# Concise Synthesis of the Calicheamicin Oligosaccharide Using the Sulfoxide Glycosylation Method

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**Abstract:** A short synthesis of the calicheamicin oligosaccharide is reported. All the glycosidic linkages have been constructed using the sulfoxide glycosylation reaction, demonstrating the efficacy of the method. A general method to introduce N–O glycosidic linkages in oligosaccharides has been developed and employed to construct the N–O bond that connects rings A and B. In the final step of the synthesis, the two halves of the calicheamicin oligosaccharide are coupled in a completely deprotected form. This convergent synthesis permits the rapid construction of derivatives of the calicheamicin oligosaccharide to test the importance of particular structural features in DNA binding.

## Introduction

Calicheamicin $\gamma_1$[1] (**1**), reported in 1987,[1] is a minor groove binder that causes double-stranded scission of DNA at oligopyrimidine runs. Calicheamicin has attracted a great deal of attention from synthetic chemists because of its unusual structure. Over the past few years it has generated several synthetic approaches of considerable sophistication.[2-4] The construction of the aglycone by Danishefsky in 1991 and the total synthesis of calicheamicin $\gamma_1$[1] by Nicolaou in 1992 represent major synthetic accomplishments.[2r,4] Calicheamicin is an intriguing natural product because it cleaves DNA site-selectively at oligopyrimidine tracts.[5] Several lines of evidence indicate that the oligosaccharide aryl tail plays a central role in DNA recognition.[5b,c,6] Moreover, NMR studies from this laboratory reveal numerous contacts between the aryl tetrasaccharide and the minor groove at the recognition sites of two different DNA duplexes.[7] The NMR studies have provided us with a picture of how calicheamicin binds in the minor groove of DNA; however, we would like to understand in greater detail how particular features of the calicheamicin oligosaccharide contribute to binding affinity and selectivity.[5c,6c,8,9] This knowledge could enable the design of other carbohydrate-based DNA binders. In order to probe the structural requirements for minor groove binding, an efficient and flexible route to the calicheamicin oligosaccharide is required.

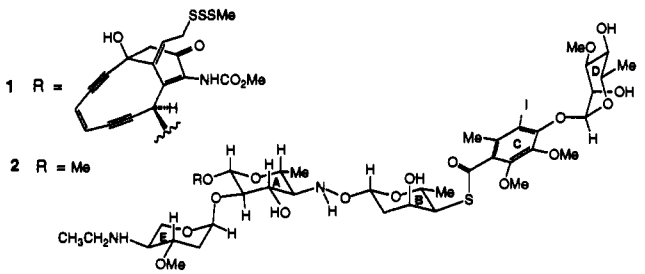


**Figure 1.** Structure of calicheamicin $\gamma^1$ **1** and the calicheamicin oligosaccharide **2**.

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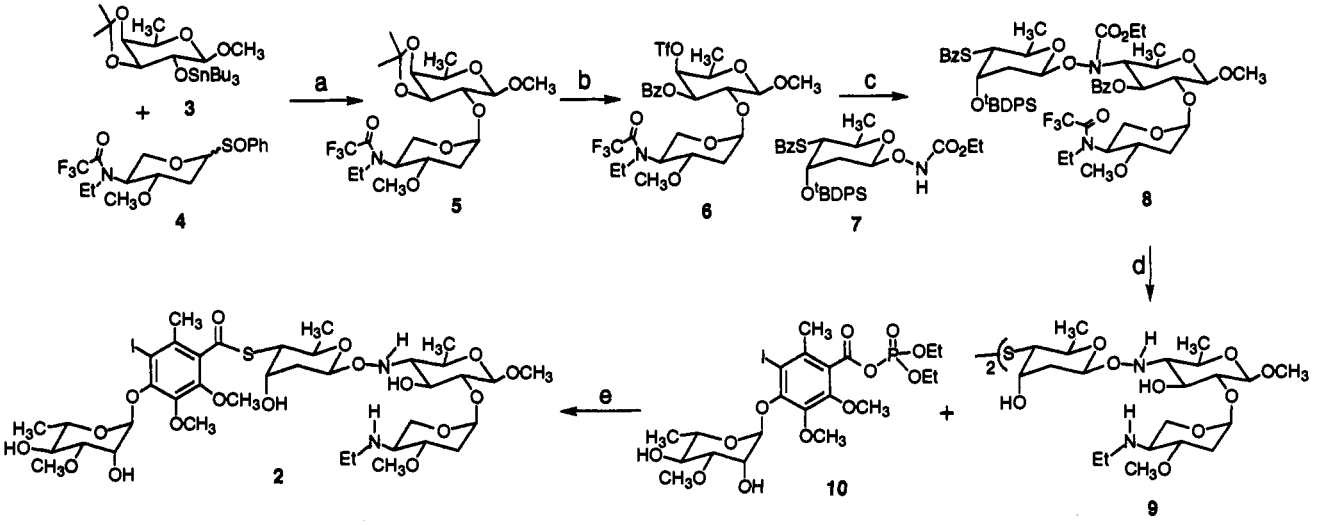
**Scheme 1.** Synthesis of the Calicheamicin Oligosaccharide[a]



[a] (a) $Tf_2O$, $Et_2O$, −78 °C to room temperature (65%); (b) TsOH, MeOH, room temperature; BzCl, py, −50 °C; $Tf_2O$, py, $CH_2Cl_2$, 0 °C (80%, 3 steps); (c) **7**, KHMDS, DMF, −10 °C, then add **6** (81%); (d) TBAF, THF, room temperature; NaOH, MeOH:EtOH, room temperature (52%, two steps); (e) $nBu_3P$, THF, room temperature; DMAP, THF, **10**, room temperature (79%, two steps).

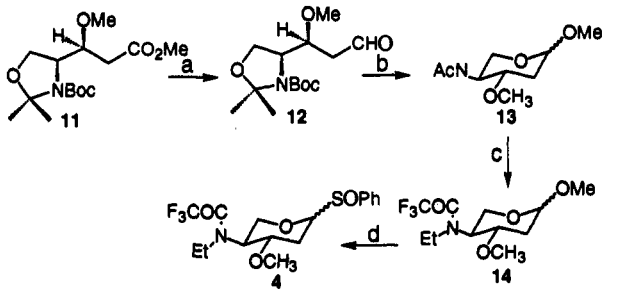
Below we report a concise synthesis of the calicheamicin oligosaccharide. All three glycosidic linkages were formed stereoselectively using the sulfoxide glycosylation reaction,[10] demonstrating the generality of the sulfoxide method for making different types of linkages.[11] In addition, the synthesis includes a general method for the introduction of the hydroxylamine glycosidic linkage, a structural feature that is critical in determining the overall shape of the calicheamicin oligosaccharide.[9b,12] The final step involves coupling two fully deprotected fragments of the oligosaccharide. This unusual approach to assembling the final target circumvents problems in deprotecting the sensitive aryl tetrasaccharide, which should increase the flexibility of the route for the construction of derivatives. The synthesis permits the rapid construction of analogs to probe the structural requirements for minor groove binding.

## Results and Discussion

Scheme 1 outlines our synthesis of the calicheamicin oligosaccharide. The sulfoxide glycosylation method was used to construct the three glycosidic linkages in fragments **5**, **7**, and **10** stereoselectively. The unusual N–O glycosidic bond was introduced stereospecifically by an $S_N2$ displacement of the axial triflate in **6** with the anion of the glycosyl urethane **7**.[3j] The deprotected ABE trisaccharide **9** and the mixed carboxylic phosphoric anhydride of the deprotected aryl rhamnose **10** are then selectively coupled in the final step using some nice chemistry developed by Masamune.[13]

*Synthesis of the ABE Trisaccharide.* The synthesis of the E ring amino sugar[3e,f,n] (Scheme 2) was patterned on Danishefsky's and Garner's work on construction of 1,2-amino alcohols.[14] The β-methoxy methyl ester **11**,[14b] derived from L-serine methyl ester, was prepared by dialkylation of the corresponding β-hydroxy acid with excess methyl triflate. DIBAL reduction of the ester produced aldehyde **12**, which on exposure to acidic methanol followed by acylation of the primary amine produced a 3:1 axial:equatorial mixture of N-acetylated methyl pyranosides **13** (58% from **11**). LAH reduction and protection with trifluoroacetic anhydride produced the protected amino sugar **14**, which was elaborated to the sulfoxide **4** by anomeric displacement with thiophenol followed by mCPBA oxidation. The E ring sulfoxide **4** was synthesized in seven steps and an overall yield of 30% from **11**.

**Scheme 2.** Synthesis of the E Ring[a]



[a] (a) DIBAL, $CH_2Cl_2$, −78 °C (86%); (b) TsOH, $ZnCl_2$, MeOH, 70 °C; $Ac_2O$, py, room temperature (67%, two steps); (c) $LiAlH_4$, $Et_2O$, room temperature; TFAA, py, room temperature (64%, two steps); (d) $BF_3{\cdot}Et_2O$, PhSH, $CH_2Cl_2$, −40 °C to room temperature; mCPBA, $CH_2Cl_2$, −78 °C to −20 °C (82%, two steps).

The E ring sulfoxide **4** was activated with triflic anhydride at −78 °C and then coupled to the stannyl alkoxide of the readily available fucose derivative **3** (Scheme 1).[15] The desired α-linked disaccharide **5** was isolated in 65% yield. The high α-selectivity (12:1 α:β) results from equilibration of the initially formed mixture of anomers as the temperature is increased to 0 °C.[16] Equilibration depends on carrying out the glycosylation reaction in the absence of base. The fact that the acid-labile isopropylidene ketal remains intact during the reaction underscores the mildness of the sulfoxide method. Deprotection of the ketal and selective benzoylation at A-3 followed by triflation at A-4 gave the AE disaccharide **6**, ready for coupling to the B ring (Scheme 1).

The B ring was obtained from D-fucose (Scheme 3) using the method of Giese to give acetyl 3,4-di-*O*-acetyl-2,6-dideoxy-α-D-*lyxo*-hexopyranoside (**15**).[17] Selective hydrolysis of the ano-

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(12) Walker, S.; Gupta, V.; Gange, D.; Kahne, D. *J. Am. Chem. Soc.*, in press.

(13) (a) Masamune, S.; Kamata, S.; Diakur, J.; Sugihara, Y.; Bates, G. S. *Can. J. Chem.* **1975**, *53*, 3693. (b) Spessard, G. O.; Chan, W. K.; Masamune, S. *Org. Synth.* **1983**, *61*, 134. The original work employed metal thiolates for the phosphate ester coupling. We have found that DMAP catalyzes the reaction efficiently.

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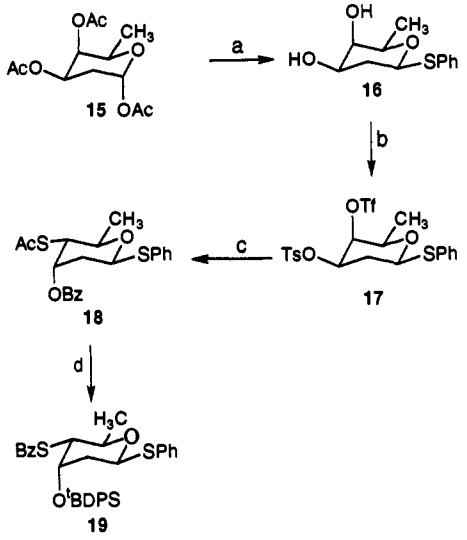
(15) Schuler, H. R.; Slessor, K. N. *Can. J. Chem.* **1977**, *55*, 3280.

(16) The product will decompose if the temperature goes above 25 °C.

(17) Giese, B.; Groninger, K. S.; Witzel, T.; Korth, H. G.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 233.

**Scheme 3.** Synthesis of the B Ring[a]




[a] (a) Amberlite IR-120(plus) resin, THF:$H_2O$, 70 °C; $(PhS)_2$, $nBu_3P$, $CH_2Cl_2$, room temperature; NaOMe, MeOH, room temperature (91%); (b) NaH, TsCl, THF, −78 °C to −60 °C; $Tf_2O$, py, $CH_2Cl_2$, 0 °C to room temperature (57%, two steps); (c) KSAc, DMF, 0 °C; KOBz, 18-C-6, DMF, 50 °C (52%, two steps); (d) LAH, $Et_2O$, 0 °C; BzCl, TEA, DMAP, $CH_2Cl_2$, 78 °C; *tert*-butyldiphenylsilyl triflate, pyridine, $CH_2Cl_2$, 25 °C (69%, three steps).

meric acetate and conversion of the resulting lactol to the sulfide followed by deprotection under basic conditions gave the diol **16**. Selective tosylation of the equatorial B3 hydroxyl followed by triflation of the B4 axial hydroxyl gave **17**. Sequential $S_N2$ displacement of the more reactive axial B4 triflate with potassium thioacetate followed by displacement of the equatorial B3 tosylate with potassium benzoate gave the sulfide **18** (15% overall yield over seven steps from **15**). B ring **18** was reduced with LAH, and then the thiol was selectively benzoylated, and finally the remaining alcohol was protected as the *tert*-butyldiphenylsilyl ether **19** (69%, three steps).

With the synthesis of the B sugar completed, we set out to construct the N–O glycosidic bond that links the A sugar to the B sugar. In the first synthesis of the calicheamicin oligosaccharide, the hydroxylamine glycosidic bond was made by reducing a glycosyl oxime.[4a] Although a 2:1 selectivity in favor of the desired isomer was ultimately achieved, the stereochemical outcome of reduction proved to be highly sensitive to small changes in the structure of the glycosyl oxime.[3c,d,4] We believe that glycosidic N–O linkages may be useful structural elements in the design of other oligosaccharides that bind to DNA, and we therefore wanted a more reliable method to construct the hydroxylamine glycosidic linkage. We opted for a strategy that relies on an $S_N2$ displacement. Hence, the A ring in our synthetic route was constructed with an axial triflate at A-4 (*vide supra*) for displacement by an appropriate hydroxylamine derivative.

Initial investigations of the $S_N2$ displacement strategy showed that a neutral hydroxylamine derivative did not displace the axial triflate in an A ring model system; instead, it facilitated elimination of the triflate (Scheme 4, eq 1). This result was not entirely unexpected: $S_N2$ displacements using neutral nucleophiles are frequently problematic in sugar systems. However, since anionic nucleophiles such as azide and thiolate readily effect $S_N2$ displacements in sugars,[18] we reasoned that an anionic hydroxylamine derivative might work where the neutral nucleophile did not. Accordingly, we carbethoxylated the perbenzylated glycosyl hydroxylamine so that it could be easily deprotonated. We found that the anionic nucleophile produced by deprotonation of the glycosyl urethane readily displaced the axial triflate to form the C–N bond with complete stereochemical control.[3j] We were delighted to find that the base-labile protecting groups of the coupled product can be removed under extremely mild conditions (Scheme 4, eq 2). This result was even more pleasing because *N*-hydroxyurethane is commercially available, and we anticipated making the necessary glycosyl urethane directly from the B ring sulfoxide. We expected the carboethoxy group, which activates the nitrogen for deprotonation during the $S_N2$ displacement reaction, to *deactivate* the nitrogen during the glycosylation reaction so that O-glycosylation would take place preferentially. In fact, direct glycosylation of *N*-hydroxyurethane with perbenzylated glucose sulfoxide cleanly gave O-glycosylated product (72%, unoptimized).

Achieving stereochemical control in the construction of $\beta$ linkages to 2-deoxy sugars such as the B ring in calicheamicin is a challenging problem in oligosaccharide synthesis.[19] The Nicolaou and Danishefsky groups have elegantly constructed the $\beta$ linkage to the B ring stereospecifically using two different approaches.[3m,4] We wanted a synthetic route that could be readily adapted to other glycosyl donors, and we therefore examined ways to glycosylate *N*-hydroxyurethane directly with a B ring sulfoxide (Scheme 5). The first approach we examined involved using the bulky silyl group on the B3 axial alcohol of the sulfoxide of **19** to try and favor nucleophilic attack from the $\beta$ face. This approach gave good glycosylation yields (76%) and moderate $\beta$-selectivity (2:1 $\beta$:$\alpha$). The second approach involved treating the activated sulfoxide of **18** with *O*-stannyl-*N*-hydroxyurethane.[20] The desired O-glycosylated product was obtained in moderate yield (39%) but with excellent $\beta$-stereoselectivity (12:1 $\beta$:$\alpha$).[21] The lower yield in the second case is due to the instability of the glycosyl donor and the fact that we cannot activate the sulfoxide for glycosylation in the presence of the stannyl alkoxide (as we do with the neutral nucleophile in the first approach). Nevertheless, as Thiem has shown for other glycosylation reactions,[20] stannyl alkoxides can be very effective in sulfoxide glycosylation reactions involving more stable glycosyl donors (*vide infra*). In any event, the synthesis of the B ring urethane set the stage for the stereospecific N–C bond construction to produce the core trisaccharide.

Urethane **7** was deprotonated with 1.2 equiv of potassium bis(trimethylsilyl)amide in DMF at −10 °C and treated with 1.5 equiv of the AE triflate **6** to give the ABE core trisaccharide **8** in 81% yield (Scheme 1). The silyl ether of **8** was then cleaved with tetrabutylammonium fluoride in THF. Without further purification, the trisaccharide was fully deprotected under basic conditions to give the ABE trisaccharide **9** as the disulfide. We have found that our method for making the N–O bond via an $S_N2$ displacement works in a range of other systems. In fact, it has been adopted by Danishefsky for the synthesis of the esperamicin and calicheamicin oligosaccharides.[3k,m]

*Synthesis of the CD Aryl Rhamnose Fragment.* The synthesis of the CD fragment is shown in Scheme 6. The D ring sulfide **20**, readily available from L-rhamnose,[22] was deketalized, selectively methylated at D3, pivaloylated at D2, and oxidized with mCPBA to the sulfoxide **22**. The D ring sulfoxide was synthesized in 40% yield over seven steps.

The C ring was synthesized starting from the Nicolaou hexasubstituted aromatic system (Scheme 6)[23] by reduction with

(18) (a) Binkley, R. W.; Ambrose, M. G. *J. Carbohydr. Chem.* **1984**, *3*, 1. (b) Knapp, S.; Kukkola, P. J.; Sharma, S.; Dhar, T. G. M.; Naughton, A. B.J. *J. Org. Chem.* **1990**, *55*, 5700.

(19) Review: Thiem, J.; Klaffke, W. *Top. Curr. Chem.* **1990**, *154*, 285.

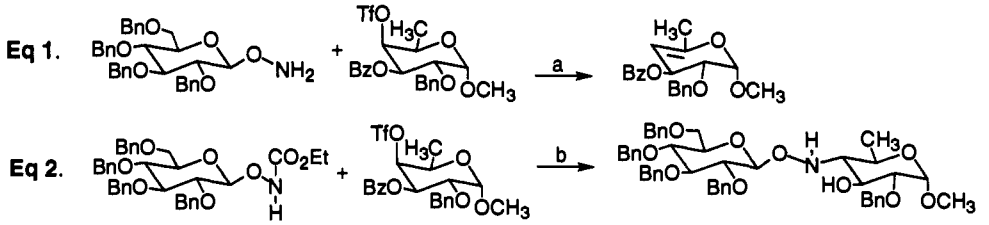
(20) Thiem, J.; Klaffke, W. *J. Org. Chem.* **1989**, *54*, 2006.

(21) The stereochemical outcome may be due to the combined effects of anchimeric assistance from the ester at C3 and the use of a stannyl alkoxide as a nucleophile: (a) Wiesner, K.; Tsai, T. Y. R.; Jin, H. *Helv. Chim. Acta* **1985**, 68, 300. (b) Reference 19.

(22) Prepared from peracetylated L-rhamnose according to a published procedure: Ferrier, R.J.; Furneaux, R. H. In *Methods in Carbohydrate Chemistry;* BeMiller, J. N., Whistler, R. L., Eds.; Academic Press: New York, 1980; Vol. VIII, p 251.

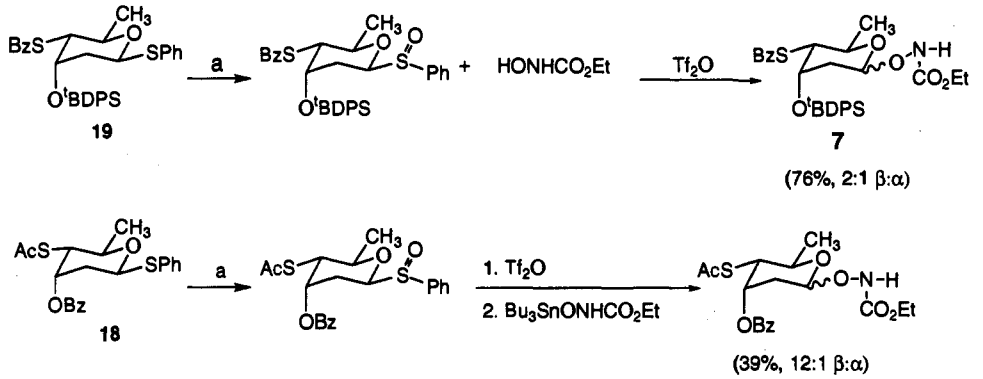
(23) Nicolaou, K. C.; Ebata, T.; Stylianides, N. A.; Groneberg, R. D.; Carrol, P. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1097.

**Scheme 4.** Model Studies for Introduction of N–O Bonds into Oligosaccharides[a]



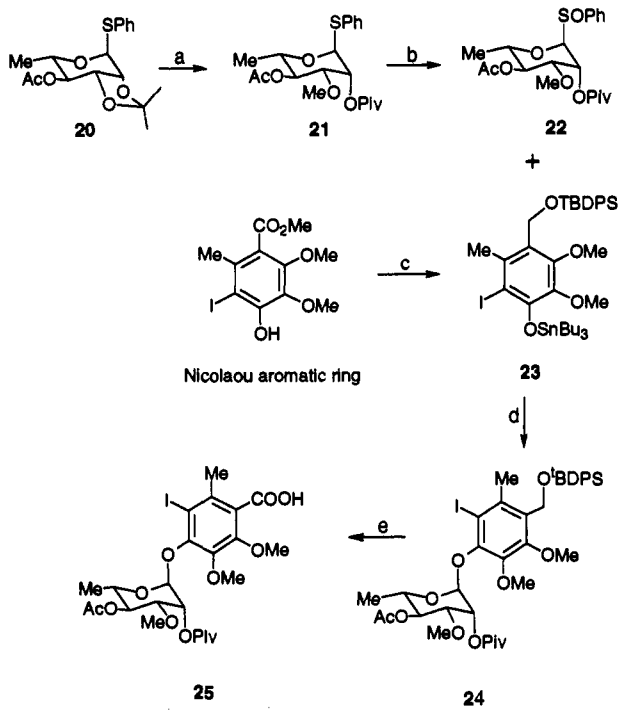

[a] (a) Excess Glu-ONH$_2$, DMF, 1.5 h, room temperature; (b) NaH–Et$_2$O–HMPA, 30 min, room temperature (82%); NaOH (solid)–MeOH, 1 h, room temperature (80%).

**Scheme 5.** Formation of the N–O Glycosidic Linkage to the B Ring[a]




[a] (a) mCPBA, $CH_2Cl_2$, –78 °C; DMS.

**Scheme 6.** Synthesis of the CD Rings of the Calicheamicin Oligosaccharide[a]




[a] (a) HOAc, THF:$H_2O$, 70 °C ; $Bu_2SnO$, DMF, 80 °C then $CH_3I$; PivCl, py, 80 °C (60%, three steps); (b) mCPBA, $CH_2Cl_2$, –78 °C to room temperature; (c) DIBAL-H, $CH_2Cl_2$, 78 °C; *tert*-butyl(Ph)$_2$SiCl, imidazole, DMF, 65 °C (94%, two steps); $(Bu_3Sn)_2O$, benzene; (d) **22** and $Tf_2O$, 2,6-dimethyl-di-*tert*-butyl-4-aminopyridine, $CH_2Cl_2$, –78 °C then add **23** (99%); (e) TBAF, THF, room temperature; $RuCl_3$ (catalyst), $NaIO_4$, $CCl_4$:$CH_3CN$:$H_2O$ (2:2:3), 0 °C (66%, two steps).

DIBAL followed by protection as the *tert*-butyldiphenylsilyl ether (94%, two steps).[24] This phenol was transformed to the corresponding stannyl alkoxide **23** and glycosylated with the activated D ring sulfoxide **22** to give the desired CD precursor **24** in quantitative yield. Complete stereochemical control was achieved by neighboring group participation of the D2 pivaloyl ester. Unlike many other glycosyl donors, glycosyl sulfoxides can be activated for glycosylation at low temperature even in the presence of several electron-withdrawing substituents.[10] In fact, we believe the sulfoxide method is better than other glycosylation methods when neighboring group participation is used to control the stereochemical outcome.[11a,c] Removal of the silyl group followed by ruthenium oxidation of the primary alcohol using the Sharpless method[25] gave the acid **25**.

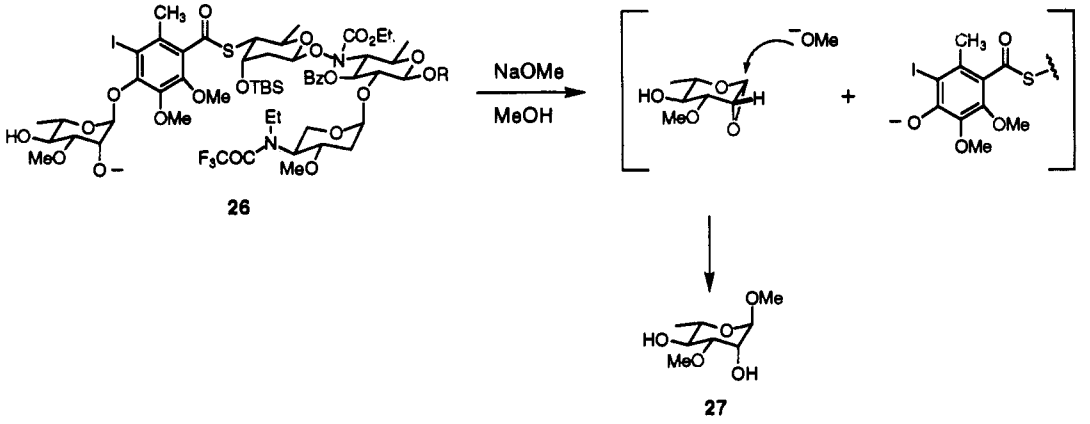
*Coupling of the CD and ABE Fragments.* The idea of coupling the fully deprotected CD and ABE fragments grew out of the discovery that the calicheamicin oligosaccharide is sensitive to basic conditions. Basic deprotection of the fully protected aryl tetrasaccharide derivative **26** resulted in cleavage of the aryl rhamnose linkage (Scheme 7). The methyl glycoside **27**, presumably formed from the intermediate epoxide, was isolated from the reaction. We have also observed migration of the CD thioester to the B3 axial alcohol under basic conditions. While we might have been able to circumvent these problems by manipulating protecting groups, this was not an appealing solution. Manipulating protecting groups in sugar systems can be complicated, and minor changes sometimes affect the outcome of reactions. In addition, protecting group manipulations add costly steps. Accordingly, we decided to investigate the possibility of coupling the fully deprotected CD and ABE fragments using chemistry developed by Masamune for the selective coupling of a phosphate ester to a thiolate in the presence of an alcohol.[13]

As anticipated, the glycosidic linkage in the aryl rhamnose acid **25** proved to be stable to basic conditions (LiOH), presumably because the phenolate is a poor leaving group with a carboxylate in the para position. The deprotected aryl rhamnose acid was then readily converted to the phosphate ester **10** using diethyl chlorophosphate and triethylamine. The disulfide of the ABE trisaccharide (**9**, Scheme 1) was reduced with tributylphosphine, and the resulting B4 thiolate was acylated *in situ* with phosphate ester **10** to give the calicheamicin $\gamma_1^I$ oligosaccharide (**2**) in 79%

(24) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975.

(25) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

**Scheme 7.** Base-Catalyzed Fragmentation of the D Ring from the Protected Calicheamicin Oligosaccharide




yield (from **9**). The coupling is selective even in the presence of the secondary amine on the E ring and several secondary alcohols.

## Conclusion

We have developed an efficient and convergent synthesis of the calicheamicin $\gamma_1^I$ oligosaccharide which employs the glycosyl sulfoxide method to introduce all the glycosidic bonds. Notable features of the synthesis include a general method for the stereospecific construction of N–O glycosidic linkages and a strategy for assembling the final target from fully deprotected fragments. This strategy allows us to circumvent protecting group problems that otherwise arise in the synthesis of the molecule. Our short and modular construction allows for the rapid synthesis of derivatives of the calicheamicin oligosaccharide that can be used to probe the importance of particular structural features in DNA recognition.

## Experimental Section

*General Methods.* NMR spectra were recorded on a GE QE-300 FT, a JEOL GSX 270 FT, or a JEOL GSX 500 FT NMR spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) with reference to internal solvent. Coupling constants ($J$) are reported in hertz (Hz). Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). Mass spectra were obtained on a Kratos MS50 spectrometer.

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.[26]

All reactions were carried out under argon or nitrogen atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise noted.

**4-(*S*)-(2-formyl-1(*S*)-methoxyethyl)-2,2-dimethyl-3-(*tert*-butoxycarbonyl)oxazolidine (12).** To a solution of hydroxy acid[14b] (500 mg, 1.73 mmol) and 3-*N*,*N*-diisobutylamino)-2,4-dimethylpentane (2.5 mL, 8.97 mmol, 5.2 equiv) in 10 mL of $CH_2Cl_2$ at 25 °C was added $CH_3OSO_2CF_3$ (0.9 mL, 7.95 mmol, 4.6 equiv) over 10 min. The reaction was stirred at 25 °C for 1 h and then refluxed at 40 °C for 20 h. The mixture was poured into saturated $NaHCO_3$ (50 mL) and extracted with $CH_2Cl_2$ (2 × 50 mL). The combined organic layers were dried over $Na_2SO_4$, concentrated, and purified by flash chromatography (20% EtOAc/petroleum ether) to give 400 mg (73%) of **11** as a colorless oil: $R_f$ 0.5 (30% EtOAc/petroleum ether); $^1$H NMR ($CDCl_3$, 500 MHz, 50 °C, mixture of rotamers) $\delta$ 4.25 (br, 2 H), 4.12 (d, $J$ = 9.5 Hz, 1 H), 4.03 (br t, $J$ = 9.1 Hz, 1 H), 3.81 (s, 3 H, COOMe), 3.51 (s, 3 H, OMe), 2.67 (d, $J$ = 16.1 Hz, 1 H), 2.55 (dd, $J$ = 16.2, 9.9 Hz, 1 H), 1.69 (br s, 3 H), 1.62 (s, 9 H), 1.56 (s, 3 H).

To a solution of **11** (1.24 g, 3.91 mmol) in 8.0 mL of $CH_2Cl_2$ at –78 °C was added dropwise a solution of DIBAL in toluene (1.0 M solution in toluene, 4.3 mL, 4.30 mmol, 1.1 equiv) over 10 min. The mixture was stirred at –78 °C for 1 h, quenched with a slow addition of MeOH, warmed to 25 °C, and poured into saturated $NaHCO_3$ (200 mL). The aqueous layer was extracted with $CH_2Cl_2$ (2 × 100 mL), and the combined organic layers were dried over $Na_2SO_4$, concentrated, and purified by flash chromatography (20% EtOAc/petroleum ether) to give 980 mg (87%) of **12** as a colorless oil. $R_f$ 0.4 (30% EtOAc/petroleum ether); $^1$H NMR ($CDCl_3$, 300 MHz, mixture of rotamers) $\delta$ 9.80 and 9.76 (2s, 1 H, CHO), 4.27 (br s, 1 H), 4.14 (br m, 1 H), 4.02 (d, $J$ = 9.6 Hz, 1 H), 3.94 (t, $J$ = 9.6 Hz, 1 H), 3.44 and 3.37 (2s, 3 H, OMe), 2.65–2.55 (m, 2 H), 1.54, 1.49, and 1.45 (3s, 15 H).

**Methyl 2,4-Dideoxy-3-*O*-methyl-4-(*N*-acetylamino)-α,β-L-xylopyranoside (13).** To a solution of aldehyde **12** (980 mg, 3.4 mmol) in 10 mL of MeOH were added anhydrous $ZnCl_2$ (50 mg, 0.37 mmol, 0.11 equiv) and $TsOH{\cdot}H_2O$ (50 mg, 0.26 mmol, 0.08 equiv), and the resulting mixture was heated to reflux for 24 h. The solvent was removed, and the crude cyclized amine was dried via azeotropic distillation with toluene (2 × 10 mL) and taken to the next step without further purification.

To a solution of the intermediate amine in 10 mL of pyridine was added excess $(CH_3CO)_2O$ (3 mL), and the mixture was stirred at 25 °C for 12 h. Pyridine was removed under reduced pressure, and the residue was dissolved in $CH_2Cl_2$. The resulting suspension was filtered, concentrated, and purified by flash chromatography (5% MeOH/EtOAc) to give 555 mg (80%) of **13** as a mixture of anomers (α: β, 7:2): $R_f$ 0.3 (α), 0.2 (β) (5% MeOH/EtOAc); $^1$H NMR ($CDCl_3$, 500 MHz) α-anomer, $\delta$ 6.16 (br d, $J$ = 5.5 Hz, 1 H, NH), 4.63 (dd, $J$ = 2.9, 5.1 Hz, 1 H, H-1), 3.89–3.86 (m, 2 H), 3.53–3.48 (m, 2 H), 3.35 (s, 3 H, 3-OMe), 3.32 (s, 3 H, 1-OMe), 2.01 (s, 3 H, OAc), 1.93–1.89 (m, 1 H, H-2), 1.72–1.69 (m, 1 H, H-2′); β-anomer, $\delta$ 6.26 (br d, $J$ = 6.2 Hz, 1 H, NH), 4.54 (t, $J$ = 3.7 Hz, 1 H, H-1), 4.25 (dd, $J$ = 2.9, 12.1 Hz, 1 H), 3.92–3.90 (m, 1 H), 3.40–3.35 (m, 7 H), 3.27 (dd, $J$ = 4.4, 11.7 Hz, 1 H), 2.14 (s, 3 H, OAc), 2.05–2.01 (m, 1 H, H-2), 1.80–1.76 (m, 1 H, H-2′); MS (relative intensity) $m/e$ 202 ($M^+$ – 1, 2.6), 172 (4.4), 144 (31.2); HRMS $C_9H_{16}O_4N_1$ calcd ($M^+$ – H) 202.1079, found 202.1090.

**Methyl 2,4-Dideoxy-3-*O*-methyl-4-(*N*-(trifluoroacetyl)-*N*-ethylamino)-α,β-L-xylopyranoside (14).** To a solution of **13** (427 mg, 2.10 mmol) in 40 mL of $Et_2O$ at 0 °C was added $LiAlH_4$ (1.0 M solution in $Et_2O$, 4.2 mL, 4.2 mmol, 2.0 equiv) over 15 min. After 30 min, the reaction was warmed to 25 °C and stirred for 20 h. The reaction was quenched with EtOAc, and the mixture was concentrated to afford the crude ethylamine as a white solid. The crude product was dried by azeotropic distillation with toluene (2 × 4 mL) and taken to the next step without further purification.

To a solution of the crude intermediate ethylamine in 10 mL of $CH_2Cl_2$ were added excess pyridine (2 mL) and $(CF_3CO)_2O$ (1 mL) at 0 °C, and the mixture was gradually (2 h) warmed to 25 °C and stirred overnight. The reaction was quenched over saturated $NaHCO_3$ (20 mL) and extracted with $CH_2Cl_2$ (2 × 15 mL). The combined organic layers were dried over $Na_2SO_4$, filtered, concentrated, and purified by flash chromatography (30% EtOAc/petroleum ether) to give 383 mg (64%, two steps) of **14** as a mixture of anomers (α-major): $R_f$ 0.3 (30% EtOAc/petroleum ether); $^1$H NMR ($CDCl_3$, 270 MHz, mixture of rotamers) α-anomer, $\delta$ 4.78 (br s, 1 H, H-1), 4.37–4.13 (m, 1 H), 3.88–3.30 (m, 5 H), 3.33, 3.31, 3.29, and 3.28 (4s, 6 H, OMe), 2.42–2.30 (m, 1 H, H-2), 1.56–1.43 (m, 1 H, H-2′), 1.26–1.15 (t, 3 H, $CH_2CH_3$); $^{13}$C NMR ($CDCl_3$, 75 MHz) α-anomer, $\delta$ 158.2, 157.7, 117.0 (q, $J_{FC}$ = 288 Hz), 116.9 (q, $J_{FC}$ = 288 Hz), 99.4, 72.1, 71.7, 60.1, 59.1, 58.7, 57.0, 56.4, 55.7, 55.4, 39.4, 36.4, 35.4, 15.4, 13.8; MS (relative intensity) $m/e$ 284 ($M^+$ – 1,

(26) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

0.3), 254 ($M^+$ – 31, 5.7), 222 (25.0); HRMS $C_{11}H_{17}O_4N_1F_3$ ($M^+$ – H) calcd 284.1110, found 284.1128.

**2,4-Dideoxy-3-*O*-methyl-4-(*N*-(trifluoroacetyl)-*N*-ethylamino)-1-phenylsulfinyl-α,β-L-xylopyranose (4).** To a solution of the *N*-trifluoroacetamide **14** (193 mg, 0.677 mmol) in 5.0 mL of $CH_2Cl_2$ at –40 °C were added $C_6H_5SH$ (75 μL, 0.745 mmol, 1.1 equiv) and $BF_3{\cdot}Et_2O$ (125 μL, 1.016 mmol). After being stirred at –40 °C for 3 h, the reaction was allowed to warm to 25 °C over 30 min. The reaction was quenched with excess $Et_3N$ (0.2 mL), and the crude mixture was purified by flash chromatography (step gradient from neat petroleum ether to 20% EtOAc/petroleum ether) to afford 240 mg (97%) of the sulfide as a mixture of anomers: $R_f$ 0.25 (10% EtOAc/petroleum ether); $^1$H NMR ($CDCl_3$, 270 MHz, mixture of rotamers) α-anomer, δ 7.50-7.24 (m, 5 H, ArH), 5.66 (br t, 1 H, H-1), 4.76 (t, $J$ = 10 Hz, 1 H, H-5), 4.40–4.15 (m, 1 H), 3.78–3.60 (m, 1 H), 3.55–3.39 (m, 3 H), 3.35 (s, 3 H, OMe), 2.61–2.53 (m, 1 H, H-2), 2.02–1.89 (m, 1 H, H-2′), 1.31–1.21 (m, 3 H, $CH_2CH_3$); β-anomer, δ 7.50–7.24 (m, 5 H, ArH), 4.84 (dd, $J$ = 10, 2 Hz, 1 H, H-1), 4.35–4.19 (m, 2 H), 3.89 (dd, 1 H), 3.60–3.40 (m, 2 H), 3.39 (s, 3 H, OMe), 3.10 (dt, 1 H, H-4), 2.64–2.56 (m, 1 H, H-2), 1.72–1.55 (m, 1 H, H-2′), 1.31–1.20 (m, 3 H, $CH_2CH_3$); $^{13}$C NMR ($CDCl_3$, 67.5 MHz), a mixture of α and β anomers, δ 157.1, 156.9, 134.7, 134.0, 133.4, 133.2, 131.8, 131.5, 131.1, 130.9, 129.0, 128.9, 127.8, 127.5, 127.4, 127.1, 116.1 (q, $J_{FC}$ = 288 Hz), 84.3, 84.1, 83.3, 83.1, 75.1, 74.1, 72.1, 71.5, 67.1, 65.4, 63.3, 60.3, 59.1, 56.8, 56.5, 55.9, 45.6, 45.5, 38.9, 38.7, 37.2, 36.5, 35.8, 35.6, 14.8, 14.1, 13.3, 13.2; MS (relative intensity) $m/e$ 362 ($M^+$ – 1, 1.6), 254 (34.5), 222 (99.1).

To a solution of the sulfide in 12 mL of $CH_2Cl_2$ at –78 °C was added mCPBA (100 mg, 0.468 mmol, 1.0 equiv, 80% from Sigma). The mixture was warmed to 0 °C over 1 h, quenched with saturated $NaHCO_3$ (15 mL), and extracted with $CH_2Cl_2$ (2 × 10 mL). The combined organic layers were dried over $Na_2SO_4$, filtered, concentrated, and purified by flash chromatography (40% EtOAc/petroleum ether) to give 170 mg (96%) of **4** as a white solid: $R_f$ 0.2–0.25 (40% EtOAc/petroleum ether); $^1$H NMR ($CDCl_3$, 300 MHz, mixture of rotamers) β-anomer, δ 7.69–7.56 (m, 5 H, ArH), 4.36 (dd, $J$ = 1.7, 10.9 Hz, 1 H, H-1), 4.33 (dt, $J$ = 10.2, 4.3 Hz, 1 H, H-3), 4.15 (t, $J$ = 10.9 Hz, 1 H, H-5), 3.91 (dd, $J$ = 4.3, 10.9 Hz, 1 H, H-5′), 3.50–3.30 (m, 2 H, $CH_2CH_3$), 3.32 (s, 3 H, OMe), 3.10 (dt, $J$ = 4.3, 10.9 Hz, 1 H, H-4), 2.44 (ddd, $J$ = 1.7, 4.3 12.6 Hz, 1 H, H-2), 1.38 (q, $J$ = 13 Hz, 1 H, H-2′), 1.30–1.15 (t, $J$ = 7.3 Hz, 3 H, $CH_2CH_3$).

**Methyl 6-Deoxy-3,4-*O*-isopropylidene-2-*O*-[2,4-dideoxy-3-*O*-methyl-4-(*N*-(trifluoroacetyl)-*N*-ethylamino)-α-L-xylopyranosyl]-β-D-galactopyranoside (5).** To a solution of methyl 6-deoxy-3,4-*O*-isopropylidene-β-D-galactopyranoside[15] (106 mg, 0.486 mmol) in toluene (5 mL) at 25 °C was added crushed 4-Å sieves (500 mg), and the resulting suspension was stirred at 25 °C for 30 min. $(Bu_3Sn)_2O$ (124 μL, 0.242 mmol, 0.5 equiv) was then added, and the mixture was heated to 70 °C under argon for 1 h. The reaction was filtered through a plug of Celite, and the filtrate was concentrated to give **3** as an oil, which was dried by azeotropic distillation with toluene and brought on to the next step without further purification.

To a solution of E ring sulfoxide **4** (108 mg, 0.285 mmol) in 10 mL of $Et_2O$ at -60 °C was added $(CF_3SO_2)_2O$ (48 μL, 0.285 mmol). The reaction was stirred at -60 °C for 5 min, and then the solution of stannyl alkoxide **3** in 2.0 mL of $Et_2O$ was added dropwise over 5 min. The mixture was gradually (1 h) warmed to 0 °C. The reaction was monitored carefully until completion (15 min) and quenched with saturated $NaHCO_3$ (5.0 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL), and the combined organic layers were dried over $Na_2SO_4$, filtered, concentrated, and purified by flash chromatography (35% EtOAc/petroleum ether) to give 99 mg (74%) of AE disaccharide **5** as a 12:1 (α:β) mixture of anomers. The anomers were separated by flash chromatography (30% EtOAc/petroleum ether) to afford 87 mg (65%) of **5**: $R_f$(α-anomer) 0.45 (40% EtOAc/petroleum ether); $R_f$(β-anomer) 0.42 (40% EtOAc/petroleum ether); $^1$H NMR ($CDCl_3$, 270 MHz, mixture of rotamers) α-disaccharide, δ 5.48 and 5.41 (2 br d, $J$ = 2.3 Hz, 1 H, E-1), 4.45 (br t), 4.32–4.10 (m and d, $J$ = 8.3 Hz, 3 H, A-1), 3.99–3.96 (m, 1 H), 3.89–3.75 (m), 3.66 (q, $J$ = 7.6 Hz, 4H, $CH_2CH_3$), 3.51 (s, E-OMe), 3.53–3.33 (m, 6 H), 3.31 and 3.30 (2s, 3 H, A-OMe), 2.41–2.32 (m, 1 H, E-2), 1.52 (s, 3 H, $Me_2C$), 1.57–1.46 (m, 1 H, E-2′), 1.43-1.39 (2d, $J$ = 6.3 Hz, 3 H, A-Me), 1.34 (s, 3 H, $Me_2C$), 1.28–1.17 (2t, $J$ = 7.3 Hz, 3 H, $CH_2CH_3$); β-disaccharide, δ 4.83 (dd, $J$ = 2.3, 9.6 Hz, 1 H, E-1), 4.29 (dt, $J$ = 4.3, 10.2 Hz, 1 H, E-5), 4.12 (2d, $J$ = 8.6 Hz, 1 H, A-1), 4.07–3.97 (m, 2 H), 3.84–3.77 (m, 2 H), 3.65 (dt, $J$ = 2.3, 7.3 Hz, 1 H), 3.53 and 3.52 (2s, 3 H, E-OMe), 3.58–3.32 (m, 3 H), 3.33 and 3.32 (2s, 3 H, A-OMe), 3.30–3.20 (dt, $J$ = 4.9, 10.2 Hz, 1 H, E-5), 2.48-2.35 (m, 1 H, E-2), 1.52 (s, 3 H, $Me_2C$), 1.48–1.43 (m, 1 H, E-2′), 1.41 (d, $J$ = 6.6 Hz, 3 H, A-Me), 1.35 (s, 3 H, $Me_2C$), 1.25–1.16 (2t, $J$ = 7.3 Hz, 3 H, $CH_2CH_3$); HRMS $C_{19}H_{29}O_8N_1F_3$ ($M^+$ – $CH_3$) calcd 456.1845, found 456.1854.

**Methyl 3-*O*-Benzoyl-6-deoxy-2-*O*-[2,4-dideoxy-3-*O*-methyl-4-(*N*-(trifluoroacetyl)-*N*-ethylamino)-α-L-xylopyranosyl]-4-triflyl-β-D-galactopyranoside (6).** To a solution of AE disaccharide **5** (87 mg, 0.185 mmol) in wet MeOH (5 mL MeOH and one drop of $H_2O$) at 25 °C was added $TsOH{\cdot}H_2O$ (10 mg, 0.05 mmol, 0.3 equiv). The hydrolysis was complete in 1 h and was neutralized with excess anhydrous $Na_2CO_3$ (500 mg), filtered through Celite, concentrated, and purified by flash chromatography (5% MeOH/EtOAc) to afford 72 mg (90%) of diol: $R_f$ 0.2 (5% MeOH/EtOAc); $^1$H NMR ($CDCl_3$, 270 MHz, mixture of rotamers) δ 5.56 and 5.46 (2d, $J$ = 2.0 Hz, 1 H, E-1), 4.56 (t, $J$ = 10.9 Hz, 1 H), 4.36 (dt, $J$ = 5.0, 10.2 Hz, 1 H), 4.21 and 4.20 (2d, $J$ = 7.6 Hz, 1 H, A-1), 4.16 (t, $J$ = 10.9 Hz, 1 H), 3.88–3.74 (m, 1 H), 3.53 (s, E-OMe), 3.70–3.36 (m, 11 H), 3.32 and 3.31 (2s, 3 H, A-OMe), 2.74 (d, $J$ = 8.6 Hz, 1H,), 2.63 (d, $J$ = 9.6 Hz, 1 H), 2.48–2.42 (m, 1 H, OH), 2.07 (dd, $J$ = 2.3, 7.6 Hz, 1 H, E-2), 1.57–1.44 (m, 1 H, E-2′), 1.34 and 1.33 (2d, $J$ = 6.6 Hz, 3 H, A-Me), 1.26 and 1.20 (2t, $J$ = 7.3 Hz, 3 H, $CH_2CH_3$); $^{13}$C NMR ($CDCl_3$, 67.5 MHz) δ 157.7, 157.0, 116.7 (q, $J_{FC}$ = 288 Hz), 116.6 (q, $J_{FC}$ = 288 Hz), 103.0, 102.6, 97.7, 97.1, 94.1, 75.8, 75.4, 75.2, 73.8, 72.7, 72.5, 71.1, 70.7, 70.4, 70.2, 59.4, 58.5, 58.3, 57.1, 56.5, 56.2, 55.8, 38.5, 35.4, 34.6, 16.2, 16.1, 14.7, 13.2; MS (m/e, int) 430 ($M^+$ – 1, 0.7), 400 ($M^+$ – 31, 2.1), 254 (44.0).

To a solution of the intermediate diol in 10 mL of $CH_2Cl_2$ at –50 °C was added a solution of $Et_3N$ (0.32 mL, 2.28 mmol, 4.0 equiv) and DMAP (21 mg, 0.17 mmol, 0.3 equiv) in $CH_2Cl_2$ (2.0 mL). $C_6H_5COCl$ (100 μL, 0.86 mmol, 1.5 equiv) was added dropwise, and the reaction was maintained at –50 °C for 4 h. The reaction was quenched with addition of excess MeOH (1 mL) and gradually warmed to 25 °C. The resulting mixture was poured into saturated $NaHCO_3$ and extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic layers were dried over $Na_2SO_4$, concentrated, and purified by flash chromatography (35% EtOAc/petroleum ether) to give 218 mg (71%) of the 3-*O*-benzoyl ester-4-ol: $R_f$ 0.25 (35% EtOAc/petroleum ether); $^1$H NMR ($CDCl_3$, 270 MHz, mixture of rotamers) δ 8.06 (d, $J$ = 6.9 Hz, 2 H, ArH), 7.60 (t, $J$ = 7.3 Hz, 1 H, ArH), 7.47 (t, $J$ = 7.2 Hz, 2 H, ArH), 5.21–5.12 (m, 2 H, A-3 and E-1), 4.56 and 4.26 (2br t, 1 H), 4.37 (d, $J$ = 7.6 Hz, 1 H, A-1), 4.19 (t, $J$ = 11.0 Hz, 1 H), 4.09–3.94 (m, 2 H), 3.82–3.63 (m, 2 H), 3.57 (s, 3 H, E-OMe), 3.55–3.30 (m, 3 H), 3.21 and 3.19 (2s, 3 H, A-OMe), 2.21–2.10 (dt, $J$ = 4.6, 12.9 Hz, 1 H, E-2), 2.02–1.95 (br t, 1 H, E-2′), 1.37–1.33 (2d, $J$ = 6.3 Hz, 3 H, A-Me), 1.26–1.16 (2t, $J$ = 6.9 Hz, 3 H, $CH_2CH_3$); MS (relative intensity), $m/e$ 504 ($M^+$ – 31, 0.2), 254 (81.5), 222 (100); HRMS $C_{23}H_{14}O_8NF_3$ ($M^+$ – $OCH_3$) calcd 504.1845, found 504.1858.

To a solution of the 3-*O*-benzoyl-4-ol intermediate (84 mg, 0.157 mmol) in 5.0 mL of $CH_2Cl_2$ at 0 °C were added pyridine (38 μL, 0.471 mmol, 3.0 equiv) and $(CF_3SO_2)_2O$ (40 μL, 0.236 mmol, 1.5 equiv), and the mixture was allowed to stir at 0 °C for 30 min. The reaction was quenched with $H_2O$ (10 mL) and extracted with $CH_2Cl_2$ (3 × 10 mL), and the organic layers were dried over $Na_2SO_4$. The crude mixture was concentrated and purified by flash chromatography (25% EtOAc/petroleum ether) to give the triflate **6** (94 mg, 90%) as an off-white solid: $R_f$ 0.5 (35% EtOAc/petroleum ether); $^1$H NMR ($CDCl_3$, 270 MHz, mixture of rotamers) δ 8.08 (d, $J$ = 7.2 Hz, 2 H, ArH), 7.66–7.60 (m, 1 H, ArH), 7.52–7.46 (m, 2 H, ArH), 5.36 and 5.34 (2dd, $J$ = 3.0, 10.2 Hz, 1 H, A-3), 5.21 and 5.15 (2d, $J$ = 2.0 Hz, 1 H, E-1), 5.12 and 5.11 (2s, 1 H, A-4), 4.45 (d, $J$ = 7.6 Hz, 1 H, A1), 4.61 (t, $J$ = 10.9 Hz, 1 H), 4.30 (dt, $J$ = 10.2, 4.6 Hz, 1 H), 4.19–3.94 (m, 2 H), 3.81 and 3.66 (2dt, $J$ = 4.6, 9.9 Hz, 1 H), 3.60 and 3.59 (2s, 3 H, E-OMe), 3.58–3.27 (m, 3 H), 3.20 and 3.17 (2s, 3 H, A-OMe), 2.10 (m, 1 H, E-2), 1.42–1.16 (m, 7 H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 166.1, 158.2, 157.5, 134.8, 134.6, 130.5, 129.5, 129.4, 129.0, 128.9, 123.5 (q, $J_{FC}$ = 368 Hz), 117.0 (q, $J_{FC}$ = 288 Hz), 116.9 (q, $J_{FC}$ = 288 Hz), 114.4 (q, $J_{FC}$ = 368 Hz), 103.5, 103.2, 99.2, 98.6, 86.1, 86.0, 74.4, 73.0, 71.8, 71.5, 71.2, 69.3, 69.0, 60.4, 59.2, 58.9, 58.0, 57.4, 57.0, 56.4, 39.2, 36.4, 35.2, 17.0, 15.3, 13.9; FABMS (relative intensity) $m/e$ 685 ($M^+$ + $H_2O$, 99), 668 ($M^+$ + 1, 100).

**Phenyl 2,6-Dideoxy-1-thio-β-D-*lyxo*-hexopyranoside (16).** To a solution of acetyl 3,4-di-*O*-acetyl-2,6-dideoxy-α-D-*lyxo*-hexopyranoside[17] (4.95 g, 18 mmol) in 100 mL of 10:1 THF–$H_2O$ was added Amberlite IR-120(plus) resin (25 g), and the suspension was heated to 70 °C for 10 h. The reaction was filtered and concentrated, and the residue was partitioned in $CH_2Cl_2/H_2O$ (300 mL/300 mL). The aqueous layer was extracted with $CH_2Cl_2$ (2 × 150 mL), and the combined organic layers

were dried over $Na_2SO_4$, filtered, and concentrated. The crude Cl lactol anomers were dried by azeotrope with toluene (3 × 50 mL) and taken to the next step without further purification.

To the mixture of lactol anomers in 200 mL of $CH_2Cl_2$ were added $(C_6H_5S)_2$ (7.9 g, 38 mmol, 2.0 equiv) and $(n\text{-}C_4H_9)_3P$ (11.2 mL, 45mmol, 2.5 equiv) in 200 mL of $CH_2Cl_2$, and the reaction was maintained at 25 °C for 2 h. The solvent was evaporated, and the oily residue containing the mixture of anomeric sulfides was loaded directly onto a column. Purification by flash chromatography (step gradient from neat petroleum ether to 25% EtOAc/petroleum ether) afforded 3.3 g of **15** ($\beta$-anomer) along with 700 mg of the $\alpha$-anomer. Only the $\beta$-anomer was carried over to the next step.

To a solution of **15** (3.3 g, 10 mmol) in 120 mL of MeOH was added $NaOCH_3$ (540 mg, 10 mmol, 1.0 equiv), and the reaction was stirred at 25 °C overnight. The reaction was neutralized with 5.0 g of Amberlite IR-120(plus) resin, filtered, concentrated, and purified by flash chromatography (70% EtOAc/petroleum ether) to afford 2.2 g (51%, three steps) of **16** as a white solid: $R_f$ 0.35 (40% EtOAc/petroleum ether); $^1$H NMR ($CDCl_3$, 270 MHz) $\delta$ 7.53–7.40 (m, ArH, 2 H), 7.32–7.18 (m, ArH, 3 H), 4.67 (dd, $J$ = 12, 2 Hz, 1 H, H-1), 3.76–3.62 (m, 1 H, H-3), 3.76–3.45 (m, 2 H, H-4, H-5), 2.27 (ddd, $J$ = 13, 4.9, 1.6 Hz, 1 H, H-2$_{eq}$), 1.72 (dd, $J$ = 12.5, 11.9, 1 H, H-2$_{ax}$), 1.30 (d, $J$ = 6.3 Hz, 3 H, H-6); $^{13}$C NMR ($CDCl_3$, 67.5 MHz) $\delta$ 133.9, 131.4, 128.9, 127.5, 82.3, 74.6, 70.4, 69.7, 34.6, 17.1; HRMS $C_{12}O_3S_1H_{16}$ ($M^+$) calcd 240.0820, found 240.0812.

**Phenyl 2,6-Dideoxy-3-*O*-tosyl-4-*O*-triflyl-1-thio-$\beta$-D-*lyxo*-hexopyranoside (17).** To a solution of diol **16** (7.0 g, 29 mmol) in 800 mL of THF at 25 °C was added NaH (3.5 g, 87 mmol, 3.0 equiv, 60% in mineral oil). After complete deprotonation, the suspension was cooled to −78 °C, and TsCl (13.8 g, 72.5 mmol, 2.2 equiv) in 100 mL of THF was added dropwise over 15 min. The reaction was warmed to −60 °C over 2 h and quenched with saturated $NH_4Cl$. The solvent was removed under reduced pressure, and the residue was partitioned in $CH_2Cl_2$/saturated NaCl (400 mL/400 mL). The aqueous layer was extracted with $CH_2Cl_2$ (2 × 200 mL), dried over $Na_2SO_4$, filtered, concentrated, and purified by flash chromatography to give 8.5 g (74%) of tosylate: $R_f$ 0.5 (30% EtOAc/petroleum ether); $^1$H NMR ($CDCl_3$, 270 MHz) $\delta$ 7.8–7.2 (m, 9 H, ArH), 4.62 (dd, $J$ = 11.2, 2.3 Hz, 1 H, H-1), 4.58–4.52 (m, 1 H, H-3), 3.69 (d, $J$ = 2.6 Hz, 1 H, H-4), 3.5 (q, $J$ = 6.6 Hz, 1 H, H-5), 2.42 (s, 3 H, $CH_3$-aromatic), 2.14–1.88 (m, 3 H, H-2 and OH), 1.27 (d, $J$ = 6.6 Hz, 3 H, H-6); $^{13}$C NMR ($CDCl_3$, 67.5 MHz) $\delta$ 145.2, 133.7, 133.1, 132.0, 130.0, 128.9, 127.8, 127.6, 81.8, 79.1, 68.4, 31.4, 21.6, 16.9.

To a solution of tosylate (8.5 g, 21.5 mmol) in 500 mL of $CH_2Cl_2$ at 0 °C was added pyridine (5.2 mL, 64.5 mmol, 3 equiv) followed by $(CF_3SO_2)_2O$ (5.4 mL, 32.3 mmol, 1.5 equiv), and the reaction was maintained at 0 °C for 30 min and then at 25 °C for an additional 10 min. The reaction was poured into $H_2O$ and extracted with $CH_2Cl_2$ (3 × 200 mL), dried over $Na_2SO_4$, concentrated, and purified by flash chromatography (25% EtOAc/petroleum ether) to afford 9.1 g (80%) of **17** as an off-white solid: $R_f$ 0.35 (20% EtOAc/petroleum ether); $^1$H NMR ($CDCl_3$, 270 MHz) $\delta$ 7.74–7.19 (m, 5 H, ArH), 4.83 (d, $J$ = 2.3, 1 Hz, 1 H, H-4), 4.73–4.63 (m, 2 H, H-3 and H-1), 3.66 (q, $J$ = 6.6 Hz, 1 H, H-5), 2.39 (s, 3 H, $CH_3$-aromatic), 2.11–1.98 (m, 2 H, H-2), 1.31 (d, $J$ = 6.4 Hz, 3 H, H-6); $^{13}$C NMR ($CDCl_3$, 67.5 MHz) $\delta$ 145.7, 132.8, 132.5, 132.2, 130.0, 129.0, 128.2, 127.9, 118.4 (q, $J_{FC}$ = 320 Hz), 83.1, 81.7, 74.1, 72.8, 32.1, 21.7, 17.3; FABMS (relative intensity) $m/e$ 527 ($M^+$ + 1, 8.6) 417 (20.9).

**Phenyl 4-*S*-Acetyl-3-*O*-benzoyl-2,6-dideoxy-1,4-dithio-$\beta$-D-*ribo*-hexopyranoside (18).** To a solution of triflate (2.1 g, 4.03 mmol) in 50 mL of DMF at 0 °C was added $CH_3COSK$ (510 mg, 4.43 mmol, 1.1 equiv) in 5.0 mL DMF over 5 min, and the resulting suspension was maintained at 0 °C for 3 h. The DMF was removed under reduced pressure, and the residue was partitioned in $CH_2Cl_2/H_2O$ (200 mL/200 mL). The mixture was extracted with $CH_2Cl_2$ (2 × 75 mL), dried over $Na_2SO_4$, concentrated, and purified by flash chromatography (25% EtOAc/petroleum ether) to give 1.1 g (60%) of the 4-*S*-acetyl-3-tosylate: $R_f$ 0.3 (20% EtOAc/petroleum ether); $^1$H NMR ($CDCl_3$, 270 MHz) $\delta$ 7.75 (m, 9 H, ArH), 4.73–4.57 (m, 2 H, H-1 and H-3), 3.62–3.5 (m, 1 H, H-5), 3.12 (t, $J$ = 10.5 Hz, 1 H, H-4), 2.45 (ddd, $J$ = 12, 5, 2 Hz, 1 H, H-2$_{eq}$), 2.38 (s, 3 H, $CH_3$-aromatic), 2.08 (s, 3 H, SAc), 1.87 (q, $J$ = 12 Hz, 1 H, H-2$_{ax}$), 1.25 (d, $J$ = 6.6 Hz, 1 H, H-6); $^{13}$C NMR ($CDCl_3$, 67.5 MHz) $\delta$ 193.1, 144.8, 134.0, 132.8, 132.2, 129.7, 129.0, 128.9, 127.9, 81.2, 78.4, 75.0, 49.9, 39.3, 30.6, 21.6, 19.3.

To a solution of sulfide 4-*S*-acetyl-3-tosylate (1.0 g, 2.2 mmol) in 30 mL of DMF were added $C_6H_5COOK$ (3.0 g, 18.7 mmol, 8.5 equiv) and 18-crown-6 (2.3 g, 8.8 mmol, 4.4 equiv), and the resulting suspension was heated at 50 °C for 4 h. The DMF was removed under reduced pressure, and the residue was taken up in $CH_2Cl_2/H_2O$ (100 mL/100 mL) and extracted with $CH_2Cl_2$ (2 × 50 mL). The combined organic layers were dried over $Na_2SO_4$, filtered, concentrated, and purified by flash chromatography (15% EtOAc/petroleum ether) to afford 777 mg (86%) of **18**: $R_f$ 0.3 (15% EtOAc/petroleum ether); $^1$H NMR ($CDCl_3$, 270 MHz) $\delta$ 7.82–7.02 (m, 10 H, ArH), 5.23 (m, 1 H, 3-H), 4.89 (dd, $J$ = 12, 2 Hz, 1 H, H-1), 3.86 (dt, $J$ = 6.3, 4.6 Hz, 1 H, H-5), 3.52 (dd, $J$ = 10.5, 2.6 Hz, 1 H, H-4), 2.16 (td, $J$ = 13, 3 Hz, 1 H, H-2$_{eq}$), 2.08 (s, 3 H, SAc), 1.91 (dt, $J$ = 12, 2.6 Hz, 1 H, H-2$_{ax}$), 1.14 (d, $J$ = 6.3, 1 H, H-6); $^{13}$C NMR ($CDCl_3$, 67.5 MHz) $\delta$ 193.4, 165.2, 133.4, 133.3, 132.0, 129.7, 129.0, 128.5, 127.6, 80.0, 73.2, 71.6, 48.0, 36.7, 30.6, 19.3; FABMS (relative intensity) $m/e$ 403 ($MH^+$, 2.4) 355 (5.9) 343 (6.5).

**Phenyl 4-*S*-Benzoyl-3-((*tert*-butyldiphenylsilyl)-2,6-dideoxy-1,4-dithio-$\beta$-D-*ribo*-hexopyranoside (19).** B ring sulfide **18** (254 mg, 0.63 mmol, 1.0 equiv) was dissolved in 10 mL of $Et_2O$, cooled to 0 °C, and treated with a dropwise addition of $LiAlH_4$ (2.52 mmol, 2.52 mL of a 1.0 M solution in $Et_2O$) by syringe. The reaction was complete in 10 min and was carefully quenched with saturated aqueous $NH_4Cl$. The reaction was poured into a separatory funnel containing 10 mL of $CH_2Cl_2$ and 10 mL of saturated aqueous $NH_4Cl$, and the mixture was extracted (3 × 10 mL $CH_2Cl_2$). The organic layers were combined, dried over $Na_2SO_4$, filtered, evaporated to an oil, and dried by azeotrope with toluene (3 × 5 mL) and 10 mL of $CH_2Cl_2$.

To a solution of the thiol in 10 mL of $CH_2Cl_2$ was added dropwise by syringe at −78 °C benzoyl chloride (133 mg, 0.94 mmol, 1.5 equiv), followed by a cannula addition of TEA (255 mg, 2.52 mmol, 4 equiv) and DMAP (10 mg, 0.05 mmol) in 1 mL of $CH_2Cl_2$. The reaction was gradually warmed to 0 °C and followed closely by TLC. After 0.5 h at −78 °C and 1 h at 0 °C, the reaction was quenched with MeOH, warmed to room temperature, evaporated, and placed directly onto a column of silica gel (gradient 10–20% EtOAc/petroleum ether) to give 170 mg (75%) of the thioester-3-ol as a clear, colorless oil: $R_f$ 0.32 (25% EtOAc/petroleum ether); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.98 (d, $J$ = 7.7 Hz, 1 H), 7.63–7.29 (m, 4 H), 5.3 (dd, $J$ = 12.1, 2.2 Hz, 1 H), 4.71 (s, 1 H, 3-OH), 4.24 (m, 1 H), 4.11 (dq, $J$ = 11.5, 6.4 Hz, 1 H), 2.23 (ddd, $J$ = 13.8, 2.7, 2.6 Hz, 1 H), 2.12 (ddd, $J$ = 14.0, 11.6, 2.7 Hz, 1 H), 1.36 (d, $J$ = 6.3 Hz, 3 H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 189.7, 136.6, 134.1, 133.8, 133.7, 131.4, 128.75, 128.7, 127.4, 127.2, 79.5, 71.5, 68.1, 51.1, 39.1, 19.6; FABMS $C_{19}H_{20}S_2O_3$ ($MH^+$) calcd 361.0932, found 361.0954.

The 4-thioester-3-ol B ring sulfide (160 mg, 0.44 mmol) was dried by toluene azeotrope (3 × 5 mL) and dissolved in 10 mL of $CH_2Cl_2$. To this solution was added pyridine (140 mg, 1.77 mmol, 4 equiv) by syringe. The reaction was cooled to −78 °C and treated with a solution of *tert*-butyldiphenylsilyl triflate (342 mg, 0.88 mmol, 2 equiv) in 2 mL of $CH_2Cl_2$. The reaction was warmed to 25 °C and stirred for 12 h. The reaction was quenched with 2 mL of MeOH, evaporated, and placed directly on a flash column to give 198 mg (80%) of the silyl ether **19** as a colorless oil: $R_f$ 0.67 (25% EtOAc/petroleum ether); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.98–7.34 (m, 20 H), 5.36 (dd, $J$ = 11.2, 2.1 Hz, 1 H), 4.31 (d, $J$ = 2.4 Hz, 1 H), 4.26 (dq, $J$ = 10.8, 6.3 Hz, 1 H), 3.75 (dd, $J$ = 10.7, 2.3 Hz, 1 H), 1.91 (ddd, $J$ = 14.0, 2.7, 2.6 Hz, 1 H), 1.81 (ddd, $J$ = 13.6, 11.4, 2.2 Hz, 1 H), 1.35 (d, $J$ = 6.3 Hz, 3 H), 1.12 (s, 9 H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 190.2, 136.8, 136.1, 135.8, 135.4, 133.6, 133.4, 132.7, 131.7, 129.8, 129.7, 129.5, 128.7, 128.5, 127.6, 127.5, 127.2, 79.9, 72.5, 70.6, 52.1, 51.2, 39.2, 27.1, 19.4; FABMS $C_{35}H_{38}S_2O_3Si$ ($MNa^+$) calcd 621.1930, found 621.1938.

**Ethyl ((4-*S*-Benzoyl-3-((*tert*-butyldiphenylsilyl)oxy)-2,6-dideoxy-4-thio-$\beta$-D-*ribo*-hexopyranosyl)oxy)carbamate (7).** The protected B sulfide **19** (217 mg, 0.38 mmol, 1.0 equiv) was dissolved in 10 mL of $CH_2Cl_2$, cooled to −78 °C, and treated with a cannula addition of mCPBA (97 mg of a 64% reagent (SIGMA, 0.36 mmol, 0.95 equiv) in 3 mL of $CH_2Cl_2$. The reaction was warmed to −10 °C, followed closely by TLC (25% EtOAc/petroleum ether), and quenched after 30 min with 0.25 mL of DMS. The reaction was evaporated and placed directly onto a flash column ($SiO_2$, 25% EtOAc/petroleum ether) to give 168 mg (76%) of the intermediate sulfoxide as a viscous oil. This material was brought immediately to the next step as a mixture of sulfoxide anomers: $R_f$ 0.12 and 0.26 (25% EtOAc/petroleum ether).

The sulfoxide (112 mg, 0.19 mmol, 1.0 equiv), 2,6-di-*tert*-butyl-4-methyl piperidine (79 mg, 0.38 mmol, 2.0 equiv), and *N*-hydroxyurethane (60 mg, 0.57 mmol, 3.0 equiv) were combined and dried by azeotrope with toluene (3 × 5 mL). To this mixture was added 10 mL of $CH_2Cl_2$, and the reaction was cooled to −78 °C and treated with a dropwise addition of triflic anhydride (59 mg, 0.21 mmol, 1.1 equiv). TLC (25% EtOAc/petroleum ether) showed formation of both O-glycosylated material (less

polar) and N-glycosylated material (more polar) as well as some persisting lactol (sulfoxide that has been activated by triflic anhydride and reacts with $H_2O$ on $SiO_2$ plate). The reaction was treated with an additional 1.1 equiv of triflic anhydride and warmed to –50 °C. TLC now showed just O- and N-glycosylated urethane. The reaction was quenched after 30 min with saturated aqueous $NaHCO_3$, warmed to room temperature, and extracted with 3 × 10 mL of $CH_2Cl_2$. The layers were combined, dried over $Na_2SO_4$, filtered, evaporated to an oil, and purified by flash chromatography (25% EtOAc/petroleum ether) to give 92 mg (76%) of the B urethane **7** as a 2:1 mixture of $\beta$:$\alpha$ anomers. This mixture was further purified by HPLC (10% *tert*-BuOMe/hexane) to give 58 mg of the pure $\beta$-anomer: $R_f$ 0.45 (25% EtOAc/petroleum ether); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.85–7.20 (m, 15 H), 5.32 (dd, $J$ = 9.7, 1.4 Hz, 1 H), 4.31–4.20 (m, 2 H, overlapping 5-H and 3-H protons), 3.67 (dd, $J$ = 10.6, 2.6 Hz, 1 H), 2.05 (ddd, $J$ = 13.3, 3.2, 2.2 Hz, 1 H), 1.66 (ddd, $J$ = 12.6, 10.1, 2.3 Hz, 1 H), 1.34 (d, $J$ = 6.3 Hz, 3 H), 1.30 (t, $J$ = 7.1 Hz, 3 H); $^{13}$C NMR (67.5 MHz, $CDCl_3$) $\delta$ 190.1, 157.0, 136.8, 136.2, 136.0, 133.4, 133.3, 132.8, 129.9, 129.8, 128.5, 127.7, 127.5, 127.3, 101.8, 70.3, 62.1, 51.1, 36.7, 29.7, 27.2, 19.6, 19.1, 14.5; FABMS $C_{20}H_{38}S_2O_3Si$ ($MH^+$) calcd 594.2345, found 594.2365.

**Phenyl 4-*O*-Acetyl-6-deoxy-3-*O*-methyl-2-*O*-pivaloyl-1-thio-$\alpha$-L-mannopyranoside (21).** To a solution of L-rhamnose anomeric sulfide[22] (23.9 g, 61 mmol) in 200 mL of MeOH at 25 °C was added 3.2 g (61 mmol, 1.0 equiv) of NaOMe. The reaction was stirred at 25 °C for 24 h and neutralized with 65 g of Amberlite IR-120(plus) acidic resin. The resin was filtered off, and the filtrate was concentrated under reduced pressure. The residue was dissolved in $CH_2Cl_2$ (500 mL) and washed with water (2 × 300 mL). The organic phase was dried over $Na_2SO_4$, filtered, and concentrated to afford the triol as a white solid, which was taken to the next step without futher purification: $R_f$ 0.25 (80% EtOAc/petroleum ether); $^1$H NMR ($CDCl_3$, 270 MHz) $\delta$ 7.45–7.23 (m, 5 H, ArH), 5.5 (s, 1 H, H-1), 4.25 (d, $J$ = 1.6 Hz, 1 H, H-2), 4.21 (dq, $J$ = 10, 6 Hz, 1 H, H-5), 3.82 (dd, $J$ = 10, 1.6 Hz, 1 H, H-3), 3.6 (t, $J$ = 10 Hz, 1 H, H-4), 1.34 (d, $J$ = 6 Hz, 1 H, H-6); $^{13}$C NMR ($CDCl_3$, 67.5 MHz) $\delta$ 133.9, 131.3, 129.0, 127.3, 87.8, 73.2, 72.6, 72.2, 69.4, 17.5; HRMS $C_{12}H_{16}O_4S$ ($M^+$) calcd 256.0768, found 256.0759.

To the crude triol (61 mmol) in 250 mL of acetone at 25 °C was added 16.5 g (121 mmol, 2.0 equiv) of anhydrous $ZnCl_2$ and 10 drops of 85% $H_3PO_4$. The reaction was maintained at 25 °C for 24 h and neutralized with 10 g of $NaOCH_3$. The reaction mixture was filtered through Celite and concentrated. The crude 2,3-isopropylidene ketal-4-ol was dissolved in 250 mL of pyridine, and $(CH_3CO)_2O$ (11.5 mL, 122 mmol, 2.0 equiv) was added. The reaction was maintained at 25 °C for 10 h, after which pyridine was removed under reduced pressure. The crude product was diluted in 500 mL of $CH_2Cl_2$, washed (2 × 250 mL) with 1 N HCl, dried over $Na_2SO_4$, concentrated, and purified by flash chromatography (20% EtOAc/petroleum ether) to afford **20**, which was dissolved in 210 mL of AcOH:$H_2O$:THF (3:1:3) and heated at 70 °C for 48 h. The solvent was removed under reduced pressure, and the residue was diluted with 500 mL of $CH_2Cl_2$, washed with saturated $NaHCO_3$ (200 mL) and water (3 × 300 mL), dried over $Na_2SO_4$, and purified by flash chromatography (60% EtOAc/petroleum ether) to give 12.1 g (66%, four steps) of the diol as a white solid: $R_f$ 0.2 (40% EtOAc/petroleum ether); $^1$H NMR ($CDCl_3$, 270 MHz) $\delta$ 7.48–7.45(m, 2 H, ArH), 7.35–7.27 (m, 3 H, ArH), 5.53 (d, $J$ = 1.3 Hz, 1 H, H-1), 4.90 (t, $J$ = 9.2 Hz, 1 H, H-4), 4.29 (dq, $J$ = 9.6, 6 Hz, 1 H, H-5), 4.22–4.20 (m, 1 H, H-2), 3.88 (dd, $J$ = 9.6, 3.3 Hz, 1 H, H-3), 3.15–2.94 (br s, 2 H, OH), 2.16 (s, 3 H, OAc), 1.23 (d, $J$ = 6.3 Hz, 3 H, H-6); $^{13}$C NMR ($CDCl_3$, 67.5 MHz) $\delta$ 172.1, 133.8, 131.3, 129.1, 127.5, 87.4, 75.5, 72.4, 70.7, 67.0, 21.0, 17.3; HRMS $C_{14}H_{18}O_5S$ ($M^+$) calcd 298.0870, found 298.0869.

To a solution of the diol acetate (12.1 g, 39.4 mmol) in 200 mL of DMF was added 5 g of crushed 4-Å sieves and $Bu_2SnO$ (15 g, 59.1 mmol, 1.5 equiv). The reaction was heated at 80 °C for 5 h, and $CH_3I$ (7.4 mL, 118.2 mmol, 3.0 equiv) was added. The reaction was maintained for an additional 6 h at this temperature, cooled to 25 °C, and filtered through Celite. The solvent was removed under vacuum, and the residue was dissolved in 400 mL of $CH_2Cl_2$, washed with $H_2O$ (2 × 200 mL), dried over $Na_2SO_4$, concentrated, and purified by flash chromatography (60% EtOAc/petroleum ether) to afford 10.1 g (79%) of the 3-methyl ether-2-ol: $R_f$ 0.4 (50% EtOAc/petroleum ether); $^1$H NMR ($CDCl_3$, 270 MHz) $\delta$ 7.5–7.2 (m, 5 H, ArH), 5.55 (d, $J$ = 1.3 Hz, 1 H, H-1), 5.03 (t, $J$ = 9.6 Hz, 1 H, H-4), 4.3 (m, 1 H, H-2), 4.21 (dq, $J$ = 9.6, 6.3 Hz, 1 H, H-5), 3.50 (dd, $J$ = 9.3, 3.3 Hz, 1 H, H-3), 3.43 (s, 3 H, OMe), 2.6 (d, $J$ = 2 Hz, 1 H, OH), 2.09 (s, 3 H, OAc), 1.16 (d, $J$ = 6.5 Hz, 3 H, H-6).

To a solution of the 3-methyl ether-2-ol (1.09 g, 3.4 mmol) in 35 mL of pyridine was added 3.44 mL (27.2 mmol, 8.0 equiv) of $(CH_3)_3COCl$. The reaction was heated at 60 °C for 6 h, and pyridine was removed under vacuum. The residue was diluted in 100 mL of $CH_2Cl_2$, washed with 1 N HCl (2 × 50 mL) and $H_2O$ (50 mL), dried over $Na_2SO_4$, and purified by flash chromatography (10% EtOAc/petroleum ether) to give 1.13 g (82%) of **21** as a white solid: $R_f$ 0.65 (15% EtOAc/petroleum ether); $^1$H NMR ($CDCl_3$, 270 MHz) $\delta$ 7.58–7.53 (m, 5 H, ArH), 5.65–5.64 (m, 1 H, H-2), 5.49 (d, $J$ = 1.3 Hz, 1 H, H-1), 5.13 (t, $J$ = 9.9 Hz, 1 H, H-4), 4.38 (dq, $J$ = 9.8, 6.2 Hz, 1 H, H-5), 3.67 (dd, $J$ = 9.6 Hz, 1 H, H-3), 3.43 (s, 3 H, OMe), 2.2 (s, 3 H, OAc), 1.33 (s, 9 H, $CMe_3$), 1.31 (d, $J$ = 6 Hz, 3 H, H-6); $^{13}$C NMR ($CDCl_3$, 67.5 MHz) $\delta$ 177.9, 170.0, 133.6, 131.9, 129.2, 127.8, 86.2, 77.7, 72.7, 69.2, 67.7, 57.4, 39.1, 27.1, 21.0, 17.5; HRMS $C_{20}H_{28}O_6S$ ($M^+$) calcd 396.1606, found 396.1608.

**4-*O*-Acetyl-6-deoxy-3-*O*-methyl-2-*O*-pivaloyl-1-phenylsulfinyl-$\alpha$-L-mannopyranose (22).** To a solution of sulfide **21** (509 mg, 1.25 mmol) in 100 mL of distilled $CH_2Cl_2$ at –78 °C was added a solution of mCPBA (300 mg, 1.38 mmol, 1.1 equiv, 80% from Sigma) in 5.0 mL of $CH_2Cl_2$. The reaction was maintained at –78 °C for 30 min, and then at 0 °C for 20 min, and then was quenched over saturated $NaHCO_3$ (200 mL). The aqueous layer was extracted with $CH_2Cl_2$ (2 × 25mL), dried over $Na_2SO_4$, filtered, concentrated, and purified by flash chromatography (35% EtOAc/petroleum ether) to give 486 mg (92%) of **22** as a white solid: $R_f$ 0.15 (15% EtOAc/petroleum ether); $^1$H NMR ($CDCl_3$, 270 MHz) $\delta$ 7.7–7.5 (m, 5 H, ArH), 5.82 (dd, $J$ = 3.3, 2 Hz, 1 H, H-2), 5.03 (t, $J$ = 9.5 Hz, 1 H, H-4), 4.49 (d, $J$ = 1.6 Hz, 1 H, H-1), 4.19 (dq, $J$ = 9.6, 6.3 Hz, 1 H, H-5), 3.93 (dd, $J$ = 9.6, 3.3 Hz, 1 H, H-3), 3.35 (s, 3 H, OMe), 2.08 (s, 3 H, OAc), 1.6 (d, $J$ = 6.4 Hz, 3 H, H-6).

**2-((*tert*-Butyldiphenylsiloxy)methyl)-3,4-dimethoxy-6-iodo-5-((tributylstannyl)oxy)toluene (23).** DIBAL (36 mL, 1.0 M solution in $CH_2Cl_2$, 36 mmol, 3.5 equiv) was added to a solution of 2-carbomethoxy-3,4-dimethoxy-5-hydroxy-6-iodotoluene[23] (3.6 g, 10.2 mmol) in 250 mL of $CH_2Cl_2$ at –78 °C. The reaction was stirred at –78 °C for 10 min, and then at 25 °C for 5 min, and then was quenched with EtOAc. The mixture was diluted with $H_2O$ (200 mL), and the aqueous phase was acidified with a dropwise addition of concentrated AcOH and extracted with $CH_2Cl_2$ (3 × 150 mL). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated. The crude primary alcohol was dried by toluene azeotrope (3 × 25 mL) and taken to the next step without further purification.

To a solution of the crude primary alcohol in 200 mL of DMF was added imidazole (1.7 g, 25.5 mmol, 2.5 equiv), followed by *tert*-butyl-$(Ph)_2SiCl$ (6.6 mL, 25.5 mL, 2.5 equiv), and the solution was heated at 65 °C for 2 h. DMF was removed under reduced pressure, and the residue was diluted in $CH_2Cl_2$ (300 mL) and washed once with water (200 mL). The organic layers were dried over $Na_2SO_4$, filtered, concentrated, and purified by flash chromatography (10% EtOAc/petroleum ether) to afford 8.2 g (94%, two steps) of the silyl ether as an oil: $R_f$ 0.4 (10% EtOAc/petroleum ether); $^1$H NMR ($CDCl_3$, 270 MHz) $\delta$ 7.72–7.79 (m, 4 H, ArH), 7.43-7.34 (m, 6 H, ArH), 6.21 (s, 1 H, OH), 4.75 (s, 2 H, $CH_2$), 3.84 (s, 3 H, OMe), 3.66 (s, 3 H, OMe), 2.48 (s, 3 H, Me), 1.05 (s, 9 H, $CMe_3$); $^{13}$C NMR ($CDCl_3$, 67.5 MHz) $\delta$ 151.3, 148.8, 137.5, 136.6, 135.8, 133.6, 129.6, 127.5, 125.0, 84.8, 61.1, 60.8, 58.5, 26.9, 24.7, 19.3; FABMS (relative intensity) *m/e* 563 ($MH^+$), 562 ($M^+$, 3.2), 561 ($M^+$ – 1, 9.5).

$(Bu_3Sn)_2O$ (177 $\mu$L, 0.34 mmol, 0.6 equiv) was added to a suspension of the phenol and crushed 4-Å molecular sieves (319 mg, 0.567 mmol, 1.0 equiv) in 15 mL of benzene. The reaction was heated to reflux for 4 h, and the sieves were removed by filtration through a plug of Celite. The residue **23** was dried by toluene azeotrope (2 × 5 mL), kept under argon, and used immediately for glycosidation.

**2-((*tert*-Butyldiphenylsiloxy)methyl)-5-[(4-*O*-acetyl-6-deoxy-3-*O*-methyl-2-*O*-pivaloyl-$\alpha$-L-mannopyranosyl)oxy]-3,4-dimethoxy-6-iodotoluene (24).** To a solution of the D ring sulfoxide **22** (476 mg, 1.13 mmol, 2.0 equiv) and 2,6 di-*tert*-butyl-4-methylpyridine (255 mg, 1.13 mmol, 2.0 equiv) in 25 mL of $CH_2Cl_2$ at –60 °C was added $(CF_3SO_2)_2O$ (210 $\mu$L, 1.24 mmol). The solution was stirred at –60 °C for 30 min, and stannyl phenoxide **23** in 5.0 mL of $CH_2Cl_2$ was added dropwise over a period of 5 min. After 30 min, the reaction flask was removed from the –60 °C bath, stirred at 25 °C for 3 min, and quenched over saturated $NaHCO_3$ (50 mL). The aqueous layer was extracted with $CH_2Cl_2$ (2 × 10 mL), dried over $Na_2SO_4$, concentrated, and purified by flash chromatography (20% $Et_2O$/petroleum ether) to give 480 mg (99%) of **24** as a colorless oil: $R_f$ 0.35 (25% $Et_2O$/petroleum ether); $^1$H NMR ($CDCl_3$, 270 MHz) $\delta$ 7.69–7.66 (m, 4 H, ArH), 7.44–7.33 (m, 6 H, ArH), 5.78 (dd, $J$ = 3, 2 Hz, 1 H, H-2), 5.47 (d, $J$ = 1.7 Hz, 1 H, H-1), 5.09 (t, $J$ = 9.9 Hz, 1 H, H-4), 4.75 (s, 2 H, $CH_2$), 4.38 (dq, $J$ = 10, 6 Hz, 1 H, H-5), 4.02 (dd, $J$ = 9.6, 3 Hz, 1 H, H-3), 3.75 (s, 3 H, OMe),

3.63 (s, 3 H, OMe), 3.4 (s, 3 H, OMe), 2.49 (s, 3 H, Me-aromatic), 2.11 (s, 3 H, OAc), 1.24 (s, 9 H, $CMe_3$), 1.19 (d, $J$ = 6.2, 3 H, H-6), 1.03 (s, 9 H, $CMe_3$); $^{13}C$ NMR ($CDCl_3$, 67.5 MHz) $\delta$ 177.6, 170.2, 153.0, 149.7, 142.9, 138.0, 135.8, 133.5, 129.6, 129.1, 127.6, 101.1, 93.8, 77.2, 72.3, 69.0, 67.7, 61.3, 60.7, 58.6, 57.5, 39.1, 27.2, 26.9, 25.5, 21.1, 19.3, 17.6.

**4-[(4-*O*-Acetyl-6-deoxy-3-*O*-methyl-2-*O*-pivaloyl-α-L-mannopyranosyl)oxy]-2,3-dimethoxy-5-iodo-6-methylbenzoic acid (25).** TBAF (10.8 mL of 1.0 M solution in THF, 10.8 mmol, 4.0 equiv) was added to a solution of **24** (2.3 g, 2.68 mmol) in 150 mL of THF at 25 °C, and the reaction was stirred for 4 h. The solvent was evaporated, and the residue was purified by flash chromatography (40% EtOAc/petroleum ether) to afford 1.37 g (2.24 mmol, 84%) of the alcohol: $R_f$ 0.2 (30% EtOAc/petroleum ether); $^1H$ NMR ($CDCl_3$, 270 MHz) $\delta$ 5.72 (dd, $J$ = 3, 2 Hz, 1 H, H-2), 5.48 (d, $J$ = 1.6 Hz, 1 H, H-1), 5.06 (t, $J$ = 10 Hz, 1 H, H-4), 4.71 (s, 2 H, $CH_2$), 4.33 (dq, $J$ = 9.8, 6.3 Hz, 1 H, H-5), 4.01 (dd, $J$ = 9.6, 3 Hz, 1 H, H-2), 3.86 (s, 3 H, OMe-aromatic), 3.80 (s, 3 H, OMe-aromatic), 3.38 (s, 3 H, OMe), 2.52 (s, 3 H, Me-aromatic), 2.09 (s, 3H, OAc), 1.21 (s, 9 H, $CCMe_3$), 1.16 (d, $J$ = 6.3 Hz, 3 H, H-6); $^{13}C$ NMR ($CDCl_3$, 67.5 MHz) $\delta$ 177.6, 170.2, 153.1, 149.8, 143.0, 137.0, 129.0, 100.9, 94.0, 76.5, 72.2, 69.0, 67.6, 61.6, 60.8, 58.1, 57.5, 39.0, 27.1, 25.2, 21.0, 17.5.

To a biphasic solution of the primary alcohol (1.37 g, 2.24 mmol) in 63 mL of $CCl_4$:$CH_3CN$:$H_2O$ (1:1:3) were added $NaIO_4$ (1.9 g, 9 mmol, 4.0 equiv) and $RuCl_3 \cdot H_2O$ (120 mg, 0.25 equiv) at 0 °C. The solution was vigorously stirred at 0 °C for 1 h and then at 25 °C for 1.5 h. The reaction was diluted with $CH_2Cl_2$ (200 mL) and $H_2O$ (200 mL), and the $CH_2Cl_2$ layer was withdrawn. The aqueous phase was then acidified with concentrated AcOH and extracted with $CH_2Cl_2$ (5 × 100 mL). The combined organic layers were dried over $Na_2SO_4$, filtered, concentrated, and purified by flash chromatography (55% EtOAc/petroleum ether with 1% AcOH) to afford 1.1 g (79%) of the carboxylic acid **25** as an off-white solid: $R_f$ 0.3 (50% EtOAc/petroleum ether with 1% AcOH); $^1H$ NMR ($CDCl_3$, 270 MHz) $\delta$ 5.74 (dd, $J$ = 3, 2 Hz, 1 H, H-2), 5.58 (d, $J$ = 1 Hz, 1 H, H-1), 5.08 (t, $J$ = 9.9 Hz, 1 H, H-4), 4.32 (dq, $J$ = 9.9, 6 Hz, 1 H, H-5), 4.02 (dd, $J$ = 10, 3 Hz, 1 H, H-3), 3.94 (s, 3 H, OMe-aromatic), 3.84 (s, 3 H, OMe-aromatic), 3.38 (s, 3 H, OMe), 2.48 (s, 3 H, Me-aromatic), 1.24 (s, 9 H, $CCMe_3$), 1.16 (d, $J$ = 6 Hz, 3 H, H-6); $^{13}C$ NMR ($CDCl_3$, 67.5 MHz) $\delta$ 177.7, 171.0, 170.2, 151.5, 151.4, 142.9, 134.7, 124.5, 100.9, 93.5, 76.9, 72.2, 69.2, 67.6, 61.8, 61.0, 57.5, 39.1, 27.1, 26.2, 21.0, 17.6; FABMS (relative intensity) $m/e$ 625 ($MH^+$, 2.4), 499 (2.9), 338 (3.8), 321 (10.9).

**Bis(ethyloxy)phosphinoyl-4-[(6-deoxy-3-*O*-methyl-α-L-mannopyranosyl)oxy]-5-Iodo-2,3-dimethoxy-6-methylbenzoate (10).** LiOH (375 μL of 2.0 M solution in $H_2O$, 0.75 mmol, 5.0 equiv) was added to a solution of the acid (94 mg, 0.15 mmol) in 6.5 mL of THF:$H_2O$ (3:1) and stirred at 25 °C for 24 h. The reaction was quenched by adding dropwise a solution of 10:1 THF:AcOH until the solution was shown to be acidic by pH paper. All solvents were removed under vacuum, and the residual acetic acid was stripped off with a toluene azeotrope. The crude acid was purified by flash chromatography (10% MeOH/EtOAc with 1% AcOH) to give 63 mg (84%) of the 2,4-diol as an off-white solid: $R_f$ 0.25 (10% MeOH/EtOAc with 1% AcOH); $^1H$ NMR ($CDCl_3$, 270 MHz) $\delta$ 5.66 (d, $J$ = 2 Hz, 1 H, H-1), 4.54 (dd, $J$ = 3, 2 Hz, 1 H, H-2), 4.25 (dq, $J$ = 9.7, 6 Hz, 1 H, H-5), 3.98 (s, 3 H, OMe-aromatic), 3.93 (s, 3 H, OMe-aromatic), 3.84 (dd, $J$ = 9.6, 3.3 Hz, 1 H, H-3), 3.67 (t, $J$ = 9.6 Hz, 1 H, H-4), 3.61 (s, 3 H, OMe), 2.49 (s, 3H, Me-aromatic), 1.32 (d, $J$ = 6 Hz, 1 H, H-6); $^{13}C$ NMR ($CDCl_3$, 67.5 MHz) $\delta$ 170.9, 152.3, 152.0, 144.5, 134.5, 128.3, 104.9, 93.8, 81.7, 72.4, 72.3, 68.2, 62.0, 61.5, 57.5, 26.2, 18.0; HRMS $C_{16}H_{21}O_9I$ ($M^+$) calcd 498.0388, found 498.0402.

To a solution of CD acid (28.4 mg, 0.057 mmol) in 2.0 mL of THF at 25 °C were added 10 μL (0.074 mmol, 1.3 equiv) of $Et_3N$ and 10 μL of $ClPO(OEt)_2$ (0.071 mmol, 1.25 equiv). The reaction was stirred for 20 min and filtered through Celite to remove insoluble $Et_3N \cdot HCl$. The solvent was evaporated under reduced pressure, and the oily residue was loaded directly onto a short silica gel column (10 mm × 8 cm, 5% MeOH/EtOAc) to give 22 mg (51%) of **10**, which was used immediately for the next step: $R_f$ 0.5 (5% MeOH/EtOAc); $^1H$ NMR ($CDCl_3$, 270 MHz) $\delta$ 5.75 (d, $J$ = 1 Hz, 1 H, H-1), 4.45 (dd, $J$ = 3.3, 1.3 Hz, 1 H, H-2), 4.29 (q, $J$ = 7.5, 2 H, $CH_2$), 4.19-4.04 (m, 3 H, $CH_2$), 3.90 (s, 3 H, OMe-aromatic), 3.85 (dq, $J$ = 9.6, 3 Hz, 1 H, H-3), 3.82 (s, 3 H, OMe-aromatic), 3.62 (t, $J$ = 9.5 Hz, 1 H, H-4), 3.55 (s, 3 H, OMe), 2.44 (s, 3 H, Me-aromatic), 2.35–2.10 (br s, 2 H, OH), 1.4–1.22 (m, 9 H, H-6).

**Methyl 4,6-Dideoxy-4-[*N*-[[2,6-dideoxy-4-*S*-benzoyl-3-((*tert*-butyldiphenyl-silyl)oxy)-4-thio-β-D-*ribo*-hexopyranosyl]oxy]-*N*-[ethoxycarbonyl]amino]-2-*O*-[2,4-dideoxy-4-(*N*-(trifluoroacetyl)-*N*-ethylamino)-3-*O*-methyl-α-L-xylopyranosyl]]-β-D-glucopyranoside (8).** The B ring urethane **7** (10 mg, 0.017 mmol) was dissolved in 1 mL of DMF, cooled to −10 °C, and treated with a dropwise addition of potassium bis(trimethylsilyl)-amide (0.02 mmol, 1.2 equiv, 0.5 M solution in toluene) by syringe over 5 min. Deprotonation was allowed to proceed for 20 min, at which time a solution of the AE triflate **6** (17 mg, 0.026 mmol, 1.5 equiv) in 1 mL of DMF was added dropwise by cannula. The reaction was stirred at −10 °C for 45 min and was quenched with 1 mL of saturated aqueous $NH_4Cl$. The reaction was extracted with $CH_2Cl_2$ (3 × 10 mL), and the organic layers were combined, dried over anhydrous $Na_2SO_4$, filtered, evaporated to an oil, and purified by radial chromatography to give 15 mg (81%) of the protected core trisaccharide **8** as a colorless oil: $R_f$ 0.66 (60% $Et_2O$/ pet ether); $^1H$ NMR (300 MHz, $CDCl_3$, mixture of rotamers) $\delta$ 7.15–8.09 (m, 20 H), 6.28 (bs, 1 H), 5.20–5.29 (m, 1 H), 4.95–5.08 (m, 1 H), 3.90–4.67 (m, 6 H), 3.60–3.82 (m, 4 H), 3.57 (s, 3 H, A ring-OMe), 3.26–3.55 (m, 5 H), 3.16 and 3.21 (2s, 3 H, E ring OMe), 1.97–2.25 (m, 2 H), 0.82–1.56 (m, 14 H), 1.08 (s, 9 H, *tert*-butyl signal); $^{13}C$ NMR (67.5 MHz, $CDCl_3$, mixture of rotamers) $\delta$ 190.3, 165.8, 165.7, 165.4, 165.3, 157.4, 157.2, 136.8, 136.7, 136.2, 136.0, 133.7, 133.6, 133.4, 133.38, 133.3, 133.2, 133.1, 132.9, 132.4, 129.8, 129.7, 128.7, 128.6, 128.54, 128.5, 128.4, 127.5, 127.3, 126.9, 102.6, 102.4, 102.3, 98.2, 97.9, 97.8, 97.4, 71.1, 70.92, 70.88, 70.7, 70.6, 62.54, 62.5, 62.44, 60.4, 59.8, 59.7, 58.6, 58.5, 58.4, 57.4, 57.1, 56.8, 56.6, 55.9, 55.7, 53.4, 50.84, 50.79, 41.3, 38.6, 37.6, 37.5, 35.7, 34.7, 31.6, 29.3, 29.0, 27.6, 27.1, 22.6, 21.0, 20.4, 19.6, 18.9, 17.8, 14.3, 14.2, 14.1, 14.0, 13.3, 11.4; FABMS $C_{84}H_{69}N_2SO_{14}SiF_3$ ($MNa^+$) calcd 1133.4088, found 1133.4078.

**Bis[methyl 4,6-dideoxy-2-*O*-[2,4-dideoxy-4-(*N*-ethylamino)-3-*O*-methyl-α-L-xylopyranosyl]-4-[[(2,6-dideoxy-4-thio-β-D-*ribo*-hexopyranosyl)oxy]amino]-β-D-galactopyranoside] Disulfide (9).** To a solution of protected ABE trisaccharide **8** (10.0 mg, 0.009 mmol) in 1.0 mL of THF was added excess TBAF (40 μL, 1.0 M solution in THF, 4.0 equiv), and the reaction was stirred for 6–24 h. The reaction was taken up in $CH_2Cl_2$, washed with aqueous brine, dried over anhydrous $Na_2SO_4$, filtered, and evaporated. The residue was taken up in 1.0 mL of absolute EtOH. To this solution was added excess NaOH (1.2 mL of 3.0 M solution in MeOH), and the clear solution was maintained at 25 °C for 2.5 h. The reaction was diluted with MeOH (2 mL) and neutralized with a dropwise addition of concentrated AcOH until pH paper indicated the solution to be slightly basic to neutral. The solvent was evaporated to give a white solid, which was triturated with EtOAc for 2 h. The suspension was filtered through Celite, and TLC (25% MeOH/diethyl ether) of the filtrate showed deprotected ABE disulfide dimer 9 and several nonpolar components. The nonpolar components were isolated by short flash chromatography (25% MeOH/diethyl ether) and resubjected to reaction conditions. The products were combined to give the deprotected ABE dimer **9** (2.2 mg, 52%) isolated as a white solid: $R_f$ 0.15 (25% MeOH/$Et_2O$); $^1H$ NMR ($CD_3OD$, 500 MHz) $\delta$ 5.38 (s, 1 H, E-1), 4.98 (dd, $J$ = 9.5, 1.5 Hz, 1 H, B-1), 4.34 (m, 1 H, B-3), 4.16 (d, $J$ = 7.7 Hz, 1 H, A-1), 3.97-3.84 (m, 3 H, A-3, B-5, and E-5), 3.76–3.68 (br m, 1 H, E-5′), 3.65–3.53 (br m, 2 H, A-5 and E-3), 3.48 (s, 3 H, A-OMe), 3.36 (s, 3 H, E-OMe), 3.3 (1 H, A-2; buried under solvent peak), 2.93–2.78 (br m, 3 H, $NCH_2$, E-4), 2.7 (dd, $J$ = 11, 3 Hz, 1 H, B-4), 2.46–2.37 (br m, 1 H, E-$2_{eq}$), 2.2 (t, $J$ = 10 Hz, 1 H, A-4), 1.95 (1 H, B-$2_{eq}$; buried under water peak), 1.64–1.56 (m, 1 H, B-$2_{ax}$), 1.46 (br m, 1 H, E-$2_{ax}$), 1.37 (d, $J$ = 6.2 Hz, 3 H, H-6), 1.36 (d, $J$ = 6.2 Hz, 3 H, H-6), 1.2 (br t, $J$ = 7 Hz, 3 H, $NCH_2CH_3$).

**Methyl 4,6-Dideoxy-4-[[[2,6-dideoxy-4-*S*-[4-[[6-deoxy-3-*O*-methyl-α-L-mannopyranosyl]oxy]-5-Iodo-2,3-dimethoxy-6-methylbenzoyl]-4-thio-β-D-*ribo*-hexopyranosyl]oxy]amino]-2-*O*-[2,4-dideoxy-4-(*N*-ethylamino)-3-*O*-methyl-α-L-xylopyranosyl]]-β-D-glucopyranoside (2).** To a solution of ABE dimer **9** (4.6 mg, 4.64 mmol) in 1.5 mL of deoxygenated THF at 25 °C was added excess ($n$-$C_4H_9)_3P$ (50 μL, 210 mmol, 45 equiv). After 20 min, TLC (3:1 ether:MeOH) showed the disulfide reduction to be complete. The CD phosphate ester **10** (14 mg, 18.6 mmol, 2 equiv) in 0.5 mL of THF and DMAP (6.8 mg, 56 mmol, 12 equiv) were added, and the reaction was stirred at 25 °C for 5 h. The solvent was evaporated under reduced pressure, and the residue was loaded directly onto the column. Flash chromatography with 6:1 $Et_2O$/MeOH afforded 7.1 mg (79%, two steps) of the calicheamicin oligosaccharide **2** as a white solid: $R_f$ 0.15 (6:1 $Et_2O$:MeOH); $^1H$ NMR ($CD_3OD$, 500 MHz) $\delta$ 5.58 (d, $J$ = 1.8 Hz, 1 H, D-1), 5.38 (bs, 1 H, E-1), 5.05 (dd, $J$ = 10.3, 1.8 Hz, 1 H, B-1), 4.45 (t, $J$ = 2.5 Hz, 1 H, D-2), 4.21 (m, 4 H, B-3 and A-1), 4.15 (m, 1 H, D-5), 4.02 (dq, $J$ = 10.6, 6.2 Hz, 1 H, B-5), 3.91 (t, $J$ = 9.5 Hz, 1 H, A-3), 3.89 (t, $J$ = 10.8 Hz, 1 H, E-5 axial), 3.89 (s, 3 H, aromatic-OMe), 3.83 (s, 3 H, aromatic-OMe), 3.74 (dd, $J$ = 9.2, 2.9 Hz, 1 H, D-3), 3.72–3.67 (m, 2 H, B-4 and E-5 equatorial), 3.65 (m, 1 H, A-5), 3.57 (t, $J$ = 9.5 Hz, 1 H, D-4), 3.53 (m, 4 H, E-3 and OMe), 3.49

(s, 3 H, OMe), 3.31 (dd, $J$ = 8.8, 7.7 Hz, 1 H, A-2), 2.82–2.68 (m, 3 H, E-4 and $NCH_2$), 2.42 (ddd, $J$ = 12.8, 2.9, 1.5 Hz, 1 H, E-2 equatorial), 2.35 (s, 3 H, aromatic-Me), 2.24 (t, $J$ = 9.9 Hz, 1 H, A-4), 1.96 (dt, $J$ = 12.5, 2.9 Hz, 1 H, B-2 equatorial), 1.74 (ddd, $J$ = 12.8, 10.3, 2.6 Hz, 1 H, B-2 axial), 1.45 (ddd, $J$ = 13.2, 11.0, 3.7 Hz, 1 H, E-2 axial), 1.36 (d, $J$ = 6.6 Hz, 3 H, A-6 or B-6 methyl), 1.34 (d, $J$ = 6.2 Hz, 3 H, A-6 or B-6 methyl), 1.20 (d, $J$ = 6.2 Hz, 3 H, D-6 methyl), 1.16 (t, $J$ = 7.0 Hz, 3 H, $NCH_2CH_3$); $^{13}C$ NMR ($CD_3OD$, 67.5 MHz, 38 unique carbons) $\delta$ 194.2 (C=O), 153.2, 152.0, 144.6, 134.5, 131.8, 105.0, 103.8, 101.4, 99.7, 94.2, 81.7, 80.3, 77.0, 72.5, 72.3, 72.1, 71.2, 70.5, 69.3, 69.2, 68.2, 62.3, 61.5, 59.9, 57.5, 56.9, 56.2, 52.5, 42.7, 38.9, 35.0, 30.7, 25.7, 19.4, 18.6, 18.0, 14.3; FABMS $C_{38}H_{61}N_2O_{17}SI$ (relative intensity) $m/e$ 977 ($MH^+$, 26), 395 (13.9), 367 (7.7), 321 (100).

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