Pergamon

Tetrahedron, Vol. 53, No. 26, pp. 8825-8836, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00571-1

Stereoselective Synthesis of 2-Deoxy-β-glycosides From Glycal Precursors. 1. Stereochemistry of the Reactions of D-Glucal Derivatives with Phenylsulfenyl Chloride and Phenylselenenyl Chloride

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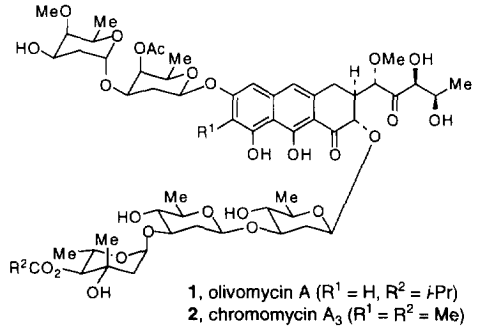
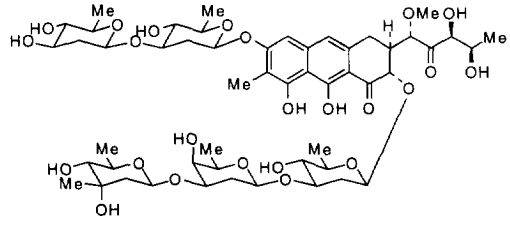
Abstract: *The stereoselectivity of the reactions of D-glucal derivatives with PhSCl and PhSeCl is dependent on the presence of an electronegative heteroatom substituent at C(6) and the nature of the functionality at C(4). The C(6)-substituent influences the conformational preferences of the D-glucal derivatives, and greatest stereoselectivity is obtained with those glycals that preferentially exist in the inverted $^5H_4$ half-chair conformation **28b**. A polar substituent at C(4) increases the selectivity by stabilizing the episulfonium /episelenonium ion intermediates **31b** and **33**.*

In connection with our work[1-3] on the synthesis of the aureolic acid antitumor antibiotics,[4-7] we were confronted with the problem of the stereoselective synthesis of 2-deoxy-β-glycosides:[8-11] three out of the five glycosidic linkages are β in olivomycin A (**1**) and chromomycin A_3 (**2**), whereas all five of the glycosidic bonds are β in mithramycin (**3**).[12] Although 2-deoxy-α-glycosides are generally easily prepared from glycals or activated 2-deoxysugar precursors,[9,11] the synthesis of 2-deoxy-β-glycosides has proved to be a much more difficult undertaking.[2] With a few exceptions,[13-17] the most extensively developed strategy for synthesis of 2-deoxy-β-glycosides utilizes donors with equatorial C(2) heteroatom substituents (e.g., -Br,[18] -SAr,[19-25] -SePh,[26] -OAc,[27,28] -NHCHO[28,29] and 1,2-epoxy[30]) that are removed reductively after the glycosylation event.



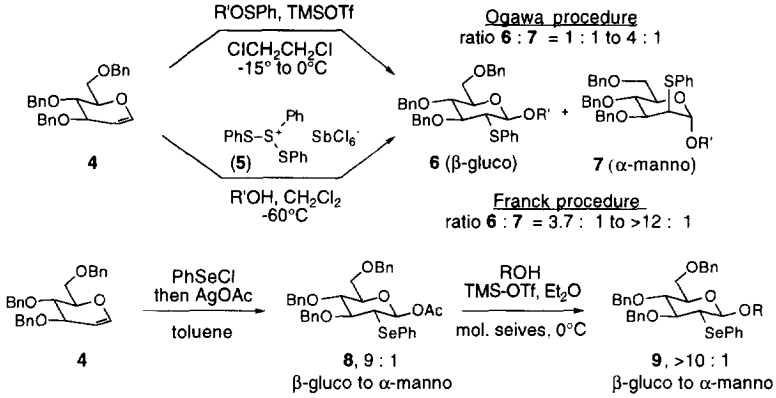
1, olivomycin A (R^1 = H, R^2 = *i*-Pr)
2, chromomycin A_3 (R^1 = R^2 = Me)



3, mithramycin

In 1990 when our studies on the synthesis of the aureolic acid glycosides began in earnest, we were interested in developing a synthetic strategy that would permit easy access to a range of oligosaccharide analogs, which in turn would permit us to probe the nature of the interactions of the aureolic acid oligosaccharides with DNA.[31-36] As such, a synthetic strategy that utilized glycals as the ultimate glycosyl donors was particularly attractive, since this would permit the synthesis of both α- and β-glycosides from a common precursor.[9,37] Based on these considerations, we were immediately attracted to the work of Ogawa, Franck and Beau who developed reasonably selective routes to 2-deoxy-β-glycosides via the reactions of glycals with electrophilic sulfur and selenium reagents.[20,23,24,26] However, detailed examination of the

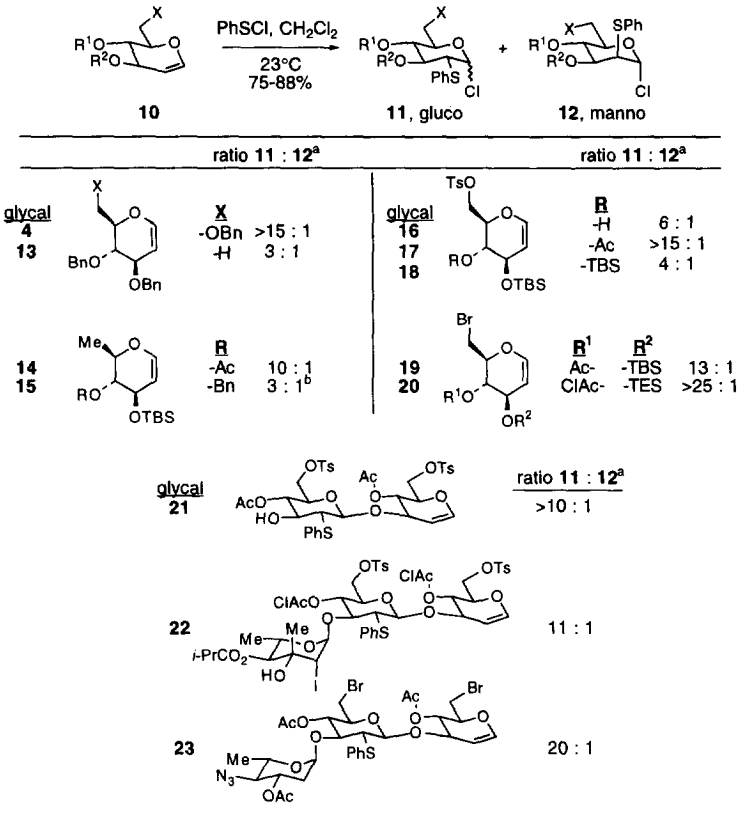
available literature revealed that the stereochemical control features of these reactions were not readily apparent. For example, stereoselectivity varied considerably with changes in the nature of the glycal protecting groups (and the identity of the C(6)-substituent) in the Ogawa and Beau methods,[20,26] while considerable variation in selectivity also occurred with structural changes in the alcohol acceptor used in the Franck procedure.[23,24] Accordingly, we decided to decouple the glycosidation step from the glycal activation step, along the lines pioneered by Beau,[26] in hope that the critical stereochemical control features of these glycosidation protocols could be defined. We report herein the results of our investigation of the reactions of glycals with phenylsulfenyl chloride (PhSCl) and phenylselenenyl chloride (PhSeCl). Our studies of the glycosidation reactions of the resulting 2-thiophenyl- and 2-selenophenyl-α-D-*gluco*-pyranosyl donors are described in the accompanying manuscript.[38]



Results and Discussion. Results of the reactions of several D-glucal or D-rhamnal derivatives with PhSCl are summarized in Table 1. These reactions were typically performed by addition of 1.1 equiv. of PhSCl[39] to a 0.2 M solution of glycal in CH_2Cl_2. In most cases, the reactions were complete within a 1 h period. Mixtures of three products were typically observed: α-**11**, β-**11** (*gluco* configuration), and α-**12** (*manno* configuration). In the majority of cases, the product ratios were determined by integration of diagnostic ^1H resonances for each product in the ^1H NMR spectrum of the crude reaction mixtures. Typically, H-1 for the β- gluco products appeared at δ 5.17-5.42 as a doublet, $J_{1,2}$ = 8.1-9.5 Hz, with H-2 appearing at δ 3.20-3.38 as a doublet of doublets, $J_{1,2}$ = 8.1-9.5 Hz. For the α-gluco chlorides (α-**11**), H-1 and H-2 typically appeared at δ 5.81 - 6.23 and δ 3.38 - 3.75, respectively, with $J_{1,2}$ = 3.1 - 4.0 Hz. Finally, H-1 and H-2 for the α-manno chlorides **12** appeared at δ 5.93 - 6.25 (br s) and 3.75 - 3.91 (br d, $J_{2,3}$ = 4.0 - 4.5 Hz). In the majority of cases, the chloride mixtures were converted to the corresponding glycosyl acetates (via reaction with AgOAc) or to the corresponding lactols (by treatment with either Ag_2CO_3, AgOTf-N,N,N'N'-tetramethylurea, or DBU in aqueous THF), which were separable and easily characterized (see Experimental Section).

The most striking observation is that the stereoselectivity of these reactions is highly dependent on the nature of the substituents at C(4) and C(6). Schmidt reported in 1988 that the reaction of tri-*O*-benzyl-D-glucal **4** with PhSCl was highly selective for the β-gluco product.[21] We determined that the selectivity of this reaction is at least 15 : 1 according to the NMR analysis described above. However, the gluco : manno selectivity realized with several 6-deoxy glucal derivatives (e.g., **13**,[26] and **15**) was only 3 : 1 favoring **11**. Selectivity was considerably better with D-rhamnal derivative **14** (10 : 1), however in initial experiments 3 : 1 mixtures of **11** and **12** were obtained.[40] In view of the fact that glycal tosylate **16**[41] is a precursor of **14**, we also explored the reactions of this compound and its derivatives with PhSCl. As shown in the table, while the stereoselectivity

Table 1. Addition of PhSCl to D- Glucal Derivatives



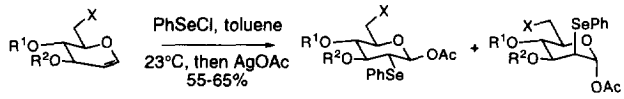
(a) Product ratios determined by ^{1}H NMR analysis of the crude reaction products, unless noted otherwise. (b) Product ratio determined after conversion of the chloride to the lactol (Ag_2CO_3,THF, H_2O).

of the reaction of **16** with PhSCl is moderate (6 : 1), excellent selectivity (>15 : 1) was obtained with its acetate derivative, **17**. Excellent results have also been obtained with the 6-bromo glycal derivatives **19** and **20**, as well as with the more complex di- and trisaccharide glycals **21**,[1] **22**[3] and **23**.[42] However, it should be noted that use of a TBS ether protecting group for C(4)-OH leads to diminished selectivity (see **18**).

Because the stereoselectivity of the glycal functionalization step is excellent with substrates containing C(6)-tosyl or -bromo substituents and acetyl (or chloroacetyl) protecting groups at C(4)-OH (e.g., **16-23**), we have used such derivatives as key intermediates in our work on the synthesis of the aureolic acid di- and trisaccharides.[1-3] The glycosyl tosylate and bromide derivatives have proven to be well behaved synthetic intermediates, presumably owing to the inductive effect of the adjacent pyran oxygen atom which stabilizes the C(6)-X unit with respect to (unwanted) substitution and elimination reactions. This observation also served as the basis of the sulfonate ester linker strategy that we recently introduced in our work on solid-phase synthesis of 6-deoxy oligosaccharides.[43]

Results of reactions of several glycals in the D-glucal or D-rhamnal series with PhSeCl are summarized in Table 2. These reactions were performed in toluene, as described by Beau.[26] The crude anomeric chlorides were treated with AgOAc to give the β-gluco (**24**) and α-manno (**25**) acetates, which in most cases were

Table 2. Addition of PhSeCl to D-Glucal Derivatives



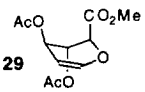
10 **24**, β-gluco **25**, α-manno

glycal	X	ratio **24** : **25**[a]	glycal	ratio **24** : **25**[a]
4	-OBn	>7 : 1[b]	**16**	10 : 1
13	-H	1 : 1[c]		
26		4-6 : 1[d]	**27**	>15 : 1

(a) Ratios determined by ^{1}H NMR analysis of crude reaction mixtures. (b) 9 : 1 selectivity has been reported for this reaction (ref. 26). (c) 6 : 1 selectivity has been reported (ref. 26). (d) 10 : 1 selectivity has been reported previously (ref. 26).

separable by chromatography. Here also, stereoselectivity was generally better with substrates containing heteroatom substituents at C(6) (compare results with **4**[2] vs. those for **13** and **26**[26]), with the best selectivity again being obtained with the 6-tosyl and 6-bromo glycals, **16** and **27**, respectively.[44] It should also be noted that the stereoselectivities for the reactions of PhSeCl with glycals **4**, **13** and **26** are lower than the values for these substrates reported by Beau.[26] It is unclear if the poor selectivity in these cases is due to equilibration of episelenonium ion intermediates.

Glycals are well-known to be conformationally flexible,[45-47] and therefore it is necessary to consider the possibility that both the normal half-chair **28a** ($^4H_5$ conformation) and the conformationally inverted isomer **28b** ($^5H_4$ conformation) contribute to the distribution of products in these reactions.[47,48] NMR studies reported by Thiem indicate that the $^5H_4$ conformation becomes increasingly important for D-glucal derivatives when the C(5) substituent becomes more electronegative; in fact, glucal **29** exists preferentially (93% at ambient temperature) in the indicated $^5H_4$ conformation.[47] Moreover, both Thiem and Horton have suggested that the production of β-gluco products in the iodoglycosidation reactions of D-glucal derivatives can be explained by invoking the involvement of the conformationally inverted glycals (c.f., **28b**, **29**).[47,48]

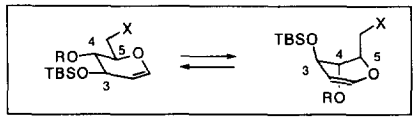


29

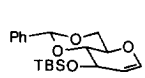
Partial ^{1}H NMR data for glycals **14**, **17** and **19**, along with data for the conformationally rigid glycal **30a** are summarized below. These data, particularly the $J_{4,5}$ data, are clearly indicative of the conformational preferences of these systems. The relative amounts of the $^4H_5$ and $^5H_4$ conformations for **14**, **17** and **19** were estimated by using the expressions $[^4H_5] + [^5H_4] = 1$, and $[^5H_4] = (J_{obs} - J_{ee}) / (J_{aa} - J_{ee})$, using values of J_{aa} = 11.6 Hz and J_{ee} = 2.0 Hz determined from fitting calculations for the maximum axial-axial ($J_{4,5}$) and minimum equatorial-equatorial ($J_{4,5}$) coupling constants, respectively.[45,47] Based on these calculations, glycal **14** is estimated to be a ca. 2 : 1 mixture dominated by the $^4H_5$ conformation, whereas **17** and **19** are ca. 2 : 1 to 3 : 1 mixtures in which the conformationally inverted $^5H_4$ structures predominate.

These observations raised the question if any correlation exists between the stereoselectivity of the reactions of PhSCl and PhSeCl with the glycals in Tables 1 and 2, and their conformational preferences? Because PhS(Se)X addition to the glycals is almost certainly slow compared to $^5H_4 \Leftrightarrow {}^4H_5$ conformational interconversion, especially for reactions that are performed at 0 °C to 23 °C, it follows that the product

Conformational Analysis of D-Glucal Derivatives



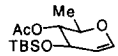
28a ($^4H_5$) **28b** ($^5H_4$)



30a

$J_{3,4}$ = 7.2 Hz
$J_{4,5}$ = 10.0 Hz

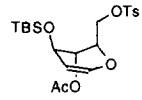
(conformation **28b** is not accessible to **30a**)



14

$J_{3,4}$ = 6.1 Hz
$J_{4,5}$ = 8.1 Hz

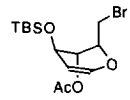
28a : **28b** = 65 : 35



17

$J_{3,4}$ = 4.2 Hz
$J_{4,5}$ = 4.6 Hz

28a : **28b** = 25 : 75



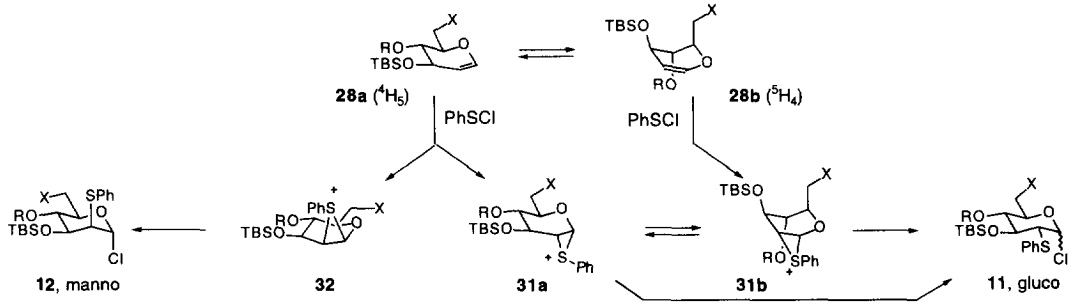
19

$J_{3,4}$ = 4.2 Hz
$J_{4,5}$ = 4.9 Hz

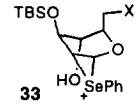
28a : **28b** = 30 : 70

distribution is determined by the relative energies of the competing transition states and not the distribution of ground state conformers **28a** and **28b**. That is, this is a situation where the Curtin-Hammett principle must apply. Consideration of the possible modes of reactivity available to the pair of glycal conformers suggests that the diastereofacial selectivity of **28a** should be less pronounced than that of **28b**. Addition of PhSCl to the bottom (α) face of **28a** (leading to episulfonium ion **31a**) should be favored relative to top (β) face addition (leading to episulfonium ion **32**), owing to nonbonded interactions of the PhS- unit with the adjacent TBS ether in **32**, as well as the propensity of D-glucal derivatives to react with electrophiles preferentially on the α face.[24,49,50] However, based on data reported for electrophilic additions reactions of glycals that are locked into the $^4H_5$ conformation,[24] it is probable that the diastereofacial selectivity of **28a** should not be overwhelmingly large. On the other hand, the two faces of conformation **28b** are differentiated to a much greater extent: the upper (β) face is hindered by two axial (or pseudo-axial) substituents, while the bottom (α) face is shielded only by the axial C(4)-OR group. It is conceivable that when the latter substituent is an acyloxy group, as in glycals **14**, **17** and **19-23**, the transition state leading to episulfonium ion **31b** could be stabilized by a charge-dipole interaction.[48] If this analysis is correct, and further assuming that the transition states for these addition reactions are half-chair-like, then glycals that preferentially adopt conformation **28b** (e.g., **16-23**, Table 1) should exhibit higher diastereofacial selectivity in reactions with PhSCl than glycals that exist preferentially in the normal half-chair conformation **28a** (e.g., **14**, **30**). Analogous arguments can be invoked to rationalize the excellent selectivity realized in the phenylselenylation reactions of glycals **16** and **27**, in which case an axial

Mechanistic Hypothesis:
Stereochemistry of Addition of PhSCl to D-Glucal Derivatives

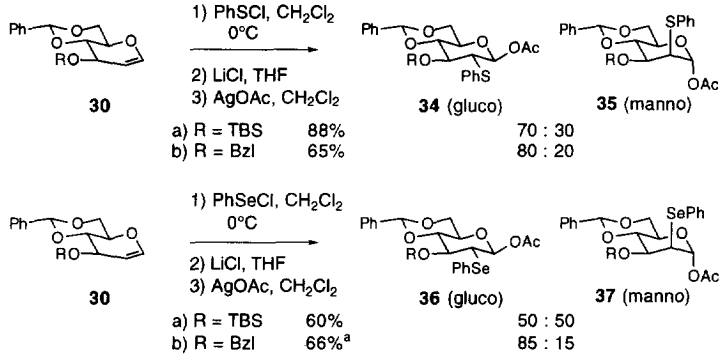


C(4)-hydroxyl group in the $^5H_4$ conformation might interact with the α epi-selenonium ion (e.g., **33**), thereby stabilizing the transition state leading to **33** relative to all other possibilities.



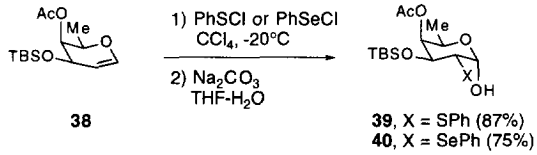
33

Support for this analysis is provided by the results of reactions of the conformationally rigid glycals **30a** and **30b** summarized below. The selectivity achieved in these experiments ranged from 1 : 1 to 5 : 1,[51] showing clearly that the diastereofacial selectivity of glucals in the normal ($^4H_5$) half-chair conformation is only modest at best. It follows, then, that the excellent selectivity realized with glycals **16-23** and **27** must be due to the involvement of the conformationally inverted glycal, **28b**.



(a) This example was performed by using the one-pot sequence summarized in Table 2.

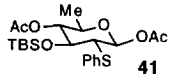
In summary, we have demonstrated that the stereoselectivity of the reactions of D-glucal derivatives (*arabino* configuration) with PhSCl and PhSeCl is highly dependent on the presence of an electronegative heteroatom substituent at C(6),[52] as well as on the functionality at C(4) (e.g., -OAc for the reactions with PhSCl, and -OH for the reactions with PhSeCl). The C(6) substituent strongly influences the conformational preferences of the D-glucal derivatives, and greatest stereoselectivity is obtained with those glycals that exist preferentially in the inverted conformation **28b** (e.g., **16-23**, Table 1). In this respect, the reactions of glucals with PhSCl are strikingly different than their reactions with arylbis(arylthio)sulfonium salts, which are insensitive to the conformational preferences of the glycal substrates.[24] Although we have not performed a systematic study of the stereoselectivity of the reactions of glycals with *lyxo*, *ribo*, and *xylo* configurations, we note in closing that the presence of a polar C(6) substituent is not a requirement for excellent selectivity in the functionalization of D-fucal derivatives such as **38** (*lyxo* configuration).[2]



38

39, X = SPh (87%)
40, X = SePh (75%)

Experimental Section[53]



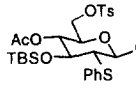
41

Acetyl 4-O-Acetyl-3-O-(*tert*-butyldimethyl)silyl-2,6-dideoxy-2-thiophenyl-β-D-glucopyranoside (41). To a 23 °C solution of glucal **14** (98 mg, 0.34 mmol) in CH_2Cl_2 (1.7 mL) was added PhSCl (0.041 mL, 0.37 mmol). The solution was stirred for 25 min at 23 °C and then concentrated in vacuo. The resulting yellow oil was dissolved in THF (1.1 mL) and then the solution was saturated with LiCl. After being stirred at 23 °C for 2 h, the mixture was diluted with CH_2Cl_2 and filtered through Celite. The filtrate was dried over Na_2SO_4, filtered, and concentrated in vacuo to give a pale yellow

oil. ^{1}H NMR analysis of the crude anomeric chlorides revealed a gluco : manno ratio of ca. 10 : 1. [Characteristic ^{1}H NMR data for the α-gluco chloride: δ 6.02 (d, J = 3.2 Hz, 1 H); for the β-manno chloride: δ 6.08 (br s, 1 H)]. The mixture of anomeric chlorides was then dissolved in HOAc (1.7 mL) and AgOAc (0.114 g, 0.683 mmol) was added. The mixture was stirred at 23 °C for 1.75 h, then diluted with CH_2Cl_2 and filtered through Celite. The filtrate was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to give a yellow oil. Purification of the crude product by flash chromatography with 5% EtOAc/hexanes followed by 10% EtOAc/hexanes afforded the desired pyranosides (0.121 g, 78% yield) as a 1 : 1 : 8 mixture of the α-manno, α-gluco, and β-gluco pyranosides, respectively. The β-gluco and α-manno pyranoside were inseparable and therefore characterized as a mixture. Data for **41**β: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60-7.21 (m, 5 H), 5.70 (d, J = 9.2 Hz, 1 H), 4.83 (app. t, J = 9.2 Hz, 1 H), 3.72 (dd, J = 10.2, 8.4 Hz, 1 H), 3.54 (m, 1 H), 3.31 (dd, J = 10.2, 9.5 Hz, 1 H), 2.13 (s, 3 H), 1.70 (s, 3 H), 1.18 (d, J = 6.0 Hz, 3 H), 0.89 (s, 9 H), 0.21 (s, 3 H), 0.09 (s, 3 H); IR (neat) 1750 (br), 1585 cm^{-1}; HRMS calcd for $C_{18}H_{25}O_6SiS$ (M^+-*t*-Bu) 397.1141, found 397.1155. *Anal.* Calcd. for $C_{22}H_{34}O_6SSi$: C, 58.12; H, 7.54. Found: C, 58.01; H, 7.26.

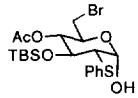
^{1}H NMR data for the α-manno pyranoside: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60-7.21 (m, 5 H), 6.13 (d, J = 2.8 Hz, 1 H), 5.00 (app. t, J = 8.6 Hz, 1 H), 4.31 (dd, J = 8.4, 4.6 Hz, 1 H), 3.90 (m, 1 H), 3.59 (dd, J = 4.6, 2.8 Hz, 1 H), 2.10 (s, 3 H), 2.06 (s, 3 H), 1.26 (d, J = 6.7 Hz, 3 H), 0.89 (s, 3 H), 0.09 (s, 3 H), 0.05 (s, 3 H).

Data for the α-gluco acetate (**41**α): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44-7.21 (m, 5 H), 6.16 (d, J = 3.5 Hz, 1 H), 4.84 (dd, J = 9.9, 9.2 Hz, 1 H), 3.99 (dd, J = 10.6, 8.8 Hz, 1 H), 3.86 (m, 1 H), 3.31 (dd, J = 10.6, 3.5 Hz, 1 H), 2.20 (s, 3 H), 2.13 (s, 3 H), 1.13 (d, J = 6.3 Hz, 3 H), 0.89 (s, 9 H), 0.18 (s, 3 H), 0.12 (s, 3 H); IR (neat): 1760, 1745, 1585 cm^{-1}; HRMS calcd for $C_{18}H_{25}O_6SiS$ (M^+-*t*-Bu) 397.1141, found 397.1135. *Anal.* Calcd. for $C_{22}H_{34}O_6SSi$: C, 58.12; H, 7.54. Found: C, 58.35; H, 7.28.



42

1,4-Di-O-acetyl-3-O-(*tert*-butyldimethylsilyl)-2-deoxy-2-(phenylthio)-6-*p*-toluenesulfonyl-β-D-glucopyranose (42). To a stirred, 23 °C solution of 1.35 g (2.97 mmol) of **17**[2,54] in 15 mL of CH_2Cl_2 was added 0.5 mL of PhSCl. After several minutes the mixture was concentrated *in vacuo* and the yellow residue was diluted with 10 mL of THF. This solution was saturated with LiCl and the mixture was stirred 2-3 h. The solution was diluted with CH_2Cl_2 and filtered through Celite using a fine grain sintered glass funnel. The filtrate was dried over Na_2SO_4 and concentrated in vacuo. Analysis of the crude product by ^{1}H NMR indicated that this material consisted of a ca. 94 : 6 mixture of α-gluco chloride (δ 5.89 (d, J = 3.2 Hz, H-1), 3.42 (dd, J = 10.4, 3.2 Hz, H-2)) and the β-manno chloride (δ 5.93 (br s, H-1), 3.75 (br d, J = 4.0 Hz, H-2)); diagnostic resonances for β-**11** (observed before the LiCl step) are δ 5.42 (d, J = 8.9 Hz, H-1) and 3.42 (dd, J = 8.9, 8.9 Hz, H-2)). This material was diluted with 15 mL of glacial acetic acid and treated with 2 g of AgOAc. After 1.5 h, the mixture was diluted with CH_2Cl_2 and filtered through Celite. The filtrate was washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated. Chromatography of the resulting residue on silica gel eluting with EtOAc-hexanes (1.5 : 8.5 then 2 : 8) gave 1.6 g (86 % overall from **17**) of **42** as a white foam: $[\alpha]_D^{23}$ +4.0° (c=4.0, $CDCl_3$); ^{1}H NMR (400 MHz) δ 7.60 (d, 2 H of AA'BB', J = 8.3 Hz), 7.35-7.13 (complex overlapping signals, 7 H), 5.69 (d, J = 8.8 Hz, H-1), 4.89 (dd, J = 9.6 8.4 Hz, H-4), 4.09 - 3.98 (AB of ABX, 2 H), 3.75 (dd, J = 9.8, 8.6 Hz, H-3), 3.73-3.67 (m, 1 H), 3.23 (dd, J = 9.6, 8.4 Hz, H-2), 2.36 (s, 3 H), 2.02 (s, 3 H), 1.63 (s, 3 H), 0.79 (s, 9 H), 0.11 (s, 3 H), 0.00 (s, 3 H); IR ($CDCl_3$) 1752, 1593 cm^{-1}. *Anal.* Calcd for $C_{29}H_{34}O_9S_2Si$: C,55.75 ; H, 6.45. Found: C, 55.50; H, 6.57.

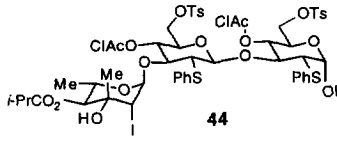


43

4-O-Acetyl-6-bromo-3-O-(tert-butyldimethyl)silyl-2,6-dideoxy-2-thiophenyl-α-D-glucopyranose (43). A solution of glycal **19**[55] (1.54 g, 4.20 mmol) in CH_2Cl_2 (45 mL) was treated with neat phenylsulfenyl chloride[39] (850 mg, 5.88 mmol) at 0°C. The ice bath was removed and the reaction stirred for 1 h while warming to ambient temperature. The mixture was concentrated under reduced pressure to give the crude glycosyl chlorides (13 : 1 *gluco* (**11**) : *manno*(**12**)). The residue was dissolved in a mixture of CH_3CN (50 mL) and H_2O (11 mL) and stirred with Ag_2CO_3 (10.2 g, 37.0 mmol) overnight. The mixture was diluted with THF and filtered through Celite; the Celite bed washed several times with EtOAc. The filtrate was concentrated and the crude product was purified by chromatography

(silica gel, 10% EtOAc-hexanes) to give the lactol **43** (1.84 mg, 89% yield as ca. 11 : 1 mixture of anomers favoring the α-OH anomer shown. Data for α-**43**: Rf = 0.71 (20% EtOAc-hexanes); $[\alpha]_D^{25}$ +22.3° (c 4.60, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.45-7.18 (m, 5 H), 5.32 (d, *J* = 3.1 Hz, 1 H), 4.90 (dd, *J* = 9.5, 8.4 Hz, 1 H), 4.19 (ddd, *J* = 9.5, 7.4, 3.1 Hz, 1 H), 4.16 (dd, *J* = 10.3, 8.4 Hz, 1 H), 3.30 (br s, 1 H, -OH), 3.29 (dd, *J* = 10.3, 3.1 Hz, 1 H), 2.15 (s, 3 H), 0.85 (s, 9 H), 0.14 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 135.2, 131.4, 130.5, 129.0, 126.8, 93.0, 75.0, 70.5, 70.4, 55.9, 32.0, 25.8, 21.5, 18.0, -3.6, -4.3; IR ($CHCl_3$) 3580, 3340 (br), 1740, 1580 cm^{-1}. *Anal.* Calcd for $C_{20}H_{31}SiSBrO_5$: C, 48.87; H, 6.36. Found: C, 48.87; H, 6.20.

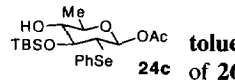
Partial ^1H NMR data for the minor β-anomer (β-**43**): 5.07(dd, J = 7.9, 8.7 Hz, 1 H, H-4), 4.80 (dd, J = 8.1, 6.0 Hz, 1 H, H-1), 3.81 (dd, *J* = 9.5, 7.9 Hz, 1 H, H-3), 3.08 (dd, *J* = 9.5, 8.1 Hz, 1 H, H-2).



44

4-O-Chloroacetyl-3-O-[4-O-chloroacetyl-2-deoxy-3-O-(2,6-dideoxy-2-iodo-4-O-isobutyryl-3-C-methyl-α-L-mannopyranosyl)-2-phenylthio-6-O-(*p*-toluenesulfonyl)-β-D-glucopyranosyl]-6-O-(*p*-toluenesulfonyl)-α-D-glucopyranose (44). PhSCl (15 μL) was added to a stirred, 23 °C solution of C-D-E trisaccharide glucal **22**[3] (50 mg, 0.0416 mmol) in CH_2Cl_2 (0.7 mL). The mixture was stirred for 30 min, then the solvent was evaporated *in vacuo*. The ^1H-NMR spectrum of the crude product showed a mixture of the α-D-gluco-, β-D-gluco-, and α-D-mannopyranosyl chlorides in the ratio of 35 : 56 : 9, respectively. Separation of this mixture by flash silica gel chromatography (hexane/EtOAc 2:1) afforded a mixture of the α-D-gluco- and β-D-glucopyranosyl chlorides (45 mg, 80%) and the D-glucopyranose (6 mg, 10%, resulting from hydrolysis of the glucopyranosyl chlorides).

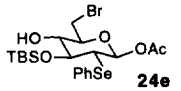
$AgOSO_2CF_3$ (27 mg, 0.105 mmol) was added to a stirred solution of the α-D-gluco- and β-D-glucopyranosyl chlorides (70 mg, 0.052 mmol), N,N,N',N'-tetramethylurea (28 μL, 0.234 mmol), and H_2O (200 μL, 11 mmol) in THF (1 mL). The mixture was stirred for 2 h in the dark, then additional $AgOSO_2CF_3$ (13 mg, 0.051 mmol) and N,N,N',N'-tetramethylurea (8 μL, 0.067 mmol) were added. The mixture was stirred for another 6 h, then was filtered through Celite and the filtrate was concentrated *in vacuo*. Purification of the crude product by flash chromatography (hexane/EtOAc 3:2) gave the trisaccharide lactol **44** (59 mg, 85%) as a white solid: R_f 0.11 (hexane/EtOAc 2:1); $[\alpha]_D^{28}$ +5.0° (c 0.8, $CHCl_3$); ^1H-NMR ($CDCl_3$) *ca.* 85:15 mixture of α- and β-D-anomers, signals of α-D-anomer: δ 7.82 - 7.62 (m, 4 arom. H), 7.41–7.06 (m, 14 arom. H), 5.40 (d, *J* = 1.6, H-1"), 5.11 (m, H-1), 4.95 (dd, *J* = 10.0, 8.8, H-4'), 4.95 (d, *J* = 8.8, H-1'), 4.87 (d, *J* = 9.2, H-4"), 4.86 (dd, *J* = 10.8, 9.2, H-4), 4.48 (d, *J* = 2.0, H-2"), 4.30 (ddd, *J* = 10.8, 4.8, 2.8, H-5), 4.20–3.86 (m, 9 H, H-3, 2 H-6, H_2-6', CH_2Cl (2x)), 3.76 (dq, *J* = 8.8, 6.0, H-5"), 3.62–3.58 (m, H-5'), 3.56 (dd, *J* = 10.8, 8.8, H-3'), 3.22 (br. s, O*H*), 3,11 (dd, *J* = 10.8, 9.2, H-2'), 3.10 (dd, *J* = 10.8, 3.6, H-2), 2.57 (sept, *J* = 7.2, Me_2CH), 2.47 (s, CH_3-Ar), 2.43 (s, CH_3-Ar), 2.23 (s, O*H*), 1.19 (s, H_3C-C3"), 1.16 (d, *J* = 7.2, 6 H, $(H_3C)_2C$), 1.13 (d, *J* = 6.0, H_3C6"); ^{13}C-NMR ($CDCl_3$) δ 177.1, 166.3, 166.0, 145.6 , 145.1, 135.3, 133.6, 132.4, 131.9, 131.4, 130.1, 129.9, 129.0, 128.9, 128.3, 128.2, 128.1, 127.5, 126.2, 105.3, 103.3, 93.0, 81.9, 76.2, 74.3, 71.7, 70.8 (2 C), 70.7, 68.6, 67.8, 67.4, 66.7, 60.4, 55.3, 54.2, 46.2, 40.84, 40.77, 34.1, 21.7, 21.6, 20.7, 18.9, 18.8, 17.5; IR ($CHCl_3$) 3590, 3530, 1770, 1740, 1600, 1590 cm^{-1};. FAB-HRMS: calcd for $C_{53}H_{61}O_{19}Cl_2IKS_4$ ($[M+K]^+$) 1365.0732, found 1365.0774.



24c

1-O-Acetyl-3-O-(*tert*-butyldimethylsilyl)-2-deoxy-2-(phenylseleno)-6-*p*-toluenesulfonyl-β-D-glucopyranose (24c). To a stirred, 0 °C solution of 0.72 g (2.93 mmol) of **26**[26] in 10 mL of toluene was added a solution of 0.73 g (3.82 mmol) of PhSeCl in 5 mL of toluene via cannula. The reaction was monitored by TLC and when no glycal remained, 0.73 g (4.4 mmol) of AgOAc was added. After 1 h, the mixture was diluted with CH_2Cl_2 and filtered through Celite. The filtrate was washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated in vacuo. ^1H NMR analysis indicated that the crude product consisted of a 6 : 1 mixture of **24c** and **25c**. Purification of the products by chromatography on silica gel (eluting with 3% acetone in CH_2Cl_2) gave 0.93 g (63%) of the known acetate **24c**[26] as a clear oil: ^1H NMR (400 MHz) δ 7.58-7.53 (m, 2 H), 7.33-7.23 (m, 3 H), 5.74 (d, *J* = 9.4 Hz, H 1), 3.53 (dd, J= 10.6,8.2 Hz, 1 H), 3.56-3.47 (m, 1 H), 3.38-3.28 (m, 1 H), 2.17 (d, *J* = 3.6 Hz, O<u>H</u>), 1.82 (s, 3 H), 1.39 (d, *J* = 6.0 Hz, 3 H), 1.03 (s, 9 H), 0.32 (s, 3 H), 0.26 (s, 3 H); IR 3620, 3510, 1762

cm^{-1}. ^{1}H NMR data for the α-manno acetate **25c**: ^{1}H NMR (400 MHz) δ 7.63-7.58 (m 2 H), 7.33-7.23 (m, 3 H), 6.54 (d, *J* = 1.0 Hz, H-1), 4.08 (dd, *J* = 8.9, 4.8 Hz, 1 H), 3.86-3.78 (m, 1 H), 3.61 (dd, *J* = 4.8, 1.0 Hz, 1 H), 3.49 (dt, *J* = 9.1, 2.7 Hz, 1 H), 2.22 (d, *J* = 2.7 Hz, 1 H), 2.06 (s, 3 H), 1.35 (d, *J* = 6.4 Hz, 3 H), 0.92 (s, 9 H), 0.12 (s, 3 H), 0.06 (s, 3 H).



24e

1-O-Acetyl-6-bromo-3-O-(*tert*-butyldimethylsilyl)-2,6-dideoxy-2-(phenyl)seleno-β-D-glucopyranose (24e): To a stirred, 0 °C solution of 1.19 g (4.34 mmol) of **27** in 17 mL of toluene was added 1.08 g (3.82 mmol) of PhSeCl. The reaction was monitored by TLC and when no glycal remained, ca. 1.5 g (>2 equiv.) of AgOAc was added. After 1 h, the mixture was diluted with CH_2Cl_2 and filtered through Celite. The filtrate was washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated. ^{1}H NMR analysis of the crude residue indicated >15 : 1 mixture of **24e** : **25e**. Purification of the crude product by chromatography on silica gel (eluting with EtOAc-hexanes, 12: 88) gave 1.2 g (57%) of **24e**: mp. 137°C; $[\alpha]_D^{28}$ +39.4° (c 3.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.53 (m, 2 H), 7.30-7.25 (m, 3 H), 5.80 (d, *J* = 10.8 Hz, H-1), 3.70-3.58 (m, 3 H), 3.52 (m, 1 H), 3.29-3.20 (t, *J* = 10.8 Hz, H-2), 2.32 (broad s, 1 H, OH), 1.85 (s, 3 H), 0.96 (s, 9 H), 0.10 (s, 3 H), 0.00 (s, 3 H); IR ($CHCl_3$) 3609, 3500, 1751, 1578 cm^{-1}. HRMS (EI) calcd for $C_{20}H_{31}O_5SiSeBr$ (M^+) 540.0291, found 540.0298.

4,6-O-Benzylidene-3-O-(*tert*-butyldimethyl)silyl-D-glucal (30a). To a 0 °C solution of 4,6-O-benzylidene-D-glucal[56,57] (0.362 g, 1.54 mmol) and imidazole (0.316 g, 4.64 mmol) in DMF (0.7 mL) and CH_2Cl_2 (7.7 mL) was added TBS-Cl (0.349 g, 2.32 mmol). The solution was allowed to slowly warm to 23 °C and then stirred at 23 °C for 6 h. H_2O was added and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with H_2O, dried ($MgSO_4$), filtered, and concentrated in vacuo to give a solid/oil mixture. Purification of the crude product by flash chromatography (1% Et_3N, 1.5% EtOAc-hexanes) afforded **30a** (0.500 g, 93% yield) as a clear, colorless oil: $[\alpha]_D^{28}$ -65.3° (c 2.58, CH_2Cl_2); IR (neat) 3070, 3040, 2950. 2930. 2890, 2850, 1645, 1500 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52-7.33 (m, 5 H), 6.30 (dd, *J* = 6.0, 1.4 Hz, 1 H), 5.60 (s, 1 H), 4.67 (dd, *J* = 6.2, 1.9 Hz, 1 H), 4.51 (app. dt, *J* = 7.4, 1.8 Hz, 1 H), 4.35 (dd, *J* = 10.2, 4.9 Hz, 1 H), 3.89 (ddd, *J* = 10.2, 9.9, 4.9 Hz, 1 H), 3.83-3.79 (m, 2 H), 0.90 (s, 9 H), 0.10 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 137.4, 128.8, 128.0, 126.0, 105.4, 101.3, 80.6, 68.8, 68.4, 67.3, 25.8, 18.2, -4.4, -4.8; HRMS calcd for $C_{15}H_{19}O_4Si$ (M^+-*t*-Bu) 291.1052, found 291.1041. *Anal.* Calcd for $C_{19}H_{28}O_4Si$: C, 65.48; H, 8.10. Found: C, 65.61; H, 7.98.

3-O-Benzyl-4,6-O-Benzylidene-D-glucal (30b). To a 23 °C solution of 4,6-O-benzylidene-D-glucal[56,57] (0.251 g, 1.07 mmol) and DMAP (catalytic amount) in THF (7 mL) was added NaH (51 mg, 2.1 mmol) followed by benzyl bromide (0.19 mL, 1.6 mmol). The mixture was stirred for 6.5 h at 23 °C, H_2O was added and the aqueous phase was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to give a yellow solid. Purification of the crude product by flash chromatography with (1% Et_3N, 4% EtOAc-hexanes) afforded the known[58] glucal **30b** (0.321 g, 92% yield) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.26 (m, 10H), 6.36 (dd, *J* = 6.0, 1.6 Hz, 1 H), 5.65 (s, 1 H), 4.83 (dd, *J* = 6.3, 1.9 Hz, 1 H), 4.82, 4.72 (AB q, *J* = 11.6 Hz, 2 H), 4.40-4.36 (m, 2 H), 4.04 (dd, *J* = 9.8, 7.2 Hz, 1 H), 3.92 (app. dt, *J* = 4.5, 9.9 Hz, 1 H), 3.86 (dd, *J* = 10.4, 9.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 138.4, 137.2, 129.0, 128.3, 128.2, 127.7, 127.6, 126.0, 102.3, 101.2, 80.0, 73.1, 72.0, 68.6, 68.4.

Acetyl 4,6-O-Benzylidene-3-O-(*tert*-butyldimethyl)silyl-2-deoxy-2-thiophenyl-β-D-glucopyranoside (34a). This compound was prepared from glucal **30a** (0.046 g, 0.132 mmol) and PhSCl (0.025 mL, 0.23 mmol) by using the procedure described for the preparation of **41**. ^{1}H NMR analysis of the mixture of chlorides obtained after the equilibration with LiCl in THF revealed an α-gluco : α-manno ratio of 70 : 30. [Characteristic ^{1}H NMR data ($CDCl_3$) for the α-gluco chloride: δ 6.05 (d, *J* = 3.6 Hz, 1 H); for the α-manno chloride: δ 6.15 (s, 1 H)]. The α-gluco : α-manno ratio was still 70 : 30 following the reaction with AgOAc. Purification of the crude product by flash chromatography (1% Et_3N and 4% EtOAc in hexanes) afforded **34a** and **34b** (0.066g, 88% yield; 75 : 25, respectively) as clear, colorless oils.

Data for **34a**: $[\alpha]_D^{26}$ -33.6° (c 2.31, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.48-7.20 (m, 10H), 5.80 (d, *J* = 9.4 Hz, 1 H), 5.51 (s, 1 H), 4.32 (dd, *J* = 10.4, 4.4 Hz, 1 H), 3.78 (dd, *J* = 10.1, 8.2 Hz, 1 H), 3.72 (dd, *J* = 10.4, 9.4 Hz, 1 H), 3.58-3.49 (m, 2 H), 3.26 (dd, *J* = 10.1, 9.1 Hz, 1 H), 1.76 (s, 3 H), 0.87 (s, 9 H), 0.13 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 136.9, 134.8, 131.9, 129.1, 128.9, 128.2, 127.2, 126.3, 102.1, 95.1, 82.7, 72.2, 68.5, 66.5, 56.7, 25.9, 20.5, 18.4, -3.9, -4.5; IR (CH_2Cl_2) 1760, 1585, 1470 cm^{-1}; HRMS calcd for $C_{23}H_{27}O_6SiS$ (M^+-*t*-Bu) 459.1298, found 459.1291. Anal. Calcd for $C_{27}H_{36}O_6SiS$: C, 62.76; H, 7.02. Found C, 63.16; H, 6.78.

Data for **35a**: $[\alpha]_D^{26}$ -1.82° (c 1.48, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.52-7.24 (m, 10H), 6.19 (d, *J* = 1.6 Hz, 1 H), 5.61 (s, 1 H), 4.46 (m, 1 H), 4.27 (dd, *J* = 9.9, 4.6 Hz, 1 H), 3.95-3.79 (m, 3 H), 3.60 (dd, *J* = 5.0, 1.3 Hz, 1 H), 2.11 (s, 3 H), 0.86 (s, 9 H), 0.04 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 137.2, 134.7, 132.5, 129.2, 128.9, 128.1, 127.6, 126.1, 101.8, 94.8, 79.5, 68.5, 66.5, 56.7, 30.0, 25.7, 21.1, 18.3, -4.5, -4.9; IR (CH_2Cl_2) 1750, 1580 cm^{-1}; HRMS calcd for $C_{23}H_{27}O_6SiS$ (M^+-*t*-Bu) 459.1298, found 459.1291; Anal. Calcd for $C_{27}H_{36}O_6SiS$: C, 62.76; H, 7.02. Found C, 63.15; H, 6.99.

Acetyl 3-O-Benzyl-4,6-O-benzylidene-2-deoxy-2-thiophenyl-β-D-glucopyranoside (**34b**) and **Acetyl 3-O-Benzyl-4,6-O-benzylidene-2-deoxy-2-thiophenyl-α-D-mannopyranoside** (**35b**). These compounds were prepared in 4 : 1 ratio from **30b** (65% yield) by using the procedure described for the preparation of **41**. Characteristic ^1H NMR data (acetone-d_6) for the intermediate α-gluco chloride: δ 6.57 (d, *J* = 3.8 Hz, 1 H); for the α-manno chloride: δ 6.37 (d, *J* = 0.9 Hz, 1 H).

Data for **34b**: mp 143-145 °C; $[\alpha]_D^{26}$ -45.2° (c 1.48, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.50-7.26 (m, 15H), 5.81 (d, *J* = 9.1 Hz, 1 H), 5.59 (s, 1 H), 4.36, 4.34 (AB q, *J* = 10.8 Hz, 2 H), 4.35 (dd, *J* = 10.4, 5.0 Hz, 1 H), 3.79 (dd, *J* = 9.4, 8.8 Hz, 1 H), 3.75 (app. t, *J* = 10.2 Hz, 1 H), 3.64 (dd, *J* = 10.7, 8.8 Hz, 1 H), 3.52 (app. dt, *J* = 5.0, 9.7 Hz, 1 H), 3.27 (dd, *J* = 10.4, 9.1 Hz, 1 H), 1.90 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 138.0, 137.0, 133.5. 133.2, 129.0, 129.0, 128.3, 128.3, 128.2, 127.8, 125.9, 101.3, 94.6, 82.7, 78.2, 75.5, 68.4, 66.5, 54.7, 20.6; IR (CH_2Cl_2) 1760, 1580 cm^{-1}; HRMS calcd for $C_{28}H_{28}O_6S$ (M^+) 492.1606, found 492.1619; Anal. Calcd for $C_{28}H_{28}O_6S$: C, 68.27; H, 5.73. Found C, 68.18; H, 5.32.

Data for **35b**: clear, colorless oil; $[\alpha]_D^{26}$ +9.4° (c 1.41, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.58-7.26 (m, 15H), 6.27 (d, *J* = 1.3 Hz, 1 H), 5.69 (s, 1 H), 4.77, 4.69 (AB q, *J* = 12.1 Hz, 2 H), 4.31 (dd, *J* = 10.1, 4.4 Hz, 1 H), 4.28 (dd, *J* = 10.1, 4.7 Hz, 1 H), 4.18 (dd, *J* = 9.8, 9.1 Hz, 1 H), 3.97 (ddd, *J* = 10.1, 9.3, 4.3 Hz, 1 H), 3.88 (app. t, *J* = 10.1 Hz, 1 H), 3.71 (dd, *J* = 4.7, 1.6 Hz, 1 H), 2.08 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 137.9, 137.3, 134.6. 132.7, 129.2, 129.0, 128.3, 128.2, 127.8, 127.7, 127.7, 126.0, 101.6, 95.0, 79.2, 73.9, 72.4, 68.5, 66.5, 53.9, 21.0; IR (CH_2Cl_2) 1755, 1560 cm^{-1}; HRMS calcd for $C_{28}H_{28}O_6S$ (M^+) 492.1606, found 492.1617.

Acetyl 4,6-O-Benzylidene-3-O-(*tert*-butyldimethyl)silyl-2-deoxy-2-selenophenyl-β-D-glucopyranoside (**36a**) and **Acetyl 4,6-O-Benzylidene-3-O-(*tert*-butyldimethyl)silyl-2-deoxy-2-selenophenyl-α-D-mannopyranoside** (**37a**). A 1 : 1 mixture of these compounds (60% yield) was prepared from **30a** using the procedure described for the preparation of **41**, except that PhSeCl was used rather than PhSCl. Characteristic ^1H NMR data ($CDCl_3$) for the intermediate α-gluco chloride: δ 6.17 (d, *J* = 3.5 Hz, 1 H).; for the α-manno chloride: δ 6.15 (br s, 1 H).

Data for **36a**: pale yellow oil; $[\alpha]_D^{26}$ +13.0° (c 1.77, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.60-7.26 (m, 10H), 5.85 (d, *J* = 9.4 Hz, 1 H), 5.49 (s, 1 H), 4.30 (dd, *J* = 10.5, 4.9 Hz, 1 H), 3.80 (dd, *J* = 10.1, 8.2 Hz, 1 H), 3.70 (app. t, *J* = 10.1 Hz, 1 H), 3.53 (dd, *J* = 9.4, 8.2 Hz, 1 H), 3.47 (app. dt, *J* = 4.8, 9.4 Hz, 1 H), 3.25 (app. t, *J* = 9.8 Hz, 1 H), 1.83 (s, 3 H), 0.89 (s, 9 H), 0.13 (s, 3 H), -0.01 (s, 3 H); HRMS calcd for $C_{23}H_{27}O_6SiSe$ (M^+- *t*-Bu) 508.0820, found 508.0781. Anal. Calcd for $C_{27}H_{36}O_6SiSe$: C, 57.54; H, 6.44. Found C, 57.98; H, 6.44.

Data for **37a**: pale yellow oil: $[\alpha]_D^{26}$ -18.5° (c 1.1, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.65-7.26 (m, 10H), 6.18 (d, *J* = 1.3 Hz, 1 H), 5.60 (s, 1 H), 4.35 (dd, *J* = 9.0, 5.2 Hz, 1 H), 4.26 (dd, *J* = 10.2, 3.9 Hz, 1 H), 3.94-3.80 (m, 3 H), 3.71 (dd, *J* = 5.0, 1.3 Hz, 1 H), 2.09 (s, 3 H), 0.89 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 137.2, 135.2, 129.3, 128.9, 128.6, 128.2, 128.1, 126.1, 101.8, 95.1, 80.2,

68.5, 66.4, 51.7, 25.7, 21.0, 18.3, -4.5, -4.9; HRMS calcd for $C_{27}H_{37}O_6SiSe$ (M^++1) 565.1524, found 565.1511. *Anal.* Calcd for $C_{27}H_{36}O_6SiSe$: C, 57.54; H, 6.44. Found C, 57.66; H, 6.65.

Acetyl 3-O-Benzyl-4,6-O-benzylidene-2-deoxy-2-selenophenyl-β-D-glucopyranoside (36b) and **Acetyl 3-O-Benzyl-4,6-O-benzylidene-2-deoxy-2-selenophenyl-α-D-mannopyranoside (37b)**. These compounds were prepared in 66% combined yield (5 : 1 selectivity) by the one pot procedure described for the preparation of **24c** and **24e**. When prepared by using the procedure described for **36a** and **37a**, the yield was only 35% and the selectivity was 3 : 1. Characteristic ^{1}H NMR data ($CDCl_3$) for the intermediate α-gluco chloride: δ 6.14 (d, J = 3.5 Hz, 1 H).; for the α-manno chloride: δ 6.21 (br s, 1 H).

Data for **36b**: $[\alpha]_D^{26}$ +8.9° (c 0.52, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.26 (m, 15H), 5.85 (d, J = 9.4 Hz, 1 H), 5.59 (s, 1 H), 4.98, 4.77 (AB q, J = 10.8 Hz, 2 H), 4.34 (dd, J = 10.4, 5.0 Hz, 1 H), 3.78 (dd, J = 9.4, 8.8 Hz, 1 H), 3.74 (app. t, J = 10.2 Hz, 1 H), 3.61 (dd, J = 10.7, 8.8 Hz, 1 H), 3.47 (app. dt, J = 5.0, 9.8 Hz, 1 H), 3.30 (dd, J = 10.5, 9.6 Hz, 1 H), 1.96 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 138.0, 137.0, 135.9, 129.2, 129.0, 128.4, 128.3, 128.3, 128.1, 127.8, 127.0, 125.9, 101.2, 94.3, 83.0, 77.9, 75.2, 68.4, 66.4, 48.6, 20.6; IR (CH_2Cl_2) cm^{-1}; HRMS calcd for $C_{28}H_{29}O_6Se$ (M^++1) 541.1129, found 541.1138.

Data for **37b**: yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.25 m, 15H), 6.31 (d, J = 1.3 Hz, 1 H), 5.66 (s, 1 H), 4.73, 4.67 (ABq, J = 12.1 Hz, 2 H), 4.28 (dd, J = 10.1, 4.7 Hz, 1 H), 4.17 (dd, J = 9.6, 4.2 Hz, 1 H), 4.12 (dd, J = 9.8, 8.8 Hz, 1 H), 3.95 (ddd, J = 10.1, 8.8, 4.4 Hz, 1 H), 3.84 (app. t, J = 10.1 Hz, 1 H), 3.75 (dd, J = 4.4, 1.6 Hz, 1 H), 2.04 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 137.9, 137.2, 135.2, 129.3, 129.0, 128.8, 128.3, 128.2, 127.7, 126.0, 101.6, 95.4, 80.0, 74.0, 72.2, 68.5, 66.4, 49.2, 21.0; HRMS calcd for $C_{28}H_{29}O_6Se$ (M^++1) 541.1129, found 541.1108. *Anal.* Calcd for $C_{28}H_{28}O_6Se$: C, 62.34; H, 5.23. Found C, 62.58; H, 5.42.

References

1. Sebesta, D. P.; Roush, W. R. *J. Org. Chem.* **1992**, *57*, 4799.
2. Roush, W. R.; Lin, X.-F. *J. Am. Chem. Soc.* **1995**, *117*, 2236.
3. Roush, W. R.; Briner, K.; Kesler, B. S.; Murphy, M.; Gustin, D. J. *J. Org. Chem.* **1996**, *61*, 6098.
4. Remers, W. A. In *The Chemistry of Antitumor Antibiotics*; Wiley-Interscience: New York, 1979; pp. 133-175.
5. Remers, W. A.; Iyengar, B. S. In *Cancer Chemotherapeutic Agents*; W. O. Foye, Ed.; ACS: 1995; pp. 578.
6. Franck , R. W.; Weinreb, S. M. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1989; pp. 173. This article reviews synthetic efforts in this area through 1987.
7. Leading references to the work of Weinreb, Franck, Thiem, Binkley, Crich and Toshima, who have made important contributions to the synthesis of the aureolic acid antibiotics, are provided in ref. 2.
8. Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212.
9. Thiem, J.; Klaffke, W. *Topics Curr. Chem.* **1990**, *154*, 285.
10. Schmidt, R. R. In *Comprehensive Organic Synthesis*; B. M. Trost, Ed.; Wiley: 1991; Vol. 6; pp. 33-64.
11. Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503.
12. The structure of the mithramycin oligosaccharides has been revised to that shown in **3** on the basis of Patel's NMR structure determination of the (mithramycin)$_2$-Mg^{+2}-DNA complex (see ref. 32).
13. Wiesner, K.; Tsai, T. Y. R.; Jin, H. *Helv. Chim. Acta* **1985**, *68*, 300.
14. Crich, D.; Ritchie, T. *J. Chem. Soc., Chem. Commun.* **1988**, 1461.
15. Crich, D.; Ritchie, T. J. *Carbohydr. Res.* **1989**, *190*, C3.
16. Kahne, D.; Yang, D.; Lim, J. J.; Miller, R.; Paguaga, E. *J. Am. Chem. Soc.* **1988**, *110*, 8716.
17. Binkley, R. W.; Sivik, M. R. *J. Carbohydr. Chem.* **1991**, *10*, 399, and references cited therein.
18. Thiem, J.; Gerken, M. *J. Org. Chem.* **1985**, *50*, 954, and references therein.
19. Nicolaou, K. C.; Ladduwahetty, T.; Randall, J. L.; Chucholowski, A. *J. Am. Chem. Soc.* **1986**, *108*, 2466.
20. Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1987**, *28*, 2723.
21. Preuss, R.; Schmidt, R. R. *Synthesis* **1988**, 694.
22. Ramesh, S.; Franck, R. W. *J. Chem. Soc., Chem. Commun.* **1989**, 960.

23. Ramesh, S.; Kaila, N.; Grewal, G.; Franck, R. W. *J. Org. Chem.* **1990**, *55*, 5.
24. Grewal, G.; Kaila, N.; Franck, R. W. *J. Org. Chem.* **1992**, *57*, 2084.
25. Hashimoto, S.; Yanagiya, Y.; Honda, T.; Ikegami, S. *Chem. Lett.* **1992**, 1511.
26. Perez, M.; Beau, J.-M. *Tetrahedron Lett.* **1989**, *30*, 75.
27. Trumtel, M.; Veyriéres, A.; Sinaÿ, P. *Tetrahedron Lett.* **1989**, *30*, 2529.
28. Trumtel, M.; Tavecchia, P.; Veyriéres, A.; Sinaÿ, P. *Carbohydr. Res.* **1989**, *1989*, 29.
29. Tavecchia, P.; Trumtel, M.; Veyriéres, A.; Sinaÿ, P. *Tetrahedron Lett.* **1989**, *30*, 2533.
30. Gervay, J.; Danishefsky, S. *J. Org. Chem.* **1991**, *56*, 5448.
31. Gao, X.; Mirau, P.; Patel, D. J. *J. Mol. Biol.* **1992**, *223*, 259.
32. Sastry, M.; Patel, D. J. *Biochemistry* **1993**, *32*, 6588.
33. Walker, S.; Valentine, K. G.; Kahne, D. *J. Am. Chem. Soc.* **1990**, *112*, 6428.
34. Silva, D. J.; Kahne, D. E. *J. Am. Chem. Soc.* **1993**, *115*, 7962.
35. Silva, D. J.; Goodnow, R., Jr.; Kahne, D. *Biochemistry* **1993**, *32*, 463.
36. Silva, D. J.; Kahne, D.; Kraml, C. M. *J. Am. Chem. Soc.* **1994**, *116*, 2641.
37. Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380.
38. Roush, W. R.; Sebesta, D. P.; James, R. A. *Tetrahedron* **1997**, *53*, 8837, the following paper in this issue.
39. Mueller, W. H.; Butler, P. E. *J. Am. Chem. Soc.* **1968**, *90*, 2075.
40. The factors responsible for the range of results obtained with **14** are not obvious at present.
41. Crich, D.; Ritchie, T. J. *Carbohydr. Res.* **1990**, *197*, 324.
42. The synthesis of trisaccharide glycal **23** will be described elsewhere (Roush, W. R.; James, R. A., unpublished research).
43. Hunt, J. A.; Roush, W. R. *J. Am. Chem. Soc.* **1996**, *118*, 9998.
44. These studies were guided by the results reported by Perez and Beau (ref. 26), who observed that the best selectivity in the reactions of 6-deoxy glucal derivatives with PhSeCl was obtained with glycals containing unprotected hydroxyl groups at C(4).
45. Rico, M.; Santoro, J. *Org. Magn. Res.* **1976**, *8*, 49.
46. Chalmers, A. A.; Hall, R. H. *J. Chem. Soc., Perkin Trans. 2* **1974**, 728.
47. Thiem, J.; Ossowski, P. *J. Carbohydr. Chem.* **1984**, *3*, 287.
48. Horton, D.; Priebe, W.; Sznaidman, M. *Carbohydr. Res.* **1990**, *205*, 71.
49. Kaila, N.; Blumenstein, M.; Bielawska, H.; Franck, R. W. *J. Org. Chem.* **1992**, *57*, 4576.
50. Franck, R. W.; Kaila, N.; Blumenstein, M.; Geer, A.; Huang, X. L.; Dannenberg, J. J. *J. Org. Chem.* **1993**, *58*, 5335.
51. The diastereoselectivity of the reactions of **30a,b** with PhSCl and PhSeCl was the same, within experimental error, when checked at the stage of the glycosyl chlorides or acetates.
52. In addition to the iodoglycosidation reactions of glycals already noted (refs. 47-48), the C(6)-substituent is also known to influence the stereoselectivity of bromination reactions of glycals (Horton, D.; Priebe, W.; Varela, O. *J. Org. Chem.* **1986**, *51* 3479).
53. For general experimental details, see: Roush, W. R.; Lin, X.-F. *J. Am. Chem. Soc.* **1995**, *117*, 2236. Unless otherwise noted, all compounds purified by chromatography are sufficiently pure (>95% by ^{1}H NMR analysis) for use in subsequent reactions.
54. Sebesta, D. P. Ph. D. Thesis, Indiana University, 1992.
55. Details of the synthesis of **19** are provided in the Supplementary Material section of the paper cited in ref. 3.
56. Sharma, M.; Brown, R. K. *Can. J. Chem.* **1966**, *44*, 2825.
57. Bedretti, V.; Mallet, J.-M.; Sinaÿ, P. *Carbohydr. Res.* **1993**, *244*, 247.
58. Fernandez-Mayoralas, A.; Marra, A.; Trumtel, M.; Veyrierès, A.; Sinaÿ, P. *Carbohydr. Res.* **1989**, *188*, 81.

Acknowledgement. We thank the National Institutes of Health (GM 38907 and RR 10537) for support of this research program. We also thank Dr. Karin Briner and Mr. Ray James for contributing several of the examples reported in Table 1.

(*Received* 6 *January* 1997; *revised* 5 *March* 1997; *accepted* 12 *March* 1997)