Chemistry of 1-Alkoxy-1-glycosyl Radicals: The Manno- and Rhamnopyranosyl Series. Inversion of α- to β-Pyranosides and the Fragmentation of Anomeric Radicals

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Received July 3, 1995[⊗]

The formation and stereoselective quenching of 1-mannopyranosyl radicals by a tributyltin hydride-mediated intramolecular 1,5-hydrogen abstraction sequence is described. A competing process is 1,4-hydrogen atom abstraction leading principally to glucopyran-2-ulosides. Fragmentation of the anomeric radical resulting in the formation of ring opened products is a problem in certain series. The chemistry is dictated to a considerable extent by the nature of the protecting groups employed with the 4,6-benzylidene series and, for rhamnose, the Ley 3,4-dispiroketal, being particularly susceptible to the 1,4-hydrogen atom abstraction but less to the fragmentation. Photochemical conditions are described, in which these side reactions are practically eliminated, and applied to the inversion of an α- to a β-mannoside in a disaccharide.

Introduction

The preparation and reactions of 1-alkoxy-1-glycopyranosyl radicals has long been a subject of interest in this laboratory. The fascination stems from the high propensity of these pyramidal, σ-type radicals[1] for quenching by thiols and stannanes along the axial direction[2] which permits the highly stereoselective formation of equatorial glycosides,[3,4] most notably the 2-deoxy-β-glycopyranosides of interest to many groups because of their presence in numerous biologically active natural products and due to the problems inherent in their synthesis.[5,6] The 1,2-cis-equatorial type glycosides (β-mannopyranosides and β-rhamnopyranosides) occur widely in nature as, for example, in the common core pentasaccharide of the N-linked glycoproteins,[7] in various mannans and glycosphingolipids,[8] and in lipopolysaccharides,[9] and present a very considerable challenge to the synthetic chemist. Several protocols for the highly stereoselective and even stereospecific generation of 1,2-cis-equatorial glycosides have been developed in recent years,[10] enabling the synthesis of β-mannopyranoside containing oligosaccharides,[11] but none are completely general and there is still much leeway for improved methods. We, and Curran and co-workers,[12] reasoned that preparation of the much more readily available α-mannopyranosides,[13] followed by intramolecular hydrogen atom abstraction to give the

[⊗] Abstract published in *Advance ACS Abstracts,* December 15, 1995.

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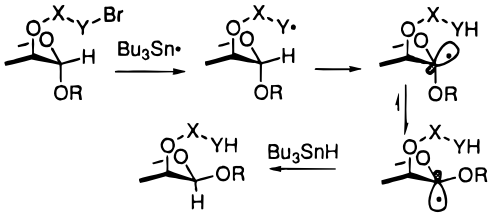
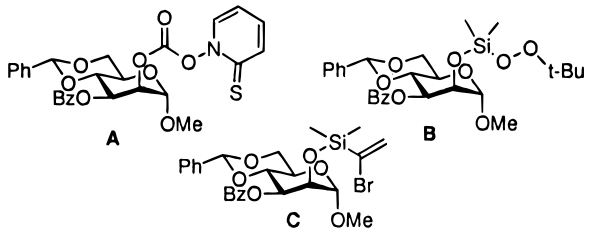
Scheme 1



1-alkoxy-1-mannopyranosyl radical, and finally axial quenching by a stannane (Scheme 1) would represent an attractive entry into β-mannopyranosides. We set out below the successful implementation of this reaction scheme and describe a number of interesting side reactions encountered in the course of this work.[14]

Results and Discussion

Intramolecular δ-hydrogen atom abstraction through six-membered cyclic transition states by aminium radical cations and alkoxy radicals has a long and venerable history[15−17] and is supported by calculations.[18] It was therefore natural that our early attempts at implementation of the above scheme focused on the generation of typical, oxygen centered, electrophilic radicals suitably disposed so as to abstract the anomeric hydrogen atom through six-membered cyclic transition states. In such a system the radical precursor must necessarily be bound to the carbohydrate moiety via the hydroxy group at C-2 which limits the choice somewhat. Attempts at the in situ generation of systems such as **A**[19,20] and **B**,[21] followed by photolysis and/or thermolysis, provided no evidence for anomeric hydrogen atom abstraction, but it was never clear whether these failures were due to the instability of the radical precursor, or alternative modes of decomposition of any radicals generated. Attention was therefore turned to more stable tethers and, following their highly successful application in δ-hydrogen atom abstractions by the Curran[22] and other groups,[23] the use of vinyl radicals.[24] Of the various possibilities, the most readily prepared was **C** but here, too, no abstraction of the anomeric hydrogen was observed on treatment with tributyltin hydride and AIBN despite the use of syringe pump techniques. A similar result was noted by Curran.[12] Given the success of Curran at δ-hydrogen atom abstraction with bromovinyl silyl ethers in less conformationally rigid systems,[22] this latter failure was ascribed to the relative rigidity of the system and the inability of the intermediate vinyl radical to access the required transition state. We therefore sought to construct a tether with the least possible conformational constraints. This essentially meant that the abstracting radical would have to be a simple, nucleophilic, alkyl radical. Intramolecular hydrogen atom abstraction in carbohydrates by alkyl radicals, other than from the anomeric position, had previously been reported by De Mesmaeker and co-workers.[25,26]



To this end, treatment of the alcohol **1** with 1,2-dibromo-2-methoxypropane, prepared in situ from 2-methoxypropene and bromine, and *N*,*N*-dimethylaniline in CH_2Cl_2 gave the mixed acetal **2** in 62% isolated yield. This acetal was isolated as an approximately equimolar mixture of two diastereomers, which we have thus far been unable to separate. Tributyltin hydride and AIBN were added dropwise to a solution of this acetal in benzene at reflux under Ar resulting in the formation of a relatively complex reaction mixture which was then stirred with moist silica gel to achieve hydrolysis of the O-2 acetal functionality. Subsequent silica gel chromatography enabled the isolation of three major products (Table 1, entry 1) and a number of minor byproducts. The major products were the desired β-mannoside **3**, the

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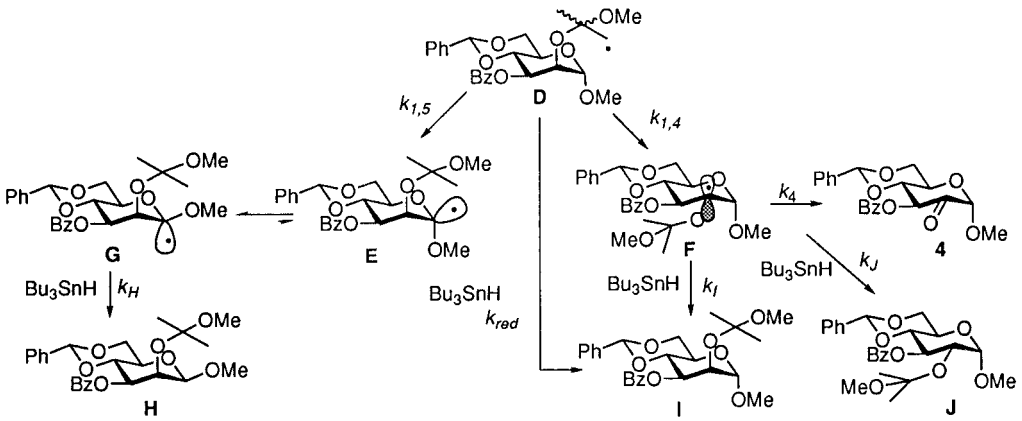
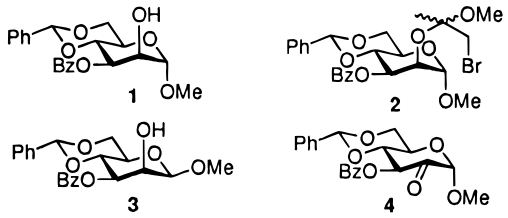
Scheme 2



α-mannoside **1**, and the ketone **4**. Repetition of the reaction with tributyltin deuteride gave the same three major products (Table 1, entry 2). Deuterium was incorporated into **3** at the anomeric site, but not into either **1** or **4**. Evidently, **3** arises from the desired δ-hydrogen atom abstraction process, inversion of the anomeric radical, and axial quenching by the stannane. The α-mannoside **1** is the result of failure of the δ-hydrogen atom abstraction process, rather than of equatorial quenching of any anomeric radical as shown by the lack of incorporation of deuterium. The formation of the ketone **4** was somewhat unexpected as 1,4-hydrogen atom abstraction reactions, through five-membered cyclic transition states, are much less common than their 1,5-counterparts.[27] Its structure was established by synthesis of an authentic sample by TPAP/NMNO[28] oxidation of **1**, and the anomeric configuration was rigorously established by the double irradiation of H-3 leading to the nuclear Overhauser enhancement of H-5 and of the anomeric methoxy group.



The results are best discussed in terms of Scheme 2. The initial radical **D** abstracts hydrogen from C-1 to give **E** or from C-2 to give **F** with the ratio of **E** to **F** being $k_{1,5}/k_{1,4}$. Radical **E** inverts to **G** which is quenched by the stannane at rate $[Bu_3SnH]k_H$ to give **H** which, after deprotection, provides **3**. Radical **F**, on the other hand, either suffers fragmentation to the ketone **4** with rate constant k_4 or is quenched by the stannane to give **I** and **J** with rates $[Bu_3SnH]k_I$ and $[Bu_3SnH]k_J$, respectively. Product **I**, the precursor to **1**, is also formed by direct quenching of radical **D** by the stannane with rate $[Bu_3SnH]k_{red}$. An increase in the stannane concentration should (i) increase the yield of **I** (→ **1**) by increasing the rate of quenching of **D** and of **F**; (ii) decrease the yield of **4**, by trapping of **F**; (iii) decrease the yield of **H** (→ **3**), by trapping of **D**. The ratio of **I** to **J** will evidently depend on the ratio of the rate constants k_I and k_J as well as on the concentration of stannane, with less **J** at higher concentrations.[29] Only minor amounts of the gluco-isomer **5**, from hydrolysis of **J**, are seen at low concentration of stannane.

To improve the ratio of **3**:**1** it is necessary to slow down the quenching of the initial radical **D** by the stannane. This effectively means reducing the concentration of the stannane or employing a poorer hydrogen atom donor. Attempts at dropwise addition of the stannane over significantly longer periods than the 5 h of the initial reaction were unproductive, presumably owing to the failure of one or more of the intermolecular steps in the chain sequence under such dilute conditions. Thus attention was turned to other methods. A common approach to maintaining a minimum stannane concentration is the use of a catalytic quantity of a stannyl chloride in the presence of a borohydride reducing agent.[30,31] Heating **2** in *tert*-butyl alcohol at reflux with a catalytic quantity of trimethyltin chloride and sodium cyanoborohydride under AIBN initiation provided a cleaner reaction mixture, devoid of the ketone **4**, but with no improvement in the **3:1** ratio (Table 1, entry 3). When tris(trimethylsilyl)silane,[32] with its lower reactivity toward the quenching of simple nucleophilic alkyl radicals,[33] was employed in place of the stannane, as much as 45% of the substrate **2** was recovered indicating a breakdown of the chain reaction (Table 1, entry 4). More surprising, however, was the absence of **3** but not of **4** from the reaction mixture. Use of an excess of tris(trimethylsilyl)silane resulted in consumption of the substrate and the isolation of **1** and **4**, but again not of **3** (Table 1, entry 5). With hindsight (*vide infra*) the

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(28) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

(29) The quenching stereoselectivity of such radicals must be a function of the trap employed, of the radical conformation, and of any C-2 substituent. The methyl 2-deoxy-α-glucopyranos-2-yl radical adds to activated alkenes with good selectivity from the equatorial site, but related C-2 substituted radicals are trapped with moderate selectivity along the axial direction by both oxygen and tributyltin deuteride. (a) Giese, B.; Groninger, K. *Tetrahedron Lett.* **1984**, *25*, 2743. (b) Moutel, S.; Prandi, J. *Tetrahedron Lett.* **1994**, *35*, 8163. (c) Horton, D.; Priebe, W.; Sznaidman, M. L. *J. Org. Chem.* **1993**, *58*, 1821.

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(31) The effectiveness of this protocol in 1,5-hydrogen atom abstractions with vinyl and aryl radicals has been demonstrated by Curran.[22]

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(33) The rate constants for the trapping of primary alkyl radicals by Bu_3SnH and TMS_3SiH respectively at 25 °C are 2.4×10^6 and 1.4×10^5 s^{-1}. (a) Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739. (b) Chatgilialoglu, C.; Dickhaut, J.; Giese, B. *J. Org. Chem.* **1991**, *56*, 6399.

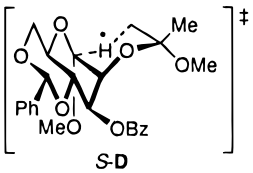
Table 1. Intramolecular Hydrogen Atom Abstraction Reactions with 2

entry	substrate concn (mM)[a]	reagent (mol equiv)	reagent concn (mM)[b]	addition time (h)	additional reaction time (h)	temp (°C)	α-mannoside **1**: % yield	β-mannoside **3**: % yield	ketone **4**: % yield
1	18.5	Bu_3SnH (1.3)	97	5	1	78	34	30	22
2	18.5	Bu_3SnD (1.3)	97	5	1	78	35	31 {[1-^{2}H]-**3**}	22
3	50	Me_3SnCl (0.1) + $NaBH_3CN$ (2.0)	5	0	4	~80	52	31	0
4[c]	46.5	TMS_3SiH (1.0)	9	0.25	1	78	35	0	10
5	23	TMS_3SiH (2.3)	125	0.25	1	78	60	0	22
6	31	Bu_3SnH (1.4)	65	5 min	1	78	57	34	0
7	18.5	Bu_3SnH (1.0)	18.5	0	1.5	rt + *hν*	59	30	0

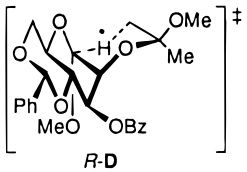
[a] Represents the initial concentration of the substrate, before addition of Bu_3SnH. [b] Represents the concentration of the Bu_3SnH solution added to the substrate. [c] 45% of unreacted **2** was also recovered from this reaction.

absence of **3** is readily understood in terms of the fragmentation of the anomeric radical **E/G** before quenching by the slow hydrogen atom donor TMS_3SiH. Two further experiments (Table 1, entries 6 and 7) involved the rapid addition over 5 min of tributyltin hydride to **2** in benzene at reflux, and the photolysis at room temperature of **2** and tributyltin hydride, respectively. Both of these experiments were clean, and devoid of the ketone **4**, with the only products being **1** and **3**. Thus, changing the concentration of tin hydride (or silane) changes the ratio of **1** and **3** as expected. It also changes the ratio of **3** and **4**.

The formation of **2** as a 1:1 diastereomeric mixture prompts the interesting question of whether one epimer is responsible for the 1,5-hydrogen atom abstraction leading to **E** and so **3**, and the other the 1,4-abstraction resulting in the formation of **F** and so **4**. Thus, it is readily seen that the *S*-isomer of radical **D** may adopt a chairlike transition state for the hydrogen atom abstraction in which the requirements of the anomeric effect are fully satisfied. On the other hand, the *R*-isomer has the pendant methoxy group equatorial to the chairlike transition state, which is consequently higher in energy perhaps promoting a switch to the more flexible five-membered transition state of the 1,4-abstraction. Unfortunately, our inability at present to separate the two diastereomers has prevented any experimental investigation of this hypothesis.[34]

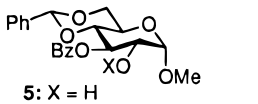


S-**D**

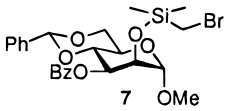


R-**D**

Looking to broaden the scope of this chemistry the methyl α-glucopyranosyl system **6** was prepared by the standard method from **5** and subjected, in benzene at reflux, to dropwise addition of tributyltin hydride and AIBN. After hydrolysis, no evidence for the formation of a β-glucoside was found and the only product isolated, aside from recovered **5**, was the ketone **4** in 70% yield. Evidently, in this example 1,4-hydrogen atom abstraction occurs exclusively. The fickleness of the system was further demonstrated when reduction of the (bromomethyl)silane **7** with tributyltin hydride (and Bu_3SnD) and AIBN failed to provide any evidence for intramolecular hydrogen atom abstraction, be it of the 1,4- or 1,5-type. These failures are probably best interpreted in terms of relatively minor structural modifications[35] preventing attainment of the transition state for 1,5-hydrogen atom abstraction rather than, for **7**, any stabilization afforded to the abstracting radical by the silicon atom.[36]



5: X = H
6: X = C(OMe)(CH_2Br)Me



7

In the rhamnopyranosyl series, the mixed acetal **11**, readily prepared from **8** in the normal manner, was treated with tributyltin hydride and AIBN in benzene to give a mixture of products, which after hydrolysis with Dowex, yielded **8**, **14**, **15**, and **18** (Table 2, entry 1). The first of these (**8**) results from quenching of the initial radical. The second (**14**), somewhat unexpectedly, was shown by NMR spectroscopy and mass spectrometry to be methyl 3-*O*-benzoyl-4-deoxy-α-L-rhamnopyranoside. This product must arise from a highly unusual, but not unprecedented,[37,38] attack of the stannyl radical on the carbonyl oxygen of the benzoyl ester followed by fragmentation. The anticipated β-glycoside **15** was isolated in a meager 3% yield. The major product, assigned structure **18**, results from the fragmentation of the anomeric radical before quenching by the stannane. In order to provide a cleaner reaction mixture, devoid of the deoxygenation type product, the 3,4-di-*O*-benzylrhamnopyranoside **9** was prepared and converted to the mixed acetal **12**. Treatment of this substance with tributyltin hydride and AIBN, either by rapid addition, as to **11**, or dropwise over 4 h (Table 2, entries 2 and 3) resulted in isolation of the reduction product **9**, the fragmentation product **19**, and for the rapid addition only the β-rhamnoside **16**. The absence of any ketone, formed by 1,4-hydrogen atom abstraction and fragmentation of the 2-pyranosyl radical, was again noteworthy. The very significant yields of ring opened products **18** and **19** from these experiments suggested that the 1-alkoxy-1-glycosyl radical in the rhamnopyranose series undergoes fragmentation much more readily than that in the mannopy-

(34) For a discussion of a similar anomeric effect in radical cyclizations see: Lopez, J. C.; Gomez, A. M.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1994**, 1533.

(35) The SiOC bond angle in simple silyl ethers is typically ~120° and the Si−O bond length 1.64 Å: Sheldrick, W. S. In *The Chemistry of Organosilicon Compounds*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1989; Vol. 1, p 227 and references therein.

(36) For a recent discourse on the stabilization of carbon radicals by α- and β-silicon see: Hwu, J. R.; Chen, B.-L.; Shiao, S.-S. *J. Org. Chem.* **1995**, *60*, 2448 and references therein cited.

(37) For the cleavage tertiary benzoate esters with Bu_3SnH see: Redlich, H.; Neumann, H.-J.; Paulsen, H. *Chem. Ber.* **1977**, *110*, 2911.

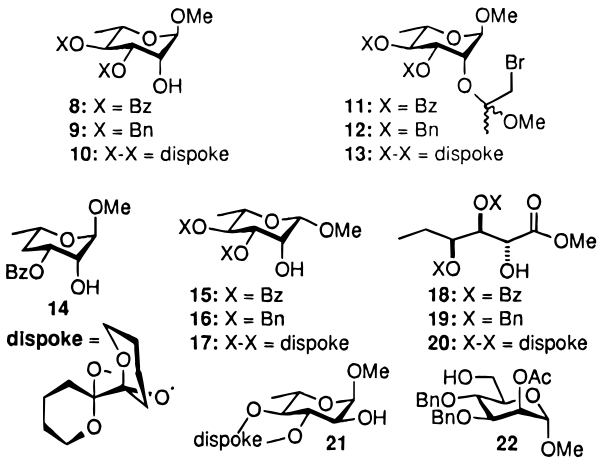
(38) It is possible that the cleavage of this particular benzoate ester by Bu_3SnH is accelerated by the β-oxygen effect: (a) Barton, D. H. R.; Hartwig, W.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1982**, 447. (b) Crich, D.; Beckwith, A. L. J.; Chen, C.; Yao, Q.; Davison, I. G. E.; Longmore, R. W.; Anaya de Parrodi, C.; Quintero-Cortes, L.; Sandoval-Ramirez, J. *J. Am. Chem. Soc.* **1995**, *117*, 8757. (c) Roberts, B. P.; Steel, A. J. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2411.

Table 2. Fragmentation and Inversion Reactions

entry	substrate	substrate concn (mM)[a]	Bu_3SnH equiv/concn (mM)[b]	addition time (h)	additional reaction time (h)	temp (°C)	α-mannosides (% yield)	β-mannosides (% yield)	fragmentation (% yield)	1,4-H abstr. (% yield)
1	**11**	25	1.5/340	0	10	78	**8** (29), **14** (13)	**15** (3)	**18** (43)	–
2	**12**	25	1.5/100	0	10	78	**9** (51)	**16** (8)	**19** (17)	–
3	**12**	25	1.5/160	4	4	78	**9** (64)	**16** (0)	**19** (18)	–
4	**13**	25	1.5/190	0	7	78	**10** (68)	**17** (4)	**20** (9)	–
5	**13**	25	1.5/130	6	3	78	**10** (37)	**17** (6)	**20** (42)	**21** (15)
6	**28**	25	1.5/120	5	3	78	**24** (57)	**32** (0)	**39** (31)	–
7	**29**	25	1.5/120	5	3	78	**25** (68)	**33** (3)	**36** (15)	–
8	**30**	25	1.5/120	5	3	78	**26** (63)	**34** (0)	**37** (14)	–
9	**31**	25	1.5/120	5	3	78	**27** (74)	**35** (0)	**38** (13)	–
10	**2**	25	1.5/120	5	3	78	**1** (19)	**3** (21)	**42** (9)	**4** (6)
11	**11**	13	1.2/120	0	3	rt, hυ	**8** (89)	**15** (11)	**18** (0)	–
12	**11**	13	1.2/120	2	3	rt, hυ	**8** (75)	**15** (25)	**18** (0)	–

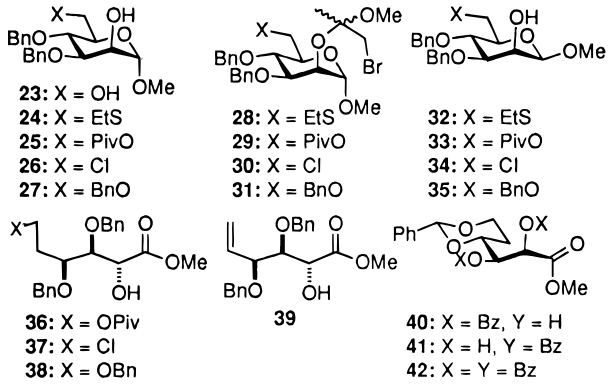
[a] Represents the initial concentration of the substrate, before addition of Bu_3SnH. [b] Represents the concentration of the Bu_3SnH solution added to the substrate.

ranose series initially studied. We reasoned that this might be the consequence, in the absence of the severely constraining 4,6-*O*-benzylidene group, of a more conformationally mobile pyranose ring being able to adopt the geometry required for fragmentation or, alternatively, that of the absence of a polar substituent at C-6.



To probe the conformation question we turned to the 1,2-dispiroketal (dispoke) blocking group introduced by Ley for the protection of trans-diols. Treatment of methyl α-L-rhamnopyranoside with 2,2′-bis(dihydropyran) as described by Ley, followed by workup with ethylene glycol, led to a complex mixture of products from which **10** was isolated in low but sufficient yield.[39] Reaction with dibromomethoxypropane in the usual manner then gave **13**. Rapid addition of tributyltin hydride to **13** at reflux in benzene gave 4% of the β-rhamnoside **17** and 9% of the fragmentation product **20** together with a substantial proportion of the reduction product **10**. Dropwise addition of the stannane over 6 h resulted in the isolation of 42% of the fragmentation product, 6% of the β-rhamnoside, and 15% of the 6-deoxygluco-, or α-quinovopyranoside (**21**), evidence for 1,4-hydrogen atom abstraction (Table 2, entries 4 and 5).

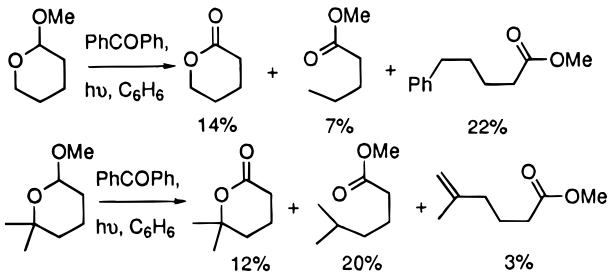
In order to probe the role of electronegative substituents at C-6 on the fragmentation reaction the mannose derivatives **24**–**27** were synthesized by standard means from **22** or **23** and converted to the mixed acetals **28**–**31**. These derivatives, in benzene at reflux, were then treated with tributyltin hydride and AIBN dropwise over 5 h. The results were approximately the same in each case with the isolation of the simple reduction product and of the fragmentation product. The similar yields of the fragmentation products **36**, **37**, and **38** (Table 2, entries 7–9), and indeed that of **19** obtained under very similar conditions (Table 2, entry 3), suggests that the nature of the substituent at C-6 has no significant effect on the fragmentation reaction. The 4,6-benzylidene derivative **2** was also subjected to these reaction conditions. As before, the reaction mixture was complex, but careful chromatography enabled isolation of the reduction product **1**, the β-mannoside **3**, the ketone **4**, and an inseparable mixture of two isomeric benzoates **40** and **41**, benzoylation of which gave the dibenzoate **42** (Table 2, entry 10). It is noteworthy that only with the benzylidene acetal **2**, the dispiroacetal **13** (Table 2, entries 5 and 10) and, in the gluco-series, the benzylidene acetal **6** is any evidence for hydrogen atom abstraction at C-2 observed. We therefore conclude that imposing a relatively rigid chairlike conformation on the pyranose ring promotes somewhat the 1,4-abstraction reaction. Finally, in this series of reactions, we subjected **11** to the photolytic conditions found to be optimum for **2**. As indicated in Table 2 (entries 11 and 12) these reactions were much cleaner, and slow addition of the tributyltin hydride over 2 h resulted in a 1:3 mixture of β- and α-rhamnopyranosides without complicating fragmentation or deoxygenation reactions.



The fragmentation of the 1-alkoxy-1-glycosyl radicals, and the effect of the protecting groups on it, is of some interest. Such radicals may cleave in the exocyclic mode to give the aglycone radical and a lactone, or in the endocyclic mode to give esters, as observed here. 2-Meth-

(39) (a) Ley, S. V.; Boons, G.-J.; Leslie, R.; Woods, M.; Hollinshead, D. M. *Synthesis* **1993**, 689. (b) Edwards, P. J.; Entwhistle, D. A.; Genicot, C.; Ley, S. V.; Visentin, G. *Tetrahedron Asym.* **1994**, *5*, 2609.

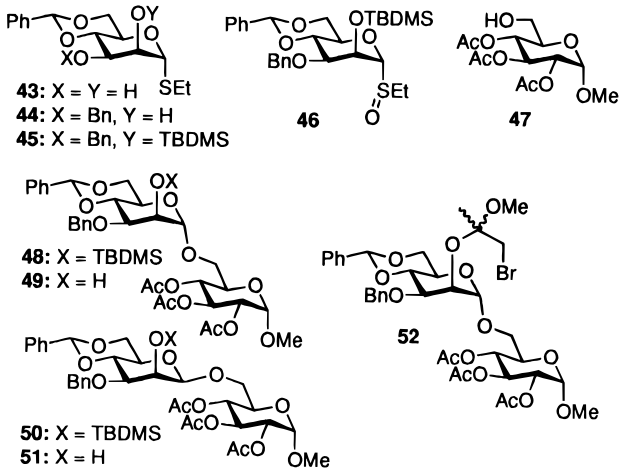
Scheme 3



oxy-2-tetrahydropyranyl radicals were initially thought to undergo preferential fragmentation in the exocyclic mode to give δ-valerolactone:[40] a preference which was explained in terms of stereoelectronic effects with the required coplanarity between the singly occupied orbital and the σ*-orbital of the scissile bond being more readily accessible in the exocyclic mode.[41] However, subsequent work showed endocyclic cleavage to be a competing, and even the major, pathway (Scheme 3).[2a,42] Increased substitution at C-6 of the 2-tetrahydropyranyl system (corresponding to C-5 in the carbohydrate numbering scheme) favors endocyclic fragmentation (Scheme 3).[43]

If we assume the anomeric radical to be fully pyramidalized then, in order for the singly occupied orbital to be coplanar with the scissile bond, fragmentation must occur from the higher energy configuration with the aglycone axial and the radical equatorial. The inversion of configuration of such radicals is estimated[1a] to have a barrier of <6 kcal mol^{-1} and so such a situation is certainly possible. Alternatively, a boat or twist-boat conformation must be invoked. Presumably, the slower fragmentation in the 4,6-benzylidene series reflects a subtle conformational effect, possibly compounded by some residual π-character in the anomeric radical, whereby the configuration and conformation required for fragmentation is of higher energy than in the other series studied.

Finally, having defined optimum conditions for mannoside inversion, we turned to the synthesis of a disaccharide. Ethyl α-thiomannoside[44] was converted to its 4,6-benzylidene derivative **43**, with benzaldehyde dimethylacetal, which was subsequently benzylated selectively at O-3, via its 2,3-(dibutylstannyl)acetal,[45] to give **44** in 80% yield. Silylation with *tert*-butyldimethylsilyl triflate then gave **45** in 95% yield. In view of the somewhat sterically hindered nature of the glycosyl donor we chose to adopt the Kahne sulfoxide glycosylation procotol[46] for coupling to the aglycone. Treatment of **45** with magnesium monoperoxphthalate[47] in aqueous THF gave the sulfoxide **46** in 90% yield as an unassigned diastereomer. Treatment of a mixture of **46**, the aglycone **47**, and 2,6-di-*tert*-butyl-4-methylpyridine in ether at −78 °C with triflic anhydride followed by warming to 0 °C over 1 h enabled the isolation of the α-mannoside **48** and its β-isomer **50** in 58 and 6% yield, respectively. Desilylation with TBAF in THF then gave the hygroscopic disaccharide **49** in 86% yield. Reaction of **49** with dibromomethoxypropane according to the standard protocol provided the radical precursor **52**. Photolysis of **52** at room temperature with dropwise addition of tributyltin hydride and AIBN over 2 h, followed by stirring with Dowex resulted in the isolation of a mixture of the α- and β-mannosides **49** and **51** in the ratio 3:1. The reaction mixture was devoid of any byproducts arising from hydrogen atom abstraction from C2 and fragmentation of the anomeric radical. The β-mannoside **51** was identical with an authentic sample obtained by desilylation of **50**.



In conclusion, conditions have been established for the inversion of α- to β-mannosides without interference by detrimental side reactions. The β:α ratio is governed by the intramolecular hydrogen atom abtraction step which at present is relatively inefficient. In order for preparatively useful β:α-ratios to be obtained it will be necessary to improve the rate of this step.

Experimental Section

General. Melting points were recorded on a Thomas hotstage microscope and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were run in $CDCl_3$ at 300 and 75 MHz, respectively. Chemical shifts are downfield from tetramethylsilane as internal standard. All solvents were dried and distilled by standard procedures. All reactions were run under a dry nitrogen or argon atmosphere. THF was distilled, under N_2, immediately prior to use from sodium benzophenone ketyl. Ether refers to diethyl ether. Microanalyses were conducted by Midwest Microanalytical, Indianapolis, IN.

Methyl 3-*O*-Benzoyl-4,6-benzylidene-α-D-mannopyranoside (1). Alcohol **1** was prepared essentially according to the literature protocol.[48] Mp 130−132 °C, lit.[48] mp 131−132 °C; $[\alpha]_D = -24°$ (c = 1.3, CH_2Cl_2); ^{1}H-NMR, δ: 3.39 (s, 3H), 3.85−4.00 (m, 2H), 4.20−4.40 (m, 3H), 4.79 (d, 1H, J = 1.5 Hz), 5.56 (dd, 1H, J = 3.25, 10.23 Hz), 5.60 (s, 1H), 7.25−7.70 (m, 8H), 8.05−8.15 (m, 2H); ^{13}C-NMR, δ: 55.0, 63.7, 68.7, 69.5, 71.4, 76.0, 101.5, 101.7, 126.1, 128.1, 128.3, 128.9, 129.7, 133.1, 137.1, 165.6.

Preparation of Carbohydrate 1-Bromo-2-methoxy-2-propyl Ethers. Method A. The substrate (1 mmol) was dissolved in CH_2Cl_2 (2 mL) under Ar and cooled to 0−5 °C in an ice−water bath. 2-Methoxypropene (104 μL, 1.1 mmol) and *N*-bromosuccinimide (0.196 g, 1.1 mmol) were then added, and

(40) Yamagashi, T.; Yoshimoto, T.; Minami, K. *Tetrahedron Lett.* **1971**, 2795.
(41) (a) Perkins, M. J.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 2* **1975**, 77. (b) Rynard, C. M.; Thankachan, C.; Tidwell, T. T. *J. Am. Chem. Soc.* **1979**, *101*, 1196.
(42) McKelvey, R. D. *Carbohydr. Res.* **1975**, *42*, 187.
(43) Bernasconi, C.; Cottier, L.; Descotes, G. *Bull. Soc. Chim. Fr.* **1977**, 101.
(44) Pedretti, V.; Veyrieres, A.; Sinay, P. *Tetrahedron* **1990**, *46*, 77.
(45) David, S.; Hanessain, S. *Tetrahedron* **1985**, *41*, 643.
(46) (a) Kahne, D.; Walker, S.; Cheng, Y.; Engen, D. V. *J. Am. Chem. Soc.* **1989**, *111*, 6881. (b) Kim, S.-H.; Augeri, D.; Yang, D.; Kahne, D. *J. Am. Chem. Soc.* **1994**, *116*, 1766. (c) Raghavan, S.; Kahne, D. *J. Am. Chem. Soc.* **1993**, *115*, 1580. (d) Sliedregt, L. A. J. M.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1994**, *35*, 4015.
(47) Heaney, H. *Aldrichim. Acta* **1993**, *26*, 35.
(48) Seymour, F. R. *Carbohydr. Res.* **1974**, *34*, 65.

the mixture was stirred at ice bath temperature for 1 h and then warmed to room temperature and stirred for an additional 24 h. The reaction mixture was then diluted with CH_2Cl_2 (10 mL) and quenched with saturated aqueous $NaHCO_3$ (4 mL). The organic layer was washed with brine (2 × 3 mL), dried ($MgSO_4$), and concentrated under vacuum. The crude reaction mixture typically consisting of the product (20−25%) and unreacted substrate (75−80%) was then purified by chromatography on silica gel, eluting with 5−8/1 hexane/ethyl acetate, to give the desired ethers as approximately 1:1 mixtures of diastereomers.

Preparation of Carbohydrate 1-Bromo-2-methoxy-2-propyl Ethers. Method B. To a stirred solution of 2-methoxypropene (0.7−0.75 M, 1.5 equiv with respect to substrate) in CH_2Cl_2 under Ar at −78 °C was added bromine (1.5 equiv with respect to substrate) dropwise via a syringe. The solution was stirred for 30 min at −78 °C before an ice cold solution of the substrate (0.8 M) and *N*,*N*-dimethylaniline (1.5 equiv with respect to substrate) in CH_2Cl_2 was added dropwise over 10 min. The reaction mixture was stirred for 2 h at −78 °C then for 12−24 h at room temperature before dilution with CH_2Cl_2, washing with saturated aqueous $NaHCO_3$ and brine, and drying ($MgSO_4$). After evaporation of the volatiles chromatography on silica gel (eluent: typically hexane/ethyl acetate 50/1 → 10/1 → 3/1) provided the desired ethers as approximately 1:1 mixtures of diastereomers typically in 60−70% yield. Residual substrate could be recovered as a more polar fraction.

Methyl 4,6-*O*-Benzylidene-3-*O*-benzoyl-2-*O*-(1-bromo-2-methoxy-2-propyl)-α-D-mannopyranoside (2). A 1:1 diastereomeric mixture prepared by protocol B from **1** in 62% yield as a white foam. $[\alpha]_D = -40°$ ($c = 2.86$); ^{1}H-NMR, δ: 1.51 + 1.37 (2 × s, 3H), 3.28 + 3.19 (2 × s, 3H), 3.43 + 3.40 (2 × s, 3H), 3.29−3.58 (m, 2H), 3.85−4.00 (m, 2H), 4.19−4.35 (m, 2H), 4.43−4.48 (m, 1H), 4.80 + 4.77 (2 × d, $J = 1.7$ Hz, 1H), 5.54 + 5.53 (2 × dd, $J = 3.1$, 10.5 Hz, 1H), 5.64 + 5.63 (2 × s, 1H), 7.26−7.35 (m, 3H), 7.35−7.50 (m, 4H), 7.50−7.62 (m, 1H), 8.00−8.15 (m, 2H); ^{13}C-NMR, δ: 21.4, 22.0, 35.2, 49.5, 50.1, 55.1, 55.9, 63.8, 64.0, 68.9, 68.92, 70.2, 70.3, 70.4, 70.6, 76.1, 76.8, 100.6, 101.0, 101.3, 101.6, 101.69, 101.7, 126.1, 128.2, 128.3, 128.4, 128.9, 129.7, 129.9, 130.1, 133.0, 133.1, 137.3, 165.8, 166.0; υ_{max}: 1721, 1382, 1096 cm^{-1}. Anal. Calcd for $C_{25}H_{29}BrO_8$: C, 55.87; H, 5.44. Found: C, 55.49; H, 5.54.

Methyl 4,6-*O*-Benzylidene-3-*O*-benzoyl-2-*O*-(1-bromo-2-methoxy-2-propyl)-α-D-glucopyranoside (6). A 1:1 diastereomeric mixture prepared by protocol A from **5**[49] in 22% yield as a white foam. $[\alpha]_D = +26.3°$ ($c = 0.3$); ^{1}H-NMR, δ: 1.48 + 1.46 (2 × s, 3H), 3.12−3.60 (m, 2H), 3.29 + 3.24 (2 × s, 3H), 3.47 (s, 3H), 3.70−3.83 (m, 2H), 3.91−4.04 (m, 1H), 4.04−4.18 (m, 1H), 4.30−4.36 (m, 1H), 4.93 + 4.89 (2 × d, $J = 3.5$ Hz, 1H), 5.53 + 5.52 (2 × s, 1H), 6.78 + 6.75 (2 × dd, $J = 9.3$, 9.5 Hz, 1H), 7.20−7.35 (m, 3H), 7.34−7.50 (m, 4H), 7.50−7.62 (m, 1H), 8.00−8.15 (m, 2H); ^{13}C-NMR, δ: 21.7, 22.4, 34.8, 35.3, 49.0, 50.0, 55.0, 55.2, 62.2, 62.3, 69.0, 70.3, 70.4, 71.3, 72.1, 79.7, 79.8, 99.8, 99.9, 101.3, 101.37, 101.4, 101.6, 126.0, 126.1, 128.1, 128.4, 128.85, 128.9, 129.6, 129.7, 129.9, 130.0, 133.0, 136.9, 165.2, 165.1; υ_{max}: 1726, 1376, 1108 cm^{-1}. Anal. Calcd for $C_{25}H_{29}BrO_8$: C, 55.87; H, 5.44. Found: C, 55.59; H, 5.77.

Methyl 4,6-*O*-Benzylidene-3-*O*-benzoyl-2-*O*-[(bromomethyl)dimethylsilyl]-α-D-mannopyranoside (7). Bromomethyl dimethylsilyl chloride (0.34 mL, 2.44 mmol) was added to a solution of **1** (630 mg, 1.63 mmol) and DMAP (298 mg, 2.44 mmol) in CH_2Cl_2 (4 mL) stirred at 15−18 °C under Ar. After stirring overnight at room temperature the precipitate was removed by filtration and the filtrate diluted with CH_2Cl_2 (15 mL), washed with saturated aqueous $NaHCO_3$ (2 × 5 mL) and brine (2 × 5 mL). The organic layer was dried (Na_2SO_4) and the solvent evaporated to give a residue which after chromatography on silica gel (eluent: pentane/ethyl acetate 5/1) gave the title compound as a colorless oil which crystallized from hexane (624 mg, 77%) as white needles. Mp 134 °C; ^{1}H-NMR, δ: 0.19 (s, 3H), 0.25 (s, 3H), 2.44 (d, $J = 0.7$ Hz, 2H), 3.44 (s, 3H), 3.89−4.05 (m, 2H), 4.23−4.37 (m, 2H), 4.43 (dd, $J = 1.7$, 3.2 Hz, 1H), 4.73 (d, $J = 1.7$ Hz, 1H), 5.51 (dd, $J = 3.2$, 10.3 Hz, 1H), 5.65 (s, 1H), 7.25−7.65 (m, 8H), 8.02−8.15 (m, 2H); ^{13}C-NMR, δ: 16.0, 55.1, 64.2, 68.8, 71.0, 71.4, 75.9, 101.7, 102.3, 126.1, 128.2, 128.4, 128.9, 129.8, 130.0, 133.2, 137.3, 165.9; υ_{max}: 1722, 1276, 1132 cm^{-1}. Anal. Calcd for $C_{24}H_{29}BrO_7Si$: C, 53.63; H, 5.44. Found: C, 53.83; H, 5.50.

General Protocol for Radical Reactions. The radical precursor was dissolved in benzene at the concentration given in Tables 1 and 2 and either heated to reflux or photolyzed at room temperature in a Rayonet photoreactor (254 nm through Pyrex) while a solution of tributyltin hydride and AIBN (5 mol %) in benzene (concentrations and equivalents given in Tables 1 and 2) was added dropwise with a motor driven syringe pump. When the addition was complete, reflux, or photolysis, was continued for the time indicated in the tables before the solvent was removed under vacuum and the residue taken up in chloroform and stirred overnight with moist silica gel or, better, Dowex 50 (H^+). The products were isolated by filtration, evaporation, and chromatography on silica gel. For entries 4 and 5 of Table 1, the same protocol was followed except that the stannane was replaced by tris(trimethylsilyl)-silane.

Methyl 3-*O*-Benzoyl-4,6-benzylidene-β-D-mannopyranoside (3).[50] An oil. ^{1}H-NMR, δ: 3.50−3.60 (m, 1H), 3.61 (s, 3H), 3.93 (t, 1H, $J = 10.3$ Hz), 4.31 (t, 1H, $J = 10.0$ Hz), 4.39 (m, 1H), 4.40 (dd, 1H, $J = 4.9$, 10.4 Hz), 4.64 (d, 1H, $J = 1.0$ Hz), 5.30 (dd, 1H, $J = 3.2$, 10.2 Hz), 5.61 (s, 1H), 7.25−7.70 (m, 8H), 8.05−8.15 (m, 2H); ^{13}C-NMR, δ: 57.3, 67.1, 68.6, 69.6, 72.6, 75.5, 101.7, 102.0, 126.1, 128.2, 128.4, 129.7, 129.9, 130.1, 133.2, 133.6, 166.0.

Methyl 3-*O*-Benzoyl-4,6-benzylidene-1-α-D-arabinohexopyranosid-2-ulose (4). Preparation of an Authentic Sample. A mixture of alcohol **1** (1 g, 2.6 mmol), *N*-methylmorpholine *N*-oxide (450 mg, 3.8 mmol), and powdered 4 Å molecular sieves in CH_2Cl_2 (10 mL) was stirred at room temperature and treated with tetrapropylammonium perruthenate[28] (45 mg, 0.13 mmol). The reaction mixture was stirred for 3 h at room temperature and then filtered through a plug of silica gel eluting with ether and ethyl acetate. After removal of the volatiles the residue was purified by chromatography on silica gel (eluent: pentane/ethyl acetate 3/1) to yield the title ketone as an oil (0.9 g, 90%) whose spectral data were in accord with those recorded in the literature.[51] ^{1}H-NMR, δ: 3.53 (s, 3H), 3.89 (t, $J = 9.1$ Hz, 1H), 4.01 (dd, $J = 9.2$, 10.7 Hz, 1H), 4.33−4.52 (m, 2H), 4.85 (s, 1H), 5.59 (s, 1H), 6.01 (d, $J = 10.8$ Hz), 7.30−7.65 (m, 8H), 8.05−8.15 (m, 2H).

Reaction of 2 with Trimethyltin Chloride and Sodium Cyanoborohydride. The substrate **2** (54 mg), trimethyltin chloride (2 mg), AIBN (3.3 mg), and sodium cyanoborohydride (12.6 mg) were heated to reflux under Ar in *tert*-butyl alcohol/benzene (2 mL) for 4 h. The solvents were removed under vacuum, and the residue was diluted with ether and filtered on a plug of silica gel eluting with ethyl acetate. The filtrate was concentrated under vacuum and taken up in dichloromethane (10 mL) and stirred with moist silica gel for 5 h. The silica gel was then removed by filtration and washed copiously with dichloromethane and ether. Concentration and purification by preparative TLC on silica gel (eluent: pentane/ethyl acetate 2/1) gave the β-mannoside **3** (12 mg, 31%) and the α-mannoside **1** (20 mg, 52%).

Methyl 3,4-Di-*O*-benzyl-α-L-rhamnopyranoside (9). This compound was prepared essentially as described for the methoxyethoxy dibenzylrhamnopyranoside.[52] A mixture of L-rhamnose monohydrate (3.00 g, 16.5 mmol) and acetyl bromide (13.6 mL, 184 mmol) was stirred for 1 h at room temperature and then concentrated to dryness by distillation with toluene at 40 °C. The residue was dissolved in ni-

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tromethane (14 mL), cooled to 0 °C, and treated with 2,6-lutidine (11.3 mL) and methanol (9.0 mL). After stirring at room temperature overnight the reaction mixture was diluted with toluene and thoroughly washed with 5% aqueous $NaHCO_3$. The organic layer was concentrated then stirred with benzyl chloride (86.0 mL) and powdered KOH (43.0 g) at 120 °C for 3 h. After cooling and dilution with toluene the reaction mixture was washed with water, concentrated, and chromatographed on silica gel which had been pretreated with 5% Et_3N in hexane (eluent: hexane → hexane/ethyl acetate 3/1) to give the crude, oily orthoester. This preparation was then treated with $BF_3{\cdot}Et_2O$ (54 μL) in CH_2Cl_2 (63 mL) for 5 min at room temperature, the solution washed with brine and dried (Na_2SO_4). Removal of the solvent and chromatography on silica gel (eluent: hexane/ethyl acetate 3/1) gave the acetate of the title product, which was dissolved in methanol (50 mL) and treated with sodium (60 mg) for 2 h at room temperature. Dowex (50W-X8, H^+ form) was then added slowly until the solution was neutral. After filtration, concentration afforded the title compound as an oil (2.70 g, 51%). $[\alpha]_D = -48.5°$ (c = 1.51, $CHCl_3$); ^{1}H-NMR, δ: 1.30 (d, J = 6.2 Hz, 3H), 2.52 (d, J = 1.7 Hz, 1H), 3.33 (s, 3H), 3.44 (t, J = 9.2 Hz, 1H), 3.64−3.72 (m, 1H), 3.81 (dd, J = 3.4, 9.2 Hz, 1H), 4.01 (t, J = 1.7 Hz, 1H), 4.60−4.70 (m, 4H), 4.88 (d, J = 10.9 Hz, 1H), 7.23−7.36 (m, 10H); ^{13}C-NMR, δ: 17.8, 54.7, 67.1, 68.4, 71.9, 79.8, 80.0, 100.0, 127.7, 127.8, 127.9, 128.3, 128.5, 137.9, 138.3; υ_{max}: 3569, 2908, 1494, 1450, 1388, 1357, 1212, 1128, 1102, 1058, 979.2 cm^{-1}. Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.25; H, 7.24.

Methyl 3,4-*O*-(Octahydro-2,2′-bipyran-2,2′-yl)-α-L-rhamnopyranoside (10). A mixture of methyl α-L-rhamnopyranoside[53] (1.92 g, 10.75 mmol), 2,2′-bis(3,4-dihydro-2*H*-pyran)[54] (2.52 g, 14.5 mmol) and camphor-10-sulfonic acid (50 mg) in $CHCl_3$ (40 mL) was heated to reflux for 2 h. Ethylene glycol (2 mL) was then added and reflux maintained for a further 1 h. The resulting brown solution was diluted with CH_2Cl_2, washed with saturated, aqueous $NaHCO_3$ and then brine, and dried (Na_2SO_4). After concentration, purification by chromatography on silica gel (eluent: hexane/ethyl acetate 5/1) gave the title compound as an oil (0.987 g, 26.7%). $[\alpha]_D = -117.0$ (c = 0.5, CH_3Cl), lit.[39] $[\alpha]_D = -87.9$ (c = 1, $CHCl_3$); ^{1}H-NMR, δ: 1.29 (d, J = 5.8 Hz, 3H), 1.45−1.85 (m, 12H), 2.42 (bs, 1H), 3.34 (s, 3H), 3.60−3.80 (m, 6H), 3.92 (bs, 1H), 3.97 (dd, J = 3.2, 9.5 Hz, 1H), 4.67 (bs, 1H); ^{13}C-NMR, δ: 16.7, 18.0, 18.1, 24.8, 24.9, 28.4, 28.6, 54.7, 60.6, 60.8, 66.4, 67.4, 69.8, 97.1, 97.4, 100.9; υ_{max}: 3581, 2945, 1466, 1453 cm^{-1}. Anal. Calcd for $C_{17}H_{28}O_7$: C, 59.29; H, 8.19. Found: C, 59.43; H, 8.16.

Methyl 3,4-Di-*O*-benzoyl-2-*O*-(1-bromo-2-methoxy-2-propyl)-α-L-rhamnopyranoside (11). Prepared as a diastereomeric mixture in 65% yield from methyl 3,4-di-*O*-benzoyl-α-L-rhamnopyranoside (**8**)[55] by protocol B. Mp 34−36 °C; ^{1}H-NMR, δ: 1.29−1.49 (m, 6H), 3.16 + 3.27 (2 × s, 3H), 3.30−3.37 (m, 1H), 3.44 (s, 3H), 3.43−3.55 (m, 1H), 4.02 (m, 1H), 4.44−4.46 (m, 1H), 4.74 + 4.78 (2 × d, J = 1.7 Hz, 1H), 5.52−5.59 (m, 2H), 7.28−7.36 (m, 4H), 7.42−7.50 (m, 2H), 7.88−7.94 (m, 4H); ^{13}C-NMR, δ: 17.7, 21.7, 22.1, 35.16, 35.2, 49.6, 49.9, 55.18, 55.20, 66.5, 66.6, 69.9, 70.2, 71.4, 71.5, 71.58, 71.6, 99.8, 100.2, 101.3, 101.6, 128.3, 128.36, 128.4, 129.6, 129.7, 133.1, 133.2, 165.77, 165.8, 165.9, 166.0; υ_{max}: 2982, 2937, 1721, 1600, 1447 cm^{-1}. Anal. Calcd for $C_{25}H_{29}BrO_8$: C, 55.88; H, 5.44. Found: C, 55.81; H, 5.50. The substrate was recovered in 27% yield from this experiment.

Methyl 3,4-Di-*O*-benzyl-2-*O*-(1-bromo-2-methoxy-2-propyl)-α-L-rhamnopyranoside (12). Prepared as a diastereomeric mixture in 60% yield from **9** by protocol B. ^{1}H-NMR, δ: 1.31 (d, J = 6.2 Hz, 3H), 1.50 + 1.52 (2 × s, 3H), 3.30−3.31 (4 × s, 6H), 3.32−3.68 (m, 4H), 3.80−3.86 (m, 1H), 4.14−4.19 (m, 1H), 4.57−4.95 (m, 5H), 7.24−7.35 (m, 10H); ^{13}C-NMR, δ: 18.0, 18.1, 21.7, 22.3, 35.5, 36.0, 49.4, 49.6, 54.7, 67.6, 68.0, 69.3, 70.0, 72.5, 72.6, 75.1, 75.2, 79.0, 79.2, 80.2, 80.3, 99.8, 100.3, 101.0, 101.3, 127.5, 127.6, 127.8, 127.9, 128.3, 138.3, 138.4, 138.6; υ_{max}: 2934, 1626, 1604, 1494 cm^{-1}. Anal. Calcd for $C_{25}H_{33}BrO_6$: C, 58.94; H, 6.53. Found: C, 58.90; H, 6.39. The substrate was recovered in 32% yield from this experiment.

Methyl 2-*O*-(1-Bromo-2-methoxy-2-propyl)-3,4-*O*-(octahydro-2,2′-bipyran-2,2′-yl)-α-L-rhamnopyranoside (13). Prepared as a diastereomeric mixture in 62% yield from (**10**) by protocol B. ^{1}H-NMR, δ: 1.27 (d, J = 6.0 Hz, 3H), 1.40−1.80 (m, 15H), 3.30−3.42 (m, 7H), 3.51−3.73 (m, 7H), 3.92−3.98 (m, 1H), 4.01−4.06 (m, 1H), 4.57+4.59 (2 × d, J = 1.5 Hz, 1H); ^{13}C-NMR, δ: 16.9, 18.2, 18.3, 21.9, 22.1, 24.8, 24.9, 25.0, 28.4, 28.43, 28.7, 35.6, 36.6, 49.4, 49.7, 54.5, 54.6, 60.5, 60.54, 60.7, 66.1, 66.2, 66.7, 66.71, 67.5, 67.51, 69.4, 70.0, 96.6, 96.9, 97.0, 100.9, 101.0, 101.3, 101.4. The substrate was recovered in 27% yield.

Methyl 3-*O*-Benzoyl-4-deoxy-α-L-rhamnopyranoside (14). An oil. $[\alpha]_D = -1.9°$ (c = 1.37, $CHCl_3$); ^{1}H-NMR, δ: 1.19 (d, J = 6.3 Hz, 3H), 1.78 (q, J = 11.5 Hz, 1H), 2.00 (d, J = 12.0 Hz, 1H), 2.37 (td, J = 4.8, 11.5 Hz, 1H), 3.47 (s, 3H), 3.72−3.92 (m, 2H), 4.65 (d, J = 3.7 Hz, 1H), 4.69−4.78 (m, 1H), 7.42 (t, J = 8.0 Hz, 2H), 7.55 (tt, J = 1.4, 8.0 Hz, 1H), 8.00 (dd, J = 1.4, 8.0 Hz, 2H); ^{13}C-NMR, δ: 17.4, 33.7, 55.2, 65.9, 67.2, 72.1, 98.5, 128.4, 129.6, 130.0, 133.2, 165.5; υ_{max}: 3572, 2936, 1716, 1447 cm^{-1}; MS, m/z: 266 ($M^{+\bullet}$).

Methyl 3,4-Di-*O*-benzoyl-β-L-rhamnopyranoside (15). Mp 148−151 °C; $[\alpha]_D = +63.7°$ (c = 0.35, $CHCl_3$); ^{1}H-NMR, δ: 1.35 (d, J = 6.2 Hz, 3H), 2.35 (bs, 1H), 3.59 (s, 3H), 3.68−3.74 (m, 1H), 4.33 (d, J = 3.0 Hz, 1H), 4.60 (s, 1H), 5.27 (dd, J = 3.0, 9.8 Hz, 1H), 5.60 (t, J = 9.8 Hz, 1H), 7.30−7.38 (m, 4H), 7.45−7.50 (m, 2H); ^{13}C-NMR, δ: 17.6, 57.0, 69.3, 70.6, 71.1, 73.8, 100.3, 128.3, 129.6, 129.9, 133.2, 133.24, 165.6, 166.0; υ_{max}: 2930, 1724, 1322 cm^{-1}. Anal. Calcd for $C_{21}H_{22}O_7$: C, 65.28; H, 5.74. Found: C, 65.12; H, 5.73.

Methyl 3,4-Di-*O*-benzoyl-5,6-dideoxy-L-*lyxo*-hexonate (18). $[\alpha]_D = -72.5°$ (c = 6.0, $CHCl_3$); ^{1}H-NMR, δ: 0.98 (t, J = 7.4 Hz, 3H), 1.75−1.88 (m, 2H), 3.40 (d, J = 6.7 Hz, 1H), 3.65 (s, 3H), 4.37 (t, J = 6.7 Hz, 1H), 5.49 (dd, J = 4.0, 6.7 Hz, 1H), 5.57−5.63 (m, 1H), 7.39−7.45 (m, 4H), 7.52−7.58 (m, 2H), 8.01−8.07 (m, 4H); ^{13}C-NMR, δ: 9.6, 24.0, 52.9, 69.5, 73.3, 74.2, 128.4, 128.4, 129.2, 129.7, 129.73, 133.2, 133.4, 165.8, 166.2, 172.4; υ_{max}: 3523, 2936, 1724, 1457, 1266 cm^{-1}. Anal. Calcd for $C_{21}H_{22}O_7$: C, 65.28; H, 5.74. Found: C, 65.34; H, 5.82.

Methyl 3,4-Di-*O*-benzyl-β-L-rhamnopyranoside (16). $[\alpha]_D = +15.4°$ (c = 0.68, $CHCl_3$); ^{1}H-NMR, δ: 1.36 (d, J = 6.1 Hz, 3H), 2.38 (s, 1H), 3.25−3.40 (m, 1H), 3.51−3.53 (m, 5H), 4.09 (s, 1H), 4.29 (d, J = 1.1 Hz, 1H), 4.62−4.79 (m, 3H), 4.94 (d, J = 10.8 Hz, 1H), 7.26−7.40 (m, 10H); ^{13}C-NMR, δ: 17.9, 56.9, 68.4, 71.4(2), 75.5, 79.7, 81.4, 100.6, 127.8, 127.9, 128.1, 128.4, 128.5, 137.8, 138.3; υ_{max}: 3574, 2936, 1450 cm^{-1}. Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.41; H, 7.30.

Methyl 3,4-Di-*O*-benzyl-5,6-dideoxy-L-*lyxo*-hexonate (19). $[\alpha]_D = +3.18°$ (c = 4.25, $CHCl_3$); ^{1}H-NMR, δ: 0.89 (t, J = 7.5 Hz, 3H), 1.55−1.70 (m, 1H), 1.70−1.85 (m, 1H), 3.55 (q, J = 5.0 Hz, 1H), 3.63 (d, J = 7.1 Hz, 1H), 3.75 (s, 3H), 3.80 (t, J = 5.0 Hz, 1H), 4.50 (dd, J = 5.0, 7.1 Hz, 1H), 4.57 (s, 2H), 4.63 (d, J = 11.7 Hz, 1H), 4.73 (d, J = 11.7 Hz, 1H), 7.26−7.42 (m, 10H); ^{13}C-NMR, δ: 9.9, 23.0, 52.3, 71.6, 72.9, 73.3, 80.1, 81.6, 127.8, 127.9, 128.2, 128.4, 137.9, 173.2; υ_{max}: 3506, 2961, 1736, 1455 cm^{-1}. Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.14; H, 7.22.

Methyl 3,4-*O*-(Octahydro-2,2′-bipyran-2,2′-yl)-β-L-rhamnopyranoside (17). $[\alpha]_D = -76.4°$ (c = 0.61, $CHCl_3$); ^{1}H-NMR, δ: 1.34 (d, J = 6.1 Hz, 3H), 1.40−1.92 (m, 12H), 2.34 (bs, 1H), 3.44−3.54 (m, 1H), 3.54 (s, 3H), 3.58−3.80 (m, 6H), 4.01 (bs, 1H), 4.40 (bs, 1H); ^{13}C-NMR, δ: 16.8; 17.9, 18.1, 24.9, 28.3, 28.6, 56.9, 60.5, 60.8, 67.0, 69.5, 69.6, 70.7, 97.0, 97.4, 101.1; υ_{max}: 3579, 2937, 1444 cm^{-1}. Anal. Calcd for $C_{17}H_{28}O_7$: C, 59.29; H, 8.19. Found: C, 59.49; H, 8.27.

Methyl 3,4-*O*-(Octahydro-2,2′-bipyran-2,2′-yl)-α-L-quinovopyranoside (21). $[\alpha]_D = -145.9°$ (c = 0.73, $CHCl_3$); ^{1}H-NMR, δ: 1.25 (d, J = 6.2 Hz, 3H), 1.40−1.89 (m, 12H), 2.06 (d, J = 8.3 Hz, 1H), 3.30 (t, J = 9.7 Hz, 1H), 3.39 (s, 3H), 3.55−3.94 (m, 7H), 4.73 (d, J = 3.9 Hz, 1H); ^{13}C-NMR, δ: 16.8, 18.1, 24.87, 24.9, 28.5 (2), 55.1, 60.6, 60.7, 65.7, 69.5, 70.3, 70.5, 96.8,

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99.5; υ_{max}: 3563, 2952, 1441 cm^{-1}. Anal. Calcd for $C_{17}H_{28}O_7$: C, 59.29; H, 8.19. Found: C, 59.44; H, 8.25.

Methyl 3,4-*O*-(Octahydro-2,2′-bipyran-2,2′-yl)-5,6-dideoxy-L-*lyxo*-hexonate (20). $[\alpha]_D = -118.0°$ ($c = 0.86$, $CHCl_3$); ^{1}H-NMR, δ: 1.02 (t, $J = 7.2$ Hz, 3H), 1.22−1.89 (m, 14H), 2.97 (d, $J = 6.8$ Hz, 1H), 3.55−3.67 (m, 4H), 3.68−3.82 (m, 4H), 3.86 (dd, $J = 3.0$, 9.6 Hz, 1H), 4.25 (dd, $J = 3.0$, 6.8 Hz, 1H); ^{13}C-NMR, δ: 9.8, 18.1, 18.2, 23.3, 24.9, 25.1, 28.2, 28.6, 52.4, 60.5, 60.8, 68.5, 71.4, 73.5, 95.7, 96.2, 172.8; υ_{max}: 3553, 2945, 1732, 1466 cm^{-1}. Anal. Calcd for $C_{17}H_{28}O_7$: C, 59.29; H, 8.19. Found: C, 58.88; H, 8.18.

Methyl 2-*O*-Acetyl-3,4-di-*O*-benzyl-α-D-mannopyranoside (22). To a stirred solution of 3,4,6-tri-*O*-acetyl-1,2-(1-methoxyethylidene)-β-D-mannospyranose[56] (8.27 g, 22.8 mmol) in methanol (400 mL) was added sodium (20 mg). After stirring overnight the solution was neutralized by addition of Dowex (50W-X8, H^+), filtered, and concentrated to give a syrup which was directly dissolved in 2,6-lutidine (70 mL) and treated with trityl chloride (7.00 g, 24.9 mmol) and stirred at 40 °C for 16 h. The solution was then filtered, treated with benzyl chloride (25.0 mL, 217 mmol) and sodium hydride (60% in oil, 5.3 g, 132.5 mmol), and heated to 120 °C for 3 h. After cooling to room temperature the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with chloroform. The extracts were washed with brine, dried (Na_2SO_4), concentrated, and chromatographed on silica gel that had been washed with 5% triethylamine in hexane (eluent: hexane/ethyl acetate 5/1) to give 3,4-di-*O*-benzyl-1,2-(1-methoxyethylidene)-6-*O*-trityl-β-D-mannospyranose. This was then dissolved in CH_2Cl_2 (300 mL) and treated with $BF_3{\cdot}OEt_2$ (0.2 mL) for 5 min, followed by addition of trifluoroacetic acid (20 mL), then water (20 mL). After stirring overnight at room temperature the reaction mixture was washed with water, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), concentrated, and purified by chromatography on silica gel (eluent: hexane/ethyl acetate 5/1 → 2/1) to give the title compound as an oil (5.27 g, 56%). $[\alpha]_D = +18.7°$ ($c = 1.5$, $CHCl_3$); ^{1}H-NMR, δ: 1.90 (bs, 1H), 2.13 (s, 3H), 3.33 (s, 3H), 3.65 (dt, $J = 9.7$, 3.6 Hz, 1H), 3.70−3.85 (m, 3H), 3.96 (dd, $J = 3.3$, 9.3 Hz, 1H), 4.51 (d, $J = 11.3$ Hz, 1H), 4.58 (d, $J = 10.9$ Hz, 1H), 4.66 (s, 1H), 4.68 (d, $J = 11.3$ Hz, 1H), 4.90 (d, $J = 10.9$ Hz, 1H), 5.35 (dd, $J = 1.8$, 3.3 Hz, 1H), 7.24−7.35 (m, 10H); ^{13}C-NMR, δ: 21.0, 54.9, 62.2, 68.6, 71.6, 71.7, 74.1, 75.2, 78.0, 98.9, 127.7, 127.8, 127.9, 128.0, 128.37, 128.4, 137.9, 138.3, 170.3; υ_{max}: 3693, 3606, 2929, 1743, 1600 cm^{-1}. Anal. Calcd for $C_{23}H_{28}O_7$: C, 66.33; H, 6.78. Found: C, 66.22; H, 6.79.

Methyl 3,4-Di-*O*-benzyl-α-D-mannopyranoside (23).[57] Sodium (20 mg) was added to a solution of **22** (0.949 g, 2.28 mmol) in methanol (30 mL), and the resulting mixture was stirred overnight, before treatment with Dowex (50W-X8, H^+) until neutral. Filtration and concentration under vacuum gave **23** as an oil (0.853 g, 100%). $[\alpha]_D = +72.7°$ ($c = 0.11$, $CHCl_3$); ^{1}H-NMR, δ: 2.15 (bs, 1H), 2.66 (bs, 1H), 3.32 (s, 3H), 3.59−3.67 (m, 1H), 3.72−3.86 (m, 4H), 4.01 (bs, 1H), 4.64 (d, $J = 11.0$ Hz, 1H), 4.68 (s, 2H), 4.75 (d, $J = 1.5$ Hz, 1H), 4.87 (d, $J = 11.0$ Hz, 1H), 7.24−7.35 (m, 10H); ^{13}C-NMR, δ: 54.7, 62.1, 68.3, 71.3, 72.1, 74.0, 75.2, 80.0, 100.2, 127.8, 127.9, 128.4, 128.6, 137.8, 138.3; υ_{max}: 3584, 2926, 1497 cm^{-1}.

Methyl 3,4-Di-*O*-benzyl-6-deoxy-6-(ethylthio)-α-D-mannopyranoside (24). A mixture of **22** (0.982 g, 2.36 mmol) and tosyl chloride (0.899 g, 4.72 mmol) was stirred overnight at room temperature in pyridine (5 mL) and then diluted with water (100 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The extracts were washed with 1 M HCl, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), concentrated, and purified by chromatography on silica gel (eluent: hexane/ethyl acetate 5/1) to yield the 6-*O*-tosyl derivative. Butyllithium (1.6 M in hexane, 3.5 mL) was added at −78 °C to ethanethiol (30 mL) followed, after warming to room temperature, by the above tosylate, and the mixture was stirred at room temperature for 3 days. The volatiles were then removed under vacuum, and the residue was extracted with chloroform. Concentration of the chloroform extracts under vacuum gave the title compound as an oil (0.849 g, 86%). $[\alpha]_D = +58.4°$ ($c = 0.86$, $CHCl_3$); ^{1}H-NMR, δ: 1.25 (t, $J = 7.4$ Hz, 3H), 2.51 (bs, 1H), 2.55−2.72 (m, 3H), 2.95 (dd, $J = 2.1$, 13.6 Hz, 1H), 3.40 (s, 3H), 3.67 (t, $J = 9.0$ Hz, 1H), 3.72−3.82 (m, 1H), 3.86 (dd, $J = 3.3$, 9.0 Hz, 1H), 4.03 (bs, 1H), 4.62−4.75 (m, 4H), 4.92 (d, $J = 11.1$ Hz, 1H), 7.25−7.37 (m, 10H); ^{13}C-NMR, δ: 14.6, 27.0, 33.3, 54.7, 68.2, 71.7, 71.9, 75.2, 77.0, 80.2, 99.7, 127.7, 127.8, 127.84, 128.4, 128.5, 137.7, 138.2; υ_{max}: 3580, 2918, 1599 cm^{-1}. Anal. Calcd for $C_{33}H_{30}O_5S$: C, 66.00; H, 7.22. Found: C, 66.02; H, 7.30.

Methyl 3,4-Di-*O*-benzyl-6-*O*-pivaloyl-α-D-mannopyranoside (25). To a solution of methyl 3,4-di-*O*-benzyl-α-D-mannopyranoside (**23**) (0.853 g, 2.28 mmol) in pyridine (8 mL) at 0 °C was added a solution of pivaloyl chloride (0.42 mL, 3.42 mmol) in CH_2Cl_2 (4 mL) by syringe pump over 6 h. The reaction mixture was poured in water (100 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The extracts were washed with 1 M HCl, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), concentrated, and purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 5/1) to give the title compound as an oil (1.003 g, 96%). $[\alpha]_D = +50.5°$ ($c = 2.14$, $CHCl_3$); ^{1}H-NMR, δ: 1.20 (s, 9H), 3.34 (s, 3H), 3.71 (t, $J = 8.8$ Hz, 1H), 3.75−3.83 (m, 1H), 3.87 (dd, $J = 3.3$, 8.8 Hz, 1H), 4.01 (bs, 1H), 4.20 (dd, $J = 5.6$, 11.7 Hz, 1H), 4.41 (dd, $J = 1.8$, 11.7 Hz, 1H), 4.56 (d, $J = 10.7$ Hz, 1H), 4.67 (s, 2H), 4.73 (d, $J = 1.5$ Hz, 1H), 4.87 (d, $J = 10.7$ Hz, 1H), 7.24−7.35 (m, 10H); ^{13}C-NMR, δ: 27.2, 38.8, 54.7, 63.3, 68.1, 69.4, 72.0, 74.3, 75.2, 80.1, 100.0, 127.9, 127.95, 128.0, 128.03, 128.5, 128.6, 137.7, 137.9, 178.2; υ_{max}: 3572, 2972, 1722 cm^{-1}. Anal. Calcd for $C_{26}H_{34}O_7$: C, 68.10; H, 7.47. Found: C, 67.82; H, 74.7.

Methyl 3,4-Di-*O*-benzyl-6-chloro-6-deoxy-α-D-mannopyranoside (26). To a solution of methyl 3,4-di-*O*-benzyl-α-D-mannopyranoside (**23**) (29.6 mg, 0.08 mmol) in pyridine (1 mL) at 0 °C was added triphenylphosphine (41.4 mg, 0.16 mmol) and tetrachloromethane (10.5 μL, 0.11 mmol), followed by stirring overnight at room temperature. After dilution with water, the reaction mixture was extracted with CH_2Cl_2, and the extracts were washed with 1 M HCl, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), concentrated, and chromatographed on silica gel (eluent: hexane/ethyl acetate 3/1) to give the title compound as an oil (25.0 mg, 81%). $[\alpha]_D = +47.1°$ ($c = 1.6$, $CHCl_3$); ^{1}H-NMR, δ: 2.55 (bs, 1H), 3.39 (s, 3H), 3.71−3.92 (m, 5H), 4.05 (bs, 1H), 4.66 (d, $J = 11.8$ Hz, 1H), 4.68 (d, $J = 11.0$ Hz, 1H); 4.73 (d, $J = 11.0$ Hz, 1H), 4.82 (d, $J = 1.5$ Hz, 1H), 4.96 (d, $J = 11.8$ Hz, 1H), 7.24−7.40 (m, 10H); ^{13}C-NMR, δ: 44.7, 55.0, 68.2, 70.7, 72.0, 75.0, 75.3, 80.1, 100.3, 127.65, 127.7, 127.9, 128.0, 128.5, 128.6, 137.7, 138.1; υ_{max}: 3569, 2917, 1498 cm^{-1}. Anal. Calcd for $C_{21}H_{25}ClO_5$: C, 64.20; H, 6.41. Found: C, 63.98; H, 6.35.

Methyl 3,4-Di-*O*-benzyl-2-(1-bromo-2-methoxy-2-propyl)-6-deoxy-6-(ethylthio)-α-D-mannopyranoside (28). Prepared by protocol B and isolated in 66% yield together with 21% of substrate. ^{1}H-NMR, δ: 1.23 (t, $J = 7.4$ Hz, 3H), 1.48 + 1.50 (2 × s, 3H), 2.60 (q, $J = 7.4$ Hz, 2H), 2.65−2.73 (m, 1H), 2.94 (dd, $J = 2.0$, 13.5 Hz, 1H), 3.2−3.45 (m, 7H), 3.51−3.56 (m, 1H), 3.68−3.79 (m, 2H), 3.85−3.89 (m, 1H), 4.14−4.19 (m, 1H), 4.59−4.66 (m, 3H), 4.69−4.75 (m, 1H), 4.91 + 4.95 (2 × d, $J = 11.4$ Hz, 1H), 7.24−7.35 (m, 10H); ^{13}C-NMR, δ: 14.8, 21.6, 22.3, 26.6, 26.7, 33.5, 35.4, 35.8, 49.3, 49.8, 54.7, 69.0, 69.7, 71.9, 72.3, 72.4, 75.0 (2), 77.2, 77.3, 79.1, 79.3, 99.6, 100.1, 100.7, 101.2, 127.6, 127.7, 127.8, 128.3, 138.1, 138.2, 138.4; υ_{max}: 2927, 1453, 1360 cm^{-1}. Anal. Calcd for $C_{27}H_{37}BrO_6S$: C, 56.94; H, 6.55. Found: C, 57.04; H, 6.60.

Methyl 3,4-Di-*O*-benzyl-2-(1-bromo-2-methoxy-2-propyl)-6-*O*-pivaloyl-α-D-mannopyranoside (29). Prepared by protocol B and isolated in 62% yield together with 25% of substrate. ^{1}H-NMR, δ: 1.20 (s, 9H), 1.49 + 1.50 (2 × s, 3H), 3.29 + 3.30 + 3.31 + 3.32 (4 × s, 6H), 3.34−3.40 (m, 1H), 3.47−3.52 (m, 1H), 3.67−3.76 (m, 1H), 3.78−3.92 (m, 2H), 4.14−4.19 (m, 1H), 4.25−4.41 (m, 2H), 4.49−4.55 (m, 1H), 4.59−4.68 (m, 2H), 4.69−4.77 (m, 1H), 4.85 + 4.94 (2 × d, $J = 10.8$ Hz, 1H), 7.24−7.35 (m, 10H); ^{13}C-NMR, δ: 21.7, 22.3, 27.2, 35.2, 35.7, 38.9, 49.3, 49.9, 54.8, 63.0, 66.9, 69.7, 70.1, 70.2,

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72.5, 72.6, 74.3, 75.2, 79.0, 79.1, 99.7, 100.1, 101.0, 101.3, 127.7, 127.8, 127.83, 127.9, 128.4, 138.1, 178.2; υ_{max}: 2953, 1722, 1281 cm^{-1}. Anal. Calcd for $C_{30}H_{41}BrO_8$: C, 59.11; H, 6.78. Found: C, 58.75; H, 6.78.

Methyl 3,4-Di-*O*-benzyl-2-(1-bromo-2-methoxy-2-propyl)-6-chloro-6-deoxy-α-D-mannopyranoside (30). Prepared by protocol B and isolated in 66% yield together with 15% of substrate. ^{1}H-NMR, δ: 1.48 + 1.52 (2 × s, 3H), 3.31 + 3.34 (2 × s, 6H), 3.34−3.40 (m, 1H), 3.49−3.57 (m, 1H), 3.70−3.91 (m, 5H), 4.15−4.19 (m, 1H), 4.58−4.80 (m, 4H), 4.91 + 4.95 (2 × d, J = 10.9 Hz, 1H), 7.24−7.30 (m, 10H); ^{13}C-NMR, δ: 21.6, 22.3, 35.4, 35.7, 45.0, 49.4, 49.7, 55.0, 68.9, 69.6, 71.3, 71.5, 72.3, 72.5, 75.2, 75.3, 78.9, 79.1, 99.6, 100.4, 101.0, 101.3, 127.7, 127.8, 127.9, 128.4, 138.1, 138.16; υ_{max}: 2939, 1455, 1363 cm^{-1}. Anal. Calcd for $C_{25}H_{32}BrClO_6$: C, 55.21; H, 5.93. Found: C, 55.44; H, 5.93.

Methyl 3,4,6-Tri-*O*-benzyl-2-(1-bromo-2-methoxy-2-propyl)-α-D-mannopyranoside (31). Prepared from methyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (**27**)[58] in 60% yield by method B. $[\alpha]_D$ = +21.2° (c = 1.87); ^{1}H-NMR, δ: 1.55 + 1.54 (2 × s, 3H), 3.33 + 3.32 (2 × s, 3H), 3.38 + 3.37 (2 × s, 3H), 3.35−3.60 (m, 2H), 3.70−3.85 (m, 3H), 3.85−3.98 (m, 2H), 4.21 (m, 1H), 4.45−4.95 (m, 7H), 7.10−7.50 (m, 15H); ^{13}C-NMR, δ: 21.7, 22.8, 35.4, 35.8, 49.4, 49.8, 54.7, 69.0, 69.2, 69.3, 69.8, 71.7, 71.8, 72.4, 72.5, 73.2, 73.21, 74.6, 74.9, 79.1, 79.2, 99.8, 100.3, 100.9, 101.2, 127.4, 127.5, 127.6, 127.61, 127.7, 127.8, 128.2, 128.3, 128.34, 138.2, 138.3, 138.4, 138.5; υ_{max}: 2916, 1457, 1104, 1071 cm^{-1}. Anal. Calcd for $C_{32}H_{39}BrO_7$: C, 62.44; H, 6.39. Found: C, 62.31; H, 6.47.

Methyl 3,4-Di-*O*-benzyl-5,6-dideoxy-L-*lyxo*-hexenonate (39). $[\alpha]_D$ = −28.7° (c = 0.72, $CHCl_3$); ^{1}H-NMR, δ: 3.32 (d, J = 7.0 Hz, 1H), 3.69 (s, 3H), 3.79 (dd, J = 3.8, 6.5 Hz, 1H), 4.10 (t, J = 6.5 Hz, 1H), 4.37 (d, J = 11.5 Hz, 1H), 4.41 (dd, J = 3.8, 7.0 Hz, 1H), 4.60 (d, J = 11.5 Hz, 1H), 4.69 (d, J = 11.7 Hz, 1H), 4.75 (d, J = 11.7 Hz, 1H), 5.36 (d, J = 6.3 Hz, 1H), 5.37 (d, J = 17.1 Hz, 1H), 5.84−5.97 (m, 1H), 7.24−7.32 (m, 10H); ^{13}C-NMR, δ: 52.3, 70.9, 71.6, 74.0, 81.4, 82.3, 119.8, 127.7, 127.8, 128.0, 128.3, 134.5, 137.8, 138.0, 172.8; υ_{max}: 3534, 3033, 2955, 1740, 1497 cm^{-1}. Anal. Calcd for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C, 70.51; H, 6.92.

Methyl 3,4-Di-*O*-benzyl-6-*O*-pivaloyl-β-D-mannopyranoside (33). $[\alpha]_D$ = −8.1° (c = 0.58, $CHCl_3$); ^{1}H-NMR, δ: 1.20 (s, 9H), 3.44−3.51 (m, 1H), 3.52 (s, 3H), 3.58 (dd, J = 3.1, 9.0 Hz, 1H), 3.81 (t, J = 9.3 Hz, 1H), 4.09 (d, J = 2.6 Hz, 1H), 4.21 (dd, J = 6.1, 11.7 Hz, 1H), 4.33 (d, J = 1.1 Hz, 1H), 4.45 (dd, J = 2.3, 11.7 Hz, 1H), 4.59 (d, J = 10.7 Hz, 1H), 4.68 (d, J = 11.9 Hz, 1H), 4.77 (d, J = 11.9 Hz, 1H), 4.94 (d, J = 10.7 Hz, 1H), 7.26−7.40 (m, 10H); ^{13}C-NMR, δ: 27.2, 38.8, 56.7, 63.2, 66.0, 71.5, 73.3, 74.3, 75.3, 81.3, 100.6, 128.0, 128.1, 128.5, 137.6, 137.9, 178.2; υ_{max}: 3570, 2968, 1725 cm^{-1}. Anal. Calcd for $C_{26}H_{34}O_7$: C, 68.10; H, 7.47. Found: C, 67.91; H, 7.57.

Methyl 3,4-Di-*O*-benzyl-5-deoxy-6-*O*-pivaloyl-*lyxo*-hexonate (36). $[\alpha]_D$ = +32.1° (c = 1.77, $CHCl_3$); ^{1}H-NMR, δ: 1.15 (s, 9H), 1.62 (bs, 1H), 1.88−1.94 (m, 1H), 2.01−2.06 (m, 1H), 3.38 (d, J = 6.3 Hz, 1H), 3.72 (s, 3H), 3.74−3.84 (m, 2H), 4.06−4.12 (m, 2H), 4.45−4.49 (m, 2H), 4.59 (d, J = 11.0 Hz, 1H), 4.61 (d, J = 11.6 Hz, 1H), 4.70 (d, J = 11.6 Hz, 1H), 7.24−7.34 (m, 10H); ^{13}C-NMR, δ: 27.2, 29.8, 38.7, 52.5, 60.8, 71.7, 73.3, 73.5, 76.5, 80.4, 127.9, 128.2, 128.5, 137.5, 137.6, 172.9, 178. 3; υ_{max}: 3531, 2958, 1723, 1480 cm^{-1}. HRMS, calcd for $C_{26}H_{35}O_7$ (M + H): 459.2383. Found: 459.2370.

Methyl 3,4-Di-*O*-benzyl-6-chloro-5,6-dideoxy-*lyxo*-hexonate (37). $[\alpha]_D$ = +35.5° (c = 0.44, $CHCl_3$); ^{1}H-NMR, δ: 2.05−2.14 (m, 2H), 3.27 (d, J = 5.9 Hz, 1H), 3.55 (dd, J = 5.6, 7.2 Hz, 2H), 3.72 (s, 3H), 3.84 (t, J = 4.5 Hz, 1H), 3.89−3.94 (m, 1H), 4.44 (dd, J = 4.5, 5.9 Hz, 1H), 4.50 (d, J = 11.1 Hz, 1H), 4.61 (d, J = 11.7 Hz, 1H), 4.64 (d, J = 11.1 Hz, 1H), 4.69 (d, J = 11.7 Hz, 1H), 7.24−7.32 (m, 10H); ^{13}C-NMR, δ: 33.5, 41.5, 52.5, 71.4, 73.5, 73.7, 80.2, 128.0, 128.2, 128.5, 137.7, 172.8; υ_{max}: 3526, 3033, 2955, 1738, 1497 cm^{-1}. Anal. Calcd for $C_{21}H_{25}ClO_5$: C, 64.20; H, 6.41. Found: C, 64.30; H, 6.55.

Methyl 3,4,6-Tri-*O*-benzyl-5-deoxy-*lyxo*-hexonate (38). $[\alpha]_D$ = −6.1° (c = 0.57, $CHCl_3$); ^{1}H-NMR, δ: 1.85−1.95 (m, 1H), 1.96−2.10 (m, 1H), 3.44−3.52 (m, 2H), 3.54 (d, J = 6.9 Hz, 1H), 3.69 (s, 3H), 3.80 (t, J = 4.8 Hz, 1H), 3.84−3.92 (m, 1H), 4.38 (d, J = 11.8 Hz, 1H), 4.43 (d, J = 11.8 Hz, 1H), 4.44−4.49 (m, 2H), 4.55 (d, J = 11.0 Hz, 1H), 4.58 (d, J = 11.6 Hz, 1H), 4.67 (d, J = 11.6 Hz, 1H), 7.24−7.32 (m, 10H); ^{13}C-NMR, δ: 30.5, 52.3, 66.3; 71.6, 72.9, 73.1, 73.3, 77.3, 80.3, 127.6, 127.7, 127.8, 128.0, 128.2, 128.3, 128.4, 137.8, 128.3, 173.1; υ_{max}: 3532, 3067, 2954, 1743 cm^{-1}. Anal. Calcd for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94. Found: C, 72.30; H, 6.82.

Methyl 2,3-Di-*O*-benzoyl-4,6-benzylidene-5-deoxy-*lyxo*-hexonate (42). Radical fragmentation of **2** led to the isolation of an inseparable mixture of the 2- and 3- benzoates **40** and **41** in 9% isolated yield. To facilitate identification this mixture was benzoylated under standard conditions to give the title dibenzoate. $[\alpha]_D$ = +73.3° (c = 0.3, $CHCl_3$); ^{1}H-NMR, δ: 1.68 (broad d, J = 12.6 Hz, 1H), 2.13 (dq, J = 4.7, 12.6 Hz, 1H), 3.64 (s, 3H), 4.02 (dt, J = 2.8, 12.6 Hz, 1H), 4.32 (broad dd, J = 4.7, 12.6 Hz, 1H), 4.38−4.45 (m, 1H), 5.49 (s, 1H), 5.70 (d, J = 6.3 Hz, 1H), 5.81 (dd, J = 4.7, 6.3 Hz, 1H), 7.28−7.33 (m, 3H), 7.40−7.47 (m, 6H), 7.54−7.62 (m, 2H), 8.03−8.08 (m, 4H); ^{13}C-NMR, δ: 26.7, 52.6, 66.4, 70.4, 72.7, 75.0, 101.2, 126.0, 128.2, 128.5 (2), 128.8, 130.0, 133.5, 133.7, 138.0, 165.3, 165.5, 168.1; υ_{max}: 2957, 2930, 1727, 1452 cm^{-1}. HRMS, calcd for $C_{28}H_{26}O_8$ (M + H): 491.1706. Found: 491.1709.

Ethyl 3-*O*-Benzyl-4,6-*O*-benzylidene-1-deoxy-1-thio-α-D-mannopyranoside (44). A mixture of ethyl 4,6-*O*-benzylidene-1-deoxy-1-thio-α-D-mannopyranoside (**43**)[59] (4.22 g, 13.51 mmol) and dibutyltin oxide (4.05 g, 16.2 mmol) was heated to reflux in methanol (130 mL) for 1 h, before concentration under vacuum, dilution with DMF (100 mL), and treatment, at room temperature, with benzyl bromide (3.5 mL, 29.7 mmol). The reaction mixture was then heated to 110 °C for 30 min, cooled to room temperature, and poured into a two-phase mixture of ethyl acetate and saturated aqueous $NaHCO_3$. After separation, the organic layer was washed with brine, dried (Na_2SO_4), concentrated, and purified by column chromatography (eluent: hexane/ethyl acetate 10/1 → 3/1) to give the title compound as an oil (4.35 g, 80%). $[\alpha]_D$ = +145.2° (c = 1.45, $CHCl_3$); ^{1}H-NMR, δ: 1.27 (t, J = 7.4 Hz, 3H), 2.55−2.64 (m, 2H), 2.81 (s, 1H), 3.86−3.91 (m, 2H), 4.09−4.16 (m, 2H), 4.19−4.24 (m, 2H), 4.68 (d, J = 11.7 Hz), 4.84 (d, J = 11.7 Hz, 1H), 5.35 (s, 1H), 5.60 (s, 1H), 7.29−7.38 (m, 8H), 7.46−7.50 (m, 2H); ^{13}C-NMR, δ: 14.8, 24.9, 63.7, 68.6, 71.4, 73.1, 75.8, 79.1, 84.0, 101.6, 126.0, 127.8, 128.0, 128.2, 128.5, 128.9, 137.4, 137.7; υ_{max}: 3688, 3606, 2930, 1602 cm^{-1}. Anal. Calcd for $C_{22}H_{26}O_5S$: C, 65.65; H, 6.51. Found: C, 65.46; H, 6.51.

Ethyl 3-*O*-Benzyl-4,6-*O*-benzylidene-2-*O*-(*tert*-butyldimethylsilyl)-1-deoxy-1-thio-α-D-mannopyranoside (45). A solution of alcohol **44** (4.00 g, 9.94 mmol) and *tert*-butyldimethylsilyl triflate (3.4 mL, 14.9 mmol) and 2,6-lutidine (2.9 mL, 25 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 30 min and then washed with 1 M HCl, saturated aqueous $NaHCO_3$, and brine, and dried (Na_2SO_4). Concentration and chromatography on silica gel (eluent: hexane/ethyl acetate 25/1) gave the title compound as an oil (4.88 g, 95%). $[\alpha]_D$ = +78.3° (c = 4.1, $CHCl_3$); ^{1}H-NMR, δ: 0.10 (s, 3H), 0.12 (s, 3H), 0.95 (s, 9H), 1.30 (t, J = 7.4 Hz, 3H), 2.55−2.71 (m, 2H), 3.81−3.90 (m, 2H), 4.16−4.26 (m, 4H), 4.70 (d, J = 12.0 Hz, 1H), 4.82 (d, J = 12.0 Hz, 1H), 5.15 (s, 1H), 5.65 (s, 1H), 7.25−7.41 (m, 8H), 7.50−7.54 (m, 2H); ^{13}C-NMR, δ: 15.0, 18.2, 25.2, 25.8, 64.7, 68.7, 72.8, 76.1, 79.4, 86.7, 101.4, 126.1, 127.4, 127.8, 128.1, 128.14, 128.8, 137.7, 138.4; υ_{max}: 2954, 1602, 1471 cm^{-1}. Anal. Calcd for $C_{28}H_{40}O_5SSi$: C, 65.08; H, 7.80. Found: C, 65.04; H, 7.74.

Ethyl 3-*O*-Benzyl-4,6-*O*-benzylidene-2-*O*-(*tert*-butyldimethylsilyl)-1-deoxy-1-thio-α-D-mannopyranoside *S*-Oxide (46). To a solution of **45** (2.09 g, 4.0 mmol) in THF (25 mL) and water H_2O (2 mL) at 0 °C was added portionwise magnesium monperoxyphthalate (0.9 g) until all the substrate was consumed. The reaction mixture was then concentrated and extracted with ether. The extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), con-

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centrated, and purified by chromatography on silica gel (eluent: hexane/ethyl acetate 5/1) to give the title sulfoxide as an oil (1.94 g, 90%). $[\alpha]_D = -0.12°$ (c = 0.85, $CHCl_3$); ^{1}H-NMR, δ: 0.09 (2 s, 6H), 0.88 (s, 9H), 1.38 (t, J = 7.5 Hz, 3H), 2.63−2.71 (m, 1H), 2.92−2.99 (m, 1H), 3.61−3.70 (m, 1H), 3.76 (t, J = 10.0 Hz, 1H), 3.99 (dd, J = 3.1, 10.0 Hz, 1H), 4.17 (dd, J = 4.4, 10.0 Hz, 1H), 4.23 (t, J = 10.0 Hz, 1H), 4.41 (d, J = 1.3 Hz, 1H), 4.69−4.75 (m, 2H), 4.81 (d, J = 11.8 Hz, 1H), 5.61 (s, 1H), 7.24−7.35 (m, 8H), 7.42−7.45 (m, 2H); ^{13}C-NMR, δ: 5.8, 25.8, 43.9, 67.4, 68.3, 70.2, 73.2, 75.7, 78.0, 95.3, 101.6, 126.0, 127.6, 127.9, 128.2, 129.0, 137.2, 138.1; υ_{max}: 3005, 2930, 1603 cm^{-1}. Anal. Calcd for $C_{28}H_{40}O_6SSi$: C, 63.12; H, 7.57. Found: C, 62.98; H, 7.68.

Methyl 2,3,4-Tri-*O*-acetyl-6-*O*-[3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(*tert*-butyldimethylsilyl)-α-D-mannopyranosyl]-(1→6)-α-D-glucopyranoside (48) and Methyl 2,3,4-Tri-*O*-acetyl-6-*O*-[3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(*tert*-butyldimethylsilyl)-*β*-D-mannopyranosyl]-(1→6)-α-D-glucopyranoside (50). To a stirred solution of **46** (0.106 g, 0.199 mmol), **47** (0.190 g, 0.60 mmol),[60] and 2,6-di-*tert*-butyl-4-methylpyridine (44.9 mg, 0.22 mmol) in ether (10 mL) at −78 °C was added, dropwise, triflic anhydride (36.6 μL). The cloudy reaction mixture was stirred at −78 °C for 1 h and then allowed to warm to 0 °C over 1 h and maintained at that temperature for a further 1 h, before it was quenched with saturated aqueous $NaHCO_3$, washed with brine, dried (Na_2SO_4), concentrated, and purified by silica gel chromatography (eluent: hexane/ethyl acetate 5/1) to give the α-linked disaccharide **48** as an oil (90.2 mg, 59%) and the β-linked disaccharide **50**, also an oil (9.1 mg, 6%). The α-linked disaccharide **48**: $[\alpha]_D = +69.7°$ (c = 1.4, $CHCl_3$); ^{1}H-NMR, δ: 0.07 (s, 3H), 0.09 (s, 3H), 0.90 (s, 9H), 2.02 (s, 6H), 2.08 (s, 3H), 3.33 (s, 3H), 3.52 (dd, J = 2.2, 11.4 Hz, 1H), 3.66−3.86 (m, 4H), 3.86−3.96 (m, 1H), 4.04 (dd, J = 1.5, 2.9 Hz, 1H), 4.10 (t, J = 9.4 Hz, 1H), 4.19 (dd, J = 4.4, 9.8 Hz, 1H), 4.69 (d, J = 1.5 Hz, 1H), 4.70 (d, J = 12.0 Hz, 1H), 4.81 (d, J = 12.0 Hz, 1H), 4.85−4.92 (m, 2H), 5.06 (t, J = 9.8 Hz, 1H), 5.46 (t, J = 9.8 Hz, 1H), 5.60 (s, 1H), 7.24−7.39 (m, 8H), 7.47−7.51 (m 2H); ^{13}C-NMR, δ: −5.2, −4.5, 18.1, 20.6, 25.7, 55.2, 64.4, 65.0, 67.9, 68.8, 70.3, 70.7, 71.1, 72.9, 75.2, 79.0, 96.5, 101.5, 126.1, 127.3, 127.9, 128.0, 128.7, 137.7, 138.6, 169.4, 170.1; υ_{max}: 2955, 1751, 1465 cm^{-1}. Anal. Calcd for $C_{39}H_{54}O_{14}Si$: C, 60.45; H, 7.02. Found: C, 60.18; H, 6.97. The β-linked disaccharide **50**: $[\alpha]_D = +40.0°$ (c = 0.6, $CHCl_3$); ^{1}H-NMR, δ: 0.13 (s, 3H), 0.16 (s, 3H), 1.25 (s, 9H), 2.01 (s, 3H), 2.04 (s, 3H), 2.07 (s, 3H), 3.25−3.34 (m, 1H), 3.40 (s, 3H), 3.43−3.55 (m, 2H), 3.84−4.10 (m, 3H), 4.09 (t, J = 9.4 Hz, 1H), 4.17 (d, J = 2.6 Hz, 1H), 4.26−4.32 (m, 2H), 4.72 (d, J = 12.4 Hz, 1H), 4.78 (d, J = 12.4 Hz, 1H), 4.85 (dd, J = 3.6, 9.8 Hz, 1H), 4.93 (d, J = 3.6 Hz, 1H), 5.05 (t, J = 9.8 Hz, 1H), 5.50 (t, J = 9.8 Hz, 1H), 5.60 (s, 1H), 7.24−7.41 (m, 8H), 7.48−7.52 (m, 2H); ^{13}C-NMR, δ: −4.9, −4.2, 18.5, 20.7, 25.9, 55.5. 67.6, 68.3, 68.6, 68.7, 68.8, 70.0, 70.8, 71.1, 72.14, 77.7, 78.7, 96.5, 101.4, 102.5, 126.0, 127.4, 127.7, 128.1, 128.13, 128.8, 137.5, 138.3, 169.7, 170.1; υ_{max}: 2932, 1749, 1602 cm^{-1}. Anal. Calcd for $C_{39}H_{54}O_{14}Si$: C, 60.45; H, 7.02. Found: C, 60.12; H, 7.02.

Methyl 2,3,4-Tri-*O*-acetyl-6-*O*-(3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranosyl)-(1→6)-α-D-glucopyranoside (49). To a solution of **48** (140 mg, 0.18 mmol) was added tetrabutylammonium fluoride (1.0 M in THF, 1.0 mL, 1.0 mmol) in THF (1 mL), followed by stirring for 1 h at room temperature. The reaction mixture was then diluted with ether, washed with 1 M HCl, saturated aqueous $NaHCO_3$, and brine, dried (Na_2CO_3), concentrated, and purified by chromatography on silica gel (eluent: hexane/ethyl acetate 2/1) to give the disaccharide **49** as an oil (102.6 mg, 86%). $[\alpha]_D = +110.4°$ (c = 1.4, $CHCl_3$); ^{1}H-NMR, δ: 2.00 (s, 3H), 2.01 (s, 3H), 2.06 (s, 3H), 2.64 (s, 1H), 3.34 (s, 3H), 3.53 (dd, J = 2.1, 11.4 Hz, 1H), 3.71−3.95 (m, 5H), 4.03−4.09 (m, 2H), 4.20 (dd, J = 4.0, 9.4 Hz, 1H), 4.70 (d, J = 11.7 Hz, 1H), 4.83−4.92 (m, 4H), 5.06 (t, J = 9.8 Hz, 1H), 5.45 (t, J = 9.8 Hz, 1H), 5.58 (s, 1H), 7.24−7.38 (m, 8H), 7.45−7.49 (m, 2H); ^{13}C-NMR, δ: 20.6, 55.3, 63.4, 65.3, 67.8, 68.7, 69.8, 70.3, 70.7, 73.1, 75.3, 78.6, 96.6, 99.9, 101.6, 126.0, 127.8, 127.9, 128.1, 128.4, 128.8, 137.5, 137.9, 169.4, 170.1; υ_{max}: 3688, 2937, 1752, 1601 cm^{-1}. HRMS, calcd for $C_{33}H_{41}O_{14}$ (M + H): 661.2496. Found: 661.2493.

Methyl 2,3,4-Tri-*O*-acetyl-6-*O*-(3-*O*-benzyl-4,6-*O*-benzylidene-*β*-D-mannopyranosyl)-(1→6)-α-D-glucopyranoside (51). The conditions used for desilylation of **48** above were applied to **50** resulting in the recovery of 65% of **50** and the isolation of **51** as an oil (31%). $[\alpha]_D = +49.9°$ (c = 2.0, $CHCl_3$); ^{1}H-NMR, δ: 1.99 (s, 3H), 2.00 (s, 3H), 2.05 (s, 3H), 2.53 (s, 1H), 3.27−3.35 (m, 1H), 3.36 (s, 3H), 3.52−3.65 (m, 2H), 3.85 (t, J = 10.3 Hz, 1H), 3.92−4.00 (m, 2H), 4.08−4.15 (m, 2H), 4.30 (dd, J = 4.9, 10.4 Hz, 1H), 4.49 (d, J = 0.9 Hz, 1H), 4.73−4.91 (m, 4H), 4.96 (t, J = 10.1 Hz, 1H), 5.46 (t, J = 10.1 Hz, 1H), 5.58 (s, 1H), 7.24−7.37 (m, 8H), 7.45−7.49 (m, 2H); ^{13}C-NMR, δ: 20.7, 55.3, 66.9, 68.2, 68.4, 68.5, 69.0, 69.6, 70.0, 70.8, 72.5, 78.3, 96.4, 100.9, 101.5, 126.0, 127.8, 127.84, 128.2, 128.4, 128.9, 137.4, 137.9, 169.9, 170.0, 170.1; υ_{max}: 3683, 2938, 1750, 1601 cm^{-1}. HRMS, calcd for $C_{33}H_{41}O_{14}$ (M + H): 661.2496. Found: 661.2500.

Methyl 2,3,4-Tri-*O*-acetyl-6-*O*-[3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(1-bromo-2-methoxy-2-propyl)-α-D-mannopyranosyl]-(1→6)-α-D-glucopyranoside (52). This mixed acetal was prepared from **51** as a mixture of two diastereomers by protocol B (34% recovered substrate). It was isolated in 62% yield as an oil. ^{1}H-NMR, δ: 1.42 + 1.53 (2 × s, 3H), 1.95−2.10 (m, 9H), 3.10−3.42 (m, 7H), 3.42−3.61 (m, 2H), 3.70−3.93 (m, 5H), 4.09−4.21 (m, 3H), 4.67−4.92 (m, 5H), 4.99−5.08 (m, 1H), 5.45 + 5.48 (2 × d, J = 9.5 Hz, 1H), 5.60 + 5.61 (2 × s, 1H), 7.24−7.37 (m, 8H), 7.47−7.51 (m, 2H); ^{13}C-NMR, δ: 20.7, 21.6, 22.4, 25.0 25.3, 35.2, 35.9, 49.5, 49.6, 50.0, 55.2, 55.3, 64.2, 65.4, 67.9, 68.8, 68.9, 69.0, 69.6, 70.3, 70.8, 70.9, 72.9, 73.2, 73.3, 74.4, 74.6, 78.6, 78.7, 96.5, 96.53, 99.7, 100.2, 101.4, 101.5, 101.6, 101.7, 126.1, 127.4, 127.55, 127.6, 127.8, 128.1, 128.2, 128.7, 128.8, 137.6, 137.7, 138.1, 138.3, 138.5, 169.5, 170.1; υ_{max}: 2936, 1751, 1602 cm^{-1}.

Acknowledgment. We are grateful to NSF (CHE 9222697) for support of this work. D.C. is a Fellow of the A. P. Sloan Foundation.

Supporting Information Available: Copies of ^{1}H- and ^{13}C-NMR spectra of **13**, **14**, **36**, **42**, **49**, **51**, and **52** (14 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.

JO951194H

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