Efficient Intramolecular Glycosylation Supported by a Rigid Spacer

Matthias Müller, Ursula Huchel, Armin Geyer, and Richard R. Schmidt*

Fakultät Chemie, Universität Konstanz, Fach M 725, D-78457 Konstanz, Germany

Received January 26, 1999

The *m*-xylylene moiety was employed as rigid spacer in intramolecular glycoside bond formation. Fifteen-membered macrocycle formation starting from 6-*O*-linked donor and 6- and 4-*O*-linked acceptor (**5a,b**, **6b**) led exclusively to β(1-4)- and β(1-6)-linked compounds **7**β and **8**β, respectively, which gave cellobioside and gentiobioside derivatives. The glycosylation yields could be improved by 14-membered macrocycle formation. In the four cases studied, the donor was 6-*O*-linked to the spacer. For the acceptor linkage to the spacer and the accepting hydroxy group, relative D-/L-*threo*- and D-/L-*erythro*-arrangements were chosen. Standard glycosylation conditions led in three cases (**13**, **14**, **23**) only to β-linkage in high yield (**16**β, **17**β, **25**β). For the transformation of **24**, having a D-*erythro*-arrangement in the acceptor moiety, the α-anomer **26**α was preferentially obtained. Limitation of the conformational space of the donor and the acceptor as in **31**, which is stereochemically identical with **24**, led to the corresponding α-glycoside **32**α in 87% yield. Synthesis of a pseudo mirror image of **23** [having 6-(D)/3-(D-*threo*)-arrangement], namely **35**, having 3(L)/6-(L-*threo*)-arrangement of the donor and acceptor moieties, expectedly gave only α-glycoside **36**α in very high yield. Thus, the efficiency and versatility of this conceptual approach to intramolecular glycoside bond formation is exhibited.

Glycosyl transfer within the active site of an enzyme can be regarded as an intramolecular process in which the anomeric center of the glycosyl donor and the accepting moiety are held in close proximity to ensure regio- and diastereoselective glycoside bond formation (Scheme 1).[1,2] To enforce a similar in vitro reaction course, various approaches to intramolecular glycoside bond formation have been studied.[3−14] These approaches are mainly based on attachment of the acceptor via a spacer Y to the 2-hydroxy group of the donor[3−10] ("functional-substituent-based approach") or, alternatively, to the leaving group of the donor[11−14] ("leaving-group-based approach"), and varying results have been obtained. The functional-substituent-based approach, generating five-membered cyclic transition states (Y = SiR_2, CR_2),[3,5−7] resulted generally in good anomer selectivity. However, the anomer selectivity is dependent on the configuration of the 2-hydroxy group (β-2-OH → β-glycoside; α-2-OH → α-glycoside), and depending on the spacer type, this process may even violate the ring closure rules,[15] thus favoring unwanted competing reactions. With larger spacer systems at the 2-hydroxy group (Y = CO−CH_2−CH_2−CO−)[8] or at any other position of the donor,[9,10] as a result of missing steric constraints, often not only was the anomer selectivity found to be low but also the yields were modest. For some cases of leaving-group-based reactions, an intermolecular reaction course could even be verified, though model considerations favored intramolecularity of the process.[13]

The close proximity between glycosyl donor and glycosyl acceptor in the active site of an enzyme is generated by specific binding between the enzyme and the substrate, leading to a structurally rigid array composed of large rings that enforce (regio- and) diastereoselective glycoside bond formation.[16] To extend this concept to face-selective intramolecular glycoside bond formation, a rigid spacer concept was proposed by us (Scheme 1),[17] which

(1) (a) Schmidt, R. R.; Dietrich, H. *Angew. Chem.* **1991**, *109*, 1348−1349; *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1328−1329. (b) Schmidt, R. R.; Frische, K. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1747−1750. (c) Amann, F.; Schaub, C.; Müller, B.; Schmidt, R. R. *Chem. Eur. J.* **1998**, *4*, 1106−1115.

(2) (a) Sinnott, L. M. *Chem. Rev.* **1990**, *90*, 1171−1202. (b) Legler, G. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 319−384.

(3) Barresi, F.; Hindgaul, O. J. *J. Am. Chem. Soc.* **1991**, *113*, 9376−9377; *Synlett* **1992**, 759−761; *Can. J. Chem.* **1994**, *72*, 1447−1465.

(4) Preuss, R.; Jung, K.-H.; Schmidt, R. R. *Liebigs Ann. Chem.* **1992**, 377−382.

(5) Stork, G.; Kim, G. J. *J. Am. Chem. Soc.* **1992**, *114*, 1087−1088.

(6) Bols, M. J. *Chem. Soc., Chem. Commun.* **1992**, 913−914; *Acta Chem. Scand.* **1996**, *50*, 931−937.

(7) Ito, Y.; Ogawa, T. *Angew. Chem.* **1994**, *106*, 1843−1845; *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1765−1767; *J. Am. Chem. Soc.* **1997**, *119*, 5562−5566.

(8) (a) Ziegler, T.; Lau, R. *Tetrahedron Lett.* **1995**, *36*, 1417−1420. (b) Lau, R.; Schüle, G.; Schwaneberg, U.; Ziegler, T. *Liebigs Ann.* **1995**, 1745−1754. (c) Schüle, G.; Ziegler, T. *Liebigs Ann.* **1996**, 1599−1607. (d) Ziegler, T.; Lemanski, G. *Eur. J. Org. Chem.* **1998**, *163*, 3−170; *Angew. Chem.* **1998**, *110*, 3367−3369; *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3129−3132.

(9) (a) Valverde, S.; Gomez, A. M.; Hernandez, A.; Herradon, B.; Lopez, J. C. *J. Chem. Soc., Chem. Commun.* **1995**, 2005−2006. (b) Valverde, S.; Gomez, A. M.; Lopez, J. C.; Herradon, B. *Tetrahedron Lett.* **1996**, *37*, 1105−1108.

(10) Yamada, H.; Imamura, K.; Takahashi, T. *Tetrahedron Lett.* **1997**, *38*, 391−394.

(11) (a) Schmidt, R. R.; Stumpp, M. *Liebigs Ann. Chem.* **1983**, 1249−1259. (b) Schmidt, R. R. In *Carbohydrates − Synthetic Methods and Applications in Medicinal Chemistry*; Ogura, H., Hasegawa, A., Suami, T., Eds.; Kodanasha Ltd.: Tokyo, 1992; 68−88. (c) Behrendt, M. E.; Schmidt, R. R. *Tetrahedron Lett.* **1993**, *34*, 6733−6736.

(12) Iimori, T.; Shibazaki, T.; Ikegami, S. *Tetrahedron Lett.* **1996**, *37*, 2267−2270.

(13) Scheffler, G.; Schmidt, R. R. *Tetrahedron Lett.* **1997**, *38*, 2943−2946; *J. Org. Chem.* **1999**, in press.

(14) Mukai, C.; Itoh, T.; Hanaoka, M. *Tetrahedron Lett.* **1997**, *38*, 4595−4598.

(15) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734−736; 738−741.

(16) In a way, this phenomenon is also effective in the intramolecular transglycosidation in cyclodextrin formation.

(17) Huchel, U.; Schmidt, R. R. *Tetrahedron Lett.* **1998**, *39*, 7693−7694.

10.1021/jo990132e CCC: $18.00
Published on Web 07/29/1999

Scheme 1

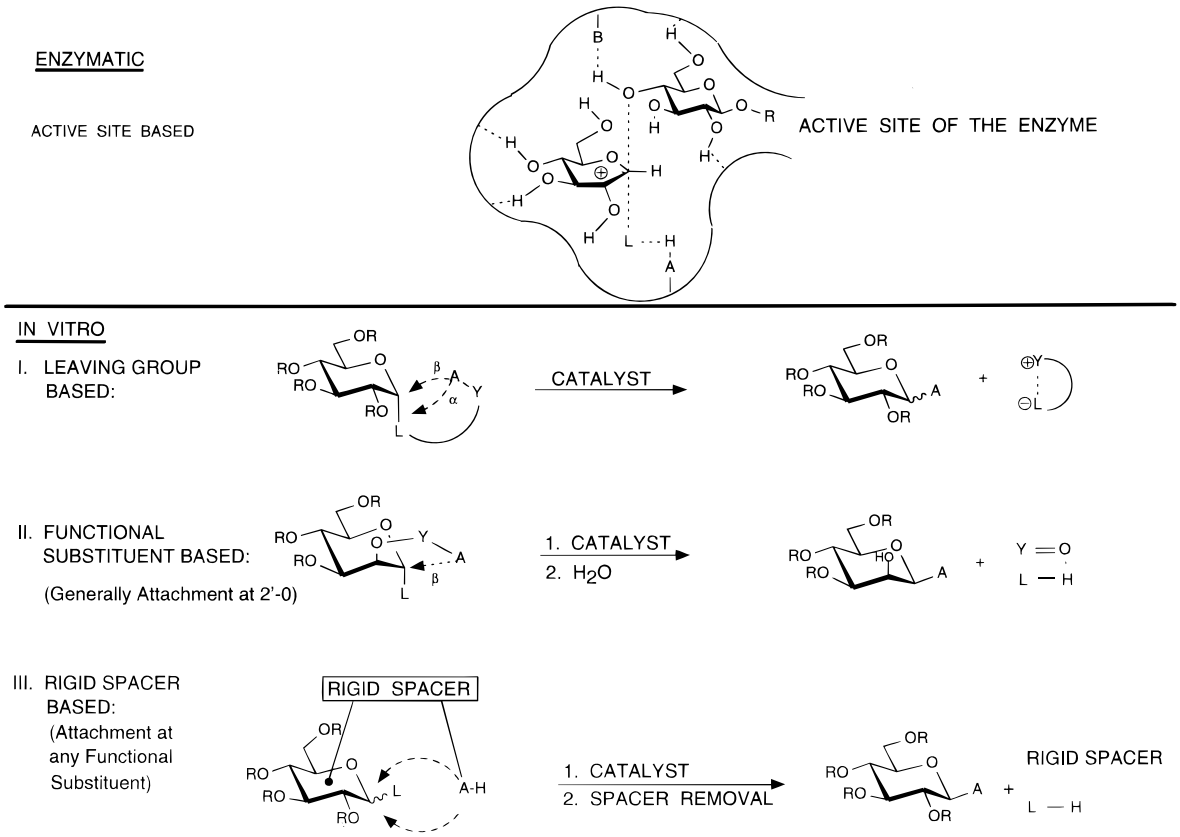


Table 1. Transformation of 5a,b into 7β

educt	conc (mol/L)	reaction conditions	yield of 7β (%)
5a	0.01	NIS (1.3 equiv), TMSOTf (0.1 equiv), CH_2Cl_2, room temperature	65
5b	0.1	NIS (1.3 equiv), TMSOTf (0.1 equiv), Toluene, room temperature	46
	0.05		56
	0.01		63

as a result of geometrical constraints should lead to the desired diastereocontrol.

This concept can be now verified with the *m*-xylylene residue as rigid spacer.[17] Attachment of the donor, for instance, via the 6-hydroxy group of D-glucose corresponding to β-face attachment [6(β)] (Scheme 2), can be readily performed. In the acceptor, any cyclic 1,3- or 1,2-*threo*- or -*erythro*-diol arrangement, structural entities common to all sugar residues, will allow for attachment to the spacer and will also provide the desired accepting hydroxy group. As shown below, this design keeps the reacting centers at proper distance and enforces the desired diastereoselection in the glycosylation step via the formation of macrocyclic rings (14- and 15-membered rings) from which the products can be readily liberated.

Results and Discussion

Generation of 15-Membered Macrocycles. For the investigation of this concept, ethyl β-thioglucoside **1a**[18] and 4-penten-1-yl glucoside **1b** (α:β = 9:1)[19] were transformed with α,α'-dibromoxylene (**2**) in the presence of NaH as base and 15-crown-5 as supporting reagent into 6-*O*-linked derivatives **3a** and **3b**, respectively (Scheme 3). Treatment of known 4,6-*O*-unprotected glucoside **4**[20] with dibutyltin oxide in toluene and then reaction with **3a,b** in the presence of tetrabutylammonium iodide afforded the desired 6a,6b-*O*-linked intermediates **5a** and **5b** (**5a**: 41%; **5b**: 64%). Correspondingly, direct reaction of **3b** with **4** in the presence of NaH and 15-crown-5 gave, besides **5b**, the 4a,6b-*O*-linked intermediate **6b**. Activation of **5a** with *N*-iodo-succinimide (NIS, 1.3 equiv) and trimethylsilyl trifluoromethanesulfonate (TMSOTf, 0.1 equiv)[21] in CH_2Cl_2 at room temperature afforded the desired (1-4)-linked disaccharide moiety, which is part of the 15-membered macrocycle **7**β, as the only monomeric product (Table 1). The β-configuration could be assigned with the help of NMR data (2b-H: $J_{1,2}$ = 7.4 Hz). Activation of the pentenyloxy group in **5b** with NIS/TMSOTf[19] afforded also **7**β. The yield is, as expected, concentration-dependent (Table 1), and intermolecular oligomer formation seems to be the competing reaction. Thus, it is exhibited that diastereofacial control in the intramolecular glycosylation step is independent of the glycosyl donor configuration and even at room temperature one anomer is exclusively generated. Hydrogenolytic *O*-debenzylation of **7**β and then *O*-acetylation afforded known cellobioside **9**β,[22] which was structurally assigned by homo- and heteronuclear NMR spectra.

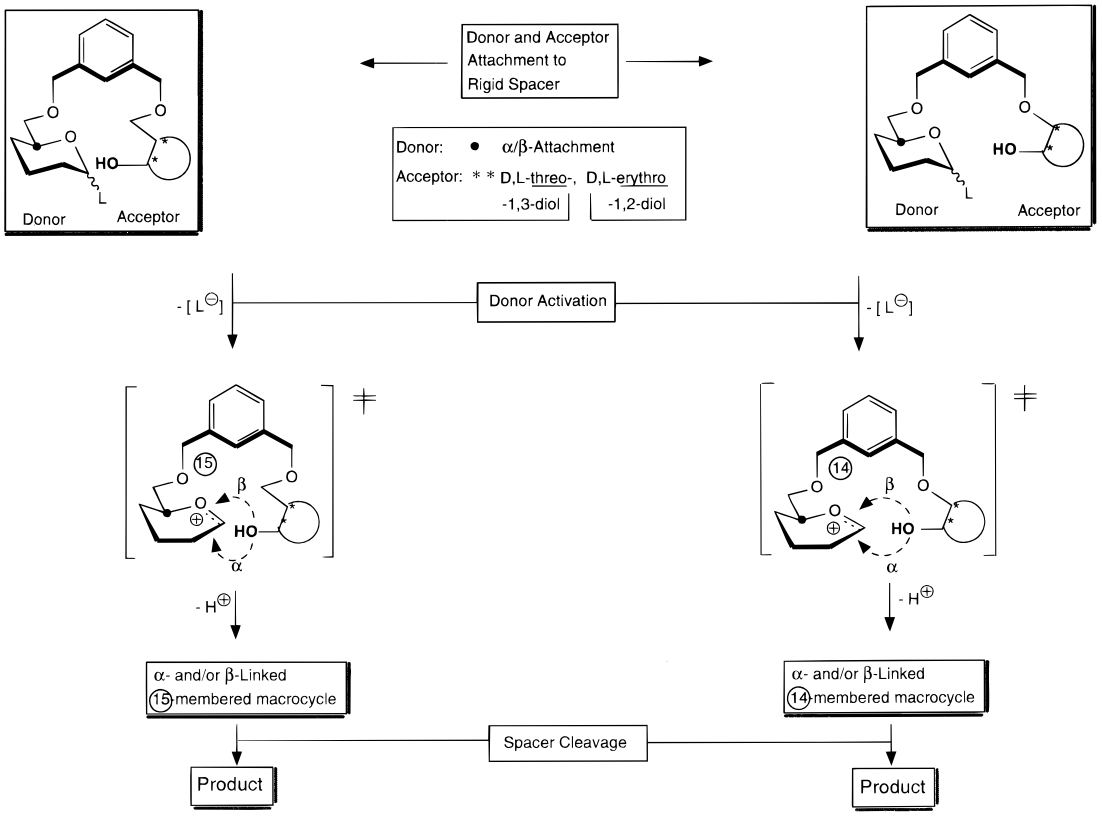
(18) Garegg, P. J.; Kvarnström, I.; Niklasson, A.; Svensson, S. C. T. *J. Carbohydr. Chem.* **1993**, *12*, 933−935.

(19) (a) Mootoo, D. R.; Konradsson, P.; Udodong, U. E.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583−5584. (b) Hondier, S.; Vottero, P. J. A. *Angew. Chem.* **1994**, *106*, 365−367; *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 354−355.

(20) Bell, D. J.; Lorber, J. *J. Chem. Soc.* **1940**, 453−455.

(21) (a) Veeneman, G. H.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331−1334. (b) Konradsson, P.; Udodon, U. E.; Fraser-Reid, B. *Tetrahedron Lett.* **1990**, *31*, 4313−4316.

Scheme 2



Detailed NMR studies[23] of compound **7**β and molecular mechanics simulations (MM^+, HyperChem) showed that the generally observed *syn* β(1-4)-arrangement of the glucopyranose residues a and b is readily accessible (Figure 1). There is also some flexibility between the benzene ring on one side and the disaccharide moiety on the other side. Thus, β-face attachment of the glycosyl donor at the 6-position to the spacer which is linked via the 6-hydroxy group to a 5,4-L-*threo*-arranged acceptor moiety as in **5** [designation: 6(β)/6(5,4-L-*threo*)-arrangement; see Table 2] provides β-face selective glycosylation. However, also from model considerations, high conformational flexibility in this system can be deduced. Therefore, the intermolecular reaction can compete with the formation of the 15-membered ring.

Not surprisingly, a similar result is obtained when the attachment of the acceptor to the spacer is reversed as in **6b**, i.e., the donor/spacer combination **3b** is linked via the 4-hydroxy group to a 4,6-*O*-unprotected L-*threo*-arranged acceptor to yield **6b** [having 6(β)/4(4,5-L-*threo*)-arrangement]. Activation of **6b** with NIS/TMSOTf in toluene at room temperature afforded the 15-membered ring β(1-6)-linked **8**β in 72% yield. The conformational assignment (Figure 1) exhibited again, as observed for **7**β, some flexibility between the benzene ring and the disaccharide moiety.[23] Hydrogenolytic *O*-debenzylation of **8**β and then *O*-acetylation afforded known gentiobioside derivative **10**β,[24] which was structurally assigned by homo- and heteronuclear NMR spectra.

Generation of 14-Membered Macrocycles. From the preceding results, it can be concluded that only β-face selective ring closure to a 15-membered ring is observed for a system that has the *m*-xylylene residue as rigid spacer, β-face attachment of the donor, and L-*threo*-1,3-diol arrangement in the acceptor moiety. However, the product yields of ~70% in this system are not yet satisfactory. On the basis of conformational studies with **7**β and **8**β,[23] ring closure to a 14-membered ring was envisaged to further limit the conformational space of the donor and/or the acceptor moiety and to favor the intramolecular reaction course. This idea was also supported by model considerations, which exhibited practically strain-free access to 14-membered rings that contain the *m*-xylylene residue as rigid spacer.

To this end, donor/spacer-linked intermediate **3a** was treated with 2,3-*O*-unprotected glucose derivative **11**[25] in the presence of NaH as base in DMF, affording mainly 2-*O*-linked compound **13** (Scheme 4; 2-*O*/3-*O*-attachment = 5:1), which had 6(β)/2(2,3-L-*threo*)-arrangement. Glycosylation under standard conditions furnished 14-membered macrocycle **16**β in 81% yield, thus resulting in the desired high glycoside yield combined with exclusive β-selectivity. Conformational studies with **16**β, based on NMR experiments and molecular mechanics simulations (Figure 2), demonstrated that the glycosidic linkage possesses the unusual *anti*-conformation.[23] Hydrogenolytic *O*-debenzylation of **16**β and then *O*-acetylation afforded

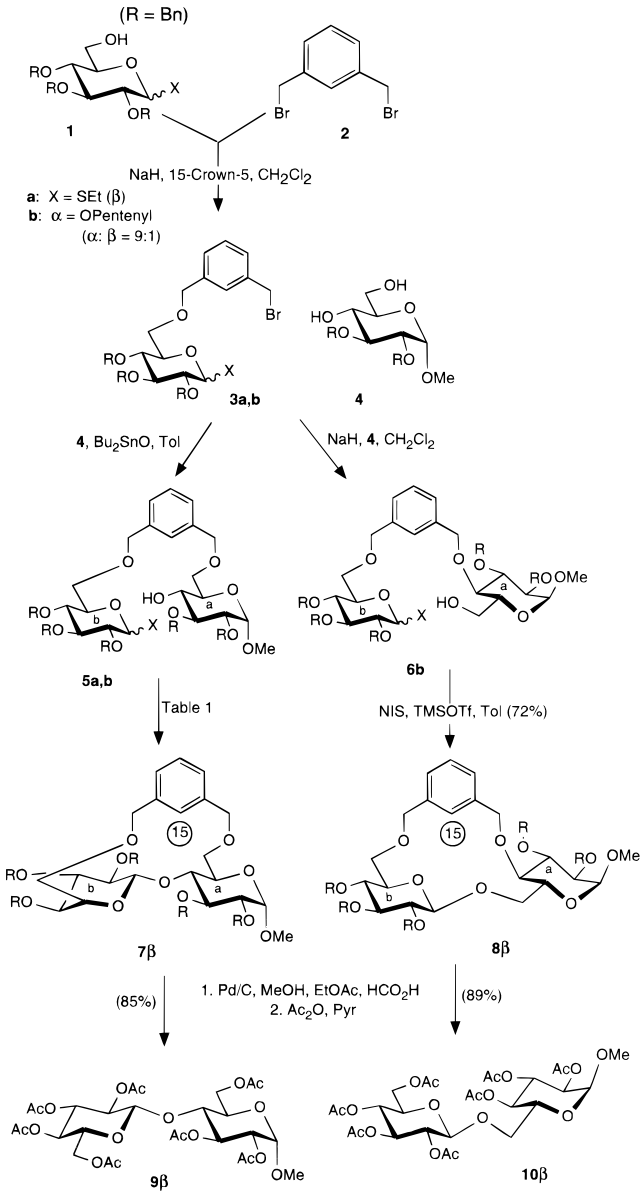
(22) Gi, C. T.; Ishihara, H.; Tejima, S. *Chem. Pharm. Bull.* **1978**, *26*, 1570−1575.

(23) (a) ^{1}H and ^{13}C assignments by DQF-COSY and HMQC spectra. For details, see: Geyer, A.; Huchel, U.; Schmidt, R. R. *Magn. Reson. Chem.* **1999**, *37*, 145−148. (b) The figures show energy minized average conformations of a 100 ps molecular dynamics simulation. *J*-Coupling-derived torsion angles and ROE-derived distances served as experimental restraints. Ten snapshots from each calculation are also shown. Three overlayed structures of **32**α differ in the exocyclic torsion of ring b, where conformational averaging was observed. NMR and modelling procedures are described in ref 23a.

(24) Kochetkov, N. K.; Klimov, E. M.; Malysheva, N. N.; Demchenko, A. V. *Carbohydr. Res.* **1991**, *212*, 77−91.

(25) Hall, D. M. *Carbohydr. Res.* **1980**, *86*, 158−160.

Scheme 3



known β(1-3)-linked disaccharide **18**β,[26] which was structurally assigned by homo- and heteronuclear NMR spectra.

Besides the 6(β)/2(L-*threo*)-arrangement, as in **14**, the other three stereochemically possible 1,2-diol arrangements also were investigated in order to elucidate the influence of the donor attachment (α and β) versus the influence of the relative acceptor configuration (D,L-*threo*, -*erythro*) on the facial selectivity in the glycosylation step. To this end, **3a** was treated with 4-*O*-unprotected galactose derivative **12** in the presence of NaH as base and in DMF as the solvent to afford 4a-*O*-linked intermediate **14**; reaction with DDQ in CH_2Cl_2 furnished 3a-*O*-unprotected **15**, which had 6(β)/4(4,3-L-*erythro*)-arrangement. Glycosylation under standard conditions afforded the glycosidic linkage in 83% yield, and only β-product **17**β was obtained. The preferred conformation is depicted in Figure 2, exhibiting *syn*-conformation for the glycosidic linkage in the 14-membered ring, which seems to be accessible without any steric strain. Hydrogenolytic

(26) Takeo, K. *Carbohydr. Res.* **1977**, *59*, 258−260.

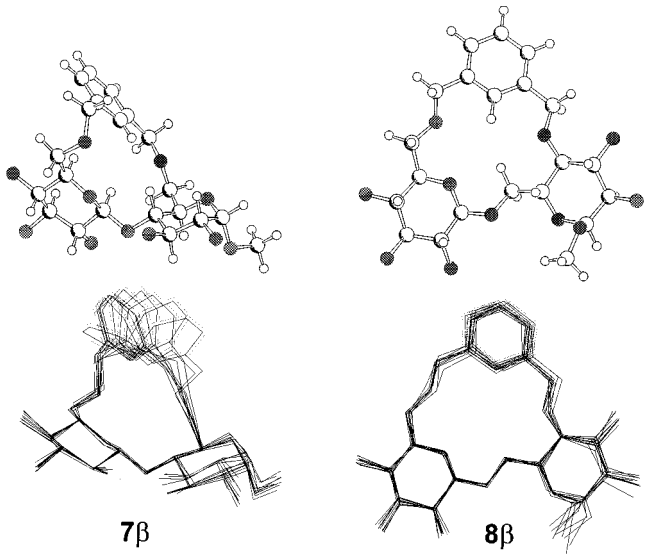


Figure 1. Energy minimized average conformations of **7**β and **8**β.[23b]

Table 2. Gycoside Bond Formation Results

		results			
compd	rel config donor/acceptor	compd	ring size	linkage	yield (%)
5a,b	6(β)/6(5,4-L-*threo*)	**7*β***	15	Glcβ(1−4)Glc	65
6b	6(β)/4(4,5-L-*threo*)	**8*β***	15	Glcβ(1−6)Glc	72
13	6(β)/2(2,3-L-*threo*)	**16*β***	14	Glcβ(1−3)Glc	81
15	6(β)/4(4,3-L-*erythro*)	**17*β***	14	Glcβ(1−3)Gal	84
23	6(β)/3(3,4-D-*threo*)	**25*β***	14	Glcβ(1−4)Glc	84
24	6(β)/3(3,4-D-*erythro*)	**26**α,***β***	14	Glcα/β(1−4)Gal	77
31	6(β)3(3,4-D-*erythro*)	**32**α	14	Glcα(1−4)Gal	87
35	3(β)/6(5,4-L-*threo*)	**36**	14	Glcα(1−4)Glc	93

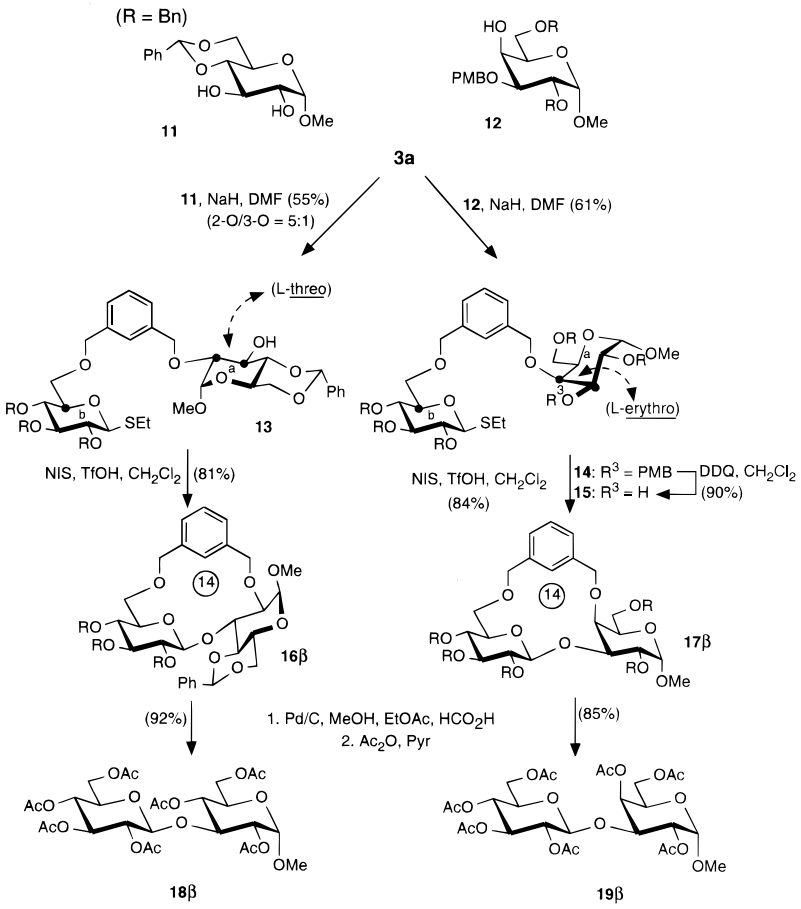
O-debenzylation of **17**β and then *O*-acetylation led to known β(1-3)-linked disaccharide **19**β,[27] which was structurally assigned by homo- and heteronuclear NMR spectra.

D-*threo*-Linkage in the acceptor moiety could also be readily constructed from **3a**: reaction with 3-*O*-unprotected glucose derivative **20**[28] in the presence of NaH as base and 15-crown-5 as supporting agent afforded the 3a-*O*-alkylated intermediate **22** (Scheme 5). Ensuing reductive opening of the benzylidene group with $NaCN{\cdot}BH_3$ in the presence of HCl in THF[29] furnished 4a-*O*-unprotected intermediate **23**, which had the desired 6(β)/3(3,4-D-*threo*)-arrangement. The same sequence of reactions as described above led to exclusive β(1-4)-linkage, affording **25**β in 84% yield, and finally to known cellobioside **9**β.[22] The conformation of **25**β depicted in Figure 2[23] shows *syn*-arrangement for the glycosidic linkage and the limited flexibility of the benzene ring relative to the disaccharide moiety.

Finally, D-*erythro*-linkage in the acceptor moiety was investigated. To this end, 3,4-*O*-unprotected galactose intermediate **21**[30] was treated with dibutyltin oxide in toluene, and then **3a** was added to furnish the 3-*O*-linkage, thus providing the desired 6(β)/3(3,4-D-*erythro*)-

(27) Wozney, Y. V.; Backinowsky, L. V.; Kochetkov, N. K. *Carbohydr. Res.* **1979**, *73*, 282−286.
(28) Qin, H.; Grindley, T. B. *J. Carbohydr. Chem.* **1996**, *15*, 95−108.
(29) Garegg, P. J.; Hultberg, H.; Wallin, S. *Carbohydr. Res.* **1982**, *108*, 97−101.
(30) Schneider, J.; Lee, Y. C.; Flowers, H. M. *Carbohydr. Res.* **1974**, *36*, 159−166.

Scheme 4



arranged intermediate **24**. Already, model considerations had exhibited that the *β*-face of the donor is less accessible than the α-face, and this was proven by the experiment: application of standard glycosylation conditions to **24** led to glycoside bond formation in 77% yield. However, for the first time a mixture of α/*β*-anomers **26**α,*β* was obtained (α:*β* = 3:1). The structural assignments were supported by hydrogenolytic *O*-debenzylation and then *O*-acetylation, yielding α/*β*(1-4)-linked disaccharides **27**α and **27***β*.

The four sterically different systems exhibit that high glycosylation yields can be readily obtained in 14-membered ring formation and that 6-(*β*-face)-attachment of the donor to the *m*-xylylene residue as rigid spacer system yields, for D- and L-*threo*- and L-*erythro*-attachment of the acceptor, exclusively *β*-linkage; only for D-*erythro*-attachment is preferential α-linkage formation observed. These promising results led to two further questions: (i) Can the glycosylation yields be increased by further limiting the conformational space of the donor and acceptor moieties? (ii) Can α- vs *β*-glycoside bond formation in a 14-membered ring system be reached by formally inverting the relative attachment of the donor and the acceptor moieties to the rigid spacer system? Answers to these questions are given below.

Limitation of the Conformational Space of the Donor and Acceptor Moieties. The *m*-xylylene spacer provides free rotation around the benzene carbon/methylene bonds, thus permitting conformations where the reacting centers are far apart. Obviously, this large conformational space can be reduced as shown in Scheme 6 with the help of substituents in the 4- and 6-position of the xylylene residue. Because of their geometry, phenyl rings seemed to be particularly attractive as substituents because they limit the conformational space of the methylene groups but still permit S_N2 reactions at the methylene carbons to construct the required starting materials. The envisaged spacer could be readily obtained from known dimethyl-*m*-terphenyl **28**;[31] bromination with *N*-bromo-succinimide (NBS) gave bis(bromomethyl)-derivative **29** as the required precursor.

Investigation of the 6(*β*)/3(3,4-D-*erythro*)-arrangement as in **24** seemed particularly attractive for this study because in this case not only was an α/*β*-product mixture obtained but also the yield was somewhat lower compared with the other cases of 14-membered ring formation. Therefore, **29** was reacted with **1a** in the presence of NaH as base to afford 6-*O*-alkylated product **30** (Scheme 7). Treatment of **21** with dibutyltin oxide in toluene, and then with **30**, afforded the desired 3a-*O*-alkylation product **31**, which is structurally related to **24**. Glycosylation studies with **31** under the same conditions not only led to a higher yield (87%) but also greatly improved the face selectivity; only α-product **32**α was obtained. Hydrogenolytic *O*-debenzylation and then *O*-acetylation afforded as expected **27**α, and **28** could also be recovered. Results of the conformational studies of **32**α are depicted in Figure 3.[23] They exhibit *syn*-conformation for the glycosidic part; **32**α is the only cyclic compound which exhibits rotational isomerism about the exocyclic

(31) Chardonnens, L.; Chardonnens, H. *Helv. Chim. Acta* **1958**, *41*, 2109−2111.

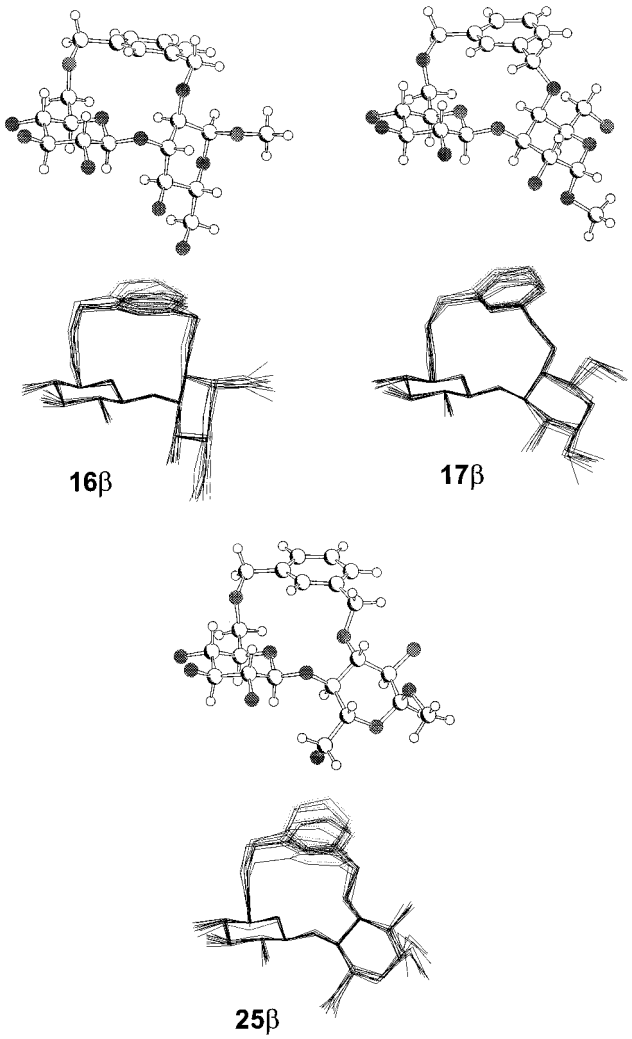


Figure 2. Energy minimized average conformations of **16***β*, **17***β*, and **25***β*.[23b]

5-6-bond of ring b. The main conformation (50%) populates the gg rotamer ($^3J_{5b-6proR} = 5.9$ Hz, $^3J_{5b-6proS} = 7.0$ Hz).

Formal Inversion of the Stereochemistry of Donor and Acceptor Attachment to the Rigid Spacer. Inversion of the relative stereochemistry of acceptor attachment can be obtained by changing the attachment site in a 1,2- or 1,3-*erythro*-diol system or by choosing enantiomeric *threo*-1,2- or 1,3-diol arrangement. For stereochemically different donor attachment, formally two alternatives exist: either inversion of the configuration of the attachment site is performed, thus going from *β*-face to α-face attachment and vice versa, or the face of the attachment is retained. However, the attachment site is on the opposite half of the pyranose plane. This pseudo-inversion of the relative stereochemistry is exhibited in Scheme 8 where, for instance, a 6(*β*)/3(D-*threo*)-arrangement should lead via transition state **A**‡ to the *β*-linked disaccharide. This experiment was already performed by the transformation of **23** into **25***β*, furnishing only *β*-linkage in 84% yield. Changing the donor attachment site to the 3(*β*)-oxygen and selecting for the acceptor attachment an L-*threo*-1,3-diol system, to retain 14-membered ring formation, should then lead via transition state **B**‡ to the α-anomer.

To test this hypothesis, **2** was reacted with 3-*O*-unprotected thioglycoside **33**, in the presence of NaH as base, to afford **34** (Scheme 9). For the acceptor attachment, 4,6-*O*-unprotected glucoside **4**[20] was treated with dibutyltin oxide in toluene, and then **34** was added to give the desired intermediate **35**. Glycosylation under standard conditions gave exclusively the α-anomer **36**α in 93% yield. Results of the conformational studies of **36**α are shown in Figure 3. The unexpectedly weak transglycosidic NOE corresponds to a gauche orientation of both glycosidic angles with ϕ (H1−C1−O4−C4) = −67° and ψ (C1−O4−C4−H4) = −55°. Further structural proof for **36**α was obtained from hydrogenolysis and then *O*-acetylation, leading to known maltoside **9**α,[32] which was structurally assigned by homo- and heteronucleoar NMR spectra.

Conclusion

The rigid *m*-xylylene spacer permits, at room temperature, highly face-selective and efficient intramolecular glycoside bond formation. This is particularly noteworthy because high anomeric control is generally not observed for glucopyranosyl and galactopyranosyl donors at room temperature unless there is anchimeric assistance. In the high yielding 14-membered ring formation, competing intermolecular glycoside bond formation plays, if at all, only a minor role. As exhibited, further potential for this intramolecular reaction is available by further limiting the conformational space of the glycosyl donor and acceptor moiety. Formal inversion of the relative stereochemical attachment of the donor and the acceptor moiety yields either α- or *β*-glycosides, as desired. Therefore, a powerful methodology for oligosaccharide synthesis in general can be based on this new conceptual approach.

Experimental Section

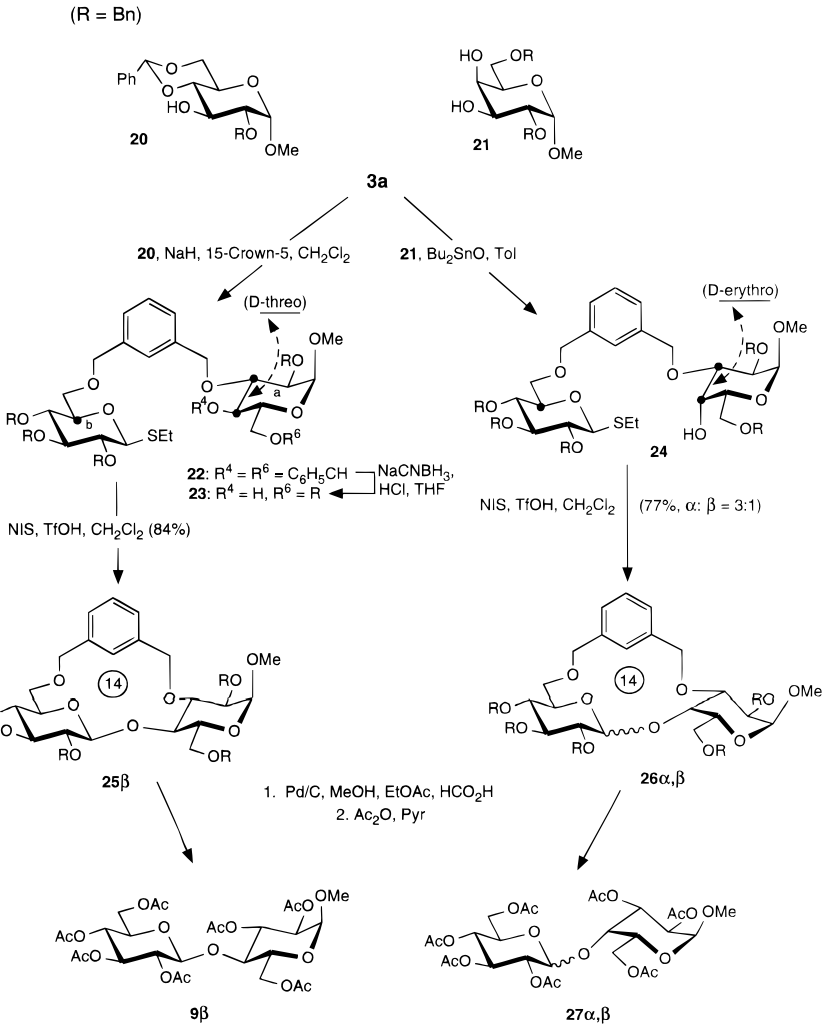
Solvents were purified in the usual way; boiling range of petroleum ether: 35−60 °C. Melting points are uncorrected. Thin-layer chromatography (TLC): plastic sheets, silica gel 60 F_{254} (layer thickness 0.2 mm). Flash chromatography: silica gel (30−60 *μ*m). Optical rotations: 1 dm cell, 20 °C. NMR spectra: DQF-COSY, HMQC, and compensated ROESY spectra were acquired on a 600 MHz NMR spectrometer at 300 K, internal standard tetramethylsilane (TMS). MALDI-MS: positive mode, 2,5-dihydroxybenzoic acid (DHB) matrix; FAB-MS: positive mode, 3-nitrobenzyl alcohol (NBOH)/NaI matrix.

General Procedure for the Synthesis of Compounds 3a,b. To a solution of **2** (528 mg, 2.0 mmol) and **1a,b** (1.0 mmol) in dry dichloromethane (10 mL) at −17 °C are added 15-crown-5 (220 *μ*L, 1.1 mmol) and sodium hydride (26 mg, 1.1 mmol), and the mixture is stirred for 8 h at −17 °C. Evaporation of the solvent and chromatography (toluene/ethyl acetate 30:1) of the residue affords compounds **3a,b**.

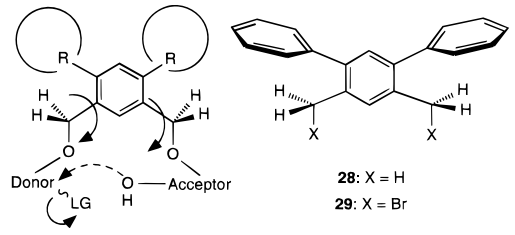
Ethyl 2,3,4-Tri-*O*-benzyl-6-*O*-(3-bromomethylbenzyl)-1-thio-*β*-D-glucopyranoside (3a). Treatment of compound **1a**[18] (495 mg) according to the general procedure affords **3a** (280 mg, 41%) as a colorless oil. TLC (toluene/ethyl acetate 6:1): R_f 0.68; $[\alpha]_D$ +16 (*c* 1, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.34 (t, 3 H, SCH_2CH_3), 2.68−2.88 (m, 2 H, SCH_2-CH_3), 3.41−3.80 (m, 6 H, 2-H, 3-H, 4-H, 5-H, 2 6-H), 4.42−4.93 (m, 11 H, 1-H, 2 7′-H, 2 8′-H, 3 PhCH_2), 7.16−7.41 (m, 19 H, 3 Ph, 2′-H, 4′-H, 5′-H, 6′-H); FAB-MS: *m*/*z* 699 $(M + Na)^+$. Anal. Calcd for $C_{37}H_{41}BrO_5S$ (677.71): C, 65.58; H, 6.09. Found: C, 65.28; H, 6.12.

(32) Dick, W. E., Jr.; Weisleder, D.; Hodge, J. E. *Carbohydr. Res.* **1971**, *18*, 115−123.

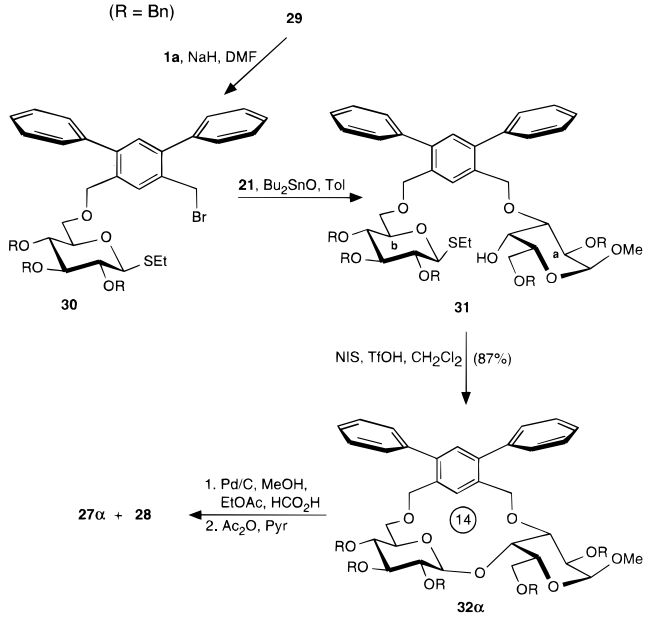
Scheme 5



Scheme 6



Scheme 7



4-Penten-1-yl 2,3,4-Tri-*O*-benzyl-6-*O*-(3-bromomethylbenzyl)-α/*β*-D-glucopyranoside (3b). Treatment of compound **1b**[19] (518 mg) according to the general procedure affords **3b** (544 mg, 78%) as a colorless oil. TLC (toluene/ethyl acetate 6:1): R_f 0.69; $[\alpha]_D$ +24 (*c* 1, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$): δ 1.69 (m, 2 H, CH_2CH_2CH), 2.12 (m, 2 H, $CH_2CH_2CH_2$), 3.39−3.81 (m, 7 H, 2-H, 3-H, 4-H, 5-H, 2 6-H, 1/2 OCH_2CH_2), 3.96 (m, 1 H, 1/2 OCH_2CH_2), 4.45−5.08 (m, 13 H, 1-H, 2 7′-H, 2 8′-H, 3 $PhCH_2$, $CH_2CH{=}CH_2$), 5.81 (m, 1 H, $CH_2CH{=}CH_2$), 7.11−7.43 (m, 19 H, 3 Ph, 1′-H, 3′-H, 4′-H, 5′-H). Anal. Calcd for $C_{40}H_{45}BrO_6$ (701.69): C, 68.47; H 6.46. Found: C, 68.72; H, 6.37.

General Procedure for the Synthesis of Compounds 5a,b. Compound **4**[20] (374 mg, 1.0 mmol) and dibutyltin oxide (274 mg, 1.1 mmol) are refluxed in toluene (10 mL) for 3 h in an apparatus for the azeotropic removal of water. Toluene (5 mL) is distilled off, and the solution is cooled to room temperature. Tetrabutylammonium iodide (406 mg, 1.1 mmol) and **3a,b** (1.0 mmol) are added. Stirring for 6 h at 90 °C, evaporation of the solvent, and chromatography (toluene → toluene/ethyl acetate 6:1) of the residue affords **5a,b**.

Ethyl 6-*O*-[3-(Methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside-6-yloxymethyl)-benzyl]-2,3,4-tri-*O*-benzyl-1-thio-*β*-D-glucopyranoside (5a). Treatment of compound **3a** (678 mg)

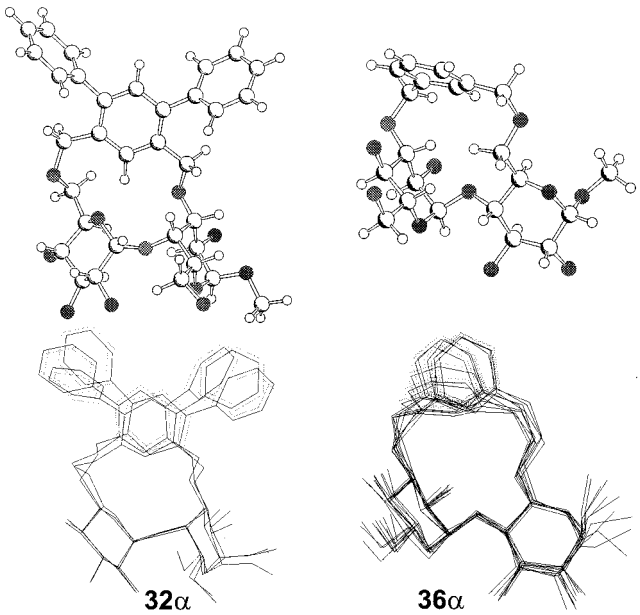
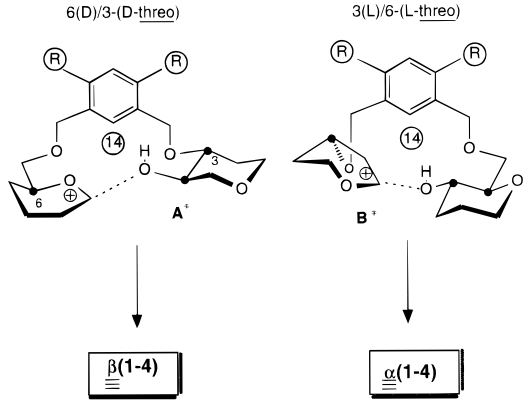


Figure 3. Energy minimized average conformations of **32**α and **36**α.[23b]

Scheme 8

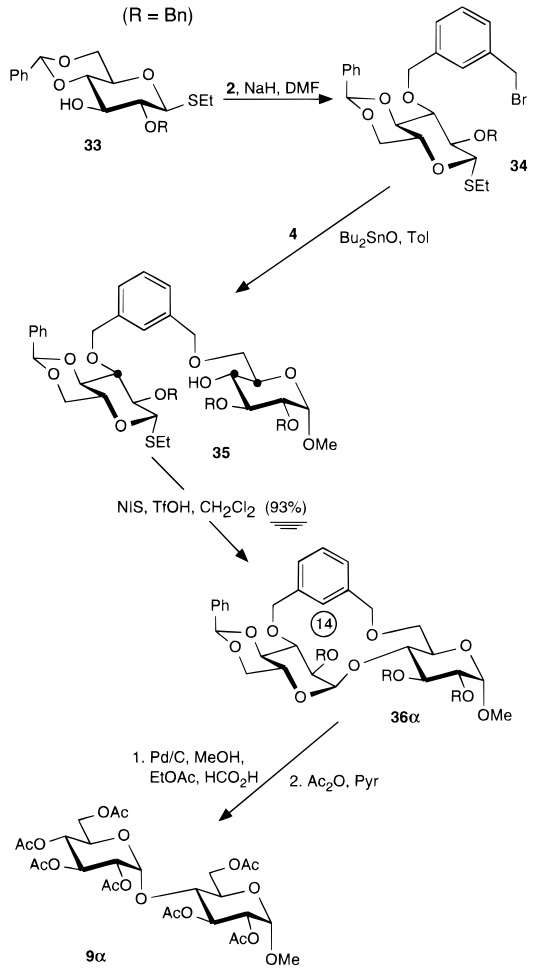


according to the general procedure affords **5a** (621 mg, 64%) as a colorless oil. TLC (toluene/ethyl acetate 6:1): R_f 0.29; $[\alpha]_D$ +26 (*c* 1, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.35 (t, 3 H, SCH_2CH_3), 2.76−2.81 (m, 2 H, SCH_2CH_3), 3.40 (s, 3 H, OCH_3), 3.46−4.95 (m, 28 H, 1a-H, 2a-H, 3a-H, 4a-H, 5a-H, 2 6a-H, 1b-H, 2b-H, 3b-H, 4b-H, 5b-H, 2 6b-H, 2 7′-H, 2 8′-H, 5 $PhCH_2$), 7.20−7.39 (m, 29 H, 5 Ph, 2′-H, 4′-H, 5′-H, 6′-H); FAB-MS: *m*/*z* 994 $(M + Na)^+$. Anal. Calcd for $C_{58}H_{66}O_{11}S$ (971.25): C, 71.73; H, 6.85. Found: C, 71.57; H, 6.52.

4-Penten-1-yl 6-*O*-[3-(Methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside-6-yloxymethyl)-benzyl]-2,3,4-tri-*O*-benzyl-α/β-D-glucopyranoside (5b). Treatment of compound **3b** (702 mg) according to the general procedure affords **5b** (408 mg, 41%) as a colorless oil. TLC (toluene/ethyl acetate 2:1): R_f 0.46; $[\alpha]_D$ +38 (*c* 1, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.67 (m, 2 H, CH_2CH_2CH), 2.09 (m, 2 H, $CH_2CH_2CH_2$), 3.36 (s, 3 H, OCH_3), 3.52−3.60 (m, 13 H, 2a-H, 3a-H, 4a-H, 5a-H, 2 6-H, 2b-H, 3b-H, 4b-H, 5b-H, 2 6-H, 1/2 OCH_2CH_2), 4.43 (m, 1 H, 1/2 OCH_2CH_2), 4.45−4.95 (m, 18 H, 1a-H, 1b-H, 2 7′-H, 2 8′-H, 5 $PhCH_2$, $CH_2CH{=}CH_2$), 5.78 (m, 1 H, $CH_2CH{=}CH_2$), 7.08−7.28 (m, 29 H, 5 Ph, 2′-H, 4′-H, 5′-H, 6′-H); MALDI-MS: *m*/*z* 1018 $(M + Na)^+$. Anal. Calcd for $C_{61}H_{70}O_{12}$ (995.22): C, 73.61; H 7.09. Found: C, 73.79; H, 7.13.

4-Penten-1-yl 6-*O*-[3-(Methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside-4-yloxymethyl)-benzyl]-2,3,4-tri-*O*-benzyl-α/β-D-glucopyranoside (6b). To a solution of **4**[20] (374 mg, 1.0 mmol) in dry dichloromethane (5 mL) are added 15-crown-5 (220 μL, 1.1 mmol) and sodium hydride (26 mg, 1.1 mmol),

Scheme 9



and then the mixture is stirred for 5 min at room temperature. Compound **3b** (702 mg, 1.0 mmol) in dichloromethane (5 mL) is added and stirred for 2 h. The solution is neutralized with an ion-exchange resin (Amberlite IR 120, H^+ form), filtered, and concentrated in vacuo. Chromatography (toluene/ethyl acetate 7:1) of the residue affords **5b** (448 mg, 45%) and **6b** (150 mg, 15%) as a colorless oil. TLC (toluene/ethyl acetate 2:1): R_f 0.45; $[\alpha]_D$ +34 (*c* 1, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.69 (m, 2 H, CH_2CH_2CH), 2.12 (m, 2 H, $CH_2CH_2CH_2$), 3.43 (s, 3 H, OCH_3), 3.49−3.82 (m, 13 H, 2a-H, 3a-H, 4a-H, 5a-H, 2 6a-H, 2b-H, 3b-H, 4b-H, 5b-H, 2 6b-H, 1/2 OCH_2CH_2), 3.95 (m, 1 H, 1/2 OCH_2CH_2), 4.36−5.08 (m, 18 H, 1a-H, 1b-H, 2 7′-H, 2 8′-H, 5 $PhCH_2$, $CH_2CH{=}CH_2$), 5.79 (m, 1 H, $CH_2CH{=}CH_2$), 7.08−7.48 (m, 29 H, 5 Ph, 2′-H, 4′-H, 5′-H, 6′-H); MALDI-MS: *m*/*z* 1018 $(M + Na)^+$. Anal. Calcd for $C_{61}H_{70}O_{12}$ (995.22): C, 73.61; H, 7.09. Found: C, 73.68; H, 7.10.

Methyl 6,6′-*O*-(1,3-Xylylene)-(2,3,4-tri-*O*-benzyl-β-D-glucopyranosyl)-(1′→4)-2,3-di-*O*-benzyl-α-D-glucopyranoside (7β). (a) Trimethylsilyl trifluoromethanesulfonate (5 μL) is added under argon at room temperature to a solution of **5b** (100 mg, 0.1 mmol) and *N*-iodosuccinimide (29 mg, 0.13 mmol) in dry toluene (10 mL); the mixture is stirred for 15 min. The solution is neutralized with triethylamine, sodium dithionite is added, and then stirring is continued until the solution is colorless. The solid is filtered off, and the solution is concentrated in vacuo. Chromatography (toluene → toluene/ethyl acetate 8:1) of the residue affords **7**β (57 mg, 63%) as a colorless oil.

(b) Trifluoromethanesulfonic acid (5 μL) is added under argon at room temperature to a solution of **5a** (97 mg, 0.1 mmol) and *N*-iodosuccinimide (29 mg, 0.13 mmol) in dry dichloromethane (10 mL), and the mixture is stirred for 15 min. The solution is neutralized with triethylamine and washed with aqueous $Na_2S_2O_4$ solution. The water phase is

extracted with dichloromethane (3 × 5 mL), and the combined organic extracts are dried ($NaSO_4$) and concentrated in vacuo. Chromatography (toluene → toluene/ethyl acetate 8:1) of the residue affords **7**β (59 mg, 65%) as a colorless oil. TLC (toluene/ethyl acetate 2:1): R_f 0.64; $[\alpha]_D$ +11 (*c* 1, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.06 (dd, 1 H, $^3J_{4,3} = {}^3J_{4,5} = 9.5$ Hz, 4b-H), 3.21 (dd, 1 H, $^3J_{5,6} = {}^3J_{5,4} = 9.5$ Hz, 5b-H), 3.36 (dd, 1 H, $^3J_{2,3} = 9.1$ Hz, $^3J_{2,1} = 7.4$ Hz, 2b-H), 3.38 (s, 3 H, OCH_3), 3.39 (dd, 1 H, $^3J_{3,2} = {}^3J_{3,4} = 9.5$ Hz, 3b-H), 3.47 (dd, 1 H, $^3J_{2,3} = 9.6$ Hz, $^3J_{2,1} = 3.7$ Hz, 2a-H), 3.58−3.63 (m, 2 H, 5a-H, 6a-H), 3.71−3.81 (m, 3 H, 3a-H, 6a-H, 6b-H), 4.22−5.02 (m, 17 H, 1a-H, 1b-H, 6b-H, 2 7′-H, 2 8′-H, 5 PhCH_2), 6.89−7.39 (m, 28 H, 5 Ph, 4′-H, 5′-H, 6′-H), 7.81 (m, 1 H, 2′-H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 69.3 (6a-C), 70.4 (5a-C), 73.6 (5b-C), 78.3 (4b-C), 78.9 (2a-C), 79.9 (3a-C), 83.5 (2b-C), 84.8 (3b-C), 98.5 (1a-C), 99.8 (1b-C); MALDI-MS: *m*/*z* 931 $(M + Na)^+$. Anal. Calcd for $C_{56}H_{60}O_{11}$ (909.11): C, 73.98; H, 6.65. Found: C, 73.89; H, 6.70.

Methyl 4,6′-*O*-(1,3-Xylylene)-(2,3,4-tri-*O*-benzyl-β-D-glucopyranosyl)-(1′→6)-2,3-di-*O*-benzyl-α-D-glucopyranoside (8β). Trimethylsilyl trifluormethanesulfonate (5 μL) is added under argon at room temperature to a solution of **6b** (100 mg, 0.1 mmol) and *N*-iodosuccinimide (29 mg, 0.13 mmol) in dry toluene (10 mL), and the mixture is stirred for 15 min. The solution is neutralized with triethylamine, sodium dithionite is added, and then stirring is continued until the solution is colorless. The solid is filtered off, and the solution is concentrated in vacuo. Chromatography (toluene→toluene/ethyl acetate 8:1) of the residue affords **8**β (65 mg, 72%) as a colorless oil. TLC (toluene/ethyl acetate 2:1): R_f 0.68; $[\alpha]_D$ +13 (*c* 1, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.11 (dd, 1 H, $^3J_{4,3} = {}^3J_{4,5} = 9.9$ Hz, 4a-H), 3.28 (s, 3 H, OCH_3), 3.31−3.42 (m, 5 H, 6a-H, 2b-H, 4b-H, 5b-H, 6b-H), 3.46 (dd, 1 H, $^3J_{2,1} = 3.6$ Hz, $^3J_{2,3} = 9.5$ Hz, 2a-H), 3.56 (dd, 1 H, $^3J_{3,2} = {}^2J_{3,4} = 9.1$ Hz, 3b-H), 3.87−3.97 (m, 3 H, 3a-H, 5a-H, 6b-H), 4.31 (d, 1 H, $^3J_{1,2} = 7.6$ Hz, 1b-H), 4.40−4.97 (m, 16 H, 1a-H, 6a-H, 2 7′-H, 2 8′-H, 5 PhCH_2), 6.91−7.34 (m, 28 H, 5 Ph, 4′-H, 5′-H, 6′-H), 7.70 (m, 1 H, 2′-H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 70.8 (5a-C), 74.3 (5b-C), 78.2 (4b-C), 79.7 (4a-C), 79.9 (2a-C), 82.0 (3a-C), 82.2 (2b-C), 84.4 (3b-C), 97.4 (1a-C), 101.8 (1b-C); MALDI-MS: *m*/*z* 931 $(M + Na)^+$. Anal. Calcd for $C_{56}H_{60}O_{11}$ (909.11): C, 73.98; H, 6.65. Found: C, 73.61; H, 6.40.

General Procedure for the Synthesis of Compounds 9α, 10β, 18β, 19β, and 27α,β. A mixture of **8**β, **16**β, **17**β, **26**α/β, **32**α, **36**α (0.02 mmol), and palladium on carbon (10%, 10 mg) in methanol/ethyl acetate (4 mL, 1:1) and formic acid (0.2 mL) is stirred under hydrogen for 20 h. After filtration and concentration in vacuo, the residue is dissolved in pyridine/acetic anhydride (4 mL, 1:1), and the mixture is stirred for 20 h. The solution is concentrated in vacuo and coevaporated with toluene.

Methyl *O*-(2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl)-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranoside (9α). Treatment of compound **35**α (16 mg) according to the general procedure and chromatography (toluene/ethyl acetate 2:1) of the residue affords known **9**α[32] (11 mg, 85%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.94, 1.96, 1.98, 1.99, 2.04, 2.08 (6 s, 21 H, COCH_3), 3.35 (s, 3 H, OCH_3), 3.89−3.92 (m, 3 H, 4a-H, 5a-H, 5b-H), 3.98 (dd, 1 H, $J_{6,6} = 12.5$ Hz, $J_{6,5} = 2.4$ Hz, 6c-H), 4.18−4.20 (m, 2 H, 6a-H, 6b-H), 4.38 (dd, 1 H, $J_{6,6} = 12.1$ Hz, $J_{6,5} = 1.8$ Hz, 6b-H), 4.71 (dd, 1 H, $J_{2,3} = 10.2$ Hz, $J_{2,1} = 3.6$ Hz, 2a-H), 4.77−4.81 (m, 2 H, 1a-H, 2b-H), 5.00 (dd, 1 H, $J_{4,3} = J_{4,5} = 9.9$ Hz, 4b-H), 5.30 (dd, 1 H, $J_{3,2} = J_{3,4} = 9.9$ Hz, 3b-H), 5.36 (d, 1 H, $J_{1,2} = 4.0$ Hz, 1b-H), 5.46 (m, 1 H, 3a-H).

Methyl *O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranoside (9β). A mixture of **7**β, **25**β (50 mg, 0.055 mmol), and palladium on carbon (10%, 8 mg) in methanol/ethyl acetate (3 mL, 1:1) and formic acid (0.3 mL) is stirred under hydrogen for 20 h. After filtration and concentration in vacuo, the residue is dissolved in pyridine/acetic anhydride (6 mL, 1:1) and is stirred for 7 h. The solution is concentrated in vacuo and coevaporated with toluene. Chromatography (toluene/ethyl acetate 2:1) affords known **9**β[22] (32 mg, 89%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.99, 2.02, 2.04, 2.07, 2.09, 2.14 (7 s, 21 H, COCH_3), 3.38 (s, 3 H, OCH_3), 3.65 (ddd, 1 H, $J_{5,6} = 2.5$, 4.4 Hz, $J_{5,4} = 10.0$ Hz, 5b-H), 3.73 (dd, 1 H, $J_{4,5} = J_{4,3} = 9.7$ Hz, 4a-H), 3.89 (ddd, 1 H, $J_{5,6} = 1.9$, 4.7 Hz, $J_{5,4} = 10.0$ Hz, 5a-H), 4.05 (ddd, 1 H, $J_{6,6} = 12.5$ Hz, $J_{6,5} = 2.5$ Hz, 6b-H), 4.14 (dd, 1 H, $J_{6,6} = 12.2$ Hz, $J_{6,5} = 5.0$ Hz, 6a-H), 4.37 (dd, 1 H, $J_{6,6} = 12.4$ Hz, $J_{6,5} = 4.4$ Hz, 6b-H), 4.48 (dd, 1 H, $J_{6,6} = 12.2$ Hz, $J_{6,5} = 2.2$ Hz, 6a-H), 4.52 (d, 1 H, $J_{1,2} = 8.0$ Hz, 1b-H), 4.82 (dd, 1 H, $J_{2,1} = 3.9$ Hz, 2a-H), 4.86 (d, 1 H, $J_{1,2} = 3.6$ Hz, 1a-H), 4.93 (dd, 1 H, $J_{2,1}$ 8.0 = Hz, $J_{2,3} = 9.1$ Hz, 2b-H), 5.07 (dd, 1 H, $J_{4,3} = J_{4,5} = 9.7$, 4b-H), 5.14 (dd, 1 H, $J_{3,4} = J_{3,2} = 9.4$ Hz, 3b-H), 5.45 (dd, 1 H, $J_{3,2} = J_{3,4} = 9.7$ Hz, 3a-H).

Methyl *O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-acetyl-α-D-glucopyranoside (10β). Treatment of compound **8**β (18 mg) according to the general procedure and chromatography (toluene/ethyl acetate 2:1) of the residue affords known **10**β[24] (11 mg, 85%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.00, 2.02, 2.03, 2.05, 2.07, 2.08, 2.09 (7 s, 21 H, COCH_3), 3.39 (s, 3 H, OCH_3), 3.55 (dd, 1 H, $J_{6,6} = 10.8$ Hz, $J_{6,5} = 6.4$ Hz, 6a-H), 3.69 (ddd, 1 H, $J_{5,6} = 2.8$ Hz, 4.7 Hz, $J_{5,4} = 10.0$ Hz, 5b-H), 3.91 (dd, 1 H, $J_{6,6} = 10.8$ Hz, $J_{6,5} = 2.0$ Hz, 6a-H), 3.95 (ddd, 1 H, $J_{5,6}$= 2.2 Hz, 6.4 Hz, $J_{5,4} = 10.2$ Hz, 5a-H), 4.13 (dd, 1 H, $J_{6,5} = 2.8$ Hz, $J_{6,6} = 12.5$ Hz, 6b-H), 4.27 (dd, 1 H, $J_{6,5} = 4.7$ Hz, $J_{6,6} = 12.4$ Hz, 6b-H), 4.55 (d, 1 H, $J_{1,2} = 8.0$ Hz, 1b-H), 4.84 (dd, 1 H, $J_{2,1} = 3.6$ Hz, $J_{2,3} = 10.2$ Hz, 2a-H), 4.91 (m, 2 H, 1a-H, 4a-H), 5.01 (dd, 1 H, $J_{2,1} = 8.0$ Hz, $J_{2,3} = 9.7$ Hz, 2b-H), 5.08 (dd, 1 H, $J_{4,3} = J_{4,5} = 9.7$ Hz, 4b-H), 5.20 (dd, 1 H, $J_{3,2} = J_{3,4} = 9.4$ Hz, 3b-H), 5.46 (dd, 1 H, $J_{3,2} = J_{3,4} = 9.7$ Hz, 3a-H).

Methyl 2,6-Di-*O*-benzyl-3-*O*-(4-methoxybenzyl)-α-D-galactopyranoside (12). Compound **21**[30] (3.74 g, 10.0 mmol) and dibutyltin oxide (2.74 g, 11.0 mmol) are refluxed in toluene (50 mL) for 5 h in an apparatus for the azeotropic removal of water. The solution is cooled to room temperature, and tetrabutylammonium iodide (4.06 g, 11.0 mmol) and *p*-methoxybenzyl chloride (1.57 g, 10.0 mmol) are added. Stirring for 1 h at 90 °C, evaporation of the solvent in vacuo, and chromatography (toluene → toluene/ethyl acetate 9:1) of the residue affords **12** (3.54 g, 72%) as a colorless oil. TLC (toluene/ethyl acetate 1:1): R_f 0.65; $[\alpha]_D$ +25 (*c* 1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.30 (s, 3 H, OCH_3), 3.54−3.93 (m, 10 H, 2-H, 3-H, 4-H, 5-H, 2 6-H, OH, PhOCH_3), 4.43−4.76 (m, 7 H, 1-H, 3 PhCH_2), 6.79 (m, 2 H, Ph), 7.19−7.30 (m, 12 H, Ph); MALDI-MS: *m*/*z* 518 $(M + Na)^+$. Anal. Calcd for $C_{29}H_{34}O_7$ (494.58): C, 70.43; H, 6.93. Found: C, 70.29; H, 6.84.

Ethyl 6-*O*-[3-(Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside-2-yloxymethyl)-benzyl]-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (13). Compound **3a** (678 mg, 1.0 mmol) in dry dimethylformamide (5 mL) is added at 0 °C to a suspension of **11** (565 mg, 2.0 mmol) and sodium hydride (26 mg, 1.1 mmol) in dry dimethylformamide (10 mL), and the mixture is stirred for 15 h at 0 °C. Concentration of the solution in vacuo and chromatography (toluene/ethyl acetate 9:1) of the residue affords **13** (404 mg, 46%) as a colorless oil. TLC (toluene/ethyl acetate 6:1): R_f 0.23; $[\alpha]_D$ +20 (*c* 1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.29 (t, 3 H, SCH_2CH_3), 2.57 (d, 1 H, $^3J_{OH,3} = 2.0$ Hz, 3a-O*H*), 2.69−2.75 (m, 2 H, SCH_2CH_3), 3.32−3.77 (m, 13 H, OCH_3, 2a-H, 4a-H, 5a-H, 6a-H, 2b-H, 3b-H, 4b-H, 5b-H, 2 6b-H), 4.09 (ddd, 1 H, $^3J_{3,2} = {}^3J_{3,4} = 9.3$ Hz, $^3J_{3,OH} = 2.0$ Hz, 3a-H), 4.20 (dd, 1 H, $^2J_{6,6} = 9.7$ Hz, $^3J_{6,5} = 4.4$ Hz, 6a-H), 4.39−4.99 (m, 12 H, 1a-H, 1b-H, 2 7′-H, 2 8′-H, 3 PhCH_2), 5.45 (s, 1 H, PhC*H*), 7.11−7.45 (m, 24 H, 4 Ph, 2′-H, 4′-H, 5′-H, 6′-H); MALDI-MS: *m*/*z* 902 $(M + Na)^+$. Anal. Calcd for $C_{51}H_{58}O_{11}S$ (879.08): C, 69.78; H, 6.65. Found: C, 69.48; H, 6.65.

Ethyl 6-*O*-[3-(Methyl 2,6-di-*O*-benzyl-3-*O*-(4-methoxybenzyl)-α-D-galactopyranoside-4-yloxymethyl)-benzyl]-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (14). Compound **12** (544 mg, 1.1 mmol) in dry dimethylformamide (5 mL) is added at 0 °C to a suspension of **3a** (678 mg, 1.0 mmol) and sodium hydride (26 mg, 1.1 mmol) in dry dimethylformamide (10 mL). The mixture is warmed to room temperature and stirred for 5 h. Concentration of the solution in vacuo and chromatography (petroleum ether/ethyl acetate 5:1 → 4:1) of the residue affords **14** (665 mg, 61%) as a colorless oil. TLC

(petroleum ether/ethyl acetate 3:1): R_f 0.25; $[\alpha]_D$ +10 (*c* 1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.30 (t, 3 H, SCH_2CH_3), 2.69−2.79 (m, 2 H, SCH_2CH_3), 3.35 (s, 3 H, OCH_3), 3.39−4.02 (m, 15 H, 2a-H, 3a-H, 4a-H, 5a-H, 2 6a-H, 2b-H, 3b-H, 4b-H, 5b-H, 2 6b-H, OCH_3), 4.35−4.95 (m, 18 H, 1a-H, 1b-H, 2 7′-H, 2 8′-H, 6 $PhCH_2$), 6.85 (m, 2 H, Ph), 7.14−7.38 (m, 31 H, Ph, 2′-H, 4′-H, 5′-H, 6′-H). Anal. Calcd for $C_{66}H_{74}O_{12}S$ (1091.37): C, 72.64; H, 6.89. Found: C, 72.38; H, 6.75.

Ethyl 6-*O*-[3-(Methyl 2,6-di-*O*-benzyl-α-D-galactopyranoside-4-yloxymethyl)-benzyl]-2,3,4-tri-*O*-benzyl-1-thio-*β*-D-glucopyranoside (15). A mixture of **14** (546 mg, 0.5 mmol) and 4,5-dichloro-3,6-dioxo-1,4-cyclohexadiene-1,2-dicarbonitrile (DDQ, 159 mg, 0.7 mmol) in dichloromethane (20 mL) and water (2 mL) is stirred at room temperature for 4 h. Dichloromethane (20 mL) is added, and the mixture is washed with aqueous $NaHCO_3$ solution (10 mL) and water (10 mL). Concentration of the solution in vacuo and chromatography (toluene/ethyl acetate 6:1) of the residue affords **15** (437 mg, 90%) as a colorless oil. TLC (toluene/ethyl acetate 3:1): R_f 0.36; $[\alpha]_D$ +22 (*c* 1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.30 (t, 3 H, SCH_2CH_3), 2.70−2.77 (m, 2 H, SCH_2CH_3), 3.31 (s, 3 H, OCH_3), 3.38−4.06 (m, 12 H, 2a-H, 3a-H, 4a-H, 5a-H, 2 6a-H, 2b-H, 3b-H, 4b-H, 5b-H, 2 6b-H), 4.42−4.93 (m, 16 H, 1a-H, 1b-H, 2 7′-H, 2 8′-H, 5 $PhCH_2$), 7.13−7.38 (m, 29 H, 5 Ph, 2′-H, 4′-H, 5′-H, 6′-H); MALDI-MS: *m*/*z* 995 $(M + Na)^+$, 1011 $(M + K)^+$. Anal. Calcd for $C_{58}H_{66}O_{11}S$ (971.22): C, 71.73; H, 6.85. Found: C, 71.64; H, 6.70.

General Procedure for the Synthesis of Compounds 16*β*, 17*β*, 25*β*, 26α/*β*, 32α, and 36α. Trifluoromethanesulfonic acid (5 μL) is added under argon at room temperature to a solution of **13**, **15**, **23**, **24**, **31**, **34** (0.05 mmol), and *N*-iodosuccinimide (22 mg, 0.10 mmol) in dry dichloromethane (5 mL), and the mixture is stirred for 30 min. The solution is washed with aqueous $NaHCO_3$ solution (1 mL) and aqueous $Na_2S_2O_3$ solution (1 mL), dried ($MgSO_4$), and concentrated in vacuo.

Methyl 2,6′-*O*-(1,3-Xylylene)-(2,3,4-tri-*O*-benzyl-*β*-D-glucopyranosyl)-(1′→3)-4,6-*O*-benzylidene-α-D-glucopyranoside (16*β*). Treatment of compound **13** (44 mg) according to the general procedure and chromatography (petroleum ether/ethyl acetate 7:1) of the residue affords **16***β* (33 mg, 81%) as a colorless oil. TLC (petroleum ether/ethyl acetate 3:1): R_f 0.32; $[\alpha]_D$ +30 (*c* 1, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.21 (d, 1 H, $^3J_{5,4}$ = 9.6 Hz, 5b-H), 3.33 (dd, 1 H, $^2J_{6,6}$ = 10.4 Hz, $^3J_{6,5}$ = 1.7 Hz, 6b-H), 3.42 (s, 3 H, OCH_3), 3.53 (dd, 1 H, $^3J_{3,2}$ = $^3J_{3,4}$ = 9.1 Hz, 3b-H), 3.60−3.68 (m, 3 H, 2b-H, 4a-H, 6a-H), 3.79−3.86 (m, 3 H, 2a-H, 5a-H, 6b-H), 3.93 (dd, 1 H, $^3J_{4,3}$ = $^3J_{4,5}$ = 9.6 Hz, 4b-H), 4.22 (dd, 1 H, $^2J_{6,6}$ = 10.1 Hz, $^3J_{6,5}$ = 4.9 Hz, 6a-H), 4.28 (d, 1-H, ^2J = 14.5 Hz, 8′-H), 4.44 (dd, 1 H, $^3J_{3,2}$ = $^3J_{3,4}$ = 9.8 Hz, 3a-H), 4.47 (d, 1 H, ^2J = 13.7 Hz, 7′-H), 4.60 (d, 1 H, ^2J = 11.3 Hz, 1/2 $PhCH_2$), 4.65 (d, 1 H, $^3J_{1,2}$ = 3.6 Hz, 1a-H), 4.69−4.76 (m, 3 H, 1b-H, $PhCH_2$), 4.83−4.88 (m, 3 H, 8′-H, $PhCH_2$), 4.98 (d, 1 H, ^2J = 11.3 Hz, 1/2 $PhCH_2$), 5.04 (d, 1 H, ^2J = 13.7 Hz, 7′-H), 5.41 (s, 1 H, PhC*H*), 7.06−7.26 (m, 21 H, 3 Ph, *m*-, *p*-benzylidene-H, 4′-H, 5′-H, 6′-H), 7.37 (m, 2 H, *o*-benzyliden-H), 8.04 (s, 1 H, 2′-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.2 (OCH_3), 62.6 (5a-C), 66.3 (6b-C), 68.7, 68.9 (2 C, 6a-C, 7′-C), 70.5 (8′-C), 72.5 (2a-C), 74.0 (5b-C), 74.5, 75.0 (2 C, 2 $PhCH_2$), 75.3, 75.4 (3 C, $PhCH_2$, 3a-C, 4a-C), 76.4 (4b-C), 82.5 (2b-C), 84.4 (3b-C), 98.1 (1a-C), 98.7 (1b-C), 100.8 (PhCH); FAB-MS: *m*/*z* 839 $(M + Na)^+$. Anal. Calcd for $C_{49}H_{52}O_{11}$ (816.35): C, 72.04; H, 6.42. Found: C, 71.48; H, 6.22.

Methyl 4,6′-*O*-(1,3-Xylylene)-(2,3,4-tri-*O*-benzyl-*β*-D-glucopyranosyl)-(1′→3)-2,6-di-*O*-benzyl-α-D-galactopyranoside (17*β*). Treatment of compound **15** (49 mg) according to the general procedure and chromatography (petroleum ether/ethyl acetate 7:1 → 6:1) of the residue affords **17***β* (38 mg, 84%) as a colorless oil. TLC (petroleum ether/ethyl acetate 3:1): R_f 0.32; $[\alpha]_D$ +14 (*c* 1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.07 (dd, 1 H, $^2J_{6,6}$ = 10.5 Hz, $^3J_{6,5}$ = 3.9 Hz, 6a-H), 3.25 (s, 3 H, OCH_3), 3.36 (m, 2 H, 5b-H, 6b-H), 3.50 (m, 2 H, 2b-H, 6a-H), 3.65 (dd, 1 H, $^3J_{3,2}$ = $^3J_{3,4}$ = 9.2 Hz, 3b-H), 3.74 (m, 2 H, 4a-H, 5a-H), 3.84 (dd, 1 H, $^3J_{3,2}$ = 10.3 Hz, $^3J_{3,4}$ = 2.9 Hz, 3a-H), 3.98 (dd, 1 H, $^3J_{2,3}$ = 10.3 Hz, $^3J_{2,1}$ = 3.7 Hz, 2a-H), 4.11 (m, 2 H, 4b-H, 6b-H), 4.32−4.41 (m, 3 H, 8′-H, $PhCH_2$), 4.49−4.51 (m, 2 H, 1a-H, 1/2 $PhCH_2$), 4.59 (d, 1 H, $^3J_{1,2}$ = 7.8 Hz, 1b-H), 4.69 (d, 1 H, ^2J = 12.4 Hz, 1/2 $PhCH_2$), 4.81−4.94 (m, 7 H, 7′-H, 8′-H, 2 1/2 $PhCH_2$), 5.00 (d, 1 H, ^2J = 11.6 Hz, 7′-H), 5.10 (d, 1 H, ^2J = 11.9 Hz, 1/2 $PhCH_2$), 7.00 (m, 1 H, 5′-H), 7.19−7.37 (m, 27 H, 5 Ph, 4′-H, 6′-H), 8.05 (s, 1 H, 2′-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.1 (OCH_3), 68.7 (6b-C), 69.9 (5a-C), 70.7 (6a-C), 70.9 (8′-C), 71.6 (4a-C), 72.6 (7′-C), 73.3, 73.5, 74.0 (4 C, 4 $PhCH_2$), 74.4 (5b-C), 75.0, 75.6 (2 C, 2 $PhCH_2$), 76.0 (2a-C), 76.9 (4b-C), 81.5 (2b-C), 82.1 (3a-C), 84.2 (3b-C), 98.6 (1a-C), 106.0 (1b-C); FAB-MS: *m*/*z* 931 $(M + Na)^+$. Anal. Calcd for $C_{56}H_{60}O_{11}$ (909.08): C, 73.99; H 6.65. Found:C, 73.61; H 6.71.

Methyl *O*-(2,3,4,6-Tetra-*O*-acetyl-*β*-D-glucopyranosyl)-(1→3)-2,4,6-tri-*O*-acetyl-α-D-galactopyranoside (18*β*). Treatment of compound **16***β* (16 mg) according to the general procedure and chromatography (toluene/ethyl acetate 3:2 → 1:1) of the residue affords known **18***β*[26] (12 mg, 92%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.91, 1.94, 1.97, 1.99, 2.03, 2.08 (6 s, 21 H, $COCH_3$), 3.34 (s, 3 H, OCH_3), 5.58 (ddd, 1 H, $J_{5,6}$ = 2.1 Hz, 4.1 Hz, $J_{5,4}$ = 9.7 Hz, 5b-H), 3.85 (m, 1 H, 5a-H), 3.98 (dd, 1 H, $J_{6,6}$ = 12.3 Hz, $J_{6,5}$ = 1.9 Hz, 6b-H), 4.05−4.08 (m, 2 H, 3a-H, 6a-H), 4.12 (dd, 1 H, $J_{6,6}$ = 12.3 Hz, $J_{6,5}$ = 4.7 Hz, 6a-H), 4.27 (dd, 1 H, $J_{6,6}$ = 12.3 Hz, $J_{6,5}$ = 4.4 Hz, 6b-H), 4.59 (d, 1 H, $J_{1,2}$ = 8.1 Hz, 1b-H), 4.79 (d, 1 H, $J_{1,2}$ = 3.6 Hz, 1a-H), 4.82−4.85 (m, 2 H, 2a-H, 2b-H), 4.92 (dd, 1 H, $J_{4,3}$ = $J_{4,5}$ = 9.7 Hz, 4a-H), 4.99 (dd, 1 H, $J_{4,3}$ = $J_{4,5}$ = 9.7 Hz, 4b-H), 5.05 (dd, 1 H, $J_{3,2}$ = $J_{3,4}$ = 9.4 Hz, 3b-H).

Methyl *O*-(2,3,4,6-Tetra-*O*-acetyl-*β*-D-glucopyranosyl)-(1→3)-2,4,6-tri-*O*-acetyl-α-D-galactopyranoside (19*β*). Treatment of compound **17***β* (18 mg) according to the general procedure and chromatography (toluene/ethyl acetate, 2/1) of the residue affords known **19***β*[27] (11 mg, 85%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.92, 1.95, 2.00, 2.04, 2.07 (5 s, 21 H, $COCH_3$), 3.33 (s, 3 H, OCH_3), 3.56 (ddd, 1 H, $J_{5,6}$ = 2.6 Hz, 3.8 Hz, $J_{5,6}$ = 9.8 Hz, 5b-H), 3.98 (dd, 1 H, $J_{6,6}$ = 10.5 Hz, $J_{6,5}$ = 6.7 Hz, 6a-H), 4.06−4.12 (m, 4 H, 3a-H, 5a-H, 6a-H, 6b-H), 4.19 (dd, 1 H, $J_{6,6}$ = 12.3 Hz, $J_{6,5}$ = 2.4 Hz, 6b-H), 4.59 (d, 1 H, $J_{1,2}$ = 7.9 Hz, 1b-H), 4.82−4.85 (m, 2 H, 1a-H, 2b-H), 5.01 (dd, 1 H, $J_{4,3}$ = $J_{4,5}$ = 9.6 Hz, 4b-H), 5.05−5.09 (m, 3 H, 2a-H, 3b-H, 4b-H), 5.37 (d, 1 H, *J* = 3.0 Hz, 4a-H).

Ethyl 6-*O*-[3-(Methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside-3-yloxymethyl)-benzyl]-2,3,4-tri-*O*-benzyl-1-thio-*β*-D-glucopyranoside (22). To a suspension of **20**[28] (137 mg, 0.36 mmol) and sodium hydride (10 mg, 0.4 mmol) in dichloromethane (3 mL) are added first 15-crown-5 (80 μL, 0.4 mmol) and then **3a** (250 mg, 0.36 mmol) in dichloromethane (2 mL). The solution is stirred for 12 h, neutralized with acetic acid, and concentrated in vacuo. Chromatography (toluene/ethyl acetate 15:1) of the residue affords **22** (176 mg, 50%) as a colorless oil. TLC (toluene/ethyl acetate 6:1): R_f 0.57; $[\alpha]_D$ +12 (*c* 1, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.28 (t, 3 H, SCH_2CH_3), 2.62−2.82 (m, 2 H, SCH_2CH_3), 3.37 (s, 3 H, OCH_3), 3.39−4.92 (m, 26 H, 1a-H, 2a-H, 3a-H, 4a-H, 5a-H, 2 6a-H, 1b-H, 2b-H, 3b-H, 4b-H, 5b-H, 2 6b-H, 2 7′-H, 2 8′-H, 4 $PhCH_2$), 7.19−7.38 (m, 24 H, 4 Ph, 2′-H, 4′-H, 5′-H, 6′-H). Anal. Calcd for $C_{58}H_{64}O_{11}S$ (969.25): C, 71.87; H, 6.65. Found: C, 71.41; H, 6.61.

Ethyl 6-*O*-[3-(Methyl 2,6-di-*O*-benzyl-α-D-glucopyranoside-3-yloxymethyl)-benzyl]-2,3,4-tri-*O*-benzyl-1-thio-*β*-D-glucopyranoside (23). A solution of hydrogen chloride (saturated in diethyl ether) is added at room temperature to a suspension of **22** (155 mg, 0.16 mmol) and sodium cyanoborohydride (82 mg, 1.3 mmol) in dry tetrahydrofuran (5 mL). At pH 1, the mixture is stirred for 1 h, water (5 mL) and diethyl ether (10 mL) are added, and the water phase is extracted with diethyl ether (3 × 10 mL). The combined organic extracts are washed with aqueous $NaHCO_3$ solution and water, dried ($MgSO_4$), and concentrated in vacuo. Chromatography (toluene/ethyl acetate 6:1) of the residue affords **23** (105 mg, 68%) as a colorless oil. TLC (toluene/ethyl acetate 6:1): R_f 0.28; $[\alpha]_D$ +19 (*c* 1, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.05 (t, 3 H, SCH_2CH_3), 2.48−2.59 (m, 2 H, SCH_2CH_3), 3.11 (s, 3 H, OCH_3), 3.14−3.54 (m, 12 H, 2a-H, 3a-H, 4a-H, 5a-H, 2 6a-H, 2b-H, 3b-H, 4b-H, 5b-H, 2 6b-H), 4.17−4.73 (m, 16 H, 1b-H, 1a-H, 2 7′-H, 2 8′-H, 5 $PhCH_2$), 6.87−

7.13 (m, 24 H, 2′-H, 4′-H, 5′-H, 6′-H, 4 Ph). $C_{58}H_{66}O_{11}S$ (971.25) FAB-MS: *m/z* 994 $(M + Na)^+$.

Ethyl 6-*O*-[3-(Methyl 2,6-di-*O*-benzyl-α-D-galactopyranoside-3-yloxymethyl)-benzyl]-2,3,4-tri-*O*-benzyl-1-thio-*β*-D-glucopyranoside (24). Compound **21**[30] (449 mg, 1.2 mmol) and dibutyltin oxide (324 mg, 1.3 mmol) are refluxed in toluene (10 mL) for 5 h in an apparatus for the azeotropic removal of water. The solution is cooled to room temperature, and then tetrabutylammonium bromide (322 mg, 1.0 mmol) and **3a** (678 mg, 1.0 mmol) are added. Stirring for 20 h at 90 °C, evaporation of the solvent, and chromatography (toluene → toluene/ethyl acetate 6:1) of the residue affords **24** (610 mg, 63%) as a colorless oil. TLC (toluene/acetone 4:1): R_f 0.40; $[\alpha]_D$ +14 (*c* 1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.31 (t, 3 H, SCH_2CH_3), 2.72−2.77 (m, 2 H, SCH_2CH_3), 3.36 (s, 3 H, OCH_3), 3.39−4.04 (m, 12 H, 2a-H, 3a-H, 4a-H, 5a-H, 2 6a-H, 2b-H, 3b-H, 4b-H, 5b-H, 2 6b-H), 4.43−4.93 (m, 16 H, 1a-H, 1b-H, 2 7′-H, 2 8′-H, 5 $PhCH_2$), 7.12−7.39 (m, 29 H, 5 Ph, 2′-H, 4′-H, 5′-H, 6′-H); MALDI-MS: *m/z* 995 $(M + Na)^+$, 1011 $(M + K)^+$. Anal. Calcd for $C_{58}H_{66}O_{11}S$ (971.22): C, 71.73; H, 6.85. Found: C, 71.52; H, 6.89.

Methyl 3,6′-*O*-(1,3-Xylylene)-(2,3,4-tri-*O*-benzyl-*β*-D-glucopyranosyl)-(1′→4)-2,3-di-*O*-benzyl-α-D-glucopyranoside (25*β*). Treatment of compound **23** (50 mg) according to the general procedure and chromatography (toluene → toluene/ethyl acetate 9:1) of the residue affords **25***β* (38 mg, 84%) as a colorless oil. TLC (toluene/ethyl acetate 2:1): R_f 0.64; $[\alpha]_D$ +24 (*c* 1, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.18 (m, 1 H, 5b-H), 3.36−3.45 (m, 6 H, 6a-H, 2b-H, 3b-H, OCH_3), 3.51−3.52 (m, 3 H, 2a-H, 5a-H, 6b-H), 3.80−3.99 (m, 5 H, 3a-H, 4a-H, 6a-H, 4b-H, 6b-H), 4.24−4.98 (m, 16 H, 1a-H, 1b-H, 2 7′-H, 2 8′-H, 5 $PhCH_2$), 7.18−7.36 (m, 23 H, 4′-H, 5′-H, 6′-H, 5 Ph), 8.51 (s, 1 H, 2′-H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 70.3 (5a-C), 74.3 (5b-C), 76.9 (4b-C), 77.9 (4a-C), 80.0 (3a-C), 81.0 (2a-C), 82.7 (2b-C), 84.7 (3b-C), 98.1 (1a-C), 103.3 (1b-C). $C_{56}H_{60}O_{11}$ (909.11) FAB-MS: *m/z* 932 $(M + Na)^+$.

Methyl 3,6′-(1,3-Xylylene)-(2,3,4-tri-*O*-benzyl-α/*β*-D-glucopyranosyl)-(1′→4)-2,6-di-*O*-benzyl-α-D-galactopyranoside (26α/*β*). Treatment of compound **24** (49 mg) according to the general procedure and chromatography (petroleum ether/ethyl acetate 9:1) of the residue affords **26**α/*β* (35 mg, 77%) as a colorless oil. TLC (petroleum ether/ethyl acetate 3:1): R_f 0.27; ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.18 (m, 1 H, 4b-H), 3.30 (m, 2b-H_β), 3.37, 3.39 (2 s, 3 H, OCH_3), 3.47 (m, 2b-H_α, 5b-H_β), 3.61−4.03 (m, 8 H, 2a-H, 3a-H, 5a-H, 2 6a-H, 3b-H, 2 6b-H), 4.27−5.11 (m, 1a-H, 4a-H, 5b-H_α, 2 7′-H, 2 8′-H, 5 $PhCH_2$), 5.12 (d, $^3J_{1,2}$ = 2.9 Hz, 1b-H_α), 5.35 (d, $^3J_{1,2}$ = 7.7 Hz, 1b-H_β), 6.95−7.34 (m, 28 H, 5 Ph, 4′-H, 5′-H, 6′-H), 8.34 (s, 1 H, 2′-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.1, 55.2 (OCH_3), 69.2 (6a-C), 70.1 (5a-C), 70.8−75.1 (7 C, 7′-C, 8′-C, 5 $PhCH_2$), 72.1 (5b-C_α), 72.1 (5b-C_β), 73.8 (6b-C), 77.0 (4a-C), 77.4 (2a-C), 78.1 (3a-C), 78.6 (4b-C_β), 80.2 (2b-C_α), 80.9 (2b-C_α, 3b-C_α), 83.2 (2b-C_β), 84.7 (3b-C_β), 98.1 (1a-C), 98.2 (1b-C_α), 99.9 (1b-C_β); FAB-MS: *m/z* 931 $(M + Na)^+$. Anal. Calcd for $C_{56}H_{60}O_{11}$ (909.08): C, 73.99; H, 6.65. Found: C, 73.74; H, 6.76.

Methyl *O*-(2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl)-(1→4)-2,3,6-tri-*O*-acetyl-α-D-galactopyranoside (27α). Methyl *O*-(2,3,4,6-Tetra-*O*-acetyl-*β*-D-glucopyranosyl)-(1→4)-2,3,6-tri-*O*-acetyl-α-D-galactopyranoside (27*β*). (a) Treatment of compound **26**α/*β* (18 mg) according to the general procedure and chromatography (toluene/ethyl acetate 3:1 → 2:1) of the residue affords first **27**α (8 mg, 61%) as a colorless solid and then **27***β* (3 mg, 23%) as a colorless oil.

(b) Treatment of compound **32**α (22 mg) according to the general procedure and chromatography (toluene/ethyl acetate 9:1 → 2:1) of the residue affords first **28** (4 mg, 77%) as a colorless solid and then **27**α (10 mg, 77%) as a colorless oil. **27**α: TLC (toluene/acetone 2:1): R_f 0.50; $[\alpha]_D$ +36 (c 0.5, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.99, 2.04, 2.05, 2.06, 2.08, 2.09 (6 s, 21 H, $COCH_3$), 3.41(s, 3 H, OCH_3), 4.03−4.17 (m, 4 H, 4a-H, 5a-H, 6a-H, 6b-H), 4.25−4.40 (m, 3 H, 5b-H, 6a-H, 6b-H), 4.88−4.97 (m, 3 H, 1a-H, 1b-H, 2b-H), 5.11−5.18 (m, 2 H 3a-H, 4b-H), 5.27 (dd, 1 H, $^3J_{2,1}$ = 3.5 Hz, $^3J_{2,3}$ = 11.2 Hz, 2a-H), 5.48 (dd, $^3J_{3,2}$ = $^3J_{3,4}$ = 9.7 Hz, 3b-H). $C_{27}H_{38}O_{18}$ (650.59) FAB-MS: *m/z* 973 $(M + Na)^+$.

27*β*: TLC (toluene/acetone 2:1): R_f 0.45; $[\alpha]_D$ +7 (c 0.5, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.00, 2.02, 2.05, 2.06, 2.08, 2.09 (6 s, 21 H, $COCH_3$), 3.34 (s, 3 H, OCH_3), 3.60 (m, 1 H, 5b-H), 3.96−4.25 (m, 6 H, 4a-H, 5a-H, 2 6a-H, 2 6b-H), 4.45 (d, 1 H, $^3J_{1,2}$ = 7.8 Hz, 1b-H), 4.82 (d, 1H, $^3J_{2,1}$ = 2.8 Hz, 1a-H), 4.85−5.22 (m, 5 H, 2a-H, 3a-H, 2b-H, 3b-H, 4b-H). $C_{27}H_{38}O_{18}$ (650.59) FAB-MS: *m/z* 973 $(M + Na)^+$.

4′,6′-Bis(bromomethyl)-*m*-terphenyl (29). A suspension of **28**[31] (1.29 g, 5.0 mmol), *N*-bromosuccinimide (3.56 g, 10.0 mmol), and azobisisobutyronitrile (20 mg) in tetrachloromethane (10 mL) is refluxed for 24 h. After the mixture cools to room temperature, the solid is filtered off and washed with tetrachloromethane. The filtrate is concentrated in vacuo. Chromatography (petroleum ether/tetrachloromethane 9:1) of the residue affords **29** (1.27 g, 61%) as colorless crystals; mp 101−103 °C. TLC (petroleum ether/tetrachloromethane 4:1): R_f 0.38; ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.48 (s, 4 H, 2 $PhCH_2$-Br), 7.17 (s, 1 H, 5′-H), 7.36 (m, 10 H, 2 Ph), 7.70 (s, 1 H, 2′-H). Anal. Calcd for $C_{20}H_{10}Br_2$ (416.15): C, 57.75; H, 3.88. Found: C, 57.54; H, 3.91.

Ethyl 2,3,4-Tri-*O*-benzyl-6-*O*-(3-bromomethyl-4,6-diphenylbenzyl)-1-thio-*β*-D-glucopyranoside (30). Compound **1a**[18] (495 mg, 1.0 mmol) in dry dimethylformamide (3 mL) is added at 0 °C to a suspension of **29** (624 mg, 1.5 mmol) and sodium hydride (26 mg, 1.1 mmol) in dry dimethylformamide (10 mL), and the mixture is stirred for 20 h at 0 °C. Concentration of the solution in vacuo and chromatography (petroleum ether/ethyl acetate 19:1) of the residue affords **30** (456 mg, 55%) as a colorless oil. TLC (petroleum ether/ethyl acetate 3:1): R_f = 0.64; $[\alpha]_D$ +5 (*c* 1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.26 (t, 3 H, SCH_2CH_3), 2.69−2.73 (m, 2 H, SCH_2CH_3), 3.39−3.71 (m, 6 H, 2-H, 3-H, 4-H, 5-H, 2 6-H), 4.42−4.93 (m, 11 H, 1-H, 2 7′-H, 2 8′-H, 3 $PhCH_2$), 7.18−7.46 (m, 26 H, 5 Ph, 5′-H), 7.70 (s, 1 H, 2′-H); MALDI-MS: *m/z* 851, 853 $(M + Na)^+$, 867, 869 $(M + K)^+$. Anal. Calcd for $C_{49}H_{49}BrO_5S$ (829.91): C, 70.92; H, 5.96. Found: C, 70.95; H, 6.07.

Ethyl 6-*O*-[3-(Methyl 2,6-di-*O*-benzyl-α-D-galactopyranoside-3-yloxymethyl)-4,6-diphenylbenzyl]-2,3,4-tri-*O*-benzyl-1-thio-*β*-D-glucopyranoside (31). Compound **21** (374 mg, 1.0 mmol) and dibutyltin oxide (274 mg, 1.1 mmol) are refluxed in toluene (10 mL) for 4 h in an apparatus for the azeotropic removal of water. The solution is cooled to room temperature, and then tetrabutylammonium bromide (355 mg, 1.1 mmol) and **30** (415 mg, 0.5 mmol) are added. Stirring for 4 h at 90 °C, evaporation of the solvent, and chromatography (toluene → toluene/ethyl acetate 19:1) of the residue affords **31** (298 mg, 53%) as a colorless oil. TLC (toluene/ethyl acetate 4:1): R_f = 0.57; $[\alpha]_D$ −1 (c 0.7, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.18 (t, 3 H, SCH_2CH_3), 2.28 (s, 1H, O*H*), 2.50−2.56 (m, 2 H, SCH_2CH_3), 3.27−3.75 (m, 15 H, 2a-H, 3a-H, 4a-H, 5a-H, 2 6a-H, 2b-H, 3b-H, 4b-H, 5b-H, 2 6b-H, OCH_3), 4.32−4.81 (m, 16 H, 1a-H, 1b-H, 2 7′-H, 2 8′-H, 5 $PhCH_2$), 7.11−7.37 (m, 36 H, 7 Ph, 5′-H), 7.64 (s, 1H, 2′-H). $C_{70}H_{74}O_{11}S$ (1123.41) FAB-MS: *m/z* 1145 $(M + Na)^+$.

Methyl 3,6′-*O*-(4,6-Diphenyl-1,3-xylylene)-(2,3,4-*O*-tribenzyl-α-D-glucopyranosyl)-(1′→4)-2,6-di-*O*-benzyl-α-D-galactopyranoside (32α). Treatment of compound **31** (56 mg) according to the general procedure and chromatography (petroleum ether/ethyl acetate 9:1 → 7:1) of the residue affords **32**α (46 mg, 87%) as a colorless oil. TLC (petroleum ether/ethyl acetate 5:1): R_f 0.18; $[\alpha]_D$ +16 (c 0.8, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.10 (dd, 1 H, $^3J_{4,3}$ = $^3J_{4,5}$ = 9.3 Hz, 4b-H), 3.29 (s, 3 H, OCH_3), 3.37 (dd, 1 H, $^3J_{4,3}$ = $^3J_{4,5}$ = 9.3 Hz, 2b-H), 3.46 (dd, 1 H, $^2J_{6,6}$ = 11.2 Hz, $^3J_{6,5}$ = 7.9 Hz, 6b-H), 3.53 (dd, 1 H, $^2J_{6,6}$ = 10.0 Hz, $^3J_{6,5}$ = 7.0 Hz, 6a-H), 3.72 (dd, 1 H, $^2J_{6,6}$ = 11.2 Hz, $^3J_{6,5}$ = 3.0 Hz, 6b-H), 3.76 (dd, 1 H, $^2J_{6,6}$ = 10.2 Hz, $^3J_{6,5}$ = 5.9 Hz, 6a-H), 3.85−3.88 (m, 2 H, 3a-H, 5a-H), 3.95 (dd, 1 H, $^3J_{3,2}$ = $^3J_{3,4}$ = 9.3 Hz, 3b-H), 4.00 (dd, 1 H, $^3J_{2,1}$ = 3.5 Hz, $^3J_{2,3}$ = 10.0 Hz, 2a-H), 4.16 (dd, 1 H, $^3J_{4,3}$ = 2.0 Hz, $^3J_{4,5}$ < 1.0 Hz, 4a-H), 4.25 (d, 1 H, ^2J = 12.1 Hz, 1/2 $PhCH_2$), 4.32 (m, 3 H, 3/2 $PhCH_2$), 4.40 (m, 1 H, 5b-H), 4.47 (d, 1 H, ^2J = 10.7 Hz, 1/2 $PhCH_2$), 4.52 (d, 1 H, ^2J = 11.9 Hz, 1/2 $PhCH_2$), 4.61−4.70 (m, 7 H, 3 $PhCH_2$, 1a-H), 4.78 (d, 1 H, ^2J = 10.9 Hz, 1/2 $PhCH_2$), 5.02 (d, 1 H, $^3J_{1,2}$ = 3.0 Hz, 1b-H), 5.13 (d, 1 H, ^2J = 13.2 Hz, 1/2 $PhCH_2$), 7.00−7.32 (m, 36 H, 7

Ph, 5′-H), 8.53 (s, 1 H, 2′-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.2 (O*C*H$_3$), 69.2 (6a-C), 70.1 (5a-C), 71.8 (Ph*C*H$_2$), 71.9 (5b-C), 72.3, 72.9, 73.2, 73.7, 73.9 (6 Ph*C*H$_2$), 74.0 (6b-C), 75.3 (Ph*C*H$_2$), 77.6 (2a-C), 77.8 (2 C, 3a-C, 4a-C), 78.3 (2b-C), 80.8 (3b-C), 80.9 (4b-C), 97.9 (1a-C), 98.6 (1b-C). $C_{68}H_{68}O_{11}$ (1061.28) FAB-MS: *m/z* 1083 $(M + Na)^+$.

Ethyl 2-*O*-Benzyl-4,6-*O*-benzylidene-6-*O*-(3-bromomethylbenzyl)-1-thio-*β*-D-glucopyranoside (34). Compound **33** (403 mg, 1.0 mmol) in dry dimethylformamide (5 mL) is added at 0 °C to a suspension of **2** (792 mg, 3.0 mmol) and sodium hydride (29 mg, 1.2 mmol) in dry dimethylformamide (10 mL), and the mixture is stirred for 2 h at 0 °C. Concentration of the solution in vacuo and chromatography (petroleum ether/ethyl acetate 19:1 → 14:1) of the residue affords **33** (316 mg, 54%) as a colorless oil. TLC (petroleum ether/ethyl acetate 3:1): R_f 0.59; $[\alpha]_D$ −31 (*c* 1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.31 (t, 3 H, SCH$_2$C*H*$_3$), 2.68−2.83 (m, 2 H, SC*H*$_2$-CH$_3$), 3.39−3.49 (m, 2 H, 2-H, 5-H), 3.66−3.81 (m, 3 H, 3-H, 4-H, 6-H), 4.32−4.38 (m, 3 H, 6-H, 2 7′-H), 4.56 (d, 1 H, $^3J_{1,2}$ = 9.8 Hz, 1-H), 4.74−4.92 (m, 4 H, PhC*H*$_2$, 2 8′-H), 5.56 (s, 1 H, PhC*H*), 7.22−7.49 (m, 14 H, 2 Ph, 2′-H, 4′-H, 5′-H, 6′-H); MALDI-MS: *m/z* 607, 609 $(M + Na)^+$. Anal. Calcd for $C_{30}H_{32}BrO_5S$ (585.57): C, 61.53; H, 5.68. Found: C, 61.60; H 5.64.

Ethyl 3-*O*-[3-(Methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside-6-yloxymethyl)-benzyl]-2-*O*-benzyl-4,6-*O*-benzylidene-1-thio-*β*-D-glucopyranoside (35). Compound **4** (374 mg, 1.0 mmol) and dibutyltin oxide (274 mg, 1.1 mmol) are refluxed in toluene (10 mL) for 4 h in an apparatus for the azeotropic removal of water. The solution is cooled to room temperature, and then tetrabutylammonium bromide (355 mg, 1.1 mmol) and **34** (293 mg, 0.5 mmol) are added. Stirring for 20 h at 90 °C, evaporation of the solvent, and chromatography (toluene → toluene/ethyl acetate 19:1) of the residue affords **35** (286 mg, 65%) as a colorless oil. TLC (toluene/ethyl acetate 4:1): R_f 0.36; $[\alpha]_D$ −17 (*c* 1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.23 (t, 3 H, SCH$_2$C*H*$_3$), 2.23 (d, 1 H, ^3J = 2.3 Hz, O*H*), 2.64−2.70 (m, 2 H, SC*H*$_2$CH$_3$), 3.27 (s, 3 H, OC*H*$_3$), 3.29−3.72 (m, 11 H, 2a-H, 3a-H, 4a-H, 5a-H, 2 6a-H, 2b-H, 4b-H, 2 6b-H), 4.25−4.93 (m, 13 H, 1a-H, 1b-H, 3b-H, 2 7′-H, 2 8′-H, 3 PhC*H*$_2$), 5.48 (s, 1 H, PhC*H*), 7.16−7.40 (m, 24 H, 4 Ph, 2′-H, 4′-H, 5′-H, 6′-H). $C_{51}H_{58}O_{11}S$ (879.08) FAB-MS: *m/z* 901 $(M + Na)^+$.

Methyl 6,3′-*O*-(1,3-Xylylene)-(2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranosyl)-(1′→4)-2,3-di-*O*-benzyl-α-D-glucopyranoside (36α). Treatment of compound **35** (44 mg) according to the general procedure and chromatography (petroleum ether/ethyl acetate 5:1 → 4:1) of the residue affords **36**α (38 mg, 93%) as a colorless oil. TLC (toluene/ethyl acetate 4:1): R_f 0.40; $[\alpha]_D$ +22 (*c* 1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.26 (dd, 1 H, $^3J_{6,6}$ = 10.6 Hz, $^3J_{6,5}$ = 7.6 Hz, 6a-H), 3.32 (dd, 1 H, $^3J_{2,1}$ = 2.9 Hz, $^3J_{2,3}$ = 10.0 Hz, 2b-H), 3.36−3.40 (m, 5 H, 4b-H, 5b-H, OC*H*$_3$), 3.44−3.48 (m, 2 H, 2a-H, 4a-H), 3.52 (dd, 1 H, $^3J_{6,6}$ = $^3J_{6,5}$ = 10.0 Hz, 6b-H), 3.75 (dd, 1 H, $^2J_{6,6}$ = 10.3 Hz, $^3J_{6,5}$ < 1.0 Hz, 6a-H), 3.92 (dd, 1 H, $^2J_{5,6}$ = 7.6 Hz, $^3J_{5,4}$ = 10.6 Hz, 5a-H), 3.97−4.00 (m, 2 H, 3a-H, 6b-H), 4.23 (dd, 1 H, $^3J_{3,4}$ = $^3J_{3,2}$ = 9.4 Hz, 3b-H), 4.43 (d, 1 H, ^2J = 13.2 Hz, 7′-H), 4.46 (d, 1 H, ^2J = 10.9 Hz, 1/2 PhC*H*$_2$), 4.51−4.54 (m, 2 H, 4.51 (d, 1 H, $^3J_{1,2}$ =3.8 Hz, 1a-H), 1/2 PhC*H*$_2$), 4.55 (d, 1 H, ^2J = 12.5 Hz, 1/2 PhC*H*$_2$), 4.62−4.66 (m, 2 H, PhC*H*$_2$), 4.73 (d, 1 H, ^2J = 13.2 Hz, 1/2 PhC*H*$_2$), 4.85−4.94 (m, 3 H, 2 8′-H, 1/2 PhC*H*$_2$), 5.21 (d, 1 H, $^3J_{1,2}$ = 2.3 Hz, 1b-H), 5.36 (s, 1 H, PhC*H*), 7.16−7.32 (m, 23 H, 4 Ph, 4′-H, 5′-H, 6′-H), 7.58 (s, 1 H, 2′-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.2 (O*C*H$_3$), 65.7 (5b-C), 67.3 (6a-C), 68.9 (6b-C), 70.0 (3b-C), 70.2 (5a-C), 71.5 (7′-C), 72.1 (4a-C), 73.2, 73.3, 73.5, 74.2 (3 Ph*C*H$_2$, 8′-C), 78.3 (3a-C), 79.0 (2b-C), 80.8 (2a-C), 81.4 (4b-C), 94.6 (1b-C), 97.6 (1a-C), 101.3 (Ph*C*H); FAB-MS: *m/z* 839 $(M + Na)^+$. Anal. Calcd for $C_{49}H_{52}O_{11}$ (816.35): C, 72.04; H, 6.42. Found: C, 71.58; H, 6.42.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

Supporting Information Available: HMQC spectra (Müller, L. *J. Am. Chem. Soc.* **1979**, *101*, 4481) of macrocyclic compounds 7*β*, 8*β*, 16*β*, 17*β*, 25*β*, 32α, and 36*β* and of protected disaccharides 9α, 9*β*, 10*β*, 18*β*, and 19*β*. HMQC spectra were acquired at 600 MHz (^{1}H) and 300 K in $CDCl_3$. Signal assignments are based on DQF-COSY and ROESY spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO990132E