamine residues groups are quite different. In the glucosamine residue, the nitrogen is encountered as its *N*-acetyl derivative. In the case of the galactosamine residue, the nitrogen is encountered in amidic linkage to one of a variety of closely related long-chain unsaturated acids. The structural diversity of the tunicamycins lies in the structural diversity of these acyl groups. The similarity of the tunicamycin congeners occasions great difficulty in their purification.[3]

However, it is not only the novelty of their structures that accounts for the interest that continues to be lavished on the tunicamycins. The inhibitory properties of tunicamycins on the biosynthesis of polysaccharides and glycoproteins are extraordinary.[4] Not only is this inhibition associated with potential antibiotic, antiviral, and even antitumor capabilities,[5] but, minimally, it marks these compounds as considerable resources for studying the fine details of the bioprocessing and organization of complex carbohydrates.[6] While the entire story has not yet been elucidated, it does seem as if the bulk of the activity of the tunicamycins resides in their ability to inhibit the transferase enzymes involved in processing UDP glucose and UDP galactose derivatives.

The structural and biological novelty of the tunicamycins also renders them worthy targets in organic synthesis. Several groups have described results arising from such synthetic studies. Given our interests in the field of complex monosaccharides,[7] it was not surprising that our laboratory would participate in this area.[8]

Even if the problem is approached via coupling of a preformed ribose derivative with a preformed galactose derivative, there remains a significant issue of stereochemistry involving the realization of the proper configuration at C5′ of the ethano bridge. Such an approach was encompassed in a most interesting disclosure from Corey and associates.[9] The actual construction of tunicaminyluracil, protected as shown in structure **21**, was accomplished by Suami and co-workers in 1983.[10] This partial synthesis of Suami involved coupling of a preformed ribose derivative with a suitably differentiated galactose-derived intermediate. The synthesis was not stereoselective in the construction of C5′ stereogenic center. An important feature of the Suami synthesis was that the amino group of the galactosamine-like section emerged as its *N*-Cbz derivative. Accordingly, it would be possible to introduce the long-chain unsaturated acyl function at this nitrogen in the final stages of a tunicamycin synthesis. The following year Suami and co-workers reported the successful use of the anomeric chloro derivative of the tunicaminyluracil residue as a "glycosylating agent" vis à vis a suitable 2-deoxy-2-acetamidoglucose glycosyl acceptor, bearing a free hydroxyl group at its anomeric carbon.[11,12] This coupling provided the novel trehalose linkage of the intact antibiotic. Subsequent deprotection and acylation of the glucosamine residue set the stage for the first complete synthesis of a naturally occurring tunicamycin (Figure 1).

In contrast to the furanose–pyranose coupling scheme of Suami, we undertook a total synthesis[13] of the aglycon.[8] Our concept involved the use of stereoselective addition[14] and condensation reactions[15] to convey the chirality of a ribose derivative (i) to the emerging side chain and, eventually, to the galactose moiety of the tunicaminyluracil target. Thus, aldehyde ii, derived initially from a stereospecific allylation of aldehyde i, served as a substrate in a cyclocondensation reaction[16] to allow access to bis(saccharide)

(1) Isolation: Takatsuka, A.; Arimak, Tamura, G. *J. Antibiot.* **1971**, *24*, 215. Takatsuka, A.; Tamura, G. *Ibid.* **1971**, *24*, 224. Takatsuka, A.; Tamura, G. *Ibid.* **1971**, *24*, 232. Takatsuka, A.; Tamura, G. *Ibid.* **1971**, *24*, 785.
(2) Structure elucidation: Ito, T.; Takatsuki, A.; Kawamura, K.; Saito, K.; Tamura, G. *Agric. Biol. Chem.* **1980**, *44*, 695.
(3) Eckardt, K. *J. Nat. Prod.* **1983**, *46*, 544.
(4) Schwartz, R. T.; Datema, R. *Trends Biochem. Sci.* **1980**, *65*. Elbein, A. D. *Ibid.* **1981**, 219.
(5) Morin, M. J.; Bernacki, R. *J. Cancer Res.* **1983**, *43*, 1669.
(6) *Tunicamycin*; Japan Scientific Press: Tokyo, 1982.
(7) Danishefsky, S. J.; DeNinno, M. P. *Angew. Chem.* **1987**, *99*, 15.
(8) For a preliminary communication describing the route from a methyl riboside derivative to peracetyltunicaminyluracil, see: Danishefsky, S.; Barbachyn, M. *J. Am. Chem. Soc.* **1985**, *107*, 7761.
(9) Corey, E. J.; Samuelson, B.; Luzzio, F. A. *J. Am. Chem. Soc.* **1984**, *106*, 3682.
(10) Suami, T.; Sasai, H.; Matsuno, K. *Chem. Lett.* **1983**, 819.
(11) Suami, T.; Sasai, H.; Matsun, K.; Suzuki, N.; Fukuda, Y.; Sakanaka, O. *Tetrahedron Lett.* **1984**, *25*, 4533. Suami, T.; Sasai, H.; Matsuno, K.; Suzuki, N. *Carbohydr. Res.* **1985**, *143*, 85. In this work Suami uses the 3-propionate ester corresponding to the 3-OTBS ether of our fully synthetic material. We also were unable to couple the very same propionate substrate used by Suami.
(12) For a recent disclosure with a similar trehalose coupling using similar substrates, see: Kominato, K.; Ogawa, S.; Suami, T. *Carbohydr. Res.* **1988**, *174*, 360.
(13) A cyclocondensation route to the ribosyl precursor, which eventually led to aldehyde **24** (vide infra), had been described.[8] Therefore, a totally synthetic route to **17** had been developed.
(14) Danishefsky, S.; DeNinno, M. P.; Phillips, G. B.; Zelle, R. E.; Lartey, P. *Tetrahedron* **1986**, *42*, 2809.
(15) Danishefsky, S. J. *Aldrichimica Acta* **1986**, *19*, 59.

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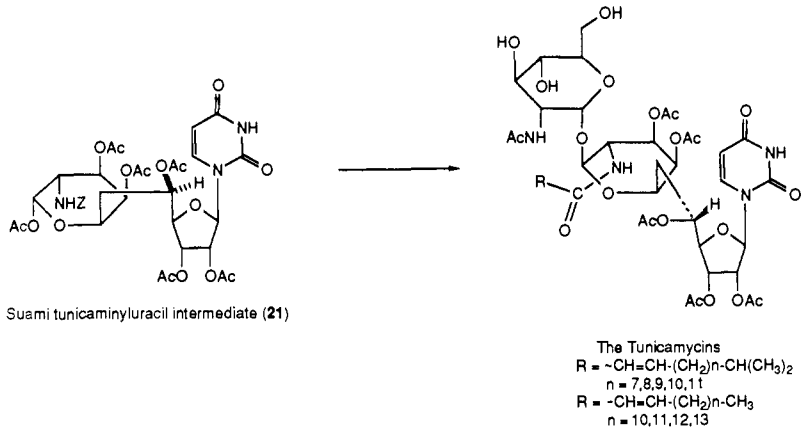

Figure 1.

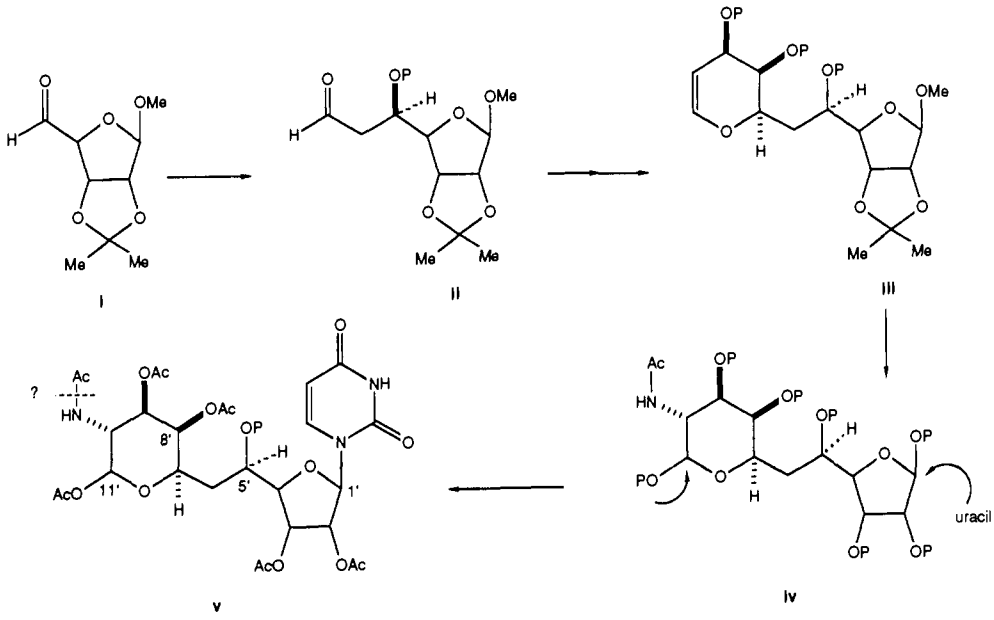

Figure 2.

iii.[17] From this point, selective functional group manipulations in the galactal region allowed us to reach intermediate iv and, eventually, the peracetyltunicaminyluracil system v.

There were, however, several serious weaknesses in that synthesis. First, the functional group manipulations from galactal derivative iii to the fully functionalized undecose derivative iv were far from efficient. Even more serious were the difficulties encountered in differentiating between the anomeric center of the "ribosyl" and "galactosyl" sectors in this intermediate. In fact, we were unable to develop chemistry that successfully dealt with this selectivity challenge. It was necessary to accept serious mixtures in the concluding phase of the effort, though eventually it proved possible to identify the ribosyl sector for nucleoside formation. A synthesis of the peracetyl derivative v was completed[8] (see Figure 2).

In view of the extreme difficulties associated with carrying out the synthesis, it was deemed impractical to attempt to distinguish the protecting group of the nitrogen on the galactosamine residue from those on the oxygens. The peracetyl pattern of substitution was generated. Of course, this would create additional difficulties if the goal were a total synthesis of tunicamycin itself, for in such a circumstance it would be necessary to accomplish a potentially awkward N-deacylation reaction. Owing to the complications in accumulating substantial amounts of fully synthetic compound v, the feasibility of such a deacylation was not investigated. Also left for the future was the matter of the final trehalose glycosidic attachment.

Mindful of the importance of the area, and cognizant of the difficulties encountered in our initial exploration, we set about to investigate a sharply modified route. In this instance, our starting material would be uracil-derived aldehyde of the type vi. *The hope was to sustain the nucleoside bond at the required ribosyl residue throughout the course of the synthesis. The ability to manage this functionality in the face of the subsequent operations would be one of the major challenges of the effort.* Given success in this regard, the aldehyde might be converted to a bis(saccharide) glycal shown as structure vii. Presumably, the steps to achieve this overall transformation would not be radically dissimilar from those that were used in the previous synthesis wherein the simpler aldehyde i was eventually converted to the bis(saccharide) glycal derivative iii[8] (Figure 3).

It was further hoped to exploit some new chemistry for the introduction of the galactosamine functionality into glycal vii. The idea was to take advantage of the Fitzsimmons cycloaddition reaction of azodicarboxylates with glycals[18] to achieve a concise solution to the stereochemical problem of the galactose segment. With this streamlined route, we hoped to reach the *N*-Cbz derivative analogous to the Suami system[10] or, in fact, that very

(16) Danishefsky, S.; Pearson, W.; Harvey, D.; Maring, C.; Springer, J. *J. Am. Chem. Soc.* **1985**, *107*, 1256.
(17) Danishefsky, S.; Maring, C.; Barbachyn, M.; Segmuller, B. *J. Org. Chem.* **1984**, *49*, 4584.
(18) Fitzsimmons, B. S.; Leblanc, Y.; Rokach, J. *J. Am. Chem. Soc.* **1987**, *109*, 285.

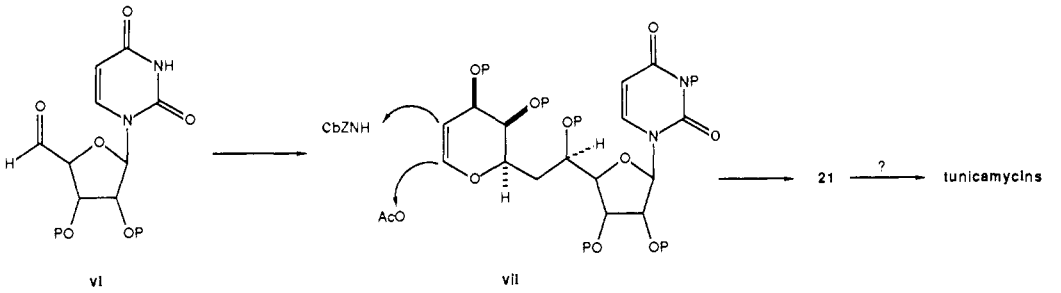

Figure 3.

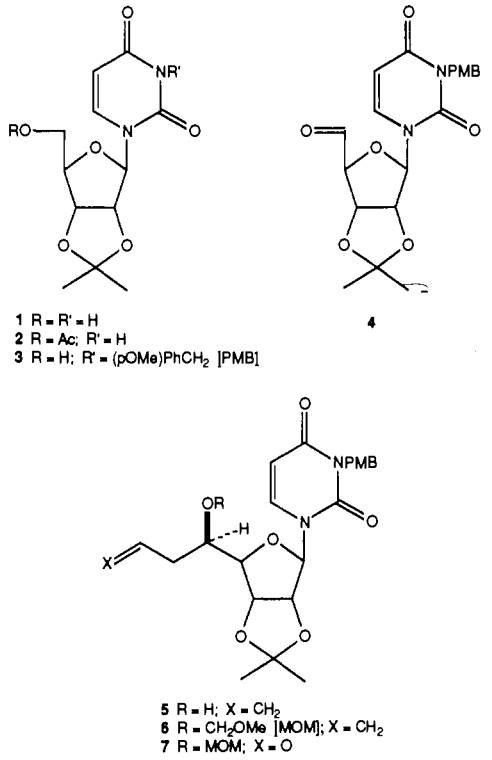

Figure 4.

compound. From that point we might then independently investigate the critical glycosylation reaction required to reach the final natural products.

Results

In this paper we provide a full account of our findings pursuant to this approach. Our starting material was the commercially available uridine derivative **1**[19] (Figure 4). Clearly, it would not be possible to carry the uracil residue in the form of its free NH group throughout the course of the synthesis. We settled upon a *p*-methoxybenzyl protecting group.[20] As will be seen, the durability of the PMB group throughout a range of reactions was one of the important findings in our investigations. Treatment of compound **1** with acetic anhydride–triethylamine gave the acetate **2** which, upon reaction with sodium hydride and *p*-methoxybenzyl bromide in DMF, followed by deacylation with potassium carbonate–methanol, afforded compound **3** in 86% overall yield. The oxidation of compound **3** to aldehyde **4** was best accomplished through a Swern type protocol.[21,22] The reaction could be carried out in large scale, and the required aldehyde was available in 79% yield. An important feasibility test as to the stability of the nucleoside linkage was successfully passed when aldehyde **4**, reacted smoothly with allyltrimethylsilane in the presence of BF_3 etherate. The homoallylic alcohol **5** was produced as a nearly homogeneous material. This type of reaction had been previously demonstrated in our laboratory with a variety of simple methyl glycoside and riboside derivatives.[14] The trace amounts (ca. 5%) of C5′ stereoisomer produced in this reaction were removed after subsequent steps.

The decision as to the proper protecting group for the new C5′ alcohol proved to be an important feature of the synthesis. After considerable trial and error (vide infra and see Figure 9), it was found that optimum success could be achieved via the methoxymethyl (MOM) derivative **6**. This compound was obtained in 96% yield from **5** under standard conditions. The time was at hand to secure the required C7′ aldehyde by oxidative fragmentation of the allyl residue. This was accomplished by hydroxylation with osmium tetroxide and subsequent treatment with lead tetraacetate. The MOM aldehyde **7** was thus available in 87% yield, as shown in Figure 4. Compound **7** was not our initial choice. The thinking that led us to its use will be described at the end of this account.

Cyclocondensation of aldehyde 7 with the previously described diene **8** was carried out under mediation by stannic chloride in methylene chloride at −78 °C. The principal product from this process was a trans silylated aldol derivative shown as **8a**. The structure of **8a** was not fully secured. Rather, the material so obtained was treated with 5% HF in acetonitrile at 0 °C. This led to a 61% overall yield of the dihydropyrone mixture **9a,b**. We note that the stereoselectivity in the cyclocondensation reaction was less than was achieved in the earlier series starting with the methyl glycoside (see Figure 2).[8] We will return to some of the intricacies involved in the facial sense of the cyclocondensation reaction after we relate the outcome of the total synthesis itself.

Examination of the NMR spectrum of the **9a,b** mixture indicated that these two components each had a cis relationship around the newly formed dihydropyrone ring. We had no way to rigorously show that the major product corresponded to the configuration (i.e., D-galacto) required to reach our target structure. Furthermore, it proved quite difficult to separate the two compounds at this stage. Accordingly, the mixture was carried further through a Luche-like reduction.[23] At this stage it was possible to obtain the major product in 64% yield as a homogeneous entity. We reiterate that one could not definitively assign the stereochemistry in the galactal sector relative to that of the ribose ring. An equivalent way of stating the matter is that given the D configuration for the ribosyl ring, the absolute configuration of the "galactyl" sector could not be known with certainty. We carried this major product further. The next step involved cleavage of the benzoyl function with potassium carbonate in methanol to provide compound **11**, which, upon acetonization with methyl isopropenyl ether afforded the desired **12** (see Figure 5).

With compound **12** in hand, we explored a novel cycloaddition reaction of azodicarboxylates with glycals, discovered by Fitzsimmons and colleagues.[18] Applied to the case at hand, this reaction would allow for the introduction of the required α-disposed amino function of the galactosamine sector. In the event, compound **12** was treated with dibenzyl azodicarboxylate under photolysis

(19) Aldrich Chemical Co.
(20) Cf.: Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 882.
(21) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(22) For a previous preparation of a related aldehyde, see Corey, E. J.; Samuelson, B. *J. Org. Chem.* **1984**, *49*, 4735.
(23) Luche, J. L.; Gemal, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 5848.

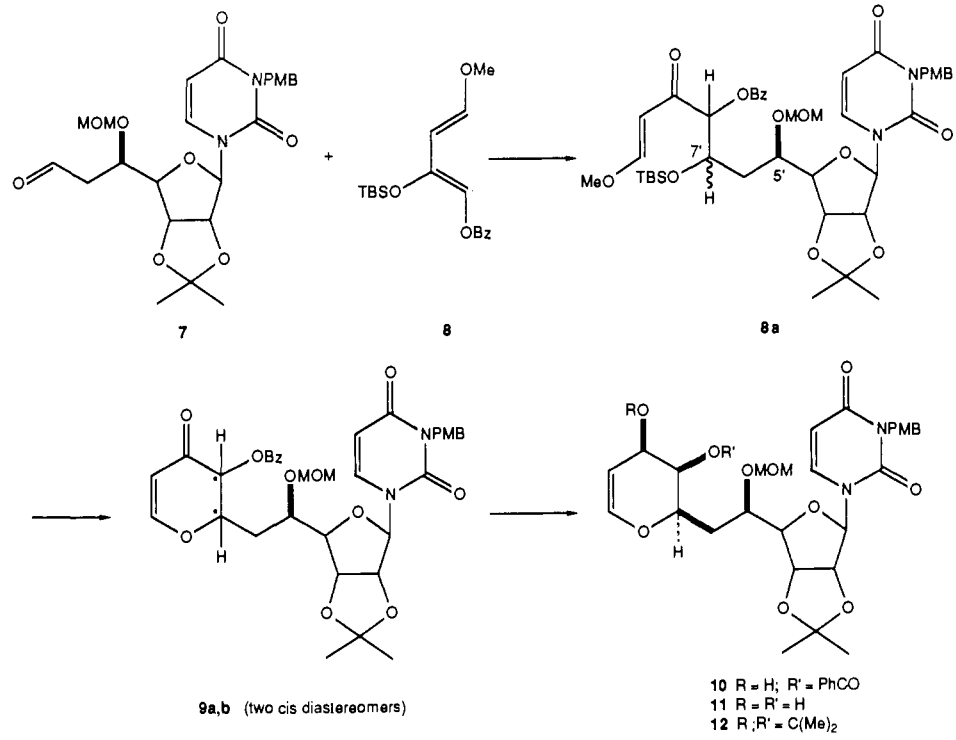

Figure 5.

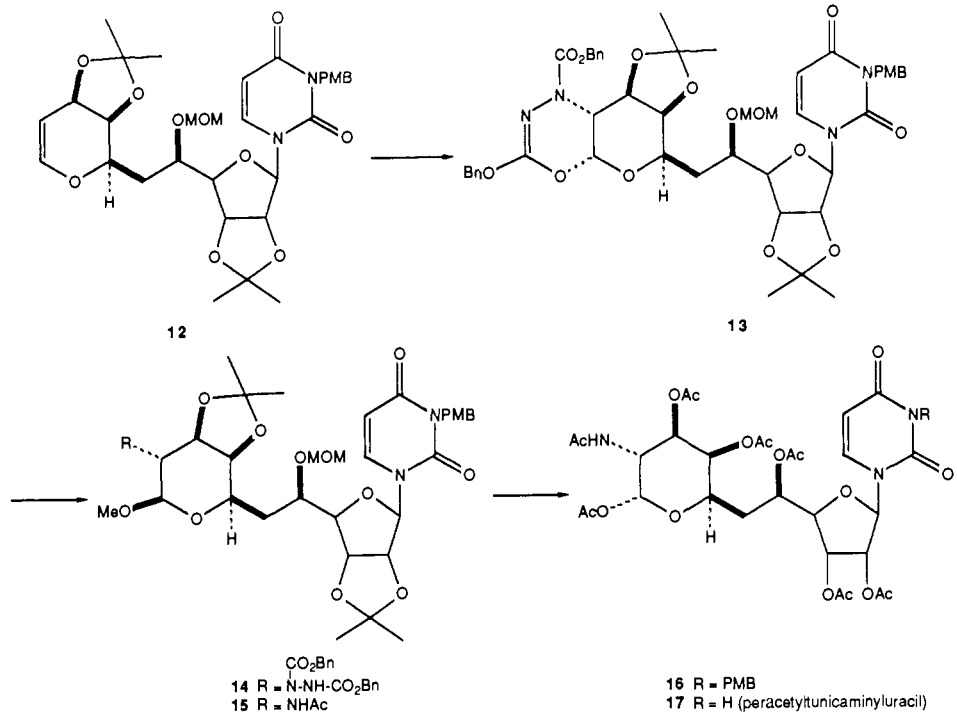

Figure 6.

condition (365 nm) in the presence of cyclohexane and methylene chloride. There was obtained an 84% yield of a 1:1 adduct to which we assigned structure **13**. Treatment of this compound with methanol in the presence of pyridinium *p*-toluenesulfonate gave the β-methyl glycoside 14.[24]

Our first goal was to confirm the stereochemistry assigned to **14** and thus to the entire series of compounds. We proceeded to correlate this series with the (peracetyltunicaminyl)uracil obtained in the previous synthesis.[8] Reaction of compound **14** with Raney nickel in the presence of methanolic acetic acid resulted in hydrogenolysis and reductive removal of the carbobenzoxy function. Acetylation of the crude amine, thus generated, afforded the *N*-acetyl derivative **15**. Cleavage of the two acetonide linkages, as well as the anomeric methoxy group, was accomplished by exposure of compound **15** to the action of 60% aqueous acetic acid under reflux. Peracetylation of the product thus obtained provided a 3:1 mixture of anomeric acetates. The major product was assigned as the α-acetoxy anomer **16**. The minor compound, the β-acetoxy anomer analogue of **16**, was not carried further. At this stage there remained only the deprotection of the imide-like nitrogen of the uracil ring. This was accomplished through the action of ceric ammonium nitrate in aqueous acetonitrile, albeit in only 59% yield. Compound **17**, obtained from this sequence, was identical with (peracetyltunicaminyl)uracil, previously ob-

(24) For the formation of glycosides from azodicarboxylate–glycal cycloadducts, see: Fitzsimmons, B. J.; Leblanc, Y.; Chan, N.; Rokach, J. *J. Am. Chem. Soc.* **1988**, *110*, 5229.

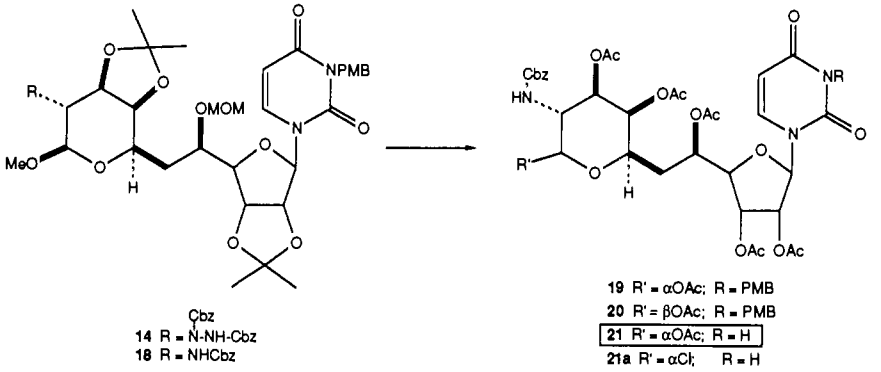

Figure 7.

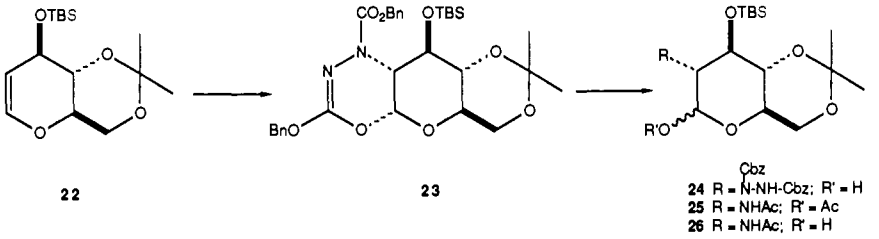

Figure 8.

tained by a total synthesis from D-ribose and previously correlated with a naturally derived sample. *This confirmation established that all of the stereochemical assignments provided above are correct and provided a firm foundation for converging on the stated goal, i.e., the Cbz derivative* ***19*** *(see Figure 6).*

We now returned to compound **14**, secure in the knowledge of its stereochemistry, and repeated the catalytic hydrogenolysis with Raney nickel. The resultant crude amine was subjected to a Schotten–Baumann like reaction[25] with aqueous sodium carbonate in THF. The *N*-Cbz derivative was obtained, though only in 70% yield. Several attempts to carry out the carbobenzoyloxylation of the amine in a nonaqueous environment using tertiary amines in the hope of improving the yield in fact led to none of the desired product.

As before, in the *N*-acetyl series, compound **18** was subjected to acetolysis, whereupon the two isopropylidene groups, the MOM function, and the anomeric ether were all removed. Peracetylation gave rise to a mixture of acetoxy anomers **19** and **20**. The major α anomer was now carried forward. Treatment of this compound with ceric ammonium nitrate[20] gave an 82% yield of the *N*-Cbz (peracetyltunicaminyl)uracil **21**. An authentic sample of this compound was not available. Nevertheless, its structure and stereochemistry can be assigned with confidence on the basis of its comparison with the closely related **17**, and rigorous comparison of the latter with authentic material.[8] Since no further stereochemical issues were addressed in the conversion of the amine derivative of **14** to **18** and thence to **21**, the configuration at every stereogenic center is secure (Figure 7).

We now explored the possibility that the glucosamine residue required to establish the trehalose linkage could also be synthesized from a suitable glycal derivative by the Fitzsimmons reaction.[18] Toward this end, the differentiated glycal derivative **22** was subjected to the cycloaddition reaction with dibenzyl azodicarboxylate. There was obtained, this time in 50% yield, the cycloadduct **23**. Treatment of this compound with aqueous acid gave rise to the hemiacetal **24**. Perhydrogenolysis (Raney nickel and hydrogen) followed by acetylation produced the anomeric mixture **25**. Selective deacylation (K_2CO_3–MeOH) of **25** gave the hemiacetal **26** (Figure 8).

A variety of attempts were now instituted to achieve the coupling of **26** with the α-acetate **21** or its corresponding chloride, **21a**. The latter case corresponds essentially to the one employed by Suami.[11,12] Unfortunately, several attempts to achieve the glycosylation were unsuccessful. In our hands the previously described conditions (Ag_2CO_3; $AgClO_4$) led first to cleavage of the acetonide linkage in **26** and thereafter to increasingly complex reaction mixtures. Apparently, even the low yield (18%) achieved in the coupling reaction by Suami and co-workers involved the use of relatively large amounts of the two components, which were derived by a relay synthesis. We have not been able to transfer this technology to our laboratory in small-scale work.

In summary, then, we have accomplished the total synthesis of the Suami intermediates **19**, **21**, and **26**. It is this coupling, for purposes of constructing the trehalose linkage, that is the last obstacle to a personal (as opposed to a formal) claim of a total synthesis.

We now describe some interesting results concerning remote effects on the diastereofacial outcome of the cyclocondensation reaction of aldehydes in this series. An account of how we arrived at aldehyde **7** would be instructive. We started by recalling that compound **27** was successfully employed in our earlier synthesis.[8] The cyclocondensation of **27** with **8** was achieved through the use of a novel two-component Lewis acid catalyst system comprised of cerium(III) acetate and BF_3 etherate. Unfortunately, all attempts to apply this catalyst system to substrates containing the intact nucleoside were unsuccessful. Apparently the catalyst system is modified or destroyed by the uracil ring. Reactions were very slow and cyclocondensations that did occur showed very little indications of stereoselectivity.

A most interesting and, at the time, disturbing result was realized with aldehyde **29**, which was the first one investigated in the nucleoside series. Since the cerium(III) acetate catalyst was ineffective, we turned to stannic chloride at −78 °C. Cyclocondensation of **29** with **8** followed by cyclization with TFA gave a single dihydropyrone (Figure 9). That the stereochemistry of this dihydropyrone corresponds to compound **30** was learned only after its attempted conversion to (peracetyltunicaminyl)uracil. Thus, starting with compound **30** and following a sequence identical with that which led to **17** from dihydropyrones **9a,b** (see Figure 7),[24] there was obtained a substance whose NMR spectrum differed in detail from that of (peracetyltunicaminyl)uracil. The multiplicities of the connected protons were virtually identical with those observed in **17**. We had no recourse but to conclude that the peracetyl compound obtained from **29** by way of dihydropyrone **30** corresponded to that shown in expression **31** *The cyclocondensation reaction of the benzyl derivative,* ***29****, had occurred entirely to produce an* L- *rather than a* D-*galactosyl moiety. In the conformer shown, this corresponds to β-face attack.* When

(25) Cf.: Bergmann, M.; Zervas, L. *Chem. Ber.* **1982**, *65*, 1192.

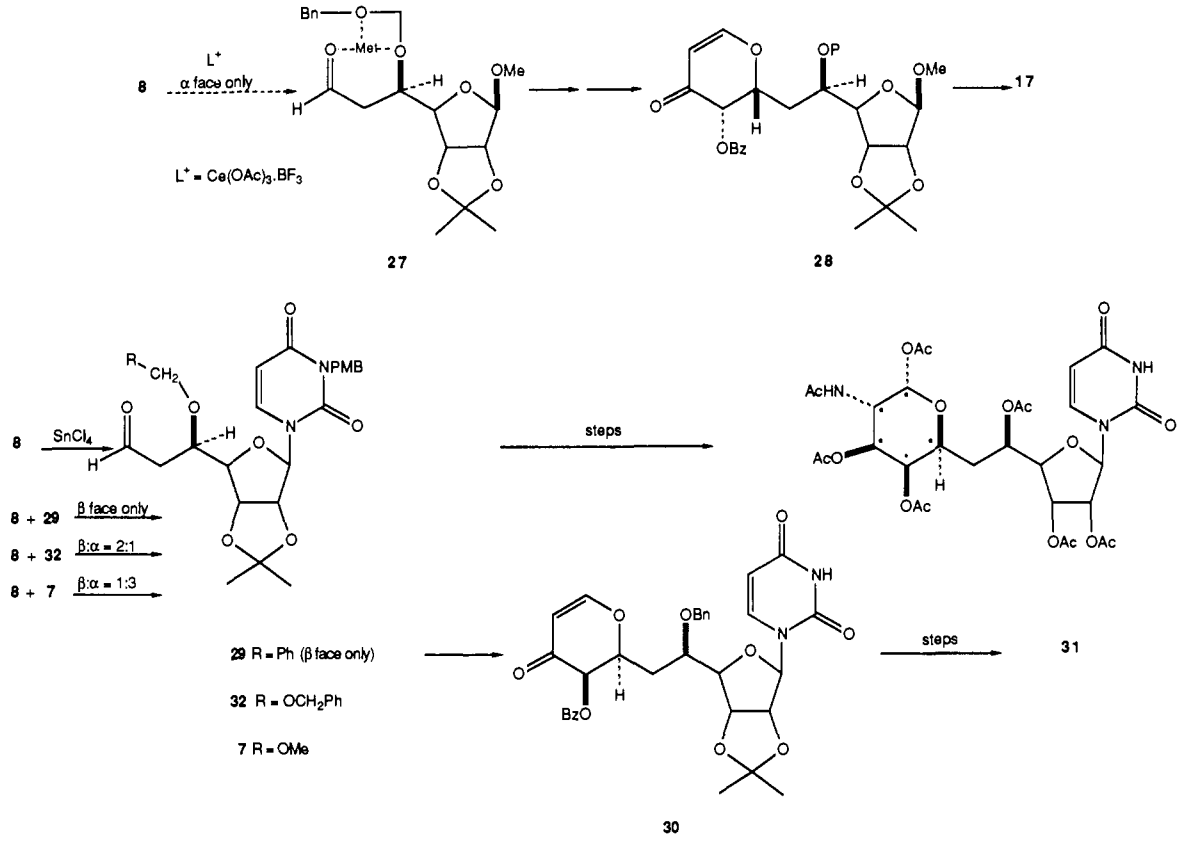

Figure 9.

this failure became apparent we next turned to aldehyde **32**. The hope was to favor the C5′ chelate ensemble implied in Figure 9.[26,27] Such a reaction would favor α-face attack (cf. **8** + **27** → **28**). As with aldehyde **7** and **29**, we were unable to use the catalyst system previously[8] employed with **27**. Through the use of the stannic chloride system, there was obtained a trans silylated aldol which, upon treatment with trifluoroacetic acid, gave rise to two dihydropyrones in a ratio of 2:1. Spectroscopic comparisons of this mixture with the one obtained from the benzyl series (cf. **30**) indicated that it was the minor product that corresponded to that required for the tunicamycin synthesis.

Thus, the stannic chloride catalyst was less efficacious at promoting C5′ chelation control than that realized by the inapplicable ceric acetate–BF_3 catalyst used in the previous synthesis. However, inclusion of one additional oxygen had at least given some of the required C5′–C7′ anti product formally corresponding to the influence of C5′ chelation control.[27] We reasoned that this desired outcome might be favored if the size of the terminal ether blocking group on the side-chain acetal function were truncated. It was from this perspective that we turned to aldehyde **7**, wherein the simple substitution of a terminating methyl group on the acetal instead of a terminating benzyl function could be investigated. *This seemingly small change tilted the facial sense of the cyclocondensation in a favorable way giving, as described above, a 3:1 ratio of compounds* **9a,b**. While we cannot be certain that the stereochemical outcome is properly attributed to C5′ chelation control, the dramatic change in going from benzyl to (benzyloxy)methylene to methoxymethylene points in that direction.[27]

Further studies involving the effects of remote stereogenic centers on the outcome of related cyclocondensation reactions with other substrates are in progress. Efforts to develop superior methodology to establish the very elusive trehalose linkage are also being pursued in simpler systems.

Experimental Section[28]

1-(5-*O*-Acetyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)uracil (2). To a solution of 2,3-*O*-isopropylidene uridine (5.0 g, 18 mmol) in 55 mL of dry methylene chloride were added triethylamine (2.6 mL, 19 mmol) and acetic anhydride (3.3 mL, 35 mmol), at room temperature. The cloudy solution went clear after ~5 min and was quenched with saturated aqueous sodium bicarbonate (100 mL). The layers were separated, and the aqueous portion was extracted with methylene chloride (2 × 100 mL). The combined organic layers were washed with brine (1 × 100 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude was purified by flash chromatography on silica gel, eluting with 3:2 ethyl acetate–hexanes and then 4:1 ethyl acetate–hexanes, to afford 5.7 g (quantitative) of the desired compound: ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.65 (brs, 1 H, uracil NH), 7.28 (d, J = 8.1 Hz, 1 H, 6-H), 5.73 (d, J = 8.1 Hz, 1 H, 5-H), 5.63 (d, J = 1.8 Hz, 1 H, 1′-H), 5.02 (dd, J = 6.4, 1.8 Hz, 1 H, 2′-H), 4.82 (dd, J = 6.4, 3.8 Hz, 1 H, 3′-H), 4.32 (m, 3 H, 4′,5′-H), 2.03 (s, 3 H, 5′-OAc), 1.56 (s, 3 H), 1.36 (s, 3 H); IR ($CHCl_3$) 3000, 1735, 1710, 1690, 1450, 1375, 1260, 1085, 1065, 1040 cm^{-1}; $[\alpha]_D$ +16.3° (c 1.10, $CHCl_3$).

1-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-3-(4-methoxybenzyl)uracil (3). To a solution of sodium hydride (1 g, 0.041 mol, 97% dry) in 40 mL of DMF, cooled to 0 °C, were added acetate **2** (12 g, 0.037 mol) in 10 mL of DMF and *p*-methoxybenzyl bromide (8.2 g, 0.041 mol) in 2 mL of DMF. The reaction was complete in 10 min (monitored by TLC), then quenched with saturated aqueous sodium bicarbonate, and extracted with ethyl acetate (3 × 75 mL). The organic layers were washed with brine (50 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude product was redissolved in 100 mL of MeOH, an excess of potassium carbonate was added, and the mixture was stirred at room temperature for 2 h. The solution was then quenched with water and extracted with ethyl acetate (3 × 100 mL), washed with brine (50 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography over silica gel (elution with 3:2 ethyl acetate–

(26) For an analysis of the stereochemical issues associated with Lewis acid induced addition of nucleophiles to aldehydes bearing proximate oxygens, see: Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.

(27) It will be noted that if the metal is chelated between the C7 aldehyde and the tetrahydrofuran oxygen, the sense of expected nucleophilic attack would correspond to that observed for aldehyde **29**. It is tempting to explain the extraordinary variation of the diastereofacial outcome in comparing the very similar aldehydes **7**, **29**, and **32** as reflecting competition between the C5′ chelate and the ring oxygen chelate. While this view accommodates the data at hand, it is merely a hypothesis.

(28) Unless otherwise specified, all products were obtained as oils or foams.

hexanes and 4:1 ethyl acetate–hexanes) yielded 12.8 g (86%) of the desired compound: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.44 (d, J = 8.6 Hz, 2 H), 7.30 (d, J = 8, 1 Hz, 1 H), 6.83 (d, J = 8.6 Hz, 2 H), 5.77 (d, J = 8.0 Hz, 1 H), 5.54 (d, J = 2.6 Hz, 1 H), 5.01 (m, 4 H), 4.30 (d, J = 2.6 Hz, 1 H), 3.90 (m, 1 H), 3.82 (m, 1 H), 3.78 (s, 3 H), 2.88 (dd, J = 7.4, 3.2 Hz, 1 H), 1.58 (s, 3 H), 1.36 (s, 3 H); IR ($CHCl_3$) 3475, 3050, 3000, 2940, 2840, 1710, 1670, 1610, 1510, 1450, 1390, 1350, 1300, 1250, 1110, 1080, 1040 cm^{-1}; $[\alpha]_D$ −15.1° (c 1.61, $CHCl_3$).

1-(2,3-*O*-Isopropylidene-β-D-*ribo*-pentodialdo-1,4-furanosyl)-3-(4-methoxybenzyl)uracil (4). Under an inert atmosphere of nitrogen, compound **3** (1.33 g, 3.29 mmol) in 3 mL of benzene, was added to a flask containing dimethyl sulfoxide (5 mL), trifluoroacetic acid (126 μL, 1.64 mmol), and pyridine (266 μL, 3.29 mmol). The mixture was cooled to ~5 °C and dicyclohexylcarbodiimide (2.10 g, 10.3 mmol) was added. The reaction mixture was stirred for 6 h, then quenched with saturated aqueous sodium bicarbonate (15 mL), and extracted with ethyl acetate (3 × 20 mL). The organic layers were washed with brine (1 × 20 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude yellow oil was placed on a flash silica gel column and eluted, respectively, with 1:1, 3:2, and 4:1 ethyl acetate–hexanes, to afford 1.05 g (79%) of the aldehyde 4: ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.24 (s, 1 H), 7.39 (d, J = 8.6 Hz, 2 H), 7.16 (d, J = 8.0 Hz, 1 H), 6.84 (d, J = 8.6 Hz, 2 H), 5.79 (d, J = 8.0 Hz, 1 H), 5.45 (s, 1 H), 5.26 (d, J = 6.3 Hz, 1 H), 5.08 (d, J = 6.6 Hz, 1 H), 4.96 (AB q, $\Delta\nu$ = 37.3 Hz, J_{AB} = 13.5 Hz), 4.53 (s, 1 H), 3.78 (s, 3 H), 1.57 (s, 3 H), 1.54 (s, 3 H); IR ($CHCl_3$) 3050, 2940, 2840, 1732, 1710, 1665, 1630, 1610, 1510, 1450, 1388, 1350, 1250 cm^{-1}; $[\alpha]_D$ −26.4° (c 0.76, $CHCl_3$); HRMS calcd for $C_{20}H_{22}H_2O_7$ 403.1505, found 403.1499.

1-(6,7,8-Trideoxy-2,3-*O*-isopropylidene-β-D-*allo*-oct-7-enofuranosyl)-3-(4-methoxybenzyl)uracil (5). Allylsilane (1.7 mL, 10.7 mmol) and boron trifluoride etherate (1.3 mL, 10.7 mmol) were added to a solution of compound **4** (860 mg, 2.14 mmol) in 30 mL of propionitrile, at −78 °C. The reaction mixture was allowed to stir for 3 h and then quenched with saturated aqueous sodium bicarbonate (15 mL). The mixture was extracted with ethyl acetate (3 × 50 mL), and organic layer was washed with brine (1 × 50 mL) and dried over magnesium sulfate. The solution was filtered and concentrated under reduced pressure. Flash chromatography over silica gel, eluting with 1:1 and then 3:2 ethyl acetate–hexanes, afforded 637 mg (67%) of **5** at a purity level of 95% (125 mg was recovered): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.44 (d, J = 8.6 Hz, 2 H), 7.31 (d, J = 8.0 Hz, 1 H), 6.83 (d, J = 8.7 Hz, 2 H), 5.85 (m, 1 H), 5.76 (d, J = 8.0 Hz, 1 H), 5.56 (d, J = 2.8 Hz, 1 H), 5.20 (m, 2 H), 5.02 (AB q, $\Delta\nu$ = 27.1 Hz, J_{AB} = 13.5 Hz), 5.03 (d, J = 3.7 Hz, 1 H), 4.98 (dd, J = 2.6, 6.6 Hz, 1 H), 4.12 (m, 1 H), 3.95 (m, 1 H), 3.82 (s, 3 H), 3.07 (br s, 1 H), 2.32 (m, 2 H), 1.57 (s, 3 H), 1.37 (s, 3 H); IR ($CHCl_3$) 3615, 3450, 3020, 2980, 2940, 1710, 1670, 1510, 1455, 1390, 1250, 1225, 1215, 1080, 1040 cm^{-1}; $[\alpha]_D$ −9.9° (c 0.69, $CHCl_3$); HRMS calcd for $C_{23}H_{28}N_2O_7$ 444.1897, found 444.1887.

1-(6,7,8-Trideoxy-2,3-*O*-isopropylidene-5-*O*-(methoxymethyl)-β-D-*allo*-oct-7-enofuranosyl)-3-(4-methoxybenzyl)uracil (6). Alcohol **5** (1.8 g, 0.004 mol) was dissolved in 30 mL of dimethylformamide at room temperature. To this was added diisopropylethylamine (7 mL, 0.04 mol) and chloromethyl methyl ether (1.52 mL, 0.02 mol). The solution was heated to reflux for 3 h, then cooled to room temperature, quenched with saturated aqueous sodium bicarbonate (100 mL), and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with 1 N aqueous hydrochloric acid (100 mL), water (2 × 100 mL), and brine (50 mL), dried over magnesium sulfate, filtered and concentrated. The crude product was chromatographed over silica gel, eluting with 1:1 hexanes–ethyl acetate to afford 1.8 g (96%) of the title compound **6**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.44 (d, J = 8.6 Hz, 2 H), 7.33 (d, J = 8.1 Hz, 1 H), 6.82 (d, J = 8.6 Hz, 2 H), 5.88 (d, J = 2.5 Hz, 1 H), 5.76 (d, J = 8.1 Hz, 1 H), 5.18 (br s, 1 H), 5.11 (m, 2 H), 5.04 (br s, 2 H), 4.94 (dd, J = 4.8, 6.6 Hz, 1 H), 4.77 (dd, J = 2.5, 6.7 Hz, 1 H), 4.68 (br s, 2 H), 4.09 (t, J = 4.3 Hz, 1 H), 3.87 (m, 1 H), 3.78 (s, 3 H), 3.38 (s, 3 H), 2.38 (m, 2 H), 1.57 (s, 3 H), 1.37 (s, 3 H); IR ($CHCl_3$) 3050, 2940, 2900, 2835, 1710, 1670, 1510, 1455, 1385, 1250, 1100, 1040 cm^{-1}; $[\alpha]_D$ +3.1° (c 1.72, $CHCl_3$); HRMS calcd for $C_{25}H_{32}N_2O_8$ 488.2159, found 488.2162.

1-(6-Deoxy-2,3-*O*-isopropylidene-5-*O*-(methoxymethyl)-β-D-*allo*-heptodialdo-1,4-furanosyl)-3-(4-methoxybenzyl)uracil (7). To a solution of compound **6** (90 mg, 0.178 mmol) in 10 mL of THF were added 226 μL (0.045 mmol) of an osmium tetroxide solution (50 mg/mL THF) and 4-methylmorpholine N-oxide (25 mg, 0.214 mmol) in 100 μL of water. The reaction mixture was stirred 4 h at room temperature, then diluted with saturated aqueous sodium bicarbonate, and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with saturated aqueous sodium bisulfite (20 mL) and brine (20 mL) and dried over magnesium sulfate. The drying agent was filtered off, and the solution was concentrated in vacuo to afford 112 mg (>100%) of the crude diol. This compound was dissolved in 6 mL of methylene chloride and cooled to 0 °C. To this solution were added sodium carbonate (15 mg, 0.178 mmol) and lead tetraacetate (79 mg, 0.178 mmol). The reaction was complete in ~5 min, then quenched with saturated aqueous sodium bicarbonate (5 mL), and extracted with ethyl acetate (3 × 15 mL). The organic portion was washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography (SiO_2) using 40% ethyl acetate in hexanes, afforded 77 mg (85%) of the desired aldehyde 7: ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.65 (br s, 1 H), 7.43 (d, J = 8.5 Hz, 2 H), 7.20 (d, J = 8.0 Hz, 1 H), 6.83 (d, J = 8.5 Hz, 2 H), 5.78 (d, J = 8.0 Hz, 1 H), 5.66 (br s, 1 H), 4.95–5.10 (m, 3 H), 4.71 (AB q, J_{AB} = 6.9 Hz, $\Delta\nu$ = 7.9 Hz), 4.37 (dd, J = 5.8, 11.6 Hz, 1 H), 4.05 (dd, J = 2.2, 4.2 Hz, 1 H), 3.79 (s, 3 H), 3.38 (s, 3 H), 2.68 (m, 2 H), 1.56 (s, 3 H), 1.34 (s, 3 H); IR ($CHCl_3$) 3050, 3000, 2945, 2935, 2835, 1715, 1670, 1510, 1450, 1385, 1250, 1110, 1040 cm^{-1}; $[\alpha]_D$ +21.2° (c 1.11, $CHCl_3$); HRMS calcd for $C_{24}H_{30}N_2O_9$ 490.1952, found 490.1974.

1-(7,11-Anhydro-8-*O*-benzoyl-6,10-dideoxy-2,3-*O*-isopropylidene-5-*O*-(methoxymethyl)-D-*threo* and L-erythro-β-D-*allo*-undec-10-eno-9-ulo-1,4-furanosyl)-3-(4-methoxybenzyl)uracil (9a,b). Aldehyde **7** (343 mg, 0.70 mmol) was dissolved in 8 mL of dry methylene chloride. The solution was cooled to −78 °C and tin tetrachloride (700 μL, of a 1.0 M solution in CH_2Cl_2) was added. The mixture was stirred for ~5 min and the diene **8** (351 mg, 1.05 mmol) in 5 mL of dry methylene chloride was added slowly (30 min) via syringe pump. The solution was stirred for 15 min, quenched with saturated aqueous sodium bicarbonate, and allowed to warm to room temperature. The reaction mixture was extracted with methylene chloride (1 × 20 mL) and ethyl acetate (3 × 20 mL), and the combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated. Flash chromatography (SiO_2) eluting with 3:1 hexanes–acetone yielded 344 mg of the desired pyrones (**9a,b**) and 358 mg of trans silylated aldol. The aldol was treated with 2 mL of a 5% HF–CH_3CN solution at 0 °C, and the conversion to pyrone was complete in 10 min. The reaction mixture was quenched with pH 7 phosphate buffer and extracted with ethyl acetate (3 × 15 mL). The organic layer was washed with brine (1 × 15 mL), dried over magnesium sulfate, filtered, and concentrated. The crude material was chromatographed (SiO_2), with 1:1 ethyl acetate–hexanes as eluant, to afford 245 mg of pyrones, an overall yield of 589 mg (61%) (ratio ~3:1 **9a** to **9b**) of the title compound: ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.03 (d, J = 7.1 Hz, 2 H), 7.57 (m, 1 H), 7.28–7.47 (m, 4 H), 7.15 (d, J = 8.0 Hz, 1 H), 6.82 (d, J = 8.7 Hz, 2 H), 5.75 (d, J = 8.0 Hz, 1 H), 5.67 (m, 2 H), 5.53 (d, J = 5.8 Hz, 1 H), 5.00 (br s, 2 H), 4.84–4.98 (m, 4 H), 4.68 (AB q, $\Delta\nu$ = 18.5 Hz, J_{AB} = 6.8 Hz), 4.08 (m, 1 H), 4.00 (m, 1 H), 3.78 (s, 3 H), 3.32 (s, 3 H), 1.8–2.2 (m, 2 H), 1.52 (s, 3 H), 1.31 (s, 3 H); IR ($CHCl_3$) 3050, 2960, 2880, 1705, 1665, 1590, 1445, 1420, 1035 cm^{-1}; $[\alpha]_D$ +25.4° (c 1.40, $CHCl_3$) (on pyrone mixture); HRMS calcd for $C_{35}H_{38}N_2O_{12}$ 678.2425, found 678.2409.

1-(7,11-Anhydro-8-*O*-benzoyl-6,10-dideoxy-2,3-*O*-isopropylidene-5-*O*-(methoxymethyl)-D-*arabino*-β-D-*allo*-undec-10-enofuranosyl)-3-(4-methoxybenzyl)uracil (10). To a mixture of pyrones **9** (224 mg, 0.33 mmol) in 5 mL of methylene chloride and 4 mL of ethanol, was added $CeCl_3 \cdot 7H_2O$ (123 mg, 0.33 mmol) at room temperature. The solution was cooled to −78 °C and sodium borohydride (13 mg, 0.33 mmol) in 2 mL of ethanol was added slowly (15 min), via syringe pump. The reaction was complete after 30 min, then carefully quenched with pH 7 phosphate buffer (3 mL), and extracted with ethyl acetate (3 × 20 mL) and methylene chloride (1 × 20 mL). The solution was dried over magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography of the crude over silica gel (ether) yielded 140 mg of desired alcohol (R_f 0.3) and 56 mg of the minor isomer (R_f 0.4) (64%). The mixed fractions were separated by HPLC (3:2 ethyl acetate–hexanes): ^{1}H NMR (250 MHz) of the desired alcohol ($CDCl_3$) δ 8.07 (d, J = 7.5 Hz, 2 H), 7.59 (m, 1 H), 7.42 (m, 4 H), 7.22 (d, J = 8.0 Hz, 1 H), 6.82 (d, J = 8.5 Hz, 2 H), 6.47 (d, J = 6.2 Hz, 1 H), 5.77 (m, 2 H), 5.44 (d, J = 4.6 Hz, 1 H), 5.00 (AB q, J_{AB} = 13.6 Hz $\Delta\nu$ = 18.0 Hz), 4.72–4.87 (m, 2 H), 4.68 (AB q, J_{AB} = 3.2 Hz, $\Delta\nu$ = 8.6 Hz), 4.35 (d, J = 9.9 Hz, 1 H), 3.97–4.11 (m, 2 H), 3.77 (s, 3 H), 3.38 (s, 3 H), 1.72–2.10 (m, 2 H), 1.50 (s, 3 H), 1.31 (s, 3 H); IR ($CHCl_3$) 3580, 3050, 3000, 2940, 2900, 2840, 1710, 1675, 1510, 1450, 1270, 1250, 1100, 1040 cm^{-1}; $[\alpha]_D$ +1.6° (c 6.70, $CHCl_3$); MS m/e 105, 122 (100).

1-(7,11-Anhydro-6,10-dideoxy-2,3-*O*-isopropylidene-5-*O*-(methoxymethyl)-D-*arabino*-β-D-*allo*-undec-10-enofuranosyl)-3-(4-methoxybenzyl)uracil (11). Potassium carbonate (267 mg, 2.10 mmol) was added to a solution of **10** (143 mg, 0.210 mmol) in 5 mL of methanol at room temperature. The reaction was completed in 15 min and then quenched with 2 mL of saturated aqueous sodium bicarbonate. More bicarbonate was added and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The organic portion was washed with brine and dried over magnesium sulfate. The drying agent was filtered off and the solution

was concentrated. Flash chromatography on silica gel (4:1 ethyl acetate–hexanes) afforded 110 mg (91%) of the diol **11**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.43 (d, J = 8.6 Hz, 2 H), 7.29 (d, J = 7.4 Hz, 1 H), 6.82 (d, J = 8.6 Hz, 2 H), 6.36 (d, J = 6.4 Hz, 1 H), 5.80 (d, J = 2.6 Hz, 1 H), 5.78 (d, J = 8.0 Hz, 1 H), 5.03 (br s, 2 H), 4.91 (m, 1 H), 4.81 (dd, J = 2.2, 6.8 Hz, 1 H), 4.66 (AB q, J_{AB} = 6.4 Hz, $\Delta\nu$ = 12.4 Hz), 4.39 (m, 1 H), 4.05 (m, 4 H), 3.77 (s, 3 H), 3.70 (m, 1 H), 3.37 (s, 3 H), 2.56 (d, J = 8.7 Hz, 1 H), 2.44 (d, J = 7.1 Hz, 1 H), 2.15 (m, 1 H), 1.72 (m, 1 H), 1.57 (s, 3 H), 1.32 (s, 3 H); IR ($CHCl_3$) 3760, 3650, 3050, 3000, 2920, 2900, 2840, 1710, 1670, 1510, 1450, 1390, 1250, 1080, 1045 cm^{-1}; $[\alpha]_D$ +9.7° (c 0.82, $CHCl_3$); MS m/e 121, 162, 231, 232, 576 (M^+).

1-(7,11-Anhydro-6,10-dideoxy-2,3:8,9-di-*O*-isopropylidene-5-*O*-(methoxymethyl)-D-*arabino*-β-D-*allo*-undec-10-enofuranosyl)3-(4-methoxybenzyl)uracil (12). 2-Methoxypropene (14.3 μL, 0.149 mmol) and a catalytic amount of pyridinium p-toluenesulfonate were added to a solution of **11** (57 mg, 0.099 mmol) in 3 mL of methylene chloride, at 0 °C. The reaction was complete in 30 min, quenched with 2 mL of saturated aqueous sodium bicarbonate, and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine (1 × 15 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography on silica gel (1:1 hexanes–ethyl acetate) afforded 53 mg (87%) of the title compound **12**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.44 (d, J = 8.6 Hz, 2 H), 7.33 (d, J = 8.1 Hz, 1 H), 6.82 (d, J = 8.6 Hz, 1 H), 6.37 (d, J = 6.2 Hz, 1 H), 5.86 (d, J = 3.1 Hz, 1 H), 5.78 (d, J = 8.1 Hz, 1 H), 5.04 (AB q, $\Delta\nu$ = 11.6 Hz, J_{AB} = 13.6 Hz), 4.92 (dd, J = 6.8, 4.8 Hz, 1 H), 4.71–4.80 (m, 2 H), 4.67 (m, 3 H), 3.98–4.12 (m, 4 H), 3.77 (s, 3 H), 3.37 (s, 3 H), 2.19 (m, 1 H), 1.72 (m, 1 H), 1.58 (s, 3 H), 1.45 (s, 3 H), 1.32 (s, 6 H); IR ($CHCl_3$) 3050, 3000, 2940, 2890, 2825, 1710, 1670, 1510, 1450, 1385, 1250, 1035 cm^{-1}; $[\alpha]_D$ +17.4° (c 1.08, $CHCl_3$); HRMS calcd for $C_{31}H_{40}N_2O_{11}$ 616.2633, found 616.2632.

3-(4-Methoxybenzyl)-1-[(11*R*)-1,2,6-trideoxy-3,4:9,10-di-*O*-isopropylidene-7-*O*-(methoxymethyl)-L-*allo*-α-D-*galacto*-undecodialdo-1,5-pyrano[2,1-*e*][2-(benzyloxy)-4-(benzyloxycarbonyl)dihydro-Δ^2-1,3,4-oxadiazinyl]-11,8-furanosyl]uracil (13). To a solution of **12** (121 mg, 0.196 mmol) in 1.0 mL of cyclohexane was added dibenzyl azodicarboxylate (293 mg, 0.982 mmol). The solution was solubilized by the addition of ~5 drops of methylene chloride. The system was purged with argon and equipped with a condenser, under nitrogen atmosphere. The mixture was irradiated (UV lamp, 365 nm) through a Pyrex filter for 24 h. The solution was concentrated and chromatographed on silica gel (4:1 followed by 3:1, hexanes–acetone) to afford 150 mg (84%) of the cycloadduct **13** (10 mg of starting material was recovered): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.21–7.55 (m, 13 H), 6.82 (d, J = 8.4 Hz, 2 H), 5.86 (d, J = 3.0 Hz, 1 H), 5.77 (d, J = 8.0 Hz, 1 H), 5.47 (d, J = 3.7 Hz, 1 H), 5.19–5.23 (m, 3 H), 5.15 (m, 1 H), 5.02 (m, 2 H), 4.92 (m, 1 H), 4.69 (AB q, $\Delta\nu$ = 6.8 Hz, J_{AB} = 6.5 Hz), 4.58 (m, 1 H), 4.39 (d, J = 10.3 Hz, 1 H), 4.02 (m, 4 H), 3.76 (s, 3 H), 3.39 (s, 3 H), 2.12 (m, 1 H), 1.78 (m, 1 H), 1.58 (s, 3 H), 1.31 (s, 6 H), 1.29 (s, 3 H); IR ($CHCl_3$) 3050, 3000, 2960, 2940, 2900, 2840, 1710, 1670, 1515, 1455, 1430, 1390, 1360, 1350, 1300, 1250, 1180, 1080, 1040 cm^{-1}; $[\alpha]_D$ –4.8° (c 1.03, $CHCl_3$).

3-(4-Methoxybenzyl)-1-[methyl (11*R*)-2-[1,2-bis(benzyloxycarbonyl)hydrazino]-2,6-dideoxy-3,4:9,10-di-*O*-isopropylidene-7-*O*-(methoxymethyl)-L-*allo*-β-D-*galacto*-undecodialdo-1,5-pyranoside-11,8-furanosyl]uracil (14). To a solution of **13** (44.7 mg, 0.049 mmol) in 2 mL of methanol at 0 °C was added a catalytic amount of pyridinium p-toluenesulfonate. The reaction was complete in 5 min and was quenched with saturated aqueous sodium bicarbonate. The reaction mixture was extracted with ethyl acetate (3 × 10 mL) and the combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography of the crude (1:1 hexanes–ethyl acetate) afforded 38 mg (83%) of the desired compound **14**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.43 (d, J = 8.5 Hz, 2 H), 7.21–7.38 (m, 11 H), 6.82 (d, J = 8.5 H, 2 H), 6.71 (br s, 1 H), 5.87 (d, J = 2.8 Hz, 1 H), 5.78 (d, J = 8.1 Hz, 1 H), 5.19–5.31 (m, 4 H), 5.02 (AB q, J_{AB} = 6.8 Hz, $\Delta\nu$ = 8.2 Hz), 4.90 (m, 2 H), 4.76 (m, 2 H), 4.63 (AB q, J_{AB} = 6.3 Hz, $\Delta\nu$ = 19.6 Hz), 4.31 (br s, 1 H), 4.11 (m, 3 H), 4.03 (m, 1 H), 3.90 (m, 1 H), 3.77 (s, 3 H), 3.43 (br s, 3 H), 3.35 (s, 3 H), 2.12 (m, 1 H), 1.78 (m, 1 H), 1.52 (s, 3 H), 1.29 (s, 9 H); IR ($CHCl_3$) 3050, 2990, 2940, 2900, 2840, 1765, 1710, 1670, 1515, 1460, 1380, 1250, 1080 cm^{-1}; $[\alpha]_D$ +22.8° (c 0.88, $CHCl_3$).

3-(4-Methoxymethyl)-1-[methyl (11*R*)-2-acetamido-2,6-dideoxy-3,4:9,10-di-*O*-isopropylidene-7-*O*-(methoxymethyl)-L-*allo*-β-D-*galacto*-undecodialdo-1,5-pyranoside-11,8-furanosyl]uracil (15). Compound **14** (97 mg, 0.103 mmol) was dissolved in 2 mL of a 60:1 methanol–acetic acid solution and transferred to a test tube. A small scoop of Raney nickel (excess) was added and the tube was fitted with a septum with a needle. The solution was hydrogenated in a Parr shaker (~40–45 psi) for 4 h. The resulting solution was filtered through Celite, eluting with methanol, and concentrated. The crude was redissolved in 2 mL of methylene chloride. Acetic anhydride (40 μL, 0.41 mmol), triethylamine (25 μL, 0.21 mmol), and a catalytic amount of 4-(dimethylamino)-pyridine were added to the solution. The acetylation was complete in 30 min; the reaction mixture was concentrated and immediately chromatographed (ethyl acetate followed by 5% methanol in ethyl acetate) to give 60 mg (83%) of the compound **15**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.43 (d, J = 8.7 Hz, 2 H), 7.30 (d, J = 8.1 Hz, 1 H), 6.82 (d, J = 8.7 Hz, 2 H), 6.00 (d, J = 7.2 Hz, 1 H), 5.89 (d, J = 3.2 Hz, 1 H), 5.79 (d, J = 8.1 Hz, 1 H), 5.03 (AB q, J_{AB} = 13.7 Hz, $\Delta\nu$ = 11.8 Hz), 4.88 (m, 2 H), 4.53–4.78 (m, 4 H), 4.11 (m, 1 H), 4.02 (m, 3 H), 3.77 (s, 3 H), 3.47 (s, 3 H), 3.40 (s, 3 H), 2.11 (m, 1 H), 2.00 (s, 3 H), 1.79 (m, 1 H), 1.58 (s, 3 H), 1.50 (s, 3 H), 1.36 (s, 3 H), 1.30 (s, 3 H); IR ($CHCl_3$) 3050, 3000, 2940, 2830, 1710, 1670, 1510, 1450, 1250, 1080, 1040 cm^{-1}; $[\alpha]_D$ 20.9° (c 0.60, $CHCl_3$); HRMS calcd for $C_{34}H_{47}N_3O_{13}$ 706.3188, found 706.3229.

1-[11(*R*)-2-Acetamido-1,3,4,7,9,10-hexa-*O*-acetyl-2,6-dideoxy-L-*allo*-α-D-*galacto*-undecodialdo-1,5-pyranose-11,8-furanosyl]-3-(4-methoxybenzyl)uracil (16). A solution of **15** (22 mg, 0.031 mmol) in 2 mL of a 60% acetic acid in water solution was heated to reflux for 3 h, then cooled to room temperature, and concentrated. The crude was redissolved in 2 mL of methylene chloride and triethylamine (50 μL, 0.374 mmol), acetic anhydride (75 μL, 0.75 mmol), and a catalytic amount of 4-(dimethylamino)pyridine were added. The reaction was complete in 15 min, then concentrated, and immediately chromatographed (ethyl acetate, 5% methanol in ethyl acetate), to afford 22 mg (86%) (mixture of anomers). HPLC separation of the mixture (ethyl acetate) gave 6 mg of α anomer **16** and 2 mg of β anomer. ^{1}H NMR (500 MHz, $CDCl_3$) (α anomer) δ 7.41 (d, J = 8.6 Hz, 2 H), 7.17 (d, J = 8.1 Hz, 1 H), 6.83 (d, J = 8.6 Hz, 2 H), 6.14 (d, J = 3.7 Hz, 1 H), 6.02 (d, J = 5.9 Hz, 1 H), 5.86 (d, J = 8.1 Hz, 1 H), 5.38 (m, 2 H), 5.22 (m, 2 H), 5.21 (dd, J = 5.9, 9.1 Hz, 1 H), 5.12 (m, 1 H), 5.02 (AB q, J_{AB} = 13.7 Hz, $\Delta\nu$ = 27.2 Hz), 4.73 (m, 1 H), 4.06 (m, 2 H), 3.78 (s, 3 H), 2.19 (s, 3 H), 2.18 (s, 3 H), 2.11 (s, 3 H), 2.08 (s, 3 H), 2.04 (s, 3 H), 2.03 (s, 3 H), 1.96 (s, 3 H), 1.25 (m, 2 H); IR ($CHCl_3$) 3050, 3000, 2990, 2820, 1740, 1670, 1510, 1450, 1375, 1200, 1050 cm^{-1}; $[\alpha]_D$ +49.5° (c 0.31, $CHCl_3$).

1-[(11*R*)-2-Acetamido-1,3,4,7,9,10-hexa-*O*-acetyl-2,6-dideoxy-L-*allo*-α-D-*galacto*-undecodialdo-1,5-pyranose-11,8-furanosyl]uracil (17). To a solution of **16** (10.0 mg, 0.012 mmol) in 800 μL of acetonitrile was added ceric ammonium nitrate (33 mg, 0.061 mmol) in 80 μL of water, and the mixture was heated to reflux for 1 h, then diluted with water, and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate, and the aqueous portion was reextracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium bisulfite (5 mL) and brine (5 mL) and then dried over magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography over silica gel (ethyl acetate, 5% methanol in ethyl acetate) afforded 5 mg (59%) of heptaacetyltunicaminyluracil (**17**), which by NMR and chromatographically was identical with the sample synthesized by our previous route.[8,29] That sample had been compared to a naturally derived sample furnished by Professor Suami.[11]

3-(4-Methoxybenzyl)-1-[methyl (11*R*)-2-[(benzyloxycarbonyl)-amino]-2,6-dideoxy-3,4:9,10-di-*O*-isopropylidene-7-*O*-(methoxymethyl)-L-*allo*-β-D-*galacto*-undecodialdo-1,5-pyranoside-11,8-furanosyl]uracil (18). A solution of compound **14** (210 mg, 0.22 mmol) in 6 mL of a 60:1 methanol–ethyl acetate solution, containing a catalytic amount of Raney nickel, was hydrogenated by using a Parr shaker (60 psi). The reaction was complete in 6 h, and then the mixture was filtered through Celite (washed with methanol) and concentrated in vacuo. The crude amine was dissolved in tetrahydrofuran (2 mL) and water (4 mL). Sodium carbonate (45 mg, 0.42 mmol) and benzyl chloroformate (60 μL, 0.40 mmol) were added, and the solution was stirred at room temperature for 1 h. Saturated aqueous sodium bicarbonate was added and the mixture was extracted with ethyl acetate. The organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography (SiO_2) of the crude, using 70% ethyl acetate in hexanes as eluant, afforded 79 mg (45%) of the compound **18**: ^{1}H NMR (490 MHz, $CCCl_3$) δ 7.41 (d, J = 8.7 Hz, 2 H), 7.28–7.38 (m, 5 H), 7.26 (d, J = 8.1 Hz, 1 H), 6.80 (d, J = 8.7 Hz, 2 H), 5.86 (d, J = 3.2 Hz, 1 H), 5.76 (d, J = 8.1 Hz, 1 H), 4.95–5.11 (m, 6 H), 4.88 (dd, J = 6.8, 4.8 Hz, 1 H), 4.73 (dd, J = 6.8, 3.2 Hz, 1 H), 4.66 (d, J = 6.6 Hz, 1 H), 4.57 (d, J = 6.6 Hz, 1 H), 4.46–4.54 (m, 1 H), 4.11 (m, 1 H), 3.94–4.08 (m, 3 H), 3.75 (s, 3 H), 3.45 (s, 3 H), 3.36 (s, 3 H), 3.10–3.20 (m, 1 H), 2.05–2.11 (m, 1 H), 1.73–1.80 (m, 1 H), 1.56 (s, 3 H), 1.49 (s, 3 H), 1.33 (s, 3 H), 1.31 (s, 3 H); IR ($CHCl_3$) 3440, 3000, 2940, 1720, 1670, 1520, 1450, 1380 cm^{-1}; $[\alpha]_D$ +21.1° (c 1.56, $CHCl_3$); HRMS (M^+ + H)

(29) Experimental procedures and full spectral characterizations of the previous route described in ref 8 are provided as Supplementary Material.

calcd for $C_{40}H_{52}O_{14}N_3$ 798.3451, found 798.3444.

1-[(11*R*)-1,3,4,7,9,10-Hexa-*O*-acetyl-2-[(benzyloxycarbonyl)amino]-2,6-dideoxy-L-*allo*-α and β-D-*galacto*-undecodialdo-1,5-pyranose-11,8-furanosyl]-3-(4-methoxybenzyl)uracil (19 and 20). Compound **18** (45 mg, 0.056 mmol) was dissolved in 4 mL of a 1:1 acetic acid–water solution, and the mixture was heated to reflux for 2 h. Then the reaction mixture was cooled to room temperature, concentrated, and pumped under reduced pressure. The crude was redissolved in methylene chloride (3 mL) and triethylamine (83 μL, 0.60 mmol), acetic anhydride (48 μL, 0.50 mmol), and a catalytic amount of 4-(methylamino)pyridine were added. The mixture was stirred at room temperature for 1 h and then filtered through a short column of silica gel, eluting with ethyl acetate, to afford a 1:1 mixture of the α:β anomers. This mixture was separated by HPLC (60% ethyl acetate in hexanes) to give 20 mg of α anomer **19** and 18 mg of β anomer **20** (75%, overall). **19**: ^{1}H NMR (490 MHz, $CDCl_3$) δ 7.42 (d, J = 8.6 Hz, 2 H), 7.34 (m, 5 H), 7.15 (d, J = 8.1 Hz, 1 H), 6.83 (d, J = 8.7 Hz, 2 H), 6.17 (d, J = 3.7 Hz, 1 H), 6.01 (d, J = 5.8, 1 H), 5.87 (d, J = 8.1 Hz, 1 H), 4.95–5.36 (m, 9 H), 4.68 (m, 1 H), 4.42–4.47 (m, 1 H), 4.02–4.10 (m, 2 H), 3.78 (s, 3 H), 2.18 (s, 3 H), 2.16 (s, 3 H), 2.13 (m, 1 H), 2.11 (s, 3 H), 2.08 (s, 3 H), 2.05 (m, 1 H), 2.04 (s, 3 H), 1.95 (s, 3 H); IR ($CHCl_3$) 3420, 3000, 1745, 1670, 1520, 1450, 1370, 1230 cm^{-1}; $[\alpha]_D$ +57.2° (c 1.23, $CHCl_3$); HRMS (M^+ + H) calcd for $C_{43}H_{50}O_{19}N_3$ 912.3039, found 912.3067.

1-[(11*R*)-1,3,4,7,9,10-Hexa-*O*-acetyl-2-[(benzyloxycarbonyl)amino]-2,6-dideoxy-L-*allo*-α-D-*galato*-undecodialdo-1,5-pyranose-11,8-furanosyl]uracil (21). To a solution of **19** (37 mg, 0.041 mmol) in 3 mL of acetonitrile were added water (300 μL) and ceric ammonium nitrate (112 mg, 0.205 mmol). The mixture was heated to reflux for 15 min, then cooled to room temperature, diluted with water (5 mL), and extracted with ethyl acetate (3 × 10 mL). The organic layers were washed with saturated aqueous sodium bicarbonate (5 mL), and the aqueous portion was reextracted with ethyl acetate (10 mL). The combined organic layers were washed with saturated aqueous sodium bisulfite and brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography (SiO_2) using 70% ethyl acetate in hexanes, afforded 27 mg (82%) of compound **21**:[30] ^{1}H NMR (490 MHz, $CDCl_3$) δ 7.62 (s, 1 H), 7.31–7.38 (m, 5 H), 7.22 (d, J = 8.2 Hz, 1 H), 6.17 (d, J = 3.2 Hz, 1 H), 5.92 (d, J = 5.7 Hz, 1 H), 5.81 (dd, J = 8.1, 2.2 Hz, 1 H), 5.30–5.36 (m, 1 H), 5.25–5.30 (m, 3 H), 5.10–5.16 (m, 4 H), 5.05 (d, J = 12.1 Hz, 1 H), 4.75 (d, J = 9.9 Hz, 1 H), 4.40–4.45 (m, 1 H), 4.04–4.08 (m, 2 H), 2.20 (s, 3 H), 2.16 (s, 3 H), 2.13 (s, 3 H), 2.10 (s, 3 H), 2.08 (s, 3 H), 1.94 (s, 3 H); IR ($CHCl_3$) 3420, 3380, 3000, 1750, 1690, 1520, 1370, 1260 cm^{-1}; $[\alpha]_D$ +63.6° (c 0.67, $CHCl_3$).

2-(Benzyloxy)-4-(benzyloxycarbonyl)-[3-*O*-(*tert*-butyldimethylsilyl)-1,2-dideoxy-4,6-*O*-isopropylidene-α-D-glucopyrano][2,1-*e*]dihydro-Δ^2-1,3,4-oxadiazine (23). To a solution of **22**[31] (317 mg, 1.06 mmol) in 2 mL of cyclohexane and 0.5 mL of methylene chloride was added dibenzyl azodicarboxylate (1.58 g, 5.28 mmol). The system was purged with argon and equipped with a condenser, under nitrogen atmosphere. The mixture was irradiated (UV lamp, 365 nm) through a Pyrex filter for 48 h. The solution was concentrated and chromatographed on silica gel (10% acetone in hexanes) to give 317 mg (50%) of the desired compound **23** (with ~50% of recovered starting material): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.20–7.55 (m, 10 H), 5.52 (d, J = 3.7 Hz, 1 H), 4.95–5.40 (m, 4 H), 4.49–4.79 (m, 1 H), 3.82–3.97 (m, 1 H), 3.56–3.82 (m, 4 H), 1.50 (s, 3 H), 1.42 (s, 3 H), 0.88 (s, 9 H), 0.20 (s, 6 H); IR ($CHCl_3$) 2940, 2920, 2880, 2840, 1770, 1720, 1650, 1450, 1290 cm^{-1}; HRMS (M^+ + H) calcd for $C_{31}H_{43}O_8N_2Si$ 599.2790, found 599.2799.

2-[1,2-Bis(benzyloxycarbonyl)hydrazino]-3-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-4,6-*O*-isopropylidene-D-glucopyranose (24). A solution containing cycloadduct **23** (175 mg, 0.293 mmol), tetrahydrofuran (6 mL), water (0.2 mL), and pyridinium p-toluenesulfonate (5 mg) was stirred at room temperature for 3 h. Then saturated aqueous sodium bicarbonate and brine were added and the mixture was extracted with ethyl acetate (4 × 15 mL). The organic portion was dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude was chromatographed (20% acetone in hexanes) to afford 160 mg (89%) of a white solid **24**: mp 157–160 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.20–7.60 (m, 10 H), 6.20–6.63 (br s, 1 H), 4.87–5.50 (m, 4 H), 3.12–4.31 (m, 5 H), 1.89 (m, 3 H), 1.42 (m, 3 H), 0.83 (s, 9 H), 0.07 (s, 6 H); IR ($CHCl_3$) 3380, 2940, 2840, 1740, 1480, 1450, 1400, 1260, 1220, 1120, 1050 cm^{-1}; HRMS (M^+ + H) calcd for $C_{31}H_{45}O_9N_2Si$ 617.2896, found 617.2868.

2-Acetamido-3-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-4,6-*O*-isopropylidene-D-glucopyranose (25). Compound **24** (74 mg, 0.12 mmol) was dissolved in 2 mL of a 60:1 methanol–acetic acid solution and 200 μL of ethyl acetate. A catalytic amount of Raney nickel was added and the compound was hydrogenated (overnight) by using a Parr shaker (60 psi). The reaction mixture was filtered through Celite, washed with methanol, and concentrated. The crude was dissolved in methylene chloride (3 mL) and triethylamine (67 μL, 0.48 mmol), acetic anhydride (34 μL, 0.36 mmol), and a catalytic amount of 4-(dimethylamino)-pyridine were added. The reaction was complete in 1 h, and the mixture was concentrated in vacuo. Flash chromatography (50% ethyl acetate in hexanes) of the residue afforded 15 mg (30%) of a mixture (α:β, 3:1, by NMR) which was separated by HPLC (40% ethyl acetate in hexanes). ^{1}H NMR (250 MHz, $CDCl_3$) (β-anomer) δ 5.79 (d, J = 8.6 Hz, 1 H), 5.31 (d, J = 9.5 Hz, 1 H), 3.71–3.97 (m, 4 H), 3.55 (dd, J = 8.5, 9.4 Hz, 1 H), 3.38 (dd, J = 9.9, 5.2 Hz, 1 H), 2.12 (s, 3 H), 1.98 (s, 3 H), 1.48 (s, 3 H), 1.42 (s, 3 H), 0.88 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H); ^{1}H NMR (250 MHz, $CDCl_3$) (α-anomer) 6.08 (d, J = 3.9 Hz, 1 H), 5.22 (d, J = 9.4 Hz, 1 H), 4.38 (ddd, J = 9.2, 5.4, 3.9 Hz, 1 H), 3.83–3.88 (m, 1 H), 3.60–3.80 (m, 4 H), 2.18 (s, 3 H), 1.99 (s, 3 H), 1.49 (s, 3 H), 1.42 (s, 3 H), 0.87 (s, 9 H), 0.09 (s, 6 H); IR ($CHCl_3$) 3430, 3000, 1750, 1670, 1520, 1370, 1260, 1130, 1070, 1020 cm^{-1}.

Acknowledgment. This research was supported by PHS Grant AI 16943. An NIH Postdoctoral Fellowship (Grant 1 F32 CA07586 to M.B. is gratefully acknowledged. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which was supported by NSF Chemistry Division Grant CHE 7916210.

Supplementary Material Available: Experimental procedures and characterizations documenting ref 8 and Figure 2 (19 pages). Ordering information is given on any current masthead page.

(30) The ^{1}H NMR spectrum (490 MHz) of this compound is virtually superimposable with that of the corresponding regions of compound **17**,[8,29] which was compared to an authentic sample.

(31) Blackburne, I. D.; Fredericks, P. M.; Guthrie, R. D. *Aust. J. Chem.* **1976**, *29*, 381.