Novel Stereoelectronic Behavior of Bicyclic Glycosyl Donors: Application to the Synthesis of Both 2-Deoxy-α- and -β-Glycosides

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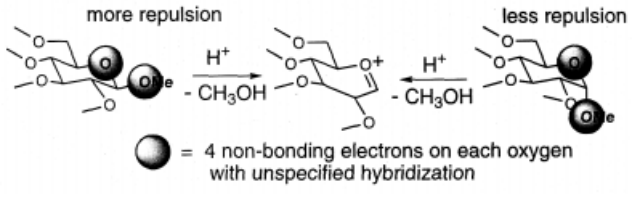
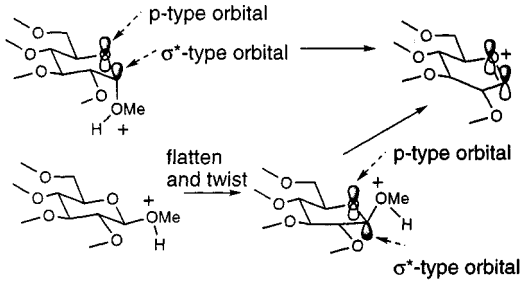
Two pairs of novel stereoisomeric, cyclic glycosyl donors exhibit different behaviors in glycosylation processes. In the pair of α-*gluco* (**1**) and β-*manno* (**2**), the former exhibits reversability with its glycoside product whereas the latter does not. In the α-*gluco* (**3**) and β-*manno* (**4**) set, the former undergoes glycosyl transfer via an isolable intermediate whereas the latter does not. The differing anomeric effects exerted in the ground states are proposed as the force which explains the differences in behavior.

The observed differences in rates of glycosyl transfer, including hydrolysis, among glycosyl donors have been the subject of analysis for decades.[1] A key issue has been the importance or even the existence of stereolectronic effects.[2] One such factor, the anomeric effect, is a force which is made manifest by the stabilization of the ground state of axial anomeric electronegative groups that overrides the steric destabilization so that axial anomers are often more stable than their corresponding equatorial anomer.[3] This stabilization is generally accepted as due, in part, to the interaction of a filled orbital on the ring oxygen atom with an antibonding orbital of the axial C−X bond. Another contribution to the anomeric effect can be viewed as an electrostatic repulsion between the n-electron pairs on the ring oxygen atom and the corresponding electron pairs on the equatorially disposed X group.[4] If the latter were the principal force operative in going from glycosyl donor through to the protonated glycosyl species that leads to transferred product, then one should predict that carbohydrates with equatorial anomeric leaving groups should be more reactive donors (higher energy ground states) than those with axial leaving groups, if one assumes that the oxonium ion is the common intermediate for both starting materials (Scheme 1).



Scheme 1. The difference in behavior of α and β glycosides: model of repulsion of nonbonding electrons

However, it is commonly assumed that the transition state for an axial leaving group is stabilized by the very same stereoelectronic force that stabilized the ground state, only more so, since the developing electron deficiency and rehybridization at the anomeric carbon atom in the axial direction induces an even stronger overlap with the filled p-type orbital on the ring oxygen atom. No such overlap is available in the early approach to the equatorial transition state, unless the normal chair of the ground state undergoes quite a bit of twisting so that the leaving group and its σ* orbital are parallel to the p orbital on the ring oxygen atom (Scheme 2).



Scheme 2. The difference in behavior of α and β glycosides: model of interaction between HOMO (p) of oxygen atom and LUMO (σ*) of carbon atom

In a classic experiment where twisting of the equatorial leaving group was inhibited by its presence in a ring, Kirby et. al. have shown that an axial epimer did solvolyze faster than its equatorial counterpart.[5] Questions remain: Is the anomeric effect in the transition state large enough to overcome the same effect in the ground state? Is the rate for axial bond cleavage and subsequent glycosyl transfer faster or slower than equatorial bond cleavage when the necessary twist motion is available to the equatorial bond? Fraser-Reid and Andrews et. al. have presented transition-state calculations which rationalize the faster equatorial bond cleavage by examining this set of questions for methyl glycosides.[6]

In our efforts to develop a useful method for the synthesis of 2-deoxy-β-glycosides, we have encountered chemistry of bicyclic donors **1**−**4** which is useful synthetically and which highlights the complexity of the problem outlined above.[7]

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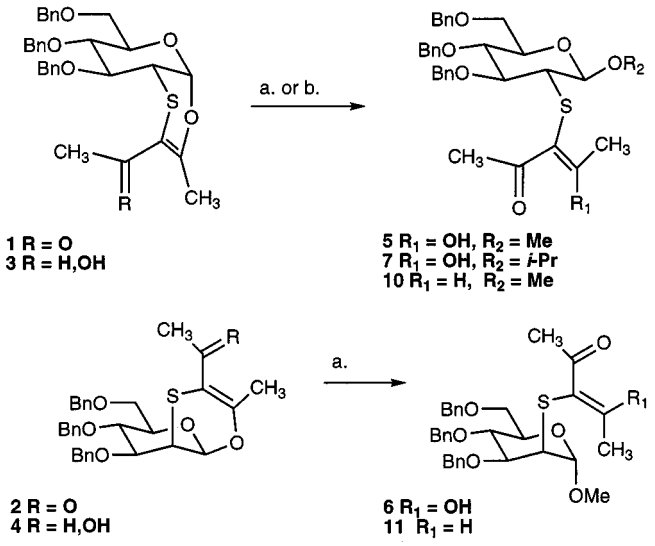
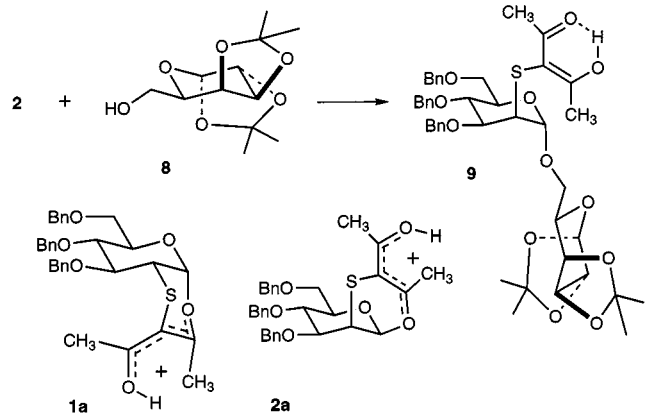
Results and Discussion

When donors **1** and **2** were stirred with methanol plus benzenesulfonic acid as catalyst and the reactions were followed by TLC to completion, the methyl glycosides **5** and **6** were obtained; the latter reaction was apparently complete approximately five times faster than the former. When donor **1** was treated with 2-propanol and methyl triflate as a catalyst, the isopropyl glycoside **7** was formed along with some α anomer (Scheme 3).



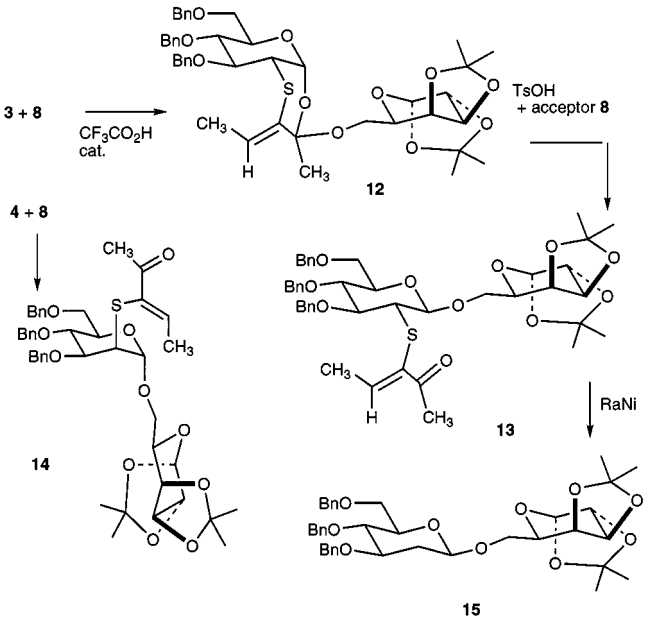
Scheme 3. a. Benzenesulfonic acid, $MeOH/CH_2Cl_2$, room temp.; b. MeOTf, $iPrOH/CH_3NO_2$

When donors **1** and **2** were treated with benzenesulfonic acid and the galactosyl acceptor **8**, only donor **2** underwent reaction to yield disaccharide **9**. This outcome was quite surprising to us since it was not obvious that presumed protonated intermediate **1a** should be dramatically different in stability or reactivity from protonated intermediate **2a** towards acceptor **8** while being similar in reactivity towards methanol (Scheme 4).



Scheme 4. The α-glycosidation of diisopropylidene galactose

When the methanolysis reactions were followed by NMR spectroscopy, an explanation became apparent. Whereas donor **2** smoothly underwent a pseudo-first-order transformation to methyl glycoside **6**, the reaction of donor **1** showed a reasonable inital rate which leveled off. This suggested that **1** plus methanol were in equilibrium with **5**. It was a simple matter to show that pure **5** rapidly converted back into **1** upon treatment with acid. Hence, the reason we did not observe glycosyl transfer to galactose acceptor **8** was that we had not employed a large excess of **8** as had been the case when methanol and 2-propanol had been used in our initial survey. The same test of methyl glycoside **6** showed no reversibility. The unexpected behavior of **1** and **5** was not unique to methanol, since parallel experiments with 2-propanol led to the same reversibility for product **7**. To compare isomers where reversibility was not an issue, we reduced donors **1** and **2** to alcohols **3** and **4**, respectively. Here too, in our initial survey, the benzenesulfonic acid catalyzed methanolysis of equatorial **4** was dramatically faster than that of axial **3**. Indeed, the reaction of **4** was complete within the 3 min, after addition of acid, required to prepare an NMR sample and obtain a spectrum of product **11**. Whereas, the conversion of **3** to **10** required approximately 50 min. In a careful study of the transfer of **3** to the galactose acceptor **8**, we observed that **12** was the initial product when trifluoroacetic acid was the catalyst. Thus, addition of **8** to the double bond of the oxathiin ring was the kinetic product and glycosyl transfer had not taken place at all. Further treatment of **12** with *p*-toluenesulfonic acid and additional acceptor **8** led to the final disaccharide product **13**.[8] To rule out an intramolecular rearrangement as the path from **12** to **13**, we prepared a simple analog of **12** by using 2-propanol and trifluoroacetic acid. Then the intermediate (not shown) was treated with *p*-toluenesulfonic acid and acceptor **8** to again afford final product **13**. In contrast, equatorial donor **4** reacted with acceptor **8** to afford **14** with no detectable intermediate. In analogy to our other glycosyl transfer work, these glycosides could be desulfurized with Raney nickel to produce 2-deoxy-glycosides (Scheme 5).



Scheme 5. Glycosidation using donors **3** and **4**

It is interesting that Sinaÿ et. al. in 1992, proposed that their experiments with anomeric mixtures of simple isopropenyl glycosides, activated by trimethylsilyl triflate actually proceeded by addition of acceptor hydroxy groups to the activated alkene.[9] Although they failed to isolate the intermediate adducts, their evidence and argumentation are convincing. Our results are different from the reports of Chenault[10] and his group. They have executed thorough studies of isopropenyl glycosides, closely related to the Sinaÿ work. However, the Chenault acid catalysis procedure is not exactly the same as that of Sinaÿ. Chenault reports, under some conditions, addition to the double bond in both α- and β-isopropenyl glycosides; but these adducts are *not* then convertible to glycosides, except in the case of water addition. Under other conditions, true glycosides are formed, but apparently not by addition to the double bond. Qualitative rate differences between α and β anomers were not reported by either Sinaÿ or Chenault.

From our series of experiments we conclude that equatorial vinyloxy leaving groups undergo glycosyl transfer faster than axial ones. Thus, whatever the factors are that contribute to the stabilization of the ground state of **1** and **3**, they fail to offer sufficient compensating stabilization of the transition state leading to formation of the oxonium ion required for glycosyl transfer. Hence, in the case of **1**, the reaction is slow and in the case of **3**, the reaction takes an indirect path relative to their counterparts with equatorial leaving groups. It is interesting that our stereoelectronic results are opposite to those of Kirby. The difference must be in Kirby's rigid tricyclic system where the ring cannot twist. Hence, the transition state with the equatorial leaving group is unable to obtain any stabilization. Models clearly show that our system is not nearly as rigid as that of Kirby.

Conclusion

In the course of development of useful methods for the synthesis of 2-deoxyglycosides by a ring-opening approach, we have uncovered differences between the behavior of anomers which were not obviously predictable. A significant difference in rate and mechanism were observed depending on the configuration of the anomeric center and also on the substituents on the bicyclic ring fused to the carbohydrate.

Experimental Section

NMR spectra were recorded with GE QE 300 and JEOL FX 400 instruments with $CDCl_3$ as solvent (*J* values in Hz). High resolution MS data was supplied by the University of Illinois Mass Spectrometry service. Low resolution data was obtained at Hunter on both Hewlett-Packard ESMS and MS instruments. Elemental analyses were performed by Robertson Microlit Laboratories Inc, Madison, NJ. Melting points were determined with a Fisher−Johns melting point apparatus. Optical rotations were determined using a Rudolph Research Autopol III automatic polarimeter. Thin-layer chromatograms were done on precoated TLC sheets of silica gel 60 F254 (E. Merck), and short/long wave ultraviolet light was used to visualize the spots. Chromatotron plates (radial chromatography) were prepared by using Kieselgel 60 PF254, gipshaltig (E. Merck). Flash chromatography was performed with silica gel (230−400 mesh). Dry THF was obtained by refluxing in the presence of sodium metal with benzenophenone as indicator, and dry dichloromethane was obtained by refluxing in the presence of P_2O_5. All other solvents were distilled or bought dry from Aldrich Chemical Co.

1-*O*,2-*S*-(2-Acetyl-1-methyl-1,2-ethenediyl)-3,4,6-tri-*O*-benzyl-2-thio-α-D-glucopyranose (1) and 1-*O*,2-*S*-(2-Acetyl-1-methyl-1,2-ethenediyl)-3,4,6-tri-*O*-benzyl-2-thio-β-D-mannopyranose (2): Refer to the published procedure.[11]

3,4,6-Tri-*O*-benzyl-1-*O*,2-*S*-[2-(1-hydroxyethyl)-1-methyl-1,2-ethenediyl]-2-thio-α-D-glucopyranose (3): To a stirred solution of the cycloadduct **1** (0.31 g; 0.57 mmol; 1 equiv.) in absolute ethanol (80 mL), $NaBH_4$ (0.11 g; 2.8 mmol; 5 equiv.) was added slowly, and the reaction was followed by TLC. After 1 h, the reaction mixture became a clear solution. The mixture was poured into a 125-mL separatory funnel and quenched with 60 mL of water. The product was extracted with three portions of CH_2Cl_2 (55 mL). All of the organic washings were combined, dried with Na_2SO_4, concentrated, and the crude product was purified using a 2-mm chromatotron plate [(1) EtOAc/petroleum ether (10:90), (2) EtOAc/petroleum ether (15:85), (3) EtOAc/petroleum ether (20:80)]. The separation afforded two major fractions, first a major diastereomer (0.150 g, 48%), followed by a second diastereomer (0.073 g, 24%). − Major component in the mixture: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (d, *J* = 4.5, 3 H), 1.5 (d, 1 H), 1.97 (s, 3 H), 3.21 (dd, *J* = 3, 10, 1 H), 3.67−4.01 (m, 5 H), 4.40−5.10 (m, 8 H), 5.52 (d, *J* = 3, 1 H), 7.10−7.50 (m, 15 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.3, 22.5, 43.0, 67.0, 69.5, 73.2, 74.5, 77.0, 79.0, 80.0, 96.0, 103.8, 128−130 (15 C), 138.7, 139.2, 145.4. − IR (neat, cm^{-1}): $\tilde{\nu}$ = 3453 (br.), 3030, 1645, 1496, 1453, 1359, 1222, 738, 698. − $C_{32}H_{36}O_6S$: calcd. 548.2232, found (FAB) 548.2235. − Minor component in the mixture: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (d, *J* = 6.3, 3 H), 1.63 (d, 1 H), 1.90 (s, 3 H), 3.20 (dd, *J* = 3, 10, 1 H), 3.60−4.10 (m, 6 H), 4.40−5.00 (m, 8 H), 5.52 (d, *J* = 3, 1 H), 7.10−7.50 (m, 15 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.6, 22.9, 42.1, 67.6, 68.7, 73, 73.8, 75.5, 79.09, 79.3, 95.0, 103.6, 127.9−128 (15C), 138.4, 138.6. − IR (neat, cm^{-1}): $\tilde{\nu}$ = 3445 (br.), 3030, 1649, 1496, 1453, 1359, 1225, 738, 697. − $C_{32}H_{36}O_6S$: calcd. 548.2232, found (FAB) 548.2235.

3,4,6-Tri-*O*-benzyl-1-*O*,2-*S*-[(2-(1-hydroxyethyl)-1-methyl-1,2-ethenediyl)]-2-thio-β-D-mannopyranose (4): To a stirred solution of **2** (0.31 g; 0.57 mmol; 1 equiv.) in absolute ethanol (35 mL) $NaBH_4$ (0.16 g; 4.3 mmol; 7.6 equiv.) was added and the reaction was followed by TLC. After 4 h, the reaction mixture became a clear solution. The mixture was quenched with water. The product was extracted with three portions of CH_2Cl_2. All of the organic washings were combined, dried with Na_2SO_4, concentrated, and the crude product was purified using a 2-mm chromatotron plate [EtOAc/petroleum ether (25:75)]. The separation afforded two major fractions, first a minor diastereomer (0.07 g, 21%), followed by a second diastereomer (0.18 g, 57%). − Minor diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (d, *J* = 6.3, 3 H), 1.896 (s, 3 H), 2.03 (s, 1 H), 3.57−3.61 (m, 1 H), 3.66 (dd, *J* = 4.5, 0.9), 3.74 (d, *J* = 3.3, 2 H), 3.93 (dd, *J* = 4.5, 8.7, 1 H), 4.06 (dd, *J* = 8.7, 9.2), 4.45−4.90 (3 AB q, 6 H), 5.07 (d, *J* = 1.2, 1 H), 7.10−7.60 (m, 15 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.8, 22.2, 40.9, 67.3, 69.0, 70.8, 73.5, 73.9, 75.3, 80.9, 92.1, 107.1, 127.6−128.6 (15 C), 137.8, 138.4, 139.1. − IR (neat, cm^{-1}): $\tilde{\nu}$ = 3445, 3030, 1656, 1603, 1497, 1454, 1362, 1235, 1911, 873, 736, 698. − $C_{32}H_{36}O_6S$ (538.7): calcd. C 70.05, H 6.54, S 6.23; found C 70.13, H 6.55, S 6.20. − Major

diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (d, *J* = 6.6, 3 H), 1.99 (s, 3 H), 3.55−3.60 (m, 1 H), 3.65−3.90 (m, 5 H), 3.94 (dd, *J* = 4.5, 8.7, 1 H), 4.10 (dd, *J* = 9, 9, 1 H), 4.40−4.90 (3 AB q, 6 H), 5.08 (d, *J* = 1.2, 1 H), 7.10−7.60 (m, 15 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.9, 21.8, 66.9, 68.8, 70.9, 73.5, 73.9, 75.4, 80.6, 92.2, 105.9, 127.6−128.6 (15 C), 137.6, 138.4, 138.5. − IR (neat, cm^{-1}): ṽ = 3441, 3030, 1667, 1602, 1497, 1454, 1362, 1236, 911, 874, 735, 698. − $C_{32}H_{36}O_6S$ (538.7): calcd. C 70.05, H 6.61, S 5.83; found C 70.13, H 6.55, S 6.20.

Methyl 3,4,6-Tri-*O*-benzyl-2-*S*-(2′,4′-dioxopent-3′-yl)-2-thio-β-D-glucopyranoside (5): To a solution of **1** (0.10 g; 0.20 mmol; 1 equiv.), in 0.5 mL of CH_2Cl_2, and 0.5 mL of CH_3OH, benzenesulfonic acid (dried by vacuum distillation after reaction with triflic anhydride) was added (0.03 g; 0.22 mmol; 1 equiv.). After stirring for 18 h (because the reaction did not go to completion), the reaction was quenched with a saturated solution of $NaHCO_3$ (aq). The aqueous fraction was then washed three times with CH_2Cl_2. The organic fractions were mixed and dried with anhydrous Na_2SO_4 and concentrated. The resulting crude product was submitted to column chromatography flash silica gel, EtOAc:hexanes (1:3)] and a white solid (0.06 g; 53%) was obtained. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.40 (s, 6 H), 2.73 (dd, *J* = 8.4, 11, 1 H), 3.36−3.34 (m, 1 H), 3.43 (s, 3 H), 3.44−3.49 (m, 1 H), 3.64 (dd, *J* = 8.8 1 H), 3.72 (d, *J* = 3, 1 H), 4.33 (d, *J* = 8.4, 1 H), 4.50−5.00 (m, 7 H), 7.10−7.60 (m, 15 H), 17.05 (s, 1 H); −^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.8, 56.5, 57.0, 69.0, 73.7, 75.1, 75.2, 79.7, 82.8, 104.4, 105.5, 128.0−128.7 (15 C), 138.2, 138.3, 138.4, 197.6. − EIMS; *m*/*z* (%): 596 (71) [M + H_4N^+], 466 (56) [$C_{28}H_{30}O_5$ + H_4N^+], 434 (21) [$C_{27}H_{38}O_4$ + H_4N^+], 168 (100), 150 (35) [$C_5H_9O_2S$ + H_4N^+], 118 (74). − $C_{33}H_{38}O_7S$ (578.7): calcd. C 68.5, H 6.6, S 5.5; found C 68.4, H 6.6, S 5.8.

Methyl 3,4,6-Tri-*O*-benzyl-2-*S*-(-2′,4′-dioxopent-3′-yl)-2-thio-α-D-mannopyranoside (6): To a solution of **2** (0.05 g; 0.084 mmol; 1 equiv.) in 0.4 mL of dry CH_2Cl_2, and 0.4 mL of dry CH_3OH, benzenesulfonic acid (dried by vacuum distillation after reaction with triflic anhydride) was added (0.02 g; 0.086 mmol; 1 equiv.) and the reaction was left to stir under N_2 for 5.5 h. The mixture was quenched with a saturated solution of $NaHCO_3$ (aq). The aqueous fraction was then washed three times with CH_2Cl_2 (60 mL). The organic fractions were mixed and dried with anhydrous $MgSO_4$ and concentrated to dryness. The residue was purified by flash chromatography [EtOAc/petroleum ether (1:4)] to give pure product (0.02 g; 43%). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.43 (s, 6 H), 3.29 (dd, *J* = 1.2, 4.5, 1 H), 3.31 (s, 3 H), 3.60−3.80 (m, 3 H), 4.00 (dd, *J* = 4.5, 9, 1 H), 4.18 (dd, *J* = 4.5, 9, 1 H), 4.50−4.90 (3 AB q, 6 H), 4.66 (d, *J* = 1.2, 1 H), 7.10−7.44 (m, 15 H), 17.18 (s, 1 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.0, 52.1, 69.4, 72.1, 72.2, 73.5, 74.9, 75.3, 79.5, 100.2, 103.1, 127.6−128.6 (15 C), 138.1, 138.6, 138.6, 198.3; − $C_{33}H_{38}O_7S$ (578.7): calcd. C 68.5, H 6.6, S 5.5; found C 68.8, H 6.5, S 5.7.

Isopropyl 3,4,6-Tri-*O*-benzyl-2-(2′,4′-dioxopent-3′-yl)-2-thio-β-D-glucopyranoside 7 and Its Anomer: The cycloadduct **1** (54 mg, 0.1 mmol) was dissolved in 0.6 mL of dry CH_3NO_2 under N_2; 2-propanol (0.2 mmol) and trimethylsilyl triflate (0.02 mmol) were added. The mixture was stirred for 20 h then quenched with 2 drops of pyridine. Flash chromatography on silica gel was used to purify the crude products, [eluent: petroleum ether/ethyl acetate (4:1), R_f = 0.8] which afforded the product as mixture of the two anomers (74%), only partially separable. ^{1}H NMR of the mixture. − ^{1}H NMR: δ = 1.19 (d, *J* = 8, 3 H), 1.28 (d, *J* = 8, 3 H), 2.40 (s, 3 H, isom.), 2.42 (s, 3 H, isom.), 2.81 (dd, *J* = 12.4, 1 H, 2-H isom.), 2.87 (dd, *J* = 10, 8, 1 H, 2-H isom.), 3.41−3.96 (m, 6 H, 6-H_2 + 3-H + 4-H + 5-H + CH *i*Pr), 4.48−4.99 (m, 7 H, CH_2 Bn + 1-H), 7.08−7.42 (m, 15 H), 16.97 (s, 1 H, OH isom.), 17.12 (s, 1 H, enolic OH isom.) − $C_{35}H_{42}O_7S$ (606.4): calcd. C 69.28, H 6.98; found C 69.07, H 6.97.

Methyl 3,4,6-Tri-*O*-benzyl-2-[(3′*Z*)-2′-oxo-3′-penten-3′-yl]-2-thio-β-D-glucopyranoside (10): To a solution of **3** (either one of the diastereomers) (0.10 g; 0.19 mmol; 1 equiv.) and trimethyl orthoformate (0.03 mL; 0.28 mmol; 1equiv.), in dry CH_2Cl_2 (0.5 mL) and dry CH_3OH (0.5 mL), benzenesulfonic acid (dried by vacuum distillation after reaction with triflic anhydride) was added (0.029 g; 0.19 mmol; 1 equiv.), and the reaction was left to stir under N_2 for 1.5 h, when the reaction was quenched with $NaHCO_3$ (aq). The aqueous fraction was then washed four times with CH_2Cl_2. The organic fractions were combined, dried withr anhydrous $MgSO_4$ and concentrated to dryness. The crude product was purified by flash chromatography [EtOAc/petroleum ether (1:4)] to give pure product (0.07 g; 68%). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.10 (d, *J* = 6.9, 3 H), 2.34 (s, 3 H), 3.09 (dd, *J* = 8.7, 10.8, 1 H), 3.38 (s, 3 H), 3.39−3.9 (m, 5 H), 4.25 (d, *J* = 8.7, 1 H), 4.50−5.00 (3 AB q, 6 H), 8.04 (q, *J* = 6.9, 1 H), 7.10−7.60 (m, 15 H); − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.9, 27.1, 54.0, 56.8, 69.1, 73.7, 75.1, 75.9, 79.3, 83.2, 105.6, 128.0−128.6 (15 C), 138.2, 138.2, 138.4, 144.3, 197.1. − IR (neat, cm^{-1}): ṽ = 3030, 1684, 1601, 1496, 1453, 1355, 1238, 736, 698. −EPIMS; *m*/*z* (%): 580 (38) [M^+ + NH_4]. − $C_{33}H_{38}O_6S$ (562.3): calcd. C 70.44, H 6.81, S 5.70; found C 70.66, H 6.86, S 6.12.

Methyl 3,4,6-Tri-*O*-benzyl-2-[(3′*Z*)-2′-dioxo-3′-penten-3′-yl)-2-thio-α-D-mannopyranoside (11): To a solution of **4** (either one of the diastereomers) (0.11 g; 0.19 mmol; 1 equiv.) and trimethyl orthoformate (0.03mL, 0.28 mmol, 1equiv.) in dry CH_2Cl_2 (0.5 mL) and dry CH_3OH (0.5 mL), benzenesulfonic acid (dried by vacuum distillation after reaction with triflic anhydride) was added (0.03 g; 0.21 mmol; 1.1 equiv.), and the reaction was left to stir under N_2 for 1.5 h, when the reaction was quenched with $NaHCO_3$ (aq). The aqueous fraction was then washed four times with CH_2Cl_2. The organic fractions were combined, dried with anhydrous $MgSO_4$ and concentrated to dryness. The crude product was purified by flash chromatography [EtOAc/petroleum ether (1:4)] to give pure product (0.10 g; 89%). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.10 (d, *J* = 6.9, 3 H), 2.36 (s, 3 H), 3.31 (s, 3 H), 3.60−3.80 (m, 4 H), 3.97 (dd, *J* = 9.9,1 H) 4.15 (dd, *J* = 4.5, 8.7, 1 H), 4.47−4.95 (m, 7 H), 7.15 (q, *J* = 6.9, 1 H), 7.17−7.60 (m, 15 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.5, 27.1, 49.5, 55.1, 69.5, 71.4, 72.0, 73.5, 74.9, 75.2, 79.0, 101.0, 127.5−128.5 (15C), 137.5, 138.5, 138.7, 148.0, 197.0. − IR (neat, cm^{-1}): ṽ = 3030, 1674, 1601, 1496, 1453, 1361, 1236, 738, 699. − EPIMS; *m*/*z* (%): 580 (39) [M^+ + NH_4]. − $C_{33}H_{38}O_6S$ (562.3): calcd. C 70.44, H 6.81, S 5.70; found C 70.11, H 6.65, S 5.70.

Alkene Adduct 12: To a solution of 1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranose (0.22 g; 0.85 mmol; 3.7 equiv.) with powdered 4-Å molecular sieves (0.1 g) in dry CH_2Cl_2 (1 mL) the major diastereomer from the reduction of **1** (0.13 g; 0.23 mmol; 1equiv.) was added, followed by trifluoroacetic acid (0.02 mL; 0.023 mmol; 1/10 equiv.). The reaction mixture was stirred at 25 °C for 5.5 h, then quenched with $NaHCO_3$ (aq), dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel [EtOAc/petroleum ether (1:3)] and the product (0.15 g; 80.4%) was obtained as a clear gel. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (s, 3 H), 1.25 (s, 3 H), 1.36 (s, 3 H), 1.45 (s, 3 H), 1.51 (s, 3 H), 1.76 (d, *J* = 6.6, 3 H), 2.80 (dd, *J* = 10.4, 2.7, 1 H), 3.50−489 (m, 18 H), 5.43 (d, *J* = 5.1, 1 H), 5.51 (d, *J* = 3, 1 H), 6.03 (q, *J* = 6.6, 1 H), 7.12−7.36 (m, 15 H); − ^{13}C NMR (75 MHz,

$CDCl_3$): δ = 15.0, 18.0, 23.0, 24.0, 24.4, 25.0, 25.9, 26.0, 26.1, 42.0, 46.0, 61.0, 62.0, 67.0, 68.0, 68.2, 68.4, 70.6, 70.7, 70.8, 71.6, 72.7, 73.0, 75.0, 75.2, 76.2, 76.3, 78.2, 78.6, 81.0, 92.0, 95.0, 96.0, 97.0, 103.0, 108.5, 108.6, 109.0, 109.4, 112.0, 127.5−130 (15 C), 138.0, 138.0, 138.2, 138.5, 147. − $C_{44}H_{54}O_{11}S$ (790.4): calcd. C 66.80, H 6.90, S 4.10; found C 66.91, H 6.90, S 3.88.

β-Glycoside 13: To a solution of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (0.43 g; 1.64 mmol; 4.2 equiv.) with powdered 4-Å molecular sieves (0.39 g) in dry CH_2Cl_2 (2 mL) the major diastereomer from the reduction of **1** (0.21 g; 0.39 mmol; 1 equiv.) was added, followed by trifluoroacetic acid (0.005 mL; 0.07 mmol; 1/6 equiv.). The reaction mixture was stirred at 25 °C for 5.5 h, then quenched with $NaHCO_3$ (aq), dried with $MgSO_4$ and concentrated in vacuo. The residue obtained was dissolved in dry CH_2Cl_2 (3.5 mL) with powdered 4-Å molecular sieves (0.41 g) and *p*-toluenesulfonic acid (PTSA) was added (0.02 g; 0.09 mmol; 1/4.5 equiv.). The mixture was stirred at 25 °C for 6 h; another fraction of PTSA (0.04 g; 0.1 mmol; 1/2 equiv.) was then added, and after stirring for 1.5 h the reaction was quenched with $NaHCO_3$ (aq), dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel [EtOAc/CH_2Cl_2 (1:2.5)], and the product (0.16 g; 53%) was obtained as a white foamy gel. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (s, 3 H), 1.25 (s, 3 H), 1.34 (s, 3 H), 1.46 (s, 3 H), 2.00 (d, *J* = 6.9, 3 H), 2.28 (s, 3 H), 3.21 (dd, *J* = 8.4, 10.5, 1 H), 3.3−4.78 (m, 18 H), 4.85 (d, *J* = 10.8, 1 H), 5.42 (d, *J* = 4.8, 1 H), 7.00 (q, *J* = 6.9, 1 H), 7.10−7.50 (m, 15 H). − ^{13}C NMR (75 MHz, CDCl3): δ = 16.9, 24.5, 24.9, 26.0, 26.1, 27.0, 52.4, 67.1, 68.8, 70.4, 70.6, 71.4. 73.5, 74.8, 77.4, 78.6, 83.0, 96.2, 104.5, 108.5, 109.2, 127.5, 127.6, 127.7, 127.8, 127.9, 128.2, 138.1, 138.1, 138.4, 144.1, 196.7. − IR (neat, cm^{-1}): $\tilde{\nu}$ = 3030, 1681, 1604, 1454, 1375, 1211, 899, 804, 736, 698. − $C_{44}H_{54}O_{11}S \cdot 3\,H_2O$ (844.4): calcd. C 62.54, H 6.44, S 3.80; found C 62.74, H 6.49, S 4.12.

α-Glycoside 9: To a solution of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (0.16 g; 0.61 mmol; 3 equiv.) and **2** (0.11 g; 0.21 mmol; 1 equiv.) in 3 mL of dry CH_2Cl_2, dry benzenesulfonic acid was added (0.042 g; 0.27 mmol; 1.3 equiv.) and the reaction was left stirring under N_2. After the acid was added, the reaction mixture′s color changed from clear to yellow and then to gray after about 20 min. When no starting material could be observed by TLC, 50 min after the benzenesulfonic acid had been added, the reaction was quenched with $NaHCO_3$ (aq). The organic fractions were dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel [EtOAc/petroleum ether (1:3)], and the product (0.1214 g; 73%) was obtained as an oil. −^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (s, 6 H), 1.41 (s, 3 H), 1.50 (s, 3 H), 2.41 (s, 6 H), 3.27 (dd, *J* = 1.5, 4.4, 1 H) 3.60−3.98 (m, 7 H), 4.06 (dd, *J* = 9.3, 9, 1 H), 4.14 (dd, *J* = 1.5, 5.9, 1 H) 4.21 (dd, *J* = 3.3, 6.9, 1 H), 4. 32 (dd, *J* = 1.9, 3.9, 1 H), 4.40−4.70 (m, 6 H), 4.86 (d, *J* = 5.5, 1 H), 4.88 (d, *J* = 1.9, 1 H), 5.50 (d, *J* = 3.8, 1 H), 7.10−7.40 (m, 15 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.8, 25.0, 25.1, 26.2, 26.3, 52.5, 65.8, 66.1, 69.1, 70.7, 70.8, 71.2, 72.4, 73.4, 74.9, 75.3, 79.4, 96.5, 99.3, 103.3, 108.7, 109.6, 128.2−128.5 (15 C), 138.1, 138.6, 138.7, 198.1. − IR (neat, cm^{-1}): $\tilde{\nu}$ = 3030, 1585, 1497, 1454, 1382, 1256, 1211, 917, 735, 698. − EPIMS; *m/z* (%): 829 (100) [M^+ + Na], 439 (12). − $C_{44}H_{54}O_{12}S$ (806.4): calcd. C 65.49, H 6.74, S 3.97; found C 65.63, H 6.55, S 4.10.

α-Glycoside 14: To a solution of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (0.07 g; 0.28 mmol; 3 equiv.) and the major diastereomer of the reduction of the top face adduct **4** (0.053 g; 0.096 mmol; 1 equiv.) in 3 mL of dry CH_2Cl_2 and 0.012 g of 4-Å molecular sieves, dry benzenesulfonic acid was added (0.016 g; 0.099 mmol; 1 equiv.) and the reaction was left stirring under N_2. After the acid was added, the reaction mixture′s color changed from clear to yellow. When no starting material could be observed by TLC, 15 min after the benzenesulfonic acid had been added, the reaction was quenched using $NaHCO_3$ (aq). The organic fractions were dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel [EtOAc/petroleum ether (1:3)], and the product (0.049 g; 64%) was obtained as an oil. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (s, 3 H), 1.33 (s, 3 H), 1.42 (s, 3 H), 1.51 (s, 3 H), 2.07 (d, *J* = 6.9, 3 H), 2.35 (s, 3 H), 3.60−3.87(m, 6 H), 3.91 (dd, *J* = 1.1, 4.9, 1 H) 4.04 (dd, *J* = 6.9, 1 H), 4.14−4.21(m, 2 H), 4.29 (dd, *J* = 1.7, 1.9, 1 H), 4.50−4.89 (m, 7 H), 4.92 (d, *J* = 0.81, 1 H), 5.49 (d, *J* = 3.8, 1 H), 7.14 (q, *J* = 6.9, 1 H), 7.18−7.40 (m, 15 H); − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.4, 24.8, 25.1, 26.2, 26.3, 27.2, 49.6, 66.1, 66.3, 69.3, 70.9, 71.1, 71.5, 72.3, 73.5, 74.9, 75.1, 78.9, 96.5, 100.0, 108.7, 109.5, 127.0−128.2 (15 C), 137.3, 138.5, 138.7, 138.8, 147.6, 196.9. − EPIMS; *m/z* (%): 803 (100) [M^+ + NH_4]. − $C_{44}H_{54}O_{11}S$ (791.0): calcd. C 66.82, H 6.88, S 4.05; found C 66.70, H 6.71, S 4.07.

1,2:3,4-Di-*O*-isopropylidene-6-*O*-{3′,4′,6′-tri-*O*-benzyl-2′-deoxy-D-*arabino*-hexopyranosyl}-β-D-galactopyranoside (15): To ca. 0.5 g of freshly prepared Raney nickel and washed first with absolute ethanol until pH = 7 was achieved, and then once with benzene, a solution of **13** (0.06 g; 0.082 mmol) in benzene (2 mL) was added and the mixture was stirred for 0.5 h. The Raney nickel was filtered off by using a pad of Celite and the solvent was evaporated. The residue was taken up in EtOAc and again filtered through a pad of Celite and purified by column chromatography [EtOAc/petroleum ether (1:6)] to give the product (0.03 g; 56.4%). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (s, 3 H), 1.32 (s, 3 H), 1.44 (s, 3 H), 1.54 (s, 3 H), 2.45 (dd, *J* = 4.9, 12.5, 1 H), 3.35−3.42 (m, 5 H), 3.53 (dd, *J* = 9.9, 1 H), 4.01 (dd, *J* = 1.8, 7.8, 1 H), 4.08 (dd, *J* = 3.3, 10.8, 1 H), 4.21 (dd, *J* = 1.8, 8.1, 1 H), 4.35 (dd, *J* = 2.4, 5.1, 1 H), 4.47−4.70 (m, 9 H), 4.95 (d, *J* = 10.8, 1 H), 5.55 (d, *J* = 4.8, 1 H), 7.10−7.45 (m, 15 H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.4, 25.0, 26.0, 26.1, 36.6, 67.9, 69.4, 70.5, 70.8, 71.3, 73.5, 74.8, 75.3, 78.2, 79.5, 96.4, 100.4, 108.6, 109.3, 127.5−128.4 (15 C), 138.4−138.6 (3 C). − IR (neat, cm^{-1}): $\tilde{\nu}$ = 3030, 1497, 1454, 1381, 1211, 900, 737, 698. − EIMS; *m/z* (%): 694 (0.4) [M^+ + NH_4], 278 (100), 203 (89), 91 (54). − $C_{39}H_{48}O_{10}$ (676.4): calcd. C 69.2, H, 7.1; found C 69.04, H 7.03.

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