On the Stereochemistry of Tethered Intermediates in *p*-Methoxybenzyl-Assisted β-Mannosylation

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We have previously developed a novel method for the stereocontrolled synthesis of β-*manno*-glycoside. Starting from 2-*O*-PMB (*p*-methoxybenzyl)-protected mannosyl donor **1**, conversion into the mixed acetal **3** under oxidative conditions followed by the activation of the anomeric position affords β-*manno*-glycoside as a single stereoisomer. Although the utility of this method has been further demonstrated in the synthesis of the core structure of Asn-linked glycan chains, there remained uncertainty with respect to the stereochemistry of the mixed acetal. In order to make a stereochemical assignment of this intermediate, diastereomeric acetals **14a**, **15a** and **14b**, **15b** were prepared from **9** + **10**/**7** and **11** + **12**/**13**, respectively. Investigations by means of NMR and a computational approach using DADAS 90 for quantifying steric hindrance, resulted in the conclusion that **14a**/**15a** derived from 2-*O*-PMB-protected **9** has an (*S*) configuration and **14b**/**15b** derived from 2-*O*-unprotected **11** has an (*R*) configuration. Based on the characteristic ^{1}H-NMR patterns inherent to the (*S*) isomers, 4,6-*O*-benzylidene-protected **30**–**35**, derived from thiomannosides **5**, **23**, **24**, **26**, **27**, were also revealed to have the (*S*) configuration.

Introduction

Stereoselective formation of β-*manno*-glycoside, which constitutes the core structure of asparagine (Asn)-linked glycoprotein oligosaccharides, has been the most challenging task in synthetic carbohydrate chemistry.[1] The difficulty arises from its unique stereochemical array of C-1/C-2 positions. Namely, 1,2-*cis* relative stereochemistry precludes the use of neighboring group participation and the equatorial orientation of the glycosidic linkage is also disfavored by virtue of an anomeric effect.[2]

Recently, we reported a novel method for the stereocontrolled synthesis of β-*manno*-glycoside[3] as an extension of the concept called intramolecular aglycon delivery (IAD).[4][5] In our approach, the *p*-methoxybenzyl (PMB)[6] group was utilized as a scaffold for making the tethered intermediate required in the IAD process. Namely, starting from 2-*O*-PMB-protected mannosyl donor **1**, treatment with DDQ in the presence of an aglycon afforded, presumably via a quinonemethide-like species **2**, the mixed acetal **3**.[7] Subsequent activation of the mannose anomeric position triggers the IAD process to afford 1,2-*cis*(β)-glycoside (Scheme 1).

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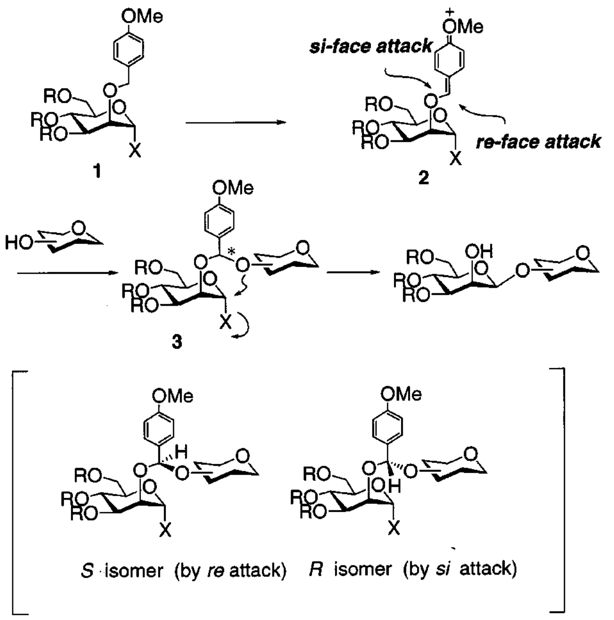

Scheme 1. Structures of diastereomeric mixed acetals

Of particular note in this strategy are its compatibility with a variety of protecting groups (acetyl, benzyl, cyclic acetal, silyl, phthalimide, *p*-methoxyphenyl) and its applicability to oligosaccharide fragment coupling. The latter feature clearly distinguishes our strategy from others and allowed us to apply it to the synthesis of the core pentasaccharide structure of the asparagine-(Asn-)linked glycoprotein oligosaccharide in a convergent and fully stereocontrolled manner.[3b,3c] Selectively protected mono-, di- and trimannosyl thioglycosides **4**,[3b] **5**,[3b] and **6**[3c] proved to be quite suitable for this purpose (Scheme 2). The yields of β-*manno*-glycosides obtained to date are as fol-

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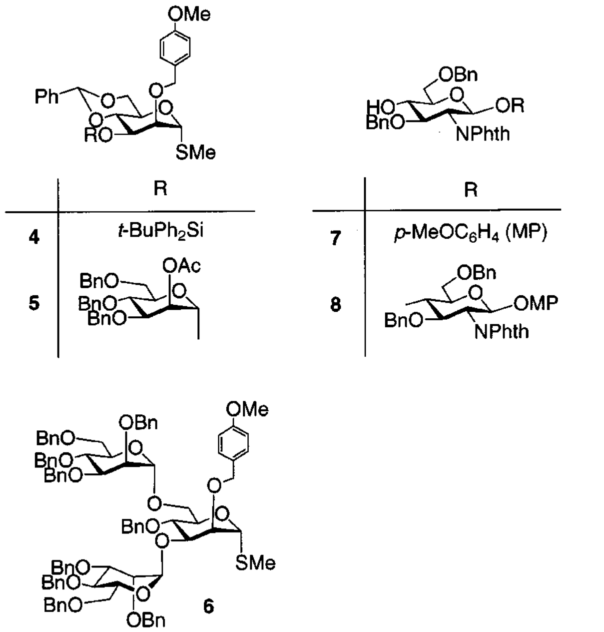
lows: 74% (1→6-linked disaccharide from **9**)[3a], 60% (1→4-linked di- and trisaccharide from **4**),[3b] 53% (1→4-linked trisaccharide from **5**)[3b] and 41% (pentasaccharide from **6**)[3c] (Table 1).



Scheme 2. Mannosyl donors and acceptors used for synthetic studies on Asn-linked glycans

Table 1. Results of PMB-assisted β-mannosylation

Donor/aglycon[a]	Yield of β-*manno*-glycoside [%][b]	Ref.
4/7	60	[3b]
4/8	60	[3b]
5/7	53	[3b]
5/8	49	[3b]
6/8	41	[3c]
9/10	52	[3a]
9/7	40	[3a]
9/18	74	[3a]

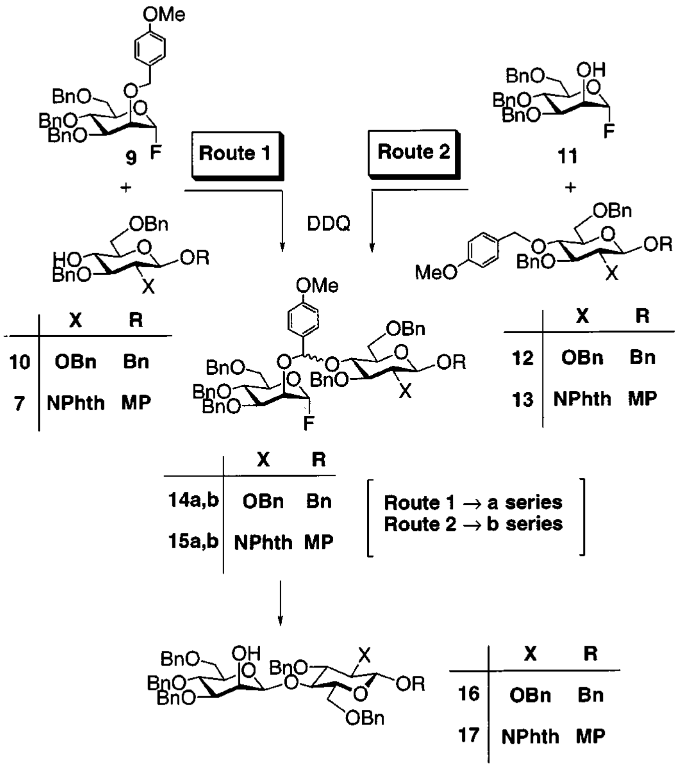
[a]Donor/aglycon ratios are from ca. 1.3 to ca. 1.5. – [b] Yields are calculated as overall from aglycon.

The success of our strategy mainly stems from the smooth formation of the mixed acetal **3** under essentially neutral conditions (DDQ, room temperature). This can be compared favorably with previously reported methods for mixed acetal formation[4,8–16] in terms of mildness of the reaction conditions, as well as operational simplicity. Additionally, by virtue of having a *p*-methoxyphenyl substituent on an acetal carbon atom, a high degree of charge delocalization can be expected during the course of the IAD process.

Although the utility of this method is quite clear, there remained uncertainty with respect to the stereochemistry of the mixed acetal. Namely, the acetalic carbon atom of **3** is stereogenic and the formation of two diastereomers is possible at this stage. Nucleophilic attack of an alcohol from the *re* and the *si* face of the presumed intermediate **2** should afford **3** as an (*S*) and (*R*) diastereomer, respectively. Therefore, the questions to be asked are: (1) Is this transformation stereoselective at all? (2) If it is stereoselective, which diastereomer is formed preferentially? (3) If the process is not stereoselective, do both isomers give IAD products with equal efficiency?

Synthesis of Diastereomeric Mixed Acetals

Due to its acyclic nature, as well as the lack of a vicinal hydrogen atom, stereochemical assignment of the mixed acetal **3** was thought to be rather problematic. In the search for a clue to solve this problem, we planned to prepare the mannosyl fluoride based mixed acetal **14** by an alternative route (Route 2). This compound was made from C-2-unprotected mannosyl fluoride **11**[17] and C-4-PMB-protected **12**. The aim was to compare this product with that obtained previously by Route 1, which was made from C-2-PMB-protected mannosyl fluoride **9** and C-4-unprotected **10**[18] (Scheme 3). Reactions were performed under conditions identical with those reported for Route 1 (DDQ, 4 Å molecular sieves/CH_2Cl_2, room temperature).



Scheme 3. Formation of diastereomeric mixed acetals

^{1}H-NMR analysis revealed that mixed acetals (**14a**,**b**), prepared as described above, are diastereomeric with each other and that both processes are substantially stereoselective to give each isomer with ≥ 95% diastereomeric purity. There are several characteristic features that clearly distinguish **14a** from **14b**. Firstly, chemical shifts of the 1-H and 2-H protons of the mannose differ by as much as ca. 1.2 and ca. 0.7 ppm, respectively (Table 2). Compared to the starting materials [$\delta_{1\text{-}H_{Man}}$ = 5.55 (**9**), 5.64 (**11**)], chemical shift deviations of **14b** are relatively small and quite a large low-field shift was observed for **14a** derived from Route 1. In addition, the signal of one of the methylene protons of the benzyl protecting group in **14a** was shifted downfield to as low as δ = 5.22. Similar trends were observed for a pair of acetals bearing a 2-phthalimide unit: **15a** [δ_H = 6.41 (1-H_{Man}), 5.40 (benzyl CH_2), 4.32 (2-H_{Man})] and **15b** [δ_H = 5.21 (1-H_{Man}), 3.75 (2-H_{Man})].

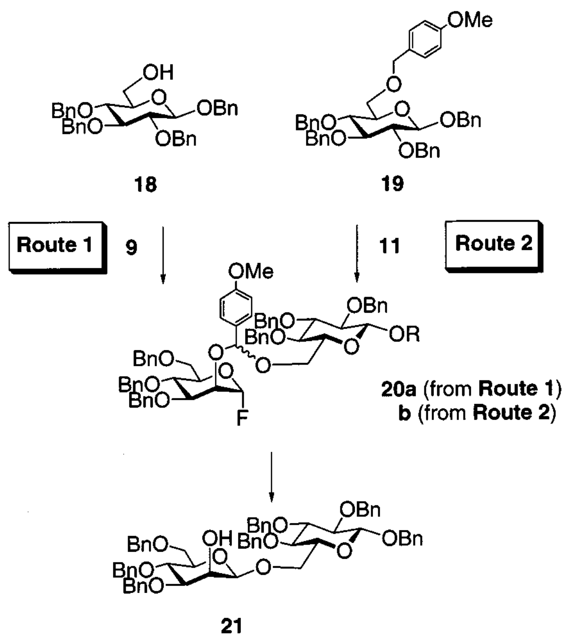
Table 2. Key ^{1}H-NMR signal of mixed acetals[a]

Mixed acetal (fluoride/aglycon) δH	^{1}Man	2Man	Acetal CH	$1_{Glc/GlcN}$
14a (9/10)	6.37	4.52	5.94	4.6
14b (11/12)	5.19	3.8	5.91	ND[b]
15a (9/7)	6.41	4.32	6.01	6.03
15b (11/13)	5.21	3.75	5.94	6.17

[a] Measured at 270 MHz in C_6D_6. – [b] Not determined.

Acetal **14b** was subjected to IAD (AgOTf, $SnCl_2$, 2,6-di-*tert*-butyl-4-methylpyridine, 4-Å molecular sieves/CH_2Cl_2) to afford β-*manno*-glycoside **16** in 47% yield, which is a nearly identical yield to that obtained previously by Route 1 (52%[3a]). This result demonstrates that the efficiency of IAD is rather insensitive to the stereochemistry of the mixed acetal as far as being effected by AgOTf/$SnCl_2$ is concerned.

A similar set of experiments was performed with the primary alcohol **18**[18] and corresponding PMB ether **19**. Thus, **18** and **19** were converted into **20** by treating with **9** (Route 1) and **11** (Route 2), respectively. ^{1}H-NMR analysis of the acetal **20a**, derived from Route 1, again revealed its stereochemical homogeneity and a characteristic downfield shift was observed for a signal assigned as 1-H_{Man}. On the other hand, acetal **20b**, derived from Route 2, proved to be a 3:2 mixture of diastereomers, with the compound having the opposite configuration to **20a** predominating. Conversion of **20a** and **20b** into β-mannoside **21** proceeded in 65%[3a,19] and 74% yield, respectively, providing additional proof that the acetal configuration is not a critical factor in the IAD process.



Scheme 4. Formation of β-1→6-linked disaccharide

Stereochemical Assignments of Mixed Acetals

Having the diastereomeric acetals **14a/b** and **15a/b** in hand, these materials were further studied by ^{1}H-NMR NOE experiments, which gave a clear indication that the spatial arrangements of substituents on the acetalic carbon atoms are markedly different in both cases. In acetals derived from Route 1 (**a** series), strong NOEs were observed between the acetal proton and 1-H_{Man}, 2-H_{Man}, and 4-H_{Glc} as well as aromatic protons of the *p*-methoxybenzyl substituent. For the other isomers (**b** series), NOE could be observed only between the 2-H_{Man} and the acetal proton.

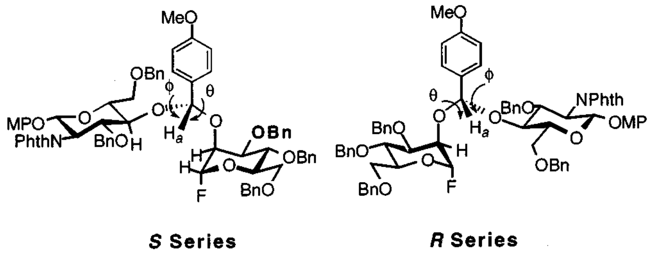
Based on this information, computational studies were performed using the program DADAS (Distance Analysis in Dihedral Angle Space) 90[20] to make stereochemical assignments of mixed acetals. In order to quantify steric repulsion under the condition that the observed NOEs should be fulfilled, calculations were performed for a pair of diastereomeric acetals **15a/b**, which were calculated as both (*S*) and (*R*) isomers. The following equation was applied to 100 initial structures for every distinct molecule (r = distance between two non-bonded atoms, R_s = a sum of van der Waals radii, R_u and R_l = upper and lower limitation of distance, A_u and A_l = upper and lower limitation of dihedral angle) (Equation 1).

$$T_p = T_r + T_n + T_t = [W_r(R_s^2 - r^2)^2] + [W_n(R_u^2 - r^2)^2 + W_n(R_l^2 - r^2)^2] + [W_t(A_u^2 - a^2)^2 + W_t(A_l^2 - a^2)^2] \quad (1)$$

soft repulsion term + NOE term + dihedral angle restriction

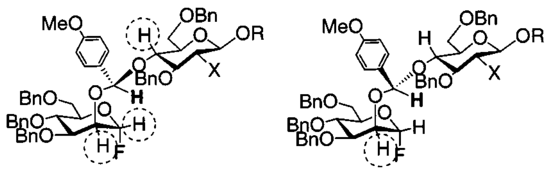
The soft repulsion term T_r is active when $r < R_s$, R_s being the sum of van der Waals radii of the two atoms. The NOE term T_n represents the observed effects under the condition

Table 3. Results of DADAS 90 calculations



15	(*R*)/(*S*)	NOE restriction (H_a →)	ϕ	θ	$T_{p(min)}$	$T_{p(max)}$
a	(*R*)	2-H_{man}	−70°	−135°	136	15000
a	(*S*)	1-H_{man}, 2-H_{man}, 4-H_{ag}, ar	100°	−50°	**27**	5855
b	(*R*)	2-H_{man}	32°	78°	**0**	34800
b	(*S*)	1-H_{man}, 2-H_{man}, 4-H_{ag}, ar	−15°	125°	221	21800

that $R_l < r < R_u$, where the lower limit R_l is 2 Å and the upper limit R_u is 3 Å for **15a** (4 NOEs); for **15b** (1 NOE) the lower limit R_l was set to be 3 Å. The dihedral angle restriction term T_t deals mostly with the acetal bond, whereas protecting groups were allowed to rotate freely. An anomeric effect was considered for the newly formed acetal bonds and was set the lower limit A_l and the upper limit A_u of angles ϕ and θ between $-90°$ and $90°$. T_p (pseudo energy) should therefore reach a minimum provided that the sterically less hindered conformation is reached under the condition that 4 NOEs for **15a** and 1 NOE for **15b** are exhibited. Table 3 shows the results of the calculations. As clearly seen by comparison of the T_p values, (*S*)-**15a** is the sterically less hindered diastereomer in comparison to (*R*)-**15a**. In contrast, in another diastereomer **15b** a reversal of relative magnitudes of T_p is observed. In this case, all conditions avoiding steric congestion were fulfilled as an (*R*) isomer (T_p = 0) in comparison to that of (*S*) isomer (i.e. 136).



14/15a **14/15b**

Figure 1. Stereochemistry of mixed acetals **14a**,**b** and **15a**,**b**; protons having NOEs to H_a (bold typeface) are marked by dotted circles

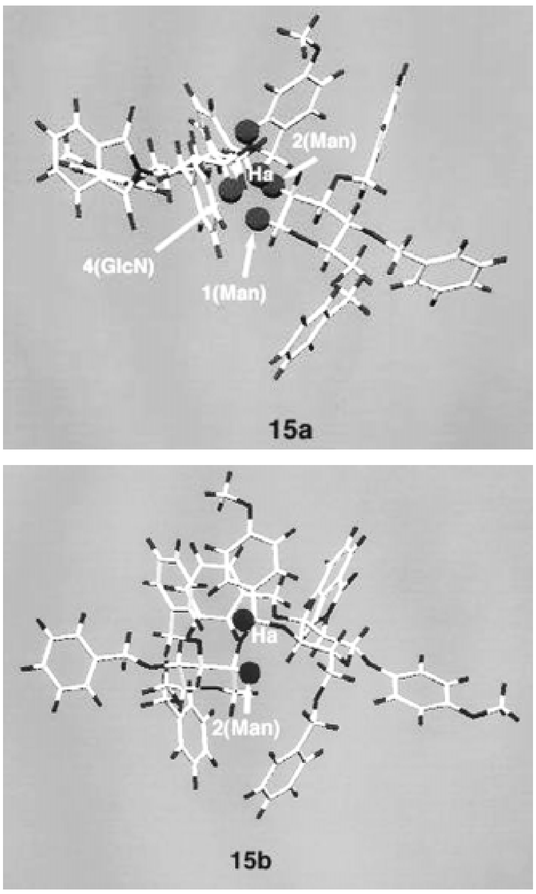
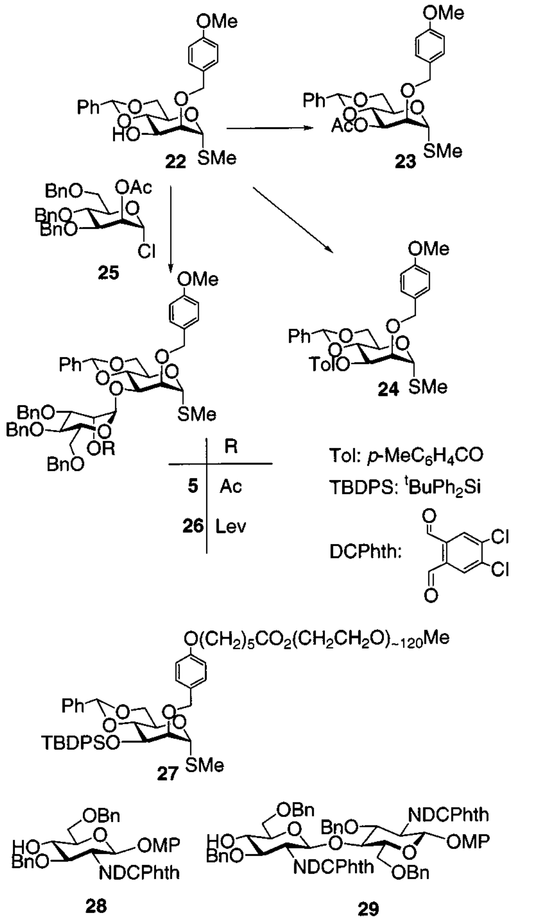


Figure 2. Computer-generated view of pseudo-energy minimum conformers of **15a** (top) and **15b** (bottom); protons H_a, 4-H_{GlcN}, 1-H_{Man}, 2-H_{Man}, and Ar-H_{PMB} (for **15a**), and H_a and 2-H_{Man} (for **15b**) are depicted as spheres

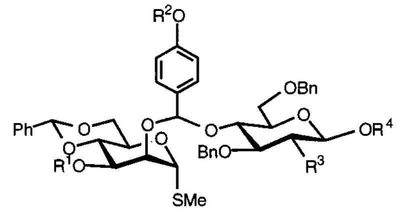
These calculations led us to the conclusion that mixed acetals formed by Route 1 and having 4 positive NOEs are (*S*) diasteromers, whilst those obtained by Route 2 and having only 1 NOE are (*R*) diastereomers (Figures 1 and 2). Since the ^{1}H-NMR patterns of (*S*) and (*R*) isomers are clearly distinct, the assignment of acetal stereochemistry is hereafter possible simply by routine ^{1}H-NMR measurement (vide infra).

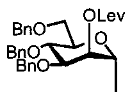
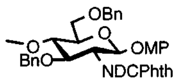
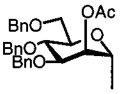
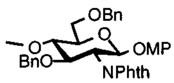
4,6-*O*-Benzylidene-protected thiomannosides **4** and **5** proved to be highly useful in the stereoselective synthesis of Asn-linked glycans[3b] and the stereochemistry of corresponding mixed acetals is of particular interest. For this reason, detailed NMR studies were performed with mixed acetals **30**−**33** (Table 4), obtained from **5**, **23**, **24**, **26**, which were in turn prepared from **22** as a key intermediate (Scheme 5). In the cases of **30**−**33**, mixed acetals were purified to give spectroscopically homogeneous compounds and isolated in 65−88% yield.[21] As summarized in Table 4, uniformly strong downfield shifts were observed for 1-H_{Man} and one benzyl methylene proton, and this fact allowed us to conclude that all of these mixed acetals have an (*S*) con-



Scheme 5. Precursors of mixed acetals **30**−**35**

Table 4. Key ^{1}H-NMR chemical sifts of thioglycoside-derived mixed acetals[a]



	R1	R2	R3	R4
30	Ac	Me	NDCPhth	OMP
31	Tol	Me	NDCPhth	OMP
32		Me	NDCPhth	
33		Me	NPhth	
34	TBDPS	$(CH_2)_5CO_2$PEGOMe	NPhth	F
35	TBDPS	$(CH_2)_5CO_2$PEGOMe	OBn	OBn

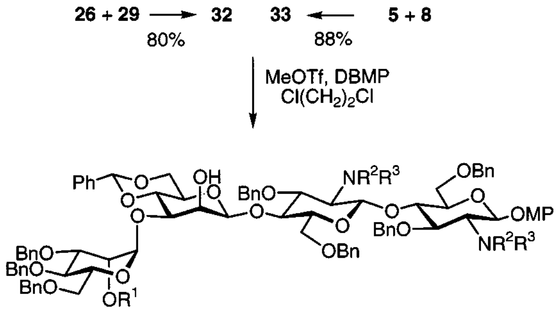
Mixed acetal	δ_H[b]					
(Thioglycoside/ aglycon)	1-H_{Man}	2-H_{Man}	Acetal CH	Ph*CH*	1-H_{GlcN}	Ref.
30 (**23**/**28**)	5.73	3.92	5.47	5.03	5.59	–
31 (**24**/**28**)	5.78	4.11	5.49	5.09	5.58	–
32 (**26**/**29**)	5.69	3.78	5.64	5.09	5.34	–
33 (**5**/**8**)	5.73	3.81	5.65	4.83	5.36	[3b]
34 (**27**/**8**)	5.63	3.29	5.35	4.80	5.87	[3e]
35 (**27**/**10**)	5.68	ND	5.46	ND	ND	[3e]

[a] Measured at 270 MHz in $CDCl_3$. – [b] Assignments for **30** and **32** were confirmed by H-H and C-H COSY experiments and those for other compounds were made by analogy.

figuration. The assignment was also supported by NOE studies for compound **30**–**32**. Namely, strong NOEs were observed between the acetal proton and 1- and 2-H of mannose and 4-H of glucosamine. In addition, in the case of polymer-supported thioglycoside **27**,[3e] the corresponding acetals **34** and **35** consist of a single stereoisomer and their configurations were assigned as (*S*).

Among the compounds listed in Table 4, mixed acetals **32** and **33** were transformed into tetrasaccharides **36a** and **36b**, respectively,[3b] by the action of methyl trifluoromethanesulfonate (MeOTf)/DBMP (Scheme 6). Compound **36**, having a 4,5-dichlorophthaloyl group as an amine-protecting group,[22] was designed to be an advanced intermediate for the synthesis of complex oligosaccharides.

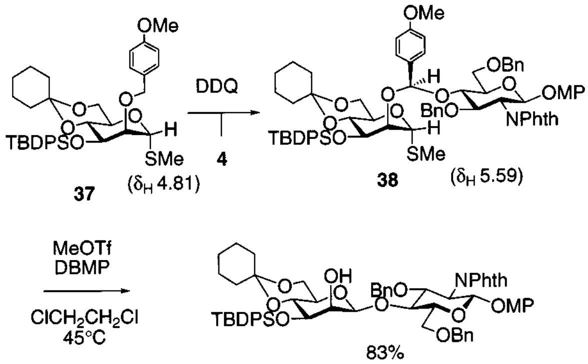
More recently it was discovered that the efficiency of β-mannoside formation can be further improved by using 4,6-



36	R1	R2,R3	yield
a	Lev	DCPhth	39%
			(43% overall based on consumed **29**)
b	Ac	Phth	55%

Scheme 6. Stereocontrolled synthesis of tetrasaccharide

cyclohexylidene-protected thioglycoside **37** (Scheme 7). Reaction with glucosamine-derived acceptor **4** afforded disaccharide **39**, via acetal **38**, in 83% yield.[23] Inspection of the ^{1}H-NMR spectrum [δ_H = 5.59 (1-H_{Man})] revealed that the stereochemistry of the acetalic carbon atom is again (*S*).



Scheme 7. Use of cyclohexylidene-protected mannosyl donor

Discussion

Isopropylidene mixed acetals and mixed silaketals were introduced by Baressi and Hindsgaul[4] and Stork and coworkers[5] as intermediates for IAD in β-D-mannosylation. These compounds were formed by bridging two alcohols under the action of dichlorodimethylsilane, or by addition of an alcohol to a vinyl ether protected carbohydrate. An *n*-pentenyl glycoside derived silaketal[24] and a glucose-derived mixed acetal[25] were used for similar purposes. Compared to the previously reported preparations of mixed acetals, the DDQ-mediated process described here seems to be operationally simpler and has applicability to a wider range of oligosaccharide structures.[26]

As far as the issue of the stereochemistry of mixed acetals **3** is concerned, it is now clear that the mixed acetal formation from the 2-*O*-PMB mannosyl donor proceeds with a uniformly high degree of diastereofacial selectivity, with attack at the *re* face of the cationic intermediate **2**. On the other hand, 2-*O*-unprotected fluoride **11** gave the (*R*) isomer **14/15b** when treated with 4-*O*-PMB-protected Glc/GlcN derivatives (**12/13**). Although the origins of these selectivities are obscure for the moment, these results strongly suggest that the stereochemical outcomes are the result of kinetic control. Additionally, it was demonstrated that IAD processes proceed with nearly equal efficiency for both diastereomers, as far as relatively reactive aglycon-derived acetals (**14**, **20**) are concerned. That the IAD process is effective for both stereoisomers, which are available by separate routes (i.e. Route 1 and Route 2 in Scheme 3), may well further broaden the flexibility of PMB-assisted β-mannosylation.

Experimental Section

General Methods: Melting points were determined with a Yanagimoto micro-melting point apparatus and are not corrected. − Optical rotations were measured with a JASCO DIP 370 Polarimeter at ambient temperature (20±3°C). − NMR spectra were recorded with a JEOL EX-270 spectrometer using Me_4Si as internal standard for $CDCl_3$ and C_6D_6 solutions. − TLC on silica gel 60 F_{254} (Merck, Darmstadt) was used to monitor the reactions and to ascertain the purity of the products. Silica gel column chromatography was performed with Merck silica gel 60 (63−200 μm) or Cica silica gel 60 N (spherical, 40−100 or 100−210 μm). − Silver trifluoromethanesulfonate (AgOTf) was recrystallized from hot toluene/*n*-hexane. All other reagents were used as received. Dichloromethane was distilled from CaH_2. All other solvents were dried and stored over freshly activated molecular sieves (3 or 4 Å). Molecular sieves were activated by heating to 180°C in vacuo for 24 h prior to use. All reactions were performed under N_2 or Ar.

Benzyl 2,3,6-Tri-*O*-benzyl-4-*O*-*p*-methoxybenzyl-β-D-glucopyranoside (12): To an ice/water-cold solution of compound **10** (1.47 g, 2.72 mmol) in DMF (15 mL) was added NaH (60%, 160 mg, 40 mmol) under a positive pressure of N_2 and the mixture was stirred for 10 min. *p*-Methoxybenzyl chloride (0.48 mL, 3.5 mmol) was added dropwise and the mixture was gradually warmed to ambient temperature. After being stirred for 18 h, the reaction was quenched with MeOH (ca. 0.5 mL) at 0°C, diluted with diethyl ether, washed successively with water and brine, dried with $MgSO_4$ and the solvent evaporated in vacuo. The residue was crystallized from cold hexane to afford 1.66 g (93%) of **12**, m.p. 98−99°C. − $[\alpha]_D$ = −16.7 (*c* = 0.72, $CHCl_3$). − ^1H NMR (270 MHz, $CDCl_3$): δ = 3.78 (s, 3 H, OMe), 4.51 (d, 1 H, 1-H), 6.80 (d, 2 H, PMB), 7.07 (d, 2 H, PMB), 7.2−7.45 (m, 20 H, Ar), $J_{1,2}$ = 7.6, J_{PMB} = 8.6 Hz. − ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 55.3(MeO), 68.9, 71.1, 73.5, 74.6, 74.9, 74.9, 75.7, 77.6, 82.3, 84.8, 102.6 (C-1). − $C_{42}H_{44}O_7$ (660.8): calcd. C 76.34, H 6.71; found C 76.18, H 6.70.

***p*-Methoxyphenyl 3,6-Di-*O*-benzyl-2-deoxy-4-*O*-*p*-methyloxybenzyl-2-phthalimido-β-D-glucopyranoside (13):** To an ice/water-cold solution of compound **7** (176 mg, 0.29 mmol) in DMF (3 mL) was added NaH (60%, 16 mg, 0.44 mmol) under a positive flush of N_2 and the mixture was stirred for 10 min. *p*-Methoxybenzyl chloride (60 μL, 0.44 mmol) was added dropwise and the mixture was gradually warmed to ambient temperature over 1 h. After being stirred for additional 2 h, the reaction was quenched with MeOH (ca. 0.1 mL) at 0°C, diluted with diethyl ether, successively washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt, 2:1) to afford 124 mg (59%) of **13**, $[\alpha]_D$ = +62.1 (*c* = 1.9, $CHCl_3$). − ^1H NMR ($CDCl_3$): δ = 3.72 (s, 3 H, MeO), 3.80 (s, 3 H, MeO), 5.63 (d, 1 H, 1-H), 6.6−7.4 (m, 18 H, Ar), 7.5−7.9 (br., 4 H, Phth); $J_{1,2}$ = 8.3 Hz. − ^{13}C NMR ($CDCl_3$) δ = 55.26, 55.53, 55.80, 68.59, 73.48, 74.70, 74.84, 75.24, 77.22, 79.16, 79.18, 97.56 (C-1). − $C_{43}H_{41}N_1O_9$ (715.8): calcd. C 72.15, H 5.77, N 1.96; found C 71.65, H 5.76, N 1.91.

Benzyl 2,3,4-Tri-*O*-benzyl-6-*O*-*p*-methoxybenzyl-β-D-glucopyranoside (19): Compound **18** (545 mg, 1.01 mmol) was treated with NaH (60%, 60 mg, 1.5 mmol) and *p*-methoxybenzyl chloride (180 μL, 1.3 mmol) in DMF (3 mL) in the same manner as described for **12**. Purification by silica gel column chromatography (hexane/AcOEt, 5:1) afforded 629 mg (94%) of **19**, m.p. 57−58°C. − $[\alpha]_D$ = 6.3 (*c* = 0.8, $CHCl_3$). − ^1H NMR (270 MHz, $CDCl_3$): δ = 3.77 (s, 3 H, MeO), 6.85 (d, 2 H, PMB), 7.1−7.45 (m, 22 H, Ar); J_{PMB} = 8.6 Hz. − ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 55.2 (MeO), 68.5, 71.1, 73.1, 74.9, 74.9, 75.7, 76.2, 77.2, 77.9, 82.3, 84.7, 102.6 (C-1). − $C_{42}H_{44}O_7$ (660.8): calcd. C 76.34, H 6.71; found C 76.16, H 6.67.

Benzyl *O*-(3,4,6-Tri-*O*-benzyl-β-D-mannopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (16). − From 11 and 12: To a stirred mixture of DDQ (26 mg, 0.11 mmol) and 4-Å molecular sieves (0.26 g) in CH_2Cl_2 (2 mL) were added compounds **11** (33.2 mg, 0.073 mmol) and **12** (60.3 mg, 0.091 mmol) as a solution in CH_2Cl_2 (3 mL) at 0°C. The mixture was stirred at 0°C for 10 min and at room temperature for 60 min. The resulting mixture was quenched with a solution of ascorbic acid (0.7%)/citric acid (1.3%)/NaOH (0.9%) in water (3 mL), diluted with AcOEt, and filtered through Celite. The filtrate was successively washed with water, aq. $NaHCO_3$ and brine, and then dried with Na_2SO_4. The solvent was evaporated, coevaporated with toluene in vacuo and the material exposed to high vacuum (ca. 1 h) to afford crude **14b**. To a flask containing 4-Å molecular sieves (0.3 g) and 2,6-di-*tert*-butyl-4-methylpyridine (DBMP, 25 mg, 0.12 mmol) was added AgOTf (30 mg, 0.12 mmol) and $SnCl_2$ (22 mg, 0.12 mmol) followed by CH_2Cl_2 (1 mL) and the mixture was cooled to ice/water temperature. **14b** was then added as a solution in CH_2Cl_2 (4 mL) and the mixture was stirred at ambient temperature for 18 h. The reaction mixture was quenched with aq. $NaHCO_3$/ice, diluted with AcOEt, and filtered through Celite. The filtrate was successively washed with water and brine, dried with $MgSO_4$, and the solvent evaporated in vacuo. The residual syrup was purified by silica gel column chromatography (hexane/AcOEt, 5:1 → 2:3) to afford 33.7 mg (47%) of **16**, m.p. 94−96°C. − $[\alpha]_D$ = +3.0 (*c* = 0.8, $CHCl_3$). − ^1H NMR (270 MHz, $CDCl_3$): δ = 2.65 (br., 1 H, OH), 3.50 (dd, 1 H, 2-H), 3.98 (br. s, 1 H, 2′-H), 4.51 (d, 1 H, 1-H), 4.64 (s, 1 H, 1′-H), 7.1−7.5 (m, 35 H, Ar); $J_{1,2}$ = 7.9, $J_{2,3}$ = 8.9 Hz. − ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 67.7, 69.0, 71.0, 71.1, 73.3, 73.4, 73.9, 74.4, 74.9, 75.1, 75.3, 75.5, 75.7, 81.5, 82.0, 83.1, 99.8 ($^1J_{CH}$ = 159 Hz), 102.6 ($^1J_{CH}$ = 159 Hz). − $C_{61}H_{64}O_{11}$ (973.2): calcd. C 75.29, H 6.62; found C 75.34, H 6.62. − In a separate experiment, **14b** was prepared from 37.1 mg (0.08 mmol) of **11** and 64.9 mg (0.098 mmol) of **12** and purified by size exclusion chromatography on Bio-Beads S-X4 (toluene); yield 85.0 mg (93%). − **From 9 and 10:** Compounds **9** (87.0 mg, 0.15 mmol) and **10** (56.3 mg) were treated with DDQ (36 mg, 0.16 mmol) in CH_2Cl_2 (3 mL), as described above, to afford crude **14a**. This material was treated with AgOTf (53 mg, 0.21 mmol)/$SnCl_2$(39 mg, 0.21 mmol)/DBMP (50 mg, 0.24 mmol) in 8 mL of CH_2Cl_2 (room temp., 5 h) and subsequent purification by silica gel column chromatography afforded 52.5 mg (52%) of **16**.

Benzyl *O*-(3,4,6-Tri-*O*-benzyl-β-D-mannopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (21). − From 11 and 19: Compounds **11** (32.4 mg, 0.072 mmol) and **19** (57.8 mg, 0.087 mmol) were transformed into **20b** in the same manner as described for **14b** in the preparation of **16**. In short, treatment of **11** and **19** with DDQ (25 mg, 0.087 mmol) in CH_2Cl_2 (5 mL) at room temperature for 70 min afforded crude **20b** (93 mg). − ^1H NMR (270 MHz, C_6D_6) δ = 4.3 [m, 2′-H, (*R*) isomer], 4.6 [m, 2′-H, (*S*) isomer], 5.88 [3/5 H, s, acetal CH, (*R*) isomer], 6.03 [dd, 3/5 H, *J* = 50 and < 1 Hz, 1′-H, (*R*) isomer], 6.04 [2/5 H, s, acetal CH, (*S*) isomer], 6.25 [d, 2/5 H, *J* = 50 Hz, 1′-H, (*S*)isomer]. − Subsequent transformation into **21** was performed using AgOTf (30 mg, 0.12 mmol), $SnCl_2$ (22 mg, 0.12 mmol), DBMP (25 mg, 0.12 mmol) and 4-Å molecular sieves (0.3 g) in 5 mL of CH_2Cl_2 (0°C, 10 min, room temp., 75 min). Purification by silica gel column chromatography afforded 52.0 mg (75%) of compound **21**, m.p. 115−117°C. − $[\alpha]_D$ = −3.0 (*c* = 1.1, $CHCl_3$). − ^1H NMR (270 MHz, $CDCl_3$): δ = 3.88 (t, 1 H, *J* = 9.2 Hz), 4.03 (d, 1 H, 2′-H), 4.22 (1 H, d, *J* = 9.9 Hz), 4.31 (s, 1 H, 1′-H), 4.50 (d, 1 H, 1-H), 7.1−7.5 (m, 35 H, Ar); $J_{1,2}$ = 7.6, $J_{2',3'}$ = 2.6 Hz. − ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 68.2, 68.7, 69.1, 71.2, 71.4, 73.5, 74.1, 74.4, 74.79, 74.83, 75.1, 75.2, 75.7, 78.0, 81.3, 82.2, 84.7, 100.3 ($^1J_{CH}$ = 159 Hz), 102.4 ($^1J_{CH}$ = 160 Hz). − $C_{61}H_{64}O_{11}$ (973.2): calcd. C 75.29, H 6.62; found C 75.26, H 6.58. − **From 9 and 18:** Compounds **9** (122.3 mg, 0.21 mmol) and **18** (80.2 mg, 0.15 mmol) were treated with DDQ (50 mg, 0.23 mmol) in 4 mL of CH_2Cl_2 to afford **20a**. This material was converted into **21** with AgOTf (74 mg, 0.29 mmol)/$SnCl_2$ (55 mg, 0.29 mmol)/DBMP (60 mg, 0.29 mmol) in 8 mL of CH_2Cl_2. Yield 94.0 mg (65%).

Mixed Acetals 14a/b and 15a/b for NOE Studies: These compounds were prepared from anomerically pure α-fluorides **9** and **11**. A typical experimental procedure is given for the preparation of **14a**: To a flask containing DDQ (16 mg, 0.070 mmol) and 4-Å molecular sieves (0.1 g) in CH_2Cl_2 was added a mixture of compounds **9** (30.2 mg, 0.0527 mmol) and **12** (34.1 mg, 0.063 mmol) as a solution in CH_2Cl_2 (1.5 mL) under ice/water cooling. The mixture was stirred at 0°C for 10 min and at room temperature for 130 min, and then quenched with a mixture of ascorbic acid (0.7%)/citric acid (1.3%)/NaOH (0.9%) in water (3 mL). The lemon-yellow suspension was diluted with AcOEt, filtered through Celite and the filtrate was successively washed with aq. $NaHCO_3$, water, and brine, dried with Na_2SO_4, and the solvent evaporated in vacuo. The residue was subjected to size exclusion chromatography on a column of Bio-Beads S-X3 (Bio-Rad) to afford **14a** (44.5 mg, 76%). − ^1H-NMR data (270 MHz, C_6D_6): **14a**: δ = 3.25 (s, 3 H, OMe), 3.9 (t, 1 H, 4-H), 4.52 (d, 1 H, 2′-H), 5.96 (s, 1 H, acetal CH), 6.38 (d, 1 H, 1′-H); $J_{3,4}$ = $J_{4,5}$ = 9, $J_{2'3'}$ = 2, J_{CH2} = 12.5 Hz, $^1J_{1',F}$ = 51.1 Hz. − **14b**: δ = 3.24 (s, 3 H, MeO), 3.75 (dd, 1 H, 2′-H), 5.19 (dd, 1 H, 1′-H), 5.22 (s, 1 H, benzyl CH_2), 5.91 (1 H, s, acetal CH); $J_{1'2'}$ < 1, $J_{2',3'}$ = 2, $J_{1',F}$ = 50 Hz. − **15a**: δ = 3.19 and 3.32 (2 s, each 3 H, OMe), 4.32 (d, 1 H, 2′-H), 4.5 (4-H), 5.05 (dd, 1 H, 2-H), 5.40 and 4.90 (ABq, each 1 H, benzylic CH_2), 6.00 (d, 1 H, 1-H), 6.02 (s, 1 H, acetal CH), 6.40 (1 H, d, 1′-H); $J_{1,2}$ = 8.6, $J_{2,3}$ = 10.6, $J_{1,F}$ = 50.9, $J_{2,3''}$ = 2, J_{CH2} = 12.5 Hz. − **15b**: δ = 3.17 and 3.26 (2 s, each 3 H, OMe), 3.78 (d, 1 H, 2′-H), 4.4 (4-H), 5.21 (d, 1 H, 1′-H), 5.94 (s, 1 H, acetal CH), 6.17 (d, 1 H, 1-H); $J_{1,2}$ = 8.6, $J_{1',F}$ = 50.8, $J_{2',3'}$ = 2 Hz.

Methyl 3-*O*-Acetyl-4,6-*O*-benzylidene-2-*O*-*p*-methoxybenzyl-1-thio-α-D-mannopyranoside (23): Acetic anhydride (2.5 mL) was added at 0°C to a solution of **22** (300 mg, 0.72 mmol) in CH_2Cl_2 (5 mL) and pyridine (2.5 mL) and stirred for 3 d at room temperature. The solution was poured into ice/water (50 mL), stirred for 30 min and diluted with CH_2Cl_2 (100 mL). The organic phase was washed with 2 N HCl (20 mL), satd. $NaHCO_3$ solution (20 mL), water (20 mL) and dried (Na_2SO_4). Removal of volatile mateials in vacuo gave 323 mg of crude product as a clear syrup. Purification by silica gel column chromatography with toluene/AcOEt (10:1) afforded 295 mg (89%) of **23** as a colorless foam, $[\alpha]_D$ = +59.6 (*c* = 1.0, $CHCl_3$). − ^1H NMR (270 MHz, $CDCl_3$): δ = 2.01, 2.13 (2 s, each 3 H, CH_3S, CH_3CO), 3.81 (s, 3 H, $CH_3OC_6H_4CH_2$), 3.89 (m, 1 H, 6-H_a), 4.05 (dd, 1 H, 2-H), 4.18 (dd, 1 H, 4-H), 4.21−4.31 (m, 2 H, 5-H, 6-H_b), 4.48, 4.63 (2 d, 1 H each, $CH_3OC_6H_4CH_2$), 5.20 (d, 1 H, 1-H), 5.21 (dd, 1 H, 3-H), 5.56 (s, 1 H, C_6H_5CH), 6.89, 7.28 (2 d, 2 H each, $CH_3OC_6H_4CH_2$), 7.32−7.48 (m, 5 H, C_6H_5CH); $J_{1,2}$ = 1.3, $J_{2,3}$ = 3.6, $J_{3,4}$ = 9.7, $J_{4,5}$ = 9.6, J_{CH2} = 11.9 Hz. − $C_{24}H_{28}O_7S$ (460.5): calcd. C 62.59, H 6.13; found C 62.73, H 6.13.

Methyl 4,6-*O*-Benzylidene-2-*O*-*p*-methoxybenzyl-1-thio-3-*O*-*p*-methylbenzoyl-α-D-mannopyranoside (24): To a solution of **22** (548 mg, 1.31 mmol) in anhydrous CH_2Cl_2 (10 mL) and pyridine (10 mL) were added at 0°C *p*-toluoyl chloride (208 μL, 1.57 mmol) and 4-dimethylaminopyridine (DMAP, 8 mg, 0.07 mmol) and the solution stirred for 20 h at room temperature. The reaction was quenched with MeOH (1 mL), stirred for 1 h and concentrated to dryness. The residue (940 mg) was purified by elution from silica gel with toluene/AcOEt, 1:0 → 10:1 to afford 475 mg (68%) of **24** as a colorless foam, $[\alpha]_D$ = +9.2 (*c* = 1.0, $CHCl_3$). − ^1H NMR (270 MHz, $CDCl_3$): δ = 2.15 (s, 3 H, CH_3S), 2.41 (s, 3 H, $CH_3OC_6H_4CO$), 3.73 (s, 3 H, $CH_3OC_6H_4CH_2$), 3.94 (m, 1 H, 6-H_a), 4.18 (dd, 1 H, 2-H), 4.24−4.40 (m, 3 H, 4-H, 5-H, 6-H_b), 4.48 and 4.60 (2 d, 1 H each, $CH_3OC_6H_4CH_2$), 5.24 (d, 1 H, 1-H), 5.46 (dd, 1 H, 3-H), 5.62 (s, 1 H, C_6H_5CH), 6.70 (m, 2 H, $CH_3OC_6H_4CH_2$), 7.16−7.46 (m, 9 H, C_6H_5CH, $CH_3OC_6H_4CH_2$, $CH_3OC_6H_4CO$), 7.93 (d, 2 H, $CH_3OC_6H_4CO$); $J_{1,2}$ = 1.2, $J_{2,3}$ = 3.5, $J_{3,4}$ = 9.7, $J_{6a,b}$ = 9.9, J_{CH2} = 11.7 Hz. − $C_{30}H_{32}O_7S$ (536.6): calcd. C 67.15, H 6.01, S 5.97; found C 67.00, H 6.02, S 5.96.

Methyl *O*-(2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-(1→3)-4,6-*O*-benzylidene-2-*O*-*p*-methoxybenzyl-1-thio-α-D-mannopyranoside (5): Methyl thiomannopyranoside **22** (1.15 g, 2.75 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (DBMP, 1.02 g, 4.95 mmol) were dissolved in anhydrous CH_2Cl_2 (25 mL) and stirred for 30 min under Ar and exclusion of light with AgOTf (1.27 g, 4.95 mmol) over freshly activated 4-Å molecular sieves (5.0 g). After cooling to −15°C, 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl chloride (**25**,[27] 1.97 g, 3.85 mmol) was added as a solution in CH_2Cl_2 (15 mL). The mixture was gradually warmed up to room temperature, stirred for 90 min and diluted with CH_2Cl_2 (100 mL). The suspension was filtered through Celite and the filtrate was washed with satd. $NaHCO_3$ solution (30 mL), 10% $Na_2S_2O_3$ solution (30 mL), and dried (Na_2SO_4). Removal of the solvent in vacuo gave a colorless foam (3.79 g), which was purified by elution from silica gel with toluene/AcOEt (10:1) to afford 2.10 g (86%) of **5** as a colorless foam, $[\alpha]_D$ = +57.0 (*c* = 1.1, $CHCl_3$). − ^1H NMR (270 MHz, $CDCl_3$): δ = 2.07, 2.09 (2 s, 3 H each, CH_3S and CH_3CO), 3.63 (s, 3 H, $CH_3OC_6H_4CH_2$), 3.64−3.79 and 4.10−4.26 (2 m, 3 H and 4 H, 3-H, 5-H, 6-H_2, 5′-H, 6′-H_2), 3.84 (dd, 1 H, 4′-H), 3.86 (dd, 1 H, 2-H), 3.88 (dd, 1 H, 4-H), 3.97 (dd, 1 H, 3′-H), 4.47 (d, 3 H, $C_6H_5CH_2$ and $CH_3OC_6H_4CH_2$), 4.60 (s, 2 H, $C_6H_5CH_2$), 4.66, 4.70, 4.87 (3 d, 1 H each, $C_6H_5CH_2$ and $CH_3OC_6H_4CH_2$), 5.15 (br. s, 1 H, 1-H), 5.30 (d, 1 H, 1′-H), 5.60 (dd, 1 H, 2′-H), 5.61 (s, 1 H, C_6H_5CH), 6.77 (m, 2 H, $CH_3OC_6H_4CH_2$), 7.03−7.47 (m, 22 H, $C_6H_5CH_2$, C_6H_5CH, and $CH_3OC_6H_4CH_2$); $J_{1,2}$ < 0.5, $J_{3,4}$ = $J_{4,5}$ = 9.7, $J_{1',2'}$ = 1.8, $J_{2',3'}$ = 3.3, $J_{3',4'}$ = 8.9 Hz. − $C_{51}H_{56}O_{12}S$ (893.1): calcd. C 68.59, H 6.32; found C 68.63, H 6.36.

Methyl *O*-(3,4,6-Tri-*O*-benzyl-2-*O*-levulinoyl-1-thio-α-D-mannopyranosyl)-(1→3)-4,6-*O*-benzylidene-2-*O*-*p*-methoxybenzyl-1-thio-α-D-mannopyranoside (26): A solution of dimannoside **5** (1.03 g, 1.16 mmol) in anhydrous CH_2Cl_2/methanol (1:1, 50 mL) was treated at 0°C with 28% NaOMe solution in methanol (20 μL, 0.1 mmol), gradually warmed to room temperature and stirred for 30 h. Concentration to dryness and coevaporation with CH_2Cl_2 (10 mL) left a brownish foam, which was levulinoylated by dissolving the intermediate in pyridine (10 mL), adding a 1 M levulinic anhydride solution in CH_2Cl_2 (5.5 mL, 5.5 mmol) and stirring the mixture for 4 d at room temperature. The solution was poured into ice/water (100 mL), stirred for 30 min and extracted with CH_2Cl_2 (250 mL). The organic layer was washed with 2 N HCl (2 × 50 mL), satd. $NaHCO_3$ solution (50 mL), dried (Na_2SO_4), and concentrated to give a brown syrup (1.4 g). Elution from silica gel with toluene/AcOEt (5:1) afforded 905 mg (82%) **26** as a colorless foam, $[\alpha]_D$ = +50.4 (*c* = 1.0, $CHCl_3$). – ^1H NMR (270 MHz, $CDCl_3$): δ = 2.07 (s, 3 H, CH_3S), 2.10 (s, 3 H, CH_{3Lev}), 2.64 (m, 4 H, CH_{2Lev}), 3.63 (s, 3 H, $CH_3OC_6H_4CH_2$), 3.66–3.91 and 4.10–4.27 (2 m, 6 H and 4 H, 2-H, 3-H, 4-H, 5-H, 6-H_2, 4′-H, 5′-H, 6′-H_2), 3.96 (3′-H), 4.45, 4.48 (3 d, 1 H each, $C_6H_5CH_2$ and $CH_3OC_6H_4CH_2$), 4.59 (s, 2 H, $C_6H_5CH_2$), 4.64, 4.67, 4.87 (3 d, 1 H each, $C_6H_5CH_2$ and $CH_3OC_6H_4CH_2$), 5.15 (d, 1 H, 1-H), 5.27 (d, 1 H, 1′-H), 5.56 (dd, 1 H, 2′-H), 5.61 (s, 1 H, C_6H_5CH), 6.77 (m, 2 H, $CH_3OC_6H_4CH_2$), 7.16–7.47 (m, 22 H, $C_6H_5CH_2$, C_6H_5CH, and $CH_3OC_6H_4CH_2$); $J_{1,2}$ = 1.0, $J_{1',2'}$ = 1.8, $J_{2',3'}$ = 3.2, $J_{3',4'}$ = 8.4 Hz. – ^{13}C NMR (67.80 MHz, $CDCl_3$): δ = 13.7 (CH_3S), 28.1 (CH_{2Lev}), 29.7 (CH_{3Lev}), 38.0 (CH_{2Lev}), 55.0 ($CH_3OC_6H_4CH_2$), 68.3 (C-2′), 68.5, 68.8 (C-6, C-6′), 71.3, 72.5, 73.3, 75.1 ($C_6H_5CH_2$, $CH_3OC_6H_4CH_2$), 77.7 (C-3′), 84.7 (C-1), 98.7 (C-1′), 101.2 (C_6H_5CH), 113.9 ($CH_3OC_6H_4CH_2$), 126.0–138.4 ($C_6H_5CH_2$, C_6H_5CH, $CH_3OC_6H_4CH_2$), 159.3 ($CH_3OC_6H_4CH_2$), 171.6 (CH_2COO), 206.0 (CH_3CO), 64.4, 72.0, 73.3, 74.3, 78.3, 79.0 (C-2, C-3, C-4, C-5, C-4′, C-5′). – $C_{54}H_{60}O_{13}S$ (949.1): calcd. C 68.34, H 6.37; found C 67.93, H 6.28.

(*S*)-*p*-Methoxybenzaldehyde [*p*-Methoxyphenyl 3,6-di-*O*-benzyl-2,4-dideoxy-2-(4,5-dichlorophthalimido)-β-D-glucopyranosid-4-yl] (Methyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-mannopyranosid-2-yl) Acetal (30): A solution of compounds **28** (100 mg, 0.15 mmol) and **23** (83 mg, 0.18 mmol) in anhydrous CH_2Cl_2 (1.5 mL) was stirred in the presence of freshly activated 4-Å molecular sieves for 30 min under exclusion of light at 0°C. DDQ (68 mg, 0.30 mmol) was then added and the deep green mixture was allowed to warm up to room temperature. After stirring for 2 h, the reaction was quenched by addition of a solution of ascorbic acid (0.7%)/citric acid (1.3%)/NaOH (0.9%) in water (7 mL), stirred until the color turned to bright yellow (10 min) and diluted with CH_2Cl_2 (50 mL). The organic phase was washed with satd. $NaHCO_3$ solution (10 mL), dried (Na_2SO_4), and the volatiles were removed in vacuo to give 150 mg (89%) of crude product. Purification by size exclusion chromatography (Bio-Beads S-X2) with toluene afforded 109 mg (65%) of **30** as a colorless foam, $[\alpha]_D$ = +44.2 (*c* = 0.65, $CHCl_3$). – ^1H NMR (270 MHz, $CDCl_3$): δ = 1.83 (s, 3 H, CH_3CO), 2.09 (s, 3 H, CH_3S), 3.64 (m, 1 H, 5-H), 3.72 (s, 3 H, $CH_3OC_6H_4$), 3.74 (dd, 1 H, 6-H_a), 3.80 (s, 3 H, $CH_3OC_6H_4$), 3.82 (dd, 1 H, 6-H_b), 3.92 (m, 2 H, 2′-H, 6′-H_a), 4.24–4.36 (m, 5 H, 3-H, 4-H, 4′-H, 5′-H, 6′-H_b), 4.47 (dd, 1 H, 2-H), 4.54, 4.60, 4.83 (3 d, 1 H each, $C_6H_5CH_2$), 5.03 (s, 1 H, C_6H_5CH), 5.18 (dd, 1 H, 3′-H), 5.31 (d, 1 H, $C_6H_5CH_2$), 5.47 (s, 1 H, $CH_3OC_6H_4CH$), 5.59 (d, 1 H, 1-H), 5.73 (br. s, 1 H, 1′-H), 6.70–6.96, 7.08–7.16 (2 m, 9 H and 4 H, $CH_3OC_6H_4$, C_6H_5CH), 7.32–7.42 (m, 10 H, $C_6H_5CH_2$), 7.70 and 7.88 (2 bs, 1 H each, DCPhth); $J_{1,2}$ = 8.4, $J_{2,3}$ = 8.6, $J_{2',3'}$ = 3.3, $J_{3',4'}$ = 9.9, J_{CH2} = 12.2, 12.4 Hz. – ^{13}C NMR (67.80 MHz, $CDCl_3$): δ = 13.6 (CH_3S), 20.8 (CH_3CO), 55.3, 55.6 (2 $CH_3OC_6H_4$), 56.2 (C-2), 64.6 (C-4′), 67.3 (C-6), 68.7 (C-6′), 70.1 (C-3′), 74.1 ($C_6H_5CH_2$), 74.3 (C-2′), 75.0 (C-5), 75.4 ($C_6H_5CH_2$), 75.6, 75.9, 77.2, 78.2 (C-3, C-4, C-4′, C-5′), 82.5 (C-1′), 97.8 (C-1), 101.4 ($CH_3OC_6H_4CH$, C_6H_5CH), 113.9, 114.4, 118.8 ($CH_3OC_6H_4$, $CH_3OC_6H_4CH$), 125.4–138.6 (C_6H_5CH, $C_6H_5CH_2$), 150.7, 155.5, 160.4 (DCPhth, $CH_3OC_6H_4$), 169.8 (CH_3CO). – $C_{59}H_{57}Cl_2NO_{15}S$ (1123.1): calcd. C 63.10, H 5.12, N 1.25; found C 63.21, H 5.11, N 1.27.

(*S*)-*p*-Methoxybenzaldehyde [*p*-Methoxyphenyl 3,6-di-*O*-benzyl-2,4-dideoxy-2-(4,5-dichlorophthalimido)-β-D-glucopyranosid-4-yl] (Methyl 4,6-*O*-benzylidene-2-deoxy-1-thio-3-*O*-toluyl-α-D-mannopyranosid-2-yl) Acetal (31): This compound was prepared by treatment of compounds **28** (150 mg, 0.23 mmol) and **24** (170 mg, 0.32 mmol) with DDQ (123 mg, 0.54 mmol) in anhydrous CH_2Cl_2 (2.3 mL) in an analogous manner as described for **30**. Purification by size exclusion chromatography (Bio-Beads S-X2) with toluene afforded 184 mg (66%) of **31** as a colorless foam, $[\alpha]_D$ = +17.4 (*c* = 1.1, $CHCl_3$). – ^1H NMR (270 MHz, $CDCl_3$): δ = 2.11 (s, 3 H, CH_3S), 2.38 (s, 3 H, $CH_3C_6H_4CO$), ca. 3.60 (m, 1 H, 5-H), 3.62 (s, 3 H, $CH_3OC_6H_4$), 3.70 (dd, 1 H, 6-H_a), 3.72 (s, 3 H, $CH_3OC_6H_4$), 3.81 (dd, 1 H, 6-H_b), 3.98 (dd, 1 H, 6′-H_a), 4.11 (d, 1 H, 2′-H), 4.31–4.39 (m, 4 H, 3-H, 4-H, 5′-H, 6′-H_b), 4.42 (dd, 1 H, 4′-H), 4.46 (dd, 1 H, 2-H), 4.55, 4.59, 4.81 (3 d, 1 H each, $C_6H_5CH_2$), 5.09 (s, 1 H, C_6H_5CH), 5.36 (d, 1 H, $C_6H_5CH_2$), 5.40 (dd, 1 H, 3′-H), 5.49 (s, 1 H, $CH_3OC_6H_4CH$), 5.58 (d, 1 H, 1-H), 5.78 (br. s, 1 H, 1′-H), 6.40 (d, 1 H, $CH_3C_6H_4CH$), 6.72, 6.83 (2 m, 2 H each, $CH_3OC_6H_4$), 6.89–7.02 (2 d, 2 H each, $CH_3C_6H_4CO$, $CH_3OC_6H_4CH$), 7.11–7.39 (m, 15 H, 2 $C_6H_5CH_2$, C_6H_5CH), 7.74 (d, 2 H, $CH_3C_6H_4CO$), 7.75, 7.90 (2 br. s, 1 H each, DCPhth); $J_{1,2}$ = 8.3, $J_{2,3}$ = 9.4, $J_{1',2'}$ < 0.5, $J_{2',3'}$ = 3.1, $J_{3',4'}$ = 9.9, $J_{4',5'}$ = 10.2, $J_{6'a,b}$ = 11.6, J_{CH2} = 12.2 Hz. – $C_{65}H_{61}Cl_2NO_{15}S$ (1199.2): calcd. C 65.10, H 5.13, N 1.17; found C 65.15, H 5.08, N 1.46.

(*S*)-*p*-Methoxybenzaldehyde {*p*-Methoxyphenyl *O*-[3,6-di-*O*-benzyl-2,4-dideoxy-2-(4,5-dichlorophthalimido)-β-D-glucopyranos-4-yl]-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-(4,5-dichlorophthalimido)-β-D-glucopyranosid-4-yl} [Methyl *O*-(3,4,6-tri-*O*-benzyl-2-*O*-levulinoyl-1-thio-α-D-mannopyranosyl)-(1→3)-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-mannopyranosid-2-yl] Acetal (32): Prepared from compounds **29** (560 mg, 0.46 mmol) and **26** (620 mg, 0.65 mmol) by treatment with DDQ (253 mg, 1.12 mmol) in CH_2Cl_2 (5 mL) in an analogous manner to that described for **30**. Purification by size exclusion chromatography (Bio-Beads S-X1) with toluene afforded 790 mg (80%) of **32** as a yellowish foam, $[\alpha]_D$ = +26.4 (*c* = 1.6, $CHCl_3$). – ^1H NMR (270 MHz, $CDCl_3$): δ = 1.84 (s, 3 H, CH_3S), 2.07 (s, 3 H, CH_{3Lev}), 2.59 (s, 4 H, CH_{2Lev}), 3.26 (s, 3 H, $CH_3OC_6H_4CH$), 3.32 and 3.41–3.63 (ddd and m, 1 H and 6 H, ring protons), 3.67 (s, 3 H, $CH_3OC_6H_4$), 3.69–3.76 (m, 3 H, ring protons, 3′′′-H), 3.78 (br. dd, 1 H, 2′′-H), 3.95, 4.07 (dd and d, 1 H each, ring protons) 4.12–4.49 (m, 16 H, ring protons, 2-H, 2′-H), 4.54 (d, 2 H, $C_6H_5CH_2$), 4.63 (br. s, 2 H, $C_6H_5CH_2$), 4.81, 4.89 (2 d, 1 H each, $C_6H_5CH_2$), 5.09 (s, 1 H, C_6H_5CH), 5.21 (d, 1 H, 1′′′-H), 5.34 (d, 1 H, 1′-H), 5.36 (d, 1 H, $C_6H_5CH_2$), 5.43 (d, 1 H, 1-H), 5.50 (br. dd, 1 H, 2′′′-H), 5.64 (s, 1 H, $CH_3OC_6H_4CH$), 5.69 (s, 1 H, 1′′-H), 6.61–6.79 (m, 6 H, $CH_3OC_6H_4$, $CH_3OC_6H_4CH$), 6.85–7.42 (m, 42 H, C_6H_5CH, $C_6H_5CH_2$), 7.68, 7.81 (2 s, 2 H each, DCPhth); $J_{1,2}$ = 8.3, $J_{1',2'}$ = 7.6, $J_{1'',2''}$ < 0.5, $J_{2'',3''}$ = 3.0, $J_{1''',2'''}$ = 1.7, J_{CH2} = 10.9, 11.6, 12.9 Hz. – ^{13}C NMR (67.80 MHz, $CDCl_3$): δ = 13.4 (CH_3S), 28.1 (CH_{2Lev}), 29.6 (CH_{3Lev}), 38.0 (CH_{2Lev}), 54.8 ($CH_3OC_6H_4CH$), 55.5 ($CH_3OC_6H_4$), 56.0 (C-2), 57.4 (C-2′), 67.0 (C-2′′′), 64.7, 69.0–78.4 (other ring C, $C_6H_5CH_2$), 82.2 (C-1′′), 97.0 (C-1′), 97.4 (C-1), 99.1 (C-1′′′), 100.3 ($CH_3OC_6H_4CH$), 100.8 (C_6H_5CH), 114.2, 114.3, 118.5 ($CH_3OC_6H_4$, $CH_3OC_6H_4CH$), 125.2–138.7 ($C_6H_5CH_2$, C_6H_5CH), 150.6, 155.3, 160.2, 165.6 (DCPhth, $CH_3OC_6H_4$), 171.2 (CH_2COO), 206.0 (CH_3CO). – $C_{117}H_{112}Cl_4N_2O_{27}S$ (2152.1): C 65.30, H 5.25, N 1.30; found C 64.83, H 5.28, N 1.23.

(*S*)-[Methyl *O*-(3,4,6-tri-*O*-benzyl-2-*O*-acetyl-1-thio-α-D-mannopyranosyl)-(1→3)-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-mannopyranosid-2-yl][*p*-methoxyphenyl *O*-[3,6-di-*O*-benzyl-2,4-dideoxy-2-phthalimido-β-D-glucopyranos-4-yl]-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosid]-*p*-methoxybenzylidene Acetal (33): Prepared from compounds **5** (165 mg, 0.18 mmol) and **8** (152 mg, 0.14 mmol) by treatment with DDQ (42 mg, 0.18 mmol) in CH_2Cl_2 (1.2 mL) in an analogous manner to that described for **30**. Purification by size exclusion chromatography (Bio-Beads S-X3) with toluene afforded 246 mg (88%) of **33** as yellowish foam. − ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.82 and 2.06 (2 s, 3 H each, SMe and Ac), 3.25 and 3.66 (2 s, 3 H each, OMe), 5.24 (d, 1 H, 1′′′-H), 5.35 (s, 1 H, benzylidene CH), 5.38 (d, 1 H, 1′-H), 5.49 (d, 1 H, 1-H), 5.61 (dd, 1 H, 2′′′-H), 5.65 (s, 1 H, acetal CH), 5.73 (s, 1 H, 1′′-H), 6.6−7.8 (m, 56 H, aromatic); $J_{1,2}$ = 8.3, $J_{1',2'}$ = 8, $J_{1''',2'''}$ = 2.0, $J_{2''',3'''}$ = 2.8 Hz). − ^{13}C NMR (67.80 MHz, $CDCl_3$): δ = 82.2 (C-1′′), 97.2, 97.6, 99.3 (C-1, -1′, -1′′′), 100.3 and 100.5 (acetal CH).

***p*-Methoxyphenyl *O*-(3,4,6-Tri-*O*-benzyl-2-*O*-levulinoyl-α-D-mannopyranosyl)-(1→3)-(4,6-*O*-benzylidene-β-D-mannopyranosyl)-(1→4)-[3,6-di-*O*-benzyl-2-deoxy-2-(4,5-dichlorophthalimido)-β-D-glucopyranosyl]-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-(4,5-dichlorophthalimido)-β-D-glucopyranoside (36a):** Mixed acetal **32** (654 mg, 0.30 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (DBMP, 218 mg, 1.06 mmol) were stirred in 1,2-dichloroethane (60 mL) with freshly activated 4-Å molecular sieves (1.5 g) under argon for 30 min. A solution of MeOTf in 1,2-dichloroethane (1 M, 1.37 mL, 1.37 mmol) was injected and the mixture stirred for 44 h at 40 °C. The reaction was quenched with triethylamine (2 mL), stirred for 15 min (color changed from yellow to brownish), diluted with CH_2Cl_2 (100 mL), and filtered through Celite. The organic phase was washed with water (2 × 30 mL), dried (Na_2SO_4), and after evaporation of the solvent the residue was subjected to size exclusion chromatography (Bio-Beads S-X1) with toluene to give 390 mg of crude **36a** and 87 mg (24%) recovered disaccharide acceptor **29**. Crude **36a** was further purified by silica gel chromatography with toluene/AcOEt, 10:1 → 5:1, to furnish another 43 mg (12%) acceptor **29** and 234 mg tetrasaccharide **36a** (39%, 43% based on consumed **29** over 2 steps) as a beige foam, $[\alpha]^{20}_D$ = +7.5 (*c* = 1.5, $CHCl_3$). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.12 (s, 3 H, CH_{3Lev}), 2.66 (m, 4 H, 2 CH_{2Lev}), 2.84 (d, 1 H, 2′′-OH), 3.12 (ddd, 1 H, 5′′-H), 3.25 (d, 1 H, 5′-H), 3.34−3.42 (m, 2 H, 5-H, 6-H_a), 3.52−3.56 (m, 3 H, 6-H_b, 6′-H_a, 6′′-H_a), 3.64 (dd, 1 H, 3′′-H), 3.66 (s, 3 H, $CH_3OC_6H_4$), 3.67−3.82 (m, 4 H, 6′-H_b, 4′′′-H, 6′′′-H_2), 3.91 (dd, 1 H, 4′′-H), 4.02 (dd, 1 H, 3′′′-H), 4.07 (m, 1 H, 2′′-H), 4.09−4.13 (m, 3 H, 4′-H, 6′′-H_b, 5′′′-H), 4.14 (2 dd, 1 H each, 3-H, 2′-H), 4.23 (dd, 1 H, 4-H), 4.25 (dd, 1 H, 3′-H), 4.30 (dd, 1 H, 2-H), 4.38 (d, 1 H, $C_6H_5CH_2$), 4.43−4.67 (m, 10 H, $C_6H_5CH_2$), 4.60 (br. s 1 H, 1′′-H), 4.81 (d, 1 H, $C_6H_5CH_2$), 4.84 and 4.87 (2 d, 1 H each, $C_6H_5CH_2$), 5.08 (d, 1 H, 1′′′-H), 5.24 (d, 1 H, 1′-H), 5.39 (d, 1 H, 1-H), 5.45 (s and dd, 1 H each, C_6H_5CH and 2′′′-H), 6.60−6.70 (m, 4 H, $CH_3OC_6H_4$), 6.82−7.44 (m, 40 H, $C_6H_5CH_2$), 7.45−7.88 (2 s and 2 br. s, 1 H each, DCPhth); $J_{1,2}$ = 8.7, $J_{2,3}$ = 10.5, $J_{3,4}$ = $J_{4,5}$ = 9.0, $J_{1',2'}$ = 8.3, $J_{4',5'}$ = 9.8, $J_{1'',2''}$ < 0.5, $J_{2'',3''}$ = 3.4, $J_{2'',OH}$ = 2.9, $J_{3'',4''}$ = 10.0, $J_{4'',5''}$ = 9.4, $J_{5'',6''a}$ = 9.5, $J_{5'',6''b}$ = 4.9, $J_{1''',2'''}$ = 1.5, $J_{2''',3'''}$ = 3.2, $J_{3''',4'''}$ = 9.0 Hz. − ^{13}C NMR (100.40 MHz, $CDCl_3$): δ = 28.1 (CH_{2Lev}), 29.8 (CH_{3Lev}), 38.0 (CH_{2Lev}), 55.5 ($CH_3OC_6H_4$), 56.0 (C-2), 56.9 (C-2′), 66.8 (C-5′′), 67.6 (C-6′), 68.0 (C-6), 68.4 (C-6′′), 68.7 (C-2′′′), 69.4 (C-6′′′), 70.6 (C-2′′), 71.6, 71.8, 72.9, 73.2, 73.6, 74.4, 74.7, 74.8, 75.1, 78.7 (C-5, C-4′, C-5′, C-4′′′, C-5′′′, $C_6H_5CH_2$), 75.8 (C-4), 76.9 (C-3), 77.2 (C-3′, C-4′′), 77.4 (C-3′′), 77.8 (C-3′′′), 96.9 (C-1′), 97.3 (C-1), 98.6 (C-1′′′), 100.6 (C-1′′), 101.4 (C_6H_5CH), 114.3, 118.5 ($CH_3OC_6H_4$), 125.3, 126.0 (DCPhth), 127.0−139.0 ($C_6H_5CH_2$,C_6H_5CH), 150.6, 155.3, 160.2, 165.6 ($CH_3OC_6H_4$, DCPhth), 171.7 (CH_2COO), 206.1 (CH_3CO); $^1J_{C1\text{-}H}$ = 163.6 (C-1), 161.4 (C-1′), 159.7 (C-1′′), 173.4 (C-1′′′) Hz. − FAB MS (positive); *m*/*z*: 2006.9, 2007.9, 2008.8, 2009.7 [M + Na]$^+$; (negative); *m*/*z*: 2083.6, 2084.6 [M − H]$^-$. − $C_{108}H_{102}Cl_4N_2O_{26}$ (1985.8): calcd. C 65.32, H 5.18, N 1.41; found C 65.44, H 5.15, N 1.43.

***p*-Methoxyphenyl *O*-(3,4,6-Tri-*O*-benzyl-2-*O*-acetyl-α-D-mannopyranosyl)-(1→3)-*O*-(4,6-*O*-benzylidene-β-D-mannopyranosyl)-(1→4)-*O*-(3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl]-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-phthal-imido-β-D-glucopyranoside (36b):** To a mixture of compound **33** (30 mg, 0.015 mmol), DBMP (9.4 mg, 0.046 mmol) and 4-Å molecular sieves (0.2 g) in 1,2-dichloroethane (1 mL) was added MeOTf (1 M in CCl_4, 46 µL, 0.046 mmol) and the mixture was stirred at 40°C. Additional portions of MeOTf (0.015 mmol) and DBMP (0.015 mmol) were added at 24 h intervals, while the stirring was continued for 4 d. The mixture was worked up as described for **32a** and the crude material was purified by size exclusion chromatography (Bio-Beads S-X4) with toluene, followed by preparative TLC (toluene/AcOEt, 5:1) to afford 15.2 mg (55%, 49% from **8**) as well as recovered **8** (3.7 mg). −Compound **36b**; $[\alpha]_D$ = +22.2 (*c* = 0.6, $CHCl_3$). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.11 (s, 3 H, Ac), 2.79 (br. s, 1 H, OH), 3.65 (s, 3 H, OMe), 4.55 (s, 1 H, 1′′-H), 5.12 (d, 1 H, 1′′′-H), 5.28 (d, 1 H, 1′-H), 5.44 (d, 1 H, 1-H), 5.45 (s, 1 H, benzylidene CH), 5.49 (dd, 1 H, 2′′′-H), 6.6−7.9 (m, 52 H, aromatic); $J_{1,2}$ = 8.8, $J_{1',2'}$ = 8.3, $J_{1''',2'''}$ = 1.5 Hz. − ^{13}C NMR (100.40 MHz, $CDCl_3$): δ = 66.8, 67.7, 68.0, 68.4, 68.6, 69.3, 70.7, 71.8, 71.9, 72.7, 73.2, 73.6, 74.4, 74.5, 74.6, 75.1, 75.8, 76.8, 77.2, 77.9, 78.9, 79.1, 97.1 (C-1′), 97.5 (C-1), 98.8 (C-1′′′), 100.6 (C-1′′), 101.4 (benzylidene CH). − $C_{105}H_{102}N_2O_{25}$ (1792.0): calcd. C 70.38, H 5.74, N 1.56; found C 70.14, H 5.84, N 1.41.

DADAS 90 Experiment: For the calculation studies 100 initial conformers for every sample (*S*)-**15a**, (*R*)-**15a**, (*S*)-**15b**, and (*R*)-**15b** were generated by using randomly generated torsion angles in DADAS 90. Bond lengths and angles of pyranose rings were based on X-ray data.[28] Anomeric fluorine was substituted by hydrogen. Minimization of pseudo energy values (T_p) was performed under the distance restrictions for NOE and soft repulsion and angle restriction for the acetal moiety by using the conjugate gradient method. T_p values for (*S*)-**15a**, (*R*)-**15a**, (*S*)-**15b**, and (*R*)-**15b** between 0 and 34800 were observed and the smallest for each individual diastereomer selected for the determination of the absolute configuration at the acetalic position. − All calculations were carried out with an IRIS Indy computer. Molgraph (DAIKIN Co. Ltd.) and Molskop (JEOL Co. Ltd.) were used as graphical editors.

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