Novel Bicylic Donors for the Synthesis of 2-Deoxy-β-Glycosides†

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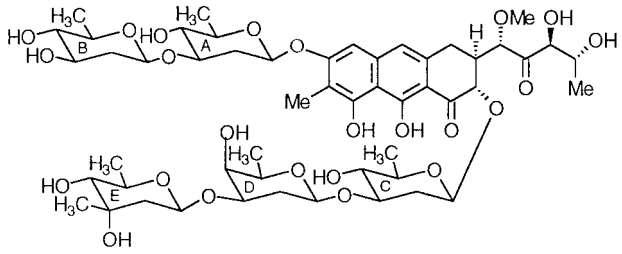
Novel bicyclic glycosyl donors have been prepared by the cycloaddition reaction of glycals with 3-thiono-2,4-pentanedione **17** followed by methylenation of the resulting ketone. Treatment of the heterocyclic donors with triflic acid in the presence of a variety of alcohol acceptors leads to the formation of β-glycosides in good yields and with excellent stereoselectivities. Desulfurization of the C-2 carbon−sulfur bonds gives the corresponding 2-deoxy-β-glycosides. This method has been extended to the synthesis of glycosidic linkages found in the aureolic acid antibiotics. Tetra-*N*-butylammonium triflate proved to be a useful additive in these glycosylation reactions, suggesting an important role for triflate anion in stabilizing intermediates which are formed.

Introduction

The 2-deoxy-β-glycosidic linkage is an important structural component in many natural products including: the aureolic acids[1] **1**, the calchiceamicins,[2] the cardiac glycosides,[3] and the angucycline antibiotics.[4] In the past two decades, more than a dozen attractive methods for the synthesis of the 2-deoxy-β-linkage have been reported, and these methods have been the subject of reviews.[5] However, thus far, no single method has been recognized as "first among equals".



1 AUREOLIC ACID

The aureolic acid antitumor antibiotics are inhibitors of DNA-dependent RNA polymerase and are known to bind as 2:1 antibiotic:Mg^{2+} complexes in the DNA minor groove.[6] Structure−activity studies have shown that the two intact oligosaccharide chains are essential for biological activity.[7] Kahne has shown that the complete C−D−E trisaccharide-aglycone[8] or, more recently, a simplified triethylene glycol−aglycone fragment[9] forms 2:1 complexes with Mg^{2+}, and these complexes interact with DNA. Because of their high toxicity, the aureolic acids have found limited therapeutic application.[1] However, because of their significant biological activity, efforts to synthesize less toxic analogues and to understand the nature of the interactions of these antibiotics with DNA are important.

As part of our ongoing interest in the synthesis of the aureolic acid antibiotics, we have previously confronted the problems inherent in the construction of the 2-deoxy-β-glycosidic linkage.[10] The aureolic acids are particularly challenging molecules, in that, 2-deoxy-β-glycosides are found both in the saccharide chains, as well as between the aglycone moiety and the saccharide chains. The A−B disaccharides are linked to phenolic residues, and the C−D−E trisaccharides to α-hydroxy ketones. A variety of approaches to the synthesis of these molecules have been reported. Most recently, in a series of papers, Roush has reviewed these methods and has described his successful approaches to forging these linkages en route to a total synthesis of the aureolic acid antibiotic olivomycin A.[11] To date, no method has been described which utilizes a common sugar donor to effect all of the glycoside linkages in this family of antibiotics.

We describe herein the results of our studies on the development of a highly selective glycosylation protocol

† Dedicated to Erwin Fleissner on the occasion of his retirement as Dean of the Division of Sciences and Mathematics at Hunter College.

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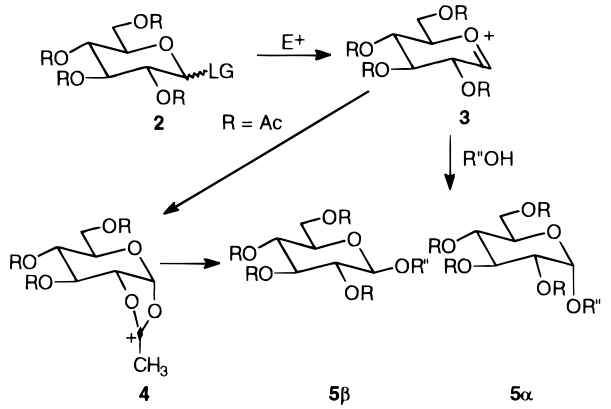
Scheme 1

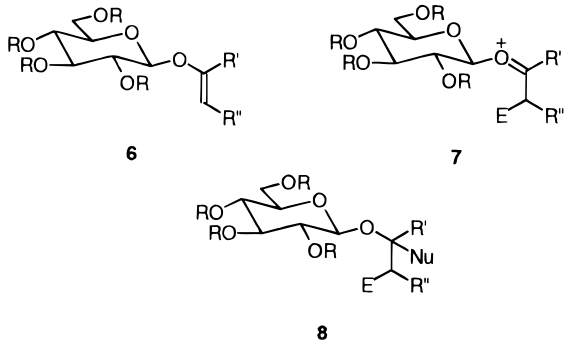


for the synthesis of 2-deoxy-β-glycosides.[12] This method utilizes a single sugar donor and gives glycosides for a variety of acceptors, including those types found in the aureolic acid antibiotics.

Background. The most common method for glycosyl transfer involves the electrophilic activation of an anomeric carbon which contains a good leaving group (Scheme 1). Examples of leaving groups which have been successfully utilized include the anomeric halides,[13,14] acetates,[15] sulfides,[16] sulfoxides,[17] phosphates and phosphites,[18] trichloroacetimidates,[19] and pentenyl glycosides.[20]

Upon activation, the anomeric group of the donor **2** departs and an oxocarbenium ion **3** is formed. This intermediate **3** is trapped by an alcohol acceptor, giving rise to a mixture of glycosides **5α** and **5*β***. Often, when the sugar donor contains an equatorial protecting group at C-2 which is capable of providing anchimeric stabilization to the developing oxocarbenium ion, such as an acetate group, a more stable dioxolenium ion **4** may be generated. Then, nucleophillic attack at the anomeric center produces exclusively the 1,2-trans glycoside **5*β***.

Recently, vinyl (alkenyl) glycosides[21−26] **6** have also been shown to possess excellent donor properties. These compounds have been prepared by: (1) methylenation of anomeric acetates;[21a,22] (2) the reaction of organometallic species with glycosyl bromides;[21b,23] (3) isomerization of allyl glycosides;[24] (4) E_1 chemistry;[25] and (5) anomeric alkoxide addition to methyl phenylpropiolate.[26] The mechanism of activation of these donors **6** is believed to involve the initial reaction of the electrophilic species (E^+) with the vinyl ether double bond leading to the formation of a cation **7**. This cation then collapses to produce an oxocarbenium ion **3** which reacts to produce a glycoside **5**. Again, neighboring group participation plays an important role in dictating the stereochemical outcome of the glycosylation reaction. In some cases, the glycosyl acceptor reacts directly with the activated double bond to give glycoside **8** which may then be rearranged to the anomeric position.[25]



None of the methods described above are particularly useful for the direct synthesis of the 2-deoxy-β-glycosidic linkage. The lack of a participating C-2 substituent makes a highly stereocontrolled and efficient glycosylation difficult. The intermediate oxocarbenium ion which is generated favors the trapping of acceptor in the axial direction due to a developing anomeric effect.[27] In addition, glycosidic bonds of 2-deoxy sugars possess low stability under acidic conditions due to the lack of a C-2 electron-withdrawing group, and hydrolysis and anomerization readily occurs.[28]

For these reasons, the most frequently employed strategy for accessing 2-deoxy-β-glycosides uses temporary equatorial blocking groups at C-2 which can be

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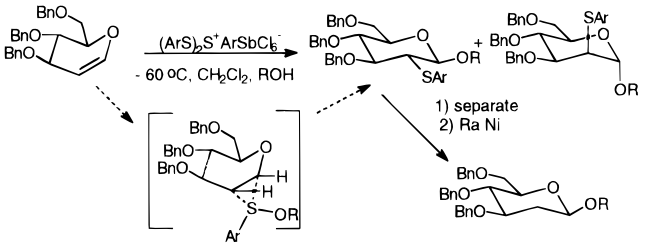
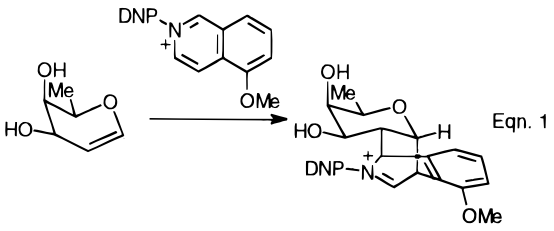
Scheme 2



removed following glycosylation. Halo-,[29,30] thiophenyl-,[31] selenophenyl-,[32] and formylamido-[33] groups have all been employed as temporary protecting groups. These moieties help stabilize the resulting glycosidic bond and are also believed to participate in the stabilization of oxocarbenium ion intermediates analogous to **3**. Often the β-stereoselectivity obtained is excellent.

Previous work in our group focused on this type of approach to 2-deoxy-β-glycosides.[10b] Addition of arylbis(arylthio)sulfonium salts and alcohols to glycals gave in some cases excellent stereoselectivities for the 2-deoxy-2-(arylthio)-β-glucosides (Scheme 2). The arylthio group at C-2 could then be removed with Raney nickel. Unfortunately, this method was not uniformly β-selective and required the use of harsh reagents, low temperatures, and anhydrous reaction conditions. With these problems in mind, we sought to develop a method which was both facile and highly selective.

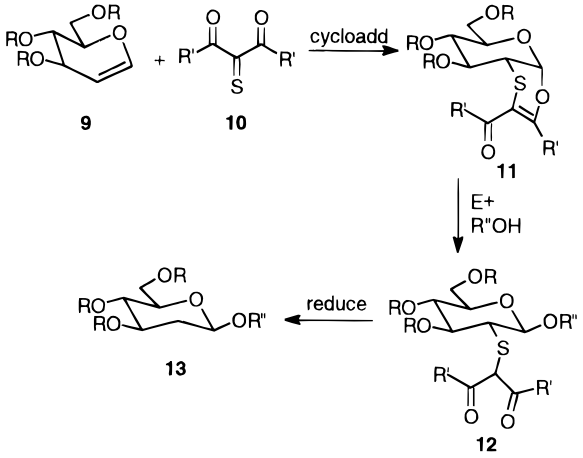
The genesis for our new concept for glycosyl transfer came from earlier work in the inverse electron demand Bradsher cycloaddition reactions of isoquinolinium salts with glycals[34] (eq 1). These reactions were both easy to carry out and gave the *cis*-1,2-dideoxy-C-glucosides as a single diastereoisomer.



Eqn. 1

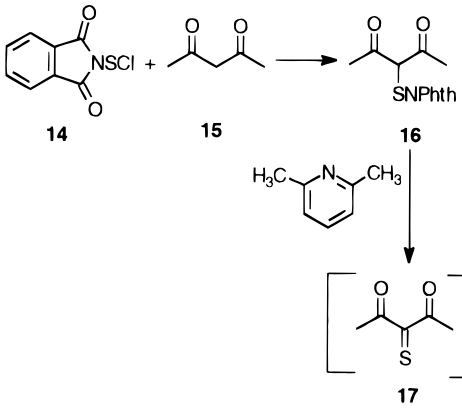
We visualized an extension of this approach to the cycloaddition reaction of a heterodiene such as **10** with a glycal **9** (Scheme 3). The resulting heterocycle **11** would be a vinyl glycoside which should possess excellent donor properties. Reaction with an electrophilic catalyst could conceivably cause cleavage of the C1−oxygen bond and in the presence of an appropriate acceptor molecule, a glycoside **12** could be formed. The acyl side chain or the C-2 sulfur could provide neighboring group participation, making the glycosylation process highly stereoselective.

Scheme 3



Later reductive removal of sulfur at C-2 would give a 2-deoxy-β-glycoside **13**.

The heterodiene system which led to the development of our new method described in this paper is the diacyl thione **17**, which is generated *in situ* from the phthalimidosulfenyl precursor **16** (eq 2).[35] In turn, **16** is easily formed from 2,4-pentanedione **15** and phthalimidosulfenyl chloride **14**.[36]



Eqn. 2

Diacyl thione **17** undergoes cycloaddition reactions with a variety of glycals under mild conditions.[35c,37−39] With tri-*O*-benzyl-D-glucal **18**, adduct **19** is obtained in 80% yield (5 days) (eq 3). A small amount of a minor diastereoisomer **20** is also formed (5%) and is easily separated from **19** by column chromatography. The adduct **22** obtained from tri-*O*-benzyl-D-galactal **21** is isolated as a single diastereoisomer (73%; 3 days) (eq 4).

The conversion of these adducts into useful glycosyl donors for the highly stereoselective synthesis of 2-deoxy-β-glycosides is the subject of this paper. Applications of the method described to the construction of important linkages found in the aureolic acid family of antibiotics will also be discussed.

Results

Our initial attempts at glycosyl transfer focused on the cleavage of the anomeric carbon−oxygen bond of adduct

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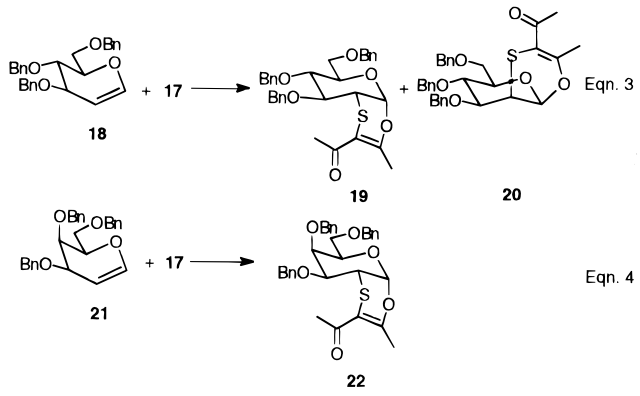
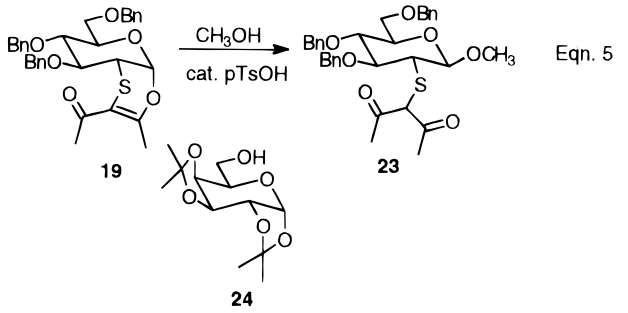


19 (eq 5).[37] Although the adduct cleanly opened to give *β*-methyl glucoside **23** when using a *p*-toluenesulfonic acid (*p*-TsOH) catalyst in methanol, a reduction in the quantity of acceptor employed or the use of the less nucleophilic acceptor, 1,2:3,4-diisopropylidenegalactopyranose (DIPG) **24**, failed to give the desired glycoside. Similarly, a change in acid catalyst to trifluoroacetic acid (TFA) or triflic acid (TfOH) failed to effect glycosylation.

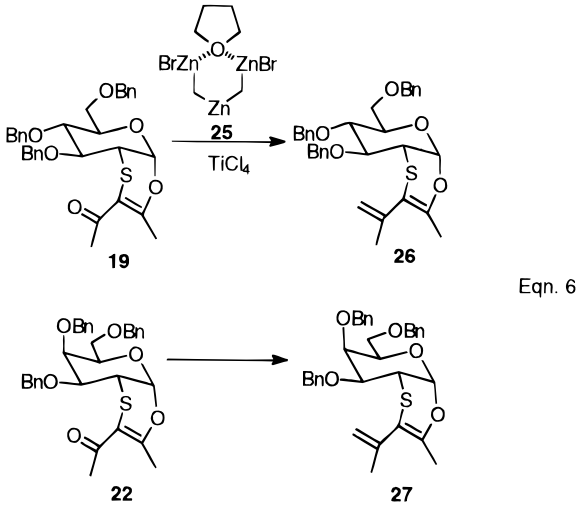


We next looked at possible methods for activating the adducts.[37,38] Olefination of the cycloadduct **19** to produce a diene would generate an extended vinyl glycoside. Treatment of **19** with methyl Wittig reagent gave diene **26** (53%). Higher yields of diene were, however, realized using commercially available Nysted Reagent[40] **25** activated by $TiCl_4$ (76%) (eq 6). Similarly, the galactose-derived cycloadduct **22** underwent methylenation with this reagent to produce **27** (69%).

Dienes **26** and **27** were easy to handle compounds which proved to be relatively stable. No decomposition of these materials was observed even after a year when they were stored at low temperatures (−20 °C).

The methylenated compounds proved to be superior glycosyl donors. Donor **26** when reacted with 2 equiv of DIPG **24** and 1 equiv of *p*-TsOH afforded modest yields of glycoside **28** (Table 1, entry 1). None of the α-glycosidic product was observed either in the ^{1}H NMR ($CDCl_3$) spectrum of the crude reaction mixture or from the analysis of fractions from column chromatography.

Structural assignments for **28** were established in part using ^{1}H-COSY (400 MHz) experiments. The anomeric



resonance of the sugar derived from the acceptor (H-1′) was a doublet centered at 5.52 ppm ($J_{1',2'} = 5.1$ Hz). The H-2′ resonance was a doublet of doublets centered at 4.28 ppm (J = 4.8, 2.2 Hz). The H-1 resonance of the newly formed glycosidic linkage appeared as a doublet centered at 4.41 ppm. The H-2 resonance was a doublet of doublets centered at 2.78 ppm. The assignment of *β* stereochemistry for the glycosidic linkage of **28** was based on the values of $J_{1,2}$ (8.4 Hz) and $J_{2,3}$ (9.0 Hz) which were indicative of a trans-trans diaxial arrangement of the protons at H-1 through H-3. In addition, ^{13}C−^{1}H connectivities for the anomeric carbons were determined by HETCOR experiments. The C-1′ resonance was assigned at 96.2 ppm and C-1 at 103.3 ppm. One bond carbon−hydrogen coupling constants ($^1J(^{13}C^1H)$) were determined for both anomeric carbons. The coupling constant for C-1′ was found to be 156 Hz, whereas ^1J for C-1 had a larger value of 178 Hz. These values are consistent with an axial and equatorial glycosidic linkage, respectively.[41]

A range of other promoters were also assayed for their effectiveness using the coupling of **26** and glycosyl acceptor **24** as a representative reaction (Table 1). With most of the other acid promoters, only *β*-glycoside **28** was again detected in the reaction mixtures. None of the glycoside resulting from addition of acceptor to the vinyl ether double bond was observed. In addition to disaccharides, unreacted starting materials and to a lesser extent (<5%) mixtures of free sugars derived by hydrolysis of **26** accounted for the mass balance from these reactions.

Falck's catalyst (PPh_3HBr),[42] gave an α:*β* mixture of glycosides (Table 1, entry 6). When aluminum(III) chloride was used as the promoter, substantial amounts of de-isopropylidenated material was obtained (Table 1, entry 5). No reaction occurred when trifluoroacetic acid was used (Table 1, entry 8). *N*-Iodosuccinimide failed to cause scission of the heterocyclic ring (Table 1, entry 9). Instead, mixtures of alkoxy iodides were obtained as a result of the addition of reagent and acceptor to both endocyclic and exocyclic double bonds.

The lanthanide triflates have been shown to be effective glycosylation catalysts.[43] However, with donor **26**, and a $Yb(OTf)_3$ catalyst, glycoside formation occurred

(37) (a) Presented in part: 209th National ACS Meeting, Anaheim, CA; April 1995; CARB 033. (b) Presented in part: 211th National ACS Meeting, New Orleans, LA; March 1996; ORGN 300.

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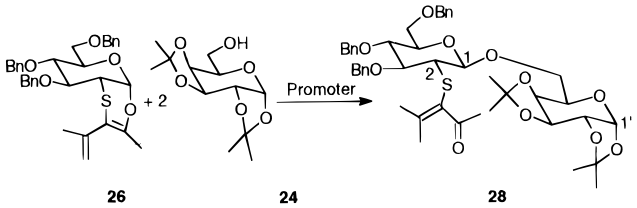
(39) (a) Capozzi, G.; Dios, A.; Franck, R. W.; Geer, A.; Marzabadi, C.; Menichetti, S.; Nativi, C.; Tamarez, M. *Agnew. Chem., Int. Ed. Engl.* **1996**, *35*, 7.

(40) Watson, A. T.; Park, K.; Wiemer, D. P.; Scott, W. J. *J. Org. Chem.* **1995**, *60*, 5102 and ref 17 therein.

(41) Bock, K.; Pedersen, C. *J. Chem. Soc., Perkin Trans. 2* **1974**, 293.

(42) Bolitt, V.; Mioskowski, C.; Lee, S. G.; Falck, J. R. *J. Org. Chem.* **1990**, *55*, 5812.

Table 1. The Effect of Promoter on Isolated Yields of Disaccharide 28



26 **24** **28**

entry	equiv of acceptor	equiv of donor	promoter	solvent	temp (°C)	time, h	yield (%) of **28**[a]
1	2	1	*p*-TsOH	CH_2Cl_2	5	5	44
2	2	1	TMSOTf	CH_2Cl_2	5	5	40
3	2	1	TfOH	CH_2Cl_2	−20	1	76
4	2	1	$BF_3{\cdot}Et_2O$	CH_2Cl_2	−20 to 5	4	42
5	2	1	$AlCl_3$	CH_2Cl_2	5	1	62[b]
6	2	1	PPh_3HBr	CH_2Cl_2	25	1	63[c]
7	2	1	$Yb(OTf)_3$[d]	CH_2Cl_2	25	48	43
8	2	1	CF_3CO_2H	CH_2Cl_2	25	24	NR
9	2	1	NIS	CH_2Cl_2	5	2	NR[e]
10	2	1	Bu_4NOTf	CH_2Cl_2	25	24	NR

[a] Yields reported are isolated yields and are calculated using the donor **26** as the limiting reagent. [b] Significant amounts of de-isopropylidenated material was also detected. [c] A mixture of disaccharides was obtained (1:10 α:β). [d] 0.3 equiv of catalyst was used. [e] Complex mixtures of alkoxy halides were formed.

Table 2. Reaction of the Gluco Diene Cycloadduct 26 with DIPG 24. Triflic Acid as the Promoter

entry	equiv of acceptor	equiv of donor	equiv of CF_3SO_3H	solvent	temp (°C)	isolated (%) yield of **28**
1	1	1	1	CH_2Cl_2	−20	22[a]
2	1.5	1	1	CH_2Cl_2	−20	53
3	2	1	1	CH_2Cl_2	−20	76
4	3	1	1	CH_2Cl_2	−20	73
5	2	1	0.5	CH_2Cl_2	−20	NR
6	2	1	0.1	CH_2Cl_2	−20	<10[b]
7	2	1	0.2[c]	CH_2Cl_2	−20	64
8	2	1	1.2	CH_2Cl_2	−20	53[d]
9	2	1	1	CH_3CN	−20	53[e]
10	2	1	1	Et_2O	−20	45[f]

[a] Polymeric material was present in the crude mixture. [b] Molecular sieves were excluded from the reaction mixture. [c] With 1 equiv of Bu_4NOTf. [d] De-isopropylidenated material was formed under these conditions. [e] Two-hour reaction time. [f] Four-hour reaction time.

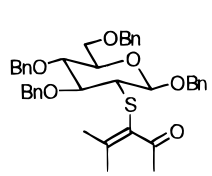
very sluggishly at room temperature to afford only a 43% yield of disaccharide after 2 days (Table 1, entry 7).

Triflic acid proved to be the promoter of choice with regards to reaction rate, product yield, and cleanliness of the reaction (Table 1, entry 3). Attempts to reduce the quantity of triflic acid resulted in prolonged reaction times and/or reduced yields (Table 2). Removal of molecular sieves from the reaction pot (Table 2, entry 6) appeared to reduce the quantity of acid required to effect glycosyl transfer, as did the addition of Bu_4NOTf (Table 2, entry 7).

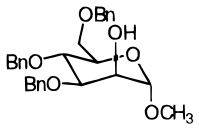
A change in solvent system to acetonitrile (Table 2, entry 9) or diethyl ether (Table 2, entry 10) also gave rise to reduced yields of disaccharide **28** when triflic acid was used. Acetonitrile has previously been shown to be an effective β-selective glycosylation solvent.[22] Intermediate α-acetonitrilium species are believed to be involved. However, for our representative reaction, only a 53% yield of β-glycoside **28** was realized even after doubling the reaction time (2 h). The use of diethyl ether as a solvent has previously been shown to enhance the ratio of 1,2-cis disaccharides obtained.[44] For our model reaction, none of the α-disaccharide was observed when this solvent was employed.

Donor **26** also reacted well with a variety of other acceptors (Table 3) under our optimized reaction conditions (1 equiv of donor, 2 equiv of acceptor, and 1 equiv of TfOH). Methyl glucoside **29** was obtained cleanly in 74% yield (Table 3, entry 1). Protected glycerol (1-*O*-hexadecyl-2-*O*-methyl-*sn*-glycerol) prepared by Bittman[45] gave glycoside **30** in 73% yield (Table 3, entry 2). Disaccharide **31** was obtained in modest yields (57%) from the reaction of **26** with methyl 2,3,4-tri-*O*-methyl-α-D-glucopyranoside.[46] The less-nucleophilic secondary sugar alcohol, methyl 6-*O*-benzyl-2,3-di-*O*-methyl-α-D-glucopyranoside,[47] produced disaccharide **32** in 67% isolated yield.

The β-glucopyranose acceptor[48] (Table 3, entry 5) gave disappointingly low yields of β-disaccharide **33** (28%) presumably due to steric effects. In addition to recovered starting materials, α-disaccharide (3%) and β-benzyl glycoside **34** (12%) were recovered from the reaction



34



35

mixture. Similar results were obtained using methyl mannoside[48] **35** as the acceptor. Seemingly, debenzylation of the sugar acceptor (at the primary OR) occurs preferentially to the nucleophilic attack by the congested C-2 hydroxy group.[49] Addition of Bu_4NOTf in conjunction with a reduction in TfOH (0.4 equiv) appeared to suppress the formation of α-disaccharide, although the

(43) Inanaga, J.; Yokoyama, Y.; Hanamoto, T. *Tetrahedron Lett.* **1993**, *34*, 2791.

(44) Igarashi, K.; Irisawa, J.; Honma, T. *Carbohydr. Res.* **1975**, *39*, 213−225.

(45) Marino-Albernas, J. R.; Bittman, R.; Peters, A.; Mayhew, E. *J. Med. Chem.* **1996**, *39*, 3241.

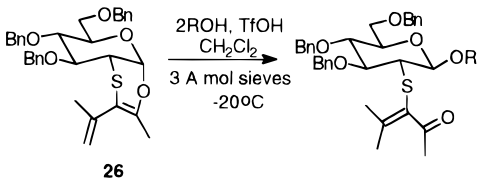
(46) Dziewiszek, K.; Zamoiski, A. *Carbohydr. Res.* **1986**, *150*, 163.

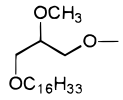
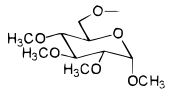
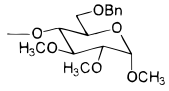
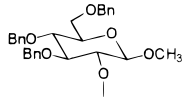
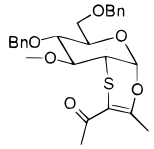
(47) Garegg, M. E. P. J.; Hultberg, H.; Oscarson, S. *J. Carbohydr. Chem.* **1983**, *2*, 305.

(48) Marzabadi, C. H.; Spilling, C. D. *J. Org. Chem.* **1993**, *58*, 3761.

(49) A similar debenzylation of a primary benzyloxy group has recently been reported: Pozgay, V.; Dubois, E. P.; Lotter, H.; Nezmelyi, A. *Carbohydr. Res.* **1997**, *303*, 165.

Table 3. Reactions of the Gluco Diene Cycloadduct 26 with Other Alcohol Acceptors

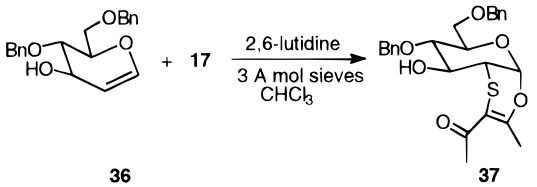


Entry	OR =	Product	Isolated Yield[a]	α:β Ratio
1	$-OCH_3$	**29**	74 %	only β
2		**30**	73 %	only β
3		**31**	57 %	only β
4		**32**	67 %	only β
5		**33**	31 %[b]	1: 9
			33 %[c]	only β
6		**38**	63 %	1:5

[a] Calculated using donor **26** as the limiting reagent. [b] 1 equiv of triflic acid was used. [c] 0.4 equiv of TfOH + 1 equiv of Bu_4NOTf.

β-benzyl glycoside was still formed in comparable amounts, and no significant improvements in yield were observed.

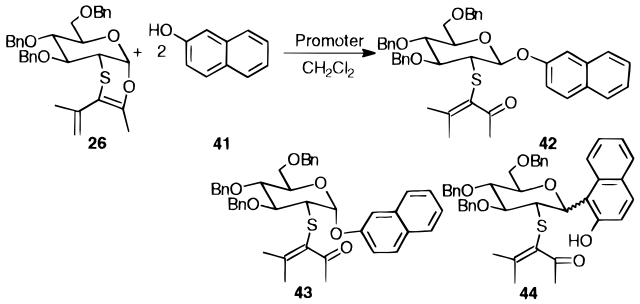
Ketone cycloadduct **37** (Table 3, entry 6) was prepared by cycloaddition of acylthione **17** with 4,6-di-*O*-benzyl-D-glucal **36** (eq 7). This acceptor also acts as an efficient glycosylating agent producing β-disaccharide **38** (53%), as well as its α-anomer (10%). Access to **38** opens the possibility for an "armed-disarmed" [20] (or "latent-active" [24]) approach to 2-deoxy-β-oligosaccharide synthesis.



Eqn. 7

The Aureolic Acid Family of Antibiotics. As part of our continuing efforts aimed at the synthesis of members of the aureolic acid family of antibiotics, we directed our glycosylation studies toward constructing 2-deoxy-β-glycosidic likages which were characteristic of this family. In particular, we were interested in the construction of the 2-deoxy-β linkages present with the acyloin portion of the molecule, the linkage with the phenolic moiety, and the construction of the 2-deoxy-β-glycoside in a galactose-based sugar framework.

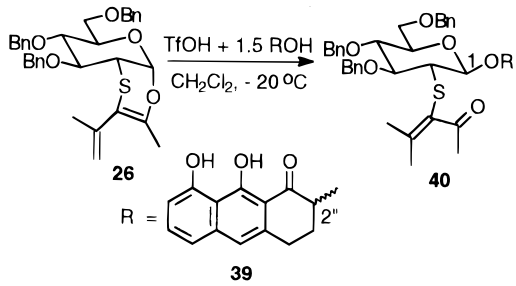
Table 4. Reaction of the Gluco Diene Cycloadduct 26 with β-Naphthol 41



entry	promoter	reaction time	% **42**[a]	% **43**[a]	% **44**[a]
1	1.0 equiv TfOH	40 min	36	12	–
2	1.0 equiv TfOH	1 h	29	11	16
3	1.0 equiv TfOH	1 h, 30 min	–	–	67
4	0.2 equiv TfOH + 1.0 equiv Bu_4NOTf	1.5 h	69	[b]	[b]

[a] Isolated yields from column chromatography using donor **26** as the limiting reagent. [b] Not isolated. Less than 5% by ^1H NMR.

Toward these ends we prepared the racemic model acyloin **39** using Kahne's procedure.[50] Using only 1.5 equiv of racemic acyloin **39** with 1 equiv of donor **26** and with 1 equiv of triflic acid, resulted in a 69% yield of a 1.3:1 mixture of glycosides **40a,b** both with the β-configuration about C-1 and *R,S*-isomeric about C-2′ (eq 8). These diastereoisomers were isolated by careful column chromatography.

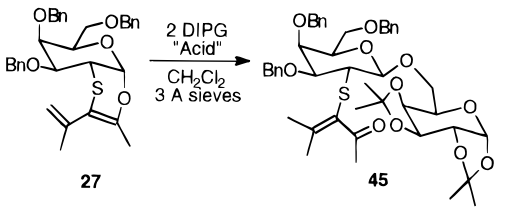


Eqn. 8

Reaction of **26** with β-naphthol **41** proved to be troublesome (Table 4). When the reaction was allowed to proceed until complete consumption of **26** was indicated by thin-layer chromatography, only the β-C-glycosidic product **44** was observed (Table 4, entry 3). Using shorter reaction times (Table 4, entries 1 and 2), mixtures of α- and β-*O*- and *C*-aryl glycosides (**42**−**44**) were obtained in low yield. Apparently, using our standard reaction conditions, epimerization at the C-1 glycosidic bond readily occurs to give the α-O-glycoside. Also, the O-glycosides undergo rapid rearrangement to their C-glycosyl analogues as previously observed by Kometani.[51] Ultimately, only the more stable β-C-glycoside **44** results. We were able to circumvent this acid-catalyzed rearrangement process by a reduction in the quantity of triflic acid used (0.2 equiv) and with the addition of 1 equiv of tetra-*N*-butylammonium triflate.

(50) Silva, D. J.; Kraml, C. M.; Kahne, D. *Biorg., & Med. Chem.* **1994**, *2*, 1251.
(51) Kometani, U.; Kondo, H.; Fujimori, Y. *Synthesis* **1988**, 1005.

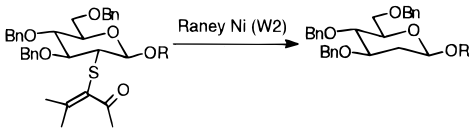
Table 5. Reaction of the Galacto Diene Cycloadduct 27 with DIPG 24

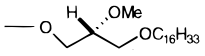
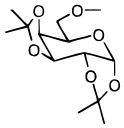
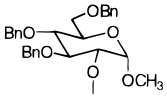
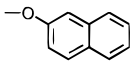


entry	acid/equiv	temp (°C)	yield of disaccharide[a]
1	TfOH/1.0	−20	nd (dec)
2	Ph_3PHBr/1.0	5	35% (1:5; α:β)
3	CF_3CO_2H/1.0	5	nd
4	TfOH/0.4 + Bu_4NOTf/1.0	−20	64% (only β)

[a] Isolated yields; calculated with donor **27** as the limiting reagent.

Table 6. Raney Nickel Desufurization of Glycosides



Entry	Compound	OR =	Product	Isolated Yield
1	**29**	—OCH_3	**46**	66 %
2	**30**		**47**	95 %
3	**28**		**48**	76 %
4	**33**		**49**	73 %
5	**42**		**50**	35 %

Using this modified procedure, β-O-glycoside **42** was obtained very cleanly (69%), with only baseline quantities of other detectable products.

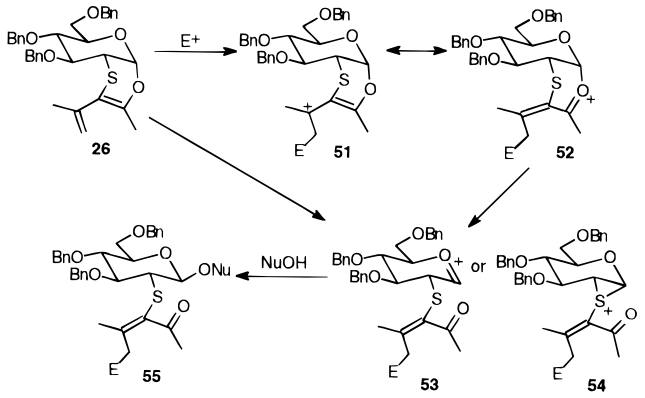
Our next goal was to see if our glycosylation protocol would be suitable for other sugar donors. The galactose-derived diene cycloadduct **27** was reacted with 2 equiv of DIPG **24** and 1 equiv of triflic acid at −20 °C (Table 5; entry 1). Unfortunately, only rapid decomposition of the donor was observed under these conditions. Several other acids were tried and also gave poor results. Only when PPh_3HBr was used (Table 5, entry 2) was any detectable quantity of disaccharide **45** observed (35%). As was seen for the gluco case when the Falck catalyst was used, a mixture of α- and β-disaccharides was obtained (1:3). Using a modified protocol (0.4 equiv of TfOH/1.0 equiv of Bu_4NOTf) (Table 5, entry 4) we again saw a dramatic improvement in both the isolated yield (64%) and observed diastereoselectivity (only β-disaccharide **45*β*** was detected) of glycosylation.

Raney Nickel Desulfurization of Glycosides. Completion of the 2-deoxy-β-glycoside synthesis required the efficient removal of the 2-thioacyl substituent. This was accomplished using Raney nickel (W2) (Table 6). In most cases the yields were good for the reduction of **28**-**30**, **33**, and **42**, although some variation in yield and reaction time was observed depending on the age and quality of the Raney nickel and upon the nature of the compound undergoing reduction.

Methyl glucoside[52] **46** was obtained in 66% isolated yield from the reduction of **29**, whereas a 95% yield was realized for the glycerol glycoside **47** derived from **30**.[45] Disaccharides **48**[10c] (from **28**) and **49** (from **33**) were also obtained in respectable yields (76 and 73%, respectively) following treatment with Raney nickel.

β-Naphthol O-glycoside **42** proved to be the most problematic example, giving only a 35% isolated yield of 2-deoxy-glycoside **50**.[11b] Tri-*O*-benzyl-D-glucal and 1,2-dideoxy-3,4,6-tri-*O*-benzyl-D-arabino-hexopyranose were isolated in substantial quantities as the result of the facile overreduction of this substrate. Cooling the reaction mixture and using other solvents failed to reduce this process. Similar low yields have been obtained by other groups when attempting to desulfurize related compounds,[53,11b] and, in some cases, the reduction was improved by changing the reducing agent to Bu_3SnH/AIBN. Unfortunately, switching reducing agents to Bu_3SnH/AIBN failed to cause desulfurization of our glycoside.

Scheme 4



Discussion

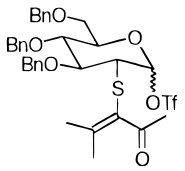
A proposed mechanism for glycosyl transfer for the heterocycles described is shown in Scheme 4. Initially, electrophilic activation of the exocyclic double bond leads to the formation of a carbocation **51**. This carbocation can be viewed as a delocalized structure with oxonium ion **52** as a major contributing form. Oxocarbenium ion **52** then further rearranges to produce **53**. Or, **53** is formed directly from **26**. This oxocarbenium ion **53** may be stabilized by electrostatic interaction with the newly liberated 2-thioacyl side chain. Or, participation by the equatorial C-2 sulfur may give rise to an intermediate thiiranium ion **54**. Either intermediate would form on the axial face of the sugar ring and therefore block this

(52) (a) Crich, D.; Ritchie, T. J. *J. Chem. Soc., Chem. Commun.* **1988**, 1461. (b) Crich, D.; Ritchie, T. *Carbohydr. Res.* **1989**, *190*, C1. (c) Crich, D.; Ritchie, T. J. *J. Chem. Soc., Perkins Trans. 1* **1990**, 945.

(53) Hashimoto, S.; Yanagiya, Y.; Honda, T.; Ikegami, S. *Chem. Lett.* **1992**, 1511.

face from attack by incoming nucleophiles. Then, exclusive backside attack to produce the 1,2-trans glycoside **55** occurs.

The fact that these reactions are not catalytic in triflic acid and are augmented by the addition of tetra-*N*-butylammonium triflate suggests that the conjugate base (TfO^-) may play a role in stabilizing intermediates which are formed in the course of the reaction thereby giving rise to enhanced yields. Triflate may serve as a stabilizing counterion for thiaranium ion **54** or for oxonium ion **53**. Or, the triflate anion may interact directly with the intermediate which is formed as a nucleophile to produce an anomeric triflate **56**. Because of a large anomeric effect,[27] the anomeric triflate **56** would be predicted to exist mainly as the axial (α) anomer. Then, in an S_N2-like fashion, nucleophilic attack by the acceptor would produce the β-glycoside **55**.



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Tetra-alkylammonium salts of halides have been used for many years as additives in the α-selective glycosylation reactions of anomeric halides with alcohol acceptors.[54] Oxonium ion−halide ion pairs or β-glycosyl halides were suggested to be intermediates in the glycosylation process.

Crich and Sun have proposed[55a] and have recently shown[55b] that anomeric triflates are the reactive intermediates in the synthesis of β-mannosides from anomeric sulfoxides using a modified Kahne glycosylation protocol.[17] They observed a pronounced decrease in β-selectivity when the alcohol protecting group at C-2 of the donor was bulky. The authors attributed this poor selectivity to the sluggish reactivity of the anomeric triflate in a sterically crowded environment and to its subsequent decomposition to an oxocarbenium ion.

The poor selectivity and low yields obtained for disaccharide **33** may be the result of retarded triflate displacement for steric reasons and the resulting decomposition of the triflate to the oxocarbenium ion **53**, followed by trapping of the alcohol acceptor in the axial direction. Likewise, this may account for the mixtures of glycosides obtained when bulky acceptor **37** was used.

Conversely, the triflate salt may help buffer the reaction medium and prevent acid-catalyzed epimerization of the glycosidic bond. In addition to suppressing α-glycoside formation in **34**, the salt also substantially reduced anomerization in the reaction of galactose donor **27** with DIPG **24** and in the reaction of donor **26** with β-naphthol **41**. The acid-catalyzed O- to C-rearrangement which is frequently observed in activated phenols was also prevented by the addition of tetra-*N*-butylammonium triflate.

(54) Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc.* **1975**, *97*, 4056.

(55) (a) Crich, D.; Sun, S. *J. Org. Chem.* **1997**, *62*, 1198. (b) While this manuscript was undergoing revision the existence of anomeric triflates as reactive intermediates was convincingly shown: Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217.

Conclusions

We have described a new method for the synthesis of 2-deoxy-β-glycosides which is both facile and highly stereoselective and which is at least comparable with existing methods for the preparation of these compounds. This method utilizes a single sugar donor type and affords glycosides for a variety of alcohol acceptors.

Several disaccharides have been prepared from both primary and secondary sugar acceptors, and we have demonstrated the utility of this method to a possible "armed-disarmed"[20] motif. Post-glycosylation processing of the disaccharides gives, in most cases, good yields of the 2-deoxy glycosides.

Our studies have led us to discover the benefits of adding tetra-*N*-butylammonium triflate to our triflate-promoted glycosylations, particularly when acid-sensitive functionalities are present or when secondary acid processes are possible.

We have been able to forge three important linkages found in the aureolic acid family of antibiotics: with an acyloin, with β-naphthol, and between two galactose moieties. An extension of this method to the synthesis of the C−D−E trisaccharide present in the aureolic acid antibiotic, mithramycin,[1] is currently being investigated. Studies aimed at optimization of the cleavage of the C-2 carbon−sulfur bond are ongoing. The reactions of the bicyclic donors with other nucleophiles is also being examined.

Experimental Section

General Information. All 1D and 2D ^1H spectra were recorded at 300 or 400 MHz, and all ^{13}C spectra were recorded at 75 MHz using $CDCl_3$ as a solvent. Melting points are uncorrected. Optical rotations were recorded under standard conditions. Low resolution mass spectra were obtained by chemical ionization (NH_3).

All reactions were performed under an inert atmosphere. Solvents were dried and distilled prior to use: diethyl ether and THF from sodium/benzophenone ketyl, CH_2Cl_2 and $CHCl_3$ from P_2O_5 , and CH_3CN from CaH_2. Anhydrous methanol, anhydrous DMF, 2,4-pentanedione, tri-*O*-acetyl-D-glucal, and Nysted reagent[40] were purchased from Aldrich Chemical Co. 1,2:3,4-Diisopropylidene-α-D-galactopyranose (DIPG) was purchased from Pfansthiel Chemical Company. Raney nickel (W2) was prepared as described in the literature[56] or was used as supplied by Aldrich. 3,4,6-Tri-*O*-benzyl-D-galactal,[57] methyl 6-*O*-benzyl-2,3-di-*O*-methyl-α-D-glucopyranoside,[47] methyl 2,3,4-tri-*O*-methyl-α-D-glucopyranoside,[46] and methyl 3,4,6-tri-*O*-benzyl-β-D-glucopyranoside[48] were prepared using published procedures. Thiophthalimide **16** and cycloadduct **19** were prepared as reported elsewhere.[35c] Molecular sieves (3A) were purchased from Aldrich Chemical Co. and were powdered and activated (150 °C oven for 12 h) prior to use. Crude products were purified by flash column chromatography on silica gel (Merck; 230−400 mesh) or on neutral alumina (BA I).

Preparation of 4,6-Di-*O*-benzyl-D-glucal (36). To a suspension of NaH (1.73 g, 43 mmol) in DMF (50 mL) was added D-glucal[58] (3.16 g, 22 mmol) portionwise as a solution in DMF (25 mL). After stirring at room temperature for 40 min, the mixture was cooled to 5 °C, and tetra-*N*-butylammonium iodide (0.31 g) and benzyl bromide (5.2 mL, 44 mmol) were added. The mixture was slowly warmed to room temperature (2 h) and was stirred an additional 48 h. The mixture was quenched with water (10 mL) and was extracted with

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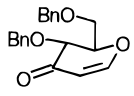
(57) Kozikowski, A. P.; Lee, J. *J. Org. Chem.* **1990**, *55*, 863.

(58) Prepared by methanolysis of tri-O-acetyl-D-glucal using Amberlite IRA-400 resin.

CH_2Cl_2 (3×, 75 mL). The combined organic fractions were extracted with additional water (5×, 100 mL) and with brine (100 mL) to afford after concentration *in vacuo* a mixture of glucals. Column chromatography (SiO_2; 15−40% ethyl acetate in petroleum ether) gave as the major products: 3,4,6-tri-*O*-benzyl-D-glucal[59] (1.65 g) and **36** (0.96 g): an oil; $[\alpha]_D$ +42.4° (c = 0.8, $CHCl_3$); IR (thin film) 3409, 3031, 2871, 1647, 1597, 1450, 1362, 1236, 1103 cm^{-1}; ^1H NMR δ 7.29−7.19 (m, 10H), 6.33 (dd, 1H, J = 6.0, 0.9 Hz), 4.74−4.48 (m, 5H), 4.28−4.26 (m, 1H), 3.93−3.89 (m, 1H), 3.75−3.74 (m, 2H), 3.61 (dd, 1H, J = 8.9, 6.3 Hz), 1.83 (br s, 1H); ^{13}C NMR δ 144.6, 128.5, 128.4, 127.9, 127.8, 127.7, 102.7, 97.4, 77.3, 76.8, 73.7, 73.6, 69.1, 68.9; MS (DEP/CI) *m/z* (rel intensity) 344 (M + NH_4) (58), 326 (100), 309 (75), 168 (61). Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.59; H, 6.79. Found: C, 73.52; H, 6.94. Also obtained was 3,6-di-*O*-benzyl-D-glucal[60] (0.08 g). No 3,4-di-*O*-benzyl-D-glucal[59] was isolated from the mixture.

Allylic oxidation[61] of **36** (0.087 g, 0.3 mmol) with MnO_2 (1.03 g, 12 mmol) in $CHCl_3$ (15 mL) afforded after 24 h, **4,6-di-*O*-benzyl-hex-1-enopyrano-3-ulose** (**57**) as a clear oil (0.054 g, 0.17 mmol, 56%), with properties consistent with similar known compounds.



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General Procedure for Cycloaddition Reactions. 2,6-Lutidine (1.0 equiv) was added to a suspension of glycal (1.0 equiv), thiophthalimide **16** (1−2 equiv), and powdered, activated, 3A molecular sieves (typically, a portion equal in weight to the weight of the combined reactants) in dry solvent (0.5−1.0 mM). The mixture was stirred at room temperature, and the reaction progress was monitored at intervals by taking an aliquot from the suspension for analysis by ^1H NMR ($CDCl_3$). When the composition of the reaction mixture showed no additional change (3−7 days), the mixture was quenched with saturated aqueous NH_4Cl and was extracted with CH_2Cl_2 (3×). The organics were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude mixtures were chromatographed (SiO_2) using gradients of ethyl acetate in petroleum ether. Removal of residual phthalimide impurities from the chromatographed fractions was accomplished by stirring with 0.1 M NaOH, followed by extraction with ethyl acetate.

1-*O*,2-*S*-(2-Acetyl-1-methyl-1,2-ethenediyl)-3,4,6-tri-*O*-benzyl-2-deoxy-2-thio-α-D-galactopyranoside (22). 3,4,6-Tri-*O*-benzyl-D-galactal (**21**) (0.48 g, 1.2 mmol), **16** (0.64 g, 2.3 mmol), and 2,6-lutidine (0.14 mL, 1.2 mmol) in $CHCl_3$ (4.7 mL) afforded **22** as an oil (0.46 g, 0.8 mmol, 73%, 4 days) following column chromatography (SiO_2, 20% EtOAc/petroleum ether): $[\alpha]_D$ +30.3° (c = 0.8, $CHCl_3$); IR (thin film) 3030, 2919, 2869, 1674, 1558, 1455, 1356, 1234, 1139, 1112, 1052 cm^{-1}; ^1H NMR δ 7.36−7.26 (m, 15H), 5.62 (d, 1H, J = 3.0 Hz), 4.89 (d, 1H, J = 13.8 Hz), 4.71−4.39 (m, 5H), 4.13−4.07 (m, 1H), 4.00 (m, 1H), 3.73 (dd, 1H, J = 10.8, 3.0 Hz), 3.60 (m, 2H), 3.53−3.44 (m, 1H), 2.29 (s, 3H), 2.25 (s, 3H); ^{13}C NMR δ 195.4, 159.3, 138.2, 137.7, 137.5, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.5, 101.9, 96.7, 75.0, 73.7, 73.6, 73.3, 72.9, 71.8, 68.4, 38.0, 30.1, 29.7; MS (DP/PCI) *m/z* (rel intensity) 564 (M + NH_4) (11), 434 (64), 309 (45), 118 (100). Anal. Calcd for $C_{32}H_{34}O_6S$: C, 70.31; H, 6.52; S, 5.87. Found: C, 69.94; H, 6.64; S, 5.87.

1-*O*,2-*S*-(2-Acetyl-1-methyl-1,2-ethenediyl)-4,6-di-*O*-benzyl-2-deoxy-2-thio-α-D-glucopyranoside (37). Glucal **36** (0.087 g, 0.27 mmol), thiophthalimide **16** (0.35 mmol), and 2,6-lutidine (0.03 mL, 0.27 mmol) in $CHCl_3$ (1.8 mL) after 6 days at room temperature afforded from chromatography (SiO_2; 25−50% EtOAc in petroleum ether): α-gluco cycloadduct **37** as an oil (0.08 g, 63%): IR (thin film) 3432, 2919, 1673, 1629, 1570, 1483, 1409, 1354, 1239, 1103, 1038 cm^{-1}; ^1H NMR δ 7.54−7.21 (m, 10H), 5.21 (d, 1H, J = 3.3 Hz), 4.83 (d, 1H, J = 11.1 Hz), 4.67 (d, 1H, J = 12.3 Hz), 4.58 (d, 1H, J = 10.8 Hz), 4.55 (d, 1H, J = 12.3 Hz), 3.95 (dd, 1H, J = 6.9, 2.1 Hz), 3.81 (dd, 1H, J = 11.1, 3.3 Hz), 3.74−3.70 (m, 2H), 3.13 (dd, 1H, J = 10.2, 3.0 Hz), 2.69 (s, 1H). 2.27 (s, 3H), 2.05 (s, 3H); MS (DEP/CI) *m/z* (rel intensity) 474 (M + NH_4) (100), 344 (71), 326 (41); and β-manno cycloadduct as a white powder (0.03 g, 24%).

General Procedure for Methylenation of Ketone Cycloadducts. To a slurry of Nysted reagent[40] (4 equiv) and ketone cycloadduct (1 equiv) in THF at −78 °C was added a 1.0 M solution of $TiCl_4$ (3 equiv) in CH_2Cl_2 over 5 min. The reaction mixture was warmed to room temperature and was stirred overnight (18 h). The mixture was cooled to 5 °C, and triethylamine (20 equiv) was added as a single portion, followed by the rapid addition of SiO_2 (Merck; 230−400 mesh). The mixture was warmed to room temperature and was filtered through a plug of SiO_2 using ethyl acetate as a wash. The filtrate was concentrated *in vacuo* to afford a crude product which was purified by column chromatography (SiO_2; 5% EtOAc/petroleum ether).

1-*O*,2-*S*-(2-Isopropenyl-1-methyl-1,2-ethenediyl)-3,4,6-tri-*O*-benzyl-2-deoxy-2-thio-α-D-glucopyranoside (26). Nysted reagent (3.84 mL, 2 mmol) and ketone cycloadduct **19** (0.29 g, 0.54 mmol) in THF (2 mL) and $TiCl_4$ (1.8 mL, 1.8 mmol) in CH_2Cl_2 were treated with triethylamine (1.73 mL, 12 mmol) and SiO_2 (0.18 g) to afford after filtration and chromatography **26** as a white solid (0.22 g, 0.4 mmol, 76%): mp 99−101 °C; $[\alpha]_D$ + 7.7° (c = 0.5, $CHCl_3$); IR (thin film) 3064, 3030, 2920, 1651, 1496, 1454, 1360, 1261, 1218, 1053 cm^{-1}; ^1H NMR δ 7.42−7.26 (m, 14H), 7.17−7.14 (m, 1H), 5.57 (d, 1H, J = 2.7 Hz), 5.57−4.51 (series of overlapping apparent AB quartets, 8H), 4.05 (dd, 1H, J = 6.9, 2.1 Hz), 3.83−3.69 (m, 4H), 3.17 (dd, 1H, J = 7.5, 2.7 Hz), 1.90 (s, 6H); ^{13}C NMR δ 142.3, 140.8, 138.3, 138.0, 137.9, 128.4, 128.1, 127.9, 127.8, 127.7, 117.8, 100.8, 94.8, 78.9, 78.6, 76.5, 75.3, 73.6, 72.6, 68.3, 43.0, 22.9, 18.6; MS (NCI/DEP) *m/z* (rel intensity) 545 (10), 544 (29), 543 (81), 224 (100). Anal. Calcd for $C_{33}H_{36}O_5S$: C, 72.77; H, 6.66; S, 5.89. Found: C, 72.63; H, 6.89; S, 5.67.

1-*O*,2-*S*-(2-Isopropenyl-1-methyl-1,2-ethenediyl)-3,4,6-tri-*O*-benzyl-2-deoxy-2-thio-α-D-galactopyranoside (27). Galacto ketone cycloadduct **22** (0.44 g, 0.81 mmol) and Nysted reagent (5.8 mL, 3.0 mmol) in THF (4 mL) and $TiCl_4$ (0.29 mL, 2.6 mmol) in CH_2Cl_2 were treated with triethylamine (2.2 mL, 16 mmol) and SiO_2 (0.26 g) to afford after filtration and column chromatography **27** as a white, oily solid at room temperature (0.31 g, 0.56 mmol, 69%): $[\alpha]_D$ +24.2° (c = 0.2, $CHCl_3$); IR (neat) 2916, 1650, 1495, 1453, 1348, 1224, 1140, 1100, 1059 cm^{-1}; ^1H NMR δ 7.36−7.16 (m, 15H), 5.52 (br s, 1H), 5.21 (d, 1 H, J = 3 Hz), 5.02−4.39 (series of apparent overlapping AB quartets, 8 H), 4.11 (apparent t, 1H, J = 6.4 Hz), 3.92 (s, 1H), 3.62 (s, 2H), 3.52 (d, 2H, J = 6.3 Hz), 1.83 (s, 3H), 1.82 (s, 3H); ^{13}C NMR δ 141.8, 140.8, 138.4, 138.1, 137.8, 128.4, 128.2, 127.9, 127.7, 127.6, 127.4, 117.5, 101.5, 95.3, 77.0, 75.6, 74.8, 73.9, 73.5, 71.3, 68.5, 39.4, 22.9, 18.5; MS (PCI/DEP/NH_3) *m/z* (rel intensity) 562 (M + NH_4) (100), 545 (M + H) (21), 434 (44), 242 (17), 168 (23). Anal. Calcd for $C_{33}H_{36}O_5S\cdot H_2O$: C, 70.44; H, 6.81; S, 5.69. Found: C, 70.79; H, 6.62; S, 5.57.

General Procedure for Triflic Acid Promoted Glycosylation. To a solution of sugar acceptor (1.5−2 equiv), diene cycloadduct (1 equiv), and powdered 3 A molecular sieves in CH_2Cl_2 at −20 °C was added triflic acid (1 equiv) as a single portion. The mixture was stirred for 1 h and then was quenched with saturated aqueous $NaHCO_3$ and was warmed to room temperature. The mixture was diluted with water and was extracted with CH_2Cl_2 (3×). The combined organics were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude products were purified by column chromatography (SiO_2, 230−400 mesh, 10−50% EtOAc in petroleum ether).

1,2:3,4-Diisopropylidene-6-*O*-{3,4,6-tri-*O*-benzyl-2-deoxy-2-*S*-(4-methyl-3-thio-pent-3-en-2-one)-β-D-glucopyranosyl}-

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α-D-galactopyranoside (28). 1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranose (**24**) (0.090 g, 0.36 mmol), gluco diene cycloadduct **26** (0.097 g, 0.18 mmol), and triflic acid (0.016 mL, 0.18 mmol) in CH_2Cl_2 (2 mL) afforded **28** as a white semisolid (0.11 g, 0.14 mmol, 76%): $[\alpha]_D$ −44.7° (c = 0.9, $CHCl_3$); IR (thin film) 2988, 2935, 1683, 1455, 1372, 1256, 1210, 1174, 1110, 1071, 1002 cm^{-1}; ^1H NMR δ 7.38−7.24 (m, 13H), 7.15−7.06 (m, 2H), 5.52 (d, 1H, J = 5.1 Hz), 4.88 (d, 1H, J = 11.1 Hz), 4.85 (d, 1H, J = 10.8 Hz), 4.73 (d, 1H, J = 10.8 Hz), 4.63−4.51 (m, 4H), 4.41 (d, 1H, J = 8.8 Hz), 4.33 (dd. 1H, J = 8.0, 1.5 Hz), 4.28 (dd, 1H, J = 4.8. 2.2 Hz), 4.06−4.02 (m, 1H), 3.98−3.94 (m, 1H), 3.71 (apparent br d, 2H, J = 2.8 Hz), 3.67−3.60 (m, 2H), 3.48−3.42 (m, 2H), 2.79 (dd, 1H, J = 8.8, 9.0 Hz), 2.42 (s, 3H), 1.99 (s, 3H), 1.85 (s, 3H), 1.55 (s, 3H), 1.42 (s, 3H), 1.33 (s, 6H); ^{13}C NMR δ 202.1, 144.8, 138.4, 138.2, 138.1, 129.7, 128.3, 128.2, 127.8, 127.7, 127.6, 127.4, 109.0, 108.4, 103.3, 96.2, 83.1, 79.1, 75.3, 74.9, 74.7, 73.6, 71.0, 70.7, 70.6, 68.7, 68.1, 66.9, 53.9, 30.2, 26.2, 26.0, 24.9, 24.4, 23.4, 22.7; MS (NCI/DEP) m/z (rel intensity) 804 (M) (69), 592 (13), 367 (100), 210 (29), 129 (54). Anal. Calcd for $C_{45}H_{56}O_{11}S$: C, 67.14; H, 7.01; S, 3.98. Found: C, 67.20; H, 7.08; S, 4.18.

Methyl 3,4,6-Tri-*O*-benzyl-2-deoxy-2-*S*-(4-methyl-3-thiopent-3-en-2-one)-β-D-glucopyranoside (29). Methanol (8 μL, 0.19 mmol), **26** (0.05 g, 0.09 mmol), and triflic acid (8 μL, 0.09 mmol) in CH_2Cl_2 (2 mL) gave **29** as a colorless oil (0.04 g, 0.07 mmol, 74%): $[\alpha]_D$ −24.6° (c = 0.3, $CHCl_3$); IR (thin film) 3030, 2912, 2866, 1684, 1540, 1456, 1362, 1206, 1113, 1074, 1049 cm^{-1}; ^1H NMR δ 7.33−7.19 (m, 13H), 7.09−7.06 (m, 2H), 4.86 (d, 1H, J = 10.8 Hz), 4.78 (d, 2H, J = 10.8 Hz), 4.69 (d, 1H, J = 10.5 Hz), 4.55 (d, 1H, J = 12.3 Hz), 4.48 (d, 1H, J = 10.5 Hz), 4.47 (d, 1 H, J = 12.3 Hz), 4.19 (d, 1H, J = 8.7 Hz), 3.65−3.64 (m, 2H), 3.58−3.52 (m, 1H), 3.42−3.32 (m, 1H), 3.37 (s, 3H), 2.68 (dd, 1H, J = 10.8, 8.7 Hz), 2.31 (s, 3H), 1.99 (s, 3H), 1.85 (s, 3H); ^{13}C NMR δ 202.0, 148.7, 138.3, 138.2, 138.0, 129.0, 128.4, 128.3, 128.2, 127.8, 127.7, 127.6, 127.5, 104.6, 82.6, 79.4, 75.7, 74.9, 74.8, 73.5, 68.8, 56.5, 55.0, 29.8, 23.8, 22.9; MS (DEP/PCI) m/z (rel intensity) 594 (M + NH_4) (100), 536 (22), 466 (60), 258 (26), 180 (35), 116 (36). Anal. Calcd for $C_{34}H_{40}O_6S$: C, 70.81; H, 6.99; S, 5.60. Found: C, 70.90; H, 6.78; S, 5.39.

Hexadecyl-2-*O*-methyl-*sn*-glyceryl-3,4,6-tri-*O*-benzyl-2-deoxy-2-*S*-(4-methyl-3-thio-pent-3-en-2-one)-β-D-glucopyranoside (30). 1-*O*-Hexadecyl-2-*O*-methyl-*sn*-glycerol (0.08 g, 0.23 mmol), **26** (0.06 g, 0.12 mmol), and triflic acid (0.01 mL, 0.12 mmol) in CH_2Cl_2 (1.5 mL) afforded **30** as a waxy, white solid (0.07 g, 0.09 mmol, 73%): $[\alpha]_D$ −21.6° (c = 0.4. $CHCl_3$); IR (neat) 3030, 2924, 2853, 1683, 1604, 1497, 1454, 1355, 1261, 1205, 1113, 1028 cm^{-1}, ^1H NMR δ 7.38−7.24 (m, 13H), 7.15−7.12 (m, 2H), 4.92−4.51 (series of overlapping ABq, 6H), 4.35 (d, 1H, J = 8.4 Hz), 3.87−3.85 (m, 1H), 3.70−3.68 (m, 1H), 3.65−3.38 (m, 8H), 3.44 (s, 3H), 2.76 (dd, 1H, J = 10.8, 8.7 Hz), 2.39 (s, 3H), 2.00 (s, 3H), 1.87 (s, 3H), 1.64−1.52 (m, 4H), 1.25 (br s, 25H), 0.90−0.86 (m, 4H); ^{13}C NMR δ 201.6, 145.6, 138.4, 138.2, 138.0, 129.6, 128.3, 128.2, 127.8, 127.7, 127.5, 127.4, 103.7, 82.9, 79.3, 79.2, 75.4, 74.9, 74.8, 74.7, 73.5, 71.7, 70.6, 69.2, 68.9, 58.0, 54.2, 31.9, 29.9, 29.7, 29.5, 29.3, 26.1, 23.5, 22.7, 22.6, 14.0; MS (NCI/DEP) m/z (rel intensity) 874 (1), 365 (21), 226 (17), 202 (100), 129 (78). Anal. Calcd for $C_{53}H_{78}O_8S$: C, 72.73; H, 8.98. Found: C, 72.80; H, 9.00.

Methyl 2,3,4-Tri-*O*-methyl-*O*-6-{3,4,6-tri-*O*-benzyl-2-deoxy-2-*S*-(4-methyl-3-thio-pent-3-en-2-one)-β-D-glucopyranosyl}-α-D-glucopyranoside (31). Methyl 2,3,4-tri-*O*-methyl-α-D-glucopyranoside (69 mg, 0.29 mmol), **26** (77 mg, 0.14 mmol), and triflic acid (0.012 mL, 0.14 mmol) in CH_2Cl_2 (1.5 mL) afforded **31** as a colorless oil (61 mg, 0.08 mmol, 57%): $[\alpha]_D$ +24.0° (c = 0.9, $CHCl_3$); IR (thin film) 2928, 1684, 1497, 1454, 1355, 1261, 1204, 1101 cm^{-1}; ^1H NMR δ 7.37−7.11 (m, 15H), 4.92−4.48 (m, 6H), 4.79 (d, 1H, J = 3.6 Hz), 4.42 (d, 1H, J = 10.2 Hz), 4.09−4.00 (m, 1H), 3.77−3.44 (m, 8H), 3.61 (s, 3H), 3.54 (s, 3H), 3.50 (s, 3H), 3.41 (s, 3H), 3.19 (dd, 1H, J = 9.0, 3.6 Hz), 3.20−3.08 (m, 1H), 2.83 (dd, 1H, J = 9.3, 9.9 Hz), 2.41 (s, 3H), 1.95 (s, 3H), 1.80 (s, 3H); ^{13}C NMR δ 202.0, 143.8, 138.4, 138.2, 138.0, 129.4, 128.3, 128.2, 127.9, 127.7, 127.5, 127.3, 127.2, 102.8, 97.2, 83.5, 83.3, 81.8, 79.8, 79.1, 77.2, 74.9, 74.7, 73.5, 70.0, 69.1, 67.9, 60.7, 60.2, 58.9, 55.2, 53.7, 30.0, 23.1, 22.6; MS (NCI/DEP) m/z (rel intensity) 780 (M) (100), 147 (24), 129 (43), 127 (28). Anal. Calcd for $C_{43}H_{56}O_{11}S$: C, 66.13; H, 7.23; S, 4.11. Found: C, 66.05; H, 7.13; S, 3.85.

Methyl 6-*O*-Benzyl-2,3-di-*O*-methyl-4-*O*-{3,4,6-tri-*O*-benzyl-2-deoxy-2-*S*-(4-methyl-3-thio-pent-3-en-2-one)-β-D-glucopyranosyl}-α-D-glucopyranoside (32). Methyl 6-*O*-benzyl-2,3-di-*O*-methyl-α-D-glucopyranose (0.095 g, 0.3 mmol), **26** (0.08 g, 0.15 mmol), and triflic acid (0.013 mL, 0.15 mmol) in CH_2Cl_2 (1.8 mL) afforded disaccharide **32** as an oil (0.084 g, 0.1 mmol, 67%): $[\alpha]_D$ +36.6° (c = 2.1, $CHCl_3$); IR (thin film) 3062, 3029, 2907, 1686, 1605, 1496, 1453, 1356, 1312, 1240, 1204, 1111, 1048 cm^{-1}; ^1H NMR δ 7.40−7.15 (m, 20H), 4.84−4.47 (series of apparent unresolved ABq, 9H), 4.24 (d, 1H, J = 8.7 Hz), 4.03−3.91 (m, 2H), 3.73−3.47 (m, 7H), 3.55 (s, 3H), 3.52 (s, 3H), 3.41 (s, 3H), 3.35−3.21 (m, 2H), 2.63 (dd, 1H, J = 12, 8.7 Hz), 2.33 (s, 3H), 1.86 (s, 3H), 1.75 (s, 3H); ^{13}C NMR δ 201.4, 141.2, 138.6, 138.4, 138.3, 137.9, 130.5, 128.5, 128.3, 128.1, 127.8, 127.7, 127.6, 127.5, 127.3, 127.2, 101.1, 97.7, 83.1, 81.4, 81.1, 79.2, 77.2, 75.3, 75.1, 74.9, 74.7, 73.5, 69.7, 68.6, 60.9, 59.1, 55.0, 54.7, 30.1, 22.8, 22.4; MS (NCI/DEP) m/z (rel intensity) 856 (7), 623 (100), 543 (35), 311 (42). Anal. Calcd for $C_{49}H_{60}O_{11}S$: C, 68.75; H, 6.95; S, 3.75. Found: C, 68.39; H, 7.09; S, 3.73.

Methyl 3,4,6-Tri-*O*-benzyl-*O*-2-{3,4,6-tri-*O*-benzyl-2-deoxy-2-*S*-(4-methyl-3-thio-pent-3-en-2-one)-β-D-glucopyranosyl}-α-D-glucopyranoside (33). Methyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (0.24 g, 0.51 mmol), **26** (0.09 g, 0.18 mmol), and triflic acid (0.015 mL, 0.18 mmol) in CH_2Cl_2 (3 mL) gave a crude mixture which following column chromatography (SiO_2, 20−40% EtOAc in petroleum ether) afforded benzyl glycoside **34** as an oil (0.013 g, 1.9×10^{-5} mol; 11%): IR (neat) 3030, 2911, 2865, 1682, 1605, 1497, 1454, 1355, 1310, 1240, 1206, 1112, 1050, 1028 cm^{-1}; ^1H NMR δ 7.39−7.25 (m, 18H), 7.16−7.13 (m, 2H), 4.93−4.83 (m, 3H), 4.76 (d, 1H, J = 10.8 Hz), 4.63−4.52 (m, 4H) 4.45 (d, 1H, J = 8.4 Hz), 3.71−3.61 (m, 3H), 3.47−3.41 (m, 2H), 2.85 (dd, 1H, J = 11.1, 8.4 Hz), 2.32 (s, 3H), 1.85 (s, 3H), 1.75 (s, 3H); ^{13}C NMR δ 201.9, 145.8, 138.3, 138.2, 138.0, 137.4, 129.5, 128.4, 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 102.6, 82.8, 79.3, 77.2, 75.5, 74.9, 73.5, 70.5, 68.9, 54.1, 30.0, 23.4, 22.6; MS (DEP/PCI) m/z (rel intensity) 670 (M + NH_4) (2), 580 (15), 562 (24), 434 (32), 360 (78), 332 (72), 196 (47), 168 (100). Further elution afforded the title compound **33** as an oil (0.05 g, 5.1×10^{-5} mol, 28%): IR (thin film) 3063, 3031, 2910, 2864, 1684, 1497, 1455, 1361, 1207, 1108 and 1028 cm^{-1}; ^1H NMR δ 7.29−7.18 (m, 26H), 7.10−7.06 (m, 4H), 4.96 (d, 1H, J = 10.8 Hz), 4.82−4.46 (series of overlapping ABq, 12H), 4.28 (d, 1H, J = 7.2 Hz), 3.82 (apparent t, 1H, J = 7.8 Hz), 3.70−3.56 (m, 8H), 3.43 (s, 3H), 3.41−3.23 (m, 2H), 2.71 (dd, 1H, J = 10.5, 8.6 Hz), 2.30 (s, 3H), 1.87 (s, 3H), 1.71 (s, 3H); ^{13}C NMR δ 201.7, 143.8, 138.9, 138.5, 138.4, 138.1, 137.9, 129.9, 128.4, 128.2, 128.0, 127.8, 127.7, 127.6, 127.5, 127.4, 127.2, 102.3, 101.1, 85.4, 83.1, 79.2, 78.3, 75.0, 74.8, 74.7, 74.6, 73.5, 68.9, 68.6, 56.6, 54.9, 30.1, 23.2, 22.5. Anal. Calcd for $C_{61}H_{68}O_{11}S{\cdot}1H_2O$: C, 71.32; H, 6.87; S, 3.12. Found: C, 71.29; H, 7.00; S, 3.18. Also isolated was 7 mg (6.9×10^{-6} mol, 3%) of an oily material tentatively identified as the isomeric α-gluco disaccharide based on its anomeric proton resonance at 5.61 ppm (d, J = 3.6 Hz).

1-*O*,2-*S*-(2-Acetyl-1-methyl-1,2-ethenediyl)-4,6-di-*O*-benzyl-*O*-3-{3,4,6-tri-*O*-benzyl-2-deoxy-2-*S*-(4-methyl-3-thio-prop-3-en-2-one)-β-D-glucopyranosyl}-α-D-glucopyranoside (38). Gluco diene cycloadduct **26** (0.05 g, 0.09 mmol), **37** (0.04 g, 0.09 mmol), and triflic acid (0.008 mL, 0.09 mmol) in CH_2Cl_2 (1.5 mL) afforded **38** as a clear oil (SiO_2; 10−40% ethyl acetate in petroleum ether) (0.05 g, 0.05 mmol, 53%): $[\alpha]_D$ +15.2 (c = 0.6, $CHCl_3$); IR (neat) 3031, 2919, 1683, 1558, 1497, 1454, 1355, 1206, 1107, 1049 cm^{-1}; ^1H NMR δ 7.36−7.14 (m, 25H), 5.54 (d, 1H, J = 3.0 Hz), 5.23 (d, 1H, J = 8.4 Hz), 4.95−4.73 (series of overlapping ABq, 6H), 4.60−4.52 (m, 4H), 4.50−4.41 (m, 2H), 4.15−4.09 (m, 1H), 3.94−3.90 (m, 1H), 3.69−3.61 (m, 4H), 3.57−3.46 (m, 1H), 3.35 (dd, 1H, J = 4.2, 2.1 Hz), 3.20 (dd, 1H, J = 9.9, 3.0 Hz), 2.77 (dd, 1H. J = 10.5, 4.2 Hz), 2.42 (s, 3H), 2.30 (s, 3H), 2.17 (s, 3H), 2.02 (s, 3H), 1.88

(s, 3H); ^{13}C NMR δ 201.0, 194.9, 160.0, 144.3, 138.7, 138.3, 138.2, 138.1, 138.0, 130.7, 128.6, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7. 127.6, 127.5, 127.4, 102.6, 102.0, 97.4, 96.4, 83.0, 79.6, 77.8, 77.7, 77.2, 75.9, 75.3, 74.9, 73.6, 73.5, 73.2, 72.8, 68.7, 55.3, 40.8, 30.3, 30.0, 23.6, 22.7, 21.4. Anal. Calcd for $C_{58}H_{64}O_{11}S_2$: C, 69.58; H, 6.44; S, 6.41. Found: C, 69.46; H, 6.38; S, 6.68. Further elution afforded 9 mg (9.0×10^{-6} mol, 10%) of an oily material tentatively identified as the α-gluco disaccharide based on the observation of an anomeric resonance at 5.16 ppm (d, J = 3.6 Hz).

1-*O*-(2,8,9-Trihydroxy-1-oxo-1,2,3,4-tetrahydroanthracen-2-yl)- 3,4,6-tri-*O*-benzyl-2-deoxy-2-*S*-(4-methyl-3-thiopent-3-en-2-one)-β-D-glucopyranoside (40). To a suspension of **26** (42 mg, 8.5×10^{-5} mol), acyloin **39** (27 mg, 0.11 mmol), and powdered 3A molecular sieves (0.101 g) in CH_2Cl_2 (2.5 mL) at −20 °C was added triflic acid (7 μL, 8.5×10^{-5} mol) as a single portion. The reaction mixture was stirred for 40 min and then was quenched with saturated aqueous $NaHCO_3$ and was worked up as previously described. Column chromatography (SiO_2, 5−10% acetone in benzene) afforded the major diastereoisomer **40a** as an orange, glassy solid (26 mg, 3.3×10^{-5} mol, 39%): $[\alpha]_D$ +34.0° (c = 0.6, $CHCl_3$); IR (thin film) 3406, 3063, 3030, 2925, 2866, 1683, 1634, 1602, 1575, 1455, 1354, 1301, 1206, 1110, 1070, 1047 cm^{-1}; ^{1}H NMR δ 15.73 (s, 1H), 9.65 (s, 1H), 7.51−7.00 (m, 18 H), 6.84 (d, 1H, J = 7.8 Hz), 4.98 (d, 1H, J = 8.4 Hz), 4.92 (d, 1H, J = 10.8 Hz), 4.83 (d, 1H, J = 10.8 Hz), 4.79 (d, 1H, J = 10.8 Hz), 4.64−4.52 (m, 4H), 3.73−3.69 (m, 2H), 3.67 (d, 1H, J = 8.7 Hz), 3.55−3.47 (m, 1H), 3.47−3.44 (m, 1H), 3.35−3.27 (m, 1H), 2.86−2.81 (m, 1H), 2.78 (dd, 1H, J = 10.8, 8.4 Hz), 2.38−2.17 (m, 2H), 2.32 (s, 3H), 1.58 (s, 3H), 1.51 (s, 3H); ^{13}C NMR δ 202.0, 201.9, 167.0, 158.6, 144.4, 140.2, 138.8, 138.7, 138.6, 138.5, 133.6. 130.7, 129.1, 129.0, 128.9, 128.8, 128.4, 128.3, 128.2, 128.1, 128.0, 118.8, 117.9, 113.1, 111.4, 110.1, 102.8, 83.2, 79.9, 77.8, 76.7, 75.5, 75.3, 74.3, 74.0, 69.3, 55.0, 30.5, 30.3, 25.9, 23.5, 22.9. Anal. Calcd for $C_{47}H_{48}O_9S\cdot H_2O$: C, 69.96; H, 6.24. Found: C, 70.10; H, 5.87. Further elution afforded slightly impure minor diastereoisomer **40b** as an orange, glassy solid (20 mg, 2.5×10^{-5} mol, 30%): IR (thin film) 3734, 2924, 1683, 1634, 1454, 1362, 1307, 1261, 1207 and 1106 cm^{-1}; ^{1}H NMR δ 15.43 (s, 1H), 9.55 (s, 1H), 7.40 (t, 1H, J = 7.8 Hz), 7.36−6.93 (m, 17H), 6.75 (d, 1H, J = 7.8 Hz), 4.82 (d, 1H, J = 10.8 Hz), 4.76 (d, 1H, J = 10.8 Hz), 4.65 (d, 1H, J = 10.8 Hz), 4.60 (d, 1H, J = 8.1 Hz), 4.47 (d, 1H, J = 10.8 Hz), 4.27 (d, 1H, J = 12.3 Hz), 4.25−4.23 (m, 2H), 4.14 (d, 1H, J = 12.3 Hz), 3.67−3.56 (m, 2H), 3.48−3.42 (m, 2H), 3.31−3.17 (m, 1H), 2.81−2.75 (m, 2H), 2.31 (s, 3H), 2.17−2.14 (m, 2H), 1.95 (s, 3H), 1.79 (s, 3H).

2-*O*-Naphthyl-3,4,6-tri-*O*-benzyl-2-deoxy-2-*S*-(4-methyl-3-thio-pent-3-en-2-one)-β-D-glucopyranoside (42). To a cooled suspension (−20 °C) of **26** (0.24 g, 0.45 mmol), **41** (0.15 g, 0.9 mmol), and powdered 3A molecular sieves (0.18 g) in CH_2Cl_2 (4.5 mL) was added triflic acid (0.04 mL, 0.45 mmol) as a single portion. The reaction mixture was stirred for 40 min and then was diluted with 0.1 M NaOH (5 mL) and was warmed to room temperature. The mixture was diluted with CH_2Cl_2 (10 mL) and was washed with 0.1 M NaOH (10 mL) and with water (3×, 10 mL). The organics were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Flash column chromatography on the crude residue (SiO_2; 5−20% ethyl acetate in petroleum ether) afforded **42** (0.11 g, 0.16 mmol, 36%) as an oil: $[\alpha]_D$ −53.9° (c = 0.5, $CHCl_3$); IR (neat) 3062, 3030, 2918, 2866, 1680, 1631, 1600, 1512, 1497, 1467, 1454, 1390, 1355, 1254, 1214, 1178, 1104, 1053, 1028 cm^{-1}; ^{1}H NMR δ 7.79−7.66 (m, 4H), 7.43−7.15 (m, 18H), 5.21 (d, 1H, J = 8.4 Hz), 4.99−4.80 (m, 3H), 4.62−4.47 (m, 3H), 3.83−3.55 (m, 5H), 3.12 (dd, 1H, J = 8.7, 12 Hz), 2.40 (s, 3H), 1.91 (s, 3H), 1.83 (s, 3H); ^{13}C NMR δ 201.6, 154.7, 147.9, 138.1, 138.0, 137.9, 134.3, 129.7, 129.2, 129.0, 128.4, 128.3, 128.1, 127.8, 127.7, 127.6, 127.56, 127.51, 127.2, 126.3, 126.2, 124.1, 118.9, 109.9, 101.2, 82.5, 79.3, 76.0, 75.2, 75.0, 73.5, 68.8, 54.3, 29.9, 23.7, 22.9; MS (NCI/DEP) *m/z* (rel intensity) 688 (2), 238 (29), 210 (41), 202 (38), 194 (45), 143 (40), 129 (100). Anal. Calcd for $C_{43}H_{44}O_6S$: C, 74.89; H, 6.38; S, 4.64. Found: C, 74.69; H, 6.37; S, 4.36.

Prolonged reaction times resulted in the formation of mixtures of α- and β-O-glycosides, as well as, β-C-glycosides. For example, when **26** (84 mg, 0.15 mmol), **41** (44 mg, 0.31 mmol), and triflic acid (13 μL, 0.15 mmol) were reacted in CH_2Cl_2 (2 mL) at −20 °C for 1 h, 15 min and then worked up and chromatographed as described above, **42** was isolated (31 mg, 4.5×10^{-5} mol, 29%). Further elution of the column afforded the α-O-naphthyl glycoside **43** (12 mg, 1.7×10^{-5} mol) as an oil: $[\alpha]_D$ +78.7° (c = 0.2, $CHCl_3$); IR (thin film) 3064, 3030, 2912, 2864, 1682, 1629, 1600, 1514, 1497, 1466, 1454, 1389, 1357, 1252, 1212, 1176, 1108, 1047, 1027 cm^{-1}; ^{1}H NMR δ 7.71−7.64 (m, 3H), 7.42−7.02 (m, 19H), 5.54 (d, 1H, J = 3.3 Hz), 4.87 (d, 1H, J = 8.7 Hz), 4.81 (d, 1H, J = 9 Hz), 4.72 (d, 1H, J = 10.8 Hz), 4.54 (d, 1H, J = 12 Hz), 4.43 (d, 1H, J = 10.8 Hz), 4.35 (d, 1H, J = 12 Hz), 4.08−3.97 (m, 1H), 3.88−3.85 (m, 1H), 3.78−3.64 (m, 2H), 3.53−3.49 (m, 1H), 3.03 (dd, 1H, J = 11.3, 3.3 Hz), 2.28 (s, 3H), 1.77 (s, 3H), 1.68 (s, 3H); MS (NCI/DEP) *m/z* (rel intensity) 688 (1), 652 (4), 543 (4), 472 (12), 287 (46), 143 (100); then, the β-C-glycoside **44** as a solid (17 mg, 2.5×10^{-5} mmol, 16%): mp 112−114 °C (Et_2O/hexanes); $[\alpha]_D$ +7.4 (c = 0.4, $CHCl_3$); IR (thin film) 3356, 3063, 3031, 2913, 2867, 1684, 1623, 1600, 1521, 1497, 1455, 1398, 1264, 1214, 1114, 1049 cm^{-1}; ^{1}H NMR δ 8.06 (m, 1H), 7.94 (s, 1H), 7.71−7.66 (m, 3H), 7.47−7.12 (m, 17H), 5.40 (d, 1H, J = 10.5 Hz), 4.98 (d, 1H, J = 11.1 Hz), 4.84 (d, 1H, J = 12.3 Hz), 4.82 (d, 1 H, J = 10.8 Hz), 4.59−4.52 (m, 2H), 4.44 (d, 1H, J = 12.3 Hz), 4.00 (apparent t, 1H, J = 9 Hz), 3.79−3.64 (m, 3H), 3.40 (apparent t, 1 H, J = 10.8 Hz), 1.97 (s, 3H), 1.27 (s, 3H), 0.83 (s, 3H); MS (PCI/DEP) *m/z* (rel intensity) 706 (M + NH_4) (7), 196 (15), 180 (100), 148 (40), 131 (40), 99 (18).

Reaction of the Galactose Donor 27 with DIPG: Triphenylphosphine Hydrogen Bromide as a Promoter. To a solution of **24** (32 mg, 0.13 mmol), **27** (34 mg, 6.3×10^{-5} mol), and powdered 3A molecular sieves in CH_2Cl_2 (0.9 mL) at 5 °C, was added triphenylphosphine hydrogen bromide (21 mg, 6.3×10^{-5} mol) as a single portion. The reaction mixture was stirred for 6 h and then quenched with saturated aqueous $NaHCO_3$ (5 mL). It was diluted with CH_2Cl_2 (10 mL) and was washed with water (3×, 10 mL). The organics were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product mixture was chromatographed (Neutral alumina (BA I); 10−20% ethyl acetate in petroleum ether) to give **1,2:3,4-Diisopropylidene-*O*-6-{3,4,6-tri-*O*-benzyl-2-deoxy-2-*S*-(4-methyl-3-thio-pent-3-en-2-one)-α-D-galactopyranosyl}-α-D-galactopyranoside (45α)** as a colorless oil (4 mg, 6.2×10^{-6} mol, 9%): ^{1}H NMR δ 7.25 (m, 15H), 5.51 (d, 1H, J = 5.1 Hz), 4.94−4.93 (m, 1H), 4.83 (d, 1H, J = 11.1 Hz), 4.74 (d, 1H, J = 11.7 Hz), 4.66−4.59 (m, 2H), 4.51−4.37 (m, 3H), 4.11−3.94 (m, 3H), 3.83 (dd, 1H, J = 10.8, 2.4 Hz), 3.76−3.61 (m, 2H), 3.60−3.52 (m, 4H), 3.34 (dd, 1H, J = 12.0, 3.3 Hz), 2.32 (s, 3H), 1.93 (s, 3H), 1.79 (s, 3H), 1.42 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H), 1.26 (s, 3H). Further elution afforded **1,2:3,4-Diisopropylidene-*O*-6-{3,4,6-tri-*O*-benzyl-2-deoxy-2-*S*-(4-methyl-3-thio-pent-3-en-2-one)-β-D-galactopyranosyl}-α-D-galactopyranoside (45β)** as a white solid (12 mg, 1.8×10^{-5} mol, 26%): mp 58−60 °C; $[\alpha]_D$ −31.4° (c = 0.7, $CHCl_3$); IR (neat) 3003, 2934, 1684, 1660, 1456, 1374, 1258, 1209, 1167, 1104, 1069 cm^{-1}; ^{1}H NMR δ 7.30−7.17 (m, 15H), 5.44 (br d, 1H, J = 5.1 Hz), 4.74 (d, 1H, J = 11.7 Hz), 4.65 (d, 1H, J = 12.3 Hz), 4.51 (d, 1H, J = 11.7 Hz), 4.49−4.42 (series of overlapping ABq, 2H), 4.36 (d, 1H, J = 6.0 Hz), 4.27 (d, 1H, J = 9 Hz), 4.21−4.18 (m, 4H), 3.97−3.88 (m, 2H), 3.82 (d, 1H, J = 2.1 Hz), 3.55−3.41 (m, 3H), 3.32 (dd, 1H, J = 11.4, 2.7 Hz), 3.07 (dd, 1H, J = 10.8, 9 Hz), 2.35 (s, 3H), 1.88 (s, 3H), 1.76 (s, 3H), 1.44 (s, 3H), 1.34 (s, 3H), 1.24 (s, 6H); ^{13}C NMR δ 202.9, 145.4, 138.5, 138.0, 133.9, 133.6, 129.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.7, 127.5, 127.4, 127.2, 109.0, 108.4, 103.1, 97.4, 96.2, 81.3, 74.4, 73.5, 73.3, 72.1, 71.8, 71.2, 70.7, 68.7, 68.6, 67.2, 51.1, 30.2, 26.2, 26.0, 25.0, 24.4, 23.5, 22.6; MS (NCI/DEP) *m/z* (rel intensity) 804 (9), 286 (13), 194 (33), 143 (100). Anal. Calcd for $C_{45}H_{56}O_{11}S$: C, 67.15; H, 7.01. Found: C, 66.94; H, 7.25.

Modified Triflic Acid Promoted Glycosylation Protocol. To a solution of donor (1 equiv), acceptor (2 equiv), and powdered 3A molecular sieves in CH_2Cl_2 at −20 °C were added

tetra-*N*-butylammonium triflate (1 equiv) and then triflic acid (0.2−0.4 equiv). The mixture was stirred at this temperature until consumption of starting materials was indicated by thin-layer chromatography. The mixture was worked up as previously described, and the crude products were chromatographed using gradients of ethyl acetate in petroleum ether.

2-*O*-Naphthyl Glycoside (42). *β*-Naphthol **41** (27 mg, 0.18 mmol), **26** (48 mg, 0.09 mmol), Bu_4NOTf (9.5 mg, 0.09 mmol), and triflic acid (16 μL, 0.02 mmol) afforded **42** (42 mg, 0.12 mmol, 69%) from chromatography.

Galactose Disaccharide (45). DIPG **24** (0.12 g, 0.44 mmol), **27** (0.12 g, 0.22 mmol), Bu_4NOTf (0.09 g, 0.22 mmol), and triflic acid (8 μL, 0.09 mmol) gave **45** (0.11 g, 0.14 mmol, 64%) following column chromatography.

General Procedure for Raney Nickel Desulfurization. The Raney nickel suspension (freshly prepared or commercially supplied) was transferred by pipet to a two-necked round-bottom flask and was washed with water (3×, 5 mL, or until the pH of the resulting supernatant was neutral to litmus paper). The slurry was then washed (2×, 5 mL) with the solvent used for carrying out the reaction. It was resuspended in solvent and, where necessary, cooled in an ice−water bath. A solution of glycoside was prepared and added to the Raney nickel suspension. The mixture was stirred until consumption of starting materials was indicated by TLC (SiO_2; vanilin/H_2SO_4 or palladium(II) chloride/HCl). The mixture was filtered through a mixed pad of Celite/SiO_2, and the pad was rinsed with a large excess of solvent. The filtrate was concentrated *in vacuo*, and the resulting crude product was chromatographed on SiO_2 using either gradients of ethyl acetate in petroleum ether or ethyl acetate in dichloromethane.

Methyl 3,4,6-Tri-*O*-benzyl-2-deoxy-*β*-D-arabino-hexopyranoside (46). To a suspension of Raney nickel (200 mg) in benzene (3 mL) at room temperature was added a solution of glycoside **29** (20 mg, 3.5×10^{-5} mol) in benzene (4 mL). After 30 min, the mixture was filtered through a mixed pad of Celite/SiO_2, and the pad was washed with benzene (100 mL) and with acetone (400 mL). The combined filtrate was concentrated *in vacuo*. Column chromatography (SiO_2, 15% ethyl acetate in petroleum ether) afforded **46** (10 mg, 2.3×10^{-5} mol, 66%) with spectroscopic properties consistent with those described in the literature.[33]

Hexadecyl-2-*O*-methyl-*sn*-glyceryl 3,4,6-tri-*O*-benzyl-2-deoxy-*β*-D-arabino-hexopyranoside (47). To a suspension of Raney nickel (250 mg) in benzene (2 mL) at room temperature was added a solution of glycoside **30** (0.04 g, 0.05 mmol) in benzene (2 mL). After 1 h, the mixture was filtered through a pad of Celite which was rinsed successively with benzene (100 mL) and then with acetone (450 mL). The combined filtrates were concentrated *in vacuo*, and the crude material was chromatographed (SiO_2, 15% ethyl acetate in petroleum ether) to afford **47** (0.03 g, 97%) with spectral characteristics consistent with those previously reported.[45]

1,2:3,4-Diisopropylidene-6-*O*-(3,4,6-tri-*O*-benzyl-2-deoxy-*β*-D-arabino-hexopyranosyl)-α-D-galactopyranoside (48). To a suspension of Raney nickel (400 mg) in benzene (5 mL) was added a solution of disaccharide **28** (38 mg, 4.7×10^{-5} mol) in benzene (4 mL). The mixture was stirred at room temperature for 1.5 h and then was filtered through a pad of Celite using benzene (100 mL) and acetone (600 mL) as washes. The combined filtrates were concentrated *in vacuo*, and the resulting crude product was chromatographed (SiO_2; 5% ethyl acetate in dichloromethane) to give **48** as a colorless oil (25 mg, 3.7×10^{-5} mol, 74%) with spectral characteristics consistent with those previously described.[10c]

Methyl 3,4,6-Tri-*O*-benzyl-*O*-2-(3,4,6-tri-*O*-benzyl-2-deoxy-*β*-D-arabino-hexopyranosyl)-*β*-D-glucopyranoside (49). To a suspension of Raney nickel (200 mg) in benzene (3 mL) at room temperature was added a solution of disaccharide **33** (34 mg, 3.3×10^{-5} mol) in benzene (4 mL). After 2 h, the mixture was filtered through a mixed pad of Celite/SiO_2, and the pad was washed with benzene (100 mL) and then with acetone (300 mL). The combined filtrate was concentrated *in vacuo*. The crude mixture was chromatographed (SiO_2; 10−20% ethyl acetate in petroleum ether) to afford **49** as a colorless oil (22 mg, 2.5×10^{-5} mol, 73%): $[\alpha]_D$ −3.9° ($c = 0.3$, $CHCl_3$); IR (neat) 3030, 2928, 2866, 1497, 1454, 1362, 1094, 1062, 1028 cm^{-1}; ^1H NMR δ 7.29−7.19 (m, 25H), 7.17−7.11 (m, 5H), 4.83−4.66 (series of overlapping ABq, 5H), 4.60−4.40 (series of overlapping ABq, 8H), 4.28 (br d, 1H, J = 6.6 Hz), 3.69−3.50 (m, 7H), 3.49−3.28 (m, 4H), 3.42 (s, 3H), 2.19−2.14 (m, 1H), 1.57 (ddd, 1H, J = 12.6, 6.3, 2.4 Hz); ^{13}C NMR δ 138.5, 138.4, 138.2, 138.0, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.4, 102.8, 100.6, 85.1, 80.4, 79.6, 78.0, 77.9, 77.4, 77.2, 77.0, 75.6, 75.4, 74.9, 73.5, 71.3, 69.3, 68.9, 56.6, 36.9. Anal. Calcd for $C_{55}H_{60}O_{10}\cdot H_2O$: C, 73.03; H, 6.66. Found: C, 73.48; H, 6.95.

2-*O*-Naphthyl 3,4,6-Tri-*O*-benzyl-2-deoxy-*β*-D-arabino-hexopyranoside (50). To a suspension of Raney nickel (200 mg) in abs ethanol (2 mL) at 5 °C was added a solution of glycoside **42** (41 mg, 6.0×10^{-5} mol) in benzene/ethanol (4 mL, 1:1). After 1 h, the mixture was filtered through a pad of Celite/SiO_2, and the pad was washed with ethanol (100 mL), benzene (100 mL), and acetone (200 mL). The combined filtrate was concentrated *in vacuo*. Repetitive column chromatography (2×) on the crude product (SiO_2; 5−10% ethyl acetate in petroleum ether) afforded slightly impure 2-deoxyglycoside **50** (12 mg, 2.1×10^{-5} mol) with spectroscopic properties consistent with those described in the literature.[11b]

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Supporting Information Available: ^1H and/or ^{13}C NMR spectra for all compounds and ^1H-COSY, $^1H-^{13}C$-HETCOR and a portion of the undecoupled $^1H-^{13}C$ spectra for compound **28** (47 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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