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Glycosylation using a one-electron-transfer, homogeneous reagent. Application to an efficient synthesis of the trimannosyl core of *N*-glycosylproteins *

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ABSTRACT

Double glycosylation of methyl 2,4-di-*O*-benzyl-β-D-mannopyranoside with ethyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-1-thio-α-D-mannopyranoside using as promoter tris(4-bromophenyl)ammoniumyl hexachloroantimonate, a stable, commercial, and crystalline radical cation, afforded after debenzoylation methyl 2,4-di-*O*-benzyl-3,6-di-*O*-(3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-β-D-mannopyranoside in excellent yield. Other mannosyl donors were also investigated.

INTRODUCTION

A precise knowledge of the primary structure of glycoprotein glycans constitutes a prerequisite for the development of glycobiology. With a few rare exceptions, the invariant (inv) glycoasparagine "core" **1**, common to all *N*-glycoproteins, results from the association, by a β-D-glycosidic linkage, of a mannotriose with di-*N*-acetylchitobiose, itself linked to an appropriate asparagine residue of the protein. The mannotriose structure of **1** thus appears as an evolutionary selected, branched structure for the anchoring of informational carbohydrate branches and was selected as a synthetic target in the field.

Partially protected trimannosides **5** and **6** were previously synthesized[1–3] in amorphous form by use of 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl chloride (**2**) as the mannosyl donor. Regiocontrolled activation of the hydroxyl groups of methyl α-D-mannopyranoside (**3**) through tributylstannylation, followed by reaction with chloride **2**, resulted[1] in a modest overall yield (7%) of **5**, which was subsequently largely improved when **2** was condensed with benzyl 2,4-di-*O*-benzyl-

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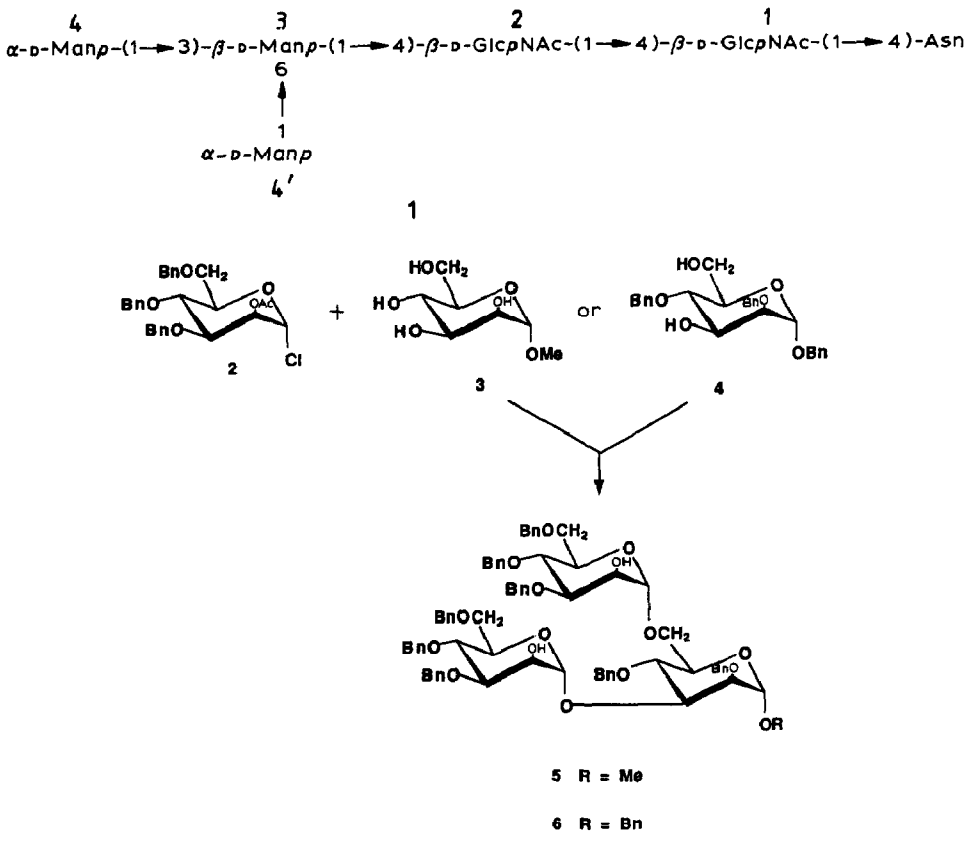
* Dedicated to Professor J. Montreuil.

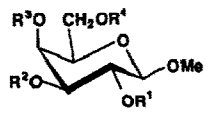


α-D-mannopyranoside (**4**), the promoter being either mercury(II) bromide–mercury(II) cyanide (49% yield of **6**)[2], or preferably silver triflate (67% of **6**)[3].

We recently reported[4] a glycosylation reaction using stable and commercially available tris(4-bromophenyl)ammoniumyl hexachloroantimonate as a conceptually new type of promoter for thioglycosides. We describe herein the application of this method to an efficient synthesis of the trimannoside **34**.

RESULTS AND DISCUSSION

Synthesis of the glycosyl acceptor **23**.—In order to mimic the β-D-mannopyranosyl linkage of the mannosyl residue *3* in the core structure **1**, methyl 2,4-di-*O*-benzyl-β-D-mannopyranoside **23** was selected as the acceptor. It was synthesized by a modification of a procedure developed by David and Fernandez-Mayoralas[5]. Ogawa and Matsui[6] first reported that stannylation of methyl β-D-galactopyranoside (**7**), followed by heating with allyl bromide during eight days at 80–85°, afforded methyl 3,6-di-*O*-allyl-β-D-galactopyranoside (**8**) and methyl 6-*O*-allyl-β-D-galactopyranoside (**9**) in 51 and 11% yield, respectively. David and



7 $R^1 = R^2 = R^3 = R^4 = H$

8 $R^1 = R^3 = H$, $R^2 = R^4 = All$

9 $R^1 = R^2 = R^3 = H$, $R^4 = All$

10 $R^3 = H$, $R^1 = R^2 = R^4 = All$

11 $R^1 = H$, $R^2 = R^3 = R^4 = All$

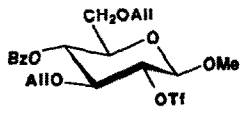
12 $R^1 = R^3 = Ac$, $R^2 = R^4 = All$

13 $R^3 = Ac$, $R^1 = R^2 = R^4 = All$

14 $R^1 = Ac$, $R^2 = R^3 = R^4 = All$

15 $R^1 = R^3 = Tf$, $R^2 = R^4 = All$

16 $R^1 = Tf$, $R^3 = H$, $R^2 = R^4 = All$



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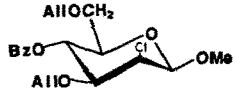

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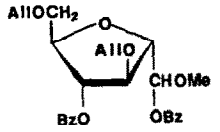

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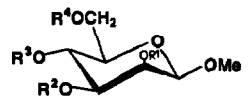
Fernandez-Mayoralas[5] improved the preparation of **8** to 61%. When stannylated **7** was heated in toluene during 6 h at 70° in the presence of allyl bromide and tetrabutylammonium iodide[7], we obtained compound **8** in 76% yield. Other products carefully isolated were methyl 6-*O*-allyl-β-D-galactopyranoside (**9**, 10%), methyl 2,3,6-tri-*O*-allyl-β-D-galactopyranoside (**10**, 8%), and methyl 3,4,6-tri-*O*-allyl-β-D-galactopyranoside (**11**, 3%). The structural assignments of **8**, **10**, and **11** were based on the expected modification of the ^1H NMR spectra upon *O*-acetylation (compounds **12**, **13**, and **14**, respectively). Compound **9** has been prepared by Ogawa and Matsui[6], but the physical properties reported {syrup, $[\alpha]_D$ −23.0° (chloroform)} are at variance with our data {mp 103–104°, $[\alpha]_D$ +7° (chloroform)}.

The bis(triflate) **15**[5] was obtained in pure form in 95% yield within 5 h at 0°, and fully characterized. A small amount (4%) of methyl 3,6-di-*O*-allyl-2-*O*-triflyl-β-D-galactopyranoside (**16**) was also separated and characterized. As reported[5], **15** reacted quantitatively with freshly prepared tetrabutylammonium benzoate in toluene solution at room temperature in 30 min to give a single product, which was identified by TLC comparison as methyl 3,6-di-*O*-benzoyl-2-*O*-triflyl-β-D-glucopyranoside (**17**). Heating for 1 h at 100° gave the known methyl 3,6-di-*O*-allyl-2,4-di-*O*-benzoyl-β-D-mannopyranoside (**20**) in 73% yield. Besides a tiny amount (1%) of persistent monobenzoate **17**, which helped to identified the primary product of the reaction by TLC comparison, two other byproducts were obtained in pure form and characterized. The 2-chloro derivative **18** (2%) was probably formed from the

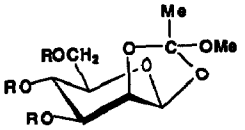


20 $R^1 = R^3 = Bz$, $R^2 = R^4 = All$

21 $R^1 = R^3 = H$, $R^2 = R^4 = All$

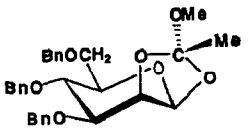
22 $R^1 = R^3 = Bn$, $R^2 = R^4 = All$

23 $R^1 = R^3 = Bn$, $R^2 = R^4 = H$

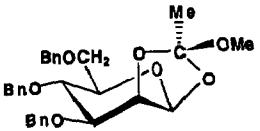


24 R = Ac

25 R = Bn



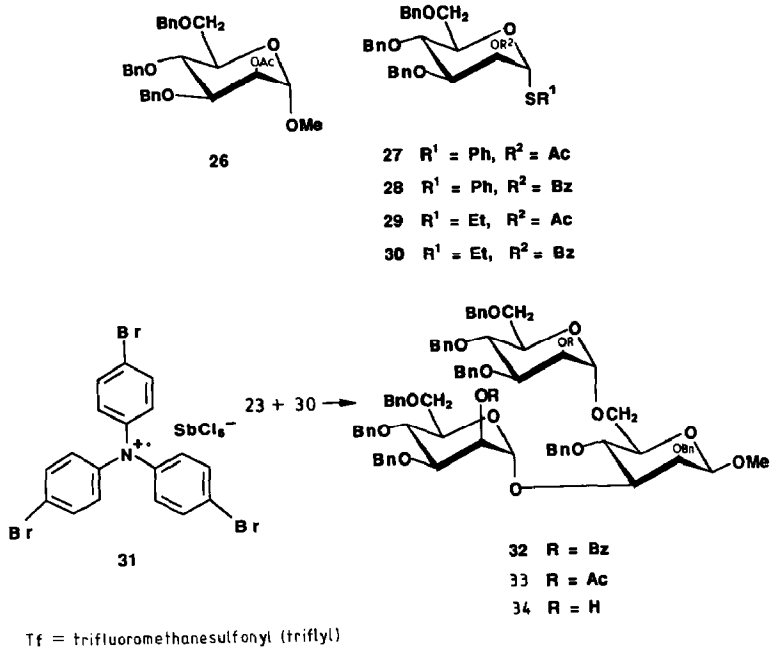
25 endo



25 exo

displacement of **17** by a putative small amount of chloride anion present in the preparation of tetrabutylammonium benzoate. A ring contraction[8] of **17** was responsible for the formation of derivative **19**. A single diastereoisomer was isolated from the reaction mixture, but the absolute configuration at C-1 was not determined. *O*-Debenzoylation of **20** gave methyl 3,6-di-*O*-allyl-β-D-mannopyranoside (**21**), which was routinely benzylated to methyl 3,6-di-*O*-allyl-2,4-di-*O*-benzyl-β-D-mannopyranoside (**22**). Finally, *O*-deallylation of **22** according to Boss and Scheffold[9] gave the desired glycosyl acceptor **23**[10] in crystalline form and in 87% yield.

Synthesis of glycosyl donors.—Known 3,4,6-tri-*O*-acetyl-β-D-mannopyranose 1,2-(methyl orthoacetate) (**24**)[11–13] was transformed into 3,4,6-tri-*O*-benzyl-β-D-mannopyranose 1,2-(methyl orthoacetate) (**25**)[14–16], which was obtained as a diasteroisomeric mixture (*exo:endo*, 17:3). The *endo* and *exo* isomers were easily separated on silica gel and characterized. Treatment of a solution of the *exo–endo* mixture **25** in acetonitrile with thiophenol and mercury(II) bromide at 60° gave a small amount of methyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (**26**)[17] (10%) and the crystalline thioglycoside donor **27** in 80% yield. This compound has previously been prepared in amorphous form by another route[18]. Deacetylation, followed by benzoylation with benzoyl chloride in pyridine, gave the amorphous donor **28** in 90% yield. Similarly, **25** was easily converted into the known glycosyl donors **29**[19] and **30**[20]. The *endo* compound of **25** was found unreactive under these conditions and could be separated from the reaction mixture at the end of the reaction. The physical properties reported[19] for **29** {syrup, $[\alpha]_D$ +73° (chloroform)} are at variance with our data {mp 50–51°, $[\alpha]_D$ +84° (chloroform)}. Physical

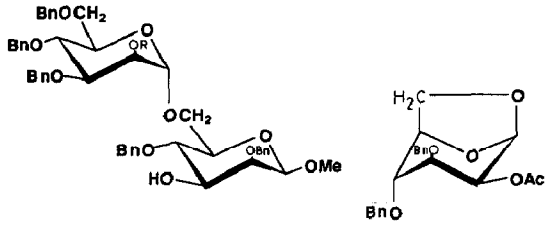


Tf = trifluoromethanesulfonyl (triflyl)

properties for **30**[20] have not been described, and ^{1}H NMR data[20] are at variance with our own data.

Glycosylation reactions.—Glycosylation of the diol **23** was now achieved by use of the activation of a thioglycoside[4] with tris(4-bromophenyl)ammoniumyl hexachloroantimonate (**31**). When ethyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-1-thio-α-D-mannopyranoside (**30**) reacted in acetonitrile at 10° for 1 h with methyl 2,4-di-*O*-benzyl-β-D-mannopyranoside (**23**) in the presence of the commercial reagent **31**, the trisaccharide methyl 3,6-di-*O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-2,4-di-*O*-benzyl-β-D-mannopyranoside (**32**) was isolated in 85% yield, and separated from 10% of the disaccharide methyl 6-*O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-2,4-di-*O*-benzyl-β-D-mannopyranoside (**35**). The disaccharide **35** was not fully characterized, but its linkage was assumed to be (1 → 6) on the basis of the higher reactivity of the primary alcohol of the acceptor. The α-D configuration at C-1′ of **35** was deduced from NMR data [^{1}H: δ 5.05 ($J_{1',2'}$ 1.8 Hz, H-1^1); ^{13}C: δ 97.62 (C-1′)]. The same yield was obtained when **28** was used as glycosyl donor, but the reaction time was extended to ~ 5 h. A somewhat lower yield (~ 75%) of trisaccharide **33** was obtained when either **27** or **29** were used as glycosyl donor. This trisaccharide **33** was found to be contaminated by a disaccharide (~ 20%) which was assumed to be **36**. For this reason, **33** and **36** were not obtained in pure form, and only their NMR data have been recorded. Deacetylation of **33** gave an almost quantitative yield of the target trisaccharide **34** identical with the one obtained from **32**. A small amount (3%) of known[21] 2-*O*-acetyl-1,6-

anhydro-3,4-di-*O*-benzyl-β-D-mannopyranose (**37**) was also separated and identi-



35 R = Bz
36 R = Ac

37

fied. The α-D configuration of the newly linked mannosyl groups of trisaccharide **32** were clearly deduced from NMR data [^{1}H: δ 5.30 ($J_{1',2'}$ 1.8 Hz, H-1'), 5.02 ($J_{1'',2''}$ 1.8 Hz, H-1''); ^{13}C: δ 99.63 ($J_{C\text{-}1',H\text{-}1'}$ 170 Hz, C-1'), 97.82 ($J_{C\text{-}1'',H\text{-}1''}$ 170 Hz, C-1'')]. Ethyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-1-thio-α-D-mannopyranoside (**30**) thus appears as an excellent glycosyl donor, when the one-electron-transfer, homogeneous reagent was used. The results reported herein demonstrate the efficiency of this novel method[4] which give an easy access to the important trisaccharide **32**. *O*-Debenzoylation of **32** gave the diol **34** to be used for the synthesis of biantennary structures.

EXPERIMENTAL

General methods.—Melting points were determined with a Büchi model 510 melting point apparatus and are uncorrected. Optical rotations were measured at 20 ± 2° with a Perkin–Elmer Model 241 polarimeter, on a solution in a 10-cm, 1-mL cell. ^{1}H NMR spectra were recorded with a Cameca 250 and a Brüker AM-400 spectrometer for solutions in $CDCl_3$ or C_6D_6 (internal Me_4Si). ^{13}C NMR spectra were recorded at 100.57 MHz with a Brüker AM-400 for solutions in $CDCl_3$ adopting δ 77.00 for the central line of $CDCl_3$. Assignments were aided by J-mod technique and proton–carbon correlation. Single and double primes refer to the mannosyl residues *4* and *4'* (or vice versa), the exact assignment has not been achieved in this work. CI(ammonia)–mass spectra were obtained with a Nermag R10-10 spectrometer. Reactions were monitored by TLC on Silica Gel 60 F_{254} (Merck) and detection by charring with H_2SO_4. Flash column chromatography was performed on Silica Gel 60 (230–400 mesh, Merck). Elemental analyses were performed by Service Central d'Analyse du C.N.R.S., BP 22, F-69390 Vernaison, France.

Allylation of methyl β-D-galactopyranoside.—A mixture of methyl β-D-galactopyranoside (**7**) (1.94 g, 10 mmol) and $(Bu_3Sn)_2O$ (9 g, 15 mmol) in toluene (50 mL) was stirred under reflux for 15 h with continuous azeotropic removal of water. Toluene (25 mL) was distilled off, and allyl bromide (10 mL) and tetrabutylammonium iodide (3.7 g, 10 mmol) were added. The solution was stirred for 6 h at 70° under Ar and concentrated. The residue was eluted from a column of silica gel (1 : 1 cyclohexane–EtOAc → EtOAc) to give, in order, **10**, **11**, **8** and **9**.

Methyl 2,3,6-tri-O-allyl-β-D-galactopyranoside (**10**). Yield, 252 mg (8%), syrup, $[\alpha]_D$ −6° (*c* 1.15, $CHCl_3$); NMR data: ^1H (400 MHz, $CDCl_3$): δ 6.02–5.84 (m, 3 H, 3 CH=), 5.36–5.13 (m, 6 H, 3 CH_2=), 4.38–4.29 (m, 1 H, OCH), 4.21 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1). 4.23–4.15 (m, 3 H, OCH_2, OCH), 4.08–4.04 (m, 2 H, OCH_2), 4.00 (dd, 1 H, $J_{4,5}$ 1.0, $J_{3,4}$ 3.5 Hz, H-4), 3.77 and 3.68 (2 dd, $J_{5,6a} = J_{5,6b}$ 5.8, $J_{6a,6b}$ 10.0 Hz, H-6a,6b), 3.55 (ddd, H-5), 3.54 (s, 3 H, OCH_3), 3.46 (dd, 1 H, $J_{2,3}$ 9.5 Hz, H-2), 3.37 (dd, 1 H, H-3), and 2.48 (br. s, 1 H, D_2O exchangeable, OH); ^{13}C: δ 135.01, 134.45, and 134.24 (3 CH=), 117.00, 117.00, and 116.33 (3 CH_2=), 104.28 (C-1), 80.06 (C-3), 73.52, 72.25, and 71.18 (3 OCH_2), 78.14, 72.90, and 66.67 (C-2,4,5), 68.78 (C-6), and 56.62 (OCH_3); MS: *m/z* 332 $(M + 18)^+$ and 315 $(M + 1)^+$.

Anal. Calcd for $C_{16}H_{26}O_6$ (314.38): C, 61.13; H, 8.34. Found: C, 60.99; H, 8.47.

Methyl 3,4,6-tri-O-allyl-β-D-galactopyranoside (**11**). Yield, 95 mg (3%), syrup, $[\alpha]_D$ −2° (*c* 1, $CHCl_3$); NMR data: ^1H (250 MHz, $CDCl_3$): δ 6.03–5.83 (m, 3H, 3 CH=), 5.37–5.11 (m, 6 H, 3 CH_2=), 4.20 (d, 1 H, J_{12} 7.9 Hz, H-1), 3.83 (ddd, 1 H, $J_{2,OH}$ 1.9, $J_{2,3}$ 9.8 Hz, H-2), 3.54 (s, 3 H, OCH_3), 3.32 (dd, 1 H, $J_{3,4}$ 2.9 Hz, H-3), and 2.43 (d, 1 H, D_2O exchangeable, OH); ^{13}C: δ 135.35, 134.54, and 134.39 (3 CH=), 117.30, 117.26, and 116.84 (3 CH_2=), 104.10 (C-1), 81.49 (C-3), 73.73, 72.38, and 71.13 (3 OCH_2), 73.45, 72.33, and 70.89 (C-2,4,5), 68.38 (C-6), and 56.84 (OCH_3); MS: *m/z* 332 $(M + 18)^+$ and 315 $(M + 1)^+$.

Anal. Calcd for $C_{16}H_{26}O_6$ (314.38): C, 61.13; H, 8.34. Found: C, 60.99, H, 8.41.

Methyl 3,6-di-O-allyl-β-D-galactopyranoside (**8**). Yield 2.1 g (76%), mp 44° (cyclohexane–EtOAc), $[\alpha]_D$ +1° (*c* 0.85, $CHCl_3$) {lit.[6] $[\alpha]_D$ +1° (*c* 0.6, $CHCl_3$)}; NMR data: ^1H (400 MHz, $CDCl_3$): δ 6.01–5.87 (m, 2 H, 2 CH=), 5.37–5.18 (m, 4 H, 2 CH_2=), 4.27–4.14 (m, 2 H, OCH_2), 4.18 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1), 4.08–4.06 (m, 2 H, OCH_2), 4.05 (dd, 1 H, $J_{4,5}$ 1.0, $J_{3,4}$ 3.3 Hz, H-4), 3.78 (dd, 1 H, $J_{5,6a}$ 6.0, $J_{6a,6b}$ 10.1 Hz, H-6a), 3.73 (dd, 1 H, $J_{2,3}$ 9.5 Hz, H-2), 3.70 (dd, 1 H, $J_{5,6b}$ 6.0 Hz, H-6b), 3.60 (ddd, 1 H, H-5), 3.56 (s, 3 H, OCH_3), 3.38 (dd, 1 H, H-3), 2.50 (d, 1 H, *J* 1.4 Hz, D_2O exchangeable, OH), and 2.45 (d, *J* 2.0 Hz, D_2O exchangeable, OH); ^{13}C: δ 134.55 and 134.48 (2 CH=), 117.75 and 117.25 (2 CH_2=), 104.02 (C-1), 80.23 (C-3), 72.47 and 70.87 (2 OCH_2), 73.45 and 70.53 (C-2,5), 66.25 (C-4), 68.98 (C-6), and 56.89 (OCH_3); MS: *m/z* 292 $(M + 18)^+$.

Anal. Calcd for $C_{13}H_{22}O_6$ (274.32): C, 56.92; H, 8.08. Found: C, 56.96; H, 7.97.

Methyl 6-O-allyl-β-D-galactopyranoside (**9**). Yield, 235 mg (10%), mp 103–104° (EtOAc), $[\alpha]_D$ +7° (*c* 1, $CHCl_3$) {lit.[6] $[\alpha]_D$ −23° (*c* 0.90, $CHCl_3$)}; NMR data: ^1H (250 MHz, $CDCl_3$): δ 6.05–5.89 (m, 1 H, CH=), 5.38–5.20 (m, 2 H, CH_2=), 4.26–4.15 (m, 2 H, OCH_2), 4.21 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1), 3.55 (s, 3 H, OCH_3); ^{13}C: δ 134.51 (CH=), 118.07 (CH_2=), 104.20 (C-1), 80.13 (C-3), 70.95 (OCH_2), 74.10 and 70.39 (C-2,5), 66.48 (C-4), 68.98 (C-6), and 57.27 (OCH_3); MS: *m/z* 252 $(M + 18)^+$ and 235 $(M + 1)^+$.

Anal. Calcd for $C_{10}H_{18}O_6$ (234.25): C, 51.28; H, 7.75, Found: C, 51.41; H, 7.68.

The structures of **8**, **10**, and **11** were confirmed by acetylation of these compounds.

Methyl 2,4-di-O-acetyl-3,6-di-O-allyl-β-D-galactopyranoside (**12**).—Yield, 92% from **8**, $[\alpha]_D$ +12° (*c* 1.1, $CHCl_3$); NMR data: ^1H (250 MHz, C_6D_6): δ 5.88–5.70 (m, 2 H, 2 CH=), 5.62 (dd, 1 H, $J_{1,2}$ 8.1, $J_{2,3}$ 10.2 Hz, H-2), 5.52 (dd, 1 H, $J_{3,4}$ 3.2, $J_{4,5} < 1$ Hz, H-4), 5.29–5.00 (m, 4 H, 2 CH_2=), 4.19 (d, 1 H, H-1), 3.33 (s, 3 H, OCH_3), 1.79 and 1.64 (2 s, 6 H, 2 Ac); ^{13}C: δ 170.16 and 169.46 (2 C=O), 134.26 and 134.23 (2 CH=), 117.50 and 117.09 (2 CH_2=), 102.09 (C-1), 76.85 (C-3), 72.43 and 70.35 (2 OCH_2), 72.37 and 70.57 (C-2,5), 68.04 (C-6), 66.55 (C-4), 56.70 (OCH_3), 20.90 and 20.79 (2 CH_3CO); MS: *m/z* 376 $(M + 18)^+$ and 359 $(M + 1)^+$.

Anal. Calcd for $C_{17}H_{26}O_8$ (358.39): C, 56.97; H, 7.31. Found: C, 56.71; H, 7.13.

Methyl 4-O-acetyl-2,3,6-tri-O-allyl-β-D-galactopyranoside (**13**).—Yield, 98% from **10**, $[\alpha]_D$ +5° (*c* 1.25, $CHCl_3$); NMR data: ^1H (400 MHz, $CDCl_3$): δ 5.98–5.81 (m, 3 H, 3 CH=), 5.42 (dd, 1 H, $J_{4,5}$ 0.9 $J_{3,4}$ 3.0 Hz, H-4), 5.32–5.12 (m, 6 H, 3 CH_2=), 4.34–4.28 (m, 1 H, OCH_2), 4.25 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1), 4.24–4.14 (m, 2 H, OCH_2), 4.05–3.92 (m, 3 H, OCH_2), 3.67 (ddd, 1 H, $J_{5,6a} = J_{5,6b}$ 6 Hz, H-5), 3.56 (s, 3 H, OCH_3), 3.55–3.37 (m, 4 H, H-2,3,6a,6b), and 2.12 (s, 3 H, Ac); ^{13}C: δ 169.81 (C=O), 134.94, 134.30 and 134.02 (3 CH=), 117.07, 116.61 and 116.08 (3 CH_2=), 104.30 (C-1), 78.43 and 78.07 (C-2,3), 73.55, 72.09 and 70.64 (3 OCH_2), 71.88 (C-5), 67.97 (C-6), 66.86 (C-4), 56.82 (OCH_3), and 20.49 (CH_3CO); MS: *m/z* 374 $(M + 18)^+$ and 357 $(M + 1)^+$.

Methyl 2-O-acetyl-3,4,6-tri-O-allyl-β-D-galactopyranoside (**14**).—Yield, 98% from **11**, $[\alpha]_D$ −9° (*c* 1.1, $CHCl_3$); NMR data: ^1H (250 MHz, $CDCl_3$): δ 6.00–5.77 (m, 3 H, 3 CH=), 5.35–5.12 (m, 7 H, H-2, 3 CH_2=), 4.29 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 3.47 (s, 3 H, OCH_3), and 2.08 (s, 3 H, Ac); ^{13}C: δ 169.54 (C=O), 135.34, 134.38, and 134.38 (3 CH=), 117.37, 116.90, and 116.85 (3 CH_2=), 102.05 (C-1), 79.93 (C-3), 73.68, 72.42, and 70.92 (3 OCH_2), 73.48, 72.42, and 71.10 (C-2,4,5), 68.33 (C-6), 56.21 (OCH_3), and 21.02 (CH_3CO); MS: *m/z* 374 $(M + 18)^+$ and 357 $(M + 1)^+$.

Anal. Calcd for $C_{18}H_{28}O_7$ (356.42): C, 60.66; H, 7.92. Found: C, 60.41; H, 7.87.

Methyl 3,6-di-O-allyl-2,4-di-O-triflyl-β-D-galactopyranoside (**15**).—Trifluoromethanesulfonic anhydride (0.5 mL, 3 mmol) was slowly added under Ar to a solution of **8** (274 mg, 1 mmol) in pyridine (0.65 mL) and CH_2Cl_2 (5 mL) cooled to −20°. The solution was kept for 5 h at 0°. Cold aq $NaHCO_3$ and CH_2Cl_2 were then added. The organic layer was separated, washed with dilute NaCl solution, dried ($MgSO_4$), and concentrated. The residue (650 mg) was eluted from a column of silica gel with 2:1 cyclohexane–EtOAc to give first amorphous **15** (512 mg, 95%), $[\alpha]_D$ +4° (*c* 1.25, $CHCl_3$); NMR data: ^1H (250 MHz, $CDCl_3$): δ 6.00–5.81 (m, 2 H, 2 CH=), 5.38–5.21 (m, 5 H, H-4, 2 CH_2=), 4.68 (dd, 1 H, $J_{1,2}$ 8.0, $J_{2,3}$ 10.0 Hz, H-2), 4.47 (d, 1 H, H-1), 3.56 (s, 3 H, OCH_3); ^{13}C: δ 133.57 and 132.48 (2 CH=), 119.57 and 117.82 (2 CH_2=), 118.36 and 118.34 (2 q, $J_{C,F}$ 320 Hz, 2 CF_3), 100.72 (C-1), 82.20 (C-2), 80.64 (C-3), 74.71 (C-5), 72.35 and 71.91 (2 OCH_2), 71.13 (C-4), 66.03 (C-6), and 57.34 (OCH_3); MS: *m/z* 556 $(M + 18)^+$ and 539 $(M + 1)^+$.

Anal. Calcd for $C_{15}H_{20}F_6O_{10}S_2$ (538.46): C, 33.46; H, 3.74. Found: C, 33.63; H, 3.75.

Methyl 3,6-di-O-allyl-2-O-triflyl-β-D-galactopyranoside (**16**).—This compound was obtained by further elution. Yield, 17 mg (4%), $[\alpha]_D$ +1° (*c* 2.5, $CHCl_3$); NMR data: ^1H (250 MHz, $CDCl_3$): δ 6.02–5.83 (m, 2 H, 2 CH=), 5.38–5.18 (m, 4 H, 2 CH_2=), 4.79 (dd, 1 H, $J_{1,2}$ 8.0, $J_{2,3}$ 9.5 Hz, H-2), 4.42 (d, 1 H, H-1), and 3.56 (s, 3 H, OCH_3); ^{13}C: δ 134.07 and 133.31 (2 CH=), 118.79 and 117.51 (2 CH_2=), 118.34 (q, $J_{C,F}$ 320 Hz, CF_3), 100.60 (C-1), 83.95 (C-2), 77.57 (C-3), 73.21 (C-5), 72.50 and 71.01 (2 OCH_2), 68.46 (C-6), 66.60 (C-4), and 57.07 (OCH_3); MS: *m/z* 424 $(M + 18)^+$ and 407 $(M + 1)^+$.

Anal. Calcd for $C_{14}H_{21}F_3O_8S$ (406.39): C, 41.38; H, 5.21. Found: C, 41.44; H, 5.30.

Reaction of **15** *with tetrabutylammonium benzoate.*—A suspension of **15** (1.9 g, 3.5 mmol) and tetrabutylammonium benzoate (10 g, 27 mmol) in toluene (40 mL) was stirred at room temperature for 0.5 h, and then heated to 100° for 1 h under Ar. The mixture was filtered through a bed of Celite which was washed with diethyl ether. The combined organic phases were concentrated and the residue was eluted from a column of silica gel with 2:1 cyclohexane–EtOAc to give, in order, **19**, **17**, **20**, and **18**.

3,6-Di-O-allyl-2,5-anhydro-4-O-benzoyl-D-mannose benzoyl methyl acetal (**19**). Yield, 203 mg (12%), $[\alpha]_D$ +20° (*c* 1.1, $CHCl_3$); NMR data: ^1H (250 MHz, $CDCl_3$): δ 8.16–8.10 (m, 4 H, Ph), 7.65–7.60 (m, 2 H, Ph), 7.52–7.46 (m, 4 H, Ph), 6.22 (d, 1 H, $J_{1,2}$ 5.5 Hz, H-1), 5.98–5.88 (m, 2 H, 2 CH=), 5.48 (dd, 1 H, $J_{3,4}$ 1.5, $J_{4,5}$ 3 Hz, H-4), 5.37–5.18 (m, 4 H, 2 CH_2=), 4.48 (ddd, 1 H, $J_{5,6a} = J_{5,6b}$ 6.5 Hz, H-5), 4.39 (dd, 1 H, $J_{2,3}$ 2.5 Hz, H-3), 4.35 (dd, 1 H, H-2), 4.32–4.17 (m, 2 H, OCH_2), 4.12–4.05 (m, 2 H, OCH_2), 3.71 (d, 2 H, H-6a,6b), and 3.52 (s, 3 H, OCH_3); ^{13}C: δ 166.07 and 165.22 (2 C=O), 134.39–128.30 (2 Ph and 2 *C*H=CH_2), 117.22 and 117.11 (2 CH_2=), 97.34 (C-1), 84.00, 83.51, 82.81, and 79.19 (C-2,3,4,5), 72.25, 70.70, and 69.54 (C-6 and 2 OCH_2), and 57.41 (OCH_3); MS: *m/z* 500 $(M + 18)^+$ and 482 $(M)^+$.

Anal. Calcd for $C_{27}H_{30}O_8$ (482.53): C, 67.21; H, 6.27. Found: C, 67.21; H, 6.32.

Methyl 3,6-di-O-allyl-4-O-benzoyl-2-O-triflyl-β-D-glucopyranoside (**17**). Yield, 18 mg (1%); ^1H NMR data (250 MHz, $CDCl_3$): δ 8.07–8.03 (m, 2 H, Bz), 7.63–7.47 (m, 3 H, Bz), 5.85–5.64 (m, 2 H, 2 CH=), 5.28 (dd, 1 H, $J_{3,4}$ 9.3, $J_{4,5}$ 9.8 Hz, H-4), 5.22–5.02 (m, 4 H, 2 CH_2=), 4.64 (dd, 1 H, $J_{1,2}$ 8.0, $J_{2,3}$ 9.3 Hz, H-2), 4.51 (d, 1 H, H-1), 3.87 (dd, 1 H, H-3), 3.78–3.71 (m, 1 H, H-5), 3.60 (s, 3 H, OCH_3); MS: *m/z* 528 $(M + 18)^+$ and 511 $(M + 1)^+$.

Methyl 3,6-di-O-allyl-2,4-di-O-benzoyl-β-D-mannopyranoside (**20**). Yield, 1.24 g (73%), mp 96–97° (aq EtOH), $[\alpha]_D$ −149° (*c* 0.75, $CHCl_3$) {lit.[5] mp 93–95° (aq EtOH), $[\alpha]_D$ −145° (*c* 1.4, $CHCl_3$)}; NMR data: ^1H (400 MHz, $CDCl_3$): δ 8.15–8.03 (m, 4 H, Bz), 7.62–7.55 (m, 2 H, Bz), 7.51–7.45 (m, 4 H, Bz), 5.89–5.80 (m, 1 H, CH=), 5.82 (dd, 1 Hz, $J_{1,2}$ 0.8, $J_{2,3}$ 3.0 Hz, H-2), 5.72–5.64 (m, 1 H, CH=), 5.52 (dd, 1 H, $J_{3,4} = J_{4,5}$ 9.6 Hz, H-4), 5.26–5.05 (m, 4 H, 2 CH_2=), 4.66 (d, 1 H, H-1), 4.19–3.99 (m, 4 H, 2 OCH_2), 3.85 (dd, 1 H, H-3), 3.82 (ddd, 1 H, $J_{5,6a} = J_{5,6b}$ 5.0 Hz, H-5), 3.73 (2d, 2 H, H-6a,6b), and 3.56 (s, 3 H, OCH_3); ^{13}C: δ 165.90 and

165.39 (2 C=O), 134.29–128.17 (2 Ph and 2 CH=), 117.58 and 116.91 (2 CH_2=), 100.02 (C-1), 76.53, 74.20, 68.98 and 68.21 (C-2,3,4,5), 72.43, 70.23 and 69.66 (C-6 and 2 OCH_2) and 57.17 (OCH_3); MS: *m/z* 500 $(M + 18)^+$ and 483 $(M + 1)^+$.

Anal. Calcd for $C_{27}H_{30}O_8$ (482.53) C, 67.21; H, 6.27. Found: C, 67.15; H, 6.01.

Methyl 3,6-di-O-allyl-4-O-benzoyl-2-chloro-2-deoxy-β-D-mannopyranoside (**18**). Yield, 28 mg (2%), mp 61–62° (EtOAc–CH_2Cl_2), $[\alpha]_D$ −83° (*c* 1, $CHCl_3$); NMR data: ^1H (400 MHz, $CDCl_3$): δ 8.04–8.02 (m, 2 H, Bz), 7.61–7.57 (m, 1 H, Bz), 7.48–7.44 (m, 2 H, Bz), 5.84–5.73 (m, 2 H, 2 CH=), 5.46 (dd, 1 H, $J_{3,4} = J_{4,5}$ 9.4 Hz, H-4), 5.25–5.06 (m, 4 H, 2 CH_2=), 4.63 (d, 1 H, $J_{1,2}$ 1.0 Hz, H-1), 4.47 (dd, 1 H, $J_{2,3}$ 3.5 Hz, H-2), 4.17–4.12 (m, 1 H, OCH_2), 3.86 (dd, 1 H, H-3), 3.77–3.74 (m, 1 H, H-5), 3.66–3.64 (m, 2 H, H-6a,6b), and 3.61 (s, 3 H, OCH_3); ^{13}C: δ 165.34 (C=O), 134.30–128.41 (2 *C*H=CH_2 and Bz), 117.97, 117.13 (2 CH_2=), 99.58 (C-1), 77.02 (C-3), 74.72 (C-2), 72.53, 70.33 and 69.71 (C-6 and 2 OCH_2), 68.47 (C-5), 59.21 (C-2) and 57.25 (OCH_3); MS: *m/z* 416, 414 $(M + 18)^+$, and 397 $(M + 1)^+$.

Anal. Calcd for $C_{20}H_{25}ClO_6$ (396.87) C, 60.53; H, 6.35. Found: C, 60.78; H, 6.45.

Tetrabutylammonium benzoate.—A solution of NaOH (18 g, 0.45 mol) in distilled water (30 mL) was added to a solution of commercial tetrabutylammonium hydrogen sulfate (34 g, 0.1 mmol) in distilled water (50 mL). Benzoic acid (24.4 g, 0.2 mol) was dissolved in this solution. CH_2Cl_2 (50 mL) was added, the upper organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic phases were dried ($MgSO_4$), concentrated, and the residual solvent co-evaporated with toluene to give a white solid (25.5 g, 70%). This very hydroscopic salt was dried under vacuum over P_2O_5 before use; ^1H NMR data (250 MHz, $CDCl_3$): δ 8.40–8.20 (m, 2 H, Bz), 7.40–7.20 (m, 3 H, Bz), 3.22–3.13 (m, 8 H, CH_2N), 1.60–1.42 (m, 8 H, CH_2CH_2N), 1.41–1.26 (m, 8 H, CH_2CH_3), and 0.93 (t, 12 H, *J* 7 Hz, CH_2CH_3).

Methyl 3,6-di-O-allyl-β-D-mannopyranoside (**21**).—Compound **20** (550 mg, 1.14 mmol) was *O*-debenzoylated with NaOMe in MeOH (20 mL) for 12 h at room temperature. After usual workup, the residue was eluted from a column of silica gel with EtOAc to give **21** (288 mg, 92%), mp 78–80° (EtOAc), $[\alpha]_D$ −88° (*c* 0.72, $CHCl_3$); ^1H NMR data (250 MHz, $CDCl_3$): δ 6.04–5.83 (m, 2 H, 2 CH=), 5.38–5.17 (m, 4 H, 2 CH_2=), 4.39 (d, 1 H, $J_{1,2}$ 1 Hz, H-1), 3.57 (s, 3 H, OCH_3), and 3.34 (dd, 1 H, $J_{5,6b}$ 3.5, $J_{6a,6b}$ 9.4 Hz, H-6b); MS: *m/z* 292 $(M + 18)^+$ and 275 $(M + 1)^+$.

Anal. Calcd for $C_{13}H_{22}O_6$ (274.32): C, 56.92; H, 8.08. Found: C, 56.63; H, 7.87.

Methyl 3,6-di-O-allyl-2,4-di-O-benzyl-β-D-mannopyranoside (**22**).—Compound **21** (200 mg, 0.73 mmol) waas benzylated in DMF (10 mL) with NaH (60% in oil, 105 mg) and benzyl bromide (0.47 mL, 4 mmol), with stirring at room temperature for 4 h. MeOH (0.2 mL) was added at 0° to destroy the excess of NaH. The solvent was evaporated and a solution of the residue in CH_2Cl_2 (10 mL) was filtered through a bed of Celite, washed with water and NaCl solution, dried ($MgSO_4$), filtered, and concentrated. The residue was eluted from a column of silica gel with 3 : 1 cyclohexane–EtOAc to give **22** (289 mg, 87%), mp 35–36° (EtOAc–cyclohe-

xane), $[\alpha]_D$ −70° (*c* 0.76, $CHCl_3$): ^1H NMR data (400 MHz, $CDCl_3$): δ 7.48–7.43 (m, 2 H, Ph), 7.38–7.27 (m, 8 H, Ph), 6.00–5.78 (m, 2 H, 2 CH=), 5.31–5.13 (m, 4 H, 2 CH_2=), 4.96 and 4.84 (2 d, 2 H, *J* 12.5 Hz, CH_2Ph), 4.92 and 4.59 (2 d, 2 H, *J* 10.8 Hz, CH_2Ph), 4.29 (br. s, 1 H, $J_{1,2} < 1$ Hz, H-1), 4.12–3.90 (m, 4 H, 2 OCH_2), 3.86 (dd, 1 H, $J_{2,3}$ 3.0 Hz, H-3), 3.81 (dd, 1 H, $J_{3,4} = J_{4,5}$ 9.5 Hz, H-4), 3.78 (dd, 1 H), $J_{5,6a}$ 2.0, $J_{6a,6b}$ 11.0 Hz, H-6a), 3.69 (dd, 1 H, $J_{5,6b}$ 5.5 Hz, H-6b), 3.53 (s, 3 H, OCH_3), 3.42 (ddd, 1 H, H-5), and 3.41 (dd, 1 H, H-3); MS: *m/z* 472 $(M + 18)^+$.

Anal. Calcd for $C_{27}H_{34}O_6$ (454.57): C, 71.34; H, 7.54. Found: C, 71.40; H, 7.49.

*Methyl 2,4-di-*O*-benzyl-β-*D*-mannopyranoside* (**23**).—A suspension of **22** (2.1 g, 4.6 mmol) and 10% Pd–C (1 g) in a mixture of water (100 mL), MeOH (20 mL), and acetic acid (4 mL) was heated to 60° with stirring for 24 h. The mixture was filtered through a bed of Celite and concentrated. The residue was eluted from a column of silica gel with 1:1 cyclohexane–EtOAc to afford **23** (1.5 g, 87%), mp 55–56° (EtOHc), $[\alpha]_D$ −85° (*c* 1.07, $CHCl_3$) {lit.[10] mp 56–58° (EtOAc–light petroleum), $[\alpha]_D$ −87° (*c* 0.8, $CHCl_3$)}; NMR data: ^1H (400 MHz, $CDCl_3$): δ 7.39–7.26 (m, 10 H, Ph), 5.03 and 4.61 (2 d, 2 H, *J* 11.9 Hz, CH_2Ph), 4.89 and 4.62 (2 d, 2 H, *J* 11.0 Hz, CH_2Ph), 4.41 (d, 1 H, $J_{1,2}$ 0.5 Hz, H-1), 3.91 (dd, 1 H, $J_{5,6a}$ 3.0, $J_{6a,6b}$ 12.0 Hz, H-6a), 3.81 (dd, 1 H, $J_{2,3}$ 4.0 Hz, H-2), 3.77 (dd, 1 H, $J_{5,6b}$ 5.5 Hz, H-6b), 3.67 (dd, 1 H, $J_{3,4}$ 9.0 Hz, H-3), 3.56 (dd, 1 H, $J_{4,5}$ 9.0 Hz, H-4), 3.54 (s, 3 H, OCH_3), and 3.33–3.27 (m, 1 H, H-5); ^{13}C: δ 138.31 and 138.29 (2 C, Ph), 128.63–127.75 (*C*H, Ph), 102.77 (C-1), 77.84, 76.67, 75.49, and 73.94 (C-2,3,4,5), 74.95 and 74.73 (2 CH_2Ph), 62.21 (C-6), and 57.28 (OCH_3); MS: *m/z* 392 $(M + 18)^+$ and 375 $(M + 1)^+$.

*3,4,6-Tri-*O*-benzyl-β-*D*-mannopyranose 1,2-(methyl orthoacetate)* (**25**).—3,4,6-Tri-*O*-acetyl-β-D-mannopyranose 1,2-(methyl orthoacetate) (**24**, *exo–endo* mixture; 12 g, 33 mmol), obtained from D-mannose[14] in a 63% yield, was deacetylated in MeOH (100 mL) by the addition of a saturated solution of NH_3 in MeOH (20 mL). The solution was kept overnight at room temperature, and then concentrated to a syrup (11 g). The residue was benzylated in DMF (500 mL) with benzyl bromide (30 mL) and NaH (60% in oil, 10 g), with stirring at room temperature for 4 h. MeOH (30 mL) was added at 0° to destroy the excess of NaH. The solvent was evaporated and a solution of the residue in dichloromethane (300 mL) was filtered through a bed of Celite, washed with water, dried ($MgSO_4$), filtered, and concentrated. The residue was eluted from a column of silica gel with 3:1 cyclohexane–EtOAc to give **25** as a 17:3 mixture of *exo–endo* isomers (15 g, 90%). Another chromatography on silica gel (CH_2Cl_2) of a sample gave first pure *endo* isomer (**25** *endo*), mp 87–88° (from cyclohexane–EtOAc), $[\alpha]_D$ +37° (*c* 1, $CHCl_3$); NMR data: ^1H (250 MHz, $CDCl_3$): δ 7.41–7.23 (m, 15 H, 3 Ph), 5.10 (d, 1 H, $J_{1,2}$ 2.5 Hz, H-1), 4.92 and 4.63 (2 d, 2 H, *J* 10.8 Hz, PhCH_2), 4.83 and 4.76 (2 d, 2 H, *J* 12.2 Hz, PhCH_2), 4.53 (s, 2 H, PhCH_2), 4.11 (dd, 1 H, $J_{2,3}$ 4.1 Hz, H-2), 4.02 (dd, 1 H, $J_{3,4} = J_{4,5}$ 9.5 Hz, H-4), 3.76 (dd, 1 H, H-3), 3.76–3.71 (m, 2 H, H-6a,b), 3.44 (s, 3 H, OCH_3), 3.47–3.40 (m, 1 H, H-5), and 1.50 (s, 3 H, CH_3); ^{13}C: δ 138.17, 138.16, and 137.84 (3 C, Ph), 128.41–127.26 (*C*H, Ph), 124.13 (*C*–OCH_3), 94.85 (C-1), 79.18,

76.00, 74.11, and 73.94 (C-2,3,4,5), 75.19, 73.18, and 72.27 (3 PhCH$_2$), 68.75 (C-6), 50.10 (OCH_3), and 23.96 (CH_3); MS: m/z 524 $(M + 18)^+$.

Anal. Calcd for $C_{30}H_{34}O_7$ (506.60): C, 71.13; H, 6.76. Found: C, 71.17; H, 6.69.

Further elution gave the pure *exo* isomer (**25** *exo*), mp 71–72° (cyclohexane–EtOAc), $[\alpha]_D$ +34° (*c* 1.35, $CHCl_3$) {lit.[14] mp 76–78°, $[\alpha]_D$ +12° (*c* 1.65, $CHCl_3$); {lit.[15] mp 75–77° (ethyl ether–light petroleum), $[\alpha]_D$ +29° ($CHCl_3$)}; ^{1}H NMR data (250 MHz, $CDCl_3$): δ 7.43–7.21 (m, 15 H, 3 Ph), 5.35 (d, 1 H, $J_{1,2}$ 2.5 Hz, H-1), 4.90 and 4.62 (2 d, 2 H, *J* 10.8 Hz, PhCH_2), 4.79 (s, 2 H, PhCH_2), 4.60 and 4.54 (2 d, 2 H, *J* 12.2 Hz, PhCH_2), 4.39 (dd, 1 H, $J_{2,3}$ 3.9 Hz, H-2), 3.93 (dd, 1 H, $J_{3,4} = J_{4,5}$ 9.3 Hz, H-4), 3.80–3.66 (m, 3 H, H-3,6a,6b), 3.46–3.38 (m, 1 H, H-5), 3.29 (s, 3 H, OCH_3), and 1.74 (s, 3 H, CH_3); ^{13}C: δ 138.14, 138.13 and 137.76 (3 C, Ph), 128.42–127.41 (*C*H, Ph), 123.89 (*C*–OCH_3), 97.43 (C-1), 78.95, 77.05, 74.07, and 73.98 (C-2,3,4,5), 76.59, 73.22, and 72.21 (3 PhCH_2), 68.86 (C-6), 49.49 (OCH_3), and 24.44 (CH_3); MS: m/z 524 $(M + 18)^+$.

Anal. Calcd for $C_{30}H_{34}O_7$ (506.60): C, 71.13; H, 6.76. Found: C, 71.23; H, 6.75.

Phenyl 2-O-acetyl-3,4,6-tri-O-benzyl-1-thio-α-D-mannopyranoside (**27**).—Thiophenol (1 mL) was added to a solution of **25** (506 mg, 1 mmol) and $HgBr_2$ (19 mg) in dry acetonitrile (5 mL). The mixture was heated to 60° under Ar for 4 h, and then concentrated. A solution of the residue in CH_2Cl_2 was washed with 5% aq NaOH (10 mL), water, dried ($MgSO_4$), and concentrated. The residue was eluted from a column of silica gel with 5:1 cyclohexane–EtOAc to give first **27** (467 mg, 80%), mp 62–63° (EtOAc–hexane), $[\alpha]_D$ +106° (*c* 1, $CHCl_3$) {lit.[18] $[\alpha]_D$ +104° (*c* 1.88, $CHCl_3$)}; NMR data: ^{1}H (250 MHz, $CDCl_3$): δ 7.49–7.45 (m, 2 H, Ph), 7.37–7.17 (m, 18 H, Ph), 5.61 (dd, 1 H, $J_{1,2}$ 1.5, $J_{2,3}$ 2.5 Hz, H-2), 5.54 (d, 1 H, H-1), 4.89 and 4.51 (2 d, 2 H, *J* 10.7 Hz, PhCH_2), 4.73 and 4.57 (2 d, 2 H, *J* 11.2 Hz, PhCH_2), 4.67 and 4.46 (2 d, 2 H, *J* 12.0 Hz, PhCH_2), 4.38–4.29 (m, 1 H, H-5), 3.98 (dd, 1 H, $J_{3,4} = J_{4,5}$ 9.3 Hz, H-4), 3.93 (dd, 1 H, H-3), 3.86 (dd, 1 H, $J_{5,6a}$ 4.4, $J_{6a,6b}$ 10.8 Hz, H-6a), 3.72 (dd, 1 H, $J_{5,6b}$ 1.8 Hz, H-6b), and 2.14 (s, 3 H, Ac); ^{13}C: δ 170.24 (C=O), 138.22, 138.12, and 137.54 (3 C, Ph), 133.64 (C, SPh), 131.72–127.53 (*C*H, Ph), 86.19 (C-1), 78.45 (C-3), 74.47 (C-4), 72.42 (C-5), 70.28 (C-2), 75.21, 73.31, and 71.86 (3 PhCH_2), 68.78 (C-6), and 21.04 (CO*C*H_3); MS: m/z 602 $(M + 18)^+$.

Anal. Calcd for $C_{35}H_{36}O_6S$ (584.74): C, 71.89; H, 6.21. Found: C, 72.20; H, 6.10.

Further elution gave methyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (**26**) (51 mg, 10%), $[\alpha]_D$ +24° (*c* 1, $CHCl_3$) {lit.[17] $[\alpha]_D$ +23° (*c* 1.15, $CHCl_3$)}.

Ethyl 2--O-acetyl-3,4,6-tri-O-benzyl-1-thio-α-D-mannopyranoside (**29**).—Thioethanol (0.5 mL) was added to a solution of **25** (506 mg, 1 mmol) and $HgBr_2$ (36 mg, 0.1 mmol) in dry acetonitrile (3 mL). The mixture was heated to 35° under Ar for 6 h and concentrated. A solution of the residue in CH_2Cl_2 was washed with 5% aq NaOH, water, dried ($MgSO_4$), and evaporated. The residue was eluted from a column of silica gel with 4:1 cyclohexane–EtOAc to give **29** as a white solid (460 mg, 85%), mp 50–51° (EtOAc–pentane), $[\alpha]_D$ +84° (*c* 1, $CHCl_3$); NMR data: ^{1}H (400 MHz, $CDCl_3$): δ 7.35–7.12 (m, 15 H, 3 Ph), 5.42 (dd, 1 H, $J_{1,2}$ 1.5, $J_{2,3}$ 2.5 Hz,

H-2), 5.31 (d, 1 H, H-1), 4.83 and 4.46 (2 d, 2 H, J 11.0 Hz, PhCH_2), 4.67 and 4.47 (2 d, 2 H, J 12.0 Hz, PhCH_2), 4.66 and 4.50 (2 d, 2 H, J 11.5 Hz, PhCH_2), 4.17–4.12 (m, 1 H, H-5), 3.92 (dd, 1 H, $J_{3,4} = J_{4,5}$ 9.0 Hz, H-4), 3.88 (dd, 1 H, H-3), 3.82 (dd, 1 H, $J_{5,6a}$ 4.0, $J_{6a,6b}$ 11.0 Hz, H-6a), 3.67 (dd, 1 H, $J_{5,6b}$ 2.0 Hz, H-6b), 2.65 (dq, 1 H, J_{vic} 7.5, J_{gem} 12.0 Hz, CHCH$_3$), 2.57 (dq, 1 H, J_{vic} 7.5, J_{gem} 12.0 Hz, CHCH$_3$), 2.14 (s, 3 H, Ac), and 1.26 (t, 3 H, J_{vic} 7.5 Hz, CH$_3$); ^{13}C: δ 170.45 (C=O), 138.53, 138.31, and 137.83 (3 C, Ph), 128.56–127.74 (*C*H, Ph), 82.55 (C-1), 78.73 (C-3), 74.66 (C-4), 71.96 (C-5), 70.67 (C-2), 75.27, 73.51 and 71.95 (3 PhCH_2), 68.93 (C-6), 25.59 (CH_2CH$_3$), 21.26 (COCH$_3$), and 15.05 (CH$_3$); MS: m/z 554 $(M + 18)^+$.

Anal. Calcd for $C_{31}H_{36}O_6S$ (536.69): C, 69.38; H, 6.76. Found: C, 69.53; H, 6.78.

Phenyl 2-O-benzoyl-3,4,6-tri-O-benzyl-1-thio-α-D-mannopyranoside (**28**).—Compound **27** (292 mg, 0.5 mmol) was *O*-deacetylated by NaOMe (0.4 mmol) in MeOH (5 mL) for 30 min at room temperature. MeOH was evaporated and the residue was treated with benzoyl chloride (0.1 mL, 0.85 mmol) in pyridine (3 mL) and CH_2Cl_2 (6 mL). The mixture was stirred for 2 h at room temperature and MeOH (0.5 mL) was added to destroy excess benzoyl chloride. Stirring was continued for 30 min. The solvent was coevaporated with toluene. The residue (0.4 g) was eluted from a column of silica gel with 6:1 cyclohexane–EtOAc to afford **28** (300 mg, 90%), syrup, $[\alpha]_D$ +69° (c 1, $CHCl_3$); NMR data: ^{1}H (250 MHz, $CDCl_3$): δ 8.08–8.04 (m, 2 H, Bz), 7.58–7.47 (m, 3 H, Oh), 7.40–7.20 (m, 20 H, Ph), 5.87 (dd, 1 H, $J_{1,2}$ 1.6, $J_{2,3}$ 2.9 Hz, H-2), 5.66 (d, 1 H, H-1), 4.91 and 4.57 (2 d, 2 H, J 10.7 Hz, PhCH_2), 4.82 and 4.60 (2 d, 2 H, J 11.3 Hz, PhCH_2), 4.72 and 4.50 (2 d, 2 H, J 11.8 Hz, PhCH_2), 4.43–4.36 (m, 1 H, H-5), 4.17 (dd, 1 H, $J_{3,4} = J_{4,5}$ 9.2 Hz, H-4), 4.05 (dd, 1 H, H-3), 3.95 (dd, 1 H, $J_{5,6a}$ 3.9, $J_{6a,6b}$ 10.8 Hz, H-6a), and 3.78 (dd, 1 H, $J_{5,6b}$ 1.7 Hz, H-6b); ^{13}C: δ 165.56 (C=O), 138.40, 138.33, and 137.66 (3 C, Ph), 133.71 (C, SPh), 129.82 (C, Bz), 133.18–127.47 (*C*H, Ph), 86.39 (C-1), 78.61 (C-3), 74.53 (C-4), 72.70 (C-5), 70.68 (C-2), 75.32, 73.38, and 71.70 (3 PhCH_2), and 69.07 (C-6); MS: m/z 664 $(M + 18)^+$.

Anal. Calcd for $C_{40}H_{38}O_6S$ (646.80): C, 74.28; H, 5.92. Found: C, 74.30; H, 5.86.

Ethyl 2-O-benzoyl-3,4,6-tri-O-benzyl-1-thio-α-D-mannopyranoside (**30**).—Compound **29** (4.3 g, 8 mmol) was *O*-deacetylated by NaOMe (4 mmol) in MeOH (30 mL) for 30 min at room temperature. MeOH was evaporated and the residue was treated with benzoyl chloride (1.2 mL, 10 mmol) in pyridine (10 mL) and CH_2Cl_2 (20 mL). The mixture was stirred for 1 h at room temperature and water (0.1 mL) was added to destroy excess benzoyl chloride. Stirring was continued for 30 min. Water and CH_2Cl_2 were added. The organic layer was separated, washed with water, dried ($MgSO_4$), and concentrated. The residue (6 g) was eluted from a column of silica gel with 80:1 toluene–EtOAc to afford **30** (4.2 g, 88%), syrup, $[\alpha]_D$ +39° (c 1, $CHCl_3$); NMR data: ^{1}H (250 MHz, $CDCl_3$): δ 8.10–8.06 (m, 2 H, Bz), 7.58–7.17 (m, 18 H, Ph), 5.71 (dd, 1 H, $J_{1,2}$ 1.6, $J_{2,3}$ 3.0 Hz, H-2), 5.45 (d, 1 H, H-1), 4.87 and 4.54 (2 d, 2 H, J 10.8 Hz, PhCH_2), 4.76 and 4.55 (2 d, 2 H, J 11.7 Hz, PhCH_2), 4.73 and 4.52 (2 d, 2 H, J 11.9 Hz, PhCH_2), 4.27–4.19 (m, 1 H, H-5),

4.13 (dd, 1 H, $J_{3,4} = J_{4,5}$ 9.0 Hz, H-4), 4.02 (dd, 1 H, H-3), 3.93 (dd, 1 H, $J_{5,6a}$ 3.6, $J_{6a,6b}$ 10.8 Hz, H-6a), 3.75 (dd, 1 H, $J_{5,6b}$ 1.7 Hz, H-6b), 2.77–2.54 (m, 2 H, CH_2CH_3), and 1.28 (t, 3 H, J 7.4 Hz, CH_3); ^{13}C: δ 165.53 (C=O), 138.32, 138.31, and 137.65 (3 C, Ph), 128.94 (C, Bz), 133.06–127.42 (*C*H, Ph), 82.51 (C-1), 78.59 (C-3), 74.41 (C-4), 71.93 (C-5), 70.78 (C-2), 75.16, 73.30, and 71.50 (3 PhCH_2), 68.93 (C-6), 25.55 (CH_2CH_3), and 14.93 (CH_3); MS: m/z 616 $(M + 18)^+$ and 599 $(M + 1)^+$.

Anal. Calcd for $C_{36}H_{38}O_6S$ (598.76): C, 72.22; H, 6.40. Found: C, 72.39; H, 6.40.

Glycosylation: general procedure[4].—A suspension of **23** (60 mg, 0.16 mmol) and 4A molecular sieves (1.5 g) in dry acetonitrile (10 mL) was stirred for 20 min under Ar. Tris(4-bromophenyl)ammoniumyl hexachloroantimonate (**31**, 500 mg), and then a solution of the donor (**27**, **28**, **29** or **30**) (0.48 mmol, 1.5 eq) in acetonitrile (5 mL) were added slowly at 0°. After stirring at 10–15° for 30 min, another portion of tris(4-bromophenyl)ammoniumyl hexachloroantimonate (100 mg) was added. The mixture was kept at room temperature for 1 h (5 h for **27** and **28**), neutralized (Et_3N), filtered through a bed of Celite, and concentrated. The residue was eluted from a column of silica gel with 3 : 1 cyclohexane–EtOAc to give first the trisaccharide **32** or **33**, then a small amount of the disaccharide **35** or **36**. A small amount of **37** was also isolated when the glycosylation was achieved with **27** or **29**.

*Methyl 3,6-di-*O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-α-*D*-mannopyranosyl)-2,4-di-*O*-benzyl-β-*D*-mannopyranoside* (**32**).—Yield, 200 mg (85%), $[\alpha]_D$ −18° (*c* 0.86, $CHCl_3$); NMR data: ^1H (400 MHz, $CDCl_3$): δ 5.72 (dd, 1 H, $J_{1',2'}$ 1.8, $J_{2',3'}$ 3.0 Hz, H-2′), 5.70 (dd, 1 H, $J_{1'',2''}$ 1.8, $J_{2'',3''}$ 2.6 Hz, H-2″), 5.30 (d, 1 H, H-1′), 5.02 (d, 1 H, H-1″), 4.27 (br. s, 1 H, $J_{1,2} < 1$ Hz, H-1), 3.83 (br. s, 1 H, $J_{2,3}$ 4.0 Hz, H-2), and 3.42 (s, 3 H, OCH_3); ^{13}C: δ 165.33 and 165.24 (2 C, C=O), 138.61, 138.48, 138.42, 138.33, 138.20, 137.78, 137.74, and 137.51 (8 C, Ph), 129.81 and 129.67 (2 C, Bz), 128.23–127.18 (*C*H, Ph), 102.55 (C-1), 99.63 (C-1′), and 97.82 (C-1″), 80.55, 77.97, 77.39, 77.16, 75.11, 74.62, 74.13, 73.99, 72.18, 71.50, 68.99, and 68.46 (12 *C*H, C-2,2′,2″, C-3,3′,3″, C-4,4′,4″, C-5,5′,5″), 75.01, 74.87, 74.75, 73.94, 73.23, 73.13, 71.54, and 70.90 (8 PhCH_2), 69.10, 68.79, and 66.45 (3 *C*H2, C-6,6′,C″), and 56.98 (OCH_3); MS: m/z 1465 $(M + 18)^+$.

Anal. Calcd for $C_{89}H_{90}O_{18} \cdot H_2O$ (1465.71): C, 72.93; H, 6.33. Found: C, 72.82; H, 6.23.

*Methyl 6-*O*-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-α-*D*-mannopyranosyl)-2,4-di-*O*-benzyl-β-*D*-mannopyranoside* (**35**).—Yield, 14 mg (10%); NMR data: ^1H (400 MHz, $CDCl_3$): δ 5.70 (dd, 1 H, $J_{1',2'}$ 1.8, $J_{2',3'}$ 2.2 Hz, H-2′), 5.04 (d, 1 H, H-1′), 4.38 (br. s, $J_{1,2} < 1$ Hz, H-1), 3.82 (br. d, 1 H, $J_{2,3}$ 4.0 Hz, H-2), and 3.49 (s, 3 H, OCH_3); ^{13}C: δ 165.40 (C=O), 138.45, 138.30, 138.19, 138.11, and 137.79 (5 C, Ph), 129.53 (C, Bz), 128.40–127.27 (*C*H, Ph), 102.52 (C-1), 97.62 (C-1′), and 57.03 (OCH_3); MS: m/z 928 $(M + 18)^+$.

*Methyl 3,6-di-*O*-(2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-*D*-mannopyranosyl)-2,4-di-*O*-benzyl-β-*D*-mannopyranoside* (**33**).—Yield, 160 mg (75%); NMR data: ^1H (250 MHz, $CdCl_3$): δ 5.48 (dd, 1 H, $J_{1',2'}$ 2.0, $J_{2',3'}$ 3.0 Hz, H-2′), 5.44 (dd, 1 H, $J_{1'',2''}$

2.0, $J_{2'',3''}$ 3.0 Hz, H-2″), 5.15 (d, 1 H, H-1′), 4.26 (br. s, 1 H, $J_{1,2} < 1$ Hz, H-1), 3.41 (s, 3 H, OCH_3), 2.14 and 2.06 (2s, 6 H, 2 Ac); ^{13}C: δ 170.20 and 169.92 (2C, C=O), 138.66, 138.53, 138.50, 138.15, 138.05, 137.80, 137.74, and 137.63 (8 C, Ph), 128.46–127.21 (*C*H, Ph), 102.56 (C-1), 99.67 (C-1′), 97.77 (C-1″), 57.04 (OCH_3), 21.05 and 20.89 (2 CH_3CO); MS: *m/z* 1341 $(M + 18)^+$.

Methyl 6-O-(2-O-acetyl-3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-2,4-di-O-benzyl-β-D-mannopyranoside (**36**).—Yield, 27 mg (20%); ^1H NMR data (250 MHz, $CDCl_3$): δ 5.46 (dd, 1 H, $J_{1',2'}$ 2.0, $J_{2',3'}$ 2.8 Hz, H-2′), 4.93 (d, 1 H, H-1′), 4.37 (d, 1 H, $J_{1,2} < 1$ Hz, H-1), 3.93 (dd, 1 H, $J_{2,3}$ 4 Hz, H-2), 3.48 (s, 3 H, OCH_3) and 2.15 (s, 3 H, Ac); MS: *m/z* 866 $(M + 18)^+$.

2-O-Acetyl-1,6-anhydro-3,4-di-O-benzyl-β-D-mannopyranose (**37**)[21].—Yield, 2 mg (3%); ^1H NMR data (400 MHz, $CDCl_3$): δ 7.37–7.25 (m, 10 H, 2 Ph), 5.43 (br. s, 1 H, H-1), 4.82 (dd, 1 H, $J_{1,2}$ 2.0, $J_{2,3}$ 5.5 Hz, H-2), 4.56–4.37 (m, 5 H, H-5, 2 CH_2Ph), 4.22 (dd, 1 H, $J_{5,6a}$ 1.0, $J_{6a,6b}$ 7.5 Hz, H-6a), 4.04–4.01 (m, 1 H, H-3), 3.75 (dd, 1 H, $J_{5,6b}$ 5.5 Hz, H-6b), 3.43 (dd, 1 H, $J_{3,4} = J_{4,5}$ 1.5 Hz, H-4) and 2.12 (s, 3 H, Ac); MS: *m/z* 402 $(M + 18)^+$.

Methyl 2,4-di-O-benzyl-3,6-di-O-(3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-β-D-mannopyranoside (**34**).—Compound **32** or **33** was *O*-deesterified by NaOMe in MeOH (20 min for **33** and overnight for **32**). The usual workup gave a residue which was eluted from a column of silica gel with 1:2 cyclohexane–EtOAc to provide an almost quantitative yield of **37** as a low melting solid, $[\alpha]_D$ +18° (*c* 0.8, $CHCl_3$); NMR data: ^1H (400 MHz, $CDCl_3$): δ 7.41–7.11 (m, 40 H, 8 Ph), 5.22 (d, 1 H, $J_{1',2'}$ 1.4 Hz, H-1′), 5.06 (d, 1 H, $J_{1'',2''}$ 1.5 Hz, H-1″), 4.25 (d, 1 H, $J_{1,2}$ 0.5 Hz, H-1), 4.10 (dd, 1 H, $J_{2'',3''}$ 3.0 Hz, H-2″), 3.98 (dd, 1 H, $J_{2',3'}$ 2.8 Hz, H-2′), 3.93 (dd, 1 H, $J_{2,3}$ 3.0 Hz, H-2), 3.42 (s, 3 H, OCH_3), and 2.36 (br., 2 H, D_2O exchangeable, 2 OH); ^{13}C: δ 138.66, 138.40, 138.36, 138.09, 138.02, 137.80, 137.76, and 137.71, (8 C, Ph), 102.57 (C-1), 101.47 (C-1′), 99.70 (C-1″), 80.82, 79.88, 79.32, 77.56, 75.00, 74.70, 74.21, 74.08, 71.69, 70.95, 68.60, and 67.69 (C-2,2′,2″, C-3,3′,3″, C-4,4′,4″, C-5,5′,5″), 74.90, 74.81, 74.63, 73.99, 73.29, 73.17, 72.02, and 71.16 (8 CH_2Ph), 69.08, 68.70, and 66.06 (C-6,6′,6″), and 56.97 (OCH_3); MS: *m/z* 1256 $(M + 18)^+$.

Anal. Calcd for $C_{75}H_{82}O_{16}$(1239.48): C, 72.68; H, 6.67. Found: C, 72.36; H, 6.51.

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