Synthetic Studies of the Tunicamycin Antibiotics. Preparation of (+)-Tunicaminyluracil, (+)-Tunicamycin-V, and 5′-*epi*-Tunicamycin-V

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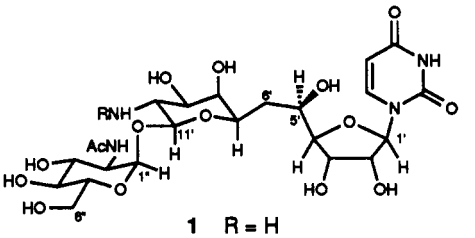
Abstract: A concise synthetic route to the tunicamycin antibiotics is described, illustrated by the preparation of (+)-tunicamycin-V (**1-V**). Key features of the synthesis include (1) the development and application of a silicon-mediated reductive coupling of aldehydes and allylic alcohols to construct the undecose core of the natural product and (2) the development of an efficient procedure for the synthesis of the trehalose glycosidic bond within the antibiotic. These innovations allow for the coupling of a uridine-derived aldehyde fragment with a performed trehalose-linked disaccharide allylic alcohol to form the carbohydrate core (**1**) of the natural product in a highly covergent manner. The resultant amino polyol is a versatile intermediate for the synthesis of any of the homologous tunicamycin antibiotics.

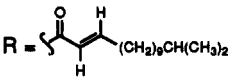
The tunicamycins, corynetoxins, and streptovirudins make up a unique class of microbial metabolites that inhibit various enzymatic processes involving the formation of phospholipid-linked intermediates. As a consequence, they elicit a range of biological responses, to include potent antimicrobial, antiviral, and antitumor activities.[1] Structurally, the more than thirty members of the class may be categorized as long-chain *N*-acyl derivatives of the core substructure **1** or, in the case of certain streptovirudins, its dihydrouracil analog. The *N*-acyl appendages vary in length and in degree of unsaturation, branching, and hydroxylation. Representative examples are depicted below.

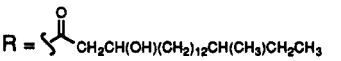
Consideration of these antibiotic structures has led to the proposal that they function as bisubstrate analogs for the enzymes they inhibit.[2] In prokaryotic systems, for example, the tunicamycins block the exchange of uridine diphosphate *N*-acetylmuramic acid pentapeptide with a phospholipid carrier, thus inhibiting cell wall biosynthesis.[3] In eukaryotic systems, they block the transfer of *N*-acetylglucosamine-1-phosphate from its UDP-activated precursor uridine diphosphate *N*-acetylglucosamine to the phospholipid dolichol phosphate, thereby inhibiting oligosaccharide biosynthesis.[4]

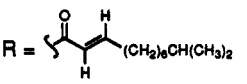
Given the substantial structural differences between the substrates of these enzymatic transformations, it is reasonable to propose that these processes might respond differently to variations in antibiotic structure and that the relative inhibitory activities of different tunicamycins might differ as a consequence. An ambiguity in most biological studies of the tunicamycins conducted thus far is that complex and varying mixtures of tunicamycins, as obtained by fermentation, are typically assayed. Separation of these mixtures is tedious, requiring the use of reverse-phase



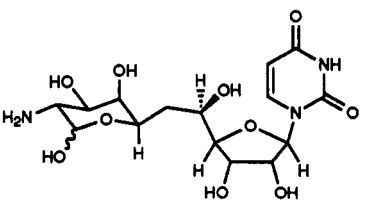
1 R = H

Tunicamycin-V (**1-V**) R = 

Corynetoxin-H19a* R = 

Streptovirudin-A_1 R = 

* Stereochemistry of acyl appendage undetermined.



Tunicaminyluracil (**2**)

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(1) Isolation and structure elucidation of tunicamycin: (a) Takatsuki, A.; Arima, K.; Tamura, G. *J. Antibiot.* **1971**, *24*, 215. (b) Kenig, M.; Reading, C. *J. Antibiot.* **1979**, *32*, 549. (c) Hamill, R. L.; U.S. Patents 4,273,225, 1980; 4,336,333, 1982. (d) Ito, T.; Kodama, Y.; Kawamura, K.; Suzuki, K.; Takatsuki, A.; Tamura, G. *Agric. Biol. Chem.* **1977**, *41*, 2303. (e) Takatsuki, A.; Kawamura, K.; Okina, M.; Kodama, Y.; Ito, T.; Tamura, G. *Agric. Biol. Chem.* **1977**, *41*, 2307. (f) Takatsuki, A.; Kawamura, K.; Kodama, Y.; Ito, T.; Tamura, G. *Agric. Biol. Chem.* **1979**, *43*, 761. (g) Ito, T.; Takatsuki, A.; Kawamura, K.; Sato, K.; Tamura, G. *Agric. Biol. Chem.* **1980**, *44*, 695. Reviews of tunicamycin: (h) Elbein, A. *Trends Biochem.* **1981**, 219. (i) *Tunicamycin*; Tamura, G., Ed.; Japan Scientific Press: Tokyo, Japan, 1982. Corynetoxins and streptovirudins: (j) Eckardt, K. *J. Nat. Prod.* **1983**, *46*, 544. (k) Vogel, P.; Patterson, D. S.; Berry, P. H.; Frahn, J. L.; Anderton, N.; Cockrum, P. A.; Edgar, J. A.; Jago, M. V.; Lanigan, G. W.; Payne, A. L.; Culvenor, C. C. J. *Aust. J. Exp. Biol. Med. Sci.* **1981**, *59*, 455. (l) Edgar, J. A.; Frahn, J. L.; Cockrum, P. A.; Anderton, N.; Jago, M. V.; Culvenor, C. C. J.; Jones, A. J.; Murray, K. E.; Shaw, K. J. *J. Chem. Soc., Chem. Commun.* **1982**, 222. (m) Thrum, H.; Eckardt, K.; Bradler, G.; Fuegner, R.; Tonew, E.; Tonew, M. *J. Antibiot.* **1975**, *28*, 514. (n) Eckardt, K.; Thrum, H.; Bradler, G.; Tonew, E.; Tonew, M. *J. Antibiot.* **1975**, *28*, 274. (o) Eckardt, K.; Ihn, W.; Tresselt, D.; Krebs, D. *J. Antibiot.* **1981**, *34*, 1631.

(2) (a) Ito, T.; Kodama, Y.; Kawamura, K.; Suzuki, S.; Takatsuki, A.; Tamura, G. *Agric. Biol. Chem.* **1979**, *43*, 1187. (b) See ref 1e.

(3) (a) Takatsuki, A.; Shimizu, K.; Tamura, G. *J. Antibiot.* **1972**, *25*, 75. (b) Tamura, G.; Sasaki, T.; Matsuhashi, M.; Takatsuki, A.; Yamasaki, M. *Agric. Biol. Chem.* **1976**, *40*, 447.

(4) (a) Takatsuki, A.; Kohno, K.; Tamura, G. *Agric. Biol. Chem.* **1975**, *39*, 2089. (b) Tkacz, J. S.; Lampen, J. O. *Biochem. Biophys. Res. Commun.* **1975**, *65*, 248.

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HPLC; thus, in practical terms, only milligram quantities of any given pure tunicamycin are available.[5] For this reason, and in light of the potent biological activity of the tunicamycins, we have developed an efficient synthetic route to the tunicamycin antibiotics,[6] described in full herein.

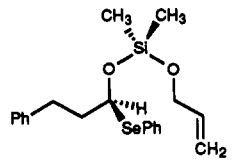
Synthetic Plan

Retrosynthetic analysis of the tunicamycins as a class suggests that one highly versatile strategy for their preparation would involve the selective *N*-acylation of the precursor **1** as the final synthetic step. Two challenges emerge upon consideration of the simplified precursor **1** as a synthetic target: (1) the construction of the undecose fragment, tunicaminyluracil (**2**), from readily available precursors and (2) the efficient formation of the trehalose disaccharide linkage with proper stereochemistry.

Given the complexity of the tunicaminyluracil substructure (**2**) in terms of stereochemistry and functionality, it is not surprising that previous efforts to synthesize the tunicamycins have focused initially on the preparation of **2**, deferring formation of the trehalose disaccharide linkage to a later stage.[7,8] These same studies have shown, however, that the latter problem is perhaps as difficult as the former. In the single reported synthesis of a natural tunicamycin prior to studies described herein, Suami *et al.*[7] described the successful late-stage formation of the trehalose linkage via a modified Koenigs–Knorr carbohydrate construction, albeit proceeding in poor yield (18%). In a detailed study, Danishefsky and co-workers[8] noted that a similar coupling reaction involving nearly identical precursors did not proceed according to precedent; these authors point out that the earlier successful coupling had been achieved with retrosynthetically derived material and was conducted on a relatively large scale. These observations proved invaluable in the development of our synthetic plan, where it was determined to conduct the trehalose bond-forming step at an early stage in the synthesis.

The undecose substructure within **1** may be viewed as the product of the coupling of uridine and galactosamine residues through carbons C5′ and C6′, respectively. Suami *et al.* employed a related coupling reaction in their synthesis of tunicaminyluracil (**2**),[7c] while Danishefsky *et al.* established this bond by an organometallic addition reaction with subsequent development of the galactosamine fragment by de novo construction.[8] Our retrosynthetic analysis of **1** also targeted the C5′–C6′ bond for disconnection; however, we planned to employ a new method for this bond formation that allowed for the use of simple precursors derived from uridine and galactosamine.[6b]

Exploratory studies had shown that when a solution of dihydrocinnamaldehyde (1 equiv) in pyridine was treated sequentially with benzeneselenol[9] (1.0 equiv, 23 °C, 15 min), excess dichlorodimethylsilane (14 equiv, 23 °C, 16 h, excess reagent removed in vacuo), and allyl alcohol (1.0 equiv, 23 °C, 1 h), the *O*-silyl hemiselenoacetals **3** were formed in high yield (>90%).[10] Subsequent exposure of *O*-silyl hemiselenoacetals **3** to tributyltin hydride (2.2 equiv) at 60 °C in toluene in the presence of the radical initiator 2,2′-azobis(isobutyronitrile) (AIBN, 0.06 equiv) led to a 7-*endo*-trig ring closure to form the siloxane **4** (62%) together with a small amount of noncyclized reduction product **5** (11%). No product arising from 6-*exo*-trig cyclization



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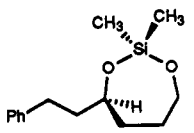

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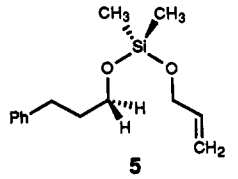
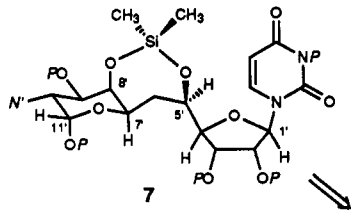


5

was observed, perhaps a consequence of the length of the Si–O bonds.[11] This procedure allowed for the mild and efficient coupling of aldehydes and allylic alcohols and generated a siloxane-protected 1,4-diol functionality, a retron that maps onto the C5′–C8′ substructure within **1**. A substrate such as the *O*-silyl hemiselenoacetal **6**, prepared from an appropriate uridine 5′-aldehyde derivative and a galactosamine-derived allylic alcohol, was thus envisioned to undergo a similar silicon-mediated reductive coupling to form the siloxane **7**. For the proposed retrosynthetic disconnection to be valid, it was critical that the newly formed stereogenic centers at C5′ and C7′ be established with correct stereochemistry. The stereochemical outcome at C7′ was predicted to be the desired *R* configuration for the following reasons: (1) glycosyl radicals are known to react to form axial bonds preferentially,[12] and (2) equatorial C–H bond formation would result in a prohibitively strained ring system. The stereochemistry of C5′, on the other hand, was less easily predicted (vide infra). To investigate the feasibility of the proposed bond formation and its potential application in a synthesis of **1**, the reductive coupling procedure was first examined in the context of a synthesis of tunicaminyluracil (**2**).



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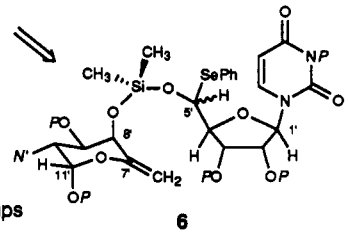


P = various protecting groups

6

Synthesis of (+)-Tunicaminyluracil (2)

To apply the hemiselenoacetal reductive coupling methodology described above in a synthesis of tunicaminyluracil (**2**), the allylic

(5) (a) Mahoney, W. C.; Duksin, D. *J. Chromatogr.* **1980**, *198*, 506. (b) See ref 1g.

(6) Preliminary accounts of this work: (a) Myers, A. G.; Gin, D. Y.; Rogers, D. H. *J. Am. Chem. Soc.* **1993**, *115*, 2036. (b) Myers, A. G.; Gin, D. Y.; Widdowson, K. L. *J. Am. Chem. Soc.* **1991**, *113*, 9661.

(7) (a) Suami, T.; Sasai, H.; Matsuno, K.; Suzuki, N. *Carbohydr. Res.* **1985**, *143*, 85. (b) Suami, T.; Sasai, H.; Matsuno, K.; Suzuki, N.; Fukuda, Y.; Sakanaka, O. *Tetrahedron Lett.* **1984**, *25*, 4533. (c) Suami, T.; Sasai, H.; Matsuno, K. *Chem. Lett.* **1983**, 819.

(8) (a) Danishefsky, S. J.; DeNinno, S. L.; Chen, S.; Boisvert, L.; Barbachyn, M. *J. Am. Chem. Soc.* **1989**, *111*, 5810. (b) Danishefsky, S.; Barbachyn, M. *J. Am. Chem. Soc.* **1985**, *107*, 7761.

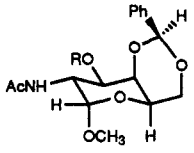
(9) Foster, D. G. *Organic Synthesis*; Horning, E. C., Ed.; John Wiley and Sons: New York, 1955; Collect. Vol. 3, pp 771–773.

(10) For existing methods for the formation of *O*-trimethylsilyl hemithio- and hemiselenoacetals, see: (a) Chan, T. H.; Ong, B. S. *Tetrahedron Lett.* **1976**, 319. (b) Dumont, W.; Krief, A. *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 540. (c) Glass, R. S. *Synth. Commun.* **1976**, *6*, 47. (d) Evans, D. A.; Truesdale, L. K.; Grimm, K. G.; Nesbitt, S. L. *J. Am. Chem. Soc.* **1977**, *99*, 5009. (e) Liotta, D.; Paty, P. B.; Johnston, J.; Zima, G. *Tetrahedron Lett.* **1978**, *5091*. (f) Sassaman, M. B.; Surya, Prakash, G. K.; Olah, G. A. *Synthesis* **1990**, 104.

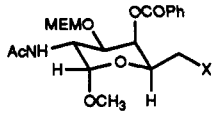
(11) The increased tendency for *endo* attack in ring systems incorporating silicon, as opposed to all-carbon systems, has been rationalized by trajectory analysis: Wilt, J. W.; Lusztyk, J.; Perran, M.; Ingold, K. U. *J. Am. Chem. Soc.* **1988**, *107*, 281.

(12) (a) Giese, B.; Dupuis, J. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 622. (b) Adlington, R. M.; Baldwin, J. E.; Basak, A.; Kozyrod, R. P. *J. Chem. Soc., Chem. Commun.* **1983**, 944. (c) Baumberger, F.; Vasella, A. *Helv. Chim. Acta* **1983**, *66*, 2210. (d) Dupuis, J.; Giese, B.; Ruegge, D.; Fischer, H.; Korth, H.-G.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 896. (e) Korth, H.-G.; Sustmann, R.; Dupuis, J.; Giese, B. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1453.

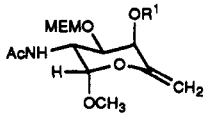
alcohol **13** was synthesized from α-methyl 2-(acetylamino)-4,6-*O*-benzylidenegalactopyranoside (**8**),[13] prepared as a single anomer in 55% yield (mp 165.0–166.3 °C, ethyl alcohol) from commercial *N*-acetylgalactosamine. In initial investigations,



8 R = H
9 R = MEM



10 X = Br
11 X = SePh



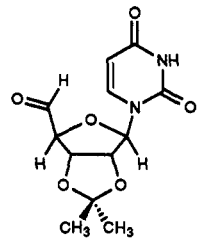
12 R^1 = COPh
13 R^1 = H

alcohol **8** was protected as the corresponding 3-*O*-*tert*-butyldimethylsilyl ether derivative; however, the silyl protecting group was later shown to be inappropriate due to its propensity to migrate upon deprotection of the C4-hydroxyl functionality. Consequently, **8** was protected as the 3-*O*-methoxyethoxymethyl (MEM) ether[14] **9** (MEM chloride (5.0 equiv), diisopropylethylamine (10 equiv), tetrahydrofuran (THF), 60 °C, 2 h, 75%). Generation of the C6-*exo*-methylene functional group from **9** was initiated by oxidative cleavage of the 4,6-*O*-benzylidene acetal. Thus, exposure of **9** to *N*-bromosuccinimide (NBS, 1.3 equiv) and barium carbonate (1.6 equiv) in refluxing carbon tetrachloride for 2 h[15] efficiently formed the bromide **10** (87%). It was necessary to employ the anomeric methyl galactopyranoside in the latter transformation because the corresponding benzyl galactopyranoside underwent competitive oxidation of the benzyl group. In efforts to generate the C6-*exo*-methylene functionality from **10** by the direct elimination of hydrogen bromide (*e.g.*, silver fluoride, pyridine;[16] triethylamine, benzene, reflux; silver carbonate, isooctane, reflux), **10** was found to be unreactive, presumably a consequence of steric shielding of the C5-hydrogen by the axial C1-methoxyl substituent. Elimination was therefore induced in a two-step procedure involving the initial treatment of the bromide **10** with benzeneselenol (3.0 equiv) in the presence of triethylamine (6.0 equiv) in refluxing dimethoxyethane (DME) for 18 h to generate the phenylselenide **11** (96%). Oxidation of the phenylselenide **11** with *m*-chloroperoxybenzoic acid (*m*-CPBA, 1.5 equiv) in carbon tetrachloride at −14 °C for 1 h, followed by thermal elimination of the resulting selenoxide (carbon tetrachloride, reflux, 5 h),[17] afforded the allylic benzoate **12** in 99% yield. Removal of the C4-benzoyl ester group of **12** was accomplished by transesterification with potassium carbonate (3.0 equiv) in methyl alcohol at 23 °C for 3 h to yield the allylic alcohol **13** (92%).

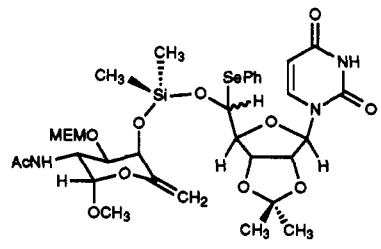
The uridine 5′-aldehyde derivative **14** was prepared as the initial coupling partner for the allylic alcohol **13** and was synthesized from commercial 2′,3′-isopropylideneuridine. Oxidation of 2′,3′-isopropylideneuridine following the procedure of Corey and Samuelsson (chromium trioxide (4.0 equiv), pyridine (8.0 equiv), acetic anhydride (4.0 equiv), dichloromethane, *N*,*N*-dimethylformamide (DMF), 23 °C, 20 min)[18] afforded **14** in 55% yield.

(13) Stoffyn, P. J.; Jeanloz, R. W. *J. Am. Chem. Soc.* **1954**, *76*, 561, 563.
(14) Corey, E. J.; Gras, J. L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809.
(15) Hanessian, S. *Carbohydr. Res.* **1966**, *2*, 86.
(16) Horton, D.; Weckerle, W. *Carbohydr. Res.* **1975**, *44*, 227.
(17) Reich, H. J.; Wollowitz, S.; Trend, J. E.; Chow, F.; Wendelborn, D. F. *J. Org. Chem.* **1978**, *43*, 1679.
(18) Corey, E. J.; Samuelsson, B. *J. Org. Chem.* **1984**, *49*, 4735.

The aldehyde **14**, like many others synthesized during the course of our investigations, underwent ready hydration and was unstable to purification by conventional chromatography on silica gel. Aldehyde **14** was partially purified in its hydrated form by flash chromatography on silica gel at −14 °C. Regeneration of the aldehyde was readily accomplished by the azeotropic removal (toluene) of water from the hydrate.



14

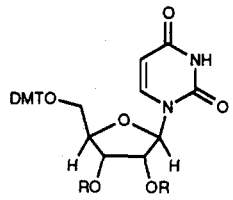


15

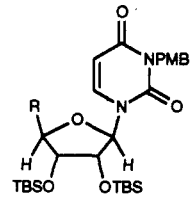
Initial attempts to construct the *O*-silyl hemiselenoacetal **15** from **14** and the allylic alcohol **13** employed the procedure developed for the coupling of hydrocinnamaldehyde and allyl alcohol (see above). Thus, treatment of the aldehyde **14** (2.0 equiv) with benzeneselenol (2.0 equiv) in pyridine at 23 °C for 1 h, addition of dichlorodimethylsilane (20 equiv, 8 h), removal of excess dichlorodimethylsilane in vacuo, and addition of a solution of allylic alcohol **13** (1 equiv) in pyridine at 23 °C produced the adducts **15** in modest yield as a 1:1 mixture of diastereomers at C5′. Purification of the diastereomers **15** proved to be difficult due to their instability to column chromatography; as a result, the crude adducts (approximately 60% pure) were subjected directly to conditions conducive to free radical cyclization. Addition of a solution of tributyltin hydride (2.5 equiv, 10 mM) and AIBN (0.05 equiv) in toluene over a period of 10 h to a solution of diastereomers **15** in refluxing toluene (1 mM), followed by treatment of the crude product mixture with potassium fluoride hydrate in methyl alcohol, afforded only the reduction product 2′,3′-isopropylideneuridine and recovered allylic alcohol **13**, indicating that trapping of the C5′-radical with tributyltin hydride was faster than cyclization.

This unfavorable result in the initial cyclization attempt prompted the preparation of a second *O*-silyl hemiselenoacetal derivative (**20**). This derivative incorporated a protecting group for the imido functionality and, with the greater steric bulk of the 2′-*O*- and 3′-*O*-sily ethers, was felt to be better disposed toward intramolecular cyclization through shielding of the C5′-radical intermediate from bimolecular trapping. Preparation of **20** began with the treatment of uridine with dimethoxytrityl chloride (1.0 equiv) in pyridine at 23 °C for 12 h.[19] The resultant dimethoxytrityl ether **16** was combined with excess *tert*-butyldimethylsilyl chloride (6.0 equiv) and imidazole (12 equiv) in DMF at 23 °C for 13 h to afford the bis(*tert*-butyldimethylsilyl) ether **17** in 93% yield from uridine. Exposure of **17** to *p*-methoxybenzyl chloride (2.0 equiv) and sodium hydride (1.5 equiv) in DMF at 0 °C for 4.5 h afforded the corresponding *N*-(*p*-methoxybenzyl) derivative. Subsequent removal of the dimethoxytrityl protecting group with a solution of benzenesulfonic acid in chloroform (2% (w/w)) at 0 °C for 5 min[20] provided the alcohol **18** in 82% yield for the two steps. The use of the *p*-methoxybenzyl protecting group for the imido functionality of uracil is precedented in the work of Danishefsky and co-workers in their synthesis of tunicaminyluracil.[8] Efforts to oxidize **18** to the corresponding aldehyde (**19**) employing a number of standard reagents (pyridinium dichromate, chromium trioxide in pyridine, or 1,3-dicyclohexylcarbodiimide and dimethyl sulfoxide) were complicated by the formation of

(19) Smith, M.; Rammler, D. H.; Goldberg, H.; Khorana, H. G. *J. Am. Chem. Soc.* **1962**, *84*, 430.
(20) Stawiński, J.; Hozumi, T.; Narang, S. A.; Bahl, C. P.; Wu, R. *Nucleic Acid Res.* **1977**, *4*, 353.

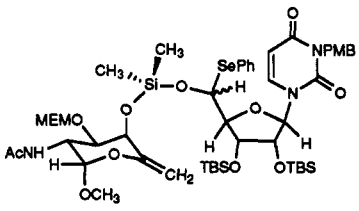


16 R = H
17 R = TBS

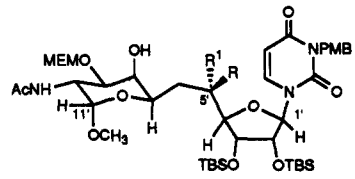


18 R = CH_2OH
19 R = CHO

byproducts that could not be readily separated from **19**. Only the Swern oxidation[21] (oxalyl chloride (6.2 equiv), dimethyl sulfoxide (9.4 equiv), triethylamine (15 equiv), dichloromethane, −78 °C, 45 min) afforded product **19** of sufficient purity (~90%) to carry on with the reductive cyclization procedure. Subjection of the crude aldehyde **19** (2.0 equiv) to the coupling conditions described above (benzeneselenol (2.0 equiv), pyridine, 23 °C; dichlorodimethylsilane (20 equiv); **13** (1 equiv)) afforded the *O*-silyl hemiselenoacetals **20** in 92% yield as a 1:1 mixture of C5′-diastereomers after purification by flash column chromatography. The stability of *O*-silyl hemiselenoacetals **20** to silica gel is notable in light of the lability of the hemiselenoacetals **15** previously encountered.



20



21 R^1 = OH, R = H
22 R^1 = H, R = OH

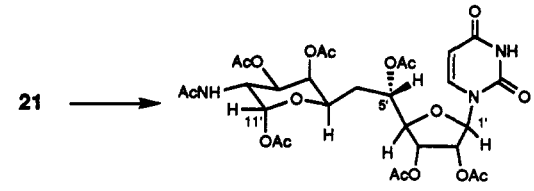
A series of experiments were performed to evaluate the feasibility of carbon–carbon bond formation within the hemiselenoacetals **20** (Table 1). Treatment of a solution of the hemiselenoacetals **20** with tributyltin hydride in the presence of a free radical initiator led to efficient intramolecular cyclization to form a mixture of epimeric adducts whose diastereomeric ratio varied markedly with the choice of solvent. Direct treatment of the crude product mixture with potassium fluoride hydrate in methyl alcohol produced the diastereomeric diols **21** and **22** in 40–80% yield from **20**. These diastereomers could be separated by preparative thin-layer chromatography or radial chromatography to afford each C5′-diastereomer in pure form. To establish the stereochemistry of the cyclization products, each of the diols **21** and **22** was separately deprotected (ceric ammonium nitrate, acetonitrile, water, 60 °C, 3 h;[22] 3 N hydrochloric acid, reflux, 3 h) and was peracetylated (acetic anhydride, 4-(*N*,*N*-dimethylamino)pyridine (DMAP), dichloromethane, 0 °C, 2 h) to give α-heptaacetyl-5′-*epi*-tunicaminyluracil (**23**) from **21** and α-heptaacetyltunicaminyluracil (**24**) from **22** after preparative thin-layer chromatography. These products were compared with an authentic sample of α-heptaacetyltunicaminyluracil (**24**), prepared from a mixture of tunicamycins according to the procedure of Tamura *et al.*[1d]

(21) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
(22) Johansson, R.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2371.

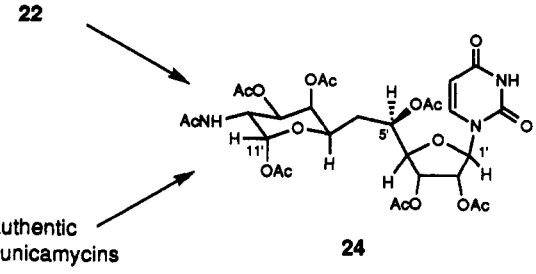
Table 1. Reductive Coupling of **20**: Solvent and Temperature Effects[a]

solvent	temperature[b] (°C)	product ratio[c] **22** (desired):**21** (undesired)
$PhCH_3$	110	1.0:3.0
$PhCH_3$	60	1.0:3.2
$PhCH_3$	50	1.0:4.2
$PhCH_3$	−78 → 23	1.0:5.3
THF	60	1.0:2.2
10% H_2O:THF	60	1.0:2.0
10% DMF:THF	60	1.0:3.0
CH_3CN	23	1.9:1.0
CH_3CN	0	2.4:1.0
CH_3CN	−5	2.9:1.0
CH_3CN	−14 → 0	3.1:1.0
$(CH_3)_2CHOH$	0	1.9:1.0
$(CH_3)_2CHOH$	−78 → 23	1.9:1.0
CH_3CH_2OH	65	1.0:1.0
CH_3CH_2OH	0	1.7:1.0
CH_3OH	0	3.7:1.0
0.06% H_2O:CH_3CN	0	2.4:1.0
0.06% H_2O:CH_3CN	−14 → 23	2.3:1.0
20% CH_3OH:CH_3CN	0	2.9:1.0
20% CH_3OH:CH_3CN	−20 → 23	2.1:1.0

[a] Reactions were performed employing 3–5 mg of **20** (1 equiv, 1 mM) and 10 equiv of Bu_3SnH. [b] Reactions performed at or below 23 °C were initiated with Et_3B and oxygen. Reactions conducted at temperatures >23 °C were initiated by the slow addition of a solution of Bu_3SnH (10 equiv) and AIBN (0.05 equiv) at 23 °C. [c] Yields were generally >70%, except for those reactions carried out in protic solvents, which afforded yields of ~40%. The major byproduct in all cases was that of hydrogen-atom addition to the radical site.



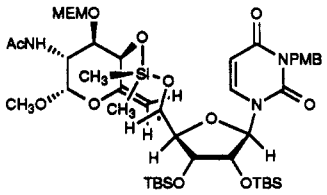
23



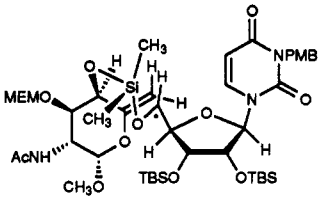
Authentic Tunicamycins

24

In general, the use of nonpolar solvents (toluene, THF) in the free radical cyclization was found to favor the formation of the undesired epimer (**21**) from **20**, whereas polar solvents (acetonitrile, methyl alcohol) favored the formation of the desired isomer **22**. Hypothetical transition structures **25** and **26** leading to these isomers, respectively, are depicted below. In both structures, attack of the C5′-radical is invoked to occur opposite the bulky *tert*-butyldimethylsilyl ether substituents. The manner in which the solvent polarity apparently influences the stereochemical outcome of the cyclization reaction is not at all evident, and the validity of transition structures **25** and **26** is certainly open to question. Nevertheless, the role of the solvent in the reaction provides a useful device for practical syntheses of either stereoisomer. The optimal protocol for the preparation of the desired stereoisomer (**22**) involved the addition of tributyltin hydride



25



26

(2.0 equiv) and triethylborane[23] (0.25 equiv) to a solution of *O*-silyl hemiselenoacetals **20** (1 mM, 1 equiv) in acetonitrile at −8 °C. Treatment of the crude product mixture with potassium fluoride hydrate in methyl alcohol and purification of the resulting diol mixture by radial chromatography afforded the pure diol **22** in 62% yield and the pure diol **21**, isolated in separate fractions, in 18% yield. Although reactions conducted in methyl alcohol produced an increased proportion of **22** relative to reactions conducted in acetonitrile, the increased formation of the reduction product **18** in methyl alcohol led to a lower absolute yield.

Deprotection of the synthetic diol **22** (ceric ammonium nitrate (5.4 equiv), acetonitrile–water, 60 °C, 3 h; 3 N hydrochloric acid, reflux, 3 h) furnished synthetic tunicaminyluracil (**2**) in crude form. Peracetylation of synthetic **2** with excess acetic anhydride and DMAP in dichloromethane at 0 °C afforded, after preparative thin-layer chromatography, α-heptaacetyltunicaminyluracil (**24**, 43%), which was shown to be identical in all respects (^{1}H NMR, ^{13}C NMR, mp, FTIR, MS, HRMS, TLC, HPLC, optical rotation) with an authentic sample.

Synthesis of (+)-Tunicamycin-V (1-V)

The establishment of an efficient method for the formation of the C5′–C6′ carbon–carbon bond of tunicaminyluracil has provided the basis for a highly convergent synthesis of the tunicamycin antibiotics. In addition to the preparation of the undecose core, the latter endeavor required the development of a method for the construction of the β,α-trehalose linkage within **1**, a crucial problem that previously had been met with only modest success. In contrast to prior work, in which the trehalose bond was formed as a late-stage synthetic operation,[7,8] the approach described herein focused on glycosidic bond formation early in the synthesis, as the initial convergent step. Construction of the C5′–C6′ bond of the tunicaminyluracil core was deferred to a later stage in the synthesis, where the mild conditions of the silicon-mediated reductive coupling methodology projected to form this bond (see above) were anticipated to be compatible with the trehalose linkage. An advantage of this strategy was that it permitted the use of relatively simple carbohydrate precursors for the synthesis of the trehalose-linked disaccharide.

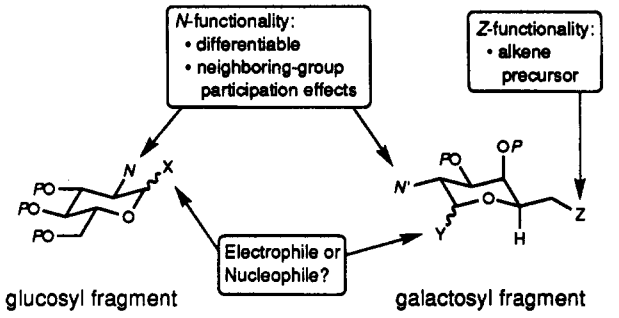
Synthesis of the β,α-Trehalose Linkage

Although the stereocontrolled synthesis of any glycosidic bond is inherently challenging, the preparation of disaccharides containing an ether linkage between anomeric carbons (trehalose linkage) is particularly so. Any such linkage is potentially disconnected retrosynthetically in two ways; in both disconnections the glycosyl acceptor (nucleophilic component) contains an anomeric hydroxyl group as the nucleophile. This compounds the difficulty of glycosidic bond formation by virtue of the poorer nucleophilicity of the anomeric hydroxyl group as compared with other alcohols and because the orientation of the anomeric hydroxyl group is ambiguous. As a consequence, trehalose-linked saccharides are seldom prepared efficiently.

The traditional method of glycosidic bond formation, originating with Koenigs and Knorr in 1901,[24] suffers from several disadvantages, to include[25] (1) the difficulty of stereocontrolled synthesis of the glycosyl halide coupling partners, (2) the thermal and hydrolytic instability of these halides, (3) the use of toxic or potentially explosive heavy-metal salts in the coupling reaction, and (4) the frequently poor efficiency of the coupling reactions, particularly with hydroxyl groups of low nucleophilicity.

For these reasons, and given the documented poor performance of the Koenigs–Knorr methodology in the context of synthesis of the tunicamycin trehalose linkage,[7,8] our studies focused on the methodology of Schmidt *et al.* for glycosidic bond formation. Also known as the trichloroacetimidate method,[26] the Schmidt protocol entails the coupling of an anomeric trichloroacetimidate (glycosyl donor) with the nucleophilic hydroxyl group of a glycosyl acceptor. Advantages of this method include (1) the ease of synthesis of trichloroacetimidates of either α- or β-configuration, (2) the thermal and hydrolytic stability of the glycosyl trichloroacetimidates, (3) mild conditions for glycosidic bond formation, typically catalyzed by Lewis acid, and (4) the efficiency and stereoselectivity of these coupling reactions. The trichloroacetimidate methodology has seen limited use in the synthesis of the disaccharides containing the trehalose linkage.[27]

In retrosynthetic analysis of the tunicamycin trehalose-linked disaccharide, primary consideration must be given to the assignment of the roles of electrophile and nucleophile to the galactosamine and glucosamine components. In addition, careful consideration must be given to the choice of protective groups for each C2-amino functionality and to the potential role of that protective group in the glycosylation reaction. Similar considerations apply to the hydroxyl groups of each sugar. In addition, the C6-substituent ("Z") of the galactosamine residue must function as a precursor to an *exo*-methylene group (C5–C6).



Protecting groups (*P*):
- stable during glycosylation and reductive coupling procedures
- easily removable in the presence of trehalose linkage

After extensive experimentation, the coupling partners **33** and **36** were found to serve as optimal substrates in an acid-promoted trichloroacetimidate glycosylation reaction to form the desired β,α-trehalose linkage (see below). This approach employed the galactosamine derivative **33** as the nucleophilic component in the

(23) Nozaki, K.; Koichiro, O.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547.

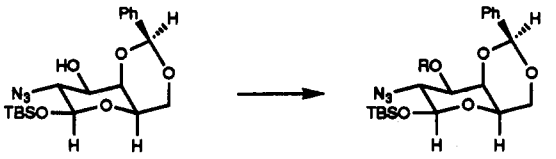
(24) Koenigs, W.; Knorr, E. *Chem. Ber.* **1901**, *34*, 957.

(25) Reviews of the Koenigs–Knorr method: (a) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155. (b) Paulsen, H. *Chem. Soc. Rev.* **1984**, *13*, 15.

(26) Reviews of the trichloroacetimidate method: (a) Schmidt, R. R. *Pure Appl. Chem.* **1989**, *61*, 1257. (b) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212.

(27) (a) Isheda, H.; Imai, Y.; Kiso, M.; Hasegawa, A.; Sakurai, T.; Azuma, I. *Carbohydr. Res.* **1989**, *195*, 59. (b) Paulsen, H.; Sumfleth, B. *Chem. Ber.* **1979**, *112*, 3203.

Table 2. Screening of 3-*O*-Protective Groups (R) for **27**[a]



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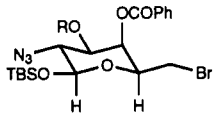
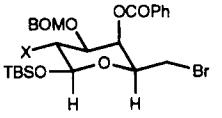
R	reagent	yield (%)	incompatibility
benzyl	benzyl bromide	84	removal during NBS-cleavage of benzylidene
SEM	SEMCl	95	removal during acid-catalyzed glycosylation
TBS	TBSCl	92	migration upon deprotection of C4-OH
acetyl	acetic anhydride	quantitative	migration to form C2-acetamide on azide reduction

[a] SEM = (trimethylsilyl)ethoxymethyl, TBS = *tert*-butyldimethylsilyl, NBS = *N*-bromosuccinimide.

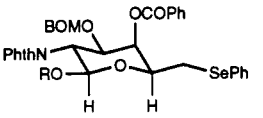
reaction. This component was synthesized from galactopyranoside **27**,[28] prepared by a four-step sequence from tri-*O*-acetyl-D-galactal in 23% yield. The 4,6-*O*-benzylidene acetal within **27** not only served to protect the C4- and C6-hydroxyl groups but also functioned as a precursor to the allylic alcohol functionality necessary for the reductive coupling that would form the undecose core of the tunicamycins. Because of concerns that the benzylidene acetal would not be stable under the acidic conditions of the glycosidic coupling procedure, the oxidative cleavage of this group was performed prior to the glycosidic coupling. Initially, it was deemed prudent to protect the C3-hydroxyl group before oxidative cleavage of the benzylidene acetal; however, after serious difficulties were encountered with four different types of protective groups (Table 2), the direct oxidative cleavage of **27**, with a free C3-hydroxyl group, was examined. Irradiation of a solution of **27** (0.077 M) in bromotrichloromethane with a 250-W sunlamp at 0 °C for 2.5 h[29] afforded the bromide **28** in 87% yield. The C3-hydroxyl group of **28** was then protected as the corresponding benzyloxymethyl (BOM) ether[30] (**29**, BOM chloride (5.0 equiv), diisopropylethylamine (5.5 equiv), dichloromethane, 55 °C, 15 h, 98%). The BOM ether **29** was found to be unreactive toward a variety of standard reagents developed for the reduction of azides,[31] presumably a consequence of steric shielding of the azido group by the adjacent *tert*-butyldimethylsilyloxy group. Only the treatment of **29** with benzeneselenol (3.0 equiv) in triethylamine at 60 °C for 2.5 h[32] efficiently formed the corresponding amine (**30**, 98%). Protection of the amine **30** with phthaloyl dichloride (2.0 equiv) in a mixture of toluene and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at 100 °C for 1.5 h afforded the phthalimide **31** in 86% yield. Displacement of the primary bromide within **31** using benzeneselenol (3.2 equiv) and triethylamine (12 equiv) in refluxing dimethoxyethane for 10 h efficiently furnished the phenylselenide **32** (95%). It was also possible to both reduce the azido group and displace the bromide by the treatment of **29** with benzeneselenol and triethylamine; however, the two-step procedure outlined above proceeded in higher yield. The phenylseleno group served as a masked form of the *exo*-methylene functionality neccessary for the planned reductive coupling protocol. Cleavage of the anomeric *tert*-butyldimethylsilyl ether **32** with triethylamine trihydrofluoride (8.7 equiv) in acetonitrile (23 °C, 6 h, 97%) produced the



28 R = H
29 R = BOM



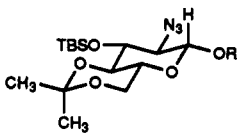
30 X = H_2N
31 X = PhthN



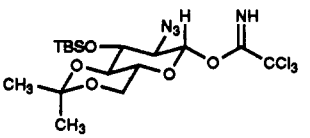
32 R = TBS
33 R = H

hemiacetal **33** as a 10:1 (β:α) mixture of anomers. The C2-phthalimido substituent is believed to favor the equatorial or β-orientation of the anomeric hydroxyl group, by virtue of a nonbonding steric interaction between a phthalimido carbonyl group and the anomeric hydroxyl group within the axial or α-anomer.[33] The β-orientation is required to prepare the trehalose linkage within the tunicamycins.

The coupling partner **36** was synthesized from the fully protected 2-azidoglucopyranoside **34**,[34] prepared by a four-step sequence in 27% yield beginning with tri-*O*-acetyl-D-glucal. Quantitative and selective cleavage of the anomeric silyl ether was accomplished by the treatment of **34** with potassium fluoride hydrate (5.5 equiv) in methyl alcohol at 23 °C for 6.5 h. Exposure of the hemiacetal **35** to a suspension of potassium carbonate (0.9 equiv) in trichloroacetonitrile and dichloromethane at 23 °C for 24 h provided the β-trichloroacetimidate **36** (64%) as well as recovered starting material (12%), after flash chromatography using triethylamine-treated silica gel.



34 R = TBS
35 R = H



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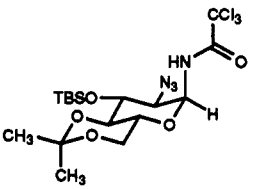

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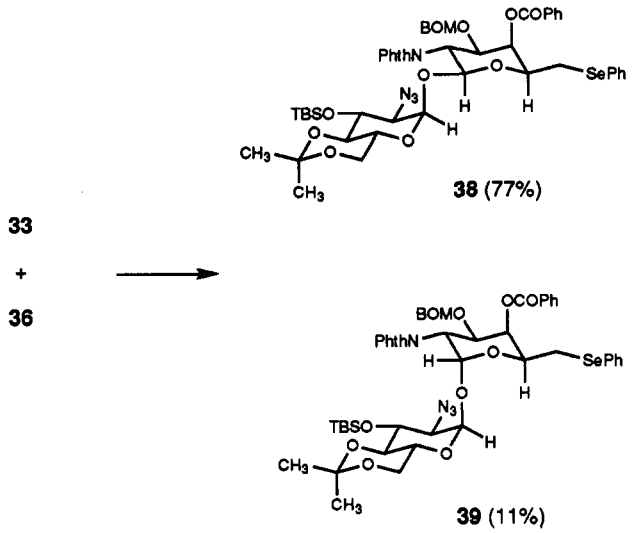
Literature procedures for the Schmidt coupling of anomeric trichloroacetimidates with alcohols typically involve the use of the Lewis acids boron trifluoride etherate or trimethylsilyl trifluoromethanesulfonate (TMSOTf).[26] Treatment of the coupling partners **33** and **36** with boron trifluoride etherate under a variety of conditions led only to the decomposition of **36**. The use of TMSOTf as catalyst did produce the coupled products **38** and **39** in low yield (<30% combined yield); the competitive rearrangement of **36** to the amide **37** accompanied this transformation. The latter coupling reaction appeared to exhibit induction periods of varying length, suggesting that trifluoromethanesulfonic acid (TfOH) might function as the actual catalyst in the reaction.[35] Indeed, coupling reactions employing

(28) Grundler, G.; Schmidt, R. R. *Liebigs Ann. Chem.* **1984**, 1826.
(29) Chana, J.; Collins, P. M.; Farina, F.; Peacock, D. J. *J. Chem. Soc., Chem. Commun.* **1988**, 94.
(30) Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97*, 6260.
(31) Scriven, E. F.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297.
(32) In our preliminary publication of this work, we were unaware of, and therefore did not cite, the following precedent for this transformation: (a) Bartra, M.; Romea, P.; Uprí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1990**, *46*, 587. (b) Bartra, M.; Felix, U.; Vilarrasa, J. *Tetrahedron Lett.* **1992**, *46*, 587. We thank Professor Vilarrasa for bringing this work to our attention.
(33) Lemiuex, R. U.; Takeda, T.; Chung, B. Y. *ACS Symp. Ser.* **1976**, *39*, 90.
(34) Kinzy, W.; Schmidt, R. R. *Liebigs Ann. Chem.* **1985**, 1537.
(35) For a related observation, see: Evans, D. A.; Kaldor, S. W.; Jones, K. J.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001.

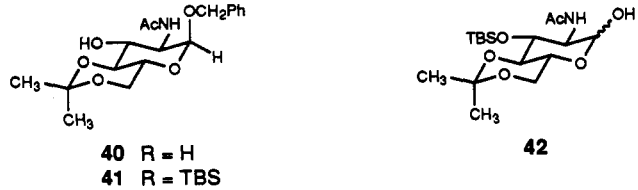
TfOH as the catalyst were found to be both rapid and efficient. In the optimum procedure, slow addition of a solution of TfOH (5% in toluene (v/v), 0.36 equiv total) to a solution of hemiacetal **33** (1 equiv) and trichloroacetimidate **36** (2.0 equiv) in dry toluene at 4-h intervals over a 24-h period at −20 °C produced the β,α-linked trehalose **38** in 77% yield after flash column chromatography. The α,α-diastereomer (**39**) was also isolated as a minor product (11%) in separate fractions. This procedure was found to be equally efficient on the milligram to 10-gram scale and represents a highly practical solution to the problem of stereocontrolled formation of the trehalose linkage within **1**.



Other Glycosylation Attempts

Prior to the development of the glycosylation procedure described above, early investigations into trehalose construction centered on a reversal of the roles of the galactosamine- and glucosamine-derived coupling partners. Initial efforts employed the *N*-acetylglucosamine derivative **42**[8] as the nucleophilic component in the glycosylation reaction. This was a logical

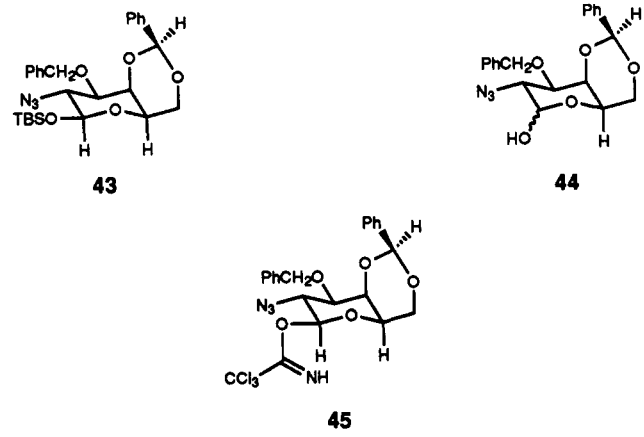
strategy to follow given that the tunicamycins contain an *N*-acetylglucosamine residue. The incompatibility of the C2-acetamido group with a leaving group at C1 (oxazoline formation) mandated that the *N*-acetylglucosamine residue serve as the nucleophilic component in the coupling reaction, if it were to be used at all. Protection of the known benzyl glucopyranoside **40**[36]



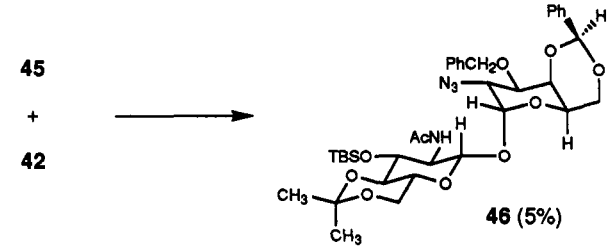
with *tert*-butyldimethylsilyl chloride (1.5 equiv) and imidazole (2.9 equiv) in DMF at 23 °C for 12 h furnished the silyl ether **41** in 98% yield. Reduction of **41** with lithium (2.0 equiv) in liquid ammonia at −78 °C produced the *N*-acetylglucosamine derivative **42** as a 2:1 (α:β) mixture of anomers in 72% yield.

(36) Hasegawa, A.; Kaneda, Y.; Amano, M.; Kiso, M.; Azuma, I. *Agric. Biol. Chem.* **1978**, *42*, 2187.

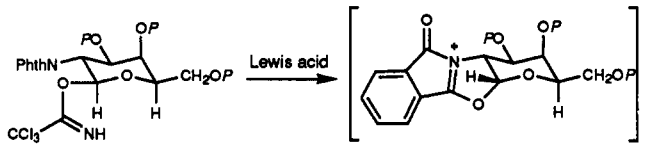
The galactose-derived trichloroacetimidate **45**, with a C2-azido substituent, was synthesized for initial coupling studies with **42**. The azido alcohol **27**, described above, was protected as its benzyl ether (**43**) using sodium hydride (1.2 equiv) and benzyl bromide (1.3 equiv) in THF at 23 °C for 8 h. Cleavage of the anomeric silyl ether with potassium fluoride hydrate in methyl alcohol at 23 °C furnished the anomeric alcohols **44** (1.5:1, α:β) in 75% yield. Treatment of the anomers **44** with excess trichloroacetonitrile and a catalytic quantity of DBU (0.05 equiv) in dichloromethane at 23 °C for 10 min afforded the β-trichloroacetimidate **45**, which was used in the coupling reaction without purification.

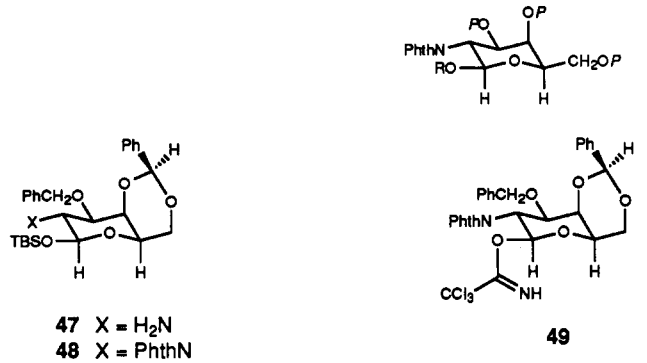


Exposure of a mixture of anomers **42** (3.0 equiv) and the trichloroacetimidate **45** (1 equiv) to TMSOTf (0.2 equiv) in dry dichloromethane at −20 °C for 6 h provided only trace quantities of coupling products; the anomeric alcohols **44** and **42** were the primary components of the reaction mixture. The disaccharide **46** containing the undesired α,β-trehalose configuration, was isolated in ~5% yield. It should be noted that this product was



formed with the incorrect stereochemistry at both anomeric positions. Although the configuration of the anomeric nucleophile (**42**) could not be controlled in any obvious way, there was ample precedent for the use of a C2-phthalimido group within the electrophilic component to direct nucleophilic attack in the desired (β) sense.[33] Toward this end, the glycosyl donor **49** was prepared, initiated by the reduction of the azido group of **43** with hydrogen sulfide in a mixture of pyridine and triethylamine (3.5:1 (v/v), 23 °C, 20 h) to furnish the amine **47** in 98% yield. Introduction of the phthalimido protecting group was accomplished by the treatment of **47** with phthaloyl dichloride (3 equiv) and DBU (6.4 equiv) in toluene at 100 °C for 3 h to provide the phthalimide **48** in 94% yield. Cleavage of the anomeric silyl ether of **48** with potassium fluoride hydrate (20 equiv) in methyl alcohol at 23 °C for 8 h and activation of the resultant hemiacetal with excess trichloroacetonitrile in dichloromethane in the presence of a catalytic amount of DBU (0.3 equiv) at 23 °C for 5 min afforded the β-trichloroacetimidate **49** in 52% yield from **48**. Treatment of a solution of the coupling partners **42** (1.7 equiv) and **49** (1 equiv) in dry dichloromethane with TMSOTf (0.9 equiv) at −20 °C for 12 h produced the desired β,α-trehalose **50** as the major product (24%) along with a significant amount of the β,β-linked diastereomer **51** (17%). Although the problem of stereochemical

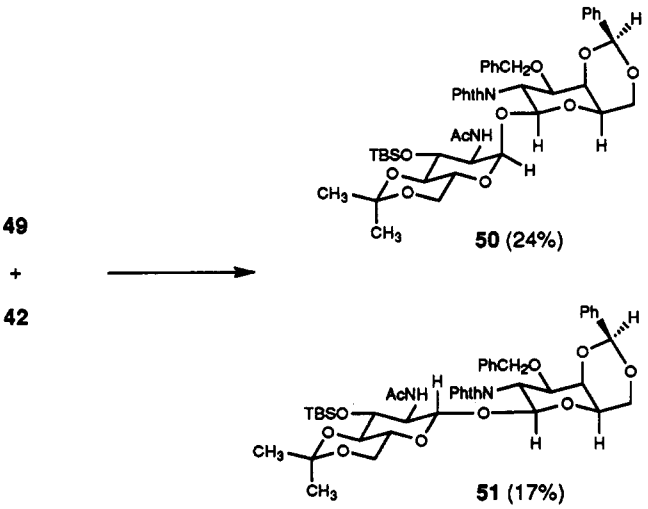




47 X = H_2N
48 X = PhthN

49

control at the anomeric center of the galactosamine residue appears to have been solved with the introduction of the phthalimido group, the anomeric center of the nucleophilic *N*-acetylglucosamine residue was poorly controlled. In addition, the coupling yield was unacceptable for preparative purposes. For these reasons, this glycosylation approach was abandoned in favor of one in which the roles of electrophile and nucleophile in the coupling reaction were interchanged, an approach that evolved into the optimized glycosylation procedure with the substrates **33** and **36** described above.



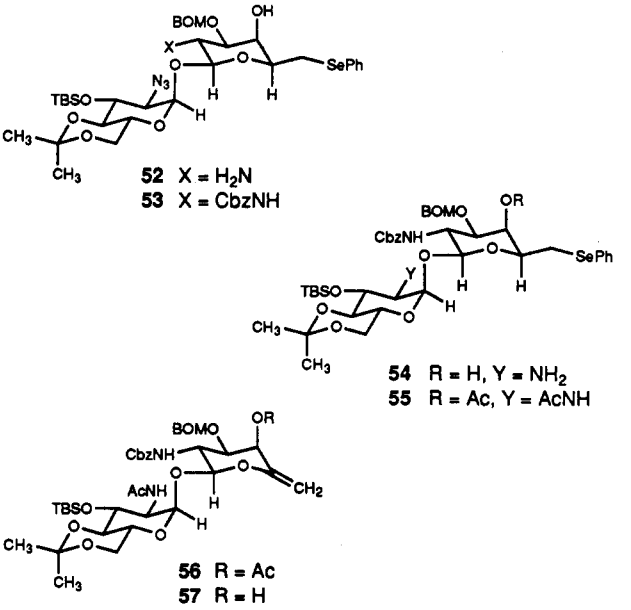
49 + 42

50 (24%)

51 (17%)

Carbon–Carbon Bond Formation: Construction of the Trisaccharide Core

With the establishment of an efficient procedure for the synthesis of the β,α-trehalose-linked disaccharide **38**, efforts turned toward the development of a procedure for its transformation to the allylic alcohol **57**, required for reductive coupling with a uridine-derived 5′-aldehyde. Because of the lability of the phthalimido substituent, we first elected to replace this protective group with the more stable benzyl carbamate group. Treatment of **38** with a mixture of hydrazine hydrate and ethyl alcohol (1:8 (v/v)) at 100 °C in a sealed tube for 12 h led to cleavage of both the phthalimido and benzoyl substituents to afford the corresponding amino alcohol **52** in 87% yield. Selective protection of the amino group as the benzyl carbamate was accomplished by the treatment of **52** with benzyl chloroformate (8.9 equiv) in pyridine at 0 °C for 30 min, furnishing the disaccharide **53** in



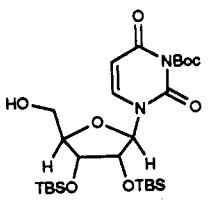
52 X = H_2N
53 X = CbzNH

54 R = H, Y = NH_2
55 R = Ac, Y = AcNH

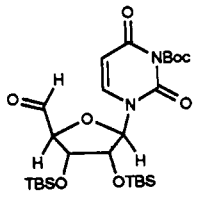
56 R = Ac
57 R = H

91% yield. The hindered azido group of **53** was smoothly reduced with benzeneselenol[32] (14 equiv) in triethylamine at 55 °C for 12 h (91%), and the resultant amino alcohol **54** was directly acetylated with acetic anhydride and pyridine (60 °C, 2.5 h, 91%), providing the diacetyl derivative **55**. Transformation of **55** to the allylic alcohol **57** proceeded efficiently in a two-step procedure involving the initial oxidation of **55** to the selenoxide (*m*-CPBA (3.5 equiv), carbon tetrachloride, 0 °C, 30 min) followed by thermolysis of the selenoxide at 65 °C for 10 h. Exposure of the resulting allylic acetate **56** to potassium carbonate (0.07 equiv) in methyl alcohol at 23 °C for 2 h produced the allylic alcohol **57** in 81% yield from **55**.

The silicon-mediated reductive coupling of the allylic alcohol **57** with a uridine-derived 5′-aldehyde coupling partner represented the final convergent step in the construction of the core structure (**1**) of the tunicamycins. The aldehyde **59** was chosen as the initial substrate for coupling. Unlike the aldehyde **19**, used in the synthesis of tunicaminyluracil (**2**), **59** does not incorporate the *p*-methoxybenzyl group for protection of the uracil imide. Although the latter protective group functioned adequately in two previous syntheses of tunicaminyluracil, the rather harsh oxidative conditions necessary for its removal[22] were believed to be incompatible with the trehalose linkage of **1**. The *tert*-butyl carbamate protective group was chosen as an alternative that was anticipated to undergo facile deprotection under mildly acidic conditions. Treatment of uridine derivative **17** with di-*tert*-butyl



58

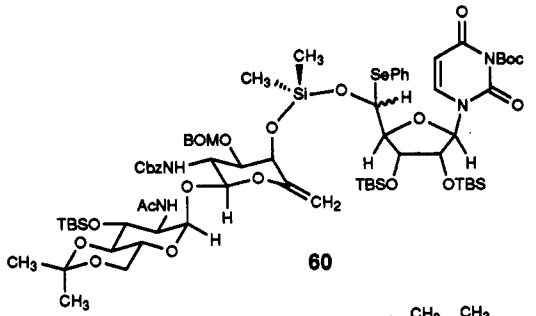


59

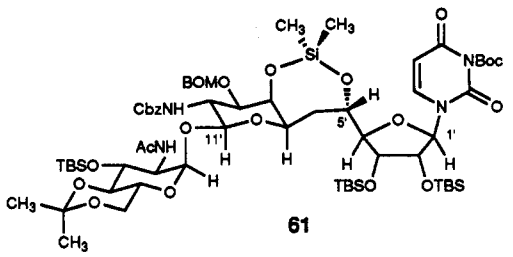
dicarbonate (2.0 equiv) and DMAP (0.06 equiv) in pyridine at 23 °C for 12 h and exposure of the resulting *tert*-butyl carbamate to trichloroacetic acid (4.6 equiv) in dichloromethane at 0 °C for 15 min furnished the alcohol **58** in 53% yield from **17**. Efficient oxidation of **58** to the corresponding aldehyde (**59**) was accomplished, as before, employing the Swern oxidation protocol (oxalyl chloride (3.0 equiv), dimethyl sulfoxide (5.0 equiv), triethylamine (10 equiv), dichloromethane, −78 °C, 25 min).

Like uridine-5′-aldehyde derivatives previously prepared, **59** was found to be unstable toward chromatography on silica gel and was therefore used in crude form for the formation of the *O*-silyl hemiselenoacetal in the next step.

The procedure for hemiselenoacetal adduct formation was similar to that used for the preparation of **20**. Thus, a deoxygenated solution of the aldehyde **59** (2.5 equiv) in toluene was treated with benzeneselenol (3.8 equiv) and pyridine (4.1 equiv) at 23 °C for 15 min, followed by a solution of dichlorodimethylsilane (10 equiv) in pyridine at 23 °C for 6 h; excess dichlorodimethylsilane and solvents were removed in vacuo, and a solution of the allylic alcohol **57** (1 equiv) in pyridine was added at 23 °C to form, within 5 min, the adduct **60** as a 5:1 mixture of C5′-epimers (50%). Free radical cyclization of **60** was induced by the dropwise addition of a solution of triethylborane in THF (1 M, 0.2 equiv) over a 15-min period to a solution of **60** (1 mM) and tributyltin hydride (2.5 equiv) in toluene at 23 °C. The



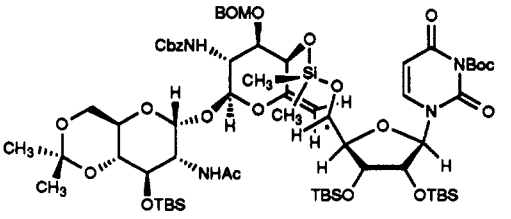
60



61

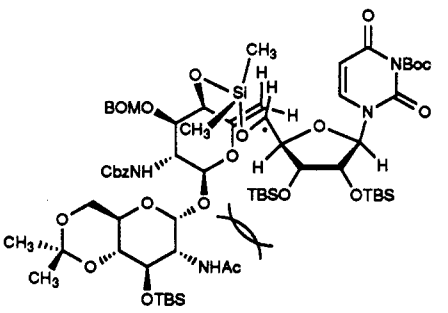
cyclic siloxane **61** was isolated in 80% yield after chromatography on silica gel. Although carbon–carbon bond formation was highly efficient, the reaction produced exclusively the *S* configuration at C5′, the configuration opposite to that of the desired product. This stereochemical assignment was determined by degradation of **61** with aqueous hydrochloric acid (3 N, reflux, 3 h), followed by peracetylation of the resulting amino polyol with acetic anhydride (40 equiv) and DMAP (51 equiv) in dichloromethane at 0 °C for 2 h, and comparison of the product with authentic samples of peracetyl α-tunicaminyluracil (**24**) and peracetyl C5′-*epi*-α-tunicaminyluracil (**23**). The observed preference for the formation of the undesired C5′-*S* diastereomer in this transformation paralleled our earlier results in studies leading to a synthesis of tunicaminyluracil. Unfortunately, the use of polar solvents in the cyclization of substrate **60**, a procedure which led to a reversal of selectivity in the previous study, failed to produce the desired diastereomer; cyclizations of **60** conducted in acetontrile, methyl alcohol, and aqueous methyl alcohol all produced **61** exclusively.

The high stereoselectivity of this free radical cyclization reaction was rationalized by invoking the two hypothetical transition structures **62** and **63**. These structures, similar to structures **25** and **26** previously invoked, depict the olefin approaching the carbon-centered radical from the side opposite to that of the bulky *tert*-butyldimethylsilyl ethers on the furanose ring. Structure **63**, which leads to the formation of the desired C5′-*R* configuration in the product, is believed to possess a destabilizing steric interaction between the disaccharide and the 3′-*O*-*tert*-butyldimethylsilyl ether. This destabilizing interaction is diminished in structure **62**. The proposed steric interaction is believed to be exacerbated in **63** relative to **26** by the additional steric shielding



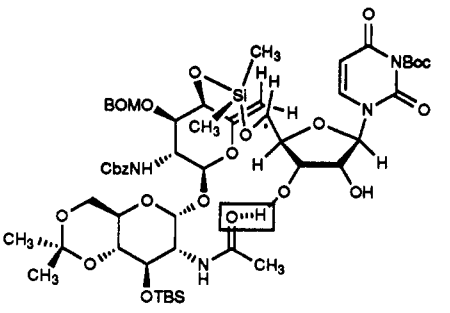
62

Hypothetical transition structure leading to undesired product. (Observed).



63

Hypothetical transition structure leading to desired product. (Not observed).



64

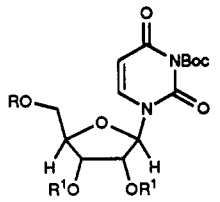
of the *N*-acetylglucosamine residue. Further consideration of structures **62** and **63** suggested that the replacement of the bulky silyloxy groups of the uridine-derived fragment with hydroxyl groups would not only eliminate the disfavorable steric interaction but might also induce an associative interaction that draws the *N*-acetylglucosamine residue closer to the furanose ring by virtue of an intramolecular hydrogen bond between the acetamide carbonyl group and the C3′-hydroxyl group. The proposed transition structure (**64**) should favor formation of the desired C5′-*R* stereochemistry in the cyclized product.

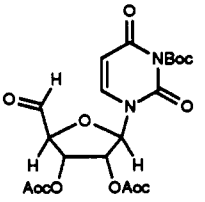
In order to test this hypothesis, it was necessary to devise a synthesis of the diol *O*-silyl hemiselenoacetal **70**. This required a protective group for the 2′- and 3′-hydroxyl groups of the uridine moiety that could be removed in the presence of the sensitive *O*-silyl hemiselenoacetal functional group. Toward this end, the aldehyde **68**, incorporating allyloxy carbonate (Aoc) protective groups[37] on the C2′- and C3′-hydroxyl groups, was prepared in a five-step sequence from 5′-*O*-dimethoxytrityluridine (**16**). Transient protection of the C2′- and C3′-hydroxyl groups within **16** (trimethylsilyl chloride (2.5 equiv), triethylamine (5.0 equiv), DMAP (0.02 equiv), dichloromethane, 23 °C, 2 h), followed by

(37) Guibe, F.; Dangles, O.; Balavoine, G. *Tetrahedron Lett.* **1986**, *27*, 2365.

(38) Schreiber, S. L.; Claus, R. E.; Reagan, J. *Tetrahedron Lett.* **1982**, *23*, 3867.

the sequential treatment of the resulting bis(trimethylsilyl) ether with di-*tert*-butyl dicarbonate (1.4 equiv) and DMAP (0.02 equiv) in pyridine at 23 °C for 12 h and then potassium fluoride hydrate (2.4 equiv) in methyl alcohol at 23 °C for 3 h, afforded the diol **65** in 79% yield. Exposure of the diol **65** to allyl chloroformate



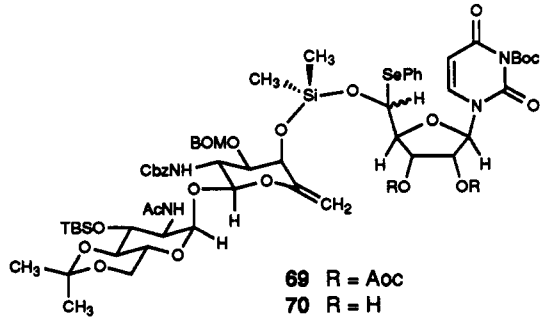


65 R = DMT, R^1 = H
66 R = DMT, R^1 = Aoc
67 R = H, R^1 = Aoc

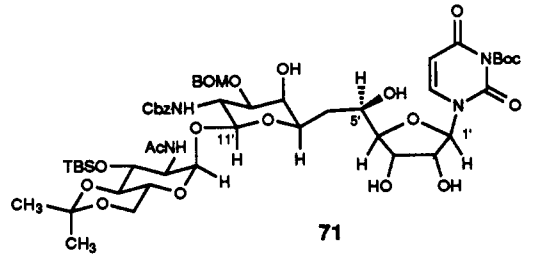
68

(10 equiv) in pyridine (–20 °C → 0 °C) produced the diallyloxy carbonate derivative (**66**) (87%). Subjection of the latter to benzenesulfonic acid (1.4 equiv) in chloroform at 23 °C for 2 min afforded the alcohol **67** in 76% yield. Swern oxidation of **67**, as previously conducted, produced multiple products, presumably a consequence of the greater lability of the aldehyde **68** due to the electron-withdrawing character of the C2′- and C3′-substituents. Oxidation of **67** with the Dess–Martin periodinane (3.0 equiv) in dichloromethane at 23 °C for 20 min, by contrast, was found to furnish the desired aldehyde (**68**), isolated as a mixture with its hydrated form. Regeneration of the aldehyde from its hydrated form was readily accomplished prior to siloxane adduct formation by azeotropic drying with toluene.

The coupling of the aldehyde **68** with the allylic alcohol **57** proceeded according to procedures described above, involving (1) the treatment of the aldehyde **68** (2.0 equiv) with benzeneselenol (3.0 equiv) and pyridine (3.0 equiv) in dry toluene at 23 °C for 15 min, (2) exposure of the resulting solution to dichlorodimethylsilane (20 equiv) at 23 °C for 4.5 h, (3) removal of excess dichlorodimethylsilane and solvents in vacuo, and (4) treatment of the residue with a solution of the allylic alcohol **57** (1 equiv) in pyridine at 23 °C for 5 min. The siloxane adducts



69 R = Aoc
70 R = H

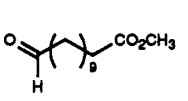


71

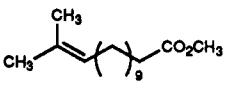
69 were isolated as an inseparable mixture of C5′-diastereomers (2:1, stereochemistry not determined) in 81% combined yield. Selective removal of the allyloxy carbonate protective groups proceeded efficiently employing a catalytic quantity of dichlorobis(triphenylphosphine)palladium (0.01 equiv) and tributyltin hydride (3.0 equiv) in moist dichloromethane at 23 °C for 6 min to afford the diols **70** in 85% yield.[37] Free radical cyclization of the diols **70** was initiated by the addition of aliquots of a solution of triethylborane (1 M, hexanes, 0.1 equiv each) at 15-min intervals to a solution of the diols **70** (1 mM) and tributyltin hydride (2.0 equiv) in toluene at 0 °C over 2 h. Subsequent treatment of the crude cyclization products with potassium fluoride hydrate (25 equiv) in methyl alcohol to remove the siloxane tether produced a mixture of tetraols epimeric at C5′ in a ratio of 7.5:1. The major product was determined to possess the desired C5′-*R* configuration by its transformation to peracetyl α-tunicaminyluracil (**24**) and comparison with an authentic sample as above. The diastereomer **71** could be separated by careful column chromatography on silica gel eluting with benzene:acetonitrile:isopropyl alcohol (12:4:1); the desired 5′-*R*-diastereomer **71** was isolated in pure form in 60% yield. This observed reversal of stereoselectivity compared to that of the cyclization of **60** supports the proposed transition structure **64**. In further support of this hypothesis, it was found that the cyclization of **70** in a protic solvent (methyl alcohol) led to an erosion in the stereoselectivity in the carbon–carbon bond-forming process (1.6:1, C5′-*R*:C5′-*S*), presumably due to disruption of the proposed intramolecular hydrogen bond. Given the complexity of the system, however, it is certainly possible that other factors may be involved.

Final Stages

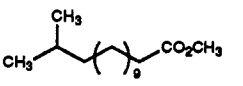
Having constructed the carbon framework of the tunicamycin antibiotics, there remained the deprotection steps and the attachment of the lipophilic *N*-acyl substituent to complete the synthesis. Tunicamycin-V, a major constituent of most fermentation broths of the natural tunicamycins, was selected for preparation, thus necessitating that the (*E*)-14-methyl-2-tetradecenoic acid side chain by synthesized. Ozonolysis of a commercial sample of cyclododecene in a mixture of dichloromethane and methyl alcohol in the presence of sodium bicarbonate (0.6 equiv) at –78 °C for 3 h and treatment of the crude product mixture with triethylamine (2.8 equiv) and acetic anhydride (5.6 equiv) in dichloroemthane at 23 °C for 6 h afforded the aldehyde **72** in 94% yield.[38] Olefination of **72** with isopropylidenetriphenylphosphorane afforded the corresponding trisubstituted olefin **73** (82%), which, upon hydrogenation under 1 atm of hydrogen with 10% palladium on carbon as catalyst in toluene at 60 °C for 12 h, furnished the methyl ester **74** in 96% yield.



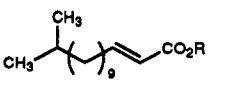
72



73



74

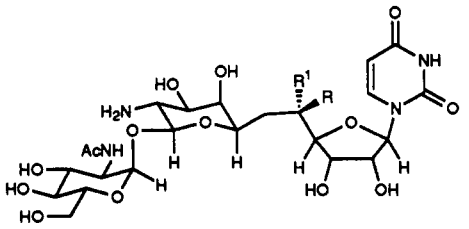


75 R = CH_3
76 R = H

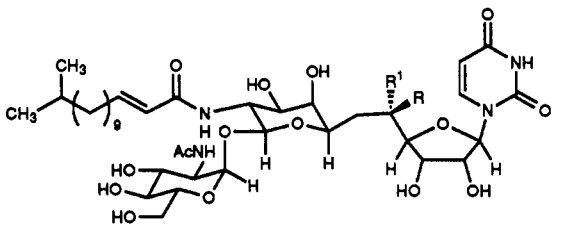
Introduction of α,β-unsaturation in the acyl chain was accomplished by the formation of the α-phenylselenide (lithium diisopropylamide (1.2 equiv), THF, –78 °C, 25 min; diphenydiselenide (2 equiv), –78 °C → 23 °C, 5.5 h) and oxidation of the crude selenide with *m*-CPBA (1.2 equiv) in dichloromethane at –78 °C for 2 h. Treatment of the oxidation mixture with dimethyl sulfide (4.9 equiv) and Et_3N (1.0 equiv) at 23 °C for 6 h induced elimination of the selenoxide to form the (*E*)-α,β-unsaturated ester **75** in 55% yield. Saponification of **75** with

aqueous sodium hydroxide in *tert*-butyl alcohol (60 °C, 1.5 h) produced the crystalline fatty acid **76** (91%).

In the final stages of the synthesis, deprotection of the tetraol **71** by catalytic transfer hydrogenolysis of both the benzyl carbamate and the (benzyloxy)methyl ether groups was performed with 10% formic acid in methyl alcohol in the presence of a catalytic amount of palladium black at 23 °C for 1.5 h. Subsequent treatment of the crude amino pentaol with 13% formic acid in methyl alcohol at 40 °C for 5 h led efficiently to hydrolysis of the isopropylidene ketal and the *tert*-butyl carbamate groups. Further treatment of the crude product from the latter reaction with excess hydrofluoric acid in a mixture of acetonitrile and methyl alcohol (1:1) at 23 °C for 2 h furnished the amino polyol **1**. Purification of **1** was achieved by chromatography with RP-18 reverse-phase silica gel eluting with pyridine:methyl alcohol:water (1:1:1.5); **1** was obtained in greater than 90% yield over the entire deprotection sequence.



1 R^1 = H, R = OH
77 R^1 = OH, R = H



1-V R^1 = H, R = OH
78 R^1 = OH, R = H

N-Acylation of **1** was accomplished under conditions similar to those described by Suami *et al.*[7] The fatty acid was activated by stirring **76** (6.0 equiv) with 1,3-dicyclohexylcarbodiimide (9.0 equiv) in dichloromethane at 23 °C for 30 min. Aliquots of the latter solution were added (1.0 equiv each) to a solution of **1** in methyl alcohol at 8-h intervals over 2 days to afford, after flash column chromatography through RP-18 reverse-phase silica gel eluting with methyl alcohol:pyridine:water (1:1:1) and trituration with chloroform, pure tunicamycin-V. It should be noted that the judicious selection of the protecting groups on the trisaccharide core (**71**) allowed for a highly efficient deprotection sequence. Thus, the entire deprotection procedure was performed without purification of any intermediate and provided, after fatty acid coupling, purified tunicamycin-V (88 mg) in 83% yield from the tetraol **71**. Synthetic **1-V** was shown to be identical in all respects (^{1}H NMR, ^{13}C NMR, melting point, mixed melting point, FTIR, HPLC, MS, HRMS, optical rotation) to that of a purified authentic sample. The route described for the synthesis of **1-V** is potentially applicable to the preparation of any of the homologous tunicamycin antibiotics by the attachment of the appropriate fatty acid side chain in the final step.

Preparation of C5′-*epi*-Tunicamycin-V

Using the synthetic route described for the preparation of tunicamycin-V (**1-V**), the C5′-*S* diastereomer **61** was efficiently transformed via the amino polyol **77** into the nonnatural tunicamycin isomer C5′-*epi*-tunicamycin-V (**78**, 74%). Thus, using the chemistry described, this stereoisomeric series of tunicamycins is also available for biological evaluation.

Summary

A convergent, stereoselective synthesis of tunicamycin-V (**1-V**) and its C5′-epimer is described. Within this synthetic route, an efficient method for carbon–carbon bond formation was developed, involving the silicon-mediated reductive coupling of aldehydes and allylic alcohols. This protocol forms the basis for the stereoselective preparation of tunicaminyluracil (**2**) and its C5′-epimer, employing the uridine derivative **19** and the galactosamine derivative **13** as the coupling partners. An attractive feature of this reductive coupling procedure is its compatibility with the sensitive trehalose glycosidic linkage within the tunicamycins. This allowed for the synthesis of the carbohydrate core (**1**) by carbon–carbon bond formation between a uridine 5′-aldehyde derivative and a trehalose-linked disaccharide allylic alcohol. Implementation of this synthetic plan led to the development of an efficient procedure for the previously problematic preparation of the β,α-trehalose linkage within the natural product, using the glycosidic coupling partners **33** and **36** in a variation of the trichloroacetimidate glycosylation method. Subsequent reductive coupling of the trehalose-linked disaccharide allylic alcohol **57** with uridine 5′-aldehyde derivatives **68** or **59** allowed for the highly convergent and selective preparation of **1** or its C5′-epimer (**77**), respectively. The synthesis of the amino polyol intermediates **1** and **77** should allow for the preparation of any of the homologous tunicamycin antibiotics in pure form, as well as of related structures of potential utility as biochemical probes.

Experimental Section

General Procedures. All reactions were performed in flame-dried round-bottom or modified Schlenk (Kjeldahl shape) flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Where necessary (so noted), solutions were deoxygenated by alternate evacuation/argon flush cycles (greater than three iterations). Organic solutions were concentrated by rotary evaporation below 30 °C at *ca.* 25 Torr (water aspirator). Flash column chromatography was performed as described by Still *et al.* employing 230–400-mesh silica gel.[39] Thin-layer chromatography (analytical and preparative) was performed using glass plates precoated to a depth of 0.25 mm with 230–400-mesh silica gel impregnated with a fluorescent indicator (254 nm).

Materials. Commercial reagents and solvents were used as received with the following exceptions. Tetrahydrofuran, ethyl ether, and dimethoxyethane were distilled from sodium benzophenone ketyl. Dichloromethane, *N*,*N*-diisopropylethylamine, diisopropylamine, triethylamine, pyridine, toluene, and acetonitrile were distilled from calcium hydride at 760 Torr. Dimethyl sulfoxide was distilled from calcium sulfate at 40 Torr and was stored over 4-Å molecular sieves. Carbon tetrachloride was distilled from phosphorus pentoxide at 760 Torr. Oxalyl chloride was distilled at 760 Torr immediately prior to use. The molarity of *n*-butyllithium solutions was determined by titration using diphenyacetic acid as an indicator (average of three determinations).[40] A mixture of homologous tunicamycins was purchased from Sigma Chemical Co.

Instrumentation. Infrared (IR) spectra were obtained using a Perkin-Elmer 1600 FTIR spectrophotometer referenced to a polystyrene standard. Data are presented as follows: frequency of absorption (cm^{-1}), and intensity of absorption (s = strong, m = medium, w = weak). Proton and carbon-13 nuclear magnetic resonance (^{1}H NMR or ^{13}C NMR) spectra were recorded with a JEOL JX-400 (400 MHz) or a GE QE-300-Plus (300 MHz) NMR spectrometer; chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$, δ 7.26; C_6HD_5, δ 7.20; CD_3COCD_2H, δ 2.04; CD_2HOD, δ 3.30). Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances), integration, coupling constant in hertz (Hz), and assignment. High-

(39) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(40) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.

performance liquid chromatography (HPLC) was conducted with a Waters 501 HPLC equipped with a Beckman ODS C18 standard reverse-phase column and an Isco V^4 absorbance detector set at 255 nm. Optical rotations were determined with a JASCO-DIP-181 polarimeter equipped with a sodium lamp source. High-resolution mass spectra were obtained from the University of California, Riverside Mass Spectrometry Facility. Melting points were recorded with a Büchi SMP-20 melting point apparatus and are uncorrected.

Methyl 2-(Acetylamino)-4,6-*O*-benzylidene-3-*O*-[(2-methoxyethoxy)-methyl]-α-D-galactopyranoside (9). Methoxyethoxymethyl chloride (4.4 mL, 30.7 mmol, 5.0 equiv) was added to a solution of methyl 2-(acetylamino)-4,6-*O*-benzylidene-α-D-galactopyranoside (**8**, 2.5 g, 7.7 mmol, 1 equiv) and diisopropylethylamine (13.5 mL, 77.3 mmol, 10.0 equiv) in tetrahydrofuran (20 mL), and the resulting solution was heated at 60 °C for 2 h. The reaction mixture was partitioned between water (600 mL) and ethyl acetate (4 × 200 mL), and the combined organic layers were dried (magnesium sulfate) and concentrated. The residue was purified by flash column chromatography (20% acetone in ethyl acetate) to give methyl 2-(acetylamino)-4,6-*O*-benzylidene-3-*O*-[(2-methoxyethoxy)methyl]-α-D-galactopyranoside (**9**, 2.37 g, 75%) as a white solid: mp 53.5–54.0 °C; R_f 0.32, 25% acetone in ethyl acetate; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.51 (m, 2 H, arom), 7.34 (m, 3 H, arom), 6.98 (s, 1 H, NH), 5.65 (s, 1 H, benzylidene acetal), 4.79 (d, 1 H, J = 7.0 Hz, MEM CH_2), 4.74 (d, 1 H, J = 3.5 Hz, H 1), 4.67 (d, 1 H, J = 7.0 Hz, MEM CH_2), 4.51 (d, 1 H, J = 3.2 Hz, H 4), 4.48 (m, 1 H, H 2), 4.12 (m, 2 H, H 6), 3.99 (dd, 1 H, J = 3.5, 11.4 Hz, H 3), 3.75 (m, 1 H, H 5), 3.69 (m, 2 H, MEM CH_2), 3.54 (m, 2 H, MEM CH_2), 3.35 (s, 3 H, CH_3O), 3.34 (s, 3 H, CH_3O), 1.85 (s, 3 H, Ac); IR (neat film) 3300 (w, br), 2898 (m), 1659 (s), 1548 (m), 1453 (w), 1370 (w), 1199 (w), 1134 (m), 1112 (m), 1050 (s), 984 (m), 792 (w), 748 (w), 760 (m) cm^{-1}; HRMS (FAB) m/z calcd for $C_{20}H_{30}NO_8$ $(MH)^+$ 412.1971, found 412.1970.

Methyl 2-(Acetylamino)-4-*O*-benzoyl-6-bromo-3-*O*-[(2-methoxyethoxy)-methyl]-α-D-galactopyranoside (10). Solid barium carbonate (1.80 g, 9.1 mmol, 1.6 equiv) and *N*-bromosuccinimide (1.32 g, 7.4 mmol, 1.3 equiv) were added sequentially to a solution of methyl 2-(acetylamino)-4,6-*O*-benzylidene-3-*O*-[(2-methoxyethoxy)methyl]-α-D-galactopyranoside (**9**, 2.34 g, 5.7 mmol, 1 equiv) in carbon tetrachloride (47 mL). The resulting suspension was deoxygenated and was heated at reflux for 2 h, during which time the reaction mixture turned orange and then yellow. After allowing the reaction mixture to cool to 23 °C, the solvent was removed in vacuo, and the residue was diluted with dichloromethane (500 mL). Solids were removed by filtration, and the filtrate was washed sequentially with 5% aqueous sodium bisulfite solution (500 mL) and saturated aqueous sodium chloride solution (300 mL). The organic layer was dried (magnesium sulfate) and concentrated, and the residue was purified by flash column chromatography (100% ethyl acetate) to afford methyl 2-(acetylamino)-4-*O*-benzoyl-6-bromo-3-*O*-[(2-methoxyethoxy)-methyl]-α-D-galactopyranoside (**10**) (2.42 g, 87%) as a white solid: mp 57.0–57.5 °C; R_f 0.50, 50% acetone in ethyl acetate; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.06 (m, 2 H, arom), 7.67 (m, 1 H, arom), 7.55 (m, 2H, arom), 7.10 (d, 1 H, J = 9.4, NH), 5.82 (d, 1 H, J = 2.0 Hz, H 4), 4.83 (d, 1 H, J = 3.5 Hz, H 1), 4.81 (d, 1 H, 7.3 Hz, MEM CH_2), 4.47 (d, 1 H, J = 7.3 Hz, MEM CH_2), 4.47 (m, 1 H, H 2), 4.25 (m, 2 H, H 3, 5), 3.81–3.50 (m, 6 H, H 6, MEM CH_2), 3.44 (s, 3 H, CH_3O), 3.37 (s, 3 H, CH_3O), 1.87 (s, 3 H, Ac); IR (neat film) 3314 (w), 2924 (w), 1723 (s), 1670 (m), 1543 (m), 1451 (w), 1370 (w), 1268 (s), 1116 (s), 1038 (s), 981 (w), 942 (w), 846 (w), 711 (m) cm^{-1}; HRMS (FAB) m/z calcd for $C_{20}H_{29}BrNO_8$ $(MH)^+$ 490.1077, found 490.1091.

Methyl 2-(Acetylamino)-4-*O*-benzoyl-6-deoxy-5,6-didehydro-3-*O*-[(2-methoxyethoxy)methyl]-6-(phenylseleno)-α-D-galactopyranoside (11). Benzeneselenol (1.81 mL, 16.5 mmol, 3.0 equiv) was added to a solution of methyl 2-(acetylamino)-4-*O*-benzoyl-6-bromo-3-*O*-[(2-methoxyethoxy)-methyl]-α-D-galactopyranoside (**10**, 2.70 g, 5.5 mmol, 1 equiv) and triethylamine (4.60 mL, 33.0 mmol, 6.0 equiv) in dimethoxyethane (40 mL), and the resulting mixture was heated at reflux for 18 h. The reaction solution was partitioned between saturated aqueous sodium bicarbonate solution (300 mL) and ethyl acetate (4 × 200 mL), and the combined organic layers were dried (magnesium sulfate) and concentrated. The residue was purified by flash column chromatography (100% ethyl acetate) to give methyl 2-(acetylamino)-4-*O*-benzoyl-6-deoxy-5,6-didehydro-3-*O*-[(2-methoxyethoxy)methyl]-6-(phenylseleno)-α-D-galactopyranoside (**11**, 2.98 g, 96%) as a white solid: mp 44.0 °C; R_f 0.24, 100% ethyl acetate; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.07 (m, 2 H, Bz arom), 7.67 (m, 1 H, Bz arom), 7.55 (m, 4 H, Bz arom, PhSe arom), 7.25 (m, 3 H, PhSe arom), 7.06 (s, 1 H, NH), 5.80 (d, 1 H, J = 2.0 Hz, H 4), 4.80 (m, 2 H, H 1, MEM CH_2), 4.47 (m, 1 H, H 2), 4.46 (d, 1 H, J = 7.3 Hz, MEM CH_2), 4.21 (m, 2 H, H 3, 5), 3.78 (m, 1 H, MEM CH_2), 3.55 (m, 3 H, MEM CH_2), 3.38 (s, 3 H, CH_3O), 3.35 (s, 3 H, CH_3O), 3.18 (dd, 1 H, J = 8.8, 12.6 Hz, H 6), 3.04 (dd, 1 H, J = 5.0, 12.6 Hz, H 6), 1.86 (s, 3 H, Ac); IR (neat film) 3316 (w), 2934 (w), 2896 (w), 1722 (s), 1674 (m), 1539 (m), 1452 (w), 1371 (w), 1269 (s), 1116 (s), 1040 (s), 981 (w), 941 (w), 711 (m) cm^{-1}; HRMS (FAB) m/z calcd for $C_{26}H_{34}NO_8Se$ $(MH)^+$ 568.1450, found 568.1437.

Methyl 2-(Acetylamino)-4-*O*-benzoyl-3-*O*-[(2-methoxyethoxy)methyl]-α-D-galactopyranoside (12). Solid *m*-chloroperoxybenzoic acid (*ca.* 60% (w/w), 2.22 g, 7.7 mmol, 1.5 equiv) was added to a solution of methyl 2-(acetylamino)-4-*O*-benzoyl-6-deoxy-5,6-didehydro-3-*O*-[(2-methoxyethoxy)methyl]-6-(phenylseleno)-α-D-galactopyranoside (**11**, 2.91 g, 5.14 mmol, 1 equiv) in carbon tetrachloride (40 mL) at −14 °C, and the resulting suspension was stirred at this temperature for 1 h. Excess oxidant was quenched by the addition of dimethyl sulfide (5.66 mL, 77.1 mmol, 15.0 equiv) and triethylamine (1.51 mL, 10.3 mmol, 2.0 equiv), and the mixture was heated at reflux for 5 h. The resulting yellow solution was partitioned between saturated aqueous sodium bicarbonate solution (400 mL) and ethyl acetate (3 × 200 mL), and the combined organic layers were dried (magnesium sulfate) and concentrated. The crude product was purified by flash column chromatography (100% ethyl acetate) to give methyl 2-(acetylamino)-4-*O*-benzoyl-3-*O*-[(2-methoxyethoxy)methyl]-α-D-galactopyranoside (**12**, 2.07 g, 99%) as a white solid: mp 44.0–44.5 °C; R_f 0.20, 100% ethyl acetate; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.04 (m, 2 H, arom), 7.65 (m, 1 H, arom), 7.54 (m, 2 H, arom), 7.19 (d, 1 H, J = 8.1 Hz, NH), 6.02 (d, 1 H, J = 3.4 Hz, H 4), 4.91 (d, 1 H, J = 3.4 Hz, H 1), 4.83 (s, 1 H, H 6), 4.81 (d, 1 H, J = 7.3 Hz, MEM CH_2), 4.78 (s, 1 H, H 6), 4.70 (m, 1 H, H 2), 4.57 (d, 1 H, J = 7.3 Hz, MEM CH_2), 4.26 (dd, 1 H, J = 3.4, 11.2 Hz, H 3), 3.75 (m, 1 H, MEM CH_2), 3.55 (m, 3 H, MEM CH_2), 3.43 (s, 3 H, CH_3O), 3.34 (s, 3 H, CH_3O), 1.89 (s, 3 H, Ac); IR (neat film) 3287 (w), 2933 (w), 17196 (s), 1663 (s), 1543 (m), 1451 (w), 1369 (w), 1266 (s), 1197 (w), 1132 (m), 1111 (s), 1025 (s), 950 (m), 884 (w), 713 (m) cm^{-1}; HRMS (FAB) m/z calcd for $C_{20}H_{28}NO_8$ $(MH)^+$ 410.1815, found 410.1810.

Methyl 2-(Acetylamino)-6-deoxy-5,6-didehydro-3-*O*-[(2-methoxyethoxy)methyl]-α-D-galactopyranoside (13). Potassium carbonate (2.0 g, 14.5 mmol, 3.0 equiv) was added to a solution of methyl 2-(acetylamino)-4-*O*-benzoyl-3-*O*-[(2-methoxyethoxy)methyl]-α-D-galactopyranoside (**12**, 2.00 g, 4.9 mmol, 1 equiv) in methyl alcohol (35 mL), and the resulting suspension was stirred at 23 °C for 3 h. The reaction mixture was partitioned between saturated aqueous sodium chloride solution (200 mL) and dichloromethane (4 × 200 mL), and the combined organic layers were dried (magnesium sulfate) and concentrated. Flash column chromatography of the residue afforded methyl 2-(acetylamino)-6-deoxy-5,6-didehydro-3-*O*-[(2-methoxyethoxy)methyl]-α-D-galactopyranoside (**13**, 1.37 g, 92%) as a white solid: mp 102.5 °C; R_f 0.20, 50% acetone in benzene; ^{1}H NMR (400 MHz, C_6D_6) δ 5.97 (d, 1 H, J = 8.6 Hz, NH), 5.12 (ddd, 1 H, J = 3.6, 8.6, 10.0 Hz, H 2), 4.95 (d, 1 H, J = 3.6 Hz, H 1), 4.77 (s, 1 H, H 6), 4.63 (s, 1 H, H 6), 4.49 (d, 1 H, J = 7.7 Hz, MEM CH_2), 4.47 (d, 1 H, J = 3.8 Hz, H 4), 4.42 (d, 1 H, J = 7.7 Hz, MEM CH_2), 4.08 (dd, 1 H, J = 3.8, 10.0 Hz, H 3), 3.48 (m, 1 H, MEM CH_2), 3.39 (d, 1 H, J = 4.1 Hz, OH), 3.34 (m, 1 H, MEM CH_2), 3.12 (s, 3 H, CH_3O), 3.11 (m, 2 H, MEM CH_2), 3.03 (s, 3 H, CH_3O), 1.68 (s, 3 H, Ac); IR (neat film) 3589–3096 (m), 2930 (m), 1660 (s), 1649 (s), 1556 (m), 1373 (w), 1249 (w), 1196 (w), 1138 (m), 1104 (s), 1038 (s), 973 (w), 944 (w) cm^{-1}; HRMS (FAB) m/z calcd for $C_{13}H_{24}NO_7$ $(MH)^+$ 306.1553, found 306.1550.

2′,3′-*O*-Bis-*tert*-butyldimethylsilyl)-5′-*O*-(dimethoxytrityl)uridine (17). Uridine (1.00 g, 4.1 mmol, 1 equiv), dimethoxytrityl chloride (1.40 g, 4.10 mmol, 1 equiv), and pyridine (7 mL) were combined, and the resulting solution was stirred at 23 °C for 12 h. The orange mixture was poured into vigorously stirred ice–water (100 mL), and the resulting yellow precipitate was isolated by filtration. The solid was dried by azeotropic removal of residual water (toluene, 3 × 3 mL) and was dissolved in *N*,*N*-dimethylformamide (3 mL). Imidazole (3.33 g, 49.0 mmol, 12.0 equiv) and *tert*-butyldimethylsilyl chloride (3.70 g, 24.5 mmol, 6.0 equiv) were added sequentially, and the resulting viscous solution was stirred at 23 °C for 13.5 h, at which point excess silyl chloride was quenched by the slow addition of methyl alcohol (10 mL). The product mixture was partitioned between water (500 mL) and ethyl acetate (3 × 200 mL), and the combined organic layers were dried (magnesium sulfate) and concentrated. The residue was purified by flash chromatography (33% ethyl acetate in hexanes) to afford 2′,3′-*O*-bis(*tert*-butyldimethylsilyl)-5′-*O*-(dimethoxytrityl)uridine (**17**, 2.95 g, 93%) as a pale yellow solid: mp 118.0–122.0 °C; R_f 0.45, 50% ethyl acetate in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1 H, NH), 8.19 (d, 1 H, J = 8.2 Hz, H

6), 7.4–7.2 (m, 9 H, arom), 6.85 (m, 4 H, arom), 5.84 (d, 1 H, J = 1.8 Hz, H 1′), 5.29 (dd, 1 H, J = 2.3, 8.2 Hz, H 5), 4.17 (m, 3 H, H 2′, 3′, 4′), 3.79 (s, 6 H, CH_3O), 3.71 (dd, 1 H, J = 1–2, 9.4 Hz, H 5′), 3.34 (dd, 1 H, J = 1–2, 10.6 Hz, H 5′), 0.90 (s, 9 H, *tert*-butyl), 0.77 (s, 9 H, *tert*-butyl), 0.18 (s, 3 H, $SiCH_3$), 0.10 (s, 3 H, $SiCH_3$), 0.03 (s, 3 H, $SiCH_3$), –0.06 (s, 3 H, $SiCH_3$); IR (neat film) 3184 (m), 3058 (m), 2930 (s), 2856 (s), 1684 (s), 1608 (m), 1509 (s), 1463 (s), 1253 (s), 1175 (m), 836 (s) cm^{-1}; HRMS (FAB) m/z calcd for $C_{42}H_{59}N_2O_8Si_2$ $(MH)^+$ 775.3810, found 775.3774.

2′,3′-*O*-Bis(*tert*-butyldimethylsilyl)-3-*N*-(*p*-methoxybenzyl)uridine (18). A solution of 2′,3′-*O*-bis(*tert*-butyldimethylsilyl)-5′-*O*-(dimethoxytrityl)-uridine (**17**, 2.90 g, 3.7 mmol, 1 equiv) in *N*,*N*-dimethylformamide (5 mL) and neat *p*-methoxybenzyl chloride (1.01 mL, 7.5 mmol, 2.0 equiv) were added sequentially to a suspension of sodium hydride (135 mg, 5.6 mmol, 1.5 equiv) in *N*,*N*-dimethylformamide (4 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 4.5 h, whereupon excess base was neutralized by the slow addition of methyl alcohol (5 mL). The resulting solution was partitioned between water (500 mL) and ethyl acetate (3 × 200 mL), and the combined organic layers were dried (magnesium sulfate) and concentrated. The residue was dissolved in a solution of benzenesulfonic acid in chloroform (2% (w/w), 20 mL) at 0 °C, and the resulting orange solution was stirred at 0 °C for 5 min. The product solution was partitioned between saturated aqueous sodium bicarbonate solution (500 mL) and ethyl acetate (3 × 200 mL), and the combined organic layers were dried (magnesium sulfate) and concentrated. Flash column chromatography of the residue (50% ethyl acetate in hexanes) afforded 2′,3′-*O*-bis(*tert*-butyldimethylsilyl)-3-*N*-(*p*-methoxybenzyl)uridine contaminated with residual *p*-methoxybenzyl alcohol. The product was purified by flash column chromatography (gradient elution: dichloromethane → 50% ethyl acetate in dichloromethane) to give pure 2′,3′-*O*-bis(*tert*-butyldimethylsilyl)-3-*N*-(*p*-methoxybenzyl)uridine (**18**, 1.82 g, 82%) as a white solid: mp 84.0 °C; R_f 0.43, 50% ethyl acetate in hexanes; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, 2 H, J = 8.8 Hz, arom), 7.39 (d, 1 H, J = 8.1 Hz, H 6), 6.80 (d, 2 H, J = 8.8 Hz, arom), 5.77 (d, 1 H, J = 8.1 Hz, H 5), 5.40 (d, 1 H, J = 6.3 Hz, H 1′), 5.07 (d, 1 H, J = 13.4 Hz, PMB CH_2), 4.99 (d, 1 H, J = 13.4 Hz, PMB CH_2), 4.62 (dd, 1 H, J = 4.6, 6.3 Hz, H 2′), 4.15 (dd, 1 H, J = 2.7, 4.6 Hz, H 3′), 4.06 (m, 1 H, H 4′), 3.91 (m, 1 H, H 5′), 3.77 (s, 3 H, CH_3O), 3.68 (m, 1 H, H 5′), 3.34 (dd, 1 H, J = unres, 5.9 Hz, OH), 0.90 (s, 9 H, *tert*-butyl), 0.80 (s, 9 H, *tert*-butyl), 0.08 (s, 3 H, $SiCH_3$), 0.07 (s, 3 H, $SiCH_3$), –0.03 (s, 3 H, $SiCH_3$), –0.19 (s, 3 H, $SiCH_3$); IR (neat film) 3456 (w, br), 2930 (m), 2857 (m), 1710 (m), 1667 (s), 1513 (m), 1462 (m), 1250 (s), 1162 (w), 1097 (w), 836 (m), 776 (m) cm^{-1}; HRMS (FAB) m/z calcd for $C_{29}H_{49}N_2O_7Si_2$ $(MH)^+$ 593.3078, found 593.3088.

2′,3′-*O*-Bis(*tert*-butyldimethylsilyl)-3-*N*-(*p*-methoxybenzyl)uridine-5′-aldehyde (19). Dimethyl sulfoxide (204 μL, 2.9 mmol, 4.7 equiv) was added dropwise to a solution of oxalyl chloride (167 μL, 1.9 mmol, 3.1 equiv) in dichloromethane (4 mL) at –78 °C, and the resulting solution was stirred at –78 °C for 5 min. To this solution was added dropwise via cannula a solution of 2′,3′-*O*-bis(*tert*-butyldimethylsilyl)-3-*N*-(*p*-methoxybenzyl)uridine (**18**, 365 mg, 0.62 mmol, 1 equiv) in dichloromethane (4 mL), and the mixture was stirred at –78 °C for 15 min. Triethylamine (669 μL, 4.8 mmol, 7.5 equiv) was added at –78 °C, and after 30 min, the cold reaction mixture was poured into saturated aqueous sodium bicarbonate solution (150 mL). The aqueous layer was extracted with ethyl acetate (2 × 100 mL), and the combined organic layers were dried (magnesium sulfate) and concentrated to afford 2′,3′-*O*-bis(*tert*-butyldimethylsilyl)-3-*N*-(*p*-methoxybenzyl)uridine-5′-aldehyde (**19**, 375 mg) as a pale yellow solid. Due to the lability of the product and its susceptibility to hydration, the uridine 5′-aldehyde derivative (**22**) was used in its crude form in the following experiment. Crude **22**: ^1H NMR (400 MHz, C_6D_6) δ 9.66 (s, 1 H, H 5′), 7.62 (m, 2 H, arom), 6.71 (m, 2 H, arom), 6.56 (d, 1 H, J = 8.0 Hz, H 6), 5.54 (d, 1 H, J = 3.9 Hz, H 1′) 5.45 (d, 1 H, J = 8.0 Hz, H 5), 5.10 (m, 1 H, H 4′), 4.63 (m, 1 H, H 3′), 4.35 (m, 1 H, H 2′), 3.28 (s, 3 H, OCH_3), 0.99 (s, 9 H, *tert*-butyl), 0.85 (s, 9 H, *tert*-butyl), 0.07, 0.05, –0.10, –0.21 (4 × $SiCH_3$); IR (neat film) 3381 (w, br), 2930 (s), 2858 (s), 1714 (s1667 (s), 1514 (s), 1462 (s), 1392 (m), 1344 (m), 1300 (m), 1250 (s), 1069 (m), 838 (s), 777 (s), 747 (w) cm^{-1}; HRMS (FAB) m/z calcd for $C_{29}H_{47}N_2O_7Si_2$ $(MH)^+$ 591.2922, found: 591.2953.

***O*-Silyl Hemiselenoacetals (20).** Freshly distilled benzeneselenol (68 μL, 0.62 mmol, 2.0 equiv) was added to a solution of 2′,3′-*O*-bis(*tert*-butyldimethylsilyl)-3-*N*-(*p*-methoxybenzyl)uridine-5′-aldehyde (**19**, 375 mg, *ca.* 0.62 mmol, *ca.* 2 equiv, azeotropically dried with two 3-mL portions of toluene) in pyridine (6 mL), and the resulting solution was deoxygenated. After stirring at 23 °C for 1 h, the reaction mixture was transferred via cannula to a solution of dichloromethylsilane (752 μL, 6.2 mmol, 20 equiv) in pyridine (6 mL). The resulting solution was deoxygenated and was stirred at 23 °C for 10 h. The cloudy yellow suspension was concentrated in vacuo at 23 °C, and the residue was suspended in toluene (3 mL). Volatiles were removed in vacuo, and the residue was diluted with a mixture of toluene and pyridine (10:1 (v/v), 6.6 mL). To the suspension was added via cannula a solution of methyl 2-(acetylamino)-6-deoxy-5,6-didehydro-3-*O*-[(2-methoxyethoxy)methyl]-α-D-galactopyranoside (**13**, 94 mg, 0.31 mmol, 1 equiv) in pyridine (2 mL), and the resulting reaction mixture was stirred at 23 °C for 10 min. The product was partitioned between a mixture of ethyl acetate and pentane (1:1 (v/v), 200 mL) and water (100 mL). The organic layer was washed with water (100 mL) and then was dried (magnesium sulfate) and concentrated. Flash column chromatography (ethyl acetate) of the residue afforded a 1:1 mixture of the C5′-diastereomers **23** (314 mg, 92%). For analytical purposes, the diastereomers could be separated by preparative thin-layer chromatography (1:1 ethyl acetate in hexanes).

20a: white solid, mp 57.0–59.0 °C; R_f 0.38, ethyl acetate; ^1H NMR (400 MHz, C_6D_6) δ 8.04 (d, 1 H, J = 8.2 Hz, H 6), 7.76 (d, 2 H, J = 8.5 Hz, PMB arom), 7.72 (d, 2 H, J = 7.0 Hz, PhSe arom), 7.10 (t, 2 H, J = 7.0 Hz, PhSe arom), 7.04 (d, 1 H, J = 7.3 Hz, PhSe arom), 6.78 (d, 2 H, J = 8.5 Hz, PMB arom), 6.71 (d, 1 H, J = 8.4 Hz, NH), 6.61 (d, 1 H, J = 6.2 Hz, H 1′), 5.90 (d, 1 H, J = 7.9 Hz, H 5), 5.90 (d, 1 H, J = 2.3 Hz, H 5′), 5.28 (d, 1 H, J = 13.2 Hz, PMB CH_2), 5.11 (d, 1 H, J = 13.2 Hz, PMB CH_2), 5.11 (m, 1 H, H 10′), 5.09 (d, 1 H, J = 3.5 Hz, H 11′), 4.67 (t, 1 H, J = 2.4 Hz, H 4′), 4.59 (s, 1 H, H 6′), 4.56 (d, 1 H, J = 7.0 Hz, MEM CH_2), 4.46 (m, 1 H, H 2′), 4.41 (d, 1 H, J = 7.0 Hz, MEM CH_2), 4.41 (d, 1 H, J = 2.9 Hz, H 8′), 4.35 (m, 1 H, H 3′), 4.31 (s, 1 H, H 6′), 4.25 (dd, 1 H, J = 2.9, 10.8 Hz, H 9′), 3.79 (m, 1 H, MEM CH_2), 3.29 (s, 3 H, CH_3O), 3.17 (m, 2 H, MEM CH_2), 3.14 (s, 3 H, CH_3O), 3.03 (m, 1 H, MEM CH_2), 3.00 (s, 3 H, CH_3O), 1.84 (s, 3 H, Ac), 1.02 (s, 9 H, *tert*-butyl), 0.99 (s, 9 H, *tert*-butyl), 0.33 (s, 3 H, $SiCH_3$), 0.24 (s, 3 H, $SiCH_3$), 0.23 (s, 6 H, $SiCH_3$), 0.20 (s, 3 H, $SiCH_3$), 0.12 (s, 3 H, $SiCH_3$); IR (neat film) 3332 (w), 2929 (m), 2856 (w), 1713 (m), 1670 (s), 1513 (m), 1455 (m), 1390 (w), 1251 (m), 1108 (m), 1038 (m), 839 (m), 777 (w), 742 (w) cm^{-1}; HRMS (FAB) m/z calcd for $C_{50}H_{80}N_3O_{14}SeSi_3$ $(MH)^+$ 1110.4113, found 1110.4136.

20b: white solid, mp 59.5–61.0 °C; R_f 0.35, ethyl acetate; ^1H NMR (400 MHz, C_6D_6) δ 7.75 (m, 5 H, H 6, PMB arom, PhSe arom), 7.12 (m, 2 H, PhSe arom), 7.07 (m, 1 H, PhSe arom), 6.78 (d, 2 H J = 8.5 Hz, PMB arom), 6.68 (d, 1 H, J = 7.3 Hz, H 1′), 6.59 (d, 1 H, J = 8.5 Hz, NH), 6.11 (d, 1 H, J = 8.2 Hz, H 5), 6.00 (d, 1 H, J = 4.7 Hz, H 5′), 5.30 (d, 1 H, J = 13.2 Hz, PMB CH_2), 5.15 (m, 1 H, H 10′), 5.12 (d, 1 H, J = 13.2 Hz, PMB CH_2), 5.01 (d, 1 H, J = 3.2 Hz, H 11′), 4.60 (m, 4 H, H 2′, 3′, 6′, MEM CH_2), 4.52 (d, 1 H, J = 2.9 Hz, H 8′), 4.49 (m, 1 H, H 4′), 4.42 (d, 1 H, J = 7.0 Hz, MEM CH_2), 4.36 (s, 1 H, H 6′), 4.26 (dd, 1 H, J = 2.9, 11.4 Hz, H 9′), 3.72 (m, 1 H, MEM CH_2), 3.29 (s, 3 H, CH_3O), 3.20 (m, 2 H, MEM CH_2), 3.11 (s, 3 H, CH_3O), 3.07 (m, 1 H, MEM CH_2), 3.02 (s, 3 H, CH_3O), 1.79 (s, 3 H, Ac), 1.04 (s, 9 H, *tert*-butyl), 0.97 (s, 9 H, *tert*-butyl), 0.39 (s, 3 H, $SiCH_3$), 0.28 (s, 3 H, $SiCH_3$), 0.27 (s, 3 H, $SiCH_3$), 0.24 (s, 3 H, $SiCH_3$), 0.12 (s, 3 H, $SiCH_3$), 0.06 (s, 3 H, $SiCH_3$); IR (neat film) 3335 (w), 2830 (m), 2856 (w), 1713 (m), 1668 (s), 1513 (w), 1455 (w), 1390 (w), 1251 (m), 1108 (m), 1039 (m), 837 (m), 775 (w), 743 (w) cm^{-1}; HRMS (FAB) m/z calcd for $C_{50}H_{80}N_3O_{14}SeSi_3$ $(MH)^+$ 1110.4113, found 1110.4111.

Diol 21. A solution of triethylborane (30 μL, 1.0 M in hexanes, 0.03 mmol, 0.2 equiv) was added to a deoxygenated solution of the siloxanes **20** (153 mg, 0.14 mmol, 1 equiv) and tributyltin hydride (185 μL, 0.69 mmol, 5.0 equiv) in toluene at –78 °C, and the resulting solution was allowed to warm to 23 °C over 4 h. Volatiles were removed in vacuo, and the residue was diluted with methyl alcohol (25 mL). Potassium fluoride hydrate (300 mg, 3.2 mmol, 16.0 equiv) was added, and the resulting suspension was stirred at 23 °C for 9 h. After dilution with dichloromethane (50 mL), the suspension was filtered, and the filtrate was concentrated. Flash column chromatography of the residue (25% acetone in ethyl acetate) afforded a 5:1 mixture of the diastereomers **21** and **22**, respectively (88 mg combined, 71%), as a white solid.

Diol 22. A solution of triethylborane (15 μL, 1.0 M in hexanes, 0.015 mmol, 0.2 equiv) was added to a deoxygenated solution of the siloxane adducts **20** (110 mg, 0.099 mmol, 1 equiv) and tributyltin hydride (53 μL, 0.20 mmol, 2.0 equiv) in acetonitrile (110 mL) at –8 °C. After 10 min, a second aliquot of triethylborane solution (5 μL, 0.005 mmol, 0.05 equiv) was added. The reaction mixture was stirred at –8 °C for 20 min, and volatiles were removed in vacuo. The residue was diluted with methyl alcohol (30 mL), and potassium fluoride hydrate (1.0 g) was added to the resulting solution. After stirring at 23 °C for 5 h, the reaction solution

was concentrated, and the residue was partitioned between saturated aqueous sodium chloride solution (70 mL) and ethyl acetate (6 × 50 mL). The combined organic layers were dried (sodium sulfate) and concentrated, and the products were isolated by radial chromatography (5% methyl alcohol in dichloromethane) to afford separate fractions of **22** (55 mg, 62%) and **21** (16 mg, 18%) as white solids.

21: mp 100.5–102.0 °C; R_f 0.50, 10% methyl alcohol in dichloromethane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, 1 H, J = 8.8 Hz, H 6), 7.44 (d, 2 H, J = 9.1 Hz, arom), 6.80 (d, 2 H, J = 9.1 Hz, arom), 6.21 (d, 1 H, J = 9.4 Hz, NH), 5.79 (d, 1 H, J = 4.5 Hz, H 1′), 5.75 (d, 1 H, J = 8.8 Hz, H 5), 5.03 (s, 2 H, PMB CH_2), 4.80 (d, 1 H, J = 7.9 Hz, MEM CH_2), 4.79 (d, 1 H, J = 3.8 Hz, H 11′), 4.67 (d, 1 H, J = 7.9 Hz, MEM CH_2), 4.50 (m, 1 H, H 10′), 4.20 (t, 1 H, J = 4.4 Hz, H 2′), 4.12 (t, 1 H, J = 4.4 Hz, H 3′), 3.95 (m, 3 H, H 5′, 7′, 8′), 3.89 (m, 2 H, H 4′, 9′), 3.84 (m, 1 H, MEM CH_2), 3.75 (s, 3 H, CH_3O), 3.72 (m, 1 H, MEMCH_2), 3.57 (m, 3 H, OH, MEM CH_2), 3.41 (s, 3 H, CH_3O), 3.37 (s, 4 H, OH CH_3O), 2.26 (m, 1 H, H 6′), 1.98 (s, 3 H, Ac), 1.79 (m, 1 H, H 6′), 0.87 (s, 9 H, *tert*-butyl), 0.83 (s, 9 H, *tert*-butyl), 0.07 (s, 3 H, $SiCH_3$), 0.06 (s, 3 H, $SiCH_3$), 0.02 (s, 3 H, $SiCH_3$), –0.02 (s, 3 H, $SiCH_3$); IR (neat film) 3600–3213 (w, br), 2930 (m), 2857 (m), 1712 (m), 1668 (s), 1514 (m), 1455 (m), 1392 (w), 1249 (m), 1109 (m), 1052 (m), 837 (m), 778 (m); HRMS (FAB) m/z calcd for $C_{42}H_{72}N_3O_{14}Si_2$ $(MH)^+$ 898.4553, found 898.4551.

22: mp 100.5–101.5 °C; R_f 0.53, 10% methyl alcohol in dichloromethane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, 2 H, J = 7.5 Hz, arom), 7.22 (d, 1 H, J = 8.3 Hz, H 6), 6.77 (d, 2 H, J = 7.5 Hz, arom), 6.16 (d, 1 H, J = 8.8 Hz, NH), 5.79 (d, 1 H, J = 8.3 Hz, H 5), 5.26 (d, 1 H, J = 7.9 Hz, H 1′), 5.06 (d, 1 H, J = 13.9 Hz, PMB CH_2), 4.95 (d, 1 H, J = 13.9 Hz, PMB CH_2), 4.81 (m, 2 H, H 2′, MEM CH_2), 4.74 (d, 1 H, J = 3.8 Hz, H 11′), 4.70 (s, 1 H, OH), 4.68 (d, 1 H, J = 7.3 Hz, MEM CH_2), 4.49 (m, 1 H, H 10′), 4.13 (d, 1 H, J = 4.4 Hz, H 2′), 4.06 (m, 2 H, H 5′, 7′), 3.98 (m, 1 H, H 4′), 3.90 (m, 2 H, H 8′, 9′), 3.82 (m, 1 H, MEM CH_2), 3.75 (s, 3 H, CH_3O), 3.74 (m, 1 H, MEM CH_2), 3.58 (m, 2 H, MEM CH_2), 3.40 (s, 3 H, CH_3O), 3.38 (s, 3 H, CH_3O), 3.10 (s, 1 H, OH), 2.04 (m, 1 H, H 6′), 1.98 (s, 3 H, Ac), 1.57 (m, 1 H, H 6′), 0.89 (s, 9 H, *tert*-butyl), 0.72 (s, 9 H, *tert*-butyl), 0.09 (s, 3 H, $SiCH_3$), 0.08 (s, 3 H, $SiCH_3$), –0.10 (s, 3 H, $SiCH_3$), –0.31 (s, 3 H, $SiCH_3$); IR (neat film) 3624–3178 (w, br), 2930 (m), 2860 (w), 1713 (m), 1667 (s), 1514 (m), 1456 (m), 1390 (w), 1250 (m), 1108 (m), 1052 (s), 876 (w), 838 (m), 775 (m) cm^{-1}; HRMS (FAB) m/z calcd for $C_{42}H_{72}N_3O_{14}Si_2$ $(MH)^+$ 898.4553, found 898.4528.

α-Heptaacetyl-5′-*epi*-tunicaminyluracil (23). Ceric ammonium nitrate (60 mg, 0.11 mmol, 5.0 equiv) was added to a solution of the diol **21** (20 mg, 0.022 mmol, 1 equiv) in a mixture of acetonitrile and water (10:1 (v/v), 3.3 mL), and the resulting solution was heated at 60 °C for 3 h. The reaction mixture was partitioned between saturated aqueous sodium chloride solution (50 mL) and ethyl acetate (3 × 50 mL), and the combined organic layers were dried (sodium sulfate) and concentrated. The residue was diluted with aqueous hydrochloric acid (3 N, 2 mL), and the resulting suspension was heated at reflux for 3 h, at which time volatiles were removed in vacuo at 23 °C. The solid residue of 5′-*epi*-tunicaminyluracil was diluted with dichloromethane (5 mL), and the resulting solution was cooled to 0 °C and treated sequentially with DMAP (120 mg, 1.0 mmol, 45 equiv) and acetic anhydride (80 μL, 0.84 mmol, 38 equiv). The reaction mixture was stirred at 0 °C for 2 h and then was diluted with ethyl acetate (50 mL). The product solution was washed sequentially with 0.5 N aqueous hydrochloric acid solution (40 mL), saturated aqueous sodium bicarbonate solution (40 mL), and saturated aqueous sodium chloride solution (40 mL). The organic layer was dried (sodium sulfate) and concentrated, and the residue was purified by preparative thin-layer chromatography (7% methyl alcohol in dichloromethane) to afford **23** as the major product (6.5 mg, 31%): R_f 0.33, 10% methyl alcohol in dichloromethane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1 H, imide NH), 7.53 (d, 1 H, J = 8.6 Hz, H 6), 6.17 (d, 1 H, J = 3.7 Hz, H 11′), 6.13 (d, 1 H, J = 5.6 Hz, H 1′), 5.85 (d, 1 H, J = 8.6 Hz, H 5), 5.44 (d, 1 H, J = 9.9 Hz, amide NH), 5.28 (d, 1 H, J = 2.9 Hz, H 8′), 5.26 (m, 1 H, H 5′), 5.22 (t, 1 H, J = 5.6 Hz, H 2′), 5.19 (dd, 1 H, J = 2.9, 12.0 Hz, H 9′), 5.11 (dd, 1 H, J = 4.0, 5.6 Hz, H 3′), 4.69 (ddd, 1 H, J = 3.7, 9.9, 12.0 Hz, H 10′), 4.22 (d, 1 H, J = 8.3 Hz, H 7′), 4.10 (d, 1 H, J = 4.0 Hz, H 4′), 2.19 (s, 6 H, Ac), 2.11 (s, 3 H, Ac), 2.11 (m, 1 H, H 6′), 2.08 (s, 3 H, Ac), 2.07 (s, 3 H, Ac), 2.02 (s, 3 H, Ac), 1.94 (s, 3 H, Ac), 1.62 (m, 1 H, H 6′); IR (neat film) 3289 (w, br), 2925 (w), 1747 (s), 1693 (s), 1546 (w), 1458 (w), 1370 (m), 1223 (s), 1123 (w), 1041 (m), 929 (w) cm^{-1}; HRMS (FAB) m/z calcd for $C_{29}H_{38}N_3O_{17}$ $(MH)^+$ 700.2201, found 700.2231.

Synthetic α-Heptaacetyltunicaminyluracil (24). Ceric ammonium nitrate (165 mg, 0.30 mmol, 5.4 equiv) was added to a solution of the diol **22** (50 mg, 0.056 mmol, 1 equiv) in a mixture of acetonitrile and water (10:1 (v/v), 5.5 mL), and the resulting solution was heated at 60 °C for 3 h. The reaction mixture was partitioned between saturated aqueous sodium chloride solution (50 mL) and ethyl acetate (3 × 50 mL), and the combined organic layers were dried (sodium sulfate) and concentrated. The residue was diluted with aqueous hydrochloric acid (3 N, 3 mL), and the resulting suspension was heated at reflux for 3 h, at which time volatiles were removed in vacuo at 23 °C. The solid residue of crude tunicaminyluracil was diluted with dichloromethane (5 mL), and the resulting solution was cooled to 0 °C and was treated sequentially with DMAP (300 mg, 2.5 mmol, 45 equiv) and acetic anhydride (200 μL, 2.1 mmol, 38 equiv). The reaction mixture was stirred at 0 °C for 2 h and then was diluted with ethyl acetate (50 mL). The product solution was washed sequentially with 0.5 N aqueous hydrochloric acid solution (40 mL), saturated aqueous sodium bicarbonate solution (40 mL), and saturated aqueous sodium chloride solution (40 mL). The organic layer was dried (sodium sulfate) and concentrated, and the residue was purified by preparative thin-layer chromatography (7% methyl alcohol in dichloromethane) to afford **24** as the major product (17 mg, 43%): mp 174.5 °C (decomp); R_f 0.31, 10% methyl alcohol in dichloromethane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1 H, imide NH), 7.21 (d, 1 H, J = 8.4 Hz, H 6), 6.12 (d, 1 H, J = 3.5 Hz, H 11′), 5.90 (d, 1 H, J = 5.9 Hz, H 1′), 5.80 (d, 1 H, J = 8.4 Hz, H 5), 5.46 (d, 1 H, J = 9.8 Hz, amide NH), 5.35 (t, 1 H, J = 5.9 Hz, H 3′), 5.27 (t, 1 H, J = 5.9 Hz, H 2′), 5.24 (d, 1 H, J = 3.3 Hz, H 8′), 5.20 (dd, 1 H, J = 3.3, 11.6 Hz, H 9′), 5.10 (m, 1 H, H 5′), 4.71 (ddd, 1 H, J = 3.5, 9.8, 11.6 Hz, H 10′), 4.07 (m, 2 H, H 4′, 7′), 2.19 (s, 3 H, Ac), 2.17 (s, 3 H, Ac), 2.12 (s, 3 H, Ac), 2.10 (s, 3 H, Ac), 2.08 (s, 3 H, Ac), 2.03 (s, 3 H, Ac), 1.95 (s, 3 H, Ac), 1.95 (obscured, 1 H, H 6′), 1.55 (ddd, 1 H, J = 1.9, 8.3, 9.9 Hz, H 6′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 170.6, 170.0, 170.0, 169.6, 169.3, 169.1 (6 × CH_3CO_2, CH_3CONH), 162.2 (C 4), 149.9 (C 2), 139.7 (C 6), 103.5 (C 5), 91.1, 88.0, 82.6 (C 1′, 4′, 11′), 72.4, 69.6, 69.6, 69.4, 68.2, 67.7 (C 2′, 3′, 5′, 8′, 9′, 10′), 46.8, 32.6 (C 6′, 7′), 23.2 (CH_3CONH), 20.9, 20.9, 20.8, 20.7, 20.5, 20.4 (6 × CH_3CO_2); IR (neat film) 3295 (w, br), 3013 (w), 1746 (s), 1694 (s), 1543 (w), 1455 (w), 1431 (w), 1373 (m), 1222 (s), 1046 (m), 933 (w), 756 (w) cm^{-1}; HRMS (FAB) m/z calcd for $C_{29}H_{38}N_3O_{17}$ $(MH)^+$ 700.2201, found 700.2177; $[\alpha]^{25}$ +65.9° (c = 1.67, $CHCl_3$).

α-Heptaacetyltunicaminyluracil (24) from Natural Tunicamycin. A solution of commercial tunicamycin (20 mg, 0.024 mmol, 1 equiv) in aqueous hydrochloric acid (3 N, 1.5 mL) was heated at reflux for 3 h, and volatiles were removed in vacuo at 23 °C. The residue was diluted with dichloromethane (3 mL), and to this solution were added DMAP (150 mg, 1.2 mmol, 50 equiv) and acetic anhydride (100 μL, 1.0 mmol, 42 equiv) in sequence, at 0 °C. The resulting solution was stirred at 0 °C for 2 h and then was diluted with ethyl acetate (50 mL). The product solution was washed sequentially with 0.5 N aqueous hydrochloric acid solution (40 mL), saturated aqueous sodium bicarbonate solution (40 mL), and saturated aqueous sodium chloride solution (40 mL) and then was dried (sodium sulfate) and concentrated. The residue was purified by preparative thin-layer chromatography (7% methyl alcohol in dichloromethane) to afford **24** as the major product (5 mg, 30%): mp 175.0 °C (decomp); R_f 0.31, 10% methyl alcohol in dichloromethane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1 H, imide NH), 7.21 (d, 1 H, J = 8.4 Hz, H 6), 6.12 (d, 1 H, J = 3.4 Hz, H 11′), 5.90 (d, 1 H, J = 5.9 Hz, H 1′), 5.80 (d, 1 H, J = 8.4 Hz, H 5), 5.47 (d, 1 H, J = 10.0 Hz, amide NH), 5.35 (t, 1 H, J = 5.9 Hz, H 3′), 5.27 (t, 1 H, J = 5.9 Hz, H 2′), 5.24 (d, 1 H, J = 3.3 Hz, H 8′), 5.20 (dd, 1 H, J = 3.3, 11.4 Hz, H 9′), 5.10 (m, 1 H, H 5′), 4.71 (ddd, 1 H, J = 3.4, 10.0, 11.4 Hz, H 10′), 4.07 (m, 2 H, H 4′, 7′), 2.19 (s, 3 H, Ac), 2.17 (s, 3 H, Ac), 2.12 (s, 3 H, Ac), 2.10 (s, 3 H, Ac), 2.08 (s, 3 H, Ac), 2.03 (s, 3 H, Ac), 1.95 (s, 3 H, Ac), 1.95 (obscured, 1 H, H 6′), 1.55 (ddd, 1 H, J = 2.0, 8.2, 9.9 Hz, H 6′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 170.6, 170.0, 170.0, 169.6, 169.3, 169.1 (6 × CH_3CO_2, CH_3CONH), 162.1 (C 4), 149.8 (C 2), 139.7 (C 6), 103.5 (C 5), 91.1, 88.0, 82.6 (C 1′, 4′, 11′), 72.4, 69.7, 69.6, 69.4, 68.2, 67.7 (C 2′, 3′, 5′, 8′, 9′, 10′), 46.8, 32.6 (C 6′, 7′), 23.2 (CH_3CONH), 20.9, 20.9, 20.8, 20.7, 20.5, 20.4 (6 × CH_3CO_2); IR (neat film) 3307 (w, br), 3023 (w), 1747 (s), 1694 (s), 1538 (w), 1455 (w), 1431 (w), 1373 (m), 1223 (s), 1046 (m), 933 (w), 756 (w) cm^{-1}; HRMS (FAB) m/z calcd for $C_{29}H_{38}N_3O_{17}$ $(MH)^+$ 700.2201, found 700.2229; $[\alpha]^{25}$ +63.4° (c = 1.33, $CHCl_3$).

***tert*-Butyldimethylsilyl 2-Azido-4-*O*-benzoyl-6-bromo-β-D-galactopyranoside (28).** A solution of *tert*-butyldimethylsilyl 2-azido-4,6-*O*-benzylidene-β-D-galactopyranoside (**27**, 4.70 g, 11.6 mmol, 1 equiv) in

bromotrichloromethane (150 mL) was divided equally among 10 sealed Pyrex tubes (10 × 1.5 cm), and the tubes were irradiated with a 275-W sunlamp at 0 °C for 2.5 h. The reaction mixtures were combined and concentrated, and the residue was purified by flash column chromatography (25% ethyl acetate in hexanes) to give *tert*-butyldimethylsilyl 2-azido-4-*O*-benzoyl-6-bromo-β-D-galactopyranoside (**28**, 4.88 g, 87%) as a colorless oil: R_f 0.40, 33% ethyl acetate in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (m, 2 H, arom), 7.63 (m, 1 H, arom), 7.50 (m, 2 H, arom), 5.63 (dd, 1 H, *J* = 3.4, 1.0 Hz, H 4), 4.63 (d, 1 H, *J* = 7.5 Hz, H 1), 3.87 (ddd, 1 H, *J* = 7.6, 5.9, 1.0 Hz, H 5), 3.71 (m, 1 H, H 3), 3.57 (dd, 1 H, *J* = 10.3, 7.5 Hz, H 2), 3.41 (m, 2 H, H 6), 2.45 (s(br), 1 H, OH), 0.98 (s, 9 H, *tert*-butyl), 0.24, 0.22 (2 × s, 2 × 3H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 133.5–128.4 (arom), 97.4, 74.0, 70.5, 70.4, 66.0, 29.1, 25.6, 25.6, 25.5, 17.8, –4.2, –5.2; IR (neat film) 3624–3248 (m, br), 2930 (m), 2858 (m), 2115 (s), 1725 (s), 1452 (w), 1362 (w), 1273 (s), 1115 (s), 1071 (s), 836 (s), 708 (s) cm^{-1}; HRMS (FAB) *m*/*z* calcd for $C_{19}H_{29}N_3O_5BrSi$ $(MH)^+$ 486.1077, found 486.1060.

***tert*-Butyldimethylsilyl 2-Azido-4-*O*-benzoyl-3-*O*-[(benzyloxy)methyl]-6-bromo-β-D-galactopyranoside (29).** (Benzyloxy)methyl chloride (26.0 mL, 188 mmol, 5.0 equiv) was added to a solution of the bromide **28** (18.3 g, 37.6 mmol, 1 equiv) and diisopropylethylamine (36.0 mL, 207 mmol, 5.5 equiv) in dichloromethane (150 mL), and the resulting solution was heated at reflux for 15 h. The reaction mixture was diluted with dichloromethane (200 mL), and the resulting solution was washed sequentially with water (50 mL) and saturated aqueous sodium chloride solution (50 mL). The organic layer was dried (sodium sulfate) and concentrated, and the residue was filtered through a short column of silica gel (17% ethyl acetate in hexanes) providing *tert*-butyldimethylsilyl 2-azido-4-*O*-benzoyl-3-*O*-[(benzyloxy)methyl]-6-bromo-β-D-galactopyranoside (**29**, 20.2 g, 89%) as a viscous oil: R_f 0.60, 33% ethyl acetate in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (m, 2 H, arom), 7.62 (m, 1 H, arom), 7.50 (m, 2 H, arom), 7.41–7.28 (m, 5 H, arom), 5.71 (dd, 1 H, *J* = 3.2, 1.0 Hz, H 4), 4.93 (d, 1 H, *J* = 7.3 Hz, OCH_2O), 4.75 (d, 1 H, *J* = 6.6 Hz, $PhOCH_2O$), 4.74 (d, 1 H, *J* = 7.3 Hz, OCH_2O), 4.64 (d, 1 H, *J* = 7.6 Hz, H 1), 4.60 (d, 1 H, *J* = 6.6 Hz, $PhCH_2O$), 3.83 (m, 1 H, H 5), 3.78 (dd, 1 H, *J* = 10.5, 3.2 Hz, H 3), 3.66 (dd, 1 H, 10.5, 7.6 Hz, H 2), 3.40 (m, 2 H, H 6), 1.00 (s, 9 H, *tert*-butyl), 0.25 (s, 3 H, $SiCH_3$), 0.24 (s, 3 H, $SiCH_3$); IR (neat film) 2930 (m), 2858 (m), 2113 (s), 1728 (s), 1602 (w), 1454 (w), 1267 (s), 1113 (s), 1027 (s), 836 (s), 784 (m), 709 (s) cm^{-1}; HRMS (FAB) *m*/*z* calcd for $C_{27}H_{35}N_3O_6BrSi$ $(M^+ - H)$ 604.1511, found 604.1479.

***tert*-Butyldimethylsilyl 2-Amino-4-*O*-benzoyl-3-*O*-[(benzoyloxy)methyl]-6-bromo-β-D-galactopyranoside (30).** A solution of *tert*-butyldimethylsilyl 2-azido-4-*O*-benzoyl-3-*O*-[(benzoyloxy)methyl]-6-bromo-β-D-galactopyranoside (**29**, 20.2 g, 33.4 mmol, 1 equiv) in triethylamine (50 mL) was added dropwise to a solution of benzeneselenol (10.2 mL, 96 mmol, 2.9 equiv) in triethylamine (150 mL) at 0 °C. The resulting solution was stirred at 0 °C for 5 min, then at 23 °C for 5 min, and finally at 60 °C for 2.5 h. The reaction mixture was concentrated in vacuo, and the yellow residue was dissolved in ethyl acetate (250 mL). The latter solution was washed sequentially with water (2 × 100 mL) and saturated aqueous sodium chloride solution (50 mL) and then was dried (sodium sulfate) and concentrated. The residue was purified by flash column chromatography (gradient elution: 20 → 33% ethyl acetate in hexanes) to furnish *tert*-butyldimethylsilyl 2-amino-4-*O*-benzoyl-3-*O*-[(benzyloxy)methyl]-6-bromo-β-D-galactopyranoside (**30**, 18.9 g, 98%) as a colorless oil: R_f 0.20, 50% ethyl acetate in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (m, 2 H, arom), 7.60 (m, 1 H, arom), 7.47 (m, 2 H, arom), 7.34–7.27 (m, 5 H, arom), 5.68 (d(br), 1 H, *J* = 2.6 Hz, H 4), 4.96 (d, 1 H, *J* = 7.1 Hz, OCH_2O), 4.74 (d, 1 H, *J* = 7.1 Hz, OCH_2O), 4.66 (d, 1 H, *J* = 11.7 Hz, $PhCH_2O$), 4.58 (d, 1 H, *J* = 7.6 Hz, H 1), 4.56 (d, 1 H, *J* = 11.7 Hz, $PhCH_2O$), 3.87 (dd(br), 1 H, *J* = 7.8, 5.6 Hz, H 5), 3.81 (dd, 1 H, *J* = 10.3, 2.6 Hz, H 3), 3.43 (dd, 1 H, *J* = 10.7, 5.4 Hz, H 6), 3.38 (dd, 1 H, *J* = 10.7, 7.8 Hz, H 6), 3.21 (dd, 1 H, *J* = 10.3, 7.6 Hz, H 2), 1.79 (m, 2 H, NH_2), 0.96 (s, 9 H, *tert*-butyl), 0.22, 0.20 (2 × s, 2 × 3 H, $Si(CH_3)_2$); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.5, 137.3–127.8 (arom), 99.4, 93.1, 77.0, 74.3, 70.0, 67.6, 54.7, 29.7, 25.8, 17.0, –3.8, –5.1; IR (neat film) 2928 (m), 2857 (m), 1722 (s), 1452 (w), 1271 (s), 1170 (m), 1109 (s), 1044 (s), 837 (s), 783 (m), 708 (m) cm^{-1}; HRMS (FAB) *m*/*z* calcd for $C_{27}H_{39}NO_6BrSi$ $(MH)^+$ 580.1739, found 580.1730.

***tert*-Butyldimethylsilyl 4-*O*-Benzoyl-3-*O*-[(benzyloxy)methyl]-6-bromo-2-phthalimido-β-D-galactopyranoside (31).** A solution of *tert*-butyldimethylsilyl 2-amino-4-*O*-benzoyl-3-*O*-[(benzyloxy)methyl]-6-bromo-β-D-galactopyranoside (**30**, 21.0 g, 36.5 mmol, 1 equiv) and triethylamine (20.0 mL, 146 mmol, 4.0 equiv) in dichloromethane (240 mL) at 0 °C was treated with phthaloyl dichloride (10.5 mL, 72.9 mmol, 2.0 equiv) and then was stirred at 0 °C for 10 min. The reaction solution was concentrated in vacuo, and the residue was diluted with a mixture of toluene and DBU (6:1 (v/v), 280 mL). The resulting green solution was heated at 100 °C for 1.5 h and then was cooled to 23 °C. Ethyl acetate (300 mL) was added, and the product solution was washed sequentially with water (2 × 100 mL) and saturated aqueous sodium chloride solution (100 mL). The organic layer was dried (sodium sulfate) and concentrated, and the residue was purified by flash column chromatography (33% ethyl acetate in hexanes) to afford *tert*-butyldimethylsilyl 4-*O*-benzoyl-3-*O*-[(benzyloxy)methyl]-6-bromo-2-phthalimido-β-D-galactopyranoside (**31**, 22.1 g, 86%) as a colorless oil: R_f 0.45, 50% ethyl acetate in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (m, 2 H, ArH), 7.84–6.98 (m, 12 H, ArH), 5.85 (d(br), 1 H, *J* = 4.4 Hz, H 4), 5.52 (d, 1 H, *J* = 8.0 Hz, H 1), 4.88 (dd, 1 H, *J* = 11.5, 4.4 Hz, H 3), 4.84 (d, 1 H, *J* = 7.3 Hz, OCH_2O, 4.56 (dd, 1 H, *J* = 11.5, 8.0 Hz, H 2), 4.53 (d, 1 H, *J* = 7.3 Hz, OCH_2O), 4.18 (s, 2 H, $PhCH_2O$), 4.08 (m, 1 H, H 5), 3.47 (m, 2 H, H 6), 0.72 (s, 9 H, *tert*-butyl), 0.14, 0.01 (2 × s, 2 × 3 H, $Si(CH_3)_2$); ^{13}C NMR (400 MHz, $CDCl_3$) δ 168.2, 167.5, 166.1, 137.2–123.1 (arom), 94.0, 94.0, 93.3, 74.4, 71.7, 69.7, 68.3, 54.9, 29.4, 25.4, 17.6, –4.0, –5.4; IR (neat film) 2955 (m), 2858 (m), 1775 (m), 1715 (s), 1267 (s), 1175 (m), 1110 (s), 1039 (s), 837 (s), 783 (m), 721 (m) cm^{-1}; HRMS (FAB) *m*/*z* calcd for $C_{35}H_{39}BrNO_8Si$ $(M^+ - H)$ 708.1628, found 708.1595.

***tert*-Butyldimethylsilyl 4-*O*-benzoyl-3-*O*-[(benzyloxy)methyl]-6-(phenylseleno)-2-phthalimido-β-D-galactopyranoside (32).** Benzeneselenol (10.6 mL, 100 mmol, 3.2 equiv) was added to a deoxygenated solution of *tert*-butyldimethylsilyl 4-*O*-benzoyl-3-*O*-[(benzyloxy)methyl]-6-bromo-2-phthalimido-β-D-galactopyranoside (**31**, 22.0 g, 31.2 mmol, 1 equiv) and triethylamine (50.0 mL, 359 mmol, 11.5 equiv) in anhydrous dimethoxyethane (280 mL), and the resulting solution was heated at 90 °C for 10 h. The reaction mixture was cooled to 23 °C and then was diluted with ethyl ether (300 mL). The resulting solution was washed sequentially with water (100 mL) and saturated aqueous sodium chloride solution (100 mL). The organic layer was dried (sodium sulfate) and concentrated, and the residue was purified by flash column chromatography (25% ethyl acetate in hexanes) to afford *tert*-butyldimethylsilyl 4-*O*-benzoyl-3-*O*-[(benzyloxy)methyl]-6-bromo-2-phthalimido-β-D-galactopyranoside (**31**, 23.3 g, 95%) as a pale yellow oil: R_f 0.40, 25% ethyl acetate in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (m, 2 H, arom), 7.84–6.98 (m, 17 H, arom), 5.78 (d(br), 1 H, *J* = 3.4 Hz, H 4), 5.74 (d, 1 H, *J* = 8.1 Hz, H 1), 4.84 (dd, 1 H, *J* = 11.2, 3.4 Hz, H 3), 4.82 (d, 1 H, *J* = 7.6 Hz, OCH_2O), 4.57 (dd, 1 H, *J* = 11.2, 8.1 Hz, H 2), 4.51 (d, 1 H, *J* = 7.6 Hz, OCH_2O), 4.17 (s, 2 H, $PhCH_2O$), 3.98 (ddd, 1 H, *J* = 8.6, 5.1, 1.0 Hz, H 5), 3.21 (dd, 1 H, *J* = 12.9, 8.6 Hz, H 6), 3.01 (dd, 1 H, *J* = 12.9, 5.1 Hz, H 6), 0.71 (s, 9 H, *tert*-butyl), 0.15, 0.02 (2 × s, 2 × 3 H, $Si(CH_3)_2$); ^{13}C NMR (300 MHz, $CDCl_3$) δ 168.6, 168.0, 166.2, 137.1–123.0 (arom), 93.9, 93.0, 73.6, 71.6, 69.6, 54.9, 28.1, 25.4, 17.5, –3.9, –5.5; IR (neat film) 2928 (m), 2849 (m), 1775 (m), 1715 (s), 1469 (w), 1389 (s), 1266 (s), 1173 (m), 1113 (s), 1038 (s), 839 (s), 783 (m), 721 (m) cm^{-1}; HRMS (FAB) *m*/*z* calcd for $C_{41}H_{44}NO_8SeSi$ $(M^+ - H)$ 786.2001, found 786.2013.

4-*O*-Benzoyl-3-*O*-[(benzoyloxy)methyl-6-(phenylseleno)-2-phthalimido-D-galactopyranose (33). Triethylamine trihydrofluoride (40.0 mL, 250 mmol, 8.7 equiv) was added to a solution of *tert*-butyldimethylsilyl 4-*O*-benzoyl-3-*O*-[(benzyloxy)methyl]-6-(phenylseleno)-2-phthalimido-β-D-galactopyranoside (**32**, 22.5 g, 28.6 mmol, 1 equiv) in acetonitrile (120 mL) contained in a 300-mL polyethylene reaction vessel. The resulting solution was stirred at 23 °C for 6 h and then was partitioned between ethyl acetate (200 mL) and water (100 mL). The organic phase was washed sequentially with water (100 mL) and saturated aqueous sodium chloride solution (100 mL) and then was dried (sodium sulfate) and concentrated. The residue was purified by flash column chromatography (gradient elution: 25 → 50% ethyl acetate in hexanes) to afford 4-*O*-benzoyl-3-*O*-[(benzyloxy)methyl]-6-(phenylseleno)-2-phthalimido-D-galactopyranose (**33**) as a mixture of anomers (>10:1, β:α, 18.6 g, 97%) as a colorless oil. The β-anomer could be obtained pure by fractional crystallization (ethyl acetate in hexanes): white needles, mp 69.0–71.0 °C; R_f 0.40, 33% ethyl acetate in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (m, 2 H, arom), 7.83–6.97 (m, 17 H, arom), 5.88 (d(br), 1 H, *J* = 2.9 Hz, H 4), 5.53 (t(br), 1 H, *J* ~ 8.1 Hz, H 1), 4.87 (dd, 1 H, *J* = 11.0, 3.2 Hz, H 3), 4.84 (d, 1 H, *J* = 7.3 Hz, OCH_2O), 4.56 (dd, 1 H, *J* = 11.2, 8.5 Hz, H 2), 4.52 (d, 1 H, *J* = 7.3 Hz, OCH_2O), 4.16 (s, 2 H, $PhCH_2O$), 4.02 (t(br), 1 H, *J* ~ 6.8 Hz, H 5), 4.74 (d(br), 1 H, *J* = 7.5 Hz, OH), 3.19 (dd, 1 H, *J* = 12.9, 7.3 Hz, H 6), 3.02 (dd, 1 H, *J* = 12.9, 6.3 Hz, H 6); ^{13}C NMR (400 MHz, C_6D_6) δ 169.0, 168.2, 166.3, 137.9–123.2 (arom), 93.9, 93.4, 74.3, 72.5, 69.8, 54.9, 28.6; IR (neat film) 3600–3300 (s), 3062 (m), 2857 (m), 1773 (m), 1714 (s), 1602

(w), 1453 (w), 1392 (s), 1268 (s), 1176 (m), 1114 (s), 1025 (s), 720 (m), cm^{-1}; HRMS (FAB) m/z calcd for $C_{35}H_{31}NO_8Se$ $(M)^+$ 673.1191, found 673.1215.

2-Azido-3-*O*-*tert*-butyldimethylsilyl)-4,6-*O*-isopropylidene-D-glucopyranose (35). Solid potassium fluoride hydrate (12.0 g, 127.5 mmol, 5.5 equiv) was added to a solution of *tert*-butyldimethylsilyl 2-azido-3-*O*-*tert*-butyldimethylsilyl)-4,6-*O*-isopropylidene-β-D-glucopyranoside (**34**, 11.0 g, 23.3 mmol, 1 equiv) in methyl alcohol (100 mL), and the resulting solution was stirred at 23 °C for 6.5 h. The reaction mixture was partitioned between ethyl acetate (700 mL) and water (300 mL). The organic layer was washed with saturated aqueous sodium chloride solution (300 mL) and then was dried (sodium sulfate) and concentrated. The residue was purified by flash column chromatography (25% ethyl acetate in hexanes) to afford a mixture of 2-azido-3-*O*-(*tert*-butyldimethylsilyl-4,6-*O*-isopropylidene-D-glucopyranose (**35**, α:β 2:1, 8.49 g, quantitative) as a clear, colorless oil: R_f 0.57, 50% ethyl acetate in hexanes; ^1H NMR (300 MHz, $CDCl_3$) δ 5.30 (t, 1 H, J = 3.6 Hz, H 1α), 5.11 (d, 1 H, J ~ 1 Hz, OHβ), 4.62 (dd, 1 H, J = 1, 8.0 Hz, H 1β), 4.19 (dd, 1 H, J = 4.0, 8.4 Hz, H 6β), 4.0–3.6 (m, H 6α & β, OHα), 3.55–3.40 (m, H 3, 4α & β), 3.30–3.10 (m, H 5, 2α & β), 1.47 (s, 3 H, CH_3), 1.46 (s, 3 H, CH_3), 1.40 (s, H, CH_3), 1.38 (s, 3 H, CH_3), 0.92 (s, 9 H, *tert*-butyl), 0.90 (s, 9 H, *tert*-butyl), 0.16 (s, 3 H, $SiCH_3$), 0.12 (s, 3 H, $SiCH_3$), 0.11 (s H, $SiCH_3$), 0.08 (s, 3 H, $SiCH_3$); IR (neat film) 3391 (w, br), 2930 (m), 2859 (m), 2111 (s), 1472 (w), 1383 (w), 1267 (m), 1124 (m), 1088 (s), 838 (s) cm^{-1}; HRMS (FAB) m/z calcd for $C_{15}H_{30}N_3O_5Si$ $(MH)^+$ 360.1955, found 360.1960.

Trichloroacetimido 2-Azido-3-*O*-(*tert*-butyldimethylsilyl)-4,6-*O*-isopropylidene-β-D-glucopyranoside (36). Potassium carbonate (3.0 g, 21.7 mmol, 0.9 equiv) was added to a solution of 2-azido-3-*O*-(*tert*-butyldimethylsilyl)-4,6-*O*-isopropylidene-D-glucopyranose (**35**, 8.40 g, 23.4 mmol, 1 equiv) in a mixture of dichloromethane and trichloroacetonitrile (5:1 (v/v), 120 mL), and the resulting solution was stirred at 23 °C for 24 h. Precipitated solids were removed by filtration, and the filtrate was concentrated. The residue was purified by flash column chromatography (10% ethyl acetate in hexanes containing 2% triethylamine) to afford trichloroacetimido 2-azido-3-*O*-(*tert*-butyldimethylsilyl)-4,6-*O*-isopropylidene-β-D-glucopyranoside (**36**, 7.53 g, 64%). Unreacted starting material, 2-azido-3-*O*-(*tert*-butyldimethylsilyl)-4,6-*O*-isopropylidene-D-glucopyranose (**35**, 1.0 g, 12%), was recovered in separate fractions. Trichloroacetimido 2-azido-3-*O*-(*tert*-butyldimethylsilyl)-4,6-*O*-isopropylidene-β-D-glucopyranoside (**36**): R_f 0.30, 20% ethyl acetate in hexanes; ^1H NMR (300 MHz, $CDCl_3$) δ 8.73 (s, 1 H, NH), 5.67 (d, 1 H, J = 6.7 Hz, H 1), 3.97 (dd, 1 H, J = 4.8, 12.1 Hz, H 6), 3.79 (t, 1 H, J = 12.1 Hz, H 6), 3.55 (m, 3 H, H 2, 3, 4), 3.35 (m, 1 H, H 5), 1.48 (s, 3 H, acetonide), 1.38 (s, 3 H, acetonide), 0.90 (s, 9 H, *tert*-butyl), 0.14 (s, 3 H, $SiCH_3$), 0.11 (s, 3 H, $SiCH_3$); IR (neat film) 3347 (w), 2930 (m), 2858 (m), 2113 (s), 1679 (s), 1472 (w), 1373 (m), 1267 (s), 1203 (m), 1173 (m), 1065 (s), 971 (m), 835 (s), 798 (s), 781 (s), 647 (m) cm^{-1}.

Disaccharide 38. 4-*O*-Benzoyl-3-*O*-[(benzyloxy)methyl]-6-(phenylseleno)-2-phthalimido-D-galactopyranose (**33**, 0.90 g, 1.34 mmol, 1 equiv), trichloroacetimido 2-azido-3-*O*-(*tert*-butyldimethylsilyl)-4,6-*O*-isopropylidene-β-D-glucopyranoside (**36**, 1.33 g, 2.64 mmol, 2.0 equiv), crushed 4-Å molecular sieves (2 g), and toluene (10 mL) were combined, and the mixture was stirred at 23 °C for 2 h. The suspension was cooled to −20 °C, and six aliquots of a solution of trifluoromethanesulfonic acid in toluene (5% (v/v), 300-μL aliquots, 0.17 mmol each, 0.06 equiv each) were added dropwise at 4-h intervals over a 24-h period. The acid catalyst was neutralized by the addition of triethylamine (100 μL), and the reaction mixture was diluted with ethyl acetate (50 mL). The product solution was filtered through a pad of Celite and was concentrated. The residue was purified by flash column chromatography (25% ethyl acetate in hexanes) to provide disaccharide **38** (1.04 g, 77%), as well as the α,α-trehalose coupling product **39** (149 mg, 11%) in separate fractions, both as colorless oils. **38**: R_f 0.36, 25% ethyl acetate in hexanes; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (m, 2 H, arom), 7.64 (m, 1 H, arom), 7.57 (m, 1 H, arom), 7.48 (m, 2 H, arom), 7.08–6.87 (m, 13 H, arom), 5.67 (d(br), 1 H, J = 3.2 Hz, H 8′), 5.64 (d, 1 H, J = 8.8 Hz, H 11′), 5.24 (dd, 1 H, J = 11.0, 8.8 Hz, H 10′), 4.94 (dd, 1 H, J = 11.0, 3.2 Hz, H 9′), 4.83 (d, 1 H, J = 3.7 Hz, H 1″), 4.81 (d, 1 H, J = 7.3 Hz, OCH_2O), 4.43 (d, 1 H, J = 7.3 Hz, OCH_2), 4.27 (d, 1 H, J = 12.2 Hz, $PhCH_2O$), 4.26 (m, 2 H, H 6″), 4.10 (d, 1 H, J = 12.2 Hz, $PhCH_2O$), 3.98 (t, 1 H, J = 9.0 Hz, H 3″), 3.65 (m, 2 H, H 5, H 5″), 3.29 (t, 1 H, J = 9.6, H 4″), 3.25 (dd, 1 H, J = 12.5, 9.0 Hz, H 6′), 2.88 (dd, 1 H, J = 12.5, 4.4 Hz, H 6′), 2.82 (dd, 1 H, J = 9.5, 3.7 Hz, H 2″), 1.39, 1.24 (2 × s, 2 × 3 H, $C(CH_3)_2$), 0.97 (s, 9 H, *tert*-butyl), 0.08, 0.06 (2 × s, 2 × 3 H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, C_6D_6) δ 169.2, 167.7, 166.2, 137.8–123.0 (arom), 101.3, 101.1, 99.4, 93.3, 74.8, 74.5, 72.3, 71.2, 69.7, 69.4, 66.4, 65.2, 62.5, 53.2, 29.1, 26.1, 25.9, 19.0, 18.3, −4.2, −5.1; IR (neat film) 2952 (s), 2856 (s), 2107 (s), 1778 (m), 1714 (s), 1580 (w), 1470 (m), 1392 (s), 1265 (s), 1125 (s), 1025 (s), 970 (m), 865 (s), 720 (s) cm^{-1}. Elem. anal. Calcd for $C_{50}H_{58}N_4O_{12}SeSi$: C, 59.22; H, 5.77; N, 5.52. Found: C, 59.13; H, 5.79; N, 5.71. **39**: R_f 0.22, (25% ethyl acetate in hexanes); ^1H NMR (400 MHz, C_6D_6) δ 8.33 (m, 2 H, arom), 7.67 (m, 1 H, arom), 7.57 (m, 2 H, arom), 7.48 (m, 1 H, arom), 7.17–6.86 (m, 13 H, arom), 6.09 (d, 1 H, J = 3.2 Hz, H 8′), 5.92 (dd, 1 H, J = 11.5, 3.2 Hz, H 9′), 5.69 (d, 1 H, J = 3.9 Hz, H 11′), 5.48 (dd, 1 H, J = 11.5, 3.9 Hz, H 10′), 5.38 (d, 1 H, J = 3.4 Hz, H 1″), 4.87 (d, 1 H, J = 7.0 Hz, OCH_2O), 4.83 (d, 1 H, J = 7.0 Hz, OCH_2O), 4.82 (m, 1 H, H 6″), 4.46 (d, 1 H, J = 12.2 Hz, $PhCH_2O$), 4.38 (d, 1 H, J = 12.2 Hz, $PhCH_2O$), 4.27 (dd, 1 H, J = 9.5, 8.8 Hz, H 6″), 3.32 (dd, 1 H, J = 12.9, 9.5 Hz, H 3″), 3.26 (m, 2 H, H 6′, 7′), 3.19 (t, 1 H, J = 9.5 Hz, H 4″), 3.12 (m, 1 H, H 5″), 2.99 (dd, 1 H, J = 12.9, 3.4 Hz, H 2″), 2.96 (dd, 1 H, J = 9.8, 3.4 Hz, H 6′), 1.18 (s, 9 H, *tert*-butyl), 1.08 (s, 3 H, CH_3), 0.95 (s, 3 H, CH_3), 0.57 (s, 3 H, $SiCH_3$), 0.42 (s, 3 H, $SiCH_3$); ^{13}C NMR (100 MHz, C_6D_6) δ 168.7, 167.9, 166.1, 138.3–123.4, 99.0, 94.8, 94.1, 93.1, 74.7, 71.9, 71.7, 70.7, 70.4, 70.3, 65.2, 65.1, 62.0, 52.1, 29.0, 28.9, 26.1, 18.7, 18.6, −3.9, −4.6; IR (neat film) 2950 (w), 2856 (w), 2108 (s), 1775 (w), 1722 (s), 1470 (w), 1386 (m), 1267 (s), 1135 (m), 1071 (m), 970 (m), 869 (m), 711 (m) cm^{-1}.

Benzyl 2-(Acetylamino)-3-*O*-(*tert*-butyldimethylsilyl)-4,6-*O*-isopropylidene-α-D-glucopyranoside (41). Imidazole (3.90 g, 57.4 mmol, 2.9 equiv) and *tert*-butyldimethylsilyl chloride (4.53 g, 29.9 mmol, 1.5 equiv) were added sequentially to a solution of benzyl 2-(acetylamino)-4,6-*O*-isopropylidene-α-D-glucopyranoside (**40**, 7.00 g, 19.9 mmol, 1 equiv) in *N*,*N*-dimethylformamide (50 mL), and the resulting solution was stirred at 23 °C for 12 h. The reaction mixture was partitioned between water (100 mL) and ethyl acetate (100 mL). The organic layer was washed with saturated aqueous sodium chloride solution (50 mL) and then was dried (sodium sulfate) and concentrated. The residue was purified by flash column chromatography (gradient elution: 33 → 50% ethyl acetate in hexanes) to afford benzyl 2-(acetylamino)-3-*O*-(*tert*-butyldimethylsilyl)-4,6-*O*-isopropylidene-α-D-glucopyranoside (**41**, 9.13 g, 98%) as a colorless oil: R_f 0.39, 33% ethyl acetate in hexanes; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 5 H, arom), 5.50 (d, 1 H, J = 9.8 Hz, NH), 4.83 (d, 1 H, J = 3.9 Hz, H 1), 4.68 (d, 1 H, J = 12.0 Hz, $PhCH_2$), 4.44 (d, 1 H, J = 12.0 Hz, $PhCH_2$), 4.23 (dt, 1 H, J = 9.8, 3.9 Hz, H 2), 3.82 (dd, 1 H, J = 10.0, 4.9 Hz, H 6), 3.74 (t, 1 H, J = 10.0 Hz, H 6), 3.68 (t, 1 H, J = 9.8 Hz, H 3), 3.67 (m, 1 H, H 5), 3.57 (t, 1 H, J = 9.8 Hz, H 4), 1.93 (s, 3 H, Ac), 1.47 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 0.84 (s, 9 H, *tert*-butyl), 0.04 (s, 3 H, $SiCH_3$), 0.03 (s, 3 H, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 136.9, 128.4, 128.1, 128.0, 99.2, 97.6, 74.7, 71.0, 69.5, 63.8, 62.2, 53.8, 28.9, 25.5, 23.2, 18.8, 18.0, −4.2, −5.1; IR (neat film) 3291 (m), 2928 (s), 2856 (m), 1653 (s), 1552 (m), 1374 (m), 1200 (m), 1131 (s), 1042 (s), 838 (s) cm^{-1}; HRMS (FAB) m/z calcd for $C_{24}H_{40}NO_6Si$ $(MH)^+$ 466.2625, found 466.2604.

2-(Acetylamino)-3-*O*-(*tert*-butyldimethylsilyl)-4,6-*O*-isopropylidene-D-glucopyranose (42). A solution of benzyl 2-(acetylamino)-3-*O*-(*tert*-butyldimethylsilyl)-4,6-*O*-isopropylidene-α-D-glucopyranoside (**41**, 0.98 g, 2.1 mmol, 1 equiv) in tetrahydrofuran (15 mL) was added dropwise via cannula to a solution of lithium metal (30 mg, 4.3 mmol, 2 equiv) in freshly distilled liquid ammonia (75 mL) at −78 °C. The resulting solution was stirred at −78 °C for 5 min, whereupon excess solid ammonium chloride (3 g) was added. The reaction mixture was allowed to warm slowly to 23 °C and was stirred at this temperature for 2 h to allow the solvent ammonia to evaporate. The residue was further concentrated in vacuo and then was purified by flash column chromatography (100% ethyl acetate) to afford an anomeric mixture of 2-(acetylamino)-3-*O*-(*tert*-butyldimethylsilyl)-4,6-*O*-isopropylidene-D-glucopyranose (**42**, 2:1 α:β, 0.60 g, 72%) as a viscous oil: R_f 0.40, 100% ethyl acetate; ^1H NMR (400 MHz, $CDCl_3$) δ 5.72 (d, 1 H, J = 9.5 Hz, NHα), 5.68 (d, 1 H, J = 5.9 Hz, NHβ), 5.19 (d, 1 H, J = 3.7 Hz, H 1α), 4.62 (d, 1 H, J = 8.0 Hz, H 1β), 4.14 (m, 2 H, H 2α,2b), 3.94 (dd, 1 H, J = 11.0, 5.4 Hz, H 6β), 3.8–3.5 (m), 3.24 (m, 1 H, H 5β), 2.05 (s, 3 H, Acβ), 2.00 (s, 3 H, Acα), 1.47 (s, 6 H, CH_3α & β), 1.40 (s, 6 H, CH_3α & β), 0.87 (s, 9 H, *tert*-butylβ), 0.85 (s, 9 H, *tert*-butylα), 0.10 (s, 3 H, $SiCH_3$β), 0.09 (s, 3 H, $SiCH_3$β), 0.06 (s, 3 H, $SiCH_3$α), 0.05 (s, 3 H, $SiCH_3$α); IR (neat film) 3300 (m, br), 2930 (m), 2856 (m), 1654 (s), 1534 (m), 1377 (s), 1200 (s), 1130 (s), 965 (w), 868 (s) cm^{-1}; HRMS (FAB) m/z calcd for $C_{17}H_{35}NO_6Si$ $(MH)^+$ 376.2155, found 376.2144.

***tert*-Butyldimethylsilyl 2-Azido-3-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside (43).** A solution of alcohol **27** (1.66 g, 4.1 mmol, 1 equiv) in tetrahydrofuran (25 mL) was added via cannula to a suspension

of sodium hydride (120 mg, 4.9 mmol, 1.2 equiv) in tetrahydrofuran (10 mL), and the resulting mixture was stirred at 23 °C for 15 min. Benzyl bromide (630 μL, 5.3 mmol, 1.3 equiv) was added, and the heterogeneous reaction mixture was heated at 60 °C for 10 h. The suspension was diluted with ethyl ether (200 mL), and the resulting ethereal solution was filtered through a short column of Celite. The filtrate was concentrated, and the residue was purified by flash column chromatography (15% ethyl acetate in hexanes) to provide *tert*-butyldimethylsilyl 2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside (**43**, 1.72 g, 85%) as a pale yellow viscous oil: R_f 0.44, 25% ethyl acetate in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (m, 2 H, arom), 7.37 (m, 8 H, arom), 5.47 (s, 1 H, benzylidene acetal), 4.74 (s, 2 H, PhCH_2), 4.52 (d, 1 H, J = 7.8 Hz, H 1), 4.24 (dd, 1 H, J = 12.2, 1.2 Hz, H 6), 4.06 (d(br), 1 H, J = 3.7 Hz, H 4), 4.00 (dd, 1 H, J = 12.2, 1.7 Hz, H 6), 3.78 (dd, 1 H, J = 10.5, 7.8 Hz, H 2), 3.32 (dd, 1 H, J = 10.5, 3.7 Hz, H 3), 3.28 (s(br), 1 H, H 5), 0.97 (s, 9 H, *tert*-butyl), 0.19 (s, 3 H, $SiCH_3$), 0.17 (s, 3 H, $SiCH_3$); IR (neat film) 2929 (w), 2857 (w), 2112 (s), 1454 (w), 1402 (w), 1365 (w), 1284 (w), 1253 (w), 1174 (m), 1108 (s), 1059 (m), 997 (m), 837 (s), 783 (w), 697 (m) cm^{-1}; HRMS (FAB) m/z calcd for $C_{26}H_{34}N_3O_5Si$ (M^+ – H) 496.2268, found 496.2289.

2-Azido-3-*O*-benzyl-4,6-*O*-benzylidene-D-galactopyranose (44). Solid potassium fluoride hydrate (0.93 g, 9.9 mmol, 5.0 equiv) was added to a solution of *tert*-butyldimethylsilyl 2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside (**43**, 0.98 g, 1.97 mmol, 1 equiv) in methyl alcohol (40 mL), and the resulting solution was stirred at 23 °C for 7 h. Ethyl acetate (100 mL) was added, and the resulting solution was washed sequentially with water (2 × 100 mL) and saturated aqueous sodium chloride solution (100 mL). The organic phase was dried (sodium sulfate) and concentrated, and the residue was purified by flash column chromatography (50% ethyl acetate in hexanes) to afford an anomeric mixture of 2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-D-galactopyranose (**44**, 1.5:1 α:β, 0.57 g, 75%) as a colorless oil: R_f 0.34, 50% ethyl acetate in hexanes; ^{1}H NMR (300 MHz, C_6D_6) δ 7.8–7.2 (m, arom), 5.26 (s, 2 H, benzylidene acetal α & β), 4.86 (t(br), 1 H, J = 3.3 Hz, H 1α), 4.54 (s, 2 H, PhCH_2 β), 4.52 (s, 2 H, PhCH_2 α), 4.16 (t, 1 H, J = 9.2 Hz, H 1β), 4.07 (d(br), 1 H, J = 11.8 Hz, H 3α), 4.05 (d(br), 1 H, J = 12.3 Hz, H 6β), 3.89 (s(br), 2 H, H 6α), 3.74 (s(br), 1 H, H 4α), 3.70 (dd, 1 H, J = 10.2, 9.2 Hz, H 2β), 3.51 (d, 1 H, J = 3.0 Hz, H 4β), 3.42 (d(br), 1 H, J = 11.8 Hz, H 2α), 3.32 (d(br), 1 H, J = 12.3 Hz, H 6β), 3.28 (s(br), 1 H, H 5α), 3.01 (dd, 1 H, J = 10.2, 3.0 Hz, H 3β), 2.59 (d, 1 H, J = 9.2 Hz, OHβ), 2.31 (s, 1 H, H 5β), 2.00 (d, 1 H, J = 3.8 Hz, OHα); IR (neat film) 3420 (w, br), 3049 (w), 2867 (w), 2112 (s), 1454 (w), 1363 (w), 1249 (w), 1170 (w), 1099 (m), 1049 (m), 995 (m), 744 (m), 698 (m) cm^{-1}; HRMS (FAB) m/z calcd for $C_{20}H_{22}N_3O_5$ $(MH)^+$ 384.1559, found 384.1548.

Trichloroacetimido 2-Azido-3-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside (45). DBU (10 μL, 0.07 mmol, 0.05 equiv) was added to a solution of 2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-D-galactopyranose (**44**, 500 mg, 1.31 mmol, 1 equiv) in a mixture of trichloroacetonitrile and dichloromethane (1:5 (v/v), 12 mL). The resulting solution was stirred at 23 °C for 10 min and then volatiles were removed in vacuo. The residue was filtered through a short column of silica gel, eluting with 33% ethyl acetate in hexanes containing 2% triethylamine to afford trichloroacetimido 2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside (**45**), which was used in the following glycosylation reaction without further purification.

Disaccharide 56. Trichloroacetimido 2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside from the previous experiment (**45**, 137 mg, ~0.26 mmol, ~1 equiv), 2-(acetylamino)-3-*O*-(*tert*-butyldimethylsilyl)-4,6-*O*-isopropylidene-D-glucopyranose (**42**, 308 mg, 0.79 mmol, 3.0 equiv), dichloromethane (2 mL), and crushed, activated 4-Å molecular sieves (200 mg) were combined, and the resulting suspension was stirred at 23 °C for 2 h. The suspension was cooled to –20 °C, and a solution of trimethylsilyl trifluoromethanesulfonate (5% (v/v) in dichloromethane, 250 μL, 0.14 mmol, 0.2 equiv total) was added portionwise at 1-h intervals over a 5-h period. The suspension was diluted with ethyl ether (10 mL) and was allowed to warm to 23 °C. Solids were removed by filtration through a short column of Celite, and the filtrate was concentrated. The residue was purified by flash column chromatography (50% ethyl acetate in hexanes) to provide disaccharide **46** (12 mg, 5%) and recovered 2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-D-galactopyranoside (**44**, 76 mg, 76%). Disaccharide **46**: R_f 0.28, 50% ethyl acetate in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.5–7.2 (m, 10 H, arom), 5.62 (d, 1 H, J = 7.8 Hz, NH), 5.44 (s, 1 H, benzylidene acetal), 5.16 (d, 1 H, J = 3.2 Hz, H 11′), 5.15 (d, 1 H, J = 8.5 Hz, H 1″), 4.71 (s, 2 H, PhCH_2), 4.17 (m, 2 H, H 6′, 8′), 4.14 (dd, 1 H, J = 10.3, 9.5 Hz, H 3″), 3.95 (m, 3 H, H 6′, 9′, 10′), 3.83 (m, 2 H, H 6″, 7′), 3.69 (t, 1 H, J = 10.3 Hz, H 4″), 3.40 (t, 1 H, J = 10.4 Hz, H 6″), 3.33 (m, 1 H, H 5″), 3.22 (m, 1 H, H 2″), 1.98 (s, 3 H, Ac), 1.45 (s, 3 H, CH_3), 1.39 (s, 3 H, CH_3), 0.87 (s, 9 H, *tert*-butyl), 0.06 (s, 3 H, $SiCH_3$), 0.04 (s, 3 H, $SiCH_3$); IR (neat film) 3286 (w), 2928 (w), 2856 (w), 2113 (s), 1657 (s), 1556 (w), 1372 (m), 1249 (m), 1099 (s), 1040 (s), 860 (m), 697 (m) cm^{-1}; HRMS (FAB) m/z calcd for $C_{37}H_{53}N_4O_{10}Si$ $(MH)^+$ 741.3531, found 741.3550.

***tert*-Butyldimethylsilyl 2-Amino-3-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside (47).** Hydrogen sulfide gas was bubbled through a solution of *tert*-butyldimethylsilyl 2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside (**43**, 500 mg, 1.01 mmol, 1 equiv) in a mixture of pyridine and triethylamine (3.5:1 (v/v), 40 mL) at 23 °C for 20 h. Volatiles were removed in vacuo at 23 °C, and the residue was partitioned between water (100 mL) and ethyl ether (100 mL). The organic layer was washed with saturated aqueous sodium chloride solution (100 mL) and then was dried (magnesium sulfate) and concentrated. The residue was purified by flash column chromatography (67% ethyl acetate in hexanes) to afford *tert*-butyldimethylsilyl 2-amino-3-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside (**47**, 465 mg, 98%) as a viscous oil: R_f 0.13, 50% ethyl acetate in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (m, 2 H, arom), 7.30 (m, 8 H, arom), 5.45 (s, 1 H, benzylidene acetal), 4.71 (d, 1 H, J = 12.0 Hz, PhCH_2), 4.63 (d, 1 H, J = 12.0 Hz, PhCH_2), 4.51 (d, 1 H, J = 7.3 Hz, H 1), 4.25 (d(br), 1 H, J = 12.2 Hz, H 6), 4.08 (d, 1 H, J = 2.7 Hz, H 4), 4.03 (dd, 1 H, J = 12.2, 1.9 Hz, H 6), 3.43 (dd, 1 H, J = 10.3, 2.7 Hz, H 3), 3.35 (s(br), 1 H, H 5), 3.27 (dd, 1 H, J = 10.3, 7.3 Hz, H 2), 0.92 (s, 9 H, *tert*-butyl), 0.17 (s, 3 H, $SiCH_3$), 0.14 (s, 3 H, $SiCH_3$); IR (neat film) 2927 (m), 2856 (m), 1454 (w), 1405 (w), 1366 (w), 1251 (w), 1172 (m), 1105 (s), 1059 (s), 1027 (m), 1002 (m), 880 (w), 836 (s), 782 (m) cm^{-1}; HRMS (FAB) m/z calcd for $C_{26}H_{38}NO_5Si$ $(MH)^+$ 472.2519, found 472.2532.

***tert*-Butyldimethylsilyl 3-*O*-Benzyl-4,6-*O*-benzylidene-2-phthalimido-β-D-galactopyranoside (48).** DBU (2.64 mL, 17.7 mmol, 6.4 equiv) and phthaloyl dichloride (1.20 mL, 8.26 mmol, 3 equiv) were added sequentially to a solution of *tert*-butyldimethylsilyl 2-amino-3-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside (**47**, 1.30 g, 2.77 mmol, 1 equiv) in toluene (15 mL), and the mixture was heated at 100 °C for 3 h. The reaction mixture was allowed to cool to 23 °C and then was diluted with ethyl ether (100 mL). The ethereal solution was washed sequentially with water (2 × 50 mL) and saturated aqueous sodium chloride solution (50 mL) and then was dried (sodium sulfate) and concentrated. The residue was purified by flash column chromatography (33% ethyl acetate in hexanes) to provide *tert*-butyldimethylsilyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-phthalimido-β-D-galactopyranoside (**48**, 1.56 g, 94%) as a colorless oil: R_f 0.57, 50% ethyl acetate in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (m, 1 H, arom), 7.71 (m, 3 H, arom), 7.60 (m, 2 H, arom), 7.39 (m, 3 H, arom), 7.10 (m, 5 H, arom), 5.51 (s, 1 H, benzylidene acetal), 5.38 (d, 1 H, J = 8.1 Hz, H 1), 4.64 (dd, 1 H, J = 11.2, 8.1 Hz, H 2), 4.62 (d, 1 H, J = 12.4 Hz, PhCH_2), 4.49 (d, 1 H, J = 12.4 Hz, PhCH_2), 4.46 (dd, 1 H, J = 11.2, 3.4 Hz, H 3), 4.3 (d, 1 H, J = 12.2 Hz, H 6), 4.20 (d, 1 H, J = 3.4 Hz, H 4), 4.08 (d, 1 H, J = 12.2 Hz, H 6), 3.50 (s(br), 1 H, H 5), 0.68 (s, 9 H, *tert*-butyl), 0.09 (s, 3 H, $SiCH_3$), 0.04 (s, 3 H, $SiCH_3$); IR (neat film) 2929 (w), 2857 (w), 1775 (w), 1714 (s), 1470 (w), 1389 (m), 1251 (w), 1172 (w), 1087 (m), 838 (m), 720 (w), 700 (w) cm^{-1}; HRMS (FAB) m/z calcd for $C_{34}H_{38}NO_7Si$ (M^+ – H) 600.2418, found 600.2422.

Trichloroacetimido 3-*O*-Benzyl-4,6-*O*-benzylidene-2-phthalimido-β-D-galactopyranoside (49). Solid potassium fluoride hydrate (4.80 g, 52 mmol, 20 equiv) was added to a solution of *tert*-butyldimethylsilyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-phthalimido-β-D-galactopyranoside (**48**, 1.55 g, 2.58 mmol, 1 equiv) in methyl alcohol (90 mL), and the resulting solution was stirred at 23 °C for 8 h. The reaction mixture was diluted with ethyl acetate (100 mL), and the resulting solution was washed sequentially with water (2 × 100 mL) and saturated aqueous sodium chloride solution (100 mL). The organic phase was dried (sodium sulfate) and concentrated, and the residue was dissolved in a mixture of dichloromethane and trichloroacetonitrile (5:1 (v/v), 24 mL). DBU (100 μL, 0.70 mmol, 0.3 equiv) was added, and the mixture was stirred at 23 °C for 5 min. Volatiles were removed in vacuo, and the residue was purified by flash column chromatography (50% ethyl acetate in hexanes with 3% triethylamine) to afford trichloroacetimido 3-*O*-benzyl-4,6-*O*-benzylidene-2-phthalimido-β-D-galactopyranoside (**49**, 876 mg, 52% from *tert*-butyldimethylsilyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-phthalimido-β-D-galactopyranoside, **48**) as a white solid: mp 154–157 °C; R_f 0.24, 50% ethyl acetate in hexanes; ^{1}H NMR (400 MHz, C_6D_6) δ 7.70 (m, 2 H, arom), 7.49 (m, 1 H, arom), 7.40 (m, 1 H, arom), 7.19–6.75 (m, 11 H, arom, H 1), 5.61 (dd, 1 H, J = 11.0, 8.8 Hz, H 2), 5.28 (s, 1 H, benzylidene

acetal), 4.76 (dd, 1 H, J = 11.0, 3.4 Hz, H 3), 4.57 (d, 1 H, J = 12.4 Hz, PhCH_2), 4.42 (d, 1 H, J = 12.4 Hz, PhCH_2), 4.15 (dd, 1 H, J = 12.4, 1.5 Hz, H 6), 3.79 (d(br), 1 H, J = 3.4 Hz, H 4), 3.37 (dd, 1 H, J = 12.4, 1.7 Hz, H 6), 2.89 (s(br), 1 H, H 5); IR (neat film) 3336 (w), 2871 (w), 1777 (w), 1715 (s), 1677 (m), 1455 (w), 1389 (s), 1297 (m), 1060 (s), 795 (m), 721 (m) cm^{-1}.

Disaccharides 50 and 51. 2-(Acetylamino)-3-*O*-(*tert*-butyldimethylsilyl)-4,6-*O*-isopropylidene-D-glucopyranose (**42**, 110 mg, 0.28 mmol, 1.7 equiv), trichloroacetimido 3-*O*-benzyl-4,6-*O*-benzylidene-2-phthalimido-β-D-galactopyranoside (**49**, 104 mg, 0.16 mmol, 1 equiv), crushed, activated 4-Å molecular sieves (200 mg), and dichloromethane (1.5 mL) were combined, and the resulting suspension was stirred at 23 °C for 2 h. The reaction mixture was cooled to −20 °C, and trimethylsilyl trifluoromethanesulfonate (50 μL, 0.26 mmol, 0.9 equiv total) was added portionwise at 4-h intervals over a 12-h period. The suspension was diluted with ethyl ether (20 mL) and was allowed to warm to 23 °C. Solids were removed by filtration through a short column of Celite, and the filtrate was washed sequentially with water (10 mL) and saturated aqueous sodium chloride solution (10 mL). The ethereal layer was dried (sodium sulfate) and concentrated, and the residue was purified by flash column chromatography (25% ethyl acetate in hexanes), providing the disaccharides **50** (34 mg, 24%) and **51** (23 mg, 17%) as colorless oils. **50**: R_f 0.11, 15% ethyl acetate in dichloromethane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.03 (m, 14 H, arom), 5.54 (s, 1 H, benzylidene acetal), 5.25 (d, 1 H, J = 8.6 Hz, H 11′), 5.24 (d, 1 H, J = 10.5 Hz, NH), 4.75 (dd, 1 H, J = 11.2, 8.6 Hz, H 10′), 4.72 (d, 1 H, J = 3.9 Hz, H 1″), 4.63 (d, 1 H, J = 12.4 Hz, PhCH_2), 4.51 (dd, 1 H, J = 11.2, 3.4 Hz, H 9′), 4.46 (d, 1 H, J = 12.4 Hz, PhCH_2), 4.30 (d, 1 H, J = 12.0 Hz, H 6′), 4.24 (d, 1 H, J = 3.4 Hz, H 8′), 4.11 (d, 1 H, J = 12.0 Hz, H 6′), 4.04 (m, 2 H, H 2″, 5″), 3.73–3.60 (m, 3 H, H 6″, 3″), 3.58 (s(br), 1 H, H 7′), 3.47 (t, 1 H, J = 9.3 Hz, H 4″), 1.43 (s, 3 H, Ac), 1.41 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3), 0.79 (s, 9 H, *tert*-butyl), 0.03 (s, 6 H, $SiCH_3$); IR (neat film) 3446 (w), 2928 (w), 2856 (w), 1774 (w), 1715 (s), 1507 (w), 1387 (m), 1174 (w), 1072 (s), 1028 (s), 868 (m), 723 (m) cm^{-1}; HRMS (FAB) m/z calcd for $C_{45}H_{57}N_2O_{12}Si$ (MH)$^+$ 845.3681, found 845.3671. **51**: R_f 0.05, 15% ethyl acetate in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86–7.05 (m, 14 H, arom), 5.74 (d, 1 H, J = 7.1 Hz, NH), 5.49 (s, 1 H, benzylidene acetal), 5.22 (d, 2 H, J = 8.3 Hz, H 11′, 1″), 4.62 (m, 2 H, H 10′, PhCH_2), 4.56 (dd, 1 H, J = 11.2, 3.4 Hz, H 9′), 4.51 (d, 1 H, J = 12.4 Hz, PhCH_2), 4.40 (t, 1 H, J = 8.6 Hz, H 3″), 4.25 (d, 1 H, J = 12.2 Hz, H 6′), 4.18 (d, 1 H, J = 3.4 Hz, H 8′), 4.05 (d(br), 1 H, J = 12.2 Hz, H 6′), 3.50 (s(br), 1 H, H 7′), 3.31 (dd, 1 H, J = 10.2, 4.6 Hz, H 6″), 3.10 (m, 2 H, H 4″, 5″), 2.82 (t, 1 H, J = 10.2 Hz, H 6″), 2.68 (m, 1 H, H 2″), 1.93 (s, 3 H, Ac), 1.28 (s, 3 H, CH_3), 1.21 (s, 3 H, CH_3), 0.80 (s, 9 H, *tert*-butyl), −0.04 (s, 6 H, $SiCH_3$); IR (neat film) 3260 (w), 2926 (w), 2849 (w), 1772 (w), 1715 (s), 1652 (m), 1393 (m), 1167 (w), 1108 (m), 1073 (s), 857 (m), 714 (m) cm^{-1}; HRMS (FAB) m/z calcd for $C_{45}H_{57}N_2O_{12}Si$ (MH)$^+$ 845.3681, found 845.3692.

Amino Alcohol 52. A 25-mL heavy-walled Pyrex tube containing a solution of disaccharide **38** (0.81 g, 0.79 mmol, 1 equiv) in a mixture of ethyl alcohol and hydrazine hydrate (8:1 (v/v), 22.5 mL) was placed under static vacuum, sealed, and then immersed in an oil bath at 100 °C for 12 h. The reaction mixture was cooled to 23 °C, and the product was partitioned between ethyl acetate (75 mL) and water (50 mL). The organic layer was washed sequentially with water (50 mL) and saturated aqueous sodium chloride solution (50 mL) and then was dried (sodium sulfate) and concentrated. The residue was purified by flash column chromatography (50% ethyl acetate in hexanes) to afford amino alcohol **52** (0.54 g, 87%) as a colorless oil: R_f 0.18, 50% ethyl acetate in hexanes; ^{1}H NMR (400 MHz, C_6D_6) δ 7.47 (m, 3 H, arom), 7.30 (m, 2 H, arom), 7.23–6.99 (m, 5 H, arom), 5.00 (d, 1 H, J = 3.7 Hz, H 1″), 4.54, 4.48 (2 × d, 2 × 1 H, J = 6.8 Hz, OCH_2O), 4.44 (m, 2 H, PhCH_2O), 4.33 (m, 2 H, H 5′, H 6″), 4.21 (t, 1 H, J = 9.5 Hz, H 3″), 4.17 (d, 1 H, J = 7.8 Hz, H 11′), 3.79 (d(br), 1 H, J = 2.9 Hz, H 8′), 3.70 (m, 1 H, H 6″), 3.43 (t, 1 H, J = 9.5 Hz, H 4″), 3.32 (m, 2 H, H 6′), 3.27 (dd, 1 H, J = 11.0, 7.8 Hz, H 10′), 3.22 (dd, 1 H, J = 11.0, 2.9 Hz, H 9′), 3.08 (m, 1 H, H 7′), 3.01 (dd, 1 H, J = 9.5, 3.7 Hz, H 2″), 1.91 (m(br), 1 H, OH), 1.45, 1.32 (2 × s, 2 × 3 H, $C(CH_3)_2$), 1.11 (s, 9 H, *tert*-butyl), 0.50 (m(br), 2 H, NH_2), 0.28, 0.21 (2 × s, 2 × 3 H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, C_6D_6) δ 138.0–127.0 (arom), 105.9, 100.6, 99.5, 94.0, 81.0, 75.2, 75.0, 71.2, 70.1, 67.2, 66.2, 64.7, 62.6, 52.6, 29.2, 28.4, 26.0, 19.0, 18.5, −3.9, −4.9; IR (neat film) 3600–2900 (m, br), 2930 (s), 2857 (s), 2107 (s), 1580 (w), 1472 (w), 1383 (m), 1265 (m), 1128 (s), 1024 (s), 970 (m), 856 (s), 737 (s) cm^{-1}; HRMS (FAB) m/z calcd for $C_{35}H_{53}N_4O_9SeSi$ (MH)$^+$ 781.2747, found 781.2731.

Benzyl Carbamate 53. To a solution of amino alcohol **52** (1.35 g, 1.73 mmol, 1 equiv) in pyridine (25 mL) at 0 °C was added benzyl chloroformate (2.30 mL, 15.0 mmol, 8.9 equiv), and the resulting mixture was stirred at 0 °C for 30 min. The reaction mixture was diluted with ethyl ether (150 mL), and the resulting solution was washed sequentially with water (3 × 75 mL) and saturated aqueous sodium chloride solution (50 mL). The ethereal solution was dried (sodium sulfate) and concentrated, and the residue was purified by flash column chromatography (33% ethyl acetate in hexanes) to provide **53** (1.35 g, 91%) as white needles: mp 114.0–115.0 °C, R_f 0.63, 33% ethyl acetate in hexanes; ^{1}H NMR (400 MHz, C_6D_6) δ 7.50–6.98 (m, 10 H, arom), 5.15 (d, 1 H, J = 12.2 Hz, PhCH_2OCO), 5.06 (m(br), 1 H, PhCH_2OCO), 5.05 (d, 1 H, J = 3.9 Hz, H 1″), 5.00 (d(br), 1 H, J = 7.8 Hz, H 11′), 4.95 (m, 1 H, NH), 4.60 (d, 1 H, J = 6.8 Hz, OCH_2O), 4.57 (d, 1 H, J = 6.8 Hz, OCH_2O), 4.47 (d, 1 H, J = 12.1 Hz, PhCH_2O), 4.45 (d, 1 H, J = 12.1 Hz, PhCH_2O), 4.25 (m, 2 H, H 5′, H 6″), 4.16 (dd, 1 H, J = 9.5, 9.0 Hz, H 3″), 4.02 (m(br), 1 H, H 10′), 3.87 (m, 1 H, H 8′), 3.67 (m, 1 H, H 6″), 3.59 (m(br), 1 H, H 9′), 3.46 (dd(br), 1 H, J = 7.3, 6.5 Hz, H 7′), 3.45 (dd, 1 H, J = 9.8, 9.0 Hz, H 4″), 3.30 (dd, 1 H, J = 12.5, 7.3 Hz, H 6′), 3.10 (dd, 1 H, J = 12.5, 6.5 Hz, H 6′), 3.03 (dd, 1 H, J = 9.8, 3.7 Hz, H 2″), 2.19 (m(br), 1 H, OH), 1.43, 1.33 (2 × s, 2 × 3 H, $C(CH_3)_2$), 1.08 (s, 9 H, *tert*-butyl), 0.28, 0.22 (2 × s, 2 × 3 H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, C_6D_6) δ 155.5, 141.9–127.0 (arom), 100.2, 99.6, 93.8, 75.3, 74.9, 70.8, 70.0, 69.6, 68.0, 67.0, 65.8, 65.0, 64.8, 62.7, 54.1, 29.2, 28.4, 26.0, 19.0, 18.5, −3.8, −4.9; IR (neat film) 3650–3175 (m, br), 3309 (s), 2930 (s), 2857 (s), 2107 (s), 1694 (s), 1556 (s), 1455 (m), 1384 (m), 1248 (s), 1023 (s), 949 (m), 860 (s), 696 (s) cm^{-1}. Elem. anal. Calcd for $C_{43}H_{57}N_4O_{11}SeSi$: C, 56.52; H, 6.29; N, 6.14. Found: C, 56.17; H, 6.29; N, 6.11.

Amino Alcohol 54. Benzeneselenol (2.50 mL, 24.0 mmol, 14.0 equiv) was added to a deoxygenated solution of benzyl carbamate **53** (1.52 g, 1.66 mmol, 1 equiv) in triethylamine (50 mL), and the resulting mixture was heated at 55 °C for 12 h. The product was partitioned between dichloromethane (150 mL) and water (150 mL), and the organic phase was dried (sodium sulfate) and concentrated. The residue was purified by flash column chromatography (33% ethyl acetate in hexanes) to afford the C2″-amino disaccharide **54** (1.35 g, 91%) as white needles: mp 172.0–174.0 °C; R_f 0.28, 50% ethyl acetate in hexanes; ^{1}H NMR (400 MHz, C_6D_6) δ 7.49–6.99 (m, 10 H, arom), 5.17 (d, 1 H, J = 12.3 Hz, PhCH_2-OCO), 5.14 (d, 1 H, J = 3.7 Hz, H 1″), 5.11 (d, 1 H, J = 12.3 Hz, PhCH_2OCO), 4.96 (m(br), 1 H, H 11′), 4.61 (d, 1 H, J = 7.1 Hz, OCH_2O), 4.59 (d, 1 H, J = 7.1 Hz, OCH_2O), 4.54 (d, 1 H, J = 12.1 Hz, PhOCH_2), 4.47 (d, 1 H, J = 12.1 Hz, PhOCH_2), 4.45 (d(br), 1 H, J = 8.3 Hz, NH), 4.31 (m, 2 H, H 5″, H 6″), 4.00 (q(br), 1 H, $J \sim$ 10.5 Hz, H 10′), 3.88 (d(br), 1 H, J = 2.9 Hz, H 8′), 3.79 (t, 1 H, J = 9.0 Hz, H 3″), 3.74 (t, 1 H, J = 10.0 Hz, H 6″), 3.52 (d(br), 1 H (obscured), H 3), 3.50 (dd, 1 H, J = 9.3, 8.7 Hz, H 4″), 3.43 (dd(br), 1 H, J = 7.3, 6.6 Hz, H 7′), 3.28 (dd, 1 H, J = 12.5, 6.6 Hz, H 6′), 3.13 (dd, 1 H, J = 12.5, 7.3 Hz, H 6′), 2.80 (dd, 1 H, J = 9.0, 3.7 Hz, H 2″), 2.61 (m(br), 1 H, OH), 1.46, 1.36 (2 × s, 2 × 3 H, $C(CH_3)_2$), 1.02 (s, 9 H, *tert*-butyl), 0.18, 0.15 (2 × s, 2 × 3 H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, C_6D_6) δ 157.0, 138.1–126.9 (arom), 102.8, 99.3, 93.7, 75.2, 75.2, 74.7, 70.1, 67.7, 67.1, 65.2, 64.8, 63.0, 58.7, 53.5, 29.4, 28.2, 26.3, 19.1, 18.6, −3.7, −4.4; IR (neat film) 3516–3100 (m, br), 3308 (m), 2928 (s), 2858 (m), 1700 (s), 1544 (s), 1478 (w), 1382 (m), 1248 (s), 1097 (s), 1038 (s), 945 (m), 864 (m), 735 (m) cm^{-1}; HRMS (FAB) m/z calcd for $C_{43}H_{61}N_2O_{11}SeSi$ (MH)$^+$ 889.3210, found 889.3210.

Disaccharide 55. The C2″-amino disaccharide **54** (1.35 g, 1.52 mmol, 1 equiv) was dissolved in a mixture of pyridine and acetic anhydride (2:1 (v/v), 30 mL), and the resulting solution was heated at 60 °C for 2.5 h. The reaction mixture was diluted with ethyl ether (100 mL), and the resulting solution was washed sequentially with water (50 mL) and saturated aqueous sodium chloride solution (30 mL). The ethereal solution was dried (sodium sulfate) and concentrated, and the residue was purified by flash column chromatography (33% ethyl acetate in hexanes) to afford **55** (1.35 g, 91%) as a colorless oil: R_f 0.63, 50% ethyl acetate in hexanes; ^{1}H NMR (400 MHz, C_6D_6) δ 7.45–6.95 (m, 10 H, arom), 6.00 (m(br), 1 H, NHAc), 5.30 (d, 1 H, J = 3.2 Hz, H 8′), 5.24 (d(br), 1 H, J = 12.5 Hz, PhCH_2OCO), 5.13 (m(br), 1 H, NHCO$_2$R), 5.08 (d, 1 H, J = 3.2 Hz, H 1″), 4.92 (d(br), 1 H, J = 12.5 Hz, PhCH_2OCO), 4.70 (d, 1 H, J = 7.3 Hz, OCH_2O), 4.55 (dt, 1 H, J = 9.3, 3.2 Hz, H 2″), 4.54 (d, 1 H, J = 12.5 Hz, PhCH_2O), 4.50 (d, 1 H, J = 7.3 Hz, OCH_2O), 4.32 (m, 2 H, H 5″, H 6″), 4.31 (d, 1 H, J = 12.5 Hz, PhCH_2O), 4.13 (q(br), 1 H, J = obscured, H 10′), 3.90 (t, 1 H, J = 9.3 Hz, H 3″), 3.74 (m, 1 H, H 6″), 3.58 (t, 1 H, J = 9.3 Hz, H 4″), 3.50 (dd, 1 H, J = 11.0, 3.2 Hz, H 9′), 3.37 (dd(br), 1 H, J = 8.1, 6.4 Hz, H 7′), 3.03 (dd, 1 H,

J = 13.5, 8.1 Hz, H 6'), 2.79 (dd, 1 H, J = 13.5, 6.4 Hz, H 6'), 2.04 (s, 3 H, NHCOCH_3), 1.57 (s, 3 H, OCOCH$_3$), 1.39, 1.32 (2 × s, 2 × 3 H, C(CH$_3$)$_2$), 0.96 (s, 9 H, *tert*-butyl), 0.08, 0.04 (2 × s, 2 × 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (100 MHz, C_6D_6) δ 170.1, 157.2, 138.1–127.3 (arom), 101.2, 99.5, 92.8, 75.3, 74.6, 73.3, 71.8, 69.9, 67.7, 67.1, 65.2, 62.8, 54.5, 54.2, 29.3, 28.2, 26.0, 23.6, 20.2, 19.2, 18.4, –3.9, –4.7; IR (neat film) 3525–3100 (m, br), 2929 (s), 2856 (m), 1722 (s), 1667 (s), 1538 (s), 1373 (s), 1296 (w), 1231 (s), 1117 (s), 1068 (s), 1027 (s), 864 (m), 737 (m) cm^{-1}; HRMS (FAB) m/z calcd for $C_{47}H_{65}N_2O_{13}SeSi$ (MH)$^+$ 973.3437, found 973.3421.

Allylic Acetate 56. Solid *m*-chloroperoxybenzoic acid (~60% (w/w), 1.38 g, 4.8 mmol, 3.5 equiv) was added to a solution of selenide **55** (1.35 g, 1.39 mmol, 1 equiv) in carbon tetrachloride (10 mL) at –15 °C. The resulting suspension was stirred at –15 °C for 20 min and then at 0 °C for 30 min. Excess oxidant was quenched by the sequential addition of dimethyl sulfide (1.20 mL, 16.0 mmol, 12.0 equiv) and triethylamine (0.5 mL, 4.0 mmol, 3.0 equiv), and the resulting solution then was heated at 65 °C for 10 h. The product was partitioned between ethyl acetate (100 mL) and saturated aqueous sodium bicarbonate solution (40 mL). The organic layer was washed sequentially with water (40 mL) and saturated aqueous sodium chloride solution (40 mL) and then was dried (sodium sulfate) and concentrated. The residue was purified by flash column chromatography (gradient elution: 33 → 50% ethyl acetate in hexanes) to provide the allylic acetate disaccharide **56** (1.09 g, 88%) as a colorless oil: R_f 0.46, 50% ethyl acetate in hexanes; ^{1}H NMR (400 MHz, C_6D_6) δ 7.26–7.06 (m, 10 H, arom), 6.25 (d(br), 1 H, J = 9.8 Hz, N*H*Ac), 5.86 (d, 1 H, J = 3.2 Hz, H 8'), 5.18 (d, 1 H, J = 12.2 Hz, PhCH_2OCO), 5.10 (d(br), 1 H, J = 7.0 Hz, N*H*CO$_2$R), 5.04 (d, 1 H, J = 3.7 Hz, H 1''), 4.97 (d(br), 1 H, J = 12.2 Hz, PhCH_2OCO), 4.69 (d, 1 H, J = 1.0 Hz, H 6'), 4.65 (ddd, 1 H, J = 9.8, 9.8, 3.7 Hz, H 2''), 4.62 (d, 1 H, J = 7.1 Hz, OCH$_2$O), 4.61 (d, 1 H, J = 6.1 Hz, H 11'), 4.54 (d, 1 H, J = 7.1 Hz, OCH$_2$O), 4.53 (d, 1 H, J = 1.0 Hz, H 6'), 4.52 (d, 1 H, J = 12.3 Hz, PhCH_2O), 4.42 (ddd, 1 H, J = 10.5, 7.0, 6.1 Hz, H 10'), 4.41 (d, 1 H, J = 12.3 Hz, PhCH_2O), 4.24 (ddd, 1 H, J = 10.5, 10.5, 5.3 Hz, H 5''), 3.96 (dd, 1 H, J = 9.8, 9.7 Hz, H 3''), 3.94 (dd, 1 H, J = 10.5, 5.3 Hz, H 6''), 3.73 (t, 1 H, J = 10.5 Hz, H 6''), 3.60 (td, 1 H, J = 10.0, 9.7 Hz, H 4''), 3.59 (dd, 1 H, J = 10.5, 3.2 Hz, H 9'), 2.13 (s, 3 H, NHCOCH_3), 1.77 (s, 3 H, OCOCH$_3$), 1.43, 1.34 (s, 9 H, *tert*-butyl), 0.17, 0.15 (2 × s, 2 × 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (100 MHz, C_6D_6) δ 169.8, 169.7, 157.2, 152.2, 137.9–127.6 (arom), 103.8, 101.2, 99.5, 93.7, 75.1, 73.9, 72.0, 70.0, 68.0, 67.2, 65.3, 62.5, 54.4, 54.2, 53.5, 29.3, 26.0, 23.5, 20.5, 19.1, 18.5, –3.9, –4.7; IR (neat film) 3530–3125 (m, br), 2952 (s), 1745 (s), 1715 (s), 1666 (s), 1523 (s), 1372 (s), 1230 (s), 1113 (s), 1023 (s), 864 (m), 698 (m) cm^{-1}; HRMS (FAB) m/z calcd for $C_{41}H_{59}N_2O_{13}Si$ (MH)$^+$ 815.3820, found 815.3786.

Allylic Alcohol 57. Solid potassium carbonate (10 mg, 0.07 mmol, 0.07 equiv) was added to a solution of the allylic acetate disaccharide **56** (0.81 g, 1.0 mmol, 1 equiv) in methyl alcohol (25 mL), and the resulting suspension was stirred at 23 °C for 2 h. The product was partitioned between ethyl acetate (100 mL) and water (40 mL). The organic layer was washed sequentially with water (40 mL) and saturated aqueous sodium chloride solution (40 mL) and then was dried (sodium sulfate) and concentrated. The residue was purified by flash column chromatography (50% ethyl acetate in hexanes) to afford allylic alcohol **57** (703 mg, 92%) as a colorless oil: R_f 0.44, 50% ethyl acetate in hexanes; ^{1}H NMR (400 MHz, C_6D_6) δ 7.29–7.08 (m, 10 H, arom), 6.06 (d(br), 1 H, J ~ 8.6 Hz, N*H*Ac), 5.17 (d, 1 H, J = 12.2 Hz, PhCH_2OCO), 5.12 (d, 1 H, J = 3.7 Hz, H 1''), 5.08 (d(br), 1 H, J ~ 8.3 Hz, N*H*CO$_2$CH$_2$Ph), 5.04 (d(br), 1 H, J = 12.2 Hz, PhCH_2OCO), 4.71 (s, 1 H, H 6'), 4.70 (d, 1 H, J = 6.5 Hz, H 11'), 4.63 (dt, 1 H, J = 10.8, 3.7 Hz, H 2''), 4.57 (m, 2 H, OCH$_2$O), 4.49 (s, 2 H, PhCH_2O), 4.45 (s, 1 H, H 6'), 4.33 (dt, 1 H, J = 8.6, 6.5 Hz, H 10'), 4.28 (dt, 1 H, J = 10.3, 5.4 Hz, H 5''), 4.23 (m, 1 H, H 8'), 4.02 (dd, 1 H, J = 10.3, 5.4 Hz, H 6''), 3.97 (dd, 1 H, J = 11.2, 10.8 Hz, H 3''), 3.75 (t, 1 H, J = 10.3 Hz, H 6''), 3.60 (dd, 1 H, J = 11.2, 10.3 Hz, H 4''), 3.58 (dd, 1 H, J = 8.6, 3.4 Hz, H 9'), 2.58 (m, 1 H, OH), 2.06 (s, 3 H, Ac), 1.47, 1.35 (2 × s, 2 × 3 H, C(CH$_3$)$_2$), 1.06 (s, 9 H, *tert*-butyl), 0.21, 0.18 (2 × s, 2 × 3 H, Si(CH$_3$)$_2$); ^{13}C NMR (100 MHz, C_6D_6) δ 170.3, 157.1, 155.9, 138.0–127.8 (arom), 102.7, 100.6, 99.6, 98.3, 94.4, 77.4, 75.2, 71.9, 70.2, 67.7, 67.2, 65.1, 62.6, 54.8, 53.8, 29.3, 26.1, 23.4, 19.2, 18.5, –3.8, –4.6; IR (neat film) 3650–3100 (s), 2928 (s), 2856 (m), 1709 (s), 1662 (s), 1534 (s), 1375 (s), 1247 (s), 1116 (s), 1026 (s), 861 (m), 780 (m), 698 (m) cm^{-1}; HRMS (FAB) m/z calcd for $C_{39}H_{57}N_2O_{12}Si$ (MH)$^+$ 773.3676, found: 773.3681. Elem. anal. Calcd for $C_{39}H_{56}N_2O_{12}Si$: C, 60.60; H, 7.30; N, 3.62. Found: C, 60.28; H, 7.13; N, 3.90.

2',3'-*O*-Bis(*tert*-butyldimethylsilyl)-3-*N*-(*tert*-butyloxycarbonyl)uridine (58). DMAP (50 mg, 0.4 mmol, 0.06 equiv) and di-*tert*-butyl dicarbonate (2.90 g, 13 mmol, 2 equiv) were added sequentially to a solution of 2',3'-*O*-bis(*tert*-butyldimethylsilyl)-5'-*O*-(dimethoxytrityl)-uridine (**17**, 5.1 g, 6.5 mmol, 1 equiv) in pyridine (50 mL) at 0 °C, and the resulting solution was stirred at 23 °C for 12 h. Volatiles were removed in vacuo, and the residue was dissolved in dichloromethane (100 mL). A solution of trichloroacetic acid (5.0 g, 30 mmol, 4.6 equiv) in dichloromethane (45 mL) was added dropwise over a 5-min period at 0 °C, and the resulting orange solution was stirred at 0 °C for 15 min. The product was partitioned between dichloromethane (150 mL) and saturated aqueous sodium bicarbonate solution (80 mL). The organic layer was dried (sodium sulfate) and concentrated, and the residue was purified by flash column chromatography (50% ethyl acetate in hexanes) to afford the product **58** (2.01 g, 53%) as a colorless oil: R_f 0.43, 50% ethyl acetate in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, 1 H, J = 8.3 Hz, H 6), 5.64 (d, 1 H, J = 8.3 Hz, H 5), 5.42 (d, 1 H, J = 5.4 Hz, H 1'), 4.43 (dd, 1 H, J = 5.4, 4.4 Hz, H 2'), 4.05 (dd, 1 H, J = 4.4, 2.9 Hz, H 3'), 3.97 (m, 1 H, H 4'), 3.82 (m, 1 H, J = 12.2 Hz, H 5'), 3.60 (m, 1 H, J = 12.2 Hz, H 5'), 2.93 (m, 1 H, OH), 1.49 (s, 9 H, *t*-Boc), 0.81 (s, 9 H, *tert*-butyl), 0.77 (s, 9 H, *tert*-butyl), –0.01, –0.02, –0.05, –0.08 (4 × s, 4 × 4 H, 4 × SiCH$_3$); IR (neat film) 3495 (w), 2930 (m), 2857 (m), 1788 (s), 1722 (s), 1678 (s), 1449 (m), 1372 (m), 1253 (s), 1151 (s), 837 (s), 778 (s) cm^{-1}; HRMS (FAB) m/z calcd for $C_{26}H_{49}N_2O_8Si_2$ (MH)$^+$ 573.3027, found 573.3032.

Uridine 5'-Aldehyde Derivative 59. Dimethyl sulfoxide (311 μL, 4.3 mmol, 5 equiv) was added dropwise to a solution of oxalyl chloride (224 μL, 2.6 mmol, 3 equiv) in dichloromethane (12 mL) at –78 °C, and the resulting solution was stirred at –78 °C for 5 min. A solution of uridine derivative **58** (500 mg, 0.87 mmol, 1 equiv) in dichloromethane (10 mL) was added via cannula, and the resulting solution was stirred at –78 °C for 15 min. Triethylamine (1.21 mL, 8.7 mmol, 10 equiv) was added, and the resulting suspension was stirred at –78 °C for an additional 25 min. The reaction mixture was poured into saturated aqueous sodium bicarbonate solution (150 mL), the aqueous layer was extracted with ethyl acetate (2 × 100 mL), and the combined organic layers were dried (sodium sulfate) and concentrated to provide crude **59** (513 mg) as a pale yellow solid. Due to the lability of the product and its susceptibility to hydration, the uridine 5'-aldehyde derivative **59** was used in its crude form in the following experiment. Crude **59**: ^{1}H NMR (400 MHz, C_6D_6) δ 9.60 (s, 1 H, H 5'), 6.62 (d, 1 H, J = 8.2 Hz, H 6), 5.55 (m, 2 H, H 1', 4'), 5.31 (d, 1 H, J = 8.2 Hz, H 5), 4.57 (m, 1 H, H 3'), 4.25 (1 H, H 2'), 1.46 (s, 9 H, *t*-Boc), 0.96 (s, 9 H, *tert*-butyl), 0.91 (s, 9 H, *tert*-butyl), 0.07, 0.03, –0.01, –0.04 (4 × SiCH$_3$); IR (neat film) 3454 (w, br), 2931 (s), 2858 (s), 1787 (s), 1725 (s), 1685 (s), 1633 (m), 1448 (s), 1372 (s), 1255 (s), 1150 (s), 1072 (m), 839 (s), 778 (s) cm^{-1}.

***O*-Silyl Hemiselenoacetals 60.** Benzeneselenol (56 μL, 0.51 mmol, 3.8 equiv) and pyridine (45 μL, 0.55 mmol, 4.1 equiv) were added sequentially to a freshly prepared, deoxygenated solution of aldehyde **59** (190 mg, ~0.34 mmol, ~2.5 equiv, azeotropically dried with 1.5 mL of toluene) in toluene (2 mL), and the resulting solution was deoxygenated. After stirring at 23 °C for 15 min, the reaction mixture was transferred via cannula to a solution of dichlorodimethylsilane (340 μL, 3.4 mmol, 10 equiv) in pyridine (2 mL). The resulting suspension was deoxygenated and was stirred in the dark at 23 °C for 6 h. The reaction mixture was concentrated in vacuo at 23 °C, and the residue was suspended in toluene (2 mL). Volatiles were removed at 23 °C, and the residue was diluted with toluene (3 mL). To the mixture was added via cannula a solution of allylic alcohol **57** (104 mg, 0.13 mmol, 1 equiv) in pyridine (2 mL), and the resulting suspension was stirred at 23 °C for 5 min. The product was partitioned between ethyl acetate (100 mL) and water (100 mL). The organic layer was dried (sodium sulfate) and concentrated, and the residue was purified by flash column chromatography (gradient elution: 33 → 50% ethyl acetate in hexanes) to afford a 5:1 mixture of C5'-diastereomers **60** (106 mg, 50%) as a colorless oil. Preparative thin-layer chromatography (50% ethyl acetate in hexanes) provided analytical samples of each diastereomer. **60a**: R_f 0.36, 50% ethyl acetate in hexanes; ^{1}H NMR (400 MHz, C_6D_6) δ 7.78 (d, 1 H, J = 8.6 Hz, H 6), 7.7–7.0 (m, 15 H, arom), 6.46 (d, 1 H, J = 9.8 Hz, NH), 6.21 (d, 1 H, J = 5.9 Hz, H 1'), 5.94 (d, 1 H, J = 8.6 Hz, H 5), 5.78 (d, 1 H, J = 3.7 Hz, H 5'), 5.23 (d, 1 H, J = 12.2 Hz, PhCH_2OCO), 5.12 (d, 1 H, J = 3.9 Hz, H 1''), 5.08 (d, 1 H, J = 12.2 Hz, PhCH_2OCO), 4.8–4.5 (m), 4.45 (m, 2 H), 4.32 (s, 1 H, H 6'), 4.31 (m, 1 H), 4.25 (dd, 1 H, J = 4.4, 2.9 Hz, H 3'), 4.22 (m, 1 H, H 2''), 3.98 (m, 2 H), 3.75 (t, 1 H, J = 10.2 Hz, H 3''), 5.90 (m, 2 H), 2.16 (s, 3 H, Ac), 1.51 (s, 9 H, *t*-Boc), 1.46, 1.35 (2 × s, 2 × 3 H, 2 × CH$_3$), 1.11, 1.03, 0.98 (3 × s, 3 × 9 H, 3 × *tert*-butyl),

0.31, 0.28, 0.27, 0.25, 0.21, 0.16, 0.15, 0.10 (8 × s, 8 × 3 H, 8 × $SiCH_3$); IR (neat film) 3324 (w), 2929 (m), 2850 (m), 1789 (s), 1724 (s), 1680 (s), 1535 (w), 1448 (m), 1371 (m), 1257 (s), 1150 (s), 1063 (s), 972 (m), 838 (s) cm^{-1}. **60b**: R_f 0.32, 50% ethyl acetate in hexanes; ^1H NMR (400 MHz, C_6D_6) δ 7.81 (d, 1 H, J = 7.6 Hz, H 6), 7.5–7.0 (m, 15 H, arom), 6.56 (d, 1 H, J = 7.6 Hz, NH), 6.40 (d, 1 H, J = 8.3 Hz, H 5), 5.83 (d, 1 H, J = 2.4 Hz, H 1″), 5.32 (d, 1 H, J = 4.15 Hz, H 5′), 5.21 (d(br), 2 H, NH), 4.67 (m, 1 H, H 2″), 4.65–4.15 (m), 4.00 (dd, 1 H, J = 10.7, 5.4 Hz, H 6″), 3.78 (t, 1 H, J = 10.7 Hz, 3.63 (dd, 1 H, J = 9.8, 8.6 Hz, H 3″), 3.56 (m, 1 H), 2.23 (s, 3 H, Ac), 1.51 (s, 9 H, *t*-Boc), 1.44, 1.36 (2 × s, 2 × 3 H, 2 × CH_3), 1.16, 1.06, 1.05 (3 × s, 3 × 9 H, 3 × *tert*-butyl), 0.40, 0.32, 0.31, 0.29, 0.28, 0.25, 0.17, 0.16 (8 × s, 8 × 3 H, 8 × $SiCH_3$); IR (neat film) 3320 (w), 2929 (m), 2857 (m), 1789 (m), 1724 (s), 1684 (s), 1527 (w), 1448 (w), 1372 (m), 1257 (s), 1114 (s), 1023 (s), 838 (s), 779 (m) cm^{-1}.

Siloxane 61. A solution of triethylborane (5 μL, 1.0 M solution in hexanes, 0.005 mmol, 0.2 equiv) was added to a deoxygenated solution of *O*-silyl hemiselenoacetals **60** (50 mg, 0.03 mmol, 1 equiv) and tributyltin hydride (20 μL, 0.07 mmol, 2.5 equiv) in toluene (30 mL) at 0 °C, and the resulting solution was stirred at 0 °C for 15 min. The solvent was removed in vacuo at 0 °C, and flash column chromatography of the residue (gradient elution: 33 → 100% ethyl acetate in hexanes) afforded siloxane **61** (36 mg, 80%) as a colorless film: R_f 0.22, 50% ethyl acetate in hexanes; ^1H NMR (400 MHz, C_6D_6) δ 7.90 (d, 1 H, J = 8.3 Hz, H 6), 6.50 (d, 1 H, J = 6.8 Hz, H 1′), 5.86 (d, 1 H, J = 9.8 Hz, NH), 5.64 (d, 1 H, J = 8.3 Hz, H 5), 5.29 (d, 1 H, J = 12.4 Hz, PhCH_2OCO), 5.17 (d, 1 H, J = 3.7 Hz, H 1″), 5.00 (d, 1 H, J = 12.4 Hz, PhCH_2OCO), 4.83 (d, 1 H, J = 8.6 Hz, NH), 4.70–4.44 (m, 7 H), 4.42 (dd, 1 H, J = 6.8, 4.4 Hz, H 2′), 4.28 (m, 1 H, J = 8.8 Hz, H 10′), 4.15 (m, 1 H, H 2″), 4.13 (m, 1 H, H5′), 4.08 (m, 1 H, H 4′), 3.93 (d, 1 H, J = H 8′), 3.88 (m, 2 H, H 4″, 6″), 3.74 (t, 1 H, J = 10.5 Hz, H 3″), 3.57 (t, 1 H, J = 9.8 Hz, H 6″), 3.49 (dd, 1 H, J = 8.8, 2.7 Hz, H 9′), 3.16 (m, 1 H, H 7′), 2.07 (s, 3 H, Ac), 1.90 (m, 2 H, H 6′), 1.51 (s, 9 H, *t*-Boc), 1.50, 1.34 (2 × s, 2 × 3 H, 2 × CH_3), 1.07, 1.06, 0.99 (3 × s, 3 × 9 H, 3 × *tert*-butyl), 0.24, 0.22, 0.17, 0.12, 0.12, 0.09, 0.06, 0.04 (8 × s, 8 × 3 H, 8 × $SiCH_3$); IR (neat film) 3329 (w), 2930 (m), 2858 (m), 1789 (m), 1726 (s), 1688 (s), 1532 (w), 1447 (m), 1372 (m), 1258 (s), 1151 (s), 1029 (s), 838 (s), 779 (m) cm^{-1}.

5′-*O*-(Dimethoxytrityl)-*N*-(*tert*-butyloxycarbonyl)uridine (65). Chlorotrimethylsilane (3.47 mL, 27.40 mmol, 2.5 equiv) was added to a solution of 5′-*O*-(dimethoxytrityl)uridine (**16**, 5.98 g, 10.94 mmol, 1 equiv), DMAP (30 mg, 0.25 mmol, 0.02 equiv), and triethylamine (7.62 mL, 54.70 mmol, 5.0 equiv) in dichloromethane (20.0 mL). The resulting white slurry was stirred at 23 °C for 2 h and then was filtered. The filtrate was concentrated, and the residual oil was passed through flash grade silica gel (33% ethyl acetate in hexanes) to yield a viscous, yellow oil (6.95 g). The intermediate bis(trimethylsilyl) ether was dissolved in pyridine (25.0 mL), and DMAP (30 mg, 0.25 mmol, 0.02 equiv) and di-*tert*-butyl dicarbonate (3.47 mL, 15.10 mmol, 1.4 equiv) were added sequentially. The resulting mixture was stirred at 23 °C for 12 h. Volatiles were removed in vacuo, and the residue was diluted with methyl alcohol (20 mL). Potassium fluoride hydrate (2.50 g, 26.56 mmol, 2.4 equiv) was added to the resulting solution, and the reaction mixture was stirred at 23 °C for 3 h. The product was partitioned between ethyl acetate (600 mL) and water (200 mL). The organic layer was washed with saturated aqueous sodium chloride solution (200 mL) and then was dried (sodium sulfate) and concentrated. The residue was purified by flash column chromatography (40% ethyl acetate in hexanes) to provide **65** (5.58 g, 79%) as a white solid: mp 93.0 °C; R_f 0.46, 67% ethyl acetate in hexanes; ^1H NMR (400 MHz, acetone-d_6) δ 7.97 (d, 1 H, J = 8.2 Hz, H 6), 7.47 (m, 2 H, arom), 7.33 (m, 6 H, arom), 7.26 (m, 1 H, arom), 6.90 (m, 4 H, arom), 5.89 (d, 1 H, J = 4.1 Hz, H 1′), 5.33 (d, 1 H, J = 8.2 Hz, H 5), 4.84 (d, 1 H, J = 5.5 Hz, OH), 4.49 (m, 1 H, H 3′), 4.37 (m, 2 H, H 4′ and OH), 4.13 (m, 1 H, H 2′), 3.78 (s, 6 H, OCH_3), 3.50 (dd, 1 H, J = 3.0, 12.1 Hz, H 5′), 3.43 (dd, 1 H, J = 2.7, 12.1 Hz, H 5′), 1.55 (s, 9 H, *tert*-butyl); IR (neat film) 3436 (w, br), 2932 (w), 1784 (s), 1716 (s), 1668 (s), 1608 (m), 1509 (m), 1446 (m), 1392 (m), 1252 (s), 1177 (w), 1147 (m) cm^{-1}; HRMS (FAB) m/z calcd for $C_{35}H_{38}N_2O_{10}$ $(M)^+$ 646.2526, found 646.2498.

2′,3′-*O*-Bis(allyloxycarbonyl)-5′-*O*-(dimethoxytrityl)-3-*N*-(*tert*-butyloxycarbonyl)uridine (66). Allyl chloroformate (10.20 mL, 95.80 mmol, 10.0 equiv) was added dropwise over a 10-min interval to a solution of diol **65** (6.20 g, 9.58 mmol, 1 equiv) in pyridine (15.50 mL, 191.6 mmol, 20.0 equiv) at −20 °C. The resulting slurry was allowed to warm to 23 °C and was stirred at this temperature for 25 min. Volatiles were removed in vacuo, and the residue was dissolved in dichloromethane (30 mL). The product was partitioned between ethyl acetate (500 mL) and water (300 mL). The organic layer was washed with saturated aqueous sodium chloride solution (300 mL) and then was dried (sodium sulfate) and concentrated. The crude product was purified by flash column chromatography (33% ethyl acetate in hexanes) to yield 2′,3′-*O*-bis(allyloxycarbonyl)-5′-*O*-(dimethoxytrityl)-3-*N*-(*tert*-butyloxycarbonyl)uridine (**66**, 6.78 g, 87%) as a white solid: mp 77.0–78.0 °C; R_f 0.53, 50% ethyl acetate in hexanes; ^1H NMR (300 MHz, C_6D_6) δ 7.57 (m, 2 H, arom), 7.40 (m, 4 H, arom), 7.36 (d, 1 H, J = 8.2 Hz, H 6), 7.20 (m, 2 H, arom), 7.07 (m, 1 H, arom), 6.80 (m, 4 H, arom), 6.26 (d, 1 H, J = 3.7 Hz, H 1′), 5.73 (m, 3 H, Aoc), 5.67 (m, 1 H, H 3′), 5.62 (m, 1 H, H 2′), 5.19 (d, 1 H, J = 8.2 Hz, H 5), 5.14 (m, 1 H, Aoc), 5.08 (m, 1 H, Aoc), 4.98 (m, 1 H, Aoc), 4.96 (m, 1 H, Aoc), 4.43 (m, 1 H, Aoc), 4.40 (m, 1 H, Aoc), 4.31 (m, 1 H, Aoc), 4.10 (m, 1 H, H 4′), 3.44 (dd, 1 H, J = 2.9, 11.5 Hz, H 5′), 3.35 (dd, 1 H, J = 2.9, 11.5 Hz, H 5′), 3.33 (s, 6 H, OCH_3), 1.45 (s, 9 H, *tert*-butyl); IR (neat film) 2935 (w), 1787 (s), 1759 (s), 1724 (s), 1682 (s), 1608 (w), 1509 (m), 1440 (m), 1372 (m), 1256 (s), 1148 (m), 1033 (w), 833 (w) cm^{-1}; HRMS (FAB) m/z calcd for $C_{43}H_{46}N_2O_{14}$ $(M)^+$ 814.2949, found 814.2900.

2′,3′-*O*-Bis(allyloxycarbonyl)-3-*N*-(*tert*-butyloxycarbonyl)uridine (67). A solution of benzenesulfonic acid (1.80 g, 11.38 mmol, 1.4 equiv) in chloroform (60.0 mL) was poured onto 2′,3′-*O*-bis(allyloxycarbonyl)-5′-*O*-(dimethoxytrityl)-3-*N*-(*tert*-butyloxycarbonyl)uridine (**66**, 6.78 g, 8.33 mmol, 1 equiv), and the resulting orange solution was stirred at 23 °C for 2 min. The product was partitioned between ethyl acetate (500 mL) and saturated aqueous sodium bicarbonate solution (300 mL). The organic layer was washed with saturated aqueous sodium chloride solution (300 mL) and then was dried (sodium sulfate) and concentrated. The residue was purified by flash column chromatography (67% ethyl acetate in hexanes) to afford **67** (3.26 g, 76%) as a white solid: mp 62.0 °C; R_f 0.42, 67% ethyl acetate in hexanes; ^1H NMR (300 MHz, C_6D_6) δ 7.01 (d, 1 H, J = 10.1 Hz, H 6), 5.96 (d, 1 H, J = 6.7 Hz, H 1′), 5.73 (m, 1 H, Aoc), 5.72 (m, 1 H, H 3′), 5.68 (m, 1 H, Aoc), 5.62 (m, 1 H, Aoc), 5.48 (dd, 1 H, J = 5.3, 6.7 Hz, H 2′), 5.34 (d, 1 H, J = 10.1 Hz, H 5), 5.20–4.94 (m, 4 H, Aoc), 4.45–4.28 (m, 3 H, Aoc), 3.95 (m, 1 H, H 4′), 3.53 (m, 1 H, H 5′), 3.30 (m, 1 H, H 5′), 2.57 (t(br), 1 H, OH), 1.45 (s, 9 H, *tert*-butyl); IR (neat film) 3499 (w, br), 2986 (w), 1784 (s), 1756 (s), 1722 (s), 1682 (s), 1451 (m), 1372 (m), 1265 (s), 1147 (m), 1100 (w), 951 (w), 786 (w) cm^{-1}; HRMS (FAB) m/z calcd for $C_{22}H_{29}N_2O_{12}$ $(MH)^+$ 513.1720, found 513.1739.

Uridine 5-Aldehyde Derivative 68. A solution of alcohol **67** (355 mg, 0.693 mmol, 1 equiv) in dichloromethane (4.0 mL) was added via cannula to a suspension of the Dess–Martin periodinane (882 mg, 2.08 mmol, 3.0 equiv) in dichloromethane (4.0 mL), and the resulting suspension was stirred at 23 °C for 20 min. The product was partitioned between ethyl acetate (130 mL) and a mixture of saturated aqueous sodium bicarbonate solution and saturated aqueous sodium thiosulfate solution (4:1 (v/v), 50 mL). The organic layer was washed with saturated aqueous sodium chloride solution (50 mL) and then was dried (sodium sulfate) and concentrated. The residue was filtered through a short column of silica gel (67% ethyl acetate in hexanes) to afford the crude aldehyde **68** (250 mg). Due to the extreme lability of the product and its high susceptibility to hydration, the crude uridine 5′-aldehyde derivative **68** was immediately used without further purification in the following experiment.

***O*-Silyl Hemiselenoacetals 69.** Benzeneselenol (81 μL, 0.74 mmol, 3.0 equiv) and pyridine (59 μL, 0.74 mmol, 3.0 equiv) were added sequentially to a deoxygenated solution of freshly prepared aldehyde **68** from the previous experiment (250 mg, ~0.5 mmol, ~2 equiv, azeotropically dried with 1.5 mL of toluene) in toluene (2 mL), and the resulting solution was deoxygenated. After stirring at 23 °C for 15 min, the reaction mixture was transferred via cannula to a solution of dichlorodimethylsilane (594 μL, 4.9 mmol, 20 equiv) in pyridine (2 mL). The resulting suspension was deoxygenated and was stirred in the dark at 23 °C for 6 h. The reaction mixture was concentrated in vacuo at 23 °C, and the residue was suspended in toluene (2 mL). The volatiles were removed at 23 °C, and the residue was diluted with toluene (3 mL). To the mixture was added via cannula a solution of allylic alcohol **57** (189 mg, 0.24 mmol, 1 equiv) in pyridine (2.5 mL), and the resulting suspension was stirred at 23 °C for 5 min. The product was partitioned between ethyl acetate (100 mL) and water (100 mL). The organic phase was dried (sodium sulfate) and concentrated, and the residue was purified by flash column chromatography (50% ethyl acetate in hexanes) to afford an inseparable mixture of diastereomers **69** (1.5:1) (296 mg, 81% total) as a white solid: mp 78.0–80.5 °C; R_f 0.59, 67% ethyl acetate in hexanes; ^1H NMR (400 MHz, C_6D_6 at 50 °C) δ 7.69 (m, arom), 7.60 (m, arom), 7.30 (m, arom), 7.14 (m, arom), 7.10–7.03 (m, arom), 6.36 (d, 1 H, J = 10.1 Hz, H 1′), 6.27 (m, 2 H, NH, H 1′), 5.97 (m), 5.91 (m, 1 H, NH), 5.85 (m, H 5′),

5.78–5.54 (m, Aoc, H 11′, H 1′, H 2′, H 3′), 5.25–4.95 (m), 4.74–4.53 (m), 4.50–4.20 (m), 4.14 (t, 1 H, J = 9.75 Hz, H 6″), 4.07–3.95 (m), 3.77 (t, 1 H, J = 9.75 Hz, H 4″), 3.65–3.56 (m), 2.18 (s, 3 H, Ac), 2.13 (s, 3 H, Ac), 1.49 (s, *t*-Boc), 1.45 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3), 1.12 (s, 9 H, *tert*-butyl), 1.09 (s, 9 H, *tert*-butyl), 0.31 (s, 3 H, $SiCH_3$), 0.28 (s, 3 H, $SiCH_3$), 0.24 (s, 3 H, $SiCH_3$), 0.21 (s, $SiCH_3$), 0.20 (s, $SiCH_3$), 0.19 (s, $SiCH_3$); IR (neat film) 3331 (w, br), 2943 (w), 1784 (m), 1760 (m), 1723 (m), 1682 (s), 1527 (w), 1450 (w), 1373 (m), 1262 (s), 1147 (m), 1079 (m), 1023 (m), 842 (w) cm^{-1}. Elem. anal. Calcd for $C_{69}H_{92}N_4O_{24}SeSi_2$: C, 55.37; H, 6.20; N, 3.74. Found: C, 55.70; H, 6.18; N, 3.82.

Diol 70. Tributyltin hydride (503 μL, 1.9 mmol, 3.0 equiv) was added to a deoxygenated solution of *O*-silyl hemiselenoacetals **69** (931 mg, 0.62 mmol, 1 equiv) and bis(triphenylphosphine)palladium(II) chloride (3 mg, 4 μmol, 0.007 equiv) in a mixture of water in dichloromethane (2% (v/v), 6 mL), and the resulting brown solution was stirred at 23 °C for 6 min. The reaction mixture immediately was subjected to flash column chromatography (gradient elution: 50 → 67% ethyl acetate in hexanes) to afford diols **70** (700 mg, 85%) as a white solid: mp 94.0–95.5 °C; R_f 0.44, 67% ethyl acetate in hexanes; ^{1}H NMR (400 MHz, C_6D_6 at 50 °C) δ 9.70 (d, 1 H, J = 9.7 Hz, H 6), 7.68–7.60 (m, arom), 6.16 (d, 1 H, J = 3.33 Hz, H 1′), 6.11 (d, 1 H, J = 10.0 Hz, NH), 6.01 (d, 1 H, J = 5.67 Hz, H 11′), 5.80 (m, 2 H, NH, H 1″), 5.70 (d, 1 H, J = 2.0 Hz, H 5′), 5.53 (d, 1 H, J = 8.67 Hz, H 5), 5.51 (d, 1 H, J = 10.0 Hz, NH), 5.27–5.15 (m), 4.73–3.95 (m), 3.84–3.73 (m), 3.64–3.55 (m), 2.13 (s, 3 H, Ac), 2.07 (s, 3 H, Ac), 1.51 (s, 9 H, *t*-Boc), 1.47 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3), 1.09 (s, 9 H, *tert*-butyl), 1.06 (s, 9 H, *tert*-butyl), 0.28 (s, 3 H, $SiCH_3$), 0.25 (s, 3 H, $SiCH_3$), 0.23 (s, $SiCH_3$), 0.22 (s, $SiCH_3$), 0.16 (s, $SiCH_3$), 0.15 (s, $SiCH_3$), 0.05 (s, $SiCH_3$), –0.17 (s, $SiCH_3$); IR (neat film) 3334 (w, br), 2931 (w), 1786 (m), 1719 (s), 1667 (s), 1540 (w), 1452 (w), 1374 (m), 1256 (s), 1120 (s), 1022 (s), 861 (m), 840 (m) cm^{-1}.

Tetraol 71. Aliquots of a solution of triethylborane (25 μL each, 1.0 M in hexanes, 0.025 mmol, 0.1 equiv each) were added to a deoxygenated solution of diols **70** (340 mg, 0.26 mmol, 1 equiv) and tributyltin hydride (138 μL, 0.51 mmol, 2.0 equiv) in toluene (300 mL) at 0 °C at 15-min intervals over a 2-h period. The resulting solution was concentrated at 0 °C, and the residue was diluted with methyl alcohol (10 mL). To this solution was added potassium fluoride hydrate (600 mg, 6.4 mmol, 25 equiv), and the resulting mixture was stirred at 23 °C for 2 h. The product was partitioned between ethyl acetate (300 mL) and saturated aqueous sodium chloride solution (150 mL). The organic layer was separated, and the aqueous layer was extracted further with ethyl acetate (100 mL). The combined organic layers were dried (sodium sulfate) and concentrated, and the residue, containing a 7.5:1 mixture of C5′-diastereomers, was purified by careful flash column chromatography (12:4:1 benzene:acetonitrile:isopropanol) to afford pure **71** (172 mg, 60%) as a white solid: mp 223.0 °C; R_f 0.34, 10% methyl alcohol in dichloromethane; ^{1}H NMR (400 MHz, $CDCl_3$ at 50 °C) δ 7.52 (d, 1 H, J = 8.1 Hz, H 6), 7.35–7.20 (m, 10 Harom), 5.83 (d, 1 H, J = 8.6 Hz, NH), 5.74 (d, 1 H, J = 8.1 Hz, H 5), 5.65 (d, 1 H, J = 4.0 Hz, H 1′), 5.18 (d, 1 H, J = 12.1 Hz, PhCH_2OCO), 5.03 (m, 2 H, H 1″, H 11′), 4.98 (d, 1 H, J = 12.1 Hz, PhCH_2OCO), 4.79 (d, 1 H, J = 6.3 Hz, OCH_2O), 4.73 (d, 1 H, J = 6.3 Hz, OCH_2O), 4.62 (d, 1 H, J = 7.5 Hz, NH), 4.56 (d, 1 H, J = 11.8 Hz, $PhCH_2$), 4.52 (d, 1 H, J = 11.8 Hz, $PhCH_2$), 4.32 (m, 2 H), 4.20–4.05 (m, 2 H), 3.96 (t, 1 H, J = 3.5 Hz, H 3′), 3.94 (m, 1 H, H6″), 3.84 (m, 1 H, H 4′), 3.82–3.71 (m, 3 H), 3.66 (t, 1 H, J = 10.1 Hz, H 6″), 3.55 (t, 1 H, J = 9.2 Hz, H 4″), 3.43 (s(br), 1 H), 3.27 (s(br), 1 H), 2.62 (s(br), 1 H), 2.20 (m, 1 H, H 6′), 1.91 (s, 3 H, Ac), 1.74 (m, 1 H, H 6′), 1.58 (s, 9 H, *t*-Boc), 1.45 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3), 0.85 (s, 9 H, *tert*-butyl), 0.08 (s, 6 H, $SiCH_3$); IR (neat film) 3354 (m, br), 2933 (m), 1784 (m), 1713 (s), 1667 (s), 1544 (m), 1449 (w), 1374 (m), 1253 (m), 1120 (s), 1079 (m), 1026 (s), 867 (w), 838 (w), 726 (m) cm^{-1}.

Aldehyde 72. Ozone was bubbled through a mixture of sodium bicarbonate (1.60 g, 19.0 mmol, 0.6 equiv) and cyclododecene (5.00 g, 30.1 mmol, 1 equiv) in a mixture of dichloromethane and methyl alcohol (10:3 (v/v), 130 mL) at –78 °C for 3 h until the solution became deep blue. To remove excess ozone, nitrogen was bubbled through the solution at –78 °C for 15 min until the solution became colorless; the reaction mixture was then allowed to warm to 23 °C. After filtration of the suspension, benzene (80 mL) was added to the filtrate, and the resulting solution was concentrated to a volume of 40 mL. The concentrate was diluted with dichloromethane (160 mL), and triethylamine (12.0 mL, 86.1 mmol, 2.8 equiv) and acetic anhydride (16.0 mL, 169.6 mmol, 5.6 equiv) were added sequentially at 23 °C over a 10-min period. After stirring for 5 h, the reaction mixture was diluted further with dichloromethane (150 mL). The solution was washed sequentially with 0.1 N aqueous hydrochloric acid (300 mL), saturated aqueous sodium bicarbonate solution (300 mL), and saturated aqueous sodium chloride solution (300 mL). The organic layer was dried (sodium sulfate) and concentrated, and the pale yellow residue was purified by flash column chromatography (10% ethyl acetate in hexanes) to give the aldehyde **72** (6.10 g, 94%) as a clear, colorless oil: R_f 0.39, 20% ethyl acetate in hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (s, 1 H, H 12), 3.62 (s, 3 H, OCH_3), 2.41 (dt, 1 H, J = 2.1, 7.5 Hz, H 2), 2.30 (t, 1 H, J = 7.5 Hz, H 2), 1.62 (m, 2 H, H 11),1.29 (m, 16 H, CH_2); IR (neat film) 2926 (s), 2853 (s), 1739 (s), 1436 (w), 1172 (m) cm^{-1}; HRMS (EI) m/z calcd for $C_{13}H_{23}O_3$ (M^+ – H) 227.1647, found 227.1641.

Methyl Ester 73. A solution of sodium bis(trimethylsilyl)amide (12.0 mL, 1.0 M in tetrahydrofuran, 12.0 mmol, 1.3 equiv) was added to a suspension of isopropyltriphenylphosphonium iodide (6.00 g, 13.9 mmol, 1.5 equiv) in tetrahydrofuran (100 mL) at –78 °C. The resulting red suspension was stirred at –78 °C for 5 min, then at 23 °C for 25 min, and finally at 0 °C for 5 min. A solution of aldehyde **72** (2.00 g, 9.25 mmol, 1 equiv) in tetrahydrofuran (25 mL) was added via cannula to the ylide solution at 0 °C, and the resulting suspension was stirred at 23 °C for 1 h. The product was partitioned between ethyl ether (500 mL) and water (300 mL). The organic layer was washed with saturated aqueous sodium chloride solution (300 mL) and then was dried (sodium sulfate) and concentrated. The resulting oil was purified by flash column chromatography (gradient elution: 3 → 5% ethyl acetate in hexanes) to afford the methyl ester **73** (1.92 g, 82%) as a clear, colorless oil: R_f 0.57, 10% ethyl acetate in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.11 (m, 1 H, H 12), 3.66 (s, 3 H, OCH_3), 3.30 (d, 2 H, J = 7.7 Hz, H 2), 1.93 (m, 1 H, H 11), 1.65 (s, 3 H, CH_3), 1.60 (s, 3 H, CH_3), 1.60 (m, 1 H, H 11), 1.27 (m, 16 H, CH_2); IR (neat film) 2925 (s), 2854 (s), 1743 (s), 1436 (m), 1376 (w), 1171 (m) cm^{-1}; HRMS (EI) m/z calcd for $C_{16}H_{30}O_2$ $(M)^+$ 254.2246, found 254.2246.

Methyl Ester 74. A solution of the methyl ester **73** (2.02 g, 7.87 mmol, 1 equiv) in toluene (20 mL) was heated at 60 °C in the presence of 10% palladium on activated carbon (300 mg) under a hydrogen atmosphere (1 atm) for 12 h. The reaction mixture was filtered through a pad of Celite, washing well with ethyl ether (150 mL). The filtrate was concentrated to afford pure **74** (1.94 g, 96%) as a clear, colorless oil: R_f 0.57, 10% ethyl acetate in hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.64 (s, 3 H, OCH_3), 2.29 (t, 2 H, J = 7.5 Hz, H 2), 1.52 (m, 1 H, H 13), 1.61–1.16 (m, 20 H, CH_2), 0.84 (d, 6 H, J = 8.3 Hz, CH_3); IR (neat film) 2925 (s), 2853 (s), 1743 (s), 1461 (w), 1436 (w), 1170 (m) cm^{-1}; HRMS (EI) m/z calcd for $C_{16}H_{32}O_2$ $(M)^+$ 256.2402, found 256.2382.

Methyl Ester 75. *n*-Butyllithium (8.15 mL, 1.3 M in hexanes, 10.6 mmol, 1.2 equiv) was added to a solution of diisopropylamine (1.86 mL, 13.3 mmol, 1.5 equiv) in tetrahydrofuran (40 mL) at –78 °C. The reaction flask was transferred briefly to an ice bath (<10 min) and then was recooled to –78 °C. A solution of **74** (2.26 g, 8.83 mmol, 1 equiv) in tetrahydrofuran (20 mL) was transferred by cannula to the cold solution of lithium diisopropylamide, and the resulting solution was stirred at –78 °C for 25 min. Solid diphenyl diselenide was added to the reaction mixture in one portion, and the resulting suspension was allowed to warm to 23 °C. The deep yellow solution was stirred at 23 °C for 5.5 h. The product was partitioned between ethyl ether (700 mL) and water (300 mL). The organic layer was washed sequentially with water (300 mL) and saturated aqueous sodium chloride solution (300 mL) and then was dried (sodium sulfate) and concentrated. Excess diphenyl diselenide was removed from the residue by flash column chromatography (gradient elution: 20 → 25% dichloromethane in hexanes). Solid *m*-chloroperoxybenzoic acid (3.13 g, 60% (w/w), 10.9 mmol, 1.2 equiv) was added to a solution of the crude selenide residue in dichloromethane (100 mL) at –78 °C, and the resulting suspension was stirred at –78 °C for 2 h. Excess oxidant was quenched by the addition of dimethyl sulfide (3.20 mL, 43.6 mmol, 4.9 equiv) and triethylamine (1.22 mL, 8.83 mmol, 1 equiv). The resulting solution was stirred at 23 °C for 6 h, and the product was partitioned between ethyl ether (500 mL) and water (300 mL). The organic layer was washed with saturated aqueous sodium chloride solution (300 mL) and then was dried (sodium sulfate) and concentrated. The residue was purified by flash column chromatography (5% dichloromethane in benzene) to afford methyl ester **75** (1.11 g, 55%) as a clear, colorless oil: R_f 0.28, 5% ethyl acetate in hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) 6.97 (dt, 1 H, J = 6.9, 15.5 Hz, H 3), 5.81 (dt, 1 H, J = 1.4, 15.5 Hz, H 2), 3.73 (s, 3 H, OCH_3), 2.20 (m, 2 H, H 4), 1.50 (m, 1 H, H 13), 1.45–1.17 (m, 16 H, CH_2), 0.82 (d, 6 H, J = 6.9 Hz, CH_3); IR (neat film) 2926

(s), 2854 (s), 1729 (s), 1658 (m), 1436 (w), 1269 (m), 1173 (w), 1042 (w) cm^{-1}; HRMS (EI) m/z calcd for $C_{16}H_{31}O_2$ $(MH)^+$ 255.2113, found 255.2313.

(*E*)-13-Methyl-2-tetradecenoic Acid (76). Methyl ester **75** (364 mg, 1.43 mmol, 1 equiv) was dissolved in a mixture of 1 M aqueous sodium hydroxide solution and *tert*-butyl alcohol (1:1 (v/v), 8 mL), and the resulting solution was heated at 60 °C for 1.5 h. The product was partitioned between ethyl acetate (100 mL) and 0.5 N aqueous hydrochloric acid solution (100 mL). The organic layer was washed with saturated aqueous sodium chloride solution (100 mL) and then was dried (sodium sulfate) and concentrated. The residue was purified by flash column chromatography (50% ethyl acetate in hexanes) to afford **76** (312 mg, 91%) as a white solid: mp 41.5 °C; R_f 0.35, 25% ethyl acetate in hexanes; ^1H NMR (300 MHz, $CDCl_3$) δ 7.09 (dt, 1 H, J = 7.1, 15.3 Hz, H 3), 5.82 (dt, 1 H, J = 1.2, 15.3 Hz, H 2), 2.22 (m, 2 H, H 4), 1.50 (m, 1 H, H 13), 1.47–1.12 (m, 16 H, CH_2), 1.86 (d, 6 H, J = 7.0 Hz, CH_3); IR (neat film) 3300–2300 (w, br), 2922 (s), 2849 (s), 1691 (s), 1651 (m), 1668 (w), 1420 (w), 1284 (w) cm^{-1}; HRMS (EI) m/z calcd for $C_{15}H_{29}O_2$ $(MH)^+$ 241.2168, found 241.2178.

Tunicamycin-V (1-V). Palladium black (60 mg) was added to a solution of tetraol **71** (140 mg, 0.13 mmol, 1 equiv) in a mixture of formic acid in methyl alcohol (10% (v/v), 10 mL), and the resulting suspension was stirred at 23 °C for 1.5 h. After filtration of the reaction mixture and concentration of the filtrate, the residue was diluted with a mixture of formic acid in methyl alcohol (13% (v/v), 10 mL), and the resulting solution was heated at 40 °C for 5 h. Following removal of volatiles in vacuo, the residue was dissolved in a mixture of methyl alcohol and acetonitrile (1:1 (v/v), 15 mL), and an aqueous solution of hydrofluoric acid (48% (w/w), 300 μL) was added. The resulting solution was stirred at 23 °C for 2 h. Concentration of the reaction mixture at 23 °C and filtration of the residue through a short column of RP-18 reverse-phase silica gel (1:1:1.5 methyl alcohol:pyridine:water) afforded the corresponding crude amino heptaol **1** (81 mg), which was used without further purification.

Solutions of the activated fatty acid **76** were prepared as follows: dichloromethane (3 mL) was added to a solid mixture of fatty acid **76** (31 mg, 0.13 mmol, 1 equiv) and 1,3-dicyclohexylcarbodiimide (40 mg, 0.19 mmol, 1.5 equiv), and the resulting suspension was stirred at 23 °C for 30 min. Freshly prepared solutions of activated **76** (1 equiv each, 6 equiv total) were added to a solution of the crude amino heptaol **1** (81 mg) in methyl alcohol (4 mL) at 8-h intervals over a period of 2 days. The reaction mixture was concentrated at 23 °C, and the residue was purified by flash column chromatography through RP-18 reverse-phase silica gel (1:1:1 methyl alcohol:pyridine:water) followed by trituration of the residue with chloroform to afford pure **1-V** (88 mg, 83% from tetraol **71**) as a white solid: mp 235–236 °C (decomp); R_f 0.60, 2:1:1 *n*-butanol:acetic acid:water; ^1H NMR (400 MHz, CD_3OD) δ 7.91 (d, 1 H, J = 8.0 Hz, H 6), 6.81 (dt, 1 H, J = 6.9, 15.5 Hz, fatty acid Hβ), 5.93 (d, 1 H, J = 15.5 Hz, fatty acid Hα), 5.92 (d, 1 H, J = 5.6 Hz, H 1'), 5.74 (d, 1 H, J = 8.0 Hz, H 5), 4.92 (d, 1 H, J = 3.9 Hz, H 1''), 4.58 (d, 1 H, J = 8.8 Hz, H 11'), 4.20 (m, 2 H, H 3', H 2'), 4.07 (m, 1 H, H 10'), 4.01 (m, 2 H, H 5', H 5''), 3.84 (m, 3 H, H 3'', H 4', H 8'), 3.77 (m, 1 H, H 7'), 3.64 (m, 4 H, H 3'', H 6'', H 9'), 3.33 (t, 1 H, J = 9.1 Hz, H 4''), 2.19 (m, 2 H, fatty acid Hγ), 2.09 (m, 1 H, H 6'), 1.92 (s, 3 H, Ac), 1.57–1.40 (m, 3 H, H 6', *i*-Pr-CH, fatty acid Hδ), 1.28 (s(br), 12 H, CH_2), 1.16 (m, 2 H, CH_2), 0.87 (d, 1 H, J = 6.7 Hz, *i*-Pr-CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ 173.5 (acetamide C=O), 169.8 (fatty acid amide C=O), 166.1 (C4), 152.6 (C2), 146.5 (C6), 142.8 (fatty acid Cβ), 125.0 (fatty acid Cα), 103.1, 102.1 (C5), 100.3 (C11'), 90.1 (C1''), 90.1, 89.6 (C1'), 75.5, 74.3, 73.3, 72.9, 72.7, 72.6, 72.1, 70.9, 68.4, 63.2, 55.0, 54.5, 40.2, 35.9, 33.0, 31.0, 30.7, 30.6, 30.5, 30.3, 29.5, 29.1, 28.5, 23.2, 23.0; IR (neat film) 3329 (s, br), 2924 (s), 2849 (m), 1667 (s, br), 1468 (m), 1267 (w), 1096 (s), 1020 (s) cm^{-1}; HRMS (FAB) m/z calcd for $C_{38}H_{63}N_4O_{16}$ $(MH)^+$ 831.4239, found 831.4229; $[\alpha]^{24}_D$ + 60.5° (c = 0.515, pyridine).

Authentic 1-V. A sample of authentic tunicamycins (25 mg) was dissolved in methyl alcohol (5 mL) at 40 °C. The solution of authentic **1-V**, in 10 separate 500-μL injections, was loaded onto a Beckman Ultrasphere ODS (C_{18}, 5 μm) rp-HPLC column (10 × 250 mm, as part of a Waters 501 HPLC system, flow = 2.00 mL/min), eluting with 85:15 (v/v) methyl alcohol:water. Fractions containing authentic 1-V were collected and pooled. The combined fractions were concentrated to afford authentic tunicamycin-V (4 mg) as a white solid: mp 233–235 °C (decomp); R_f 0.60, 2:1:1 *n*-butanol:acetic:water; ^1H NMR (400 MHz, CD_3OD) δ 7.91 (d, 1 H, J = 8.1 Hz, H 6), 6.81 (dt, 1 H, J = 6.9, 15.5 Hz, fatty acid Hβ), 5.93 (d, 1 H, J = 15.5 Hz, fatty acid Hα), 5.92 (d, 1 H, J = 5.6 Hz, H 1'), 5.74 (d, 1 H, J = 8.1 Hz, H 5), 4.92 (d, 1 H, J = 3.9 Hz, H 1''), 4.58 (d, 1 H, J = 8.6 Hz, H 11'), 4.20 (m, 2 H, H 3', H 2'), 4.07 (m, 1 H, H 10'), 4.01 (m, 2 H, H 5', H 5''), 3.84 (m, 3 H, H 3'', H 4', H 8'), 3.77 (m, 1 H, H 7'), 3.64 (m, 4 H, H 3'', H 6'', H 9'), 3.33 (t, 1 H, J = 9.1 Hz, H 4''), 2.19 (m, 2 H, fatty acid Hγ), 2.09 (m, 1 H, H 6'), 1.92 (s, 3 H, acetamide), 1.57–1.40 (m, 3 H, H 6', *i*-Pr-CH, fatty acid Hδ), 1.28 (s(br), 12 H, CH_2), 1.16 (m, 2 H, CH_2), 0.87 (d, 1 H, J = 6.7 Hz, *i*-Pr-CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ 173.5 (acetamide C=O), 169.8 (fatty acid amide C=O), 166.1 (C4), 152.6 (C2), 146.5 (C6), 142.8 (fatty acid Cβ), 125.0 (fatty acid Cα), 103.1, 102.1 (C5), 100.3 (C11'), 90.1 (C1''), 90.1, 89.6 (C1'), 75.5, 74.3, 73.3, 72.9, 72.7, 72.6, 72.1, 70.9, 68.4, 63.2, 55.0, 54.5, 40.2, 35.9, 33.0, 31.0, 30.7, 30.6, 30.5, 30.3, 29.5, 29.1, 28.5, 23.2, 23.0; IR (neat film) 3328 (s, br), 2924 (s), 2849 (m), 1666 (s, br), 1465 (m), 1267 (w), 1096 (s), 1020 (s) cm^{-1}; HRMS (FAB) m/z calcd for $C_{38}H_{63}N_4O_{16}$ $(MH)^+$ 831.4239, found 831.4250; $[\alpha]^{24}_D$ + 59.1° (c = 0.501, pyridine).

C5'-*epi*-Tunicamycin-V (78). Palladium black (45 mg) was added to a solution of tetraol **66** (55 mg, 0.039 mmol, 1 equiv) in a mixture of formic acid in methyl alcohol (10% (v/v), 10 mL), and the resulting suspension was stirred at 23 °C for 30 min. After filtration of the reaction mixture and concentration of the filtrate, the residue was diluted with a mixture of formic acid in methyl alcohol (13% (v/v), 7 mL), and the resulting solution was heated at 40 °C for 4 h. Following removal of volatiles in vacuo, the residue was dissolved in a mixture of methyl alcohol and acetonitrile (1:1 (v/v), 10 mL), and an aqueous solution of hydrofluoric acid (48% (w/w), 200 μL) then was added. The resulting solution was stirred at 23 °C for 2 h. Concentration of the reaction mixture at 23 °C and filtration of the residue through a short column of RP-18 reverse-phase silica gel (1:1:1.5 methyl alcohol:pyridine:water) afforded the corresponding crude amino hepatol **77** (22 mg), which was used without further purification.

Solutions of the activated fatty acid **76** were prepared in a manner similar to that described above: dichloromethane (1 mL) was added to a solid mixture of fatty acid **76** (14 mg, 0.06 mmol, 1.5 equiv) and 1,3-dicyclohexylcarbodiimide (20 mg, 0.10 mmol, 2.6 equiv), and the resulting suspension was stirred at 23 °C for 30 min. Freshly prepared solutions of activated **76** (1.5 equiv each, 9 equiv total) were added to a solution of the crude amino heptaol **77** (22 mg) in methyl alcohol (2 mL) at 12-h intervals over a period of 3 days. The reaction mixture was concentrated at 23 °C, and the residue was purified by flash column chromatography through RP-18 reverse-phase silica gel (1:1:1 methyl alcohol:pyridine:water) followed by trituration of the residue with chloroform to afford pure **78** (24 mg, 74% from siloxane **61**): R_f 0.60, 2:1:1 *n*-butanol:acetic acid:water; ^1H NMR (400 MHz, CD_3OD) δ 8.11 (d, 1 H, J = 8.1 Hz, H 6), 6.81 (dt, 1 H, J = 15.2, 7.0 Hz, fatty acid Hβ), 5.95 (d, 1 H, J = 15.2 Hz, fatty acid Hα), 5.93 (d, 1 H, J = 5.0 Hz, H 1'), 5.72 (d, 1 H, J = 8.1 Hz, H 5), 4.96 (d, 1 H, J = 3.5 Hz, H 1''), 4.56 (d, 1 H, J = 8.4 Hz, H 11'), 4.20 (m, 2 H, H 2', 3'), 4.05 (dd, 1 H, J = 10.7, 8.4 Hz, H 10'), 4.00–3.60 (m, 10 H), 3.42 (t, 1 H, J = 9.8 Hz), 2.20 (m, 2 H, fatty acid Hγ), 2.09 (m, 1 H, H 6'), 1.91 (s, 3 H, Ac), 1.88 (m, 1 H, H 6'), 1.60–1.15 (m, 16 H), 0.88 (s, 3 H, CH_3), 0.86 (s, 3 H, CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ 173.4 (acetamide C=O), 169.7 (fatty acid amide C=O), 166.3 (C4), 152.6 (C2), 146.6 (C6), 142.9 (fatty acid Cβ), 124.9 (fatty acid Cα), 102.8, 102.5 (C5), 100.4 (C11'), 90.1 (C1''), 90.1, 87.8 (C1'), 75.6, 74.3, 74.1, 73.1, 72.8, 72.5, 71.8, 70.8, 68.8, 62.3, 55.0, 54.4, 40.3, 35.9, 33.1, 31.1, 30.8, 30.7, 30.6, 30.4, 29.5, 29.2, 28.6, 23.3, 23.1; IR (neat film) 3399 (s, br), 2919 (m), 2849 (w), 1666 (s), 1631 (m), 1561 (w), 1461 (w), 1414 (m), 1349 (m), 1094 (m), 1023 (m) cm^{-1}; HRMS (FAB) m/z calcd for $C_{38}H_{62}N_4O_{16}$ $(MNa)^+$ 853.4059, found 853.4036.

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