Scavenging Byproducts in the Sulfoxide Glycosylation Reaction: Application to the Synthesis of Ciclamycin 0

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Abstract: We have developed a direct and efficient route for the synthesis of ciclamycin 0 using the sulfoxide glycosylation reaction to form the glycosidic linkages. In the course of completing the synthesis of ciclamycin 0, we developed new glycosylation conditions that improve the outcome of the sulfoxide reaction. The conditions involve the addition of agents that scavenge phenylsulfenyl triflate, a highly reactive byproduct that forms following activation of anomeric sulfoxides with triflic anhydride.

Introduction

The anthracycline antibiotics are a large class of glycosylated natural products which possess a wide range of biological activity.[1,2] Two of the most notable members, adriamycin (**1**) and daunomycin (**2**) (see Figure 1), have been used clinically to treat certain types of cancer. Like many other glycosylated natural products, the carbohydrates on the anthracyclines are essential for biological activity. Furthermore, even subtle changes to the carbohydrates can significantly improve biological activity and/or reduce toxicity. While this class of natural products has been studied for over 40 years, their mechanism of action and the roles of the carbohydrates are still not clear.

Our group has been interested in studying the roles of carbohydrates on glycosylated natural products for a number of years, and we were naturally drawn to the anthracycline antibiotics. We are especially interested in ciclamycin, a complex of anthracyclines isolated from *Streptomyces capoamus* that possesses good activity against tumors both in vitro and in vivo.[3,4] Since most anthracyclines in the ciclamycin complex contain the same aglycon, differences in activity and toxicity are due to differences in the oligosaccharides. Therefore, we wanted to develop a synthetic route to this class of anthracyclines that would allow us to systematically vary the oligosaccharides to shed more light on the role of the carbohydrates and the mechanisms by which these compounds work.

As part of our program to study the roles of carbohydrates on glycosylated natural products, we have been interested in improving methods to synthesize oligosaccharides to make these compounds more readily available. In 1989 we reported the use of anomeric sulfoxides as glycosyl donors and have found several advantages to using this glycosylation method: activation occurs at low temperature under mild conditions, and the activated glycosyl donor produced is extremely reactive.[5] In 1993, we began investigating the use of the sulfoxide reaction for the synthesis of ciclamycin 0, a member of the ciclamycin complex that has particularly low toxicity.[6,7] Because ciclamycin 0 has been synthesized once previously by the Danishefsky group using one of the best glycosylation methods available,[8,9] we had a standard which would allow us to compare our synthesis and glycosylation method.

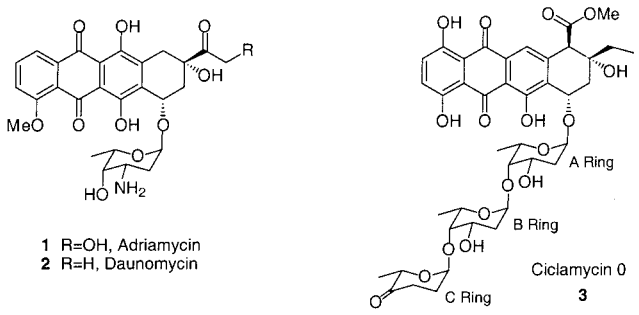

Figure 1. Anthracycline antibiotics.

Background

Several years ago, we reported the synthesis of the trisaccharide of ciclamycin 0 using the sulfoxide glycosylation reaction.[7,10] Our synthesis of the trisaccharide used a polymerization reaction in which the trisaccharide was constructed in

(1) Lown, W. Ed. *Anthracycline and Anthracenedione-Based Anticancer Agents*; Elsevier Science Publishers: Amsterdam, 1988.

(2) Priebe, W., Ed. *Anthracycline Antibiotics: New Analogues, Methods of Delivery, and Mechanisms of Action*; American Chemical Society: Washington, DC, 1995.

(3) Lima, V. Q. G.; Albert, C. A.; Lima, O. G. *An. Acad. Bras. Cienc.* **1964**, *36*, 317.

(4) Lyra, F. D. A.; Lima, O. G.; Coelho, J. S. B.; Albuquerque, M. M. F.; Maciel, G. M.; Oliviera, L. L.; Maciel, M. C. N. *An. Acad. Bras. Cienc.* **1964**, *36*, 323.

(5) Kahne, D.; Walker, S.; Cheng, Y.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881.

(6) For the isolation and characterization of ciclamycin 0, see: Bieber, L. W.; Da Silva Filho, A. A.; De Mello, J. F.; De Lima, O. G.; Do Nascimento, M. S.; Veith, H. J.; Von Der Saal, W. *J. Antibiot.* **1987**, *40*, 1335.

(7) Raghavan, S.; Kahne, D. *J. Am. Chem. Soc.* **1993**, *115*, 1580.

(8) Suzuki, K.; Sulikowski, G. A.; Friesen, R. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 8895.

(9) For recent reviews on the glycal method for the synthesis of oligosaccharides, see: (a) Thiem, J.; Klaffke, W. *Top. Curr. Chem.* **1990**, *154*, 285. (b) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1381.

(10) For lead references to the syntheses of related oligosaccharides, see: (a) Monneret, C.; Martin, A.; Pais, M. *J. Carbohydr. Chem.* **1988**, *7*, 417. (b) Thiem, J. In *Trends in Synthetic Carbohydrate Chemistry*; Horton, D., Hawkins, L. D., McGarvey, G. J., Eds.; American Chemical Society: Washington, DC, 1989; Chapter 8. (c) Horton, D.; Priebe, W.; Sznaidman, M. L. *J. Antibiot.* **1993**, *46*, 1720. (d) Kolar, C.; Bosslet, K.; Czech, J.; Gerken, M.; Hermentin, P.; Hoffmann, D.; Sedlacek, H. Chapter 4 in ref 2. (e) Animati, F.; Arcamone, F.; Berettoni, M.; Cipollone, A.; Fanciotti, M.; Lombardi, P. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1327.

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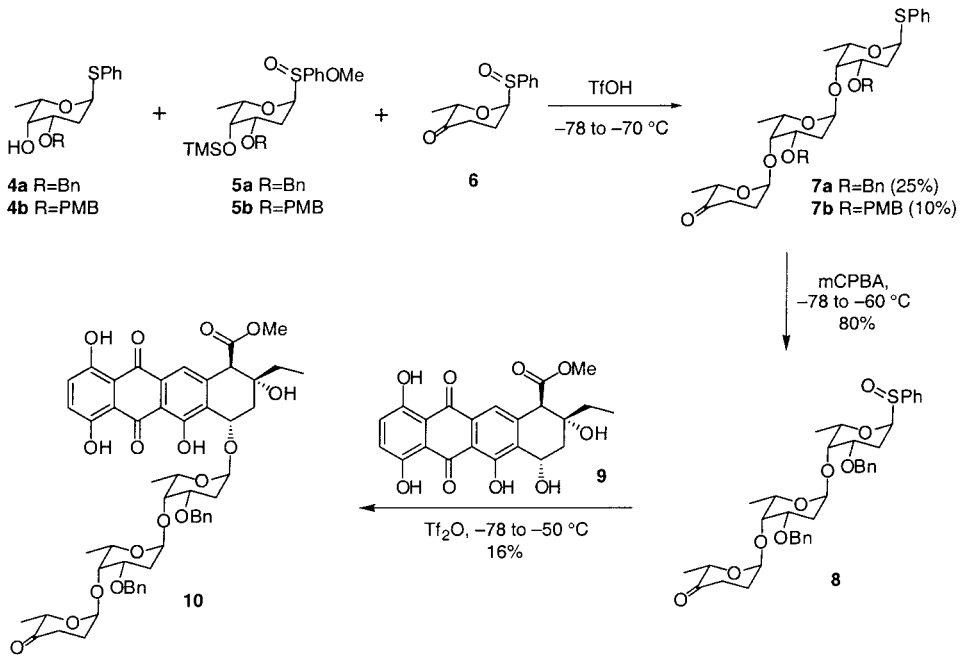
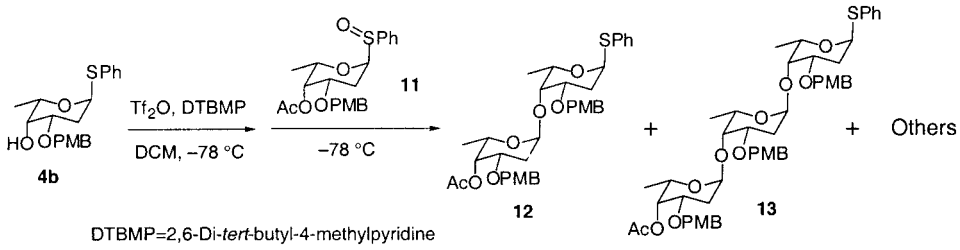
Scheme 1. One-Step Synthesis of Trisaccharides



Scheme 2. Formation of Trisaccharide **13** during the AB Glycosylation



a single reaction from three monomers, **4a**, **5a**, and **6** (see Scheme 1).[11] The reactivities of the sulfoxides and nucleophiles were tuned such that the linkage between the A ring and B ring would occur first, followed by formation of the linkage to the C ring. Using the polymerization strategy, trisaccharide **7a** could be synthesized in 25% yield in a single reaction. Oxidation of the anomeric sulfide produced trisaccharide sulfoxide **8** in 80% yield. To complete the synthesis of ciclamycin 0, we simply had to couple the trisaccharide to the aglycone ϵ-pyrromycinone (**9**)[12] and deprotect the final product (**10**). Unfortunately, the yield for glycosylating the aglycon was disappointing (16%), and we were unable to deprotect the benzyl ethers because the hydrogenation conditions also cleaved the benzylic glycosidic linkage to the aglycon.[13] To develop a good synthesis of ciclamycin 0, we needed to improve the coupling of the trisaccharide to the aglycon and modify the protecting groups on the trisaccharide.

In a model study, we found that *p*-methoxybenzyl (PMB) ethers could be deprotected with DDQ without cleaving the trisaccharide from the aglycon. Therefore, the A and B ring monomers were resynthesized with PMB protecting groups (**4b** and **5b**) and subjected to the conditions for the one-step synthesis. However, the modified monomers did not work as well in the one-step coupling reaction, and trisaccharide **7b** could only be isolated in 10% yield. A number of parameters were varied, but the one-step reaction could not be optimized further.

The substrate-dependent coupling yields suggested that the one-step reaction would not be amenable to the synthesis of large numbers of trisaccharide derivatives of ciclamycin 0. Therefore, we decided to build the trisaccharide in a stepwise manner. Our studies on the individual glycosylations led to some unexpected results which prompted a series of mechanistic investigations. On the basis of new insights into the sulfoxide reaction, we have been able to improve the glycosylation conditions, develop a better synthesis of the trisaccharide, and complete the synthesis of ciclamycin 0.

Results and Discussion

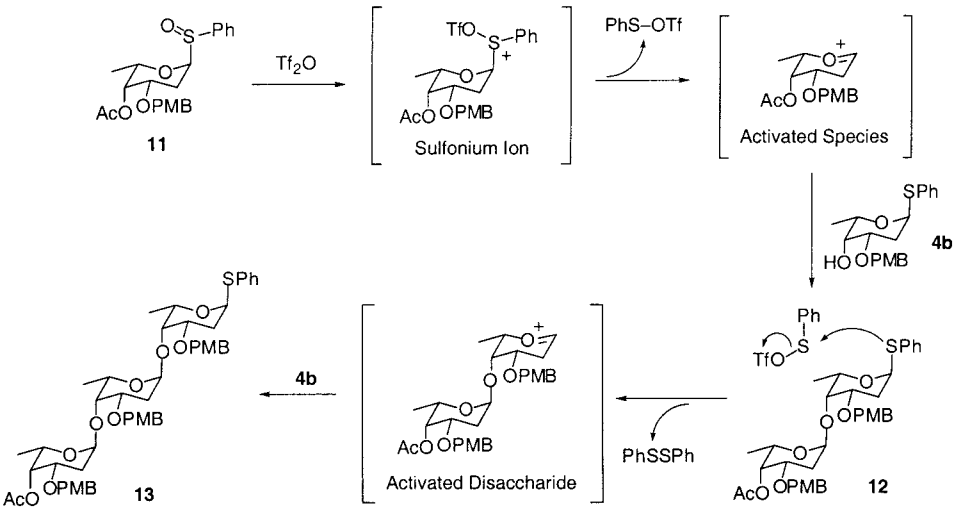
AB Glycosylation and Mechanistic Studies. We began by investigating the coupling of A ring derivative **4b** with B ring sulfoxide **11** (see Scheme 2). To prevent oligomerization, the C-4 hydroxyl of the B ring sulfoxide was protected as an acetate instead of the more labile TMS ether used in our original synthesis of the trisaccharide. In addition to this structural modification, we utilized an inverse addition procedure to activate the sulfoxide because we have found that this strategy

(11) For other one-pot syntheses of oligosaccharides, see: (a) Yamada, H.; Harada, T.; Takahashi, T. *J. Am. Chem. Soc.* **1994**, *116*, 7919 and references therein. (b) Chenault, H. K.; Castro, A. *Tetrahedron Lett.* **1994**, *49*, 9145. (c) Green, L.; Hinzen, B.; Ince, S. J.; Langer, P.; Ley, S. V.; Warriner, S. L. *Synlett* **1998**, 440 and references therein. (d) Zhang, Z.; Ollmann, I. R.; Ye, X.-S.; Wischnat, R.; Baasov, T.; Wong, C. H. *J. Am. Chem. Soc.* **1999**, *121*, 734.

(12) Pyrromycinone, **9**, was obtained by acidic hydrolysis of marcellomycin, a generous gift from Bristol-Myers Squibb. Pyrromycinone can also be obtained through known synthetic routes or through degradation of other readily available anthracyclines; see: (a) Hauser, F. M.; Mal, D. *J. Am. Chem. Soc.* **1984**, *106*, 1098. (b) Hoshino, T.; Setoguchi, Y.; Fujiwara, A. *J. Antibiot.* **1984**, *37*, 1469. (c) Krohn, K.; Kilmars, M.; Kohle, H.-J.; Ebeling, E. *Tetrahedron* **1984**, *40*, 3677.

(13) Raghavan, S. Ph.D. Thesis, Princeton University, 1994.

Scheme 3. Potential Mechanism for Trisaccharide Formation



minimizes the formation of anomeric sulfenates, thereby improving the yield of glycosylations.[14,15] Glycosylation of **4b** with **11** produced disaccharide **12** in 33% yield along with a large number of other products. Surprisingly, one of the other products formed in the reaction was a trisaccharide, **13**. Since acetates are stable to the conditions of the sulfoxide reaction, it was not immediately obvious how the trisaccharide was being formed.

One potential explanation for the formation of trisaccharide in the glycosylation of **4b** with **11** came from consideration of the byproducts that may form in the sulfoxide reaction. Activation of an anomeric sulfoxide with triflic anhydride is likely to release phenylsulfenyl triflate (see Scheme 3).[13,16,17] Others have found that alkyl and aromatic sulfenyl triflates activate anomeric sulfides rapidly at low temperature.[18,19] We reasoned that if phenylsulfenyl triflate were formed in significant amounts during the sulfoxide reaction, it might activate the anomeric sulfide of **12** and lead to the production of trisaccharide **13** (see Scheme 3). Since **4b**, **12**, and **13** each contain an anomeric sulfide, this activation process could lead to the production of a variety of oligomers which might explain why so many products were formed in the glycosylation reaction. The hypothesis that phenylsulfenyl triflate was causing problems in the reaction led us to investigate two different strategies to block phenylsulfenyl triflate mediated activation of the anomeric sulfides. The first strategy involved the addition of reagents to trap phenylsulfenyl triflate, while the second involved reducing the nucleophilicity of the sulfur atom on the A ring. As we demonstrate below, these strategies greatly improve the glycosylation reactions.

(1) Methods To Suppress Sulfide Activation: Phenylsulfenyl Triflate Scavengers. Identification of specific reagents to trap phenylsulfenyl triflate is complicated. To be effective, a trap must be reactive enough to outcompete anomeric sulfides which react rapidly with phenylsulfenyl triflate at −78 °C. In addition, the trap must react with phenylsulfenyl triflate selectively in the presence of other reactive electrophiles, such as triflic anhydride and the activated glycosyl intermediate(s). Given the high reactivity of the activated glycosyl intermediate(s), it was not obvious that any reagent would satisfy these requirements.

An extensive search of the literature suggested that unactivated alkenes might have the appropriate reactivity.[20−22] However, reaction of an alkene with phenylsulfenyl triflate would produce an episulfonium ion which might react with the alcohol acceptor (see Figure 2). To determine whether the addition of an alkene would affect the outcome of the reaction, we repeated the glycosylation of **4b** with **11** in the presence of 10 equiv of 4-allyl-1,2-dimethoxybenzene.[23] In the presence of this alkene, the glycosylation reaction appeared much cleaner by TLC and the yield of disaccharide improved considerably (from 33% to 71%). No alkylation of the starting alcohol was observed. In addition, we were able to isolate compound **14**, demonstrating that the alkene is sulfenylated in the reaction. The isolation of **14** supports the hypothesis that phenylsulfenyl triflate causes trisaccharide formation and suggests that the alkene improves the outcome by removing phenylsulfenyl triflate from the reaction mixture.

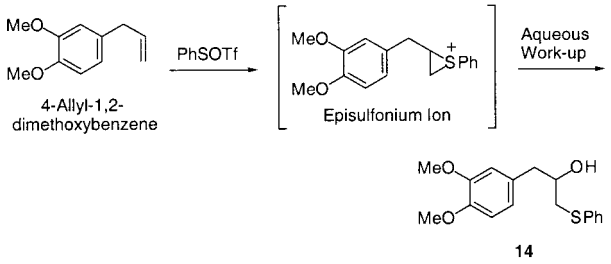


Figure 2. Sulfenylation of an alkene.

Although the addition of 4-allyl-1,2-dimethoxybenzene improved the glycosylation reaction considerably, trisaccharide

(14) Gildersleeve, J.; Pascal, R. A.; Kahne, D. *J. Am. Chem. Soc.* **1998**, *120*, 5961.

(15) For a recent application of inverse addition, see: Ge, M.; Thompson, C.; Kahne, D. *J. Am. Chem. Soc.* **1998**, *120*, 11014.

(16) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217.

(17) There may be more than one highly reactive sulfenylating agent produced in the reaction.

(18) Dasgupta, F.; Garegg, P. J. *Carbohydr. Res.* **1988**, *177*, C13.

(19) For the use of phenylsulfenyl triflate to activate sulfides, see: (a) Martichonok, V.; Whitesides, G. M. *J. Am. Chem. Soc.* **1996**, *118*, 8187. (b) Martichonok, V.; Whitesides, G. M. *Carbohydr. Res.* **1997**, *302*, 123. (c) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1998**, *120*, 435.

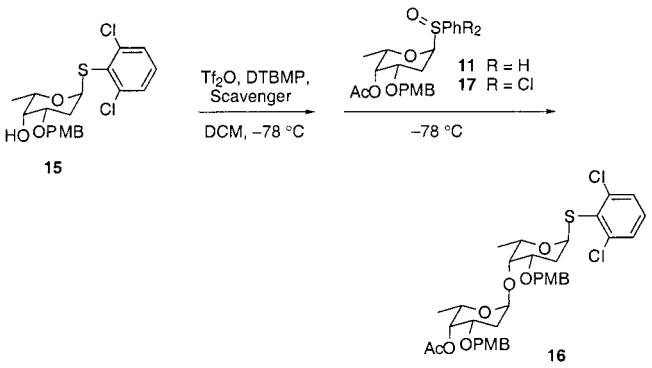
(20) Hopkins, P. B.; Fuchs, P. L. *J. Org. Chem.* **1978**, *43*, 1208.

(21) Jones, G. A.; Stirling, C. J. M.; Bromby, N. G. *J. Chem. Soc., Perkin. Trans. 2* **1983**, 385.

(22) Patai, S., Ed. *The Chemistry of Sulphenic Acids and Their Derivatives*; John Wiley and Sons, Ltd.: Chichester, 1990.

(23) This specific alkene was chosen for a number of reasons: it is commercially available and inexpensive, and has a sufficiently high boiling point to permit azeotroping with toluene along with the other starting materials prior to reaction.

Scheme 4. Glycosylation of the Modified A Ring



formation was not completely prevented. Several other traps were investigated, but none was found to be more effective than 4-allyl-1,2-dimethoxybenzene.[24] Therefore, we began investigating a second method for blocking sulfide activation.

(2) Methods To Suppress Sulfide Activation: Hindered Phenyl Sulfides. The second strategy for blocking sulfide activation involved the use of hindered sulfides. We expected that a less nucleophilic sulfide would react more slowly with phenylsulfenyl triflate, providing a better opportunity for the scavenger to remove phenylsulfenyl triflate from the reaction mixture before it could cause deleterious side reactions. Therefore, a modified A ring with a 2,6-dichlorophenyl sulfide (**15**) was synthesized; the two chlorine atoms positioned ortho to the sulfur atom were expected to decrease the nucleophilicity of the sulfur atom through steric and inductive effects. Glycosylation of the modified A ring, **15**, with sulfoxide **11** using inverse addition in the presence of 10 equiv of 4-allyl-1,2-dimethoxybenzene produced disaccharide **16** in 82% yield; no trisaccharide could be detected (see Scheme 4).[25]

Before proceeding with the completion of ciclamycin 0, we needed to establish that the 2,6-dichlorophenyl sulfide could be oxidized and used as a glycosyl donor. We were particularly concerned that the 2,6-dichlorophenyl group would cause problems during the coupling of the trisaccharide sulfoxide to the aglycon. The steric congestion and electron-withdrawing effects of the 2,6-dichlorophenyl group could decrease the rate of activation of the trisaccharide sulfoxide significantly, permitting side reactions such as anomeric sulfenate formation to occur.[14] To address this possibility, we decided to reinvestigate the AB glycosylation using a 2,6-dichlorophenyl-substituted B ring sulfoxide, **17**. This modified B ring sulfoxide was synthesized from the A ring derivative **15** by acetylation followed by oxidation with mCPBA. Glycosylation of **15** with sulfoxide **17** produced AB disaccharide **16** in 81% yield (see Scheme 4). The yield for this glycosylation is virtually identical with the yield obtained with the less hindered B ring sulfoxide **11**, indicating that the 2,6-dichlorophenyl substituent does not disrupt the AB glycosylation. These results suggested that the 2,6-dichlorophenyl substituent would not be a problem during the final coupling of the trisaccharide sulfoxide to the aglycon.

(24) Norbornylene was slightly less effective than 4-allyl-1,2-dimethoxybenzene, while vinylnorbornene, vinylnaphthalene, cyclopentene, and vinyltrimethylsilane were significantly less effective. No product was formed in the presence of triphenylphosphine or thioanisole.

(25) For comparison, glycosylation of **15** with sulfoxide **11** in the absence of a scavenger produced **16** in 45% yield along with 18% of the corresponding trisaccharide, showing that most of the improvement in yield is a result of the scavenger. However, similar improvements in yield (10−15%) are observed when the C ring sulfoxide is coupled. These modest improvements in yield achieved by incorporating the 2,6-dichlorophenyl sulfide become important when multiple glycosylations are conducted.

Formation of the ABC Trisaccharide and Completion of Ciclamycin 0. The next step in the synthesis of ciclamycin 0 involved coupling the AB disaccharide to the C ring. Glycosylations with the C ring sulfoxide have proven difficult in the past. In a model study using our original glycosylation conditions, coupling of A ring derivative **4b** with 2 equiv of C ring sulfoxide **6** produced the corresponding AC disaccharide in 33% yield. We initially thought that the low yield of this glycosylation was a result of decomposition of the C ring sulfoxide prior to activation with triflic anhydride. However, increasing the number of equivalents of sulfoxide to four resulted in a *decrease* in yield (24%), indicating that the problem was not simply due to instability of the C ring.

Our studies on the mechanism of the sulfoxide reaction suggested that other factors were responsible for the low yield. We have recently shown that anomeric sulfoxides can rearrange to sulfenates under the reaction conditions and that this process decreases the efficiency of a glycosylation reaction. In fact, we find that the C ring sulfoxide rearranges to sulfenate rapidly at −78 °C, indicating that sulfenate formation can compete with glycoside formation for this sulfoxide. However, sulfenate formation does not appear to be the only problem since increasing the number of equivalents of sulfoxide leads to a decrease in yield. One explanation for this unexpected observation comes from our studies on byproduct-mediated side reactions. As the amount of sulfoxide is increased, more byproducts are produced. Since the A ring and AC disaccharide each contain an anomeric sulfide, increased production of byproducts could lead to more extensive destruction of the starting materials and products, resulting in a decrease in yield for the reaction.

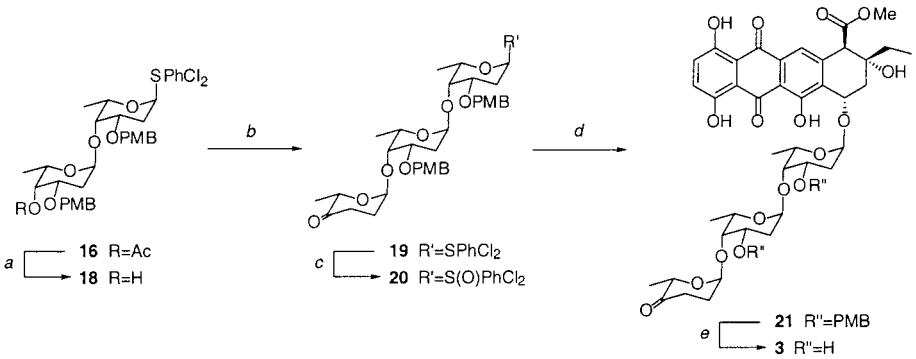
To suppress sulfenate formation and byproduct-mediated side reactions, the glycosylation of disaccharide **18** with C ring sulfoxide **6** was conducted using inverse addition in the presence of a phenylsulfenyl triflate scavenger, 4-allyl-1,2-dimethoxybenzene (Scheme 5). Using these glycosylation conditions, trisaccharide **19** was obtained in 68% yield (5:1 α/β). This glycosylation reaction provides a good illustration of how the mechanistic studies can be used to improve a difficult glycosylation reaction.

Completion of ciclamycin 0 required oxidation of the trisaccharide, attachment to the aglycon, and deprotection. Oxidation of trisaccharide **19** with mCPBA resulted in Baeyer−Villiger rearrangement of the C ring ketone. Interestingly, this problem did not occur during the oxidation of trisaccharide **7a** which contains a simple thiophenyl group on the anomeric carbon of the A ring. While mCPBA can oxidize a 2,6-dichlorophenyl sulfide (e.g., synthesis of monosaccharide **17**), the oxidation requires much warmer temperatures than usual (0 °C vs −45 °C). Apparently, the decreased rate of sulfur oxidation of trisaccharide **19** results in preferential reaction of mCPBA with the ketone of the C ring. Happily, we found that dimethyldioxirane will selectively oxidize trisaccharide **19** to sulfoxide **20** in 90% yield.[26]

The last obstacle for the synthesis of ciclamycin 0 involved coupling the trisaccharide to the aglycon. Our initial work on the coupling of **7a** to the aglycon using our original glycosylation conditions produced the benzyl-protected ciclamycin derivative **10** in 16% yield. However, the glycosylation of the aglycon **9** with trisaccharide **20** using our modified conditions proceeded smoothly to generate PMB-protected ciclamycin derivative **21** in 75% yield. Removal of the PMB ethers using DDQ completed the synthesis of ciclamycin 0.

(26) Murray, R. M.; Jeyaraman, R.; Pillay, M. K. *J. Org. Chem.* **1987**, *52*, 746.

Scheme 5. Completion of Ciclamycin 0[a]



[a] Reaction conditions: (a) LAH/Et_2O, 0 °C, 30 min (92%); (b) Tf_2O, DTBMP, 4-allyl-3,4-dimethoxybenzene, DCM, −78 °C, then **6** (68%, 5:1 α/β); (c) dimethyldioxrane, −72 to −42 °C (90%); (d) pyrromycinone (**9**) Tf_2O, DTBMP, 4-allyl-3,4-dimethoxybenzene, DCM, −78 °C, then **20** (75%); (e) DDQ, 25 °C, 30 min (60%).

Implications for the Sulfoxide Glycosylation Method. Recent studies on the mechanism of the sulfoxide reaction have demonstrated that three different intermediates can be formed, an oxonium ion, a glycosyl triflate, and a glycosyl sulfenate.[14,16] The identification and study of these intermediates has led to new methods to control stereoselectivity and improve efficiency in the reaction. The studies on byproduct formation reported in this paper provide a more complete understanding of the factors that affect the outcome of a glycosylation reaction. For example, we have found that byproducts produced during the activation of a glycosyl sulfoxide will react with anomeric sulfides, causing undesirable side reactions. This is a fairly serious problem given that sulfides are versatile intermediates for oligosaccharide synthesis and that sulfides are convenient precursors to sulfoxide donors. Fortunately, we find that alkenes added to the reaction will scavenge the byproducts and prevent decomposition of the sulfide. We should note that sulfenylating agents react with a wide range of other functional groups.[27,28] Therefore, we think the scavengers developed for the synthesis of ciclamycin 0 will be useful in many other sulfoxide glycosylation reactions. By improving our mechanistic understanding of the sulfoxide reaction, we now have a better foundation for analyzing and improving difficult glycosylation reactions.

Conclusions

Our mechanistic studies on byproducts produced in the sulfoxide reaction have led to the development of improved conditions for the reaction. By simply including an alkene such as 4-allyl-1,2-dimethoxybenzene in the reaction, the yield of a glycosylation reaction can be improved dramatically. The modified conditions for the sulfoxide reaction have been used to develop a short and efficient synthesis of ciclamycin 0. The synthesis only requires six steps from the starting monomers and proceeds with an overall yield of 17%. The directness and efficiency of our synthesis should permit the rapid assembly of derivatives which can be used to probe the relationships between structure and activity for ciclamycin 0 and related anthracyclines.

(27) For example, sulfenylating agents are known to react with alcohols, amines, and electron-rich aromatic rings. See ref 22.

(28) In addition to activating glycosyl sulfides, sulfenylating agents have been used to activate glycosyl xanthates and glycals. For activation of xanthates, see: (a) Marra, A.; Sinay, P. *Carbohydr. Res.* **1990**, *195*, 303. (b) Birberg, W.; Lonn, H. *Tetrahedron Lett.* **1991**, *32*, 7453. (c) Martichonok, V.; Whitesides, G. M. *J. Org. Chem.* **1996**, *61*, 1702. For activation of glycals, see: (d) Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1987**, *28*, 2723. (e) Ramesh, S.; Kaila, N.; Grewal, G.; Franck, R. W. *J. Org. Chem.* **1990**, *55*, 5. (f) Grewal, G.; Kaila, N.; Franck, R. W. *J. Org. Chem.* **1992**, *57*, 2084. (g) Wang, J.; Wurster, J. A.; Wilson, L. J.; Liotta, D. *Tetrahedron Lett.* **1993**, *34*, 4881.

Experimental Section

General Methods. NMR spectra were recorded on a JEOL GSX 270 or a Varian Inova 500 Fourier transform NMR spectrometer. Proton chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) unless otherwise noted. Carbon chemical shifts are reported in parts per million (ppm) downfield from TMS using the solvent CD_3COCD_3 as an internal reference unless otherwise noted. Coupling constants (*J*) are reported in hertz (Hz). Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broadened (br). Mass spectra were obtained on a VG ZAB, VG 7070, or HP 5989A (University of California, Riverside, Mass Spectrometry Facility).

Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Flash column chromatography was performed using silica gel 60 (230−400 mesh) from EM Science/Bodman.

All reactions were carried out under argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise noted. All reagents were purchased from commercial suppliers and used without further purification unless otherwise noted.

2-Hydroxy-3-(3,4-dimethoxyphenyl)propyl Phenyl Sulfide (14). $R_f = 0.32$ (7% EtOAc/methylene chloride); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.29 (m, 5H), 6.81 (d, $J = 7.9$ Hz, 1H), 6.73 (d, $J = 7.9$ Hz, 1H), 6.72 (s, 1H), 3.92, (m, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.13 (dd, $J =$ 3.9, 13.5 Hz, 1H), 2.90 (dd, $J = 7.9$, 13.5 Hz, 1H), 2.82 (m, 2H), 2.36 (m, 1H); ^{13}C NMR (CD_3COCD_3, 125.8 MHz) δ 150.7, 149.5, 138.6, 132.8, 130.3, 130.0, 127.0, 122.9, 115.0, 113.4, 72.5, 56.7, 56.6, 43.5, 41.2; HRFABMS calcd for $C_{17}H_{20}O_3S$ (M^+) 304.1133, found 304.1116.

Synthesis of the 2,6-Dichlorophenyl-Substituted A Ring Monomer (15). To a solution of 1,3,4-tri-*O*-acetyl-2,6-dideoxy-α-L-galactopyranoside (421 mg, 1.54 mmol) in 20 mL of dichloromethane at −42 °C was added 2,6-dichlorobenzenethiol (826 mg, 4.63 mmol). The reaction mixture was stirred at −78 °C for 2 h and then allowed to warm to 0 °C over 2 h. The reaction mixture was quenched by pouring it into saturated $NaHCO_3$ solution (20 mL) and allowing it to stir for 2 h. The aqueous layer was extracted with dichloromethane (3 × 10 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (20% EtOAc/petroleum ether) to afford 2,6-dichlorophenyl 3,4-di-*O*-acetyl-2,6-dideoxy-1-thio-α-L-galactopyranoside (512 mg, 85%): $R_f = 0.29$ (20% EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40 (d $J = 8.0$ Hz, 2H), 7.21 (t, $J = 8.0$ Hz, 1H), 5.82 (d, $J = 6.0$ Hz, 1H), 5.34 (ddd, $J = 3.0$, 5.0, 13.0 Hz, 1H), 5.25 (d, $J = 3.0$ Hz, 1H), 4.68 (q, $J = 6.0$ Hz, 1H), 2.43 (ddd, $J = 6.0$, 13.0, 13.0 Hz, 1H), 2.14 (s, 3H), 2.12 (m, 1H), 2.01 (s, 3H), 1.07 (d $J = 6.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 170.7, 170.1, 141.7, 131.4, 130.6, 128.9, 84.1, 69.8, 67.4, 67.3, 30.3, 21.0, 20.9, 16.5; HRFABMS calcd for $C_{16}H_{18}O_5SCl_2$ (MNa^+) 415.0149, found 415.0128.

To a solution of 2,6-dichlorophenyl 3,4-di-*O*-acetyl-2,6-dideoxy-1-thio-α-L-galactopyranoside (512 mg, 1.30 mmol) in methanol (20 mL) was added sodium methoxide (91 mg, 1.69 mmol). The reaction mixture

was stirred at room temperature for 30 min and then neutralized by addition of Amberlite I-20 acid resin. The resin was removed by filtration, and the filtrate was concentrated in vacuo to afford 2,6-dichlorophenyl 2,6-dideoxy-1-thio-α-L-galactopyranoside as a white solid (386 mg, 96%): $R_f = 0.34$ (10% EtOAc/dichloromethane); ^{1}H NMR (CD_3OD, 500 MHz) δ 7.47 (d, $J = 8.0$ Hz, 2H), 7.30 (t, $J = 8.0$ Hz, 1H), 5.72 (d, $J = 6.0$ Hz, 1H), 4.44 (q, $J = 6.5$ Hz, 1H) 3.99 (ddd, $J = 3.0$, 5.0, 12.5 Hz, 1H), 3.62 (d, $J = 3.0$ Hz, 1H), 2.31 (ddd, $J = 5.8$, 13.8, 13.8 Hz, 1H), 1.96 (dd $J = 5$, 13.5 Hz, 1H), 1.12 (d, $J = 6.5$ Hz, 1H); ^{13}C NMR (CD_3OD, 125.8 MHz) δ 142.6, 133.1, 131.8, 129.9, 86.0, 72.2, 70.2, 67.6, 33.6, 17.0; HRFABMS calcd for $C_{12}H_{14}O_3SCl_2$ (MNa^+) 330.9923, found 330.9938.

A combined solution of 2,6-dichlorophenyl 2,6-dideoxy-1-thio-α-L-galactopyranoside (604 mg, 1.96 mmol) and dibutyltin oxide (536 mg, 2.16 mmol) in benzene (25 mL) was fitted with a Dean−Stark apparatus and refluxed overnight. The reaction was cooled to room temperature, and 4-methoxybenzyl chloride (1.06 mL, 7.82 mmol) and tetrabutylammonium bromide (635 mg, 1.97 mmol) were added. The reaction was refluxed for 3.5 h, cooled to room temperature, and concentrated in vacuo. The crude reaction mixture was purified by silica gel chromatography (25% ethyl acetate/petroleum ether) to afford 2,6-dichlorophenyl 2,6-dideoxy-3-*O*-(4-methoxybenzyl)-1-thio-α-L-galactopyranoside (**15**) (833 mg, 99%): $R_f = 0.30$ (33% EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.38 (d, $J = 8.2$ Hz, 2H), 7.25 (m, 3H), 6.90 (d, $J = 8.2$ Hz, 2H), 5.76 (d, $J = 5.6$ Hz, 1H), 4.56 (s, 2H), 4.46 (q, $J = 6.6$ Hz, 1H), 3.90 (m, 1H), 3.84 (m, 1H), 3.82 (s, 3H), 2.33 (ddd, $J = 5.6$, 7.9, 11.9 Hz, 1H), 2.15 (m, 2H), 1.22 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (CD_3COCD_3, 125.8 MHz) δ 160.7, 142.7, 133.4, 132.3, 132.2, 130.6, 130.3, 115.0, 86.5, 74.9, 70.4, 70.3, 69.1, 56.0, 31.8, 17.7; HRFABMS calcd for $C_{20}H_{22}O_4NaSCl_2$ (MNa^+) 451.0514, found 451.0503.

2,6-Dichlorophenyl [4-*O*-Acetyl-2,6-dideoxy-3-*O*-(4-methoxybenzyl)-α-L-galactopyranosyl]-(1→4)-2,6-dideoxy-3-*O*-(4-methoxybenzyl)-1-thio-α-L-galactopyranoside (16). Alcohol **15** (42 mg, 0.098 mmol), 4-allyl-1,2-dimethoxybenzene (250 μL, 0.098 mmol), and 2,6-di-*tert*-butyl-4-methylpyridine (87 mg, 0.42 mmol) were combined, and residual water was removed by azeotropic distillation with toluene (3 × 10 mL). To the residue in methylene chloride (4.5 mL) was added 4 Å molecular sieves (500 mg), and the resulting suspension was stirred at room temperature for 1 h. The suspension was cooled to −78 °C, and a solution of triflic anhydride (25 μL, 0.148 mmol) in methylene chloride (350 μL) was added over 1−2 min. A solution of sulfoxide **11** (62 mg, 0.148 mmol) in methylene chloride (2.5 mL) was added via syringe over 10−15 min. After 15 min at −78 °C, the reaction was quenched with diethylamine (100 μL), filtered into saturated aqueous $NaHCO_3$ (30 mL), and extracted with methylene chloride (3 × 20 mL). The organic layers were combined, dried over Na_2SO_4, decanted, and concentrated in vacuo. The product was purified by flash chromatography (33% EtOAc/petroleum ether) to afford disaccharide **16** (58 mg, 82%): $R_f = 0.35$ (33% EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.39 (d, $J = 7.8$ Hz, 2H), 7.21 (m, 5H), 6.89 (d, $J = 7.8$ Hz, 2H), 6.83 (d, $J = 8.9$ Hz, 2H), 5.80 (d, $J = 5.3$ Hz, 1H), 5.25 (d, $J = 2.0$ Hz, 1H), 5.04 (m, 1H), 4.58 (m, 3H), 4.36 (m, 3H), 3.88 (m, 3H), 3.82 (s, 3H), 3.78 (s, 3H), 2.38 (ddd, $J = 5.3$, 12.5, 12.8 Hz, 1H), 2.16 (m, 1H), 2.12 (s, 3H), 1.98 (m, 2H), 1.13 (d, $J = 6.6$ Hz, 3H), 0.88 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (CD_3COCD_3, 125.8 MHz) δ 171.5, 160.8, 160.7, 142.7, 133.4, 132.4, 132.2, 132.1, 130.8, 130.4, 130.3, 115.0, 114.9, 100.5, 86.5, 76.2, 74.6, 72.6, 71.0, 70.9, 70.8, 70.7, 66.5, 56.1, 56.0, 32.7, 32.6, 21.4, 18.1, 17.7; HRFABMS calcd for $C_{36}H_{42}O_9NaSCl_2$ (MNa^+) 743.1824, found 743.1792.

Glycosylation Using the 2,6-Dichlorophenyl-Substituted B Ring Sulfoxide. Alcohol **15** (41 mg, 0.096 mmol), 4-allyl-1,2-dimethoxybenzene (230 μL, 1.34 mmol), and 2,6-di-*tert*-butyl-4-methylpyridine (104 mg, 0.51 mmol) were combined, and residual water was removed by azeotropic distillation with toluene (3 × 10 mL). To the residue in methylene chloride (4.5 mL) was added 4 Å molecular sieves (500 mg), and the resulting suspension was stirred at room temperature for 1 h. The suspension was cooled to −78 °C, and a solution of triflic anhydride (23 μL, 0.134 mmol) in methylene chloride (350 μL) was added over 1−2 min. A solution of sulfoxide **17** (65 mg, 0.134 mmol) in methylene chloride (3.0 mL) was added via syringe over 10−15 min. After 15 min at −78 °C, the reaction was quenched with diethylamine (100 μL), filtered into saturated aqueous $NaHCO_3$ (30 mL), and extracted with methylene chloride (3 × 20 mL). The organic layers were combined, dried over Na_2SO_4, decanted, and concentrated in vacuo. The product was purified by flash chromatography (33% EtOAc/petroleum ether) to afford disaccharide **16** (56 mg, 81%).

2,6-Dichlorophenyl [2,6-Dideoxy-3-*O*-(4-methoxybenzyl)-α-L-galactopyranosyl]-(1→4)-2,6-dideoxy-3-*O*-(4-methoxybenzyl)-1-thio-α-L-galactopyranoside (18). The disaccharide **16** (58 mg, 0.081 mmol) was taken up in diethyl ether (4 mL) and cooled to 0 °C. Lithium aluminum hydride (150 μL of 1 M LAH/ether, 0.15 mmol) was added. The reaction was stirred for 30 min and then quenched by slow addition of ethyl acetate (250 μL). After 15 min, the reaction was diluted with ethyl acetate (20 mL) and washed with water (20 mL) and saturated aqueous $NaHCO_3$ (20 mL). The aqueous layers were reextracted with ethyl acetate (20 mL), and then the organic layers were combined, dried over Na_2SO_4, decanted, and concentrated in vacuo. The product was purified by flash chromatography (50% EtOAc/petroleum ether) to afford disaccharide **18** (50 mg, 92%): $R_f = 0.40$ (50% EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.37 (d, $J = 7.9$ Hz, 2H), 7.24 (m, 5H), 6.88 (m, 4H), 5.79 (d, $J = 5.6$ Hz, 1H), 5.03 (d, $J = 2.6$ Hz, 1H), 4.63 (d, $J = 11.9$ Hz, 1H), 4.53 (d, $J = 11.9$ Hz, 1H), 4.51 (d, $J = 11.2$ Hz, 1H), 4.46 (d, $J = 11.2$ Hz, 1H), 4.32 (m, 2H), 3.87 (m, 3H), 3.82 (s, 3H), 3.79 (s, 3H), 3.71 (br s, 1H), 2.39 (ddd, $J = 5.6$, 12.6, 13.2 Hz, 1H), 2.10 (m, 2H), 1.95 (m, 2H), 1.13 (d, $J = 6.6$ Hz, 3H), 1.06 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (CD_3COCD_3, 125.8 MHz) δ 160.7, 160.66, 142.7, 133.4, 132.5, 132.4, 132.3, 132.2, 130.6, 130.3, 115.1, 115.0, 100.5, 86.5, 75.7, 74.6, 74.5, 71.2, 70.7, 70.2, 69.3, 69.2, 67.8, 56.1, 32.7, 31.4, 18.2, 18.0; HRFABMS calcd for $C_{34}H_{40}O_8NaSCl_2$ (MNa^+) 701.1719, found 701.1744.

2,6-Dichlorophenyl {(2,3,6-Trideoxy-4-ulo-α-L-hexopyranosyl)-(1→4)-[2,6-dideoxy-3-*O*-(4-methoxybenzyl)-α-L-galactopyranosyl]}-(1→4)-2,6-dideoxy-3-*O*-(4-methoxybenzyl)-1-thio-α-L-galactopyranoside (19). Alcohol **18** (50 mg, 0.074 mmol), 4-allyl-1,2-dimethoxybenzene (317 μL, 1.84 mmol), and 2,6-di-*tert*-butyl-4-methylpyridine (168 mg, 0.82 mmol) were combined, and residual water was removed by azeotropic distillation with toluene (3 × 10 mL). To the residue in methylene chloride (5.0 mL) was added 4 Å molecular sieves (500 mg), and the resulting suspension was stirred at room temperature for 1 h. The suspension was cooled to −78 °C, and a solution of triflic anhydride (28 μL, 0.168 mmol) in methylene chloride (350 μL) was added over 1−2 min. A solution of sulfoxide **6**[29] (40 mg, 0.168 mmol) in methylene chloride (3.0 mL) was added via syringe over 10−15 min. After 15 min at −78 °C, the reaction was filtered into saturated aqueous $NaHCO_3$ (30 mL) and extracted with methylene chloride (3 × 20 mL). The organic layers were combined, dried over Na_2SO_4, decanted, and concentrated in vacuo. The product was purified by flash chromatography (33% EtOAc/petroleum ether) to afford a mixture of trisaccharides (40 mg, 68%, α:β = 5:1). α-Glycoside **19**: $R_f = 0.30$ (7% EtOAc/methylene chloride); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.38 (d, $J = 7.9$ Hz, 2H), 7.22 (m, 7H), 6.86 (m, 4H), 5.78 (d, $J = 5.3$ Hz, 1H), 5.06 (br s, 1H), 5.01 (t, $J = 4.3$ Hz, 1H), 4.66 (q, $J = 6.6$ Hz, 1H), 4.51 (m, 4H), 4.34 (q, $J = 6.6$ Hz, 1H), 4.23 (q, $J = 6.6$ Hz, 1H), 3.88 (m, 4H), 3.82 (s, 3H), 3.78 (s, 3H), 2.62 (m, 1H), 1.95−2.45 (m, 7H), 1.13 (d, $J = 6.6$ Hz, 3H), 0.95 (d, $J = 6.6$ Hz, 6H); ^{13}C NMR (CD_3COCD_3, 125.8 MHz) δ 211.1, 160.6, 160.5, 142.6, 133.3, 132.3, 132.2, 132.1, 130.3, 130.2, 130.1, 115.0, 114.8, 100.3, 99.0, 86.4, 76.7, 75.6, 74.5, 73.7, 72.4, 71.0, 70.7, 70.6, 68.6, 56.0, 34.9, 32.5, 32.0, 31.1, 18.1, 18.0, 15.8; HRFABMS calcd for $C_{40}H_{48}O_{10}NaSCl_2$ (MNa^+) 813.2243, found 813.2221. β-Glycoside: $R_f = 0.28$ (7% EtOAc/methylene chloride); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.38 (d, $J = 7.9$ Hz, 2H), 7.23 (m, 5H), 6.87 (m, 4H), 5.79 (d, $J = 5.3$ Hz, 1H), 5.30 (t, $J = 3.6$ Hz, 1H), 5.06 (br s, 1H), 4.63 (d, $J = 11.6$ Hz, 1H), 4.52 (d, $J = 11.6$ Hz, 1H), 4.50 (s, 2H), 4.31 (m, 2H), 3.88 (m, 5H), 3.82 (s, 3H), 3.77 (s, 3H), 2.0−2.7 (m, 8H), 1.29 (d, $J = 6.6$ Hz, 3H), 1.13 (d, $J = 6.3$ Hz, 3H), 1.01 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (CD_3COCD_3, 125.8 MHz) δ 209.2, 160.7, 142.8, 133.4, 132.4, 132.2, 130.5, 130.4, 130.35, 130.3, 115.1, 100.7, 100.5, 86.5, 76.5, 75.7, 75.5, 75.1, 74.6,

(29) The known C ring sulfoxide **6** can be synthesized from rhamnose in seven steps (58% overall yield); see ref 7.

71.2, 71.0, 70.8, 68.0, 56.1, 35.8, 32.7, 31.9, 31.7, 18.5, 18.2, 16.4; HRFABMS calcd for $C_{40}H_{48}O_{10}NaSCl_2$ (MNa^+) 813.2243, found 813.2287.

{(2,3,6-Trideoxy-4-ulo-α-L-hexopyranosyl)-(1→4)-[2,6-dideoxy-3-*O*-(4-methoxybenzyl)-α-L-galactopyranosyl]}-(1→4)-2,6-dideoxy-3-*O*-(4-methoxybenzyl)-1-(2,6-dichlorophenylsulfinyl)-α-L-galactopyranoside (20). A solution of trisaccharide **19** (41 mg, 0.052 mmol) and sodium bicarbonate (200 mg, 2.38 mmol) in methylene chloride (3 mL) was cooled to −72 °C. Dimethyldioxirane[30] (2 mL of ∼0.05 M dimethyldioxirane in acetone, 0.10 mmol) was added, and the reaction was warmed slowly to −45 °C. The reaction was quenched with dimethyl sulfide (3 drops) and then poured into saturated $NaHCO_3$ (30 mL) and extracted three times with methylene chloride (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, decanted, and concentrated in vacuo. The crude mixture was purified by silica column chromatography (50% ethyl acetate/petroleum ether) to afford trisaccharide sulfoxide **20** (38 mg, 90%): R_f = 0.45 (50% EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.38 (m, 3H), 7.27 (m, 4H), 6.88 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 5.84 (d, J = 5.3 Hz, 1H), 5.05 (br s, 1H), 5.01 (t, J = 4.3 Hz, 1H), 4.65 (q, J = 6.6 Hz, 1H), 4.59 (s, 2H), 4.55 (d, J = 11.6 Hz, 1H), 4.48 (d, J = 11.6 Hz, 1H), 4.24 (q, J = 6.3 Hz, 1H), 4.08 (q, J = 6.6 Hz, 1H), 3.88 (m, 4H), 3.82 (s, 3H), 3.77 (s, 3H), 2.77 (m, 1H), 2.61 (m, 1H), 2.1−2.5 (m, 4H), 2.03 (m, 2H), 1.13 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H), 0.94 (d, J = 6.3 Hz, 3H); ^{13}C NMR (CD_3COCD_3, 125.8 MHz) δ 211.2, 160.7, 138.8, 137.6, 134.8, 132.3, 132.1, 130.5, 130.4, 115.1, 115.0, 100.5, 99.1, 92.5, 76.8, 75.3, 74.8, 73.8, 73.7, 72.6, 70.9, 70.8, 68.8, 56.1, 35.0, 32.2, 25.0, 18.5, 18.3, 15.9; HRFABMS calcd for $C_{40}H_{48}O_{11}NaSCl_2$ (MNa^+) 829.2192, found 829.2163.

7-*O*-{(2,3,6-Trideoxy-4-ulo-α-L-hexopyranosyl)-(1→4)-[2,6-dideoxy-3-*O*-(4-methoxybenzyl)-α-L-galactopyranosyl]-(1→4)-2,6-dideoxy-3-*O*-(4-methoxybenzyl)-α-L-galactopyranosyl}-ϵ-pyrromycinone (21). ϵ-Pyrromycinone (**9**)[12] (5 mg, 0.012 mmol), 4-allyl-1,2-dimethoxybenzene (60 μL, 0.35 mmol), and 2,6-di-*tert*-butyl-4-methylpyridine (32 mg, 0.16 mmol) were combined, and residual water was removed by azeotropic distillation with toluene (3 × 10 mL). To the residue in methylene chloride (2.5 mL) was added 4 Å molecular sieves (200 mg), and the resulting suspension was stirred at room temperature for 1 h. The suspension was cooled to −78 °C, and a solution of triflic anhydride (6 μL, 0.036 mmol) in methylene chloride (200 μL) was added over 1−2 min. A solution of trisaccharide sulfoxide **20** (28 mg, 0.035 mmol) in methylene chloride (1.5 mL) was added via syringe over 10 min. After 20 min at −78 °C, the reaction was filtered into phosphate-buffered saline (30 mL, pH 7) and extracted with methylene chloride (3 × 20 mL). The organic layers were combined, dried over Na_2SO_4, decanted, and concentrated in vacuo. The product was purified by flash chromatography (40% EtOAc/petroleum ether + 1% acetic acid) to afford protected ciclamcyin 0 (**21**) (9 mg, 75%): R_f = 0.45 (50% EtOAc/petroleum ether + 1% acetic acid); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 12.97 (s, 1H), 12.83 (s, 1H), 12.25 (s, 1H), 7.73 (s, 1H), 7.30 (m, 4H), 7.13 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 6.76 (d, J = 8.6 Hz, 2H), 5.26 (d, J = 2.0 Hz, 1H), 5.08 (br s, 1H), 4.99 (t, J = 4.0 Hz, 1H), 4.35−4.75 (m, 6H), 4.32 (s, 1H), 4.20 (q, J = 6.6 Hz, 1H), 4.12 (s, 1H), 4.02 (q, J = 6.6 Hz, 1H), 3.5−3.98 (m, 3H), 3.82 (s, 3H), 3.74 (s, 3H), 3.70 (s, 3H), 1.92−2.70 (m, 9H), 1.40−1.92 (m, 4H), 1.28 (d, J = 6.2 Hz, 3H), 1.26 (s, 1H), 0.96 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 6.6 Hz, 3H); ^{13}C NMR (CD_3COCD_3, 125.8 MHz) δ 211.2, 192.3, 187.3, 172.4, 163.5, 160.7, 160.5, 159.8, 159.1, 144.3, 134.2, 133.1, 132.4, 132.3, 131.5, 131.3, 130.5, 130.3, 129.5, 121.3, 116.2, 115.0, 114.9, 114.1, 114.0, 104.9, 103.5, 100.4, 99.1, 76.9, 75.6, 74.2, 72.6, 72.4, 72.2, 70.9, 70.8, 69.6, 68.6, 58.6, 56.2, 56.0, 53.4, 35.6, 35.0, 33.6, 32.4, 32.3, 25.0, 18.5, 18.3, 15.9, 7.7; HRMS calcd for $C_{56}H_{64}O_{19}$ (M^+) 1040.4043, found 1040.4013.

Ciclamycin 0 (3). To a solution of PMB-protected ciclamycin 0 (**20**) (0.007 g, 0.00672 mmol) in 4.0 mL of methylene chloride were added deionized water (3 drops) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.015 g, 0.0672 mmol). The reaction mixture was stirred at room temperature for 30 min. The reaction mixture was washed with water (5 mL), and the organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by preparative thin-layer chromatography (70% EtOAc/petroleum ether + 1% acetic acid) to afford 0.003 g (60%) of ciclamycin 0 (**3**) as an orange solid.[31]

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Supporting Information Available: Experimental procedures for the synthesis of **4b**, **11**, **12**, and **17**, as well as ^{1}H and ^{13}C NMR spectra for **4b** and **11**−**21** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(31) The ^{1}H, ^{13}C, and mass spectra for synthetic ciclamycin 0 were identical with the spectra reported in the literature (see refs 6 and 8).