Available online at www.sciencedirect.com
SCIENCE DIRECT®
Carbohydrate Research 338 (2003) 1073–1081
CARBOHYDRATE RESEARCH
www.elsevier.com/locate/carres

Pentafluoropropionyl and trifluoroacetyl groups for temporary hydroxyl group protection in oligomannoside synthesis

Maki Takatani,[a,b] Ichiro Matsuo,[a,b] Yukishige Ito[a,b,*]

[a]*RIKEN (The Institute of Physical and Chemical Research), 2-1 Hirosawa, Wako-shi, Saitama 351-0198, Japan*
[b]*CREST, JST, Kawaguchi, Saitama 332-1102, Japan*

Received 25 January 2003; accepted 20 February 2003

Abstract

Pentafluoropropionyl (PFP) and trifluoroacetyl (TFA) esters were demonstrated to be useful in facile oligosaccharide synthesis. These were well compatible with glycosylation conditions and removable by treatment with pyridine–EtOH, with complete preservation of acetyl groups. Analytically pure products were obtained quantitatively, simply by evaporating the reaction mixtures. Using *O*-PFP and *O*-TFA carrying glycosyl halides, trisaccharide (Manα1→2Manα1→2Man) and tetrasaccharide (Glcα1→3Manα1→2Manα1→2Man) portions of monoglucosylated high-mannose type dodecasaccharide ($Glc_1Man_9GlcNAc_2$), a putative ligand for the ER chaperon, calnexin and calreticulin, were synthesized.

Keywords: Pentafluoropropionyl and trifluoroacetyl groups; Hydroxy protection; Oligomannoside synthesis

1. Introduction

The trifluoroacetyl (TFA) group has been rarely used as a protecting group for alcohols, because it is considered to be too labile to be useful synthetically.[1] In an exceptional case, its remote participating effect was evaluated in comparison with more electron-donating acyl groups.[2] In this paper, we wish to demonstrate that TFA and, more reliably, homologous pentafluoropropionyl (PFP) esters can be used conveniently for facile oligosaccharide synthesis. These groups are stable under glycosylation conditions and can be removed under extremely mild conditions, with complete preservation of *O*-acetyl groups. By using TFA and PFP groups, concise synthetic routes to terminal trimannose (αMan1→2αMan1→2αMan **1**) and monoglucosylated trimannose (αGlc1→3αMan1→2αMan1→2αMan **2**) portions of high-mannose type glycan chain were established. These oligosaccahrides are important partial structures related to glycoprotein quality control, including folding, transport, and degradation.[3] We recently reported the synthesis of terminally glucosylated high-mannose type dodecasaccharide ($Glc_1Man_9GlcNAc_2$, **3**),[4] which is considered to be a primary ligand for the ER chaperons, calnexin (CNX) and calreticulin (CRT),[5] and obtained the first NMR-based evidence on the specific interaction between CRT and **3** (Fig. 1). In order to gain more precise understanding on the structural requirement for the recognition of CRT/CNX and other lectins involved in glycoprotein quality control, systematic preparations of various high-mannose type glycan chains and their partial structures are required.

2. Results and discussion

As the precursor of the mannose residue II of the target tri- and tetrasaccharides, crystalline 1,3,4,6-tetra-*O*-acetyl-β-D-mannose (**4a**)[6] was chosen (Scheme 1). Pozgay's procedure provided ready access to multigram amounts of this compound from D-mannose with complete avoidance of chromatographic purification. While subsequent treatment with trifluoroacetic anhydride (TFAA)–pyridine in CH_2Cl_2 uneventfully provided **4b**, we faced the technical difficulty of reproducibly obtain-

* Corresponding author. Fax: +81-48-4624680
E-mail address: yukito@postman.riken.go.jp (Y. Ito).

0008-6215/03/$ - see front matter
doi:10.1016/S0008-6215(03)00099-5

ing the corresponding glycosyl bromide **5a**, as non-reproducible results were obtained in its preparation. In any event, obtained, which was occasionally obtained, could be successfully used as a donor for α-mannosylation (with **6**[7]), and *O*-TFA proved to be highly compatible with glycosylation conditions.

Our attention was then turned to *O*-PFP derivative **4c**, which was obtained in quantitative yield by treatment with pentafluoropropionic anhydride (PFPA)[8] and pyridine in CH_2Cl_2. It was then converted to the glycosyl bromide **5b** (HBr–AcOH–Ac_2O, 60–70 °C, 1 day, 95%), which was obtained with an excellent purity.

Glycosylation of **6** with **5b** (1.5 equiv) proceeded under standard conditions (AgOTf, 4A MS/CH_2Cl_2, −20 °C–rt, 3 h) to afford **7** in 76% yield as a pure α-isomer. Although *O*-PFP group was seemingly active as a neighboring group to control the selectivity of glycosylation, explanation by an electronic factor may be more reasonable; *O*-PFP group deactivated the donor and forced the glycosylation to proceed in a stereoelectronically favored α-selective manner.[9] In fact, the electron-withdrawing trichlororacetyl (TCA) group was reported to be inactive as a neighboring group, and the 2-*O*-TCA protected glucosyl donor gave the α-glycoside exclusively.[10]

Deprotection of *O*-PFP (and *O*-TFA) was initially examined using $NaHCO_3$ as a base in aqueous dioxane. Under these conditions, selective removal of *O*-PFP was indeed possible. However, careful examination of the ^{1}H NMR spectrum revealed that substantial acetyl migration occurred, and the product was a ca. 3:1 mixture of **8** and **9** (Table 1). Separation of these compounds proved to be impractical. The use of 1,4-diazabicyclo[2,2,2]octane (DABCO) was found to be successful, although its amount and reaction time should be controlled carefully (entry 2–4). To our delight, treatment with pyridine (10 equiv) in EtOH (ca. 1:60, v/v) afforded **8** in quantitative yield, without any acetyl migration, within the detection limit of 400 MHz ^{1}H NMR (entry 6). Since the reaction proceeded quantitatively and liberated ethyl pentafluoropropionate is volatile (bp 75–76 °C), chromatographic purification was not necessary. Compound **8** was obtained in an analytically pure form simply by evaporating the reaction mixture (Fig. 2). The concentration of pyridine could be reduced (entry 7) or increased (entry 8) without loss of reaction efficiency.

For the subsequent glycosylation, 3-*O*-TFA-protected mannosyl fluoride **10** was used (Scheme 2). The latter was prepared from thioglycoside **11** via trifluoroacetylation (**12**; 95%) and SPh → F exchange under Nicolaou's conditions (NBS–DAST,[11] 53%). For the sake of full characterization, concomitantly formed β-fluoride and bromide were removed at this stage. Glycosylation of **8** was performed by using 1.5 equiv of **10**, in the presence of AgOTf, $SnCl_2$ and 4A MS in CH_2Cl_2 (−20 °C ~ rt, overnight) to give **13** in 88% yield. Subsequent deprotection of 3-*O*-TFA was performed again using pyridine–EtOH to give **14** (quantitative).

Incorporation of terminal α-Glc was achieved by using 3-*O*-acyl-4,6-*O*-benzylidene-2-*O*-*p*-methoxybenzyl-protected donor **16a**, which in turn was prepared from **15**[4] [$(ClCH_2CO)_2O$, pyridine, CH_2Cl_2, 0 °C, 1 h then, rt 10 min; 99%]. Glycosylation with **14** was performed under conditions previously optimized for 3-*O*-pivaloylated donor **16b**[4] (MeOTf, 2,6-di-*tert*-butyl-4-methylpyridine, 4A MS, 1:5 $ClCH_2CH_2Cl$–cyclohexane) to give **17** (81%) as a single isomer.

Deprotection of tri- (**13**) and tetrasaccharide (**17**) was performed in a standard manner. Thus, compound **13**

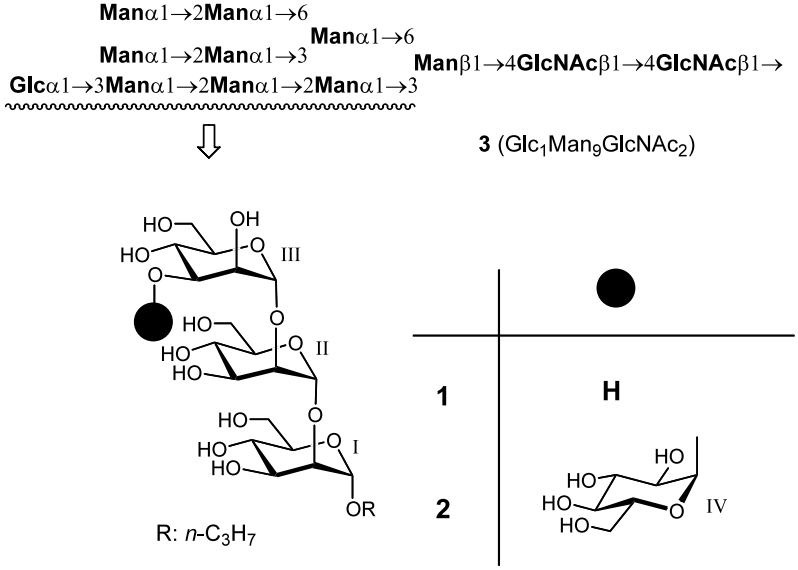
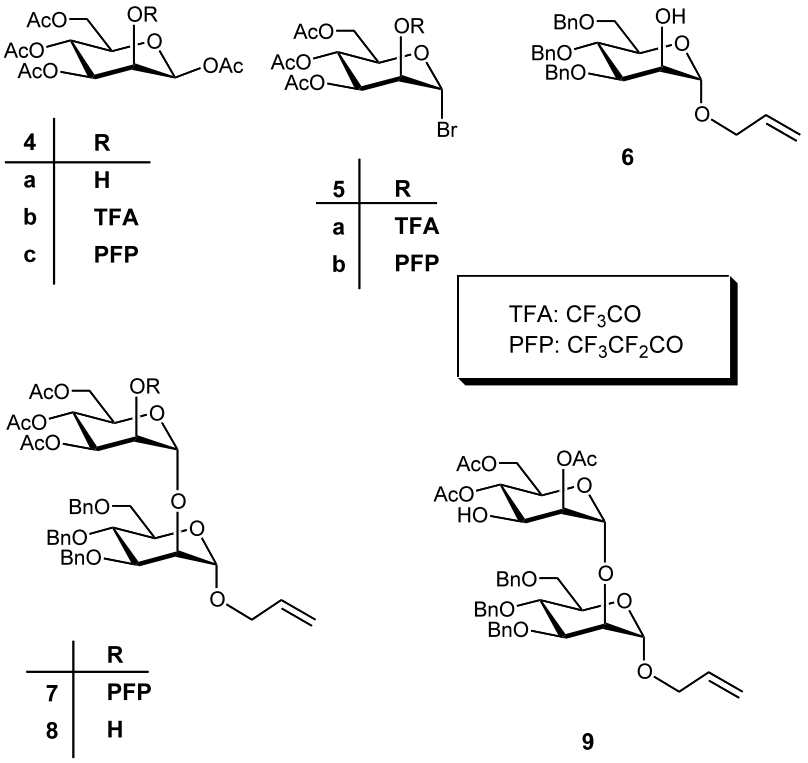


Fig. 1. Structure of high-mannose oligosaccharide associated with chaperon recognition.



Scheme 1.

Table 1
Selective deprotection of **7**

Entry	Base (equiv.)	Solvent	Temperature/time	Yield	**8/9** [a]
1	1N $NaHCO_3$ (11)	AcOEt–dioxane	rt/3 h	98%	3/1
2	DABCO (1)	EtOH	rt/1 h	quant	**8**
3	DABCO (5)	EtOH	rt/40 min	quant	3/1
4	DABCO (20)	EtOH	rt/15 min	93%	2/1
5	thiourea (3)	EtOH	70 °C/overnight	49% [b]	**8**
6	pyridine (10)	EtOH	rt/2.5 h	quant	**8**
7	pyridine (3)	EtOH	rt/6 h	quant	**8**
8	pyridine (89)	EtOH	rt/20 min	quant	**8**

[a] Estimated by ^{1}H NMR spectroscopy (400 MHz).
[b] 41% of **7** was recovered.

was subjected to deacylation (NaOMe–MeOH) followed by debenzylation (H_2, Pd/C, MeOH) to give **1** in quantitative yield. In a similar manner, tetrasaccharide **17** was converted to **2**.

It was demonstrated that previously underrated TFA and PFP esters are useful as hydroxyl protecting groups in oligosaccharide synthesis. These groups were compatible with typical glycosylation conditions and removable with complete preservation of *O*-Ac groups. Since deprotection can be performed in a workup-free manner, they may be particularly suitable in solution-phase polymer-supported oligosaccharide synthesis.[12] Further investigations along these lines are currently ongoing.

3. Experimental

3.1. General methods

Unless otherwise stated, all commercially available solvents and reagents were used without further purification. Anhydrous dichloromethane and MeOH were purchased from Kanto Chemical Co. 1,2-Dichloroethane and cyclohexane were dried over 4A molecular sieves. Optical rotations were measured with a JASCO DIP-370 digital polarimeter, using a 5 cm micro cell. High-resolution fast-atom bombardment mass spectrometry (HRFABMS) was performed on a JOEL JMS-HX-110 mass spectrometer. ^{1}H and ^{13}C

NMR spectra were recorded on a JEOL AL-400 spectrometer for solutions in $CDCl_3$ or D_2O. Chemical shifts are given in ppm and referenced to internal Me_4Si (δ_H 0.00 in $CDCl_3$), $CHCl_3$ (δ_H 7.26 in $CDCl_3$), HDO (δ_H 4.65 in D_2O), or $CDCl_3$ (δ_C 77.00). ^1H NMR assignments were made by first-order analysis of the spectra. Elemental analyses were performed with a Fisons EA1108 instrument on samples extensively dried

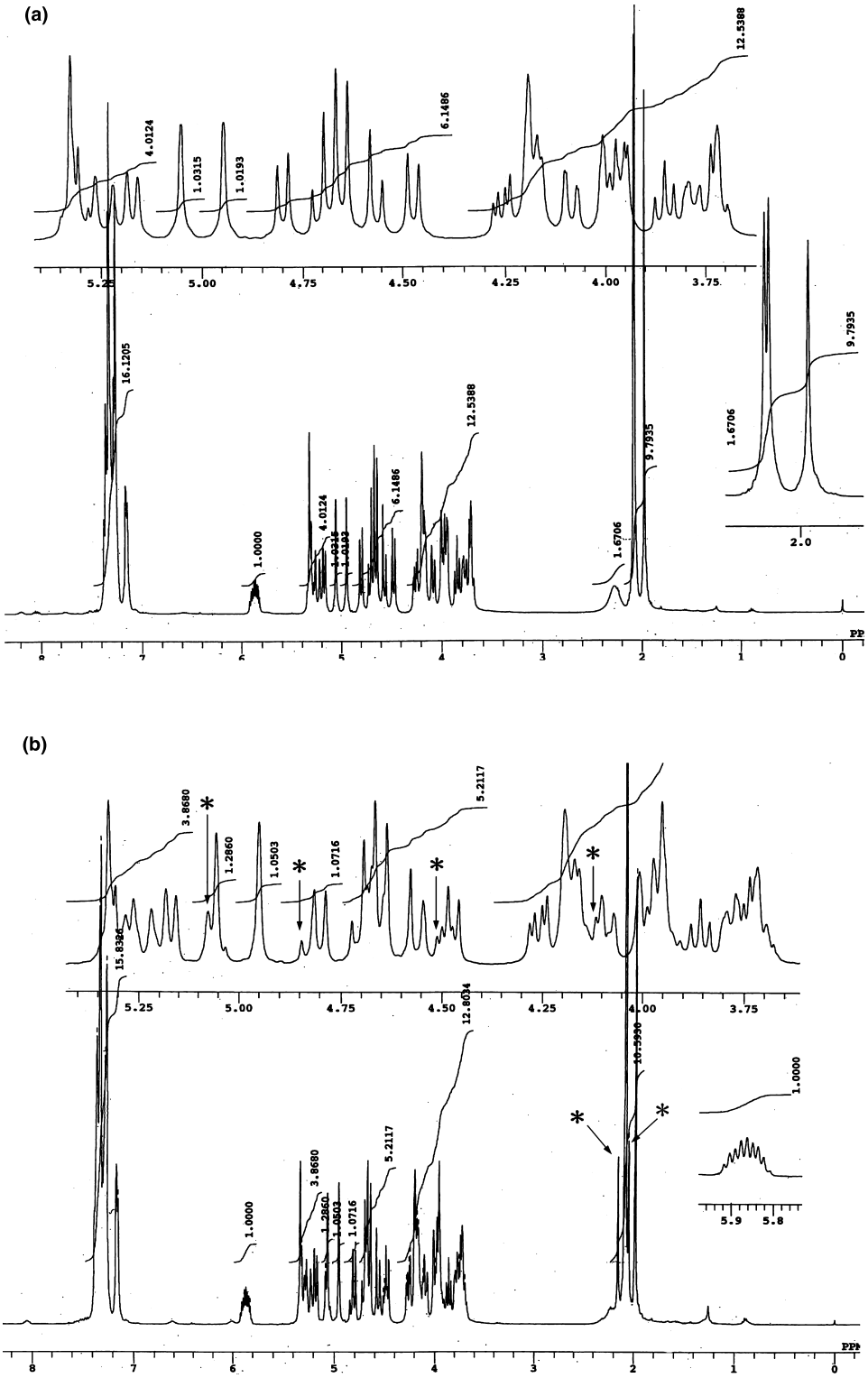
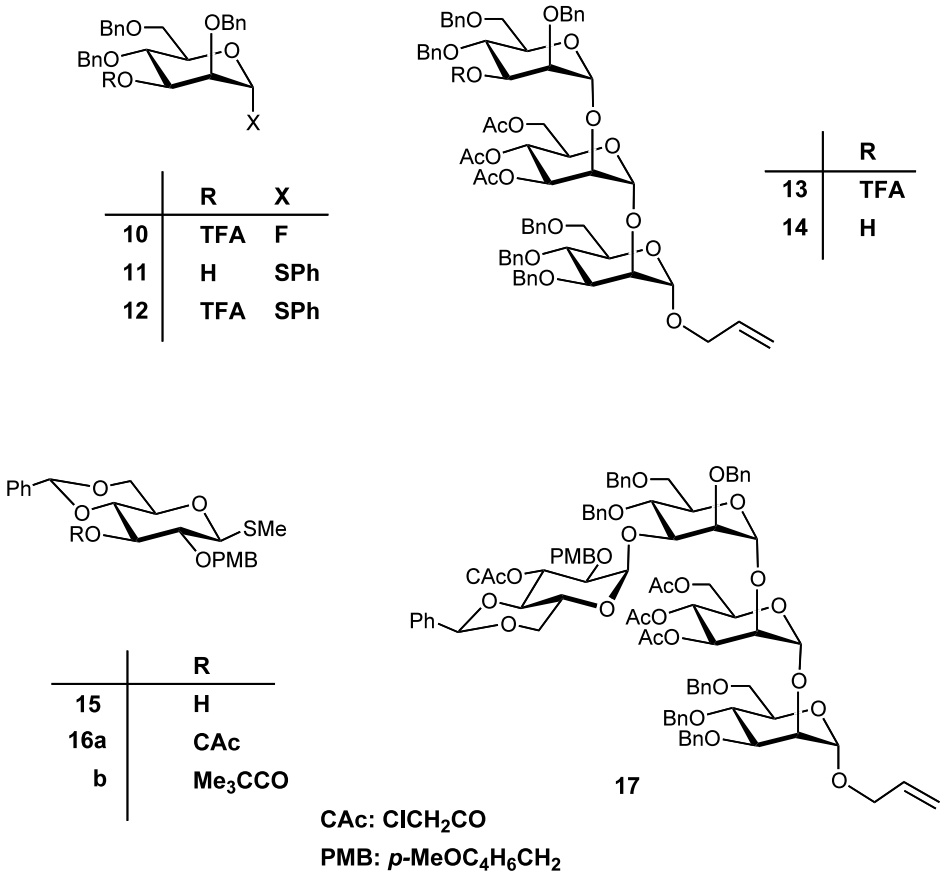


Fig. 2. ^1H NMR of crude **8** obtained by PFP removal of **7** by treatment with pyridine–EtOH (a) or $NaHCO_3$ in aq dioxane–AcOEt (b). Asterisks indicate the peaks derived from **9**.



Scheme 2.

at 50–60 °C over phosphorus pentoxide for 4–5 h in vacuo. TLC was performed on E. Merck precoated plates (20 × 20 cm; layer thickness, 0.25 mm; Silica Gel 60 F254); zones were visualized by spraying with a solution of 90:5:5 (v/v/v) MeOH–*p*-anisaldehyde–concd sulfuric acid with heating at 180 °C for ~0.5 min, and by short-wave UV light, when applicable. Flash column chromatography was performed on Silica Gel 60 (spherical type, particle size 40–100 μm; E. Merck) with the solvent systems specified, and the ratio of solvent systems was given in v/v. Organic extracts were dried over anhyd $MgSO_4$, and solutions were concentrated under diminished pressure below 50 °C.

3.2. 1,3,4,6-Tetra-*O*-acetyl-2-*O*-pentafluoropropionyl-β-D-mannopyranose (4c)

A solution of **4a** (1.00 g, 2.87 mmol) in CH_2Cl_2 (14 mL) was cooled down to ice-water temperature. With stirring pyridine (417 μL, 5.17 mmol) was added. Then, pentafluoropropionic anhydride (923 μL, 4.68 mmol) was added dropwise, and the mixture was stirred at 0 °C for 1 h. The mixture was diluted with AcOEt, and ice-chips were added to the solution. After stirring for 15 min, the layers were separated. The organic layer was washed with ice water, 0.2N HCl, and brine (twice), successively, then it was dried over $MgSO_4$ and concentrated in vacuo. Purification by silica gel column (3:2 hexane–AcOEt) afforded **4c** (1.44 g, quant). ^{1}H NMR ($CDCl_3$): δ 5.94 (s, 1 H, H-1), 5.60 (d, 1 H, *J* 2.9 Hz, H-2), 5.31 (t, 1 H, *J* 9.8 Hz, H-4), 5.23 (dd, 1 H, *J* 2.9, 9.8 Hz, H-3), 4.28 (dd, 1 H, *J* 4.6, 12.7 Hz, H-6), 4.18 (dd, 1 H, *J* 2.2, 12.7 Hz, H-6′), 3.84 (ddd, 1 H, *J* 2.2, 4.64, 9.8 Hz, H-5), 2.11 (s, 3 H, Ac), 2.09 (s, 3 H, Ac), 2.06 (s, 3 H, Ac), 2.01 (s, 3 H, Ac). ^{13}C NMR ($CDCl_3$): 170.49, 169.53, 169.06, 167.98 (4 × C=O), 89.39 (C-1), 73.16 (C-5), 72.60 (C-2), 70.04 (C-3), 64.65 (C-4), 61.45 (C-6), 20.62, 20.57, 20.54, 20.30 (4 × Ac). Anal. Calcd for $C_{17}H_{19}F_5O_{11}$: C, 41.31; H, 3.87; F, 19.22. Found: C, 40.94; H, 3.82; F, 19.10.

3.3. 3,4,6-Tri-*O*-acetyl-2-*O*-pentafluoropropionyl-α-D-mannopyranosyl bromide (5b)

Compound **4c** (552 mg, 11.2 mmol) was mixed with Ac_2O (1.5 mL) and kept at rt for 0.5 h. Then HBr–AcOH solution (3.0 mL) was added, and the mixture was kept at room temperature (rt) for 2 h and at 60–70 °C for 1 day. The resulting mixture was diluted

with AcOEt, stirred with ice-chips, washed with cold water (three times) and cold $NaHCO_3$ and brine, successively, then dried over $MgSO_4$ and concentrated in vacuo to afford crude **5b** (549 mg, 95%). ^{1}H NMR ($CDCl_3$): δ 6.37 (d, 1 H, *J* 1.7 Hz, H-1), 5.79 (dd, 1 H, *J* 3.2, 10.3 Hz, H-3), 5.67 (dd, 1 H, *J* 3.2, 1.7 Hz, H-2), 5.39 (t, 1 H, *J* 10.3 Hz, H-4), 4.31 (dd, 1 H, *J* 3.9, 12.5 Hz, H-6), 4.24 (ddd, 1 H, *J* 2.0, 3.9, 10.3 Hz, H-5), 4.19 (dd, 1 H, *J* 2.0, 12.5 Hz, H-6′), 2.10 (s, 3 H, Ac), 2.07 (s, 3 H, Ac), 1.99 (s, 3 H, Ac). ^{13}C NMR ($CDCl_3$): 170.27, 169.25, 168.87 (3 × C=O), 80.75 (C-1), 75.37 (C-2), 72.89 (C-5), 67.69 (C-3), 64.37 (C-4), 60.82 (C-6), 20.63, 20.52, 20.31 (3 × Ac).

3.4. Allyl 3,4,6-tri-*O*-acetyl-2-*O*-pentafluoropropionyl-α-D-mannopyranosyl-(1 → 2)-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (7)

A mixture of activated 4A MS (500 mg) and AgOTf (106 mg, 0.41 mmol) in CH_2Cl_2 (1 mL) was stirred at −20 °C. A solution of compound **5b** (180 mg, 0.35 mmol) and **6** (114 mg, 0.23 mmol) in CH_2Cl_2 (7 mL) was added dropwise via cannula. The mixture was gradually warmed up to rt over ∼3 h with stirring. The resulting mixture was diluted with AcOEt and stirred with ice-chips and $NaHCO_3$. After 0.5 h, the mixture was filtered through Celite, and the filtrate was washed with cold water and brine, successively. The organic extract was dried over $MgSO_4$, concentrated in vacuo and purified by silica gel column (3:1 hexane–AcOEt) to afford **7** (164 mg, 76%). ^{1}H NMR ($CDCl_3$): δ 7.39–7.25 (m, 13 H, aromatic), 7.19–7.17 (m, 2 H, aromatic), 5.88 (tdd, 1 H, *J* 5.1, 10.5, 17.3 Hz, C*H*=CH$_2$), 5.61 (dd, 1 H, *J* 1.2, 3.2 Hz, H-2^{II}), 5.45 (dd, 1 H, *J* 3.2, 10.3 Hz, H-3^{II}), 5.26 (t, 1 H, *J* 9.5 Hz, H-4^{II}), 5.26 (d, 1 H, *J* 17.3 Hz, CH=C*H*$_2$), 5.19 (d, 1 H, *J* 10.5 Hz, CH=C*H*$_2$), 5.02 (d, 1 H, *J* 1.2 Hz, H-1^{II}), 4.93 (s, 1 H, H-1^{I}), 4.84 (d, 1 H, *J* 11.0 Hz, –C*H*$_2$Ph), 4.77 (d, 1 H, *J* 11.5 Hz, –C*H*$_2$Ph), 4.65 (d, 1 H, *J* 12.7 Hz, –C*H*$_2$Ph), 4.59 (d, 1 H, *J* 11.5 Hz, –C*H*$_2$Ph), 4.56 (d, 1 H, *J* 12.7 Hz, –C*H*$_2$Ph), 4.53 (d, 1 H, *J* 11.0 Hz, –C*H*$_2$Ph), 4.23–4.11 (m, 4 H, H-5^{II}, 6^{II}, 6′^{II}, C*H*$_2$CH=CH$_2$), 4.00–3.95 (m, 3 H, H-2^{I}, 3^{I}, C*H*$_2$CH=CH$_2$), 3.90 (t, 1 H, *J* 9.0 Hz, H-4^{I}), 3.82–3.70 (m, 3 H, H-5^{I}, 6^{I}, 6′^{I}), 2.07 (s, 3 H, Ac), 1.98 (s, 3 H, Ac), 1.97 (s, 3H, Ac). ^{13}C NMR ($CDCl_3$): 170.33, 169.13, 169.07 (3 × C=O), 133.25 (*C*H=CH$_2$), 117.44 (CH$_2$CH=*C*H$_2$), 97.97 (C-1^{II}), 97.50 (C-1^{I}), 79.71 (C-3^{I}), 76.74 (C-2^{I}), 75.28 (*C*H$_2$Ph), 74.76 (C-4^{I}), 73.16 (*C*H$_2$Ph), 73.03 (*C*H$_2$Ph), 72.98 (C-2^{II}), 71.72 (C-5^{I}), 68.88 (C-5^{II}), 68.81 (C-6^{I}), 68.66 (C-3^{II}), 67.98 (*C*H$_2$CH=CH$_2$), 65.13 (C-4^{II}), 61.82 (C-6^{II}), 20.64, 20.59, 20.43 (3 × Ac). Anal. Calcd for $C_{45}H_{49}F_5O_{15}$: C, 58.44; H, 5.34; F, 10.27. Found: C, 58.28; H, 5.36; F, 10.23.

3.5. Allyl 3,4,6-tri-*O*-acetyl-α-D-mannopyranosyl-(1 → 2)-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (8)

Compound **7** (61 mg, 0.066 mmol) was dissolved in EtOH (3.3 mL). Pyridine (53 μL, 0.66 mmol) was added and stirred at rt for 2.5 h. The reaction mixture was concentrated in vacuo to afford **8** (51 mg, quant). ^{1}H NMR ($CDCl_3$): δ 7.30–7.18 (m, 13 H, aromatic), 7.09–7.07 (m, 2 H, aromatic), 5.80 (tdd, 1 H, *J* 5.4, 10.35, 17.3 Hz, C*H*=CH$_2$), 5.25–5.21 (m, 2 H, H-3^{II}, 2^{IV}), 5.17 (d, 1 H, *J* 17.3 Hz, CH=C*H*$_2$), 5.10 (d, 1 H, *J* 10.3 Hz, CH=C*H*$_2$), 4.98 (s, 1 H, H-1^{II}), 4.88 (s, 1 H, H-1^{I}), 4.73 (d, 1 H, *J* 10.7 Hz, –*C*H$_2$Ph), 4.63 (d, 1 H, *J* 12.0 Hz, –C*H*$_2$Ph), 4.58 (d, 2 H, *J* 12.0 Hz, –C*H*$_2$Ph), 4.49 (d, 1 H, *J* 12.0 Hz, –C*H*$_2$Ph), 4.40 (d, 1 H, *J* 10.7 Hz, –C*H*$_2$Ph), 4.18 (dd, 1 H, *J* 4.6, 12.2 Hz, H-6^{II}), 4.12–4.08 (m, 3 H, H-2^{II}, 5 ^{II}, C*H*$_2$CH=CH$_2$), 4.04 (d, 1 H, *J* 12.2 Hz, H-6′^{II}), 3.93–3.89 (m, 3 H, H-2^{I}, 3^{I}, C*H*$_2$CH=CH$_2$), 3.78 (t, 1 H, *J* 9.0 Hz, H-4^{I}), 3.72–3.61 (m, 3 H, H-5^{I}, 6^{I}, 6′^{I}), 2.01 (s, 3 H, Ac), 2.00 (s, 3 H, Ac), 1.90 (s, 3 H, Ac). ^{13}C NMR ($CDCl_3$): 170.45, 169.65, 169.34 (3 × C=O), 133.39 (*C*H=CH$_2$), 117.18 (CH$_2$CH=*C*H$_2$), 101.09 (C-1^{II}), 97.72 (C-1^{I}), 79.55 (C-3^{I}), 76.11 (C-2^{I}), 75.13 (*C*H$_2$Ph), 74.79 (C-4^{I}), 73.11 (*C*H$_2$Ph), 72.50 (*C*H$_2$Ph), 71.76 (C-5^{I}), 71.48 (C-3^{II}), 69.22 (C-2^{II}), 68.96 (C-6^{I}), 68.73 (C-5^{II}), 67.93 (*C*H$_2$CH=CH$_2$), 66.34 (C-4^{II}), 62.49 (C-6^{II}), 21.00, 20.86, 20.76 (3 × Ac). Anal. Calcd for $C_{42}H_{50}O_{14}$: C, 64.77; H, 6.47. Found: C, 64.63; H, 6.54.

3.6. Phenyl 2,4,6-tri-*O*-benzyl-1-thio-3-*O*-trifluoroacetyl-α-D-mannopyranoside (12)

A solution of **11** (747 mg, 1.38 mmol) in CH_2Cl_2 (6.5 mL) was cooled down to ice-water temperature. With stirring pyridine (200 μL, 2.48 mmol) was added. Then, trifluoroacetic anhydride (317 μL, 2.24 mmol) was added dropwise, and the mixture was stirred at 0 °C for 2 h and then at rt for 1 h. The mixture was diluted with AcOEt, and ice-chips were added to the solution. After being stirred for 15 min, the layers were separated. The organic layer was washed with ice-water, 0.2 N HCl, and brine (twice), successively, and then dried over $MgSO_4$ and concentrated in vacuo. Purification by silica gel chromatography (8:1 hexane–AcOEt) afforded **12** (800 mg, 91%). ^{1}H NMR ($CDCl_3$): δ 7.48–7.45 (m, 2 H, aromatic), 7.35–7.24 (m, 16 H, aromatic), 7.15–7.13 (m, 2 H, aromatic), 5.63 (d, 1 H, *J* 1.6 Hz, H-1), 5.33 (dd, 1 H, *J* 2.9, 9.5 Hz, H-3), 4.70 (d, 1 H, *J* 12.0 Hz, –C*H*$_2$Ph), 4.68 (d, 1 H, *J* 11.8 Hz, –C*H*$_2$Ph), 4.64 (d, 1 H, *J* 10.5 Hz, –C*H*$_2$Ph), 4.50 (d, 1 H, *J* 12.0 Hz, –C*H*$_2$Ph), 4.49 (d, 1 H, *J* 10.5 Hz, –C*H*$_2$Ph), 4.47 (d, 1 H, *J* 11.8 Hz, –C*H*$_2$Ph), 4.33 (ddd, 1 H, *J* 1.6, 4.3, 9.5 Hz, H-5), 4.26 (t, 1 H, *J* 9.5 Hz, H-4), 4.18 (dd, 1 H, *J* 1.6, 3.0 Hz, H-2), 3.86 (dd, 1 H, *J* 4.3, 11.1 Hz, H-6), 3.70 (dd, 1 H, *J* 1.6, 11.1 Hz, H-6′). ^{13}C NMR ($CDCl_3$):

84.86 (C-1), 78.36 (C-3), 76.13 (C-2), 75.18 (CH_2Ph), 73.51 (CH_2Ph), 72.80 (C-4), 72.57 (C-5), 72.18 (CH_2Ph), 68.49 (C-6). Anal. Calcd for $C_{35}H_{33}F_3O_6S$: C, 65.82; H, 5.21; F, 8.92; S, 5.02. Found: C, 65.48; H, 5.12; F, 8.93; S, 5.22.

3.7. 2,4,6-Tri-*O*-benzyl-1-thio-3-*O*-trifluoroacetyl-α-D-mannopyranosyl fluoride (10)

To a stirred solution of **12** (730 mg, 1.14 mmol) in CH_2Cl_2 (10 mL) was added DAST (227 μL, 1.71 mmol) and NBS (325 mg, 1.83 mmol) at −40 °C. The mixture was gradually warmed up to −10 °C and stirred overnight. After the reaction was quenched with MeOH, the mixture was diluted with AcOEt and washed with satd $NaHCO_3$, H_2O and brine, successively. The organic extract was dried over $MgSO_4$, concentrated in vacuo, and purified by silica gel chromatography (10:1 hexane–AcOEt) to afford **10** (331 mg, 53%) and the β-isomer (26 mg, 4%). ^{1}H NMR ($CDCl_3$): δ 7.37–7.26 (m, 13 H, aromatic), 7.13–7.10 (m, 2 H, aromatic), 5.62 (dd, 1 H, *J* 2.0, 49.8 Hz, H-1), 5.33 (ddd, 1 H, *J* 1.7, 3.2, 9.6 Hz, H-3), 4.69 (d, 1H, *J* 12.0 Hz, –CH_2Ph), 4.64 (s, 2 H, –CH_2Ph), 4.63 (d, 1 H, *J* 10.6 Hz, –CH_2Ph), 4.52 (d, 1 H, *J* 12.0 Hz, –CH_2Ph), 4.49 (d, 1 H, *J* 10.6 Hz, –CH_2Ph), 4.27 (t, 1 H, *J* 9.8 Hz, H-4), 4.06 (t, 1 H, *J* 2.7 Hz, H-2), 3.96 (ddd, 1 H, *J* 1.7, 3.9, 9.8 Hz, H-5), 3.81 (dd, 1 H, *J* 3.9, 11.2 Hz, H-6), 3.71 (dd, 1 H, *J* 1.7, 11.2 Hz, H-6′). ^{13}C NMR ($CDCl_3$): 105.41 (d, $^1J_{C,F}$ 223.5 Hz, C-1), 77.32 (C-3), 75.16 (CH_2Ph), 73.80 (C-5), 73.62 (CH_2Ph), 73.52 (CH_2Ph), 73.38 (d, *J* 35.0 Hz, C-2), 71.73 (C-4), 67.84 (C-6). Anal. Calcd for $C_{29}H_{28}F_4O_6$: C, 63.50; H, 5.15; F, 13.85. Found: C, 63.50; H, 5.13; F, 13.93.

3.8. Allyl 2,4,6-tri-*O*-benzyl-3-*O*-trifluoroacetyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-*O*-acetyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (13)

A mixture of activated 4A MS (180 mg), AgOTf (39 mg, 0.15 mmol) and $SnCl_2$ (28 mg, 0.15 mmol) in CH_2Cl_2 (0.5 mL) was stirred at −20 °C. A solution of compound **10** (69 mg, 0.125 mmol) and **8** (65 mg, 0.083 mmol) in CH_2Cl_2 (3.5 mL) was added dropwise via cannula. The mixture was allowed to gradually warm up to rt, and it was stirred for overnight. The resulting mixture was diluted with AcOEt and stirred with ice-chips and $NaHCO_3$. After 0.5 h, the mixture was filtered through Celite, and the filtrate was washed successively with cold water and brine. The organic extract was dried over $MgSO_4$, concentrated in vacuo, and purified by silica gel chromatography (2:1 hexane–AcOEt) to afford **13** (99 mg, 88%). ^{1}H NMR ($CDCl_3$): δ 7.37–7.07 (m, 30 H, aromatic), 5.86 (tdd, 1 H, *J* 5.6, 10.5, 17.1 Hz, C*H*=CH_2), 5.43 (dd, 1 H, *J* 3.2, 9.3 Hz, H-3^{III}), 5.36 (dd, 1 H, *J* 2.9, 9.3 Hz, H-3^{II}), 5.31 (t, 1 H, *J* 9.3 Hz, H-4^{II}), 5.27 (d, 1 H, *J* 1.7 Hz, H-1^{III}), 5.23 (dd, 1 H, *J* 1.2, 17.1 Hz, CH=CH_2), 5.16 (dd, 1 H, *J* 1.2, 10.5 Hz, CH=CH_2), 5.01 (d, 1 H, *J* 1.7 Hz, H-1^{II}), 4.93 (d, 1 H, *J* 1.5 Hz, H-1^{I}), 4.80 (d, 1 H, *J* 10.7 Hz, –CH_2Ph), 4.69–4.34 (m, 11 H, –CH_2Ph), 4.18–4.09 (m, 6 H, H-5^{II}, 6^{II}, 6′^{II}, 4^{III}, 5^{III}, CH_2CH=CH_2), 4.02–3.88 (m, 5 H, H-2^{I}, 3^{I,} 2^{II}, 2^{III}, CH_2CH=CH_2), 3.83 (t, 1 H, *J* 9.0 Hz, H-4^{I}), 3.77–3.55 (m, 5 H, H-5^{I}, 6^{I}, 6′^{I}, 6^{III}, 6′^{III}), 1.99 (s, 3 H, Ac), 1.97 (s, 3 H, Ac), 1.95 (s, 3 H, Ac). ^{13}C NMR ($CDCl_3$): 170.78, 169.39, 169.24 (3 × C=O), 133.42 (*C*H=CH_2), 117.16 (CH_2CH=*C*H_2), 100.01 (C-1^{III}), 98.79 (C-1^{II}), 97.75 (C-1^{I}), 77.70 (C-3^{III}), 76.16 (C-2^{I}), 75.96 (C-5^{III}), 75.15, 74.97 (2 × *C*H_2Ph), 74.85 (C-4^{I}, 2^{II}), 74.34, 73.06 (2 × *C*H_2Ph), 72.83 (C-4^{III}), 72.71, 72.12 (2 × *C*H_2Ph), 71.92 (C-2^{III}), 71.71 (C-5^{I}), 70.30 (C-3^{II}), 69.00 (C-6^{I}), 68.78 (C-5^{II}), 68.59 (C-6^{III}), 67.92 (*C*H_2CH=CH_2), 66.43 (C-4^{II}), 62.14 (C-6^{II}), 20.90, 20.75, 20.69 (3 × Ac). Anal. Calcd for $C_{71}H_{77}F_3O_{20}$: C, 65.23; H, 5.94; F, 4.36. Found: C, 64.98; H, 5.95; F, 4.29.

3.9. Allyl 2,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-*O*-acetyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (14)

Compound **13** (73 mg, 0.054 mmol) was dissolved in EtOH (3 mL). Pyridine (49 μL, 0.60 mmol) was added, and the mixture was stirred at rt for 2.5 h and then concentrated in vacuo to afford **14** (65 mg, quant). ^{1}H NMR ($CDCl_3$): δ 7.36–7.12 (m, 30 H, aromatic), 5.86 (tdd, 1 H, *J* 5.6, 10.5, 17.1 Hz, C*H*=CH_2), 5.35 (dd, 1 H, *J* 2.9, 9.5 Hz, H-3^{II}), 5.32 (d, 1 H, *J* 2.0 Hz, H-1^{III}), 5.27 (t, 1 H, *J* 9.0 Hz, H-4^{II}), 5.23 (dd, 1 H, *J* 1.2, 17.1 Hz, CH=CH_2), 5.16 (dd, 1 H, *J* 1.2, 10.5 Hz, CH=CH_2), 4.99 (s, 1 H, H-1^{II}), 4.93 (d, 1 H, *J* 1.5 Hz, H-1^{I}), 4.83 (d, 1 H, *J* 10.5 Hz, –CH_2Ph), 4.80 (d, 1 H, *J* 10.0 Hz, –CH_2Ph), 4.71 (d, 1 H, *J* 11.7 Hz, –CH_2Ph), 4.62 (d, 1 H, *J* 12.2 Hz, –CH_2Ph), 4.60 (d, 1 H, *J* 12.2 Hz, –CH_2Ph), 4.57 (d, 1 H, *J* 11.7 Hz, –CH_2Ph), 4.55 (d, 1 H, *J* 12.2 Hz, –CH_2Ph), 4.50 (d, 1 H, *J* 11.7 Hz, –CH_2Ph), 4.47 (d, 1 H, *J* 10.0 Hz, –CH_2Ph), 4.44 (d, 1 H, *J* 10.5 Hz, –CH_2Ph), 4.38 (d, 1 H, *J* 12.2 Hz, –CH_2Ph), 4.18–4.03 (m, 6 H, H-5^{II}, 6^{II}, 6′^{II}, 2^{III}, 5^{III}, CH_2CH=CH_2), 3.97–3.61 (m, 12 H, H-2^{I}, 3^{I}, 4^{I}, 5^{I}, 6^{I}, 6′^{I}, 2^{II}, 3^{III}, 4^{III}, 6^{III}, 6′^{III}, CH_2CH=CH_2), 1.99 (s, 6 H, Ac), 1.96 (s, 3 H, Ac). ^{13}C NMR ($CDCl_3$): 170.65, 169.90, 169.40 (3 × C=O), 133.47 (*C*H=CH_2), 117.13 (CH_2CH=*C*H_2), 100.15 (C-1^{III}), 98.66 (C-1^{II}), 97.80 (C-1^{I}), 79.27 (C-3^{I}), 77.95 (C-4^{III}), 76.44 (C-4^{I}), 76.32 (C-2^{I}, 5^{III}), 75.15 (*C*H_2Ph), 74.84 (C-2^{II}), 74.80, 73.18, 73.04, 72.61, 71.97 (5 × *C*H_2Ph), 71.64 (C-2^{III}, 5^{I}), 71.42 (C-3^{III}), 70.43 (C-3^{II}), 69.32 (C-6^{III}), 69.05 (C-6^{I}), 68.71 (C-5^{II}), 67.93 (*C*H_2CH=CH_2), 66.60 (C-4^{II}), 62.39 (C-6^{II}), 20.99, 20.80 (3 × Ac). Anal. Calcd for $C_{69}H_{78}O_{19}$: C, 68.41; H, 6.49. Found: C, 68.34; H, 6.51.

3.10. Propyl α-D-mannopyranosyl-(1→2)-α-D-mannopyranosyl-(1→2)-α-D-mannopyranoside (1)

Compound **14** (33 mg, 0.024 mmol) was dissolved in MeOH (3 mL). NaOMe–MeOH (28%, 20 μL) was added, and the mixture was stirred at rt for 5.5 h, neutralized with Amberlyst 15 (H^+), and then concentrated in vacuo. The residue was hydrogenated over $Pd(OH)_2$ (28 mg) in MeOH (3 mL) under atmospheric pressure for overnight. The catalyst was filtered off, and the filtrate was concentrated in vacuo. The residue was purified by gel filtration (Sephadex LH20, H_2O) to afford **1** (13 mg, quant). ^{1}H NMR (D_2O, *t*-BuOH at δ 1.24): δ 5.29 (s, 1 H, H-1^{II}), 5.09 (s, 1 H, H-1^{I}), 5.03 (s, 1 H, H-1^{III}), 4.10 (s, 1 H, H-2^{II}), 4.06 (t, 1 H, *J* 1.6 Hz, H-2^{III}), 3.53–3.47 (m, 1 H, CH_2CH$_2$CH$_3$), 1.60 (q, 2 H, *J* 7.2 Hz, CH$_2$CH_2CH$_3$), 0.90 (t, 3 H, *J* 7.2 Hz, CH$_2$CH$_2$CH_3). ^{13}C NMR (D_2O, *t*-BuOH at δ 30.3): 102.75 (C-1^{III}), 101.20 (C-1^{II}), 98.46 (C-1^{I}), 79.57 (C-2^{I}), 79.20 (C-2^{II}), 73.83 (C-5^{I}, 5^{II}), 73.27 (C-5^{III}), 70.90 (C-3^{I}), 70.86 (C-3^{II}), 70.55 (C-2^{III}, 3^{III}), 70.22 (*C*H$_2$CH$_2$CH$_3$), 67.68 (C-4^{I}), 67.58 (C-4 ^{II}), 67.45 (C-4^{III}), 61.73 (C-6 ^{I}, 6 ^{II}), 61.53 (C-6^{III}), 22.62 (CH$_2$*C*H$_2$CH$_3$), 10.63 (CH$_2$CH$_2$*C*H$_3$). HRFABMS: Calcd for $C_{21}H_{39}O_{16}$ $[M+H]^+$: 547.2238. Found: 547.2256.

3.11. Methyl 4,6-*O*-benzylidene-3-*O*-chloroacetyl-2-*O*-*p*-methoxybenzyl-1-thio-β-D-mannopyranoside (16a)

A solution of **15** (767 mg, 1.83 mmol) in CH_2Cl_2 (9 mL) was cooled down to ice-water temperature. Pyridine (266 μL, 3.30 mmol) was added with stirring. Then, chloroacetic anhydride (510 mg, 2.98 mmol) was added, and the mixture was stirred at 0 °C for 1 h and rt for 10 min. The mixture was diluted with AcOEt, and ice-chips were added to the solution. After being stirred for 15 min, the layers were separated. The organic layer was successively washed with ice-water, 0.2 N HCl, and brine (twice) and then dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by silica gel chromatography (3:1 hexane–AcOEt) to afford **16a** (896 mg, 99%). ^{1}H NMR ($CDCl_3$): δ 7.42–7.32 (m, 5 H, aromatic), 7.25 (d, 2 H, *J* 8.7 Hz, aromatic), 6.89 (d, 2 H, *J* 8. 7 Hz, aromatic), 5.45 (s, 1 H, benzylidene), 5.34 (t, 1 H, *J* 9.5 Hz, H-3), 4.80 (d, 1 H, *J* 10.7 Hz, –CH_2Ph), 4.57 (d, 1 H, *J* 10.7 Hz, –CH_2Ph), 4.53 (d, 1 H, *J* 9.5 Hz, H-1), 4.36 (dd, 1 H, *J* 4.9, 10.3 Hz, H-6), 3.93 (d, 1 H, *J* 14.9 Hz, CH_2Cl), 3.80 (d, 1 H, *J* 14. 9 Hz, CH_2Cl), 3.80 (s, 3 H, OMe), 3.74 (t, 1 H, *J* 10.3 Hz, H-6′), 3.61 (t, 1 H, *J* 9.5 Hz, H-4), 3.55–3.50 (m, 1 H, H-5), 3.51 (t, 1 H, *J* 9.5 Hz, H-2), 2.27 (s, 3 H, SMe). ^{13}C NMR ($CDCl_3$): 165.95 (C=O), 101.22 (benzylidene), 86.39 (C-1), 78.60 (C-2), 78.35 (C-4), 75.97 (C-3), 74.79 (*C*H$_2$Ph), 70.14 (C-5), 68.47 (C-6), 55.30 (OMe), 40.68 (*C*H$_2$Cl), 13.61 (SMe). Anal. Calcd for $C_{24}H_{27}ClO_7S$: C, 58.24; H, 5.50; Cl, 7.16; S, 6.48. Found: C, 57.91; H, 5.43; Cl, 7.34; S, 6.95.

3.12. Allyl 4,6-*O*-benzylidene-3-*O*-chloroacetyl-2-*O*-*p*-methoxybenzyl-α-D-mannopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-3-*O*-α-D-mannopyranosyl-(1→2)-3,4,6-tri-*O*-acetyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (17)

A mixture of compound **14** (32 mg, 0.026 mmol), compound **16a** (39 mg, 0.079 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP, 81 mg, 0.40 mmol) and activated 4A MS (400 mg) in $ClCH_2CH_2Cl$ (1.5 mL) and cyclohexane (7.5 mL) was stirred at rt for 0.5 h, and 1 M MeOTf in $ClCH_2CH_2Cl$ (0.4 mL, 0.40 mmol) was then added. The reaction mixture was stirred at 50 °C for 8 h and then quenched with triethylamine (0.6 mL) and diluted with AcOEt. The mixture was filtered through Celite, and the filtrate was washed with satd $NaHCO_3$ and brine. The organic extract was dried over $MgSO_4$, concentrated in vacuo and purified by PTLC (5:1 toluene–AcOEt) to afford **17** (35.0 mg, 81%). ^{1}H NMR ($CDCl_3$): δ 7.44–7.12 (m, 35 H, aromatic), 7.04 (d, 2 H, *J* 8.6 Hz, aromatic), 6.76 (d, 2 H, *J* 8.6 Hz, aromatic), 5.86 (tdd, 1 H, *J* 5.6, 10.5, 17.1 Hz, C*H*=CH$_2$), 5.72 (t, 1 H, *J* 9.5 Hz, H-3^{IV}), 5.42 (s, 1 H, benzylidene), 5.32 (s, 4 H, H-3^{II}, 4^{II}, 1^{III}, 4^{III}), 5.23 (dd, 1 H, *J* 1.2, 17.1 Hz, CH=CH_2), 5.16 (dd, 1 H, *J* 1.2, 10.5 Hz, CH=CH_2), 4.94 (s, 2 H, H-1^{I}, 1^{II}), 3.75 (s, 3 H, OMe), 2.00 (s, 3 H, Ac), 1.95 (s, 3 H, Ac), 1.86 (s, 3 H, Ac). ^{13}C NMR ($CDCl_3$): 170.59, 169.47, 169.30 (3 × C=O), 133.50 (*C*H=CH$_2$), 117.11 (CH$_2$CH=*C*H$_2$), 101.35 (benzylidene), 100.43 (C-1^{III}), 99.47 (C-1^{II}), 99.07 (C-1^{IV}), 97.82 (C-1^{I}), 75.18 (*C*H$_2$PhOMe), 73.11, 73.05, 72.39, 72.19, 71.99 (6 × *C*H$_2$Ph), 72.60 (C-3^{IV}), 70.46 (C-3^{II}), 69.39 (C-6^{III}), 69.07 (C-6^{I}), 68.71 (C-6^{IV}), 68.71 (C-5^{II}), 67.96 (*C*H$_2$CH=CH$_2$), 66.33 (C-4^{II}), 62.44 (C-6^{II}), 55.26 (OMe), 40.87 (CH$_2$Cl), 20.85, 20.80 (3 × Ac). HRFABMS Calcd for $C_{92}H_{102}ClO_{26}$ $[M+H]^+$: 1657.6348. Found: 1657.6392.

3.13. Propyl α-D-mannopyranosyl-(1→3)-α-D-mannopyranosyl-(1→2)-α-D-mannopyranosyl-(1→2)-α-D-mannopyranoside (2)

Compound **17** (29 mg, 0.017 mmol) was hydrogenated over $Pd(OH)_2$ (28 mg) in 80% aq AcOH (5 mL) and MeOH (3 mL) under atmospheric pressure overnight. The catalyst was filtered off, and the filtrate was concentrated in vacuo. The residue was dissolved in MeOH (4.5 mL) a solution of 28% NaOMe–MeOH (28 μL) was added. The mixture was stirred at rt for 2.5 h, neutralized with Amberlyst 15 (H^+), and concentrated in vacuo. The residue was purified by gel filtration (Sephadex LH20, H_2O) to afford **2** (13 mg, quant). ^{1}H NMR (D_2O, *t*-BuOH at δ 1.24): δ 5.29 (s, 1 H, H-1^{II}),

5.25 (d, 1 H, *J* 3.2 Hz, H-1^{IV}), 5.10 (s, 1 H, H-1^{I}), 5.03 (s, 1 H, H-1^{III}), 4.24 (s, 1 H, H-2^{III}), 4.11 (s, 1 H, H-2^{II}), 1.61 (q, 2 H, *J* 7.1 Hz, $CH_2CH_2CH_3$), 0.91 (t, 3 H, *J* 7.1 Hz, $CH_2CH_2CH_3$). ^{13}C NMR (D_2O, *t*-BuOH at δ 30.3): 102.73 (C-1^{III}, $^1J_{CH}$ 170.8 Hz), 101.29 (C-1^{II}, $^1J_{CH}$ 172.3 Hz), 101.03 (C-1^{IV}, $^1J_{CH}$ 171.5 Hz), 98.56 (C-1^{I}, $^1J_{CH}$ 171.7 Hz), 79.62 (C-2^{I}), 79.26 (C-2^{II}), 78.98 (C-3^{III}), 73.93, 73.45, 73.33, 72.98 (C-5^{I}, 5^{II}, 5^{III}, 5^{IV}), 70.92 (C-2^{IV}), 70.61, 70.42 (C-3^{I}, 3^{IV}), 70.34 (C-2^{III}), 70.28 ($CH_2CH_2CH_3$), 67.74, 67.64, 66.81 (C-4^{I}, 4^{III}, 4^{IV}), 61.79, 61.65, 61.57, 61.34 (C-6^{I}, 6^{II}, 6^{III}, 6^{IV}), 22.61 ($CH_2CH_2CH_3$), 10.61 ($CH_2CH_2CH_3$). HRFABMS Calcd for $C_{27}H_{49}O_{21}$ $[M+H]^+$: 709.2766. Found: 709.2798.

Acknowledgements

We thank Dr Teiji Chihara and his staff for elemental analyses and Ms. Akemi Takahashi for technical assistance. This work was partially supported by Grant-in-Aid for Scientific Research from Japan Society for the Promotion of Science (Grant No. 13480191).

References

1. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999; p 164.
2. Demchenko, A. V.; Rousson, E.; Boons, G.-J. *Tetrahedron Lett*. **1999**, *40*, 6523–6526.
3. (a) High, S. H.; Lecomte, F. J. L.; Russel, S. J.; Abell, B. M.; Oliver, J. D. *FEBS Lett*. **2000**, *476*, 38–41;
(b) Cabral, C. M.; Liu, Y.; Sifers, R. N. *Trends Biochem. Res*. **2001**, *26*, 619–624;
(c) Braakman, I. *EMBO Rep*. **2001**, *2*, 666–668.
4. (a) Matsuo, I.; Wada, M.; Manabe, S.; Yamaguchi, Y.; Otake, K.; Kato, K.; Ito, Y. *J. Am. Chem. Soc*. in press;
(b) Matsuo, I.; Wada, M.; Ito, Y. *Tetrahedron Lett*. **2002**, *43*, 3723–3725.
5. (a) Helenius, A.; Aebi, M. *Science* **2001**, *291*, 2364–2369;
(b) Spiro, R. G. *J. Biol. Chem*. **2000**, *46*, 35657–35660;
(c) Petrascu, S. M.; Branza-Nichita, N.; Negroiu, G.; Petrescu, A. J.; Dwek, R. A. *Biochemistry* **2000**, *39*, 5229–5237;
(d) For a crystal structure of CNX, see: Scrag, J. D.; Bergeron, J. J. M.; Li, Y.; Borisova, S.; Hahn, M.; Thomas, D. Y.; Cygler, M. *Mol. Cell* **2001**, *8*, 633–644.
6. Pozsgay, V.; Glaudemans, C. P. J.; Robbins, J. B.; Scheneerson, R. *Carbohydr. Res*. **1992**, *48*, 10249–10264.
7. Ogawa, T.; Nukada, T. *Carbohydr. Res*. **1985**, *136*, 135–152.
8. Kezic, S.; Jakasa, I.; Wenker, M. A. M.; Boogaard, P. J.; Monster, A. C.; de Wolff, F. A. *J. Chromatogr. B* **2000**, *749*, 265–274.
9. Paulsen, H. *Angew. Chem., Int. Ed. Engl*. **1982**, *21*, 155–173.
10. Köpper, S.; Zehavi, U. *Carbohydr. Res*. **1989**, *193*, 296–302.
11. Nicolaou, K. C.; Dolle, R. E.; Papahatjis, D. P.; Randall, J. L. *J. Am. Chem. Soc*. **1984**, *106*, 4189–4192.
12. (a) Seeberger, P. H.; Hasse, W.-C. *Chem. Rev*. **2000**, *100*, 4349–4393;
(b) Ito, Y.; Manabe, S. *Chem. Eur. J*. **2002**, *8*, 3077–3084.