The Total Synthesis of Allosamidin. Expansions of the Methodology of Azaglycosylation Pursuant to the Total Synthesis of Allosamidin. A Surprising Enantiotopic Sense for a Lipase-Induced Deacetylation

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Received February 20, 1996[⊗]

Abstract: Allosamidin, recently isolated from mycelial extracts of *Streptomyces* sp. 1713, is a powerful and selective chitinase inhibitor. The total synthesis of allosamidin is described herein. The electric eel acetylcholinesterase-mediated enantioselective hydrolysis of (*trans,trans*)-2-(benzyloxy)cyclopentene-1,3-diol diacetate accessed a monoacetyl derivative. Five additional steps produced a protected version of the aglycon ("allosamizoline") sector of allosamidin. An allal derivative stereoselectively reacted with benzenesulfonamide in the presence of a halonium source to afford a 2β-halo-1α-sulfonamidohexose. Treatment of this product with a strong base generated an intermediate 1,2-sulfonylaziridine, which was trapped with a protected allal derivative to provide a disaccharide glycal. Reiteration of this scheme gave access to the required trisaccharide. Following deprotection, the total synthesis of allosamidin was accomplished. In addition, the method, with modification, gave access to several allosamidin analogs.

Background on Allosamidin—A Paradigm Case for Chitinase Inhibition

Chitin,[1] composed substantially of an array of β-1,4-linked *N*-acetylglucosamine units, is the major component of the insect exoskeleton.[2] It is also the primary cell wall polysaccharide in several groups of fungi.[3] Chitin synthases are employed by nature to build chitinous structures, while chitinases facilitate their degradation. For example, molting fluids secreted by insects in preparation for ecdysis contain chitinases which degrade and weaken the old cuticle.[4] Also, the primary septum between mother and daughter yeast cells at the time of budding is composed primarily of chitin.[5] Accordingly, chitin-maintaining enzymes are necessary to ensure proper cell division.[6] Since chitin has a specialized role in nature, compounds capable of disrupting chitin biosynthesis are ideal targets as potential growth inhibitors of chitin containing organisms. For instance, chitin synthase inhibitors have been studied and used as inhibitors of fungal[7] and insect[8] growth.

It has been suggested that chitinase inhibitors could also function as selective insecticides[9] and fungicides.[10] Moreover, it could well be advantageous to achieve species specific chitinase inhibition. Since chitinases may function in beneficial roles, blanket inhibition of the enzyme throughout an ecosystem could be undesirable. For example, chitinases (such as those isolated from the digestive tract of certain insectivorous vertebrates) are thought to aid in digestion.[11] While no chitinous structures are known in higher order plants, plant chitinase production has been observed to increase during times of fungal infection.[12] These glycosidases appear to operate defensively against invading fungi.[13,14]

Allosamidin (**1**), isolated from mycelial extracts of *Streptomyces* sp. 1713, was heralded as an early success in the search for selective chitinase inhibitors. It (**1**) consists[15,16] of a 3,3′-*epi*-chitobiose moiety β-linked to the novel aglycon sector termed "allosamizoline" (**8**), which has the absolute configuration indicated in Figure 1.[17] Thus, the carbohydrate sector of allosamidin is a small molecule "look-alike" of chitin. A

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⊗ Abstract published in *Advance ACS Abstracts,* September 1, 1996.

(1) *Chitin, Chitosan, and Related Enzymes*; Zikakis, J. P., Ed.; Academic Press, Inc.: New York, 1984.

(2) Andersen, S. O. *Annu. Rev. Entomol.* **1979**, *24*, 29. Rudall, K. M.; Kenchington, W. *Biol. Rev.* **1973**, *49*, 597.

(3) Cabib, E.; Shematek, E. M. In *Biology of Carbohydrates*; Ginsburg, V., Robbins, P., Eds.; John Wiley & Sons, Inc.: New York, 1981; Vol. 1, p 60.

(4) Kramer, K. J.; Dziadik-Turner, C.; Koga, D. In *Comprehensive Insect Physiology Biochemistry and Pharmocology*; Kerkut, G. A., Gilbert, L. I., Eds.; Pergamon Press, Inc.: New York, 1985; p 75.

(5) Molano, J.; Bowers, B.; Cabib, E. *J. Cell Biol.* **1980**, *85*, 199.

(6) Cabib, E.; Silverman, S. J.; Shaw, J. A. *J. Gen. Microbiol.* **1992**, *138*, 97. Shaw, A. J.; Mol, P. C.; Bowers, B.; Silverman, S. J.; Valdivieso, M. H.; Durán, A.; Cabib, E. *J. Cell Biol.* **1991**, *114*, 111. Kuranda, M. J.; Robbins, P. W. *J. Biol. Chem.* **1991**, *266*, 19758. Cabib, E.; Sburlati, A.; Bowers, B.; Silverman, S. J. *J. Cell Biol.* **1989**, *108*, 1665. Cabib, E. *Adv. Enzymol. Relat. Areas Mol. Biol.* **1987**, *59*, 59.

(7) Misato, T.; Kakiki, K.; Hori, M. In *Advances in Pesticide Science*; Geissbuhler, H., Ed.; Pergamon Press: New York, 1979; p 458. Gooday, G. W. *Prog. Ind. Microbiol.* **1989**, *27*, 139.

(8) Verloop, A.; Ferrell, D. Pesticide *ACS Symp. Ser.* **1977**, *37*, 237.

(9) Muzzarelli, R. A. A. *The Insect Integument*; Hepburn, H. R., Ed.; Elsevier: New York, 1976.

(10) Sakuda, S.; Nishimoto, Y.; Ohi, M.; Watanabe, M.; Takayama, S.; Isogai, A.; Yamada, Y. *Agric. Biol. Chem.* **1990**, *54*, 1333.

(11) Lundblad, G.; Hederstedt, B.; Lind, J.; Steby, M. *Eur. J. Biochem.* **1974**, *46*, 367. Jeuniaux, C. *Nature* **1961**, *192*, 135.

(12) Mauch, F.; Hadwigwer, L. A.; Boller, T. *Plant Physiol.* **1984**, *76*, 607. Pegg, G. F.; Young, D. H. *Physiol. Plant Pathol.* **1982**, *21*, 389. Pegg, G. F.; Vessey, J. C. *Physiol. Plant Pathol.* **1973**, *3*, 207.

(13) Schlumbaum, A.; Mauch, F.; Vögeli, U.; Boller, T. *Nature* **1986**, *324*, 365. Tsukamoto, T.; Koga, D.; Ida, A.; Ishibashi, T.; Horino-Matsushige, M.; Yagishita, K.; Imoto, T. *Agric. Biol. Chem.* **1984**, *48*, 931. Boller, T.; Gehri, A.; Mauch, F.; Vögeli, U. *Planta* **1983**, *157*, 22. Nichols, E. J.; Beckman, J. M.; Hadwiger, L. A. *Plant Physiol.* **1980**, *66*, 199.

(14) Mauch, F.; Mauch-Mani, B.; Boller, T. *Plant Physiol.* **1988**, *88*, 936. Molano, J.; Polacheck, I.; Duran, A.; Cabib, E. *J. Biol. Chem.* **1979**, *254*, 4901.

(15) Sakuda, S.; Isogai, A.; Matsumoto, S.; Suzuki, A.; Koseki, K. *Tetrahedron Lett.* **1986**, *27*, 2475.

(16) Sakuda, S.; Isogai, A.; Makita, T.; Matsumoto, S.; Koseki, K.; Kodama, H.; Suzuki, A. *Agric. Biol. Chem.* **1987**, *51*, 3251.

(17) Sakuda, S.; Isogai, A.; Matsumoto, S.; Suzuki, A.; Koseki, K.; Kodama, H.; Yamada, Y. *Agric. Biol. Chem.* **1988**, *52*, 1615.

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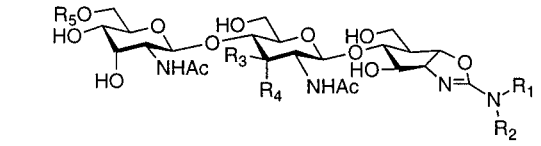
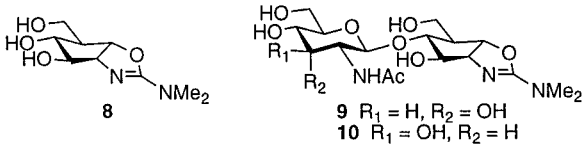


allosamidin (**1**) R_1, R_2 = CH_3; R_3, R_5 = H; R_4 = OH
demethylallosamidin (**2**) R_1 = Me; R_2, R_3, R_5 = H; R_4 = OH
didemethylallosamidin (**3**) R_1, R_2, R_3, R_5 = H; R_4 = OH
methylallosamidin (**4**) R_1, R_2, R_5 = CH_3; R_3 = H; R_4 = OH
methyl-*N*-demethylallosamidin (**5**) R_1, R_5 = Me; R_2, R_3 = H; R_4 = OH
glucoallosamidin A (**6**) R_1, R_2, R_5 = CH_3; R_3 = OH; R_4 = H
glucoallosamidin B (**7**) R_1, R_5 = CH_3; R_2, R_4 = H; R_3 = OH;



8

9 R_1 = H, R_2 = OH
10 R_1 = OH, R_2 = H

Figure 1. Structures of the Allosamidins.

recently published crystal structure of allosamidin bound in a plant chitinase/lysozyme[18] indicated that the aglycon portion was bound in the center of the active site. The aminooxazoline portion of the carbocycle serves to mimic the stabilization of positive charge at C-1 by the oxygen of the neighboring *N*-acetyl group, an apparent intermediate in the hydrolysis of chitin.

More recently, several compounds that are structurally related to allosamidin (Figure 1) were also found to exhibit strong chitinase inhibition.[19,20] In addition, the two pseudodisaccharides **9** and **10** (Figure 1) were isolated upon mild hydrolysis of allosamidin and glucoallosamidin A (**6**), respectively.[17] Finally, recent studies with isotopically labeled materials have provided information about the biosynthesis of the allosamidins.[21]

Early reports on the activity of allosamidin were concerned with the inhibition of insect chitinases. Allosamidin strongly inhibits chitinases[22] from the silkworm *Bombyx mori*, *in vitro*, while the inhibition of bacterial chitinases from *Streptomyces griseus* and *Serratia marcescens* was 500-fold less. Moreover, no inhibition was observed with yam chitinase, human or egg-white lysozymes, or β-*N*-acetyl-D-glucosaminidases from *B. mori*. Interestingly, allosamidin producing *Streptomyces* sp. AJ 9463 synthesizes two unique chitinases; one is strongly inhibited by **1**, while the other in not inhibited at concentrations of 2 mg/mL.[23] Methylallosamidin (**4**),[16] demethylallosamidin (**2**), and pseudodisaccharide **9** all displayed inhibition levels similar to **1** against *B. mori* chitinase activity.[19] In the Chitin Azure assay system, allosamidin and demethylallosamidin (**2**) inhibited *B. mori* chitinase with IC_{50} values of 0.20 and 0.25 μg/mL, respectively. However, allosamizoline (**8**) displayed no inhibition. These findings indicate that a glycosidic residue on the aglycon is essential for activity.

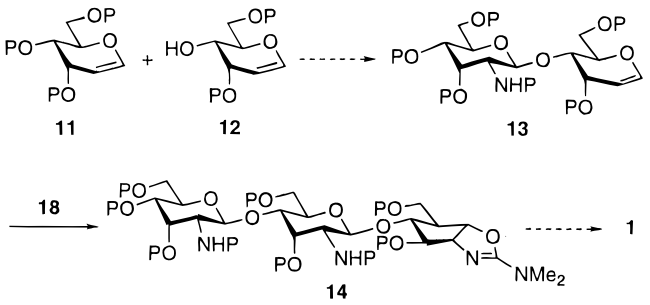
More significant than its *in vitro* chitinase inhibition is the fact that allosamidin inhibits insect growth, *in vivo*. The compound prevented larval ecdysis in all cases when injected into the fourth instar larvae of *B. mori* during the feeding stage at a dose greater than 4 μg.[24] Furthermore, administration of allosamidin to the fifth and last instar larvae of the common army worm *Leucania separata* prevented larval and pupal ecdysis, respectively.

Chitinases from several yeasts were also efficiently inhibited by the allosamidins; the level of inhibition was dependent, in a subtle way, upon the inhibitor structure. Whereas the demethylallosamidins were 10−100 times more efficient than the *N*,*N*-dimethylated analogs as inhibitors of *Candida albicans* ATCC 10231 and *Saccharomyces cerevisiae* chitinases, the *Trichoderma* sp. AF6-T8 chitinase was inhibited nearly equally by these allosamidins.[20] Didemethylallosamidin (**3**) was about 10-fold less active than **2** against *B. mori*, *Trichoderma* sp., and *Sa. cerevisiae* chitinases.[25] The configuration at C-3 of the interior sugar appears to have only a slight effect on the inhibition efficiency. It is interesting that the two pseudodisaccharides **9** and **10** inhibited the chitinase of *C. albicans* as well as the allosamidins, yet displayed no inhibition against the other yeast chitinases. Furthermore, the inhibition of *C. albicans* chitinase activity by **1** was shown to be competitive at low concentrations, while at higher concentration the inhibition is irreversible.

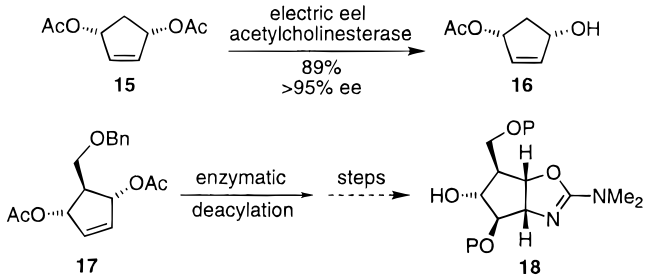
As a consequence of its novel structure and in response to the difficulties that have been encountered in attempts to obtain adequate amounts of compound for biological investigation, a program directed toward the total synthesis of allosamidin was initiated. Other laboratories have had similar goals. The large number of syntheses of aglycon **8**[26−31] and pseudotrisaccharide **1**[32−34] which have appeared in the literature attest to the high level of interest in allosamidin. In this paper, we document and expand upon our earlier disclosure which described the first total synthesis of allosamidin.[35] We do this within the broader context of azaglycosylation,[36] which is a central element in our ongoing program directed toward oligosaccharide synthesis.[37−39] We also provide some new insights into structure−activity relationships in the allosamidin series.

(18) Terwisscha van Scheltinga, A. C.; Armand, S.; Kalk, K. H.; Isogai, A.; Henrissat, B.; Dijkstra, B. W. *Biochemistry* **1995**, *34*, 15619.
(19) Isogai, A.; Sato, M.; Sakuda, S.; Nakayama, J.; Suzuki, A. *Agric. Biol. Chem.* **1989**, *53*, 2825.
(20) Nishimoto, Y.; Sakuda, S.; Takayama, S.; Yamada, Y. *J. Antibiot.* **1991**, *44*, 716.
(21) Zhou, Z.-Y.; Sakuda, S.; Kinoshita, M.; Yamada, Y. *J. Antibiot.* **1993**, *46*, 1582. (b) Zhou, Z.-Y.; Sakuda, S.; Yamada, Y. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1649.
(22) Koga, D.; Isogai, A.; Sakuda, S.; Matsumoto, S.; Suzuki, A.; Kimura, S.; Ide, A. *Agric. Biol. Chem.* **1987**, *51*, 471.
(23) Wang, Q.; Zhou, Z.-Y.; Sakuda, S.; Yamada, Y. *Biosci., Biotechnol., Biochem.* **1993**, *57*, 467.
(24) Sakuda, S.; Isogai, A.; Matsumoto, S.; Suzuki, A. *J. Antibiot.* **1987**, *40*, 296.
(25) Kinoshita, M.; Sakuda, S.; Yamada, Y. *Biosci., Biotechnol., Biochem.* **1993**, *57*, 1699.
(26) (a) Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1990**, *112*, 1261. (b) Trost, B. M. Van Vranken, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 444.
(27) (a) Takahashi, S.; Terayama, H.; Kuzuhara, H. *Tetrahedron Lett.* **1991**, *32*, 5123. (b) Nakata, M.; Akazawa, S.; Kitamura, S.; Tatsuta, K. *Tetrahedron Lett.* **1991**, *32*, 5363.
(28) (a) Simpkins, N. S.; Stokes, S.; Whittle, A. J. *Tetrahedron Lett.* **1992**, *33*, 793. (b) Simpkins, N. S.; Stokes, S.; Whittle, A. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2471.
(29) Kitahara, T.; Suzuki, N.; Koseki, K.; Mori, K. *Biosci., Biotechnol., Biochem.* **1993**, *57*, 1906.
(30) Goering, B. K.; Ganem, B. *Tetrahedron Lett.* **1994**, *35*, 6997.
(31) Shrader, W. D.; Imperiali, B. *Tetrahedron Lett.* **1996**, *37*, 599. This synthesis supports the assignment of stereochemistry of the azaglycon reported herein.
(32) (a) Maloisel, J.-L.; Vasella, A.; Trost, B. M.; Van Vranken, D. L. *J. Chem. Soc., Chem. Commun.* **1991**, 1099. (b) Maloisel, J.-L.; Vasella, A. *Helv. Chim. Acta* **1992**, *75*, 1491. (c) Maloisel, J.-L.; Vasella, A.; Trost, B. M.; Van Vranken, D. L. *Helv. Chim. Acta* **1992**, *75*, 1515.
(33) Takahashi, S. T.; Terayama, H.; Kuzuhara, H. *Tetrahedron Lett.* **1992**, *33*, 7565.
(34) Blattner, R.; Furneaux R. H.; Kemmitt, T.; Tyler, P. C.; Ferrier, R. J.; Tidén, A.-K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3411.
(35) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1991**, *113*, 5863.
(36) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 5811.
(37) Danishefsky, S. J.; Gervay, J.; Peterson, J. M.; McDonald, F. E.; Koseki, K.; Griffith, D. A.; Oriyama T.; Marsden, S. *J. Am. Chem. Soc.* **1995**, *117*, 1940.
(38) McClure, K. F.; Randolph, J.; Ruggeri, R.; Danishefsky, S. J. *Science* **1993**, *260*, 1307.
(39) Roberge, J.; Beebe, X.; Danishefsky, S. J. *Science* **1995**, *269*, 202.

Scheme 1



Scheme 2



Planning

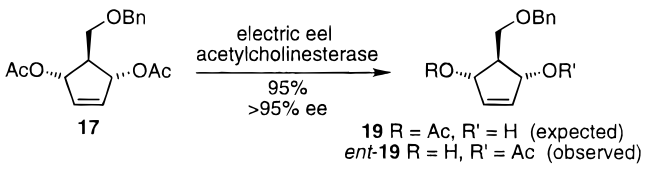
In studying the structure of allosamidin, from the perspective of an exploration in total synthesis, three problems virtually impose themselves. The carbohydrate domain consists of a novel constellation of two 2-*N*-acetylallose (All*N*Ac) residues. These are glycosidically β-linked through the 4-α-hydroxyl group of the All*N*Ac moiety at the reducing end of the carbohydrate sector. Finally, this All*N*Ac is β-linked to a substituted cyclopentyl residue, itself fused to a (dimethylamino)oxazoline ring.

Our consideration of the allosamidin synthesis began with thoughts about the construction of the glycosidic linkages (Scheme 1). We envisioned that the two allal residues **11** and **12** could be oxidatively coupled to give rise to a disaccharide glycal of type **13**. Combination of the latter (**13**) with a protected allosamizoline derivative (*cf.* **18**), in a similar fashion, would then provide core structure **14**. The allosamizoline synthon **18** would be assembled (Scheme 2) from desymmetrization of meso system **17** on the basis of precedents elegantly demonstrated by Deardorff for **15**.[40] It is with the preparation of the required antipode of a suitably protected allosamizoline derivative that our account begins.

Allosamizoline

The synthesis of the aglycon commenced with the peracetylation of the known and readily available 2-[(benzyloxy)-methyl]-4-cyclopentene-1,3-diol[41] to provide diacetate **17** in 89% yield. It was imagined that an enzyme-mediated hydrolysis of this *meso*-diacetate (**17**) would provide, enantioselectively, the monoacetate **19**. As noted above, Deardorff *et al.* had observed that the action of electric eel acetylcholinesterase (eeACE) on *meso*-diacetate **14** affords an excellent yield of alcohol **15** in >95% enantiomeric excess after one recrystallization.[40] This work was recently applied in our laboratory to the synthesis of PG $F_{2\alpha}$.[42]

Scheme 3



In the present effort, selective deacetylation of the diacetate **17** provided monoacetate *ent*-**19** in 95% yield (Scheme 3). To determine the enantioselectivity of the enzymatic hydrolysis, base-catalyzed deacetylation of **17** (K_2CO_3, methanol, THF) was used to provide the racemic monoacetate *rac*-**19** in 42% yield. Formation of the Mosher ester[43] (pyridine, (+)-MTPA-Cl, CH_2Cl_2, 0 °C) proceeded smoothly to provide a mixture of diastereomers, which could be clearly analyzed by 490 MHz ^{1}H NMR spectroscopy. Evidence for the presence of primarily one diastereomer was observed in the crude reaction mixture of the (+)-MTPA ester derived from enzymatically differentiated *ent*-**19**. Thus it was concluded at the time that *ent*-**19** had been formed in >95% enantiomeric excess (*vide infra*).

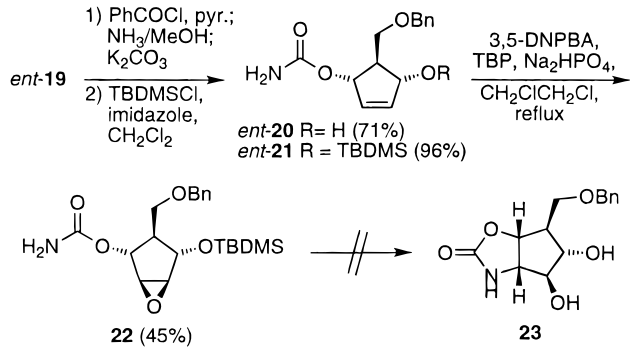
It had been anticipated that the enzymatic hydrolysis of diacetate **18** would proceed to afford the desired acetate **19**. In actual practice, however, enzymatically mediated deacylation had occurred in the opposite enantiotopic sense to that which was observed by Deardorff *et al.* with the parent diacetate **15**.[44] The absolute configuration of *ent*-**19** obtained through this route was established only upon its eventual conversion to (+)-allosamizoline (*ent*-**8**), which displayed an optical rotation opposite in sign to that observed for the naturally derived material (*vide infra*).

We note, however, that the reversal of selectivity in enzyme-mediated hydrolyses, upon substitution of the carbocyclic ring in the substrate, is not without precedent. The selectivity observed in the enzyme-mediated hydrolyses of cyclopentane diacetates has been demonstrated to bear a subtle dependence on the substitution pattern in the five-membered ring.[45−47] Thus, while it had not been known at this stage in the synthesis of allosamidin which antipode had in fact been secured, we started with what seemed, superficially, the simplest analogy. The structures drawn at this stage and in schemes thereafter, anticipate later rigorously adduced findings.

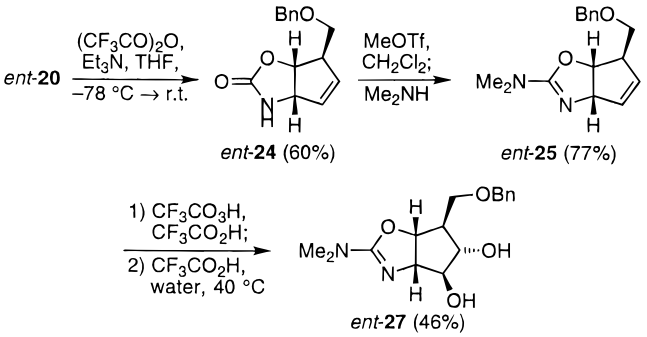
Acylation of monoacetate *ent*-**19** with phenyl chloroformate afforded a phenyl carbonate, which upon treatment with methanolic ammonia and subsequent deacetylation with added potassium carbonate provided carbamate *ent*-**20** in 71% yield (Scheme 4). The hydroxyl group was protected in the usual way with TBDMS-Cl, giving rise to silyl ether *ent*-**21** (96%). It had been anticipated that the epoxide derived from *ent*-**21** would provide a substrate appropriate for cyclization to **23**, but the olefin linkage proved to be remarkably resistant to epoxidation. Fortunately, oxidation with 3,5-dinitroperoxybenzoic acid[48] stabilized by 4,4′-thiobis(6-*tert*-butyl-3-methylphenol)[49]

(40) Deardorff, D. R.; Matthews, A. J.; McMeekin, D. S.; Craney, C. L. *Tetrahedron Lett.* **1986**, *27*, 1255.
(41) Madhavan, G. V.; Martin, J. C. *J. Org. Chem.* **1986**, *51*, *1287.*
(42) Danishefsky, S. J.; Cabal, M. P.; Chow, K. *J. Am. Chem. Soc.* **1989**, *111*, 3456.
(43) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. Dale, J. A.; Dull, J. A.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(44) Roberts and co-workers have assigned the opposite configuration to our product based on their work with porcine pancreatic lipase (see refs 71 and 72).
(45) Hultin, P. G.; Mueseler, F.-J.; Jones, J. B. *J. Org. Chem.* **1991**, *56*, 5375.
(46) Semlicka, J.; Craine, L. E.; Heeg, M.-J.; Oliver, J. P. *J. Org. Chem.* **1988**, *53*, 937.
(47) Arita, M.; Adachi, K.; Ito, Y.; Sawai, H.; Ohno, M. *J. Am. Chem. Soc.* **1983**, *105*, 4049.
(48) Rastetter, W. H.; Richard, T. J.; Lewis, M. D. *J. Org. Chem.* **1978**, *43*, 3163.
(49) Kishi, Y.; Aratani, M.; Tanino, H.; Fukuyama, T.; Goto, T.; Inoue, S.; Sugiura, S.; Kakoi, H. *J. Chem. Soc., Chem. Commun.* **1972**, 64.

Scheme 4



Scheme 5

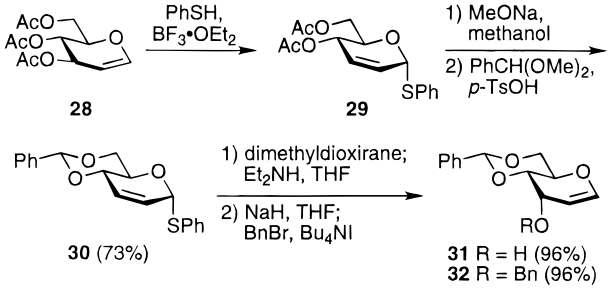


(tbp) in refluxing 1,2-dichloroethane provided a 45% yield of the desired epoxide **22**. However, all attempts to cyclize **22** to urethane **23** under basic conditions (NaH,[50] *t*-BuONa/THF,[51] or LHMDS) proved to be unsuccessful. Indeed, all of the products isolated from such reactions had lost their carbamate functionalities.

At this juncture, a synthesis of (±)-allosamizoline by Trost and Van Vranken[26a] appeared in the literature. The approach described by these authors, albeit in racemic form, was quite similar to the route which had been independently undertaken in this effort. Moreover, it began with the same starting material. In order to allow for a timely investigation of the coupling of the aglycon to a disaccharide, an intermediate in Trost's route was intercepted to allow us to complete the synthesis of the aglycon using the Stanford protocols. Treatment of a THF solution of carbamate *ent*-**20** with triethylamine/trifluoroacetic anhydride gave oxazolidinone *ent*-**24** in 60% yield (Scheme 5). Following the route published by Trost and Van Vranken, *ent*-**24** was then converted to the (dimethylamino)-oxazoline (*ent*-**25**). Epoxidation and subsequent hydration provided the corresponding α-epoxide (*ent*-**26**; 32%) and an allosamizoline derivative, now formulated as *ent*-**27** (46%).

Even as the issues associated with the synthesis of an appropriately protected aglycon derivative were being explored, development of a route to the pseudotrisaccharide region of allosamidin was progressing. The synthesis of 4,6-*O*-benzylidene-D-allal (**31**) from glucose had been reported.[52] For our purposes, however, we prepared compound **31** in a rather more concise way (Scheme 6).[53,54] Our route started with peracetylglucal **28**, which was converted by Ferrier rearrangement[55] to compound **29** following a published procedure.[56] The latter was deacetylated with methanolic sodium methoxide. The diol,

Scheme 6



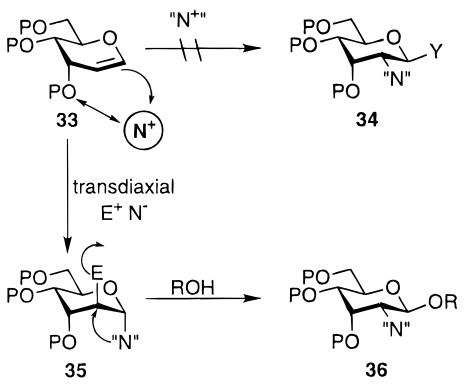
thereby obtained, was protected as its benzylidene acetal (**30**) upon treatment with benzaldehyde dimethylacetal. Attempted oxidation of sulfide **30** in the usual manner[57] with *m*-chloroperbenzoic acid (MCPBA) gave rise to a surprisingly complex mixture. However, treatment of **30** with 3,3-dimethyldioxirane[58] cleanly afforded the desired sulfoxide. The latter underwent [2,3]-sigmatropic rearrangement in the presence of diethylamine[59] to provide **31** in 96% yield. Finally, glycal **31** was *O*-benzylated to afford allal derivative **32**.

At this stage it was necessary to manipulate the glycal linkage in compound **32** such that the product would function as an azaglycosylation donor. While such capabilities were, in principle, known (nitrosyl chlorination,[60] azidonitration,[61] chloro amidation,[62] acyl nitrene addition,[63] iodophosphoramidation,[64] and dialkyl azodicarboxylate cycloaddition[65]), in the case at hand, we had to deal with a special stereochemical problem. Thus, to reach our goal structure containing All*N*Ac residues, we needed to activate the glycal in a manner which would serve to introduce the aza precursor to the α-face of **33** at C-2 (see Scheme 7). This face is clearly the more hindered as a consequence of the α-disposed ether function at C-3 in the allose series.

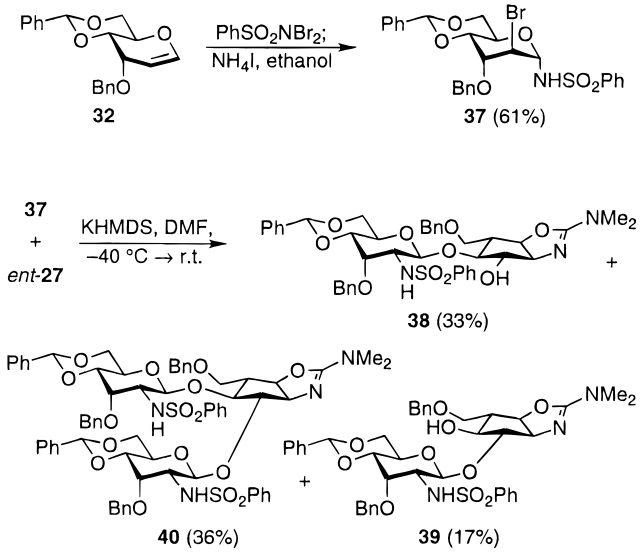
A variety of potential strategies were surveyed to address this challenge. These were summarized elsewhere.[66] Here, we focus on the one which was successfully followed. The logic involved taking advantage of a stereoelectronically (rather than steric hindrance) governed reaction. When the generalized reagent $E^+ N^-$ adds to the glycal **33** in a strictly trans-diaxial fashion (Scheme 7), the former electrophilic function emerges

(50) Roush, W. R.; Adam, M. A. *J. Org. Chem.* **1985**, *50*, 3752. Roush, W. R.; Brown, R. J.; DiMare, M. *J. Org. Chem.* **1983**, *48*, 5083.
(51) Minami, N.; Ko, S. S.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 1109.
(52) Lemieux, R. U.; Fraga, E.; Watanabe, K. A. *Can. J. Chem.* **1968**, *46*, 61. Sharma, M.; Brown, R. K. *Can. J. Chem.* **1966**, *44*, 2825.
(53) Wittman, M. D.; Halcomb, R. L.; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 1979.
(54) For recent approaches to glycals from carbohydrate precursors, see: Fernandez-Mayoralas, A.; Marra, A.; Trumtel, M.; Veyrières, A.; Sinay, P. *Tetrahedron Lett.* **1989**, *30*, 2537. Ireland, R. E.; Wilcox, C. S.; Thaisrivongs, S. *J. Org. Chem.* **1978**, *43*, 786. Eitelman, S. J.; Hall, R. H.; Jordaan, A. *J. Chem. Soc., Perkin Trans. 1* **1978**, 595.
(55) Ferrier, R. J.; Prasadi, N. *J. Chem. Soc. C* **1969**, 570.
(56) Vaverde, S.; Garcia-Ochoa, S.; Martin-Lomas, M. *J. Chem. Soc., Chem. Commun.* **1987**, 383.
(57) Kahne, D.; Walker, S.; Cheng, Y.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881.
(58) Murray, R. W.; Jeyaraman, R. J. *J. Org. Chem.* **1985**, *50*, 2847.
(59) (a) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147. (b) Tang, R.; Mislow, K. *J. Am. Chem. Soc.* **1970**, *92*, 2100.
(60) (a) Lemieux, R. U.; James, K.; Nagabhushan, T. L. *Can. J. Chem.* **1973**, *51*, 48. (b) Lemieux, R. U.; Ito, Y.; James, K.; Nagabhushan, T. L. *Can. J. Chem.* **1973**, *51*, 7. (c) Lemieux, R. U.; Nagabhushan, T. L. *Can. J. Chem.* **1968**, *46*, 413.
(61) (a) Bovin, V.; Zurabyan, S. É.; Khorlin, A. Y. *Carbohydr. Res.* **1981**, *98*, 25. (b) Lemieux, R. U.; Ratcliffe, R. M. *Can. J. Chem.* **1979**, *57*, 1244.
(62) Driguez, H.; Vermes, J.-P.; Lessard, J. *Can. J. Chem.* **1978**, *56*, 120.
(63) (a) Kozlowska-Gramsz, E.; Descotes, G. *Can. J. Chem.* **1982**, *60*, 558. (b) Kozlowska-Gramsz, E.; Descotes, G. *Tetrahedron Lett.* **1981**, *22*, 563.
(64) (a) Lafont D.; Descotes, G. *Carbohydr. Res.* **1988**, *175*, 35. (b) Lafont D.; Descotes, G. *Carbohydr. Res.* **1987**, *166*, 195.
(65) (a) Leblanc, Y.; Fitzsimmons, B. J. *Tetrahedron Lett.* **1989**, *30*, 2889. (b) Fitzsimmons, B. J.; Leblanc, Y.; Chan, N.; Rokach, J. *J. Am. Chem. Soc.* **1988**, *110*, 5229.
(66) Griffith, D. A. Ph.D. Dissertation, Yale University, New Haven, CT, 1993.

Scheme 7



Scheme 8



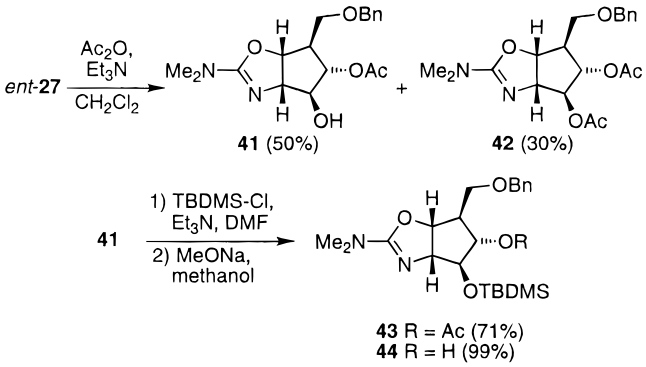
on the β-face at C-2 and the *N*-function (which serves as the *N*-acetyl precursor) enters the α-face at C-1 (**35**). *In the second stage, the E-function is expelled with suprafacial movement of the N-function to C-2 from the hindered* α*-face.*[67] In the best case scenario, the nucleophile to be glycosylated penetrates at C-1 to give the desired All*N*Ac β-glycoside **36**.

Several specific protocols discussed elsewhere were surveyed in an attempt to reduce this central paradigm to practice.[66] For the present purposes, we note that it was the pursuit of this allosamidin goal which led us to sulfonamidoglycosylation as a comprehensive method for converting glycals to 1β-glycosides of 2α-*N*-acetyl sugars, including the All*N*Ac system of interest here.

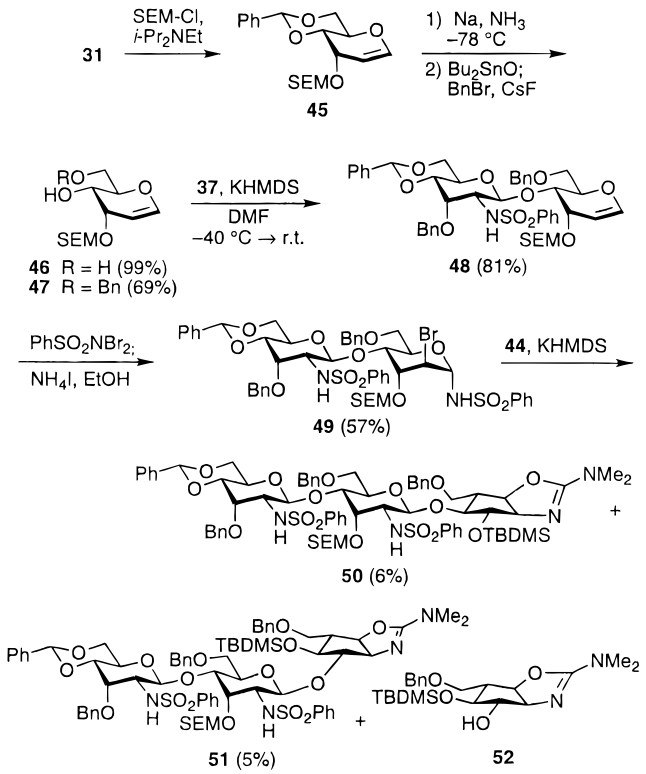
Returning to the allosamidin problem, allal derivative **32** was converted to its 2β-bromo-1α-phenylsulfonamido addition product **37**, as previously described.[36] This compound would serve as the donor for the azaglycosylation of an O-4-unprotected allal acceptor. However, with *ent*-**27** in hand, coupling to the unprotected diol was investigated (Scheme 8). We had hoped that the acceptor would react with acceptable selectivity at O-4. In practice the base-promoted coupling of bromosulfonamide **37** with this aglycon acceptor afforded 4-*O*-, 5-*O*-, and di-*O*-glycosylated products **38**, **39**, and **40** in 33, 17, and 36% yields, respectively. Therefore, prospects for positively controlled monoprotection of the diol moiety present in *ent*-**27** were examined.

To this end, diol *ent*-**27** was acetylated to provide the desired 4-*O*-protected aglycon **41** in 50% yield (Scheme 9), along with some diacetylated material (**42**, 30%). Silylation of alcohol **41** in DMF then afforded silyl ether **43** (71%), which was quantitatively deacetylated with methanolic sodium methoxide. The coupling of aglycon derivative **44** to an appropriate azaglycosylation donor could now be investigated.

Scheme 9



Scheme 10



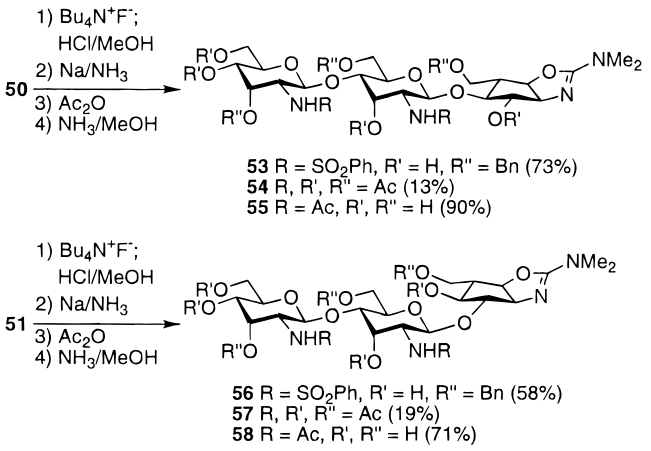
We focused our efforts on preparing a suitable disaccharide donor for coupling with **44** *en route* to reaching the pseudotrisaccharide goal series. Toward this end, we had need to identify the 4-hydroxyl group of an allal derivative as the acceptor site through differential protection of the axial hydroxyl group at C-3. Accordingly, glycal **31** upon treatment with [2-(trimethylsilyl)ethoxy]methyl chloride (SEM-Cl) gave compound **45** in quantitative yield (Scheme 10). Dissolving metal reduction of **45** afforded diol **46** (99%), which was selectively benzylated at C-6 by way of its stannylene derivative[68] to deliver alcohol **47** in 69% yield. The acceptor site had indeed been distinguished. In the event, base-promoted coupling of alcohol **47** with bromosulfonamide **37** occurred under standard conditions to provide disaccharide **48** in 81% yield (95% based on recovered **47**).

Since we had an efficient preparation of the disaccharide glycal at our disposal, it was now opportune to reiterate the

(67) Nicolau, K. C.; Ladduwahetty, T.; Randall, J. L.; Chucholowski, A. *J. Am. Chem. Soc.* **1986**, *108*, 2466.

(68) Nagashima, N.; Ohno, M. *Chem. Lett.* **1987**, 141.

Scheme 11



azaglycosylation reaction. Pursuant to this goal, glycal **48** was treated with *N*,*N*-dibromobenzenesulfonamide under the usual experimental conditions. A 57% yield of *trans*-bromosulfonamide **49** was obtained. Base-mediated coupling of **49** with aglycon derivative **44** was conducted in the usual manner. This reaction afforded only a very low yield (6%) of a 4-*O*-linked trisaccharide subsequently shown to be compound **50**. Also obtained was a 5% yield of the 3-*O*-linked trisaccharide **51** as well as recovered alcohol **44** (32%) and the 4-*O*-silylated aglycon derivative **52** (31%). The regiochemical assignments of the pseudotrisaccharides **50** and **51** were based upon 490 MHz ^{1}H NMR studies of acetylated derivatives **54** and **57** (*vide infra*). The principal message of these studies, however, was that an unanticipated migration of the silyl ether group in **44** had occurred under the strongly basic coupling conditions. This process resulted in an additional complication to an already difficult coupling.

Before dealing with the problem which this low-yielding coupling portended, we first relate the results of experiments which confidently corroborated the structural assignment of our formulated products. Fluoride-promoted deprotection of pseudotrisaccharide **50** readily cleaved the silyl ether, but these conditions failed to remove the SEM group. However, the benzylidene and SEM[69] acetal linkages were readily cleaved with 5% concentrated HCl in methanol (73%). Dissolving metal reduction of **53** provided the fully deprotected product, which was peracetylated (acetic anhydride, pyridine) to give nonaacetate **54** (13% overall). Finally, cleavage of the oxygen bound acetyl groups with methanolic ammonia afforded pseudotrisaccharide **55** (90%). While the ^{1}H NMR spectrum of compound **55** was similar to that of allosamidin (**1**), it was apparent, on closer inspection, that the spectra measured under identical conditions were not identical.

Similarly, deprotection of pseudotrisaccharide **51** proceeded in the same fashion as discussed in the sequence **50** → **55** (Scheme 11), leading, eventually, to peracetate **57** and deprotected **58**. Again, while the ^{1}H NMR spectrum of **58** was similar to that of allosamidin (**1**), there were small but clear cut differences. That trisaccharides **55** and **58** had the same molecular formula as allosamidin (**1**) was demonstrated by high-resolution mass spectrometry.

Of course, **58** and allosamidin were nonidentical, in any case, given the incorrect linkage of the aglycon and carbohydrate sectors. However, the noncongruence of what we now know to be **55** with allosamidin called for a basic structural reappraisal. One possibility was that there had been an incorrect assignment in the structure or *relative* stereochemistry of one or more of our synthetic intermediates. Alternatively, all such assignments were indeed correct, but the *absolute* configuration of our aglycon was opposite to that which was presumed by the superficial analogy of **15** and **17**, with respect to enzymatic deacetylation. We came to favor this latter interpretation.

This interpretation was confirmed. Thus, hydrogenolysis of diol *ent*-**27** provided (+)-allosamizoline (*ent*-**8**). The optical rotation observed ($[\alpha]_D$ +22.2° (*c* 0.7, water)) for *ent*-**8** was equal in magnitude but opposite in sign to the value reported ($[\alpha]^{22}_D$ −22.2° (*c* 0.5, water)) for authentic allosamizoline (**8**).[16] It is on this basis that we now confer the *ent* designation to compounds **19** and **24**−**27**.

In order to secure natural (−)-allosamizoline (**8**), the synthetic sequence outlined above would have to be conducted starting with compound **19** rather than with *ent*-**19**, as had been done. We were mindful that pig liver esterase mediated hydrolysis[70] of the parent diacetate **15** had been reported to provide the opposite enantiomer to that which had been observed with eeACE[40] and might therefore serve to produce the desired monoacetate **19**. Further complicating matters in retrospect is the fact that Cotterill *et al.*[71] had later examined the hydrolysis of diacetate **17** with porcine pancreatic lipase (PPL) and had determined by chemical correlation that the absolute configuration of the isolated monoacetate (ee > 95%) was opposite to that which was measured for the monoacetate obtained using eeACE. However, the optical rotation reported for the monoacetate from PPL deacetylation ($[\alpha]^{23}_D$ +63.2° (*c* 1.0, $CHCl_3$)) was equal in sign and magnitude to that which we had observed with eeACE. Unfortunately, the origin of this discrepancy remains unresolved,[72] although we are fully confident of our assignment since we did reach natural allosamidin (*vide infra*).

While it may have been possible to find an appropriate enzyme to produce **19**, an alternate solution was possible. It took advantage of the fact that a nearly enantiospecific, and high yielding, route to *ent*-**19** had already been developed. The idea was to so manipulate *ent*-**19** that we could enter a "product line" which would have been available from **19**, itself inaccessible when eeACE was used.

We proceeded as follows. Protection of alcohol *ent*-**19** with TBDMS-Cl gave rise to a silyl ether, which was then deacetylated with methanolic ammonia (Scheme 12). Alcohol **59**, thus produced, had the opposite absolute configuration relative to monoacetate *ent*-**19** and was obtained in quantitative yield. After installation of the carbamate in the usual way (82%), the silyl ether was cleaved with 2% aqueous HF in acetonitrile (94%). Carbamate **20** was subsequently converted to allosamizoline derivative **27** by the route used in the enantiomeric series. *Finally, hydrogenolysis of* ***27*** *provided (−)-allosamizoline (****8****), which was identical in all respects, including optical rotation, with material isolated from natural sources*.[16]

Benefiting from our hard-learned lessons in the *ent* aglycon series, the unsuitability of selective protection of diol **27** as the corresponding TBDMS ether was clear. This protection motif had been undermined by the silyl migration which had, in turn, further eroded the yield of the azaglycosylation of O-4 under basic glycosylation conditions (see Scheme 10).

Fortunately, the C-3 hydroxyl group of diol **27** could be selectively benzylated by way of stannylene methodology

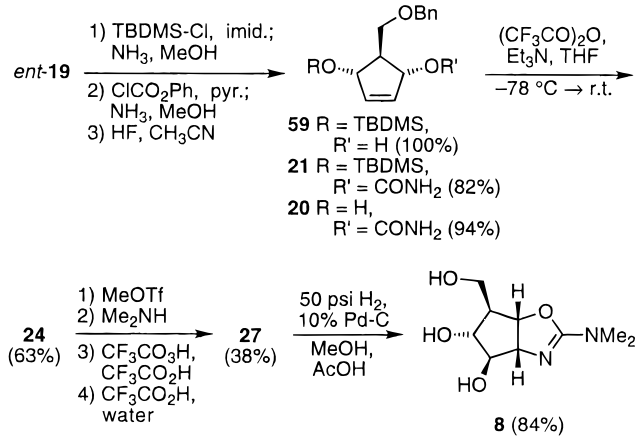
(69) Pinto, B. M.; Buiting, M. M. W.; Reimer, K. B. *J. Org. Chem.* **1990**, *55*, 2177.

(70) Laumen, K.; Reimerdes, E. H.; Schneider, M. *Tetrahedron Lett.* **1985**, *26*, 407. Laumen, K.; Schneider, M. *Tetrahedron Lett.* **1984**, *25*, 5875.

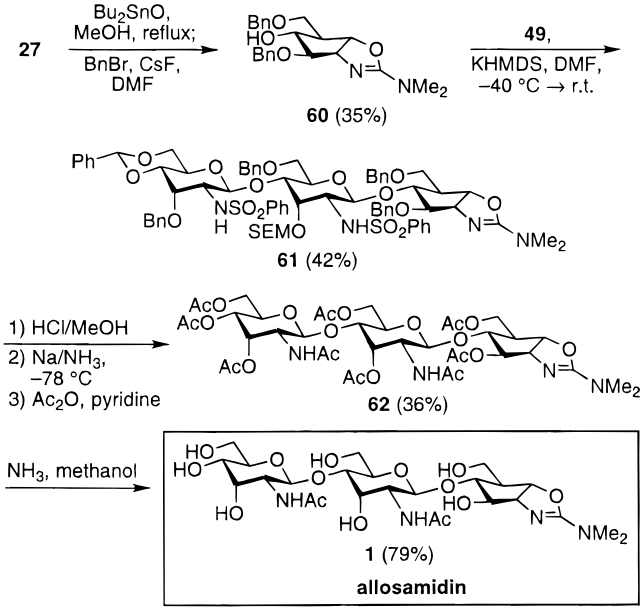
(71) Cotterill, I. C.; Cox, P. B.; Drake, A. F.; LeGrand, D. M.; Hutchinson, E. J.; Latouche, R.; Pettman, R. B.; Pryce, R. J.; Roberts, S. M.; Ryback, G.; Sik, V.; Williams, J. O. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3071.

(72) LeGrand, D.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1751.

Scheme 12



Scheme 13



(Scheme 13) to provide dibenzylated aglycon **60** in 35% yield (44% based on recovered **27**). Azaglycosylation of **60** with bromosulfonamide **49** under basic conditions provided the desired pseudotrisaccharide **61** in 42% yield (76% based on recovered **60**). Following our findings in the "allo" series, the SEM and benzylidene protecting groups were cleaved by treatment with 5% HCl in methanol. Dissolving metal reduction then deblocked the sulfonamides and benzyl ethers, and the fully deprotected product was peracetylated to provide allosamidin heptaacetate (**62**) in 36% yield from **61**. *Finally, cleavage of the acetyl esters with methanolic ammonia afforded allosamidin, identical in all respects with authentic material.*

Development of the SES Azaglycosylation Method

Preliminary studies of several compounds synthesized during this total synthesis of allosamidin were performed in collaboration with Dr. Chi-Huey Wong and Dr. David Dumas at the Scripps Research Institute. Synthetic allosamidin (**1**) showed potent chitinase inhibition, while neither natural (−)-(**8**) nor unnatural (+)-allosamizoline (*ent*-**8**) functioned as inhibitors.

Interestingly, Wong and Dumas had noted that azasugar **63** displays stronger chitinase inhibition than (−)-allosamizoline (**8**). They therefore postulated that a pseudodisaccharide or pseudotrisaccharide that included **63** might be a strong chitinase inhibitor; allodisaccharide **64**, allotrisaccharide **65**, and glucodisaccharide **66** were chosen as targets (Figure 2). Given the apparent sensitivity of various chitinases to modifications of the allosamidins, we embarked on the synthesis of analogs **64**−**66**. The synthesis of several other allosamidin analogs have recently been reported in the literature.[73−75]

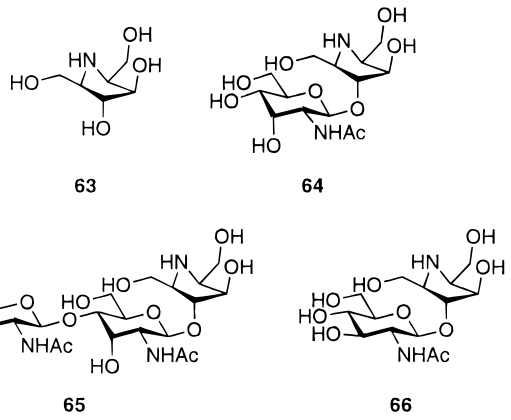
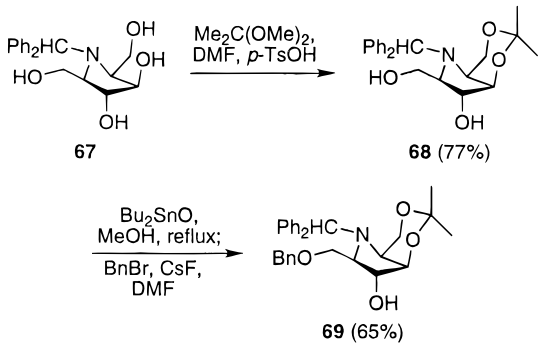


Figure 2. Structures of potential chitinase inhibitors.

Scheme 14



The syntheses of these analogs led us to explore an important new departure in the benzenesulfonamide-based azaglycosylation methodology. This expansion is described below.

Glucitol derivative **67**, prepared in a single step from commercially available 5-keto-D-fructose,[76] was kindly provided by Dumas and Wong. Initial studies concerned the selective protection of this derivative. It was hoped that acetonide formation would selectively provide the *cis*-acetonide **68**; molecular mechanics calculations indicated that the *trans*-isomer should be less stable by 5.7 kcal/mol.[77] Additionally, modeling studies suggested that ^{1}H NMR coupling constants would be diagnostic of the isomer formed. In the event, selective acetonide formation occurred smoothly with 2,2-dimethoxypropane to provide *cis*-acetonide **68** in 77% yield (Scheme 14). The observed ^{1}H NMR coupling constants were in good agreement with the values predicted for the *cis*-isomer. Moreover, long range *w*-coupling observed between H-3 and H-5 was consistent with the *cis* structure. Diol **68** was then selectively benzylated by way of the derived stannylene acetal to provide **69** in 65% yield (81% based on recovered **68**).

It was envisioned that sulfonamidoglycosylation methodology[36] would be employed to synthesize the azasugars **64**−**66**.

(73) (a) Corbett, D. F.; Dean, D. K.; Robinson, S. R. *Tetrahedron Lett.* **1993**, *34*, 1525. (b) Corbett, D. F.; Dean, D. K.; Robinson, S. R. *Tetrahedron Lett.* **1994**, *35*, 459.

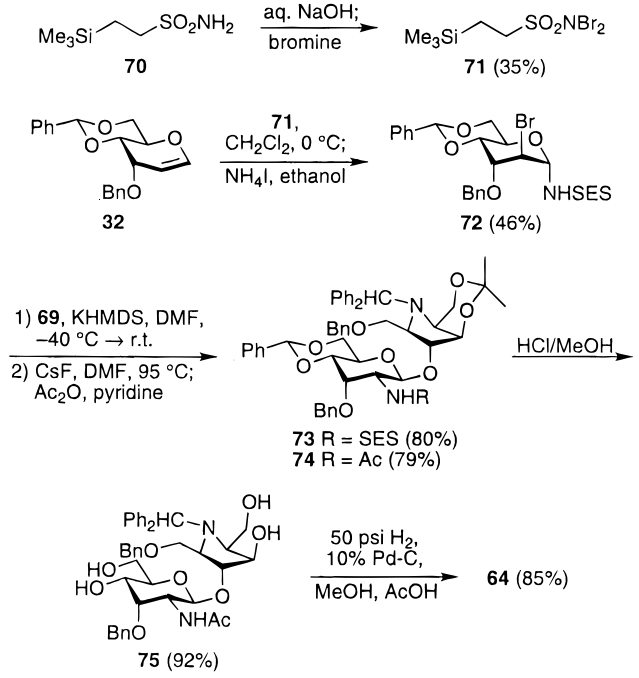
(74) Takahashi, S.; Inoue, H.; Kuzuhara, H. *J. Carbohydr. Chem.* **1995**, *14*, 273.

(75) Terayama, H.; Kuzuhara, H.; Takahashi, S.; Sakuda, S.; Yamada, Y. *Biosci., Biotechnol., Biochem.* **1993**, *57*, 2067.

(76) Reitz, A. B.; Baxter, E. W. *Tetrahedron Lett.* **1990**, *31*, 6777.

(77) Monte Carlo conformational searches using the MM3 force field as implemented in MacroModel were employed. Still, W. C. MacroModel version 3.5x, Columbia Unviversity, NY, 1992.

Scheme 15



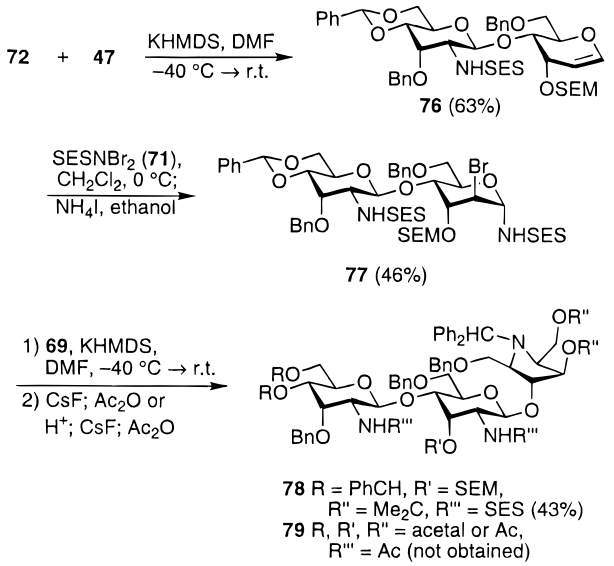
However, the intermediacy of a benzenesulfonyl moiety would necessitate deprotection by reductive desulfonylation. Such conditions could also deblock the secondary amine of the azasugar, thereby necessitating acetylation of the C-2 amine in the presence of the secondary amine. To avoid such complications, we developed the SES−sulfonamidoglycosylation method, which was subsequently used in our synthesis of the sialyl Lewis X antigen.[78] It was this methodology which was employed in the analog syntheses. The feasibility of early installation of the acetamide moiety in the allose-like sectors demonstrated the utility of the SES strategy.

The synthesis of allosyl analog **64** required the synthesis of a new *N*,*N*-dibromosulfonamide (**71**). In the event, bromination of $SESNH_2$ (**70**) in 4% aqueous sodium hydroxide gave a modest yield (35%) of *N*,*N*-dibromo-2-(trimethylsilyl)ethanesulfonamide ($SESNBr_2$, **71**) (Scheme 15). Subsequent reaction of **71** with allal derivative **32** afforded, after reduction of the remaining bromine−nitrogen bond with ammonium iodide, *trans*-bromosulfonamide **72** in 46% yield. Additional material was isolated as a mixture of *trans* and *cis* (1:1.8) isomers (26%).

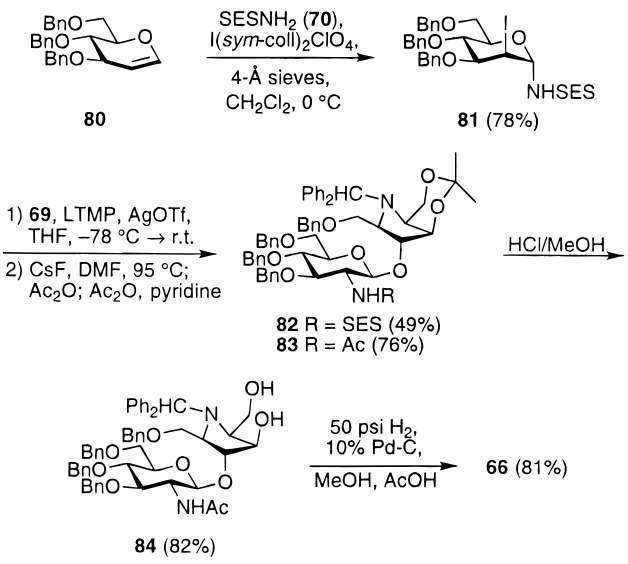
Glycosylation of azasugar **69** with **72** in the usual manner provided an 80% yield of disaccharide **73** (92% based on recovered **69**). Fluoride-promoted desulfonylation afforded an amine, which was acylated to yield **74** (79%). Next, the acetal and ketal moieties were cleaved with 5% concentrated HCl in methanol to give tetraol **75** (92%). Finally, hydrogenolysis of **75** provided the desired analog **64** in 85% yield.

The prospects for the synthesis of a trisaccharide using the SES methodology was examined. Thus, base-promoted glycosylation of glycal **47** with bromosulfonamide **72** (Scheme 16) gave disaccharide glycal **76** in 63% yield (76% based on recovered **47**). Bromosulfonamide **77**, isolated as a 6.5:1 mixture of α- and *β*-anomers from **76** in the usual fashion (46%),

Scheme 16



Scheme 17



was coupled with azasugar **69** to provide trisaccharide **78** in 43% yield (90% based on recovered **69**). Unfortunately, fluoride-promoted desulfonylation of **78** or the compound produced upon cleavage of the acetal and ketal moieties failed to provide diacetamido-containing material (**79**; R = acetal or Ac). Although the structures of the products formed after fluoride treatment are unknown, it was clear that both allose rings were not intact; only one anomeric carbon was observed by ^{13}C NMR spectroscopy.

Finally, the synthesis of the glucosyl-linked analog **66** was explored. Reaction of $SESNH_2$ (**70**) with tri-*O*-benzyl-D-glucal (**80**) and iodonium di-*sym*-collidine perchlorate provided a 78% yield of *trans*-iodosulfonamide **81** (Scheme 17). Silver-assisted glycosylation of azasugar **69** with *trans*-iodosulfonamide **81** provided a 49% yield of disaccharide **82** (83% based on recovered **69**). Desulfonylation was conducted in the presence of cesium fluoride in DMF at 95 °C. However, it was necessary to add an equivalent of acetic anhydride during the deblocking procedure to drive the reaction to completion. Acetylation of the remaining free amine provided a good yield of the acetamide (**83**, 76%). Finally, hydrogenolysis of diol **84**, obtained in 82% yield after cleavage of the acetonide present in **83**, afforded the desired disaccharide **66** in 81% yield.

(78) (a) Danishefsky, S. J.; Gervay, J.; Peterson, J. M.; McDonald, F. E.; Koseki, K.; Griffith, D. A.; Oriyama, T.; Marsden, S. P. *J. Am. Chem. Soc*. **1995**, *117*, 1940. (b) Danishefsky, S. J.; Koseki, K.; Griffith, D. A.; Gervay, J.; Peterson, J. M.; McDonald, F. E.; Oriyama, T. *J. Am. Chem. Soc*. **1992**, *114*, 8331. (c) Danishefsky, S. J.; Gervay, J.; Peterson, J. M.; McDonald, F. E.; Koseki, K.; Oriyama, T.; Griffith, D. A. *J. Am. Chem. Soc*. **1992**, *114*, 8329.

Summary

In summary, a total synthesis of allosamidin (**1**) has been achieved by way of the sulfonamidoglycosylation method. This method subsequently had a major impact on our glycal-based methodology for assembling complex oligosaccharides. Here, it was the key to assembling the novel arrangement of All*N*Ac residues and in coupling them to aglycons. From these studies we went on to apply the method to the synthesis of adhesion molecules, blood group determinants, tumor antigens, and glycopeptides. Thus, the quest for a concise solution to the challenges posed by a total synthesis of allosamidin has had a broad impact in the much larger subject of glycoconjugate constructs.[36−39] Expansion of azaglycosylation methodology to embrace SES sulfonoamidation has expanded our capability, because it enables us to deal effectively with a broader range of nitrogen-containing acceptors. It also allows for a single-step fluoride-induced unveiling of alcohols and amines initially bearing silyl ether or β-silylethylsulfonamide (SES) protecting groups.

Moreover, in the course of this journey, we encountered a surprising reversal of selectivity in the enzymatically mediated hydrolysis of *meso*-diacetate **17** during the synthesis of allosamizoline (**8**). As a result, two diastereomers of allosamidin were prepared (**55** and **58**). The synthetic strategy developed in this effort was thus applicable not only to the synthesis of allosamidin but also to analogs, whose biological profiles will be disclosed shortly. Moreover, it raises an important cautionary note in extrapolating the enantiotopic sense of enzymatic processes based upon intuitively reasonable but still superficial analogies.

Experimental Section

(1α,2*β*,3α)-2-[(Benzyloxy)methyl]-4-cyclopentene-1,3-diol Diacetate (17). To a 0 °C solution of 2-[(benzyloxy)methyl]-4-cyclopentene-1,3-diol (9.60 g, 43.6 mmol) in dichloromethane (150 mL) were added triethylamine (18.2 mL, 131 mmol), DMAP (0.53 g, 4.36 mmol), and acetic anhydride (10.3 mL, 109 mmol). The mixture was stirred 1 h and then extracted from water (200 mL) with diethyl ether (3 × 100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated, and the residue was chromatographed (silica gel, 20% ethyl acetate in hexanes) to provide the diacetate (**17**; 11.9 g, 89%) as a slightly yellowed oil: IR (neat) υ_{max} 3060, 3020, 2930, 2880, 1735, 1365, 1230, 1105, 1025 cm^{-1}; ^{1}H NMR (490 MHz, $CDCl_3$) δ 7.35−7.24 (m, 5 H, Ar*H*), 6.02 (d, J = 0.9 Hz, 2 H, olefinic), 5.53 (dd, J = 4.0, 0.8 Hz, 2 H, C*H*OAc), 4.54 (s, 2 H, OCH_2Ph), 3.71 (d, J = 5.1 Hz, 2 H, CH_2OBn), 2.40−2.35 (m, 1 H, H-2), 2.04 (s, 6 H, COCH_3); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.7, 138.2, 134.2, 128.3, 127.5, 79.1, 73.2, 69.0, 51.4, 21.1; MS (CI) *m/e* (rel intensity) 305 (M + H$^+$, 2), 246 (20), 245 (93), 155 (25), 139 (26), 137 (100), 95 (20), 91 (68). Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 67.34; H, 6.90.

[1(*S*)-(1α,4α,5*β*)]-4-(Acetyloxy)-5-[(benzyloxy)methyl]-2-cyclopenten-1-ol (*ent*-19). Diacetate **17** (20.5 g, 67.4 mmol) was rapidly stirred, while care was taken to prevent a strong vortex, with a solution of glass-distilled water (390 mL), 1.45 M NaH_2PO_4 buffer (pH 6.9, 260 mL), sodium azide (66 mg), and electric eel acetylcholinesterase (Sigma; 10 000 units, 30 mg). After 6 days, the mixture was extracted with 1:1 ethyl acetate/diethyl ether (3 × 300 mL). The combined organic layers were dried (Na_2SO_4) and concentrated, and the residue was chromatographed (silica gel, 33 → 50% ethyl acetate in hexanes) to afford the desired monoacetate *ent*-**19** (16.8 g, 95%) as a colorless liquid. A portion of *ent*-**19** was bulb-to-bulb (170 °C, 0.05 Torr) distilled: $[\alpha]_D$ +61.8° (*c* 1.1, $CHCl_3$); IR (neat) υ_{max} 3420, 3060, 3030, 2860, 1730, 1455, 1365, 1245, 1100, 1025 cm^{-1}; ^{1}H NMR (490 MHz, $CDCl_3$) δ 6.01 (dt, J = 5.7, 1.6 Hz, 1 H, H-3), 5.86 (ddd, J = 5.7, 1.9, 1.4 Hz, 1 H, H-2), 5.38 (ddt, J = 5.0, 2.2, 1.1 Hz, 1 H, H-4), 4.58 (ddt, J = 4.6, 2.0, 1.0 Hz, 1 H, H-1), 4.54 (AB_q, J = 12.2 Hz, υ = 6.9 Hz, 2 H, OCH_2Ph), 3.77 (dd, J = 9.2, 5.1 Hz, 1 H, CH*H*OBn), 3.61 (dd, J = 9.2, 7.4 Hz, 1 H, CH*H*OBn), 2.35 (br s, 1 H, O*H*), 2.28 (dq, J = 7.3, 4.9 Hz, 1 H, H-5), 2.03 (s, 3 H, COCH_3); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.6, 138.3, 137.5, 131.7, 128.3, 127.5, 79.0, 77.8, 73.3, 69.8, 55.4, 20.9; MS (CI) *m/e* (rel intensity) 263 (M + H$^+$, 50), 246 (31), 245 (82), 204 (21), 203 (79), 185 (50), 181 (20), 157 (22), 155 (43), 139 (31), 137 (81), 119 (55), 113 (24), 111 (32), 107 (30), 96 (57), 95 (76), 92 (60), 91 (100). Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68.40; H, 6.68.

***S*-Phenyl 4,6-*O*-Benzylidene-2,3-dideoxy-1-thio-α-D-*erythro*-hex-2-enopyranoside (30).** A methanolic (10 mL) solution of thioglycoside **29** (0.886 g, 2.75 mmol) was deacetylated for 1 h with 25% sodium methoxide (60 μL, 0.28 mmol). The reaction was concentrated under reduced pressure and then concentrated from added benzene (2 × 25 mL) to remove any methanol still present. A DMF solution (5 mL) of the residue was treated with benzaldehyde dimethylacetal (1.2 mL, 8.2 mmol) and *p*-toluenesulfonic acid (104 mg, 0.55 mmol). After 2 h, the reaction was heated to 30 °C under reduced pressure (10 Torr) for an additional 7 h and then concentrated under high vacuum. The greenish solid thus produced was extracted from saturated aqueous $NaHCO_3$ (75 mL) with diethyl ether (2 × 100 mL), the combined organic layers were dried ($MgSO_4$) and concentrated, and the residue was crystallized from ethyl acetate/hexanes to provide the benzylidene acetal **30** (0.572 g, 64%) as colorless needles. The mother liquor was chromatographed (silica gel, 10 → 15% ethyl acetate in hexanes) to provide additional acetal as an off-white solid (77 mg, 9%). For **30**: mp 122.5−123.5 °C; $[\alpha]_D$ +413° (*c* 1.2, $CHCl_3$); IR (KBr) υ_{max} 3050, 2990, 2940, 2900, 2880, 1580, 1480, 1385, 1310, 1135, 1110, 1085, 1020, 1005 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.57−7.26 (m, 10 H, Ar*H*), 6.12 (d, J = 10.1 Hz, 1 H, H-3), 5.96 (dt, J = 10.1, 2.5 Hz, 1 H, H-2), 5.81 (q, J = 2.2 Hz, 1 H, H-1), 5.62 (s, 1 H, O_2C*H*Ph), 4.35 (dd, J = 10.3, 4.7 Hz, 1 H, H-6$_e$), 4.29 (dq, J = 8.7, 2.0 Hz, 1 H, H-4), 4.20 (td, J = 9.2, 4.6 Hz, 1 H, H-5), 3.86 (t, J = 9.9 Hz, 1 H, H-6$_a$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 137.3, 135.2, 131.4, 129.1, 128.9, 128.3, 127.4, 127.1, 126.2, 102.1, 84.5, 75.0, 69.2, 64.3; MS (EI) *m/e* (rel intensity) 326 (M$^+$, 27), 217 (80), 171 (100), 149 (20), 143 (62), 111 (40), 91 (28), 83 (90). Anal. Calcd for $C_{19}H_{18}O_3S$: C, 69.91; H, 5.56; S, 9.82. Found: C, 69.82; H, 5.58; S, 10.01.

1,5-Anhydro-4,6-*O*-benzylidene-2-deoxy-D-*ribo*-hex-1-enopyranose (31). A solution of 3,3-dimethyldioxirane in acetone (0.04 M, ∼1 equiv) was added to a −78 °C dichloromethane solution (50 mL) of thioglucoside **30** (1.24 g, 3.80 mmol) until the sulfide (**30**) was consumed as indicated by TLC. The suspension thus produced was concentrated under reduced pressure to a colorless solid, dissolved in THF (25 mL), and treated with diethylamine (1.6 mL, 15 mmol). The reaction was stirred overnight and then extracted from brine (30 mL) with dichloromethane (2 × 100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated, and the residue was chromatographed (silica gel, 50 → 66% diethyl ether in hexanes) to provide the desired allal derivative **31** (0.853 g, 96%) as a colorless solid (mp 82.5−83.5 °C). The product was recrystallized (diethyl ether/hexanes) to provide colorless needles of **31** (0.77 g, 86%): mp 84.5−85.5 °C; $[\alpha]_D$ +206° (*c* 1.7, $CHCl_3$); IR (KBr) υ_{max} 3150, 3060, 2980, 2930, 2860, 1635, 1455, 1405, 1380, 1245, 1225, 1145, 1105, 1090, 1035 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.55−7.37 (m, 10 H, Ar*H*), 6.47 (d, J = 6.1 Hz, 1 H, H-1), 5.68 (s, 1 H, O_2C*H*Ph), 5.04 (t, J = 6.0 Hz, 1 H, H-2), 4.49 (dd, J = 10.5, 5.3 Hz, 1 H, H-6$_e$), 4.32−4.27 (m, 1 H, H-3), 4.23 (td, J = 10.2, 5.3 Hz, 1 H, H-5), 3.87 (dd, J = 10.3, 3.1 Hz, 1 H, H-4), 3.84 (t, J = 10.4 Hz, 1 H, H-6$_a$), 2.49 (d, J = 1.8 Hz, 1 H, O*H*); ^{13}C NMR (63 MHz, $CDCl_3$) δ 146.2, 137.1, 129.2, 128.3, 126.2, 101.8, 101.0, 78.1, 68.5, 63.9, 60.1.

1,5-Anhydro-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-D-*ribo*-hex-1-enopyranose (32). A THF solution (15 mL) of 4,6-*O*-benzylidene-D-allal (**31**; 3.01 g, 12.8 mmol) was added dropwise to a 0 °C suspension of sodium hydride (60% dispersion in oil; 0.62 g, 15.5 mmol) in THF (25 mL). The reaction was stirred at room temperature for 30 min, cooled to 0 °C, and then tetrabutylammonium iodide (0.52 g, 1.4 mmol) and benzyl bromide (2.0 mL, 17 mmol) were added. The mixture was stirred for 14 h at room temperature and extracted from 1:1 brine/water with diethyl ether (2 × 75 mL). The combined organic layers were dried ($MgSO_4$) and concentrated, and the orange solid was chromatographed (50 → 75% dichloromethane in hexanes) to provide the protected glycal **32** (4.01 g, 96%) as an off-white solid. A portion

was recrystallized (diethyl ether/hexanes) to provide colorless needles of **32**: mp 103−103.5 °C; $[\alpha]_D$ +163° (*c* 1.0, $CHCl_3$); IR (KBr) υ_{max} 3050, 3020, 2900, 2860, 1625, 1450, 1400, 1385, 1240, 1225, 1145, 1115, 1090, 1060, 1040, 1010 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.61−7.28 (m, 10 H, Ar*H*), 6.43 (d, J = 6.1 Hz, 1 H, H-1), 5.63 (s, 1 H, O_2CHPh), 4.98 (t, J = 6.0 Hz, 1 H, H-2), 4.96 (d, J = 12.0 Hz, 1 H, OCH*H*Ph), 4.72 (d, J = 12.0 Hz, 1 H, OCH*H*Ph), 4.51 (dd, J = 10.3, 5.3 Hz, 1 H, H-6_e), 4.38 (td, J = 10.1, 5.3 Hz, 1 H, H-5), 4.09 (dd, J = 5.9, 3.5 Hz, 1 H, H-3), 3.99 (dd, J = 10.2, 3.6 Hz, 1 H, H-4), 3.87 (t, J = 10.2 Hz, 1 H, H-6_a); ^{13}C NMR (63 MHz, $CDCl_3$) δ 145.6, 138.9, 137.5, 129.1, 128.3, 127.7, 127.4, 126.2, 102.0, 100.2, 79.5, 72.9, 68.8, 67.0, 64.5; MS (EI) *m/e* (rel intensity) 218 (54), 187 (59), 127 (15), 105 (18), 97 (43), 91 (100), 81 (16); HRMS (CI) calcd for $C_{20}H_{21}O_4$ (M + H^+) 325.1440, found 325.1432. Anal. Calcd for $C_{20}H_{20}O_4$: C, 74.06; H, 6.21. Found: C, 74.08; H, 6.34.

1,5-Anhydro-4,6-*O*-benzylidene-2-deoxy-3-*O*-[[2-(trimethylsilyl)-ethoxy]methyl]-D-*ribo*-hex-1-enopyranose (45). To a solution of 4,6-*O*-benzylidene-D-allal (**31**; 5.00 g, 21.3 mmol) in dichloromethane (20 mL) at 0 °C were added *N*,*N*-diisopropylethylamine (14.8 mL, 85 mmol) and (2-(trimethylsilyl)ethoxy)methyl chloride (7.5 mL, 43 mmol). The mixture was stirred for 5 h at room temperature, then diluted with diethyl ether (250 mL), and washed with water (2 × 50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$) and concentrated, and the residue was chromatographed (5 → 10% ethyl acetate in hexanes) to afford allal derivative **45** (7.75 g, 100%) as a colorless oil. A small portion of **45** was bulb-to-bulb distilled (190 °C, 0.06 Torr) for analysis: $[\alpha]_D$ +88.3° (*c* 1.0, $CHCl_3$); IR (neat) υ_{max} 3060, 3030, 2950, 2890, 1635, 1380, 1245, 1140, 1115, 1090, 1025 cm^{-1}; ^1H NMR (63 MHz, $CDCl_3$) δ 7.54−7.48 (m, 2 H, Ar*H*), 7.40−7.33 (m, 3 H, Ar*H*), 6.44 (d, J = 6.2 Hz, 1 H, H-1), 5.60 (s, 1 H, O_2CHPh), 4.99 (t, J = 6.0 Hz, 1 H, H-2), 4.82 (d, J = 6.9 Hz, 1 H, OCH*H*OCH_2CH_2Si), 4.49 (d, J = 6.9 Hz, 1 H, OCH*H*OCH_2CH_2Si), 4.47 (dd, J = 10.4, 5.3 Hz, 1 H, H-6_e), 4.31 (dd, J = 6.1, 3.6 Hz, 1 H, H-3), 4.25 (td, J = 10.3, 5.3 Hz, 1 H, H-5), 3.94 (dd, J = 10.4, 3.7 Hz, 1 H, H-4), 3.83 (t, J = 10.0 Hz, 1 H, H-6_a), 3.78 (td, J = 9.8, 7.1 Hz, 1 H, OCH*H*CH_2Si), 3.59 (td, J = 9.8, 7.0 Hz, 1 H, OCH*H*CH_2Si), 1.02−0.90 (m, 2 H, OCH_2CH_2Si), 0.02 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 145.7, 137.4, 128.9, 128.2, 126.1, 101.7, 100.2, 94.4, 78.6, 68.8, 65.1, 64.4, 64.0, 18.1, −1.4; MS (CI) *m/e* (rel intensity) 365 (M + H^+, 0.4), 291 (14), 245 (16), 218 (26), 217 (100), 201 (34), 179 (12), 171 (59), 149 (10), 143 (16), 111 (19), 107 (15), 103 (24), 101 (22), 91 (20), 81 (10). Anal. Calcd for $C_{19}H_{28}O_5Si$: C, 62.61; H, 7.74. Found: C, 62.39; H, 7.51.

1,5-Anhydro-2-deoxy-3-*O*-[[2-(trimethylsilyl)ethoxy]methyl]-D-*ribo*-hex-1-enopyranose (46) and 1,5-Anhydro-6-*O*-benzyl-2-deoxy-3-*O*-[[2-(trimethylsilyl)ethoxy]methyl]-D-*ribo*-hex-1-enopyranose (47). To a −78 °C solution of glycal **45** (1.28 g, 3.51 mmol) in THF (130 mL) and ammonia (370 mL) were added small pieces of sodium until a deep blue color was maintained for 1 min. The mixture was then quenched with solid NH_4Cl and concentrated with a stream of nitrogen, and the residue was extracted from 1:4 water/brine (250 mL) with chloroform (3 × 150 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to provide diol **46** as an oil (0.963 g, 99%), which was pure enough for the subsequent step.

A methanolic (40 mL) suspension of **46** (0.963 g, 3.48 mmol) and dibutyltin oxide (0.87 g, 3.5 mmol) were refluxed until homogeneous (1 h). The solution was concentrated under reduced pressure and then concentrated from benzene (3 × 50 mL) to remove any methanol still present. The stannylene acetal thus produced was rapidly stirred for 24 h with benzyl bromide (0.62 mL, 5.2 mmol) and dry cesium fluoride (0.84 g, 5.5 mmol) in DMF (20 mL). The mixture was extracted from water (250 mL) with ethyl acetate (2 × 200 mL), the combined organic layers were dried (Na_2SO_4) and concentrated, and the residue was chromatographed (silica gel, 2% Et_3N, 5 → 10 → 33 → 50% ethyl acetate in toluene) to provide the desired diprotected glycal **47** (887 mg, 69%) as a colorless oil, followed by diol **46** (200 mg, 20%) as a yellow oil. For **46**: The oil was bulb-to-bulb distilled to provide a colorless oil of **46**: $[\alpha]_D$ +228° (*c* 1.1, $CHCl_3$); IR (neat) υ_{max} 3420, 2950, 2920, 2890, 1645, 1250, 1105, 1030 cm^{-1}; ^1H NMR (63 MHz, $CDCl_3$) δ 6.45 (d, J = 5.9 Hz, 1 H, H-1), 4.93 (t, J = 5.8 Hz, 1 H, H-2), 4.80 (s, 2 H, $OCH_2OCH_2CH_2Si$), 4.06−4.01 (m, 1 H, H-3), 4.01−3.81 (m, 4 H, H-4, H-5, H-6, and H-6), 3.80−3.56 (m, 2 H, OCH_2CH_2Si), 3.55−3.49 (m, 1 H, C-6 O*H*), 3.42 (br s, 1 H, C-4 O*H*), 0.99−0.90 (m, 2 H, OCH_2CH_2Si), 0.02 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 147.0, 99.5, 94.8, 70.5, 67.7, 66.3, 63.0, 18.5, −1.0; MS (CI) *m/e* (rel intensity) 277 (M + H^+, 0.5), 201 (51), 185 (21), 157 (40), 145 (23), 129 (100), 117 (19), 111 (47), 103 (38), 101 (33), 91 (16), 85 (45), 83 (21), 81 (20). Anal. Calcd for $C_{12}H_{24}O_5Si$: C, 52.14; H, 8.75. Found: C, 52.52; H, 9.00. For **47**: $[\alpha]_D$ +190° (*c* 1.0, $CHCl_3$); IR (neat) υ_{max} 3520, 2950, 2890, 1645, 1255, 1110, 1080, 1030 cm^{-1}; ^1H NMR (490 MHz, $CDCl_3$) δ 7.40−7.25 (m, 5 H, Ar*H*), 6.49 (d, J = 6.0 Hz, 1 H, H-1), 4.92 (t, J = 5.8 Hz, 1 H, H-2), 4.81 (AB_q, J = 6.8 Hz, υ = 12.6 Hz, 2 H, $OCH_2OCH_2CH_2Si$), 4.63 (s, 2 H, OCH_2Ph), 4.06 (dd, J = 5.4, 4.2 Hz, 1 H, H-3), 3.97 (ddd, J = 10.6, 5.4, 2.2 Hz, 1 H, H-5), 3.89 (dd, J = 10.8, 2.2 Hz, 1 H, H-6), 3.87−3.83 (br m, H-4), 3.79 (dd, J = 10.8, 5.5 Hz, 1 H, H-6), 3.73−3.61 (m, 2 H, OCH_2CH_2Si), 3.22 (d, J = 8.9 Hz, 1 H, O*H*), 0.96 (t, J = 8.4 Hz, 1 H, OCH_2CH_2Si), 0.03 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 146.6, 138.1, 128.2, 127.6, 127.5, 98.6, 94.1, 74.6, 73.5, 69.7, 69.3, 66.5, 65.6, 18.0, −1.5; MS (CI) *m/e* (rel intensity) 219 (40), 201 (31), 173 (75), 155 (98), 141 (26), 129 (25), 119 (33), 107 (72), 105 (23), 103 (37), 101 (41), 91 (100). Anal. Calcd for $C_{19}H_{30}O_5Si$: C, 62.26; H, 8.25. Found: C, 62.45; H, 8.54.

***O*-[2-Benzenesulfonamido-3-*O*-benzyl-4,6-O-benzylidene-2-deoxy-D-allopyranosyl]-*β*-(1→4)-1,5-anhydro-6-*O*-benzyl-2-deoxy-3-*O*-[[2-(trimethylsilyl)ethoxy]methyl]-D-*ribo*-hex-1-enopyranose (48).** Potassium hexamethyldisilazide (0.5 M in toluene, 4.09 mmol) was added dropwise to a −40 °C stirred solution of *trans*-bromosulfonamide **37**[37] (1.09 g, 1.95 mmol) and glycal **47** (857 mg, 2.34 mmol) in DMF (15 mL). The reaction mixture was stirred for 30 min at −40 °C and then allowed to slowly warm to room temperature. After 17 h, the reaction was poured into 5:1 water/saturated aqueous NH_4Cl (300 mL) and then extracted with diethyl ether (4 × 150 mL). The combined organic layers were dried ($MgSO_4$) and concentrated, and the residue was chromatographed (silica gel, 5 → 10% ethyl acetate in toluene) to provide **48** (1.33 g, 81%) followed by recovered alcohol **47** (250 mg, 29%). For **48**: colorless foam; $[\alpha]_D$ +26.4° (*c* 1.0, CH_2Cl_2); IR (KBr) υ_{max} 3340, 3060, 3030, 2940, 2880, 1645, 1450, 1340, 1160, 1095, 1030 cm^{-1}; ^1H NMR (490 MHz, $CDCl_3$) δ 7.75−7.70 (m, 2 H, $SO_2C(CHCH)_2CH$), 7.55−7.50 (m, 1 H, $SO_2C(CHCH)_2CH$), 7.48−7.19 (m, 17 H, Ar*H*), 6.37 (d, J = 5.9 Hz, 1 H, H-1), 5.49 (s, 1 H, O_2CHPh), 5.09 (d, J = 8.4 Hz, 1 H, N*H*), 4.97 (d, J = 11.2 Hz, 1 H, OCH*H*Ph), 4.84 (d, J = 6.7 Hz, 1 H, OCH*H*OCH_2CH_2Si), 4.82 (t, J = 5.9 Hz, 1 H, H-2), 4.72 (d, J = 8.3 Hz, 1 H, H-1′), 4.68 (d, J = 6.7 Hz, 1 H, OCH*H*OCH_2CH_2Si), 4.58 (d, J = 12.0 Hz, 1 H, OCH*H*Ph), 4.46 (d, J = 11.2 Hz, 1 H, OCH*H*Ph), 4.44 (d, J = 12.0 Hz, 1 H, OCH*H*Ph), 4.33 (dd, J = 10.4, 5.2 Hz, 1 H, H-6_e′), 4.11 (dd, J = 6.0, 3.6 Hz, 1 H, H-3), 4.09 (t, J = 2.6 Hz, 1 H, H-3′), 4.02 (td, J = 9.9, 5.1 Hz, 1 H, H-5′), 3.91 (dd, J = 10.9, 3.6 Hz, 1 H, H-4), 3.78 (td, J = 10.0, 6.5 Hz, 1 H, OCH*H*CH_2Si), 3.74 (dt, J = 10.9, 2.4 Hz, 1 H, H-5), 3.72 (t, J = 10.3 Hz, 1 H, H-6_a′), 3.67 (dd, J = 9.5, 2.2 Hz, 1 H, H-4′), 3.54 (td, J = 9.9, 6.4 Hz, 1 H, OCH*H*CH_2Si), 3.46 (td, J = 8.6, 3.1 Hz, 1 H, H-2′), 3.41 (dd, J = 11.1, 2.1 Hz, 1 H, H-6), 3.34 (dd, J = 11.1, 2.9 Hz, 1 H, H-6), 1.02−0.91 (m, 2 H, OCH_2CH_2Si), 0.06 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 146.0, 141.0, 137.9, 137.6, 137.1, 132.4, 129.1, 128.8, 128.5, 128.4, 128.2, 128.0, 127.9, 127.8, 126.9, 126.0, 102.1, 100.7, 99.7, 94.7, 80.0, 76.4, 75.8, 74.9, 73.5, 72.2, 69.0, 68.0, 67.7, 64.9, 63.4, 57.2, 18.1, −1.4; MS (FAB) *m/e* (rel intensity) 868 (M + Na^+, 13), 698 (11), 373 (183), 372 (77), 266 (26), 246 (17), 245 (100), 226 (24); HRMS (FAB) calcd for $C_{45}H_{55}NNaO_{11}SSi$ (M + Na^+) 868.3165, found 868.3212. Anal. Calcd for $C_{45}H_{55}NO_{11}SSi$: C, 63.88; H, 6.55; N, 1.65; S, 3.79. Found: C, 63.93; H, 6.74; N, 1.66; S, 4.06.

***O*-[2-Benzenesulfonamido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-D-allopyranosyl]-*β*-(1→4)-6-*O*-benzyl-2-bromo-2-deoxy-3-*O*-[[2-(trimethylsilyl)ethoxy]methyl]-α-D-altropyranosyl Benzenesulfonamide (49).** A solution of glycal **48** (980 mg, 1.16 mmol) in dichloromethane (1.5 mL) was added dropwise to a stirred suspension of *N*,*N*-dibromobenzenesulfonamide (372 mg, 1.18 mmol) in dichloromethane (0.7 mL) at 0 °C. Ethanol (6 mL) and NH_4I (140 mg, 1.22 mmol) were added to the reaction after 1 h, and the resultant mixture was stirred an additional 1.5 h at room temperature, diluted with diethyl ether (250 mL), and reduced with saturated aqueous $Na_2S_2O_3$ (50 mL). The organic layer was dried ($MgSO_4$) and concentrated, and the residue

was chromatographed (silica gel, 10% ethyl acetate in toluene) to afford *trans*-sulfonamide **49** (708 mg, 57%), followed by fractions which contained a 2:1 α/β mixture of sulfonamides (144 mg, 12%). For **49**: colorless foam; IR (KBr) υ_{max} 3330, 3060, 3030, 2950, 2900, 1450, 1340, 1170, 1095 cm^{-1}; ^{1}H NMR (490 MHz, $CDCl_3$) δ 7.96−7.91 (m, 2 H, $SO_2C(CHCH)_2CH$), 7.68−7.63 (m, 2 H, $SO_2C(CHCH)_2CH$), 7.60−7.20 (m, 26 H, Ar*H*), 6.84 (d, *J* = 10.1 Hz, 1 H, N*H*), 5.51 (d, *J* = 10.1 Hz, 1 H, H-1), 5.46 (s, 1 H, O_2CHPh), 5.02 (d, *J* = 8.5 Hz, 1 H, N*H*′), 4.90 (d, *J* = 11.2 Hz, 1 H, OCH*H*Ph), 4.71 (AB_q, *J* = 6.8 Hz, υ = 15.1 Hz, 2 H, $OCH_2OCH_2CH_2Si$), 4.61 (d, *J* = 8.3 Hz, 1 H, H-1′), 4.55 (d, *J* = 12.2 Hz, 1 H, OCH*H*Ph), 4.36 (d, *J* = 12.2 Hz, 1 H, OCH*H*Ph), 4.35 (d, *J* = 11.2 Hz, 1 H, OCH*H*Ph), 4.32 (dd, *J* = 10.8, 5.3 Hz, 1 H, H-6$_e$′), 4.30 (dd, *J* = 10.0, 2.9 Hz, 1 H, H-4), 4.25 (t, *J* = 2.9 Hz, 1 H, H-3), 4.16 (d, *J* = 2.8 Hz, 1 H, H-2), 4.02 (td, *J* = 9.9, 5.2 Hz, 1 H, H-5′), 3.89 (t, *J* = 2.4 Hz, 1 H, H-3′), 3.82 (td, *J* = 9.5, 7.1 Hz, 1 H, $OCHHCH_2Si$), 3.66 (t, *J* = 10.4 Hz, 1 H, H-6$_a$′), 3.61 (td, *J* = 9.3, 7.1 Hz, 1 H, $OCHHCH_2Si$), 3.58 (dd, *J* = 9.7, 1.9 Hz, 1 H, H-4′), 3.27 (td, *J* = 8.4, 3.1 Hz, 1 H, H-2′), 3.19 (br d, *J* = 10.0 Hz, 1 H, H-5), 3.15 (dd, *J* = 11.0, 2.7 Hz, 1 H, H-6), 2.61 (dd, *J* = 10.9, 2.0 Hz, 1 H, H-6), 1.04−0.96 (m, 2 H, OCH_2CH_2Si), 0.11 (s, 9 H, $Si(CH_3)_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 141.4, 141.1, 137.7, 137.0, 132.5, 132.3, 129.1, 128.8, 128.7, 128.5, 128.3, 128.2, 128.0, 127.9, 127.7, 127.1, 127.1, 126.8, 126.0, 102.1, 100.8, 96.2, 81.9, 79.8, 77.2, 75.8, 74.8, 73.3, 71.5, 68.8, 67.6, 66.7, 66.5, 63.4, 56.9, 46.3, 18.1, −1.4; MS (FAB) *m/e* (rel intensity) 1103 (M + Na^+, 3), 1024 (10), 1023 (15), 480 (10), 373 (21), 372 (100), 356 (10), 320 (13), 318 (11), 307 (10); HRMS (FAB) calcd for $C_{51}H_{61}BrN_2NaO_{13}S_2Si$ (M + Na^+) 1103.2467, found 1103.2492. Anal. Calcd for $C_{51}H_{61}BrN_2O_{13}S_2Si$: C, 56.61; H, 5.68; N, 2.59; S, 5.93. Found: C, 56.78; H, 5.72; N, 2.58; S, 5.84.

[1(*R*)-(1α,4α,5*β*)]-5-[(Benzyloxy)methyl]-4-[(*tert*-butyldimethylsilyl)oxy]-2-cyclopenten-1-ol (59). To a 0 °C solution of monoacetate *ent*-**19** (3.95 g, 15.1 mmol) in dichloromethane (50 mL) was added imidazole (3.88 g, 57.0 mmol) and *tert*-butyldimethylsilyl chloride (4.32 g, 28.7 mmol). The mixture was stirred for 30 min, diluted with diethyl ether (200 mL), washed successively with 1 M aqueous HCl (2 × 50 mL) and saturated aqueous $NaHCO_3$ (50 mL), dried ($MgSO_4$), and concentrated. The oil thus produced was deacetylated with methanolic ammonia (150 mL) for 48 h and concentrated, and the residue was chromatographed (silica gel, 20 → 25% ethyl acetate in hexanes) to provide the desired alcohol **53** (5.10 g, 100%) as a colorless oil. A portion of **53** was bulb-to-bulb distilled (170 °C, 0.06 Torr) for analysis: $[\alpha]_D$ −49.2° (*c* 1.1, $CHCl_3$); IR (neat) υ_{max} 3370 (br), 3050, 3020, 2950, 2920, 2850, 1360, 1255, 1100, 1055 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.50−7.28 (m, 5 H, Ar*H*), 5.89 (d, *J* = 5.7 Hz, 1 H, olefinic), 5.81 (d, *J* = 5.7 Hz, 1 H, olefinic), 4.57 (AB_q, *J* = 12.0 Hz, υ = 11.3 Hz, 2 H, OCH_2Ph), 5.53 (d, *J* = 5.5 Hz, 2 H, H-1 and H-4), 3.76 (dd, *J* = 9.2, 4.5 Hz, 1 H, CH*H*OBn), 3.63 (dd, *J* = 9.2, 6.2 Hz, 1 H, CH*H*OBn), 2.50 (s, 1 H, OH), 2.12 (p, *J* = 5.4 Hz, 1 H, H-5), 0.91 (s, 9 H, $SiC(CH_3)_3$), 0.09 (s, 3 H, $SiCH_3$), 0.07 (s, 3 H, $SiCH_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 138.3, 136.0, 134.6, 128.4, 127.7, 127.6, 77.4, 76.8, 73.3, 69.0, 59.1, 25.8, 18.1, −4.5, −4.7; MS (CI) *m/e* (rel intensity) 335 (M + H^+, 1), 317 (46), 211 (24), 203 (21), 169 (28), 91 (100). Anal. Calcd for $C_{19}H_{30}O_3Si$: C, 68.22; H, 9.04. Found: C, 67.98; H, 8.75.

[1(*R*)-(1α,4α,5*β*)]-5-[(Benzyloxy)methyl]-4-[(*tert*-butyldimethylsilyl)oxy]-2-cyclopenten-1-ol Carbamate (21). To a 0 °C solution of alcohol **59** (5.10 g, 15.2 mmol) in dichloromethane (50 mL) were added pyridine (3.0 mL, 38 mmol) and phenyl chloroformate (2.3 mL, 18 mmol). The mixture was stirred for 15 min, then diluted with diethyl ether (250 mL), washed with water (50 mL), 1 M aqueous HCl (2 × 25 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL), dried ($MgSO_4$), and concentrated. The phenyl carbonate thus produced was treated for 15 h with methanolic ammonia (200 mL) and concentrated, and the residue was dissolved in diethyl ether (400 mL) and washed with 1 M aqueous NaOH (3 × 50 mL) and brine (50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated, and the residue was chromatographed (20 → 25 → 30% ethyl acetate in hexanes) to provide **21** (4.72 g, 82%) as a viscous, light-yellow oil. A portion of **21** was bulb-to-bulb distilled (180 °C, 0.040 Torr) to afford a colorless, viscous oil: $[\alpha]_D$ +3.9° (*c* 1.1, $CHCl_3$); IR (neat) υ_{max} 3490, 3340, 2950, 2930, 2860, 1720, 1595, 1390, 1365, 1310, 1105, 1055 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40−7.28 (m, 5 H, Ar*H*), 5.94−5.87 (m, 2 H, H-2 and H-3), 5.46 (5.1, 1 H, H-1), 4.95 (br s, 2 H, $OCONH_2$), 4.64 (d, *J* = 4.8 Hz, 1 H, H-4), 4.56 (AB_q, *J* = 12.1 Hz, υ = 15.1 Hz, 2 H, OCH_2Ph), 3.69 (d, *J* = 4.6 Hz, 2 H, CH_2OBn), 2.22 (p, *J* = 4.8 Hz, 1 H, H-5), 0.90 (s, 9 H, $SiC(CH_3)_3$), 0.08 (s, 3 H, $SiCH_3$), 0.06 (s, 3 H, $SiCH_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 156.8, 138.2, 138.0, 131.2, 128.2, 127.6, 127.4, 79.3, 76.6, 73.2, 68.1, 55.3, 25.8, 18.0, −4.6, −4.7; MS (CI) *m/e* (rel intensity) 378 (M + H^+, 1), 318 (31), 317 (100), 246 (43), 211 (67), 209 (21), 169 (48), 160 (27), 138 (30), 118 (36), 91 (95). Anal. Calcd for $C_{20}H_{31}O_4NSi$: C, 63.62; H, 8.28; N, 3.71. Found: C, 63.40; H, 7.99; N, 3.71.

[1(*R*)-(1α,2*β*,3α)]-2-[(Benzyloxy)methyl]-4-cyclopentene-1,3-diol Monocarbamate (20). A solution of 2% HF in acetonitrile (26 mL, 26 mmol) was added to a solution of carbamate **21** (4.71 g, 12.5 mmol) in acetonitrile (50 mL). The mixture was stirred for 9 h and then extracted from 1:3 saturated aqueous $NaHCO_3$/water (200 mL) with ethyl acetate (4 × 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated, and the residue was recrystallized (ethyl acetate/hexanes) to provide the desired carbamate **20** (2.98 g, 91%) as colorless crystals: mp 114−114.5 °C; $[\alpha]_D$ +58.0° (*c* 1.0, THF); IR (KBr) υ_{max} 3420, 3310, 3270, 3200, 2870, 1685, 1610, 1410, 1355, 1115, 1105, 1050 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40−7.28 (m, 5 H, Ar*H*), 6.02 (dt, *J* = 5.6, 1.4 Hz, 1 H, H-5), 5.91 (dt, *J* = 5.6, 1.6 Hz, 1 H, H-4), 5.33−5.28 (m, 1 H, H-1), 4.76 (br s, 2 H, $OCONH_2$), 4.62−4.55 (m, 1 H, H-3), 4.56 (s, 2 H, OCH_2Ph), 3.81 (dd, *J* = 9.2, 5.2 Hz, 1 H, CH*H*OBn), 3.63 (dd, *J* = 9.2, 7.8 Hz, 1 H, CH*H*OBn), 2.44 (d, *J* = 3.9 Hz, 1 H, O*H*), 2.31 (dq, *J* = 7.7, 4.9 Hz, 1 H, H-2); ^{13}C NMR (63 MHz, $CDCl_3$) δ 156.5, 138.1, 137.2, 132.0, 128.4, 127.7, 79.6, 78.1, 73.4, 70.0, 55.3; MS (CI) *m/e* (rel intensity) 264 (M + H^+, 9), 246 (61), 203 (65), 185 (42), 157 (22), 152 (20), 138 (67), 131 (20), 119 (56), 111 (32), 107 (36), 97 (27), 96 (50), 92 (60), 91 (100). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.73; H, 6.24; N, 5.26.

[3a(*R*)-(3aα,6α,6aα)]-6-[(Benzyloxy)methyl]-3,3a,6,6a-tetrahydro-2*H*-cyclopentoxazol-2-one (24). To a −78 °C solution of carbamate **20** (2.99 g, 11.4 mmol) in THF (250 mL) were added triethylamine (12.7 mL, 92 mmol) and trifluoroacetic anhydride (4.80 mL, 34 mmol). The reaction was warmed to room temperature over 4 h, and water (30 mL) was added. The mixture was stirred an additional 1 h, then diluted with diethyl ether (500 mL), and washed with 1 M aqueous HCl (2 × 200 mL), saturated aqueous $NaHCO_3$ (200 mL), and brine (200 mL). The organic layer was dried ($MgSO_4$) and concentrated, and the orange-yellow residue was filtered through a short plug of silica gel (66% ethyl acetate in hexanes). The yellow oil thus produced was chromatographed (silica gel, 30 → 35 → 40% ethyl acetate in dichloromethane) to provide the oxazolone **24** (1.74 mg, 63%) as an off-white solid (mp 84.5−86 °C). Recrystallization (diethyl ether/hexanes) provided colorless crystals of **24**: mp 87.5−88 °C; $[\alpha]_D$ −201° (*c* 1.0, $CHCl_3$); IR (neat) υ_{max} 3270, 2900, 2870, 1720, 1385, 1330, 1230, 1215, 1070, 1040 cm^{-1}; ^{1}H NMR (490 MHz, $CDCl_3$) δ 7.38−7.28 (m, 5 H, Ar*H*), 5.88 (dd, *J* = 5.9, 2.6 Hz, 1 H, olefinic), 5.85 (br s, 1 H, N*H*), 5.81 (dt, *J* = 5.9, 1.8 Hz, 1 H, olefinic), 5.02 (d, *J* = 7.1 Hz, 1 H), 4.72 (d, *J* = 7.1 Hz, 1 H), 4.51 (s, 2 H, OCH_2Ph), 3.58 (dd, *J* = 9.4, 4.8 Hz, 1 H, CH*H*OBn), 3.41 (dd, *J* = 9.4, 5.7 Hz, 1 H, CH*H*OBn), 3.26−3.23 (m, 1 H, H-6); ^{13}C NMR (63 MHz, $CDCl_3$) δ 159.6, 137.8, 133.6, 131.4, 128.3, 127.6, 127.4, 82.3, 73.0, 70.1, 61.7, 52.7; MS (CI) *m/e* (rel intensity) 247 (48), 246 (M + H^+, 100), 91 (75). Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.46; H, 6.18; N, 5.51.

[3a(*R*)-(3aα,6α,6aα)]-6-[(Benzyloxy)methyl]-3,6a-dihydro-*N*,*N*-dimethyl-6*H*-cyclopentoxazol-2-amine (25). Methyl trifluoromethanesulfonate (1.62 mL, 14.2 mmol) was stirred with a dichloromethane (6 mL) solution of oxazolone **24** (1.76 g, 7.18 mmol) for 5 h and then concentrated with a stream of nitrogen. Dimethylamine (56 mL) was condensed into the flask with the residue at 0 °C, and the mixture was stirred for 2 days at room temperature and then extracted from 4:1 saturated aqueous K_2CO_3/water (250 mL) with dichloromethane (3 × 100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated, and the residue was chromatographed (silica gel, 2% Et_3N, 10% methanol in ethyl acetate) to provide the aminooxazoline **25** (1.69 g, 87%) as a light-yellow oil: $[\alpha]_D$ −213° (*c* 1.1, CH_2Cl_2); IR (neat) υ_{max} 2860, 1655, 1405, 1185, 1120, 1100, 1070, 1025 cm^{-1}; ^{1}H NMR

(490 MHz, CD_2Cl_2) δ 7.37−7.26 (m, 5 H, Ar*H*), 5.85 (dt, J = 5.8, 1.9 Hz, 1 H, olefinic), 5.63 (dt, J = 5.8, 2.0 Hz, 1 H, olefinic), 4.93 (dq, J = 7.1, 1.7 Hz, 1 H), 4.84 (d, J = 7.1 Hz, 1 H), 4.51 (s, 2 H, OCH_2-Ph), 3.52 (dd, J = 9.3, 5.2 Hz, 1 H, CH*H*OBn), 3.29 (dd, J = 9.3, 7.7 Hz, 1 H, CH*H*OBn), 3.15−3.10 (m, 1 H, H-6), 2.83 (s, 6 H, N(CH_3)$_2$); ^{13}C NMR (63 MHz, CD_2Cl_2) δ 162.3, 139.0, 135.6, 130.0, 128.7, 128.0, 127.9, 86.0, 76.0, 73.6, 72.1, 53.9, 37.9; MS (EI) *m/e* (rel intensity) 272 (M^+, 31), 165 (18), 151 (15), 91 (69), 80 (18), 72 (100). Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.28. Found: C, 70.42; H, 7.22; N, 10.10.

[1a(*S*)-(1aα,1bα,4aα,5α,5aα)]-5-[(Benzyloxy)methyl]-*N*,*N*-dimethyl-1a,1b,4a,5a-tetrahydro-5*H*-oxireno[4,5]cyclopent[1,2-*d*]oxazol-3-amine (26) and 6-*O*-Benzyl-(−)-allosamizoline (27). To a 0 °C dichloromethane (8 mL) solution of aminooxazoline **25** (1.72 g, 6.32 mmol) was added 3.6 M trifluoroperacetic acid (3.51 mL, 12.7 mmol). The mixture was stirred 2 h, and water (32 mL) and sodium bisulfite (860 mg, 8.2 mmol) were added. The solution was heated to 40 °C for 5.5 h, and the reaction was extracted from water (150 mL) with dichloromethane (4 × 200 mL). The combined organic layers were dried (Na_2SO_4) and concentrated, and the residue was chromatographed (silica gel, 1% Et_3N, 5 → 10 → 20% methanol in ethyl acetate) to provide α-epoxide **26** (0.67 g, 37%) followed by diol **27** (0.84 g, 44%). The waxy, yellow solid was rechromatographed (silica gel, 1% Et_3N, 5 → 10% methanol in ethyl acetate) to provide a colorless oil of **26**: $[\alpha]_D$ −91.7° (*c* 1.0, CH_2Cl_2); IR (neat) υ_{max} 3020, 2920, 2860, 1655, 1455, 1410, 1185, 1105, 1080, 1030 cm^{-1}; ^{1}H NMR (250 MHz, CD_2Cl_2) δ 7.41−7.25 (m, 5 H, Ar*H*), 4.72 (d, J = 8.1 Hz, 1 H, H-4a), 4.50 (s, 2 H, OCH_2Ph), 4.41 (dd, J = 8.1, 1.8 Hz, 1 H, H-1b), 3.56−3.52 (m, 1 H, H-5a), 3.53 (d, J = 5.0 Hz, 2 H, CH_2OBn), 3.49 (dd, J = 2.5, 1.1 Hz, 1 H, H-1a), 2.84 (s, 6 H, N(CH_3)$_2$), 2.70 (t, J = 5.0 Hz, 1 H, H-5); ^{13}C NMR (63 MHz, CD_2Cl_2) δ 162.5, 138.6, 128.8, 128.1, 127.9, 88.1, 73.7, 70.8, 69.6, 61.5, 61.6, 47.1, 37.8; MS (EI) *m/e* (rel intensity) 288 (M^+, 42), 167 (8), 112 (100), 83 (20). Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.47; H, 6.90; N, 9.63. The off-white solid (mp 130−143 °C) was recrystallized (ethyl acetate/hexanes) to afford colorless needles of **27**: mp 143−144 °C; $[\alpha]_D$ +15.6° (*c* 1.0, CH_2Cl_2); IR (KBr) υ_{max} 3350, 3300, 2970, 2910, 2850, 1645, 1450, 1410, 1265, 1190, 1150 cm^{-1}; ^{1}H NMR (250 MHz, CD_2Cl_2) δ 7.40−7.24 (m, 5 H, Ar*H*), 6.02 (s, 2 H, O*H*), 4.74 (dd, J = 9.3, 6.6 Hz, 1 H, H-1), 4.54 (AB$_q$, J = 12.0 Hz, υ = 9.0 Hz, 2 H, OCH_2Ph), 3.96 (dd, J = 9.3, 5.0 Hz, 1 H, H-2), 3.80−3.58 (m, 4 H, H-3, H-4, H-6, and H-6), 2.85 (s, 6 H, N(CH_3)$_3$), 2.17−2.03 (m, 1 H, H-5); ^{13}C NMR (63 MHz, CD_2Cl_2) δ 162.5, 139.1, 128.6, 127.9, 127.8, 85.1, 82.5, 74.4, 73.4, 72.9, 69.3, 50.7, 37.9; MS (EI) *m/e* (rel intensity) 306 (M^+, 7), 247 (34), 245 (46), 215 (31), 190 (46), 185 (76), 141 (26), 139 (24), 138 (20), 125 (50), 113 (36), 112 (52), 97 (30), 91 (91), 89 (95), 72 (100). Anal. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.46; H, 7.47; N, 9.00.

(−)-Allosamizoline (8). A mixture of benzyl derivative **27** (30.7 mg, 0.100 mmol) and 10% Pd/C catalyst (20 mg) in 1:9 acetic acid/methanol (2 mL) was shaken for 16 h under 40 psi of H_2, filtered through Celite, and concentrated to provide the acetic acid salt of (+)-allosamizoline (**8**; 23.3 mg, 84%) as a colorless glass: $[\alpha]_D$ −21.7° (*c* 0.8, water); ^{1}H NMR (490 MHz, D_2O + 0.5% CD_3CO_2D) δ 5.35 (dd, J = 9.0, 5.2 Hz, 1 H, H-1), 4.32 (dd, J = 9.0, 4.9 Hz, 1 H, H-2), 4.07 (dd, J = 6.9, 4.9 Hz, 1 H, H-3), 3.88 (dd, J = 11.5, 4.5 Hz, 1 H, H-6), 3.82 (t, J = 7.8 Hz, 1 H, H-4), 3.72 (dd, J = 11.5, 7.3 Hz, 1 H, H-6), 3.08 (s, 6 H, N(CH_3)$_2$), 2.45−2.38 (m, 1 H, H-5); ^{13}C NMR (63 MHz, D_2O + 0.5% CD_3CO_2D) δ 161.2, 87.3, 82.2, 75.5, 64.2, 59.9, 51.9, 38.0; HRMS (FAB) calcd for $C_9H_{17}N_2O_4$ ($M + H^+$) 217.1188, found 217.1194.

3,6-Di-*O*-benzyl-(−)-allosamizoline (60). A methanolic (20 mL) suspension of diol **27** (540 mg, 1.76 mmol) and dibutyltin oxide (0.44 g, 1.8 mmol) was refluxed until the mixture became homogeneous (1 h). The solution was concentrated under reduced pressure and then concentrated from benzene (3 × 50 mL) to remove any methanol still present. The stannylene acetal was rapidly stirred in DMF (20 mL) and treated with benzyl bromide (0.31 mL, 2.6 mmol) and dry cesium fluoride (0.53 g, 3.5 mmol). After 12 h, the suspension was extracted from 0.5 M aqueous Na_2CO_3 (100 mL) with ethyl acetate (2 × 150 mL). The combined organic layers were dried (Na_2SO_4) and concentrated, and the residue was chromatographed (silica gel, 2% Et_3N, 5 → 10 → 20% ethyl acetate in toluene) to provide the desired diprotected aglycon **60** (247 mg, 35%) as a colorless solid (mp 115.5−117.5 °C), followed by recovered diol **27** (114 mg, 21%) as a colorless solid. For **60**: colorless needles (recrystallization, ethyl acetate/hexanes): mp 119−120 °C; $[\alpha]_D$ −19.6° (*c* 1.2, CH_2Cl_2); IR (KBr) υ_{max} 3170 (br), 3010, 2900, 2870, 1650, 1410, 1200, 1110, 1030 cm^{-1}; ^{1}H NMR (250 MHz, CD_2Cl_2) δ 7.45−7.23 (m, 10 H, Ar*H*), 4.82 (d, J = 11.8 Hz, 1 H, OCH*H*Ph), 4.66 (d, J = 11.8 Hz, 1 H, OCH*H*Ph), 4.64 (dd, J = 6.0, 3.0 Hz, 1 H, H-1), 4.56 (s, 2 H, OCH_2Ph), 4.16 (dd, J = 8.9, 4.6 Hz, 1 H, H-2), 3.87 (dd, J = 9.3, 7.1 Hz, 1 H, H-4), 3.86 (br s, 1 H, O*H*), 3.71−3.65 (m, 3 H, H-3, H-6, and H-6), 2.89 (s, 6 H, N(CH_3)$_2$), 2.28−2.15 (m, 1 H, H-5); ^{13}C NMR (63 MHz, CD_2Cl_2) δ 162.1, 139.2, 138.8, 128.7, 128.5, 128.2, 127.9, 127.7, 92.3, 82.5, 75.4, 73.5, 72.6, 71.9, 69.7, 51.4, 37.8; MS (CI) *m/e* (rel intensity) 397 ($M + H^+$, 1), 305 (10), 273 (29), 185 (11), 184 (100), 166 (15), 165 (58), 155 (10), 91 (44), 72 (15). Anal. Calcd for $C_{23}H_{28}N_2O_4$: C, 69.68; H, 7.12; N, 7.06. Found: C, 69.69; H, 7.09; N, 7.05.

***O*-[2-Benzenesulfonamido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-D-allopyranosyl]-*β*-(1→4)-*O*-[2-benzenesulfonamido-6-*O*-benzyl-2-deoxy-3-*O*-[[2-(trimethylsilyl)ethoxy]methyl]-D-allopyranosyl]-*β*-(1→4)-3,6-di-*O*-benzyl-(−)-allosamizoline (61).** To a −40 °C solution of *trans*-bromosulfonamide **49** (556 mg, 0.514 mmol) in DMF (1 mL) was added a DMF solution (2.5 mL) of allosamizoline derivative **60** (146 mg, 0.368 mmol), followed by dropwise addition of potassium hexamethyldisilazide (0.5 M in toluene, 2.8 mL, 1.4 mmol). The reaction mixture was stirred for 1 h at −40 °C, slowly warmed to room temperature, stirred an additional 10 h, and then extracted from 1:1 water/brine (200 mL) with diethyl ether (3 × 75 mL). The combined organic layers were dried (Na_2SO_4) and concentrated, and the residue was chromatographed (silica gel, 1% Et_3N, 0 → 10% methanol in ethyl acetate) to provide pseudotrisaccharide **61** (215 mg, 42%), followed by recovered aglycon **60** (66 mg, 45%). For **61**: colorless glass; $[\alpha]_D$ −40.6° (*c* 1.0, CH_2Cl_2); IR (KBr) υ_{max} 3330, 3190, 3060, 3030, 2880 (br), 1655, 1450, 1405, 1340 cm^{-1}; ^{1}H NMR (490 MHz, CD_2Cl_2) δ 7.85−7.81 (m, 2 H, SO_2C(C*H*CH)$_2$CH), 7.87−7.83 (m, 2 H, SO_2C(C*H*CH)$_2$CH), 7.51−7.15 (m, 31 H, Ar*H*), 5.98 (d, J = 8.2 Hz, 1 H, N*H*′), 5.46 (s, 1 H, O_2C*H*Ph), 5.12 (d, J = 8.4 Hz, 1 H, N*H*″), 4.89 (d, J = 11.3 Hz, 1 H, OCH*H*Ph), 4.68 (d, J = 6.5 Hz, 1 H, OCH*H*OCH_2CH_2Si), 4.66 (s, 2 H, OCH_2Ph), 4.60 (dd, J = 6.7, 2.1 Hz, 1 H, H-1), 4.57 (AB$_q$, J = 11.4 Hz, υ = 14.2 Hz, 2 H, OCH_2Ph), 4.56 (d, J = 8.4 Hz, 1 H, H-1″), 4.53 (d, J = 8.2 Hz, 1 H, H-1′), 4.50 (d, J = 6.5 Hz, 1 H, OCH*H*OCH_2CH_2Si), 4.44 (d, J = 11.9 Hz, 1 H, OCH*H*Ph), 4.39 (d, J = 11.3 Hz, 1 H, OCH*H*Ph), 4.34 (d, J = 11.9 Hz, 1 H, OCH*H*Ph), 4.20 (dd, J = 10.3, 5.2 Hz, 1 H, H-6$_e$″), 4.02 (dd, J = 9.0, 4.4 Hz, 1 H, H-2), 3.91 (td, J = 10.0, 5.2 Hz, 1 H, H-5″), 3.90−3.85 (m, 2 H, H-4 and H-3″), 3.80 (td, J = 9.2, 7.8 Hz, 1 H, OCH*H*CH_2Si), 3.73 (t, J = 2.7 Hz, 1 H, H-3′), 3.63 (td, J = 9.4, 7.6 Hz, 1 H, OCH*H*CH_2Si), 3.62−3.53 (m, 6 H, H-3, H-6, H-6, H-4′, H-4″, and H-6$_a$″), 3.43 (dt, J = 9.8, 2.4 Hz, 1 H, H-5′), 3.33 (AB$_q$ of ABX, J_{AB} = 11.0 Hz, J_{AX} = 3.0 Hz, J_{BX} =2.9 Hz, υ = 12.8 Hz, 2 H, H-6′ and H-6′), 3.25 (td, J = 8.3, 3.0 Hz, 1 H, H-2″), 3.18 (td, J = 8.1, 2.8 Hz, 1 H, H-2′), 2.91 (s, 6 H, N(CH_3)$_2$), 1.67−1.62 (m, 1 H, H-5), 1.10−1.05 (m, 2 H, OCH$_2$CH_2Si), 0.08 (s, 9 H, Si(CH_3)$_3$); ^{13}C NMR (63 MHz, CD_2Cl_2) δ 161.7, 142.2, 141.4, 139.6, 138.9, 138.5, 137.9, 133.0, 132.7, 129.5, 129.4, 129.2, 128.9, 128.8, 128.6, 128.5, 128.4, 128.1, 128.0, 127.7, 127.6, 127.2, 126.6, 102.5, 101.2, 99.8, 97.5, 90.6, 82.2, 81.4, 80.3, 76.8, 76.5, 75.2, 73.8, 73.6, 72.9, 72.1, 71.7, 69.4, 69.3, 68.4, 66.9, 63.9, 57.4, 56.6, 50.2, 37.9, 18.6, −1.2; HRMS (FAB) calcd for $C_{74}H_{89}N_4O_{17}S_2Si$ ($M + H^+$) 1397.5434, found 1397.5509. Anal. Calcd for $C_{74}H_{88}N_4O_{17}S_2Si$: C, 63.59; H, 6.34; H, 4.01; S, 4.59. Found: C, 63.30; H, 6.46; H, 3.94; S, 4.72.

Allosamidin Heptaacetate (62). Pseudotrisaccharide **61** (215 mg, 0.154 mmol) was treated for 4 h with 5% concentrated aqueous HCl in methanol (10 mL), and the mixture was quenched with saturated aqueous K_2CO_3, diluted with dichloromethane (100 mL), dried (Na_2SO_4), filtered through Celite, and concentrated. To a −78 °C solution of this residue in THF (2 mL) and ammonia (25 mL) were added small pieces of sodium until a deep blue color was maintained for 1 h. The mixture was quenched with solid NH_4Cl and then concentrated with a stream of nitrogen. The residue was acetylated for 2 days with pyridine (5 mL) and acetic anhydride (2 mL), concentrated under reduced pressure, and extracted from 0.5 M aqueous

Na_2CO_3 (100 mL) with dichloromethane (2 × 100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated, and the residue was chromatographed (silica gel, 1% Et_3N, 1 → 5 → 10 → 15% methanol in ethyl acetate) to provide material which was extracted from 0.5 M aqueous Na_2CO_3 (15 mL) with dichloromethane (3 × 8 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to afford allosamidin heptaacetate (**62**; 50.1 mg, 36%) as a colorless glass: $[\alpha]_D$ −35.1° (*c* 0.9, CH_2Cl_2); IR (KBr) υ_{max} 3380 (br), 2940, 1745, 1655, 1370, 1230, 1045 cm^{-1}; ^1H NMR (490 MHz, CD_2Cl_2) δ 6.30 (d, J = 8.3 Hz, 2 H, N*H*), 5.63 (t, J = 3.0 Hz, 1 H, H-3′), 5.48 (t, J = 2.9 Hz, 1 H, H-3″), 5.13 (dd, J = 6.7, 3.7 Hz, 1 H, H-3), 4.81 (dd, J = 10.3, 2.9 Hz, 1 H, H-4″), 4.75 (dd, J = 8.8, 6.4 Hz, 1 H, H-1), 4.65 (d, J = 7.7 Hz, 1 H, H-1′), 4.57 (dd, J = 11.9, 3.8 Hz, 1 H, H-6′), 4.57 (d, J = 8.6 Hz, 1 H, H-1″), 4.45 (dd, J = 11.6, 4.9 Hz, 1 H, H-6), 4.16 (dd, J = 8.8, 3.6 Hz, 1 H, H-2), 4.12−3.98 (m, 7 H), 3.91 (dt, J = 8.7, 3.4 Hz, 1 H, H-5′), 3.77 (dd, J = 9.8, 6.7 Hz, 1 H, H-4), 3.64 (dd, J = 9.0, 3.3 Hz, 1 H, H-4′), 2.88 (s, 6 H, N(C*H*$_3$)$_2$), 2.45−2.39 (m, 1 H, H-5), 2.15 (s, 3 H, COC*H*$_3$), 2.15 (s, 3 H, COC*H*$_3$), 2.11 (s, 3 H, COC*H*$_3$), 2.10 (s, 3 H, COC*H*$_3$), 2.07 (s, 3 H, COC*H*$_3$), 2.06 (s, 3 H, COC*H*$_3$), 1.93 (s, 3 H, COC*H*$_3$), 1.92 (s, 3 H, COC*H*$_3$), 1.89 (s, 3 H, COC*H*$_3$); ^{13}C NMR (63 MHz, CD_2Cl_2) δ 171.8, 171.6, 171.1, 170.4, 170.1, 170.0, 167.7, 169.5, 162.0, 100.4, 99.0, 82.6, 81.8, 80.2, 74.4, 72.5, 72.3, 70.4, 69.8, 67.0, 63.0, 62.8, 61.1, 51.8, 51.1, 49.3, 37.7, 30.0, 23.0, 22.9, 21.3, 21.1, 21.1, 21.0, 20.8, 20.7, 20.6; MS (FAB) *m/e* (rel intensity) 919 (12), 918 (47), 917 (M + H^+, 100), 307 (18), 301 (12), 289 (10), 245 (46), 225 (16); HRMS (FAB) calcd for $C_{39}H_{57}N_4O_{21}$ (M + H^+) 917.3515, found 917.3553.

Allosamidin (1). A stream of ammonia was passed over a methanolic solution (15 mL) of allosamidin heptaacetate (**62**; 50.0 mg, 0.0545 mmol) until the solution had returned to room temperature. The reaction was stirred for 3 days, concentrated, and chromatographed (Biogel P-2 gel, water) to provide allosamidin (**1**; 27 mg, 79%) as a colorless solid: mp 224→270 °C; $[\alpha]_D$ −23.9° (*c* 0.5, 0.1 M acetic acid in water); IR (KBr) υ_{max} 3370 (v br), 2920, 1650, 1545, 1410, 1375, 1060 cm^{-1}; ^1H NMR (490 MHz, D_2O + 0.5% CD_3CO_2D) δ 5.38 (dd, J = 8.8, 4.9 Hz, 1 H, H-1), 4.79 (d, J = 8.6 Hz, 1 H, H-1″), 4.78 (d, J = 8.4 Hz, 1 H, H-1′), 4.38 (dd, J = 8.8, 4.2 Hz, 1 H, H-2), 4.35 (t, J = 2.8 Hz, 1 H, H-3′), 4.29 (t, J = 5.0 Hz, 1 H, H-3), 4.06 (t, J = 2.9 Hz, 1 H, H-3″), 3.93−2.67 (m, 12 H), 3.62 (dd, J = 12.0, 6.6 Hz, 1 H, H-6′), 3.09 (s, 3 H, NC*H*$_3$Me), 3.08 (s, 3 H, NC*H*$_3$Me), 3.67−3.62 (m, 1 H, H-5), 2.08 (s, 3 H, NHCOC*H*$_3$), 2.06 (s, 3 H, NHCOC*H*$_3$); ^{13}C NMR (123 MHz, D_2O + 0.5% CD_3CO_2D) δ 174.0, 173.8, 160.6, 100.6, 99.9, 86.8, 85.0, 80.5, 76.9, 73.6, 72.6, 70.1, 69.0, 66.4, 64.2, 61.0, 60.9, 59.2, 52.9, 52.6, 51.4, 37.6, 37.4, 22.0; HRMS (FAB) calcd for $C_{25}H_{43}N_4O_{14}$ (M + H^+) 623.2776, found 623.2816.

Acknowledgment. This work was supported financially by the National Institutes of Health (PHS Grant HL 25848). We gratefully thank Prof. A. Isogai for a sample of natural allosamidin and Prof. B. M. Trost for a sample of racemic synthetic allosamizoline. We also thank Dr. D. Dumas and Prof. C. H. Wong for helpful discussions and for providing compound **67**. Kent, Bushnell, and Dox fellowships to D.A.G. are gratefully acknowledged. We are pleased to dedicate this paper to the many and continuing accomplishments of Professor Nelson Leonard.

Supporting Information Available: Experimental details and characterizations which are not part of the pathway leading to allosamidin are provided for compounds *ent*-**8**, *ent*-**20**, *ent*-**24**−*ent*-**27**, **41**−**44**, **50**−**58**, **64**, **66**−**71**, **73**−**78**, and **81**−**84** (38 pages). See any current masthead page for ordering information and Internet access instructions.

JA960526C