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Four-component one-pot synthesis of a branched *manno*-pentasaccharide: *tert*-butyldiphenylsilyl ether as an in situ removable carbohydrate-protecting group

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ABSTRACT

A branched mannose-pentasaccharide was synthesized in a convergent one-pot sequence involving chemo- and regioselective glycosylations of suitable acceptors and in situ removal of *tert*-butyldiphenylsilyl group. The process demonstrated that a combination of TMSOTf and TfOH can be used as an effective reagent for the fast and selective in situ de-protection of *tert*-butyldiphenylsilyl group, and also serve as part of the promoter system for the subsequent glycosylation reaction.

1. Introduction

Lectins are proteins having high binding specificity towards specific mono-, oligo- and poly-saccharides. Recent X-ray studies[1] of methyl α-D-mannopyranoside bound lectin, isolated from *Musa paradisiaca*, showed it contains, unlike other lectins of the same class, two mannose specific primary binding sites (PI and PII). Modelling studies also revealed that the two non-reducing ends of a branched α-*manno*-pentasaccharide ({α-D-Man*p*-(1→3)-α-D-Man*p*-(1→6)-[α-D-Man*p*-(1→6)-α-D-Man*p*-(1→3)]-α-D-Man*p*}) could effectively bind with the two primary sites PI and PII of the lectin, providing a structural explanation for the lectin's specificity for branched α-mannans only. In order to confirm the hypothesis and to study the X-ray crystallographic structure of oligosaccharide–lectin complex, conformationally locked α-benzyl glycoside of the *manno*-pentasaccharide (Fig. 1) was synthesized using a rapid and convenient synthetic strategy.

A number of one-pot glycosylation[2] approaches have been explored during the past years to minimize the overall time of the synthesis and to circumvent tedious chromatographic purification of multiple synthetic intermediates. Synthesis of oligosaccharides is often complex because of the presence of multiple hydroxyl groups and the possibility to produce stereoisomers during the glycosylation step. Many one-pot syntheses of oligosaccharides rely on differences in reactivity of the anomeric groups.[3] Pre-activation[4] or chemoselective activation[5] of the donor in presence of an acceptor also enables rapid assembly of oligosaccharides; a well established two directional glycosylation strategy. Regioselective glycosylation[6] depends on the reactivity of unprotected hydroxyl groups present in a glycosyl acceptor thus glycosylation occurs at the most reactive hydroxyl group. When the reactivity of hydroxyl groups is similar, selective protection/de-protection steps become important to avoid formation of undesired products. Thus, a major limitation of these methods is that the glycosyl acceptors cannot carry hydroxyl groups of similar reactivity, which can be avoided through in situ removal of protecting groups.[7] In this communication we described an efficient one-pot synthesis of the *manno*-pentasaccharide involving sequential chemo- and regioselective glycosylation of suitably protected acceptors, in situ removal of 6-*O*-*tert*-butyldiphenylsilyl protecting group by TMSOTf/TfOH followed by a regioselective glycosylation to form the protected target compound without purification of intermediates.

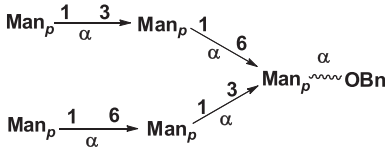

Fig. 1. Branched *manno*-pentasaccharide.

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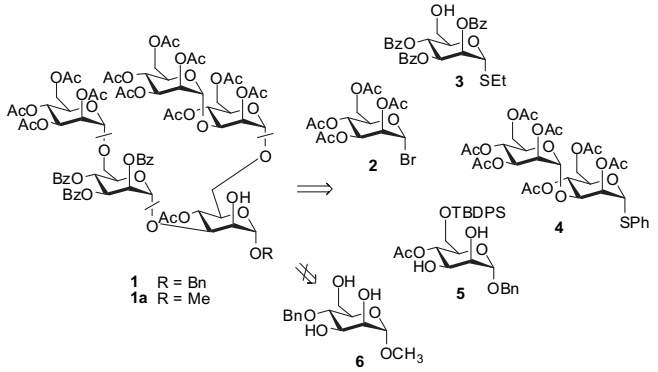
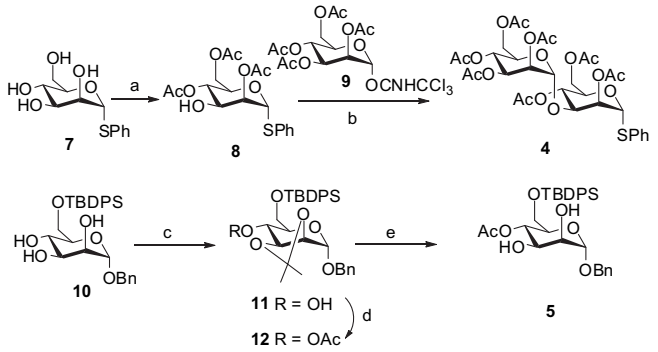
2. Results and discussion

Retrosynthetic analysis indicated that the mannose pentamer could be obtained by condensation of four moieties (Scheme 1). Building blocks **2** and **3** were prepared by literature[8,9] procedures and synthetic strategy of the building blocks **4** and **5** starting from phenyl thioglycoside[10] (**7**) and benzyl mannopyranoside[11] (**10**), respectively, are described in Scheme 2. The structures of all new products were well supported by spectroscopic and analytical data.



Scheme 1. Retrosynthetic analysis for the pentasaccharide.



Scheme 2. Synthesis of building blocks **4** and **5**. Reagents and conditions: (a) $CH(OCH_3)_3$, CSA, DMF, 10 min; 80% AcOH, 35 °C, 45 min; AcCl/Py/−40 °C, 30% based on **7**; (b) TMSOTf, CH_2Cl_2, −20 °C, 15 min, 85%; (c) 2,2-dimethoxypropane, *p*-TsOH, DMF, 12 h, 82%; (d) Ac_2O, Pyridine, 6 h, 95%; (e) 80% AcOH, 80 °C, 45 min, 75%.

Phenyl thioglycoside **7** first treated with triethylorthoacetate in presence of camphorsulfonic acid (CSA) as catalyst produced 2,3:4,6-di-*O*-orthoester, in situ ring opening of which gave 2,4- and 2,6-acyl protected thioglycosides nearly in 1:1 ratio.[12] Selective acetylation of the primary hydroxyl[13] in presence of secondary hydroxyl groups was then carried out by treating the mixture with acetyl chloride in pyridine at −40 °C to produce triacetylated phenyl thiomannopyranoside (**8**) in 30% overall yield after flash chromatography. Coupling of trichloroacetimidate donor[14] (**9**) with acceptor **8** was achieved by chemoselective activation of the former by TMSOTf[15] in CH_2Cl_2 at −20 °C to produce compound **4** in 85% yield. Neither self-condensation product of the thioglycosides nor β-stereoisomer was detected in the reaction mixture.

Initial attempts were to assemble the pentasaccharide using triol **6**[16] as an acceptor via regioselective 6-O-glycosylation with disaccharide donor **4**, was not successful because of the formation of both the 6-*O* and 3-*O* glycosylated products. This is probably due to the increased reactivity of the 3-OH group induced by the presence of free 2-OH group.[17] Different reaction conditions, including variation in the solvents (Et_2O, CH_2Cl_2, Toluene), and various promoter systems (TfOH/NIS,[18] AgOTf/NIS,[19] MeOTf,[20] DMTST,[21] $HgSO_4$[22]) were tested to improve the regioselectivity but without success.

The alternative approach employed diol acceptor **5**, prepared starting from the 6-*O* silylated benzyl mannoside **10** via 2,3-isopropylidene formation, acetylation of the remaining 4-OH group followed by removal of isopropylidene group using aqueous acetic acid. Using those already established building blocks (**4** and **5**) together with readily accessible acetobromomannose **2** and the benzoylated 6-OH thioethyl mannoside **3**, the assembly of the protected target **1** was then carried out in a one-pot sequence.

Chemoselective glycosylation of acetobromomannose **2** (1.1 equiv) and thioethyl acceptor **3** (1.0 equiv) at −20 °C in the presence of AgOTf[23] furnished disaccharide **13**. The thioethyl donor disaccharide **13** was then activated in situ by addition of NIS. Subsequent addition of diol acceptor **5** (1.0 equiv) produced regioselectively 3-*O*-glycosylated trisaccharide **14**.

All linkages and structure were established by COSY, gHSQC, HMBC and NOESY experiments. Strong correlation between H^B-1 and C^A-3, and the absence of a cross peak linking H^B-1 and C^A-2 in HMBC (Fig. 2) indicated that regioselective α-glycosylation had taken place at the *O*-3 position.

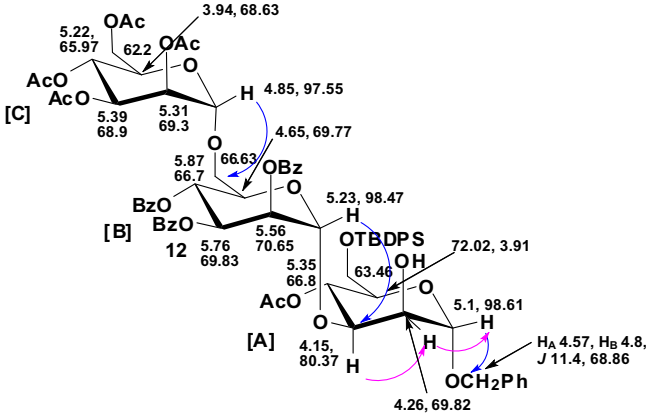
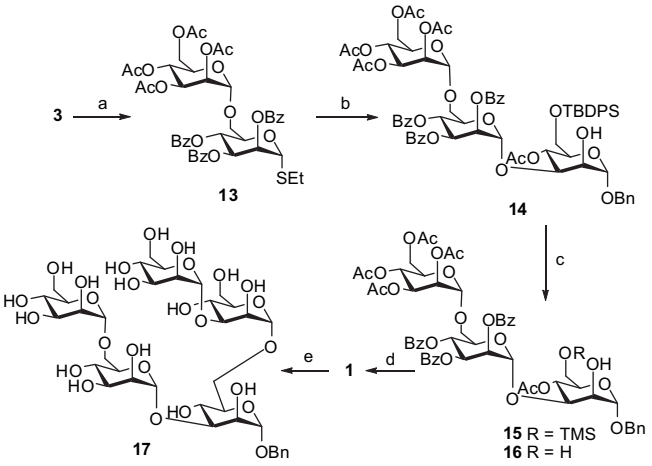


Fig. 2. Important correlations of **14** [HMBC (→), COSY (→)].

Removal of the 6-*O*-*tert*-butyldiphenylsilyl group was achieved rapidly (within 5 min) by adding TMSOTf[24] (1.5 equiv) and TfOH (2.0 equiv) at a slightly higher temperature (−5 °C) leading to diol trisaccharide acceptor **16**. Then, disaccharide thiophenyl donor **4** (1.0 equiv) together with NIS (2.5 equiv) was added into the reaction mixture. TfOH already present in the reaction mixture activated thioglycosides **4** and glycosylation proceeded through the primary 6-OH group producing the desired branched pentasaccharide **1** in 30% overall yield after column chromatography. Formation of compound **1** was characterized by ^{13}C NMR, HRMS and as well as by ^1H NMR. Traces of impurity could be detected in the ^1H NMR. Finally, de-acetylation/benzoylation was conducted at room temperature in ammonia-saturated methanol yielding **17** in good yield (Scheme 3).

The plausible mechanism for the desilylation of **14** is depicted in Fig. 3. In a separate experiment, compound **14** was first treated with TMSOTf, then with TfOH followed by the addition of anhydrous Et_3N (with in 2–3 min) to quench the reaction. HR ESI-MS of this reaction mixture indicated the presence of acceptor trisaccharide **16** along with *O*-6 trimethylsilylated trisaccharide **15** only. Acidic condition is sufficient for the cleavage of *tert*-butyldiphenylsilyl ether **14**, however longer reaction time and high reaction temperature may be required. TMSOTf generates an equilibrium[25] between **14** and TMSylated cation (B), and thus it activates TBDPSOR (**14**) and transforms it to acid-labile TMSOR **15** through heterolytic fission and TfOH acid cleavage.



Scheme 3. Synthesis of pentasaccharide **17**. Reagents and conditions: (1) One-pot sequence. (a) **2**, AgOTf, CH_2Cl_2, −20 °C, 15 min; (b) **5**, NIS, CH_2Cl_2, −20 °C, 20 min; (c) TMSOTf, −5 °C to 0 °C, 5 min, TfOH; (d) **4**, NIS, −20 °C, 15 min, 30% overall yield. (2) De-protection of **1**: (e) NH_3/MeOH, 80%.

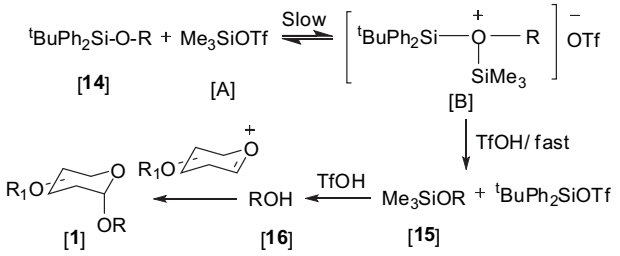


Fig. 3. Plausible mechanism for the formation of **1**.

3. Conclusion

In summary, we have developed a simple, rapid and efficient one-pot protocol for the synthesis of higher branched *manno*-oligosaccharide. Regioselective 6-O-glycosylation in presence of free 2-OH and 3-OH was not possible due to significant increase in reactivity of the 3-OH, induced by free 2-OH group. This problem was elegantly overcome by protecting the 6-OH group with *tert*-butyldiphenylsilyl ether, regioselective 3-O-glycosilation, in situ removal of the *tert*-butyldiphenylsilyl ether followed by 6-O-glycosylation sequentially. Use of TMSOTf/TfOH allows almost instantaneous removal of the *tert*-butyldiphenylsilyl ether group, which leads to a faster and effective one-pot synthesis.

4. Experimental

4.1. General information

All solvents used were distilled and/or dried before use. Evaporations were conducted below 40 °C under reduced pressure unless stated otherwise. Analytical thin-layer chromatography was performed on silica gel 60 F_{254} aluminium plates. The spots were visualized by charring with 10% (v/v) H_2SO_4 in EtOH or detected using UV light. Column chromatography and flash column chromatography were performed on 60–120 and 230–400 mesh silica gel, respectively. Optical rotations were measured with a Perkin–Elmer model 241-MC automatic polarimeter for solutions in a 1-dm cell. ^1H and ^{13}C NMR spectra were recorded in Bruker DPX 300/600 MHz and Bruker DPX 75/150 MHz spectrometer, respectively, using tetramethylsilane (δ=0.00) as an internal standard at 25 °C. ESI-MS (positive) was conducted using LC-ESI-Q-TOF micro Mass spectrometer.

*4.1.1. Phenyl 2,4,6-tri-O-acetyl-1-thio-α-D-mannopyranoside (**8**).* To a solution of compound **7** (0.1 g, 0.37 mmol) in DMF (2 ml) trimethylorthoacetate (0.01 ml, 0.81 mmol) and *p*-TsOH (10 mg) were added. The mixture was stirred for 10 min at room temperature. To the reaction mixture 2 ml 80% AcOH was added and stirred for 45 min. The solution was co-evaporated with toluene till it becomes completely acid free and dried over P_2O_5. The crude residue in 1 ml pyridine was then cooled to −40 °C and AcCl (0.18 mmol, 126 μl, 0.5 equiv based on **7**) was added. Stirring was continued for 6 h at −40 °C when TLC indicated 50% formation of a new product. MeOH (0.1 ml) was added to destroy excess AcCl and diluted with CH_2Cl_2, washed with water and evaporated to dryness. Flash chromatography generated pure **8** (0.045 mg, 30% based on **7**) as a colourless syrup. $[\alpha]_D^{24}$ +114.79 (*c* 0.57, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 2.05 (s, 3H, $COCH_3$), 2.16 (s, 3H, $COCH_3$), 4.06–4.14 (m, 2H), 4.29–4.35 (m, 1H), 4.50–4.52 (m, 1H), 5.09–5.12 (m, 1H), 5.32–5.33 (m, 1H), 5.56 (s, 1H, *H*-1), 7.26–7.47 (m, 5H, aromatic protons); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.50, 20.64, 20.73, 62.43, 68.79, 68.99, 69.38, 73.49, 85.47, 127.83, 128.96, 131.79, 132.65, 170.31, 170.51, 170.60 ppm; HRMS (ESI) calcd for $C_{18}H_{22}O_8SNa$ 421.0933 and found 421.0958.

*4.1.2. Phenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside-(1→3)-2,4,6-tri-O-acetyl-1-thio-α-D-mannopyranoside (**4**).* A solution of thioglycoside acceptor **8** (0.1 g, 0.14 mmol), trichloroacetimidate donor **9** (0.09 g, 0.15 mmol) and freshly activated molecular sieves (4 Å) in dry CH_2Cl_2 (1 ml) was stirred at −20 °C under nitrogen for 15 min when TMSOTf (5 μl) in CH_2Cl_2 was added into the reaction mixture. After 15 min TLC (R_f=0.5; 7% MeOH in CH_2Cl_2) indicated complete conversion of starting material. It was then quenched with Et_3N and stirring was continued for additional 5 min. The mixture was then diluted, filtered and concentrated. Silica gel column chromatography yielded **4** (0.15 mg, 85%) as syrup. $[\alpha]_D^{24}$ +44.00 (*c* 1.12, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ 2.00 (s, 3H, $COCH_3$), 2.05 (s, 3H, $COCH_3$), 2.07 (s, 3H, $COCH_3$), 2.15 (s, 3H, $COCH_3$), 2.16 (s, 3H, $COCH_3$), 2.18 (s, 3H, $COCH_3$), 2.22 (s, 3H, $COCH_3$), 4.09–4.11 (m, 2H), 4.16 (dd, *J*=3.6, 9.6 Hz, 1H), 4.25 (dd, *J*=1.5, 6.3 Hz, 1H), 4.27 (dd, *J*=1.8, 2.4 Hz, 1H), 4.43–4.46 (m, 1H), 5.03 (s, 1H), 5.03 (d, *J*=1.8 Hz, 1H), 5.04 (s, 1H), 5.21–5.27 (m, 2H), 5.35 (t, *J*=4.95 Hz, 1H), 5.49–5.5 (m, 1H), 5.52 (s, 1H), 7.30–7.47 (m, 4H, aromatic protons); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 20.62, 20.63, 20.71, 20.74, 20.85, 20.92, 62.5, 62.62, 65.91, 67.97, 68.11, 69.53, 69.63, 69.89, 72.25, 74.99, 85.71, 98.87, 128.20, 129.24, 131.96, 132.39, 169.59, 169.84, 169.90, 170.04, 170.32, 170.56, 170.74 ppm; HRMS (ESI) calcd for $C_{30}H_{38}O_{16}SNa$ 751.1884 and found 751.1934.

*4.1.3. Benzyl 2,3-O-isopropylidene-6-O-tert-butyldiphenylsilyl-α-D-mannopyranoside (**11**).* To a stirred solution of compound **10** (140 mg, 0.28 mol) in dry DMF (2 ml), 2,2-dimethoxypropane (0.034 g, 0.04 ml, 0.33 mol) and *p*-TsOH (20 mg) were added. The mixture was stirred at room temperature for 12 h. It was then quenched with Et_3N, concentrated to syrup, which on column chromatography (R_f=0.71; 10% EtOAc in Toluene) gave **11** (0.125 mg, 82%) as a yellow syrup. $[\alpha]_D^{24}$ +17.59 (*c* 1.22, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.07 [s, 9H, $Ph_2SiC(CH_3)_3$], 1.34 [s, 3H, $C(CH_3)_2$], 1.49 [s, 3H, $C(CH_3)_2$], 3.72–3.95 (m, 4H), 4.17 (m, 2H), 4.48 (d, *J*=11.7 Hz, 1H, OCH_2Ph), 4.69 (d, *J*=11.7 Hz, 1H, OCH_2Ph), 5.08 (s, 1H, *H*-1), 7.24–7.72 (m, 15H, aromatic protons); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.22, 26.15, 26.81, 27.9, 64.33, 68.79, 69.89, 70.3, 75.48, 78.46, 95.98, 109.46, 127.72, 127.75, 127.92, 128.23, 128.44, 129.78, 133.03, 133.19, 135.58, 135.67, 136.88 ppm; HRMS (ESI) calcd for $C_{32}H_{40}O_6SiNa$ 571.2496 and found 571.2492.

*4.1.4. Benzyl 2,3-O-isopropylidene-4-O-acetyl-6-O-tert-butyldiphenylsilyl-α-D-mannopyranoside (**12**).* Compound **11** (100 mg, 0.18 mmol) was dissolved in pyridine (1 ml) and Ac_2O (0.2 ml) was added drop wise at 0 °C. The resulting mixture was warmed

gradually to room temperature and stirred. After 6 h TLC indicated (R_f=0.84; 5% EtOAc in Toluene) complete conversion of the starting material. The reaction was quenched with methanol (0.2 ml), diluted with CH_2Cl_2 (10 ml) and washed with water and brine. The organic layer was separated and dried over Na_2SO_4 to get pure 12 (0.1 g, 95%) as a thick glass. $[\alpha]_D^{24}$ +17.01 (*c* 0.68, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.06 [s, 9H, $Ph_2SiC(CH_3)_3$], 1.34 [s, 3H, $C(CH_3)_3$], 1.55 [s, 3H, $C(CH_3)_3$], 1.93 (s, 3H, $COCH_3$), 3.64 (d, *J*=11.1 Hz, 1H), 3.74–3.88 (m, 2H), 4.19–4.27 (m, 2H), 4.56 (d, *J*=11.7 Hz, 1H, O–CH_2–Ph), 4.79 (d, *J*=11.7 Hz, 1H, O–CH_2–Ph), 5.04 (t, *J*=8.7 Hz, 1H), 5.16 (s, 1H, *H*-1), 7.24–7.71 (m, 15H, aromatic protons); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.18, 20.81, 26.41, 26.53, 26.72, 27.56, 63.13, 68.69, 69.46, 69.79, 75.84, 76.20, 95.66, 109.84, 127.60, 127.67, 127.94, 128.28, 128.45, 129.64, 133.22, 133.27, 135.59, 135.69, 136.82, 169.63 ppm; HRMS (ESI) calcd for $C_{34}H_{42}O_7SiNa$ 613.2597 and found 613.2597.

*4.1.5. Benzyl 4-O-acetyl-6-O-tert-butyldiphenylsilyl-α-D-mannopyranoside (**5**).* Compound **12** (100 mg, 0.18 mmol) dissolved in 80% AcOH (2 ml) was heated at 80 °C for 45 min when TLC (R_f=0.82; 5% MeOH in DCM) indicates formation of a new product. Column chromatography produced pure **5** (0.07 g, 75%). $[\alpha]_D^{24.0}$ +62.76 (*c* 0.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.06 [s, 9H, $Ph_2SiC(CH_3)_3$], 1.97 (s, 3H, $COCH_3$), 2.42 (br s, 1H, O*H*), 2.98 (br s, 1H, O*H*), 3.70–3.97 (m, 5H), 4.54 (d, *J*=11.7 Hz, 1H, O–CH_2–Ph), 4.76 (d, *J*=11.7 Hz, 1H, O–CH_2–Ph), 4.98–5.08 (m, 2H), 7.26–7.69 (m, 15H, aromatic protons); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.23, 20.91, 26.77, 63.21, 68.85, 70.24, 70.54, 70.84, 71.17, 98.31, 127.67, 127.72, 127.92, 128.02, 128.46, 129.71, 133.27, 135.63, 135.69, 136.99, 171.72 ppm; HRMS (ESI) calcd for $C_{31}H_{38}O_7SiNa$ 573.2284 and found 573.2277.

*4.1.6. Benzyl 6-O-(2,4,6-tri-O-acetyl-3-O-(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)-α-D-mannopyranosyl)-3-O-(2,3,4-tri-O-benzoyl-6-O-(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)-α-D-mannopyranosyl)-4-O-acetyl-α-D-mannopyranoside (**1**).* A solution of compound **3** (100 mg, 0.19 mmol) and **2** (84 mg, 0.2 mmol) in dry CH_2Cl_2 (1 ml) was stirred at −20 °C with powdered molecular sieves (4 Å) under nitrogen. After 30 min, AgOTf (10 mg) was added and stirring was continued for further 15 min when TLC (compound **13**, R_f=0.33; 20% EtOAc in Toluene) indicated complete consumption of starting materials, NIS (87 mg, 0.32 mmol) along with **5** (94 mg, 0.17 mmol) was added in it. After 20 min TLC (R_f=0.4; 3% MeOH in CH_2Cl_2) showed formation of a new product (**14**). The reaction temperature was then raised to −5 °C. TMSOTf (0.06 g, 0.3 mmol) in CH_2Cl_2 (1 ml) was added and stirring was continued for 5 min at the end of which TfOH (0.06 g, 0.4 mmol) was added to it. TLC (R_f=0.27; 3% MeOH in CH_2Cl_2) indicated formation of a new product (**16**). Compound **4** (95 mg, 0.13 mmol) and NIS (55 mg, 0.2 mmol) dissolved in CH_2Cl_2 (1 ml) were then added into the reaction mixture at −20 °C and allowed to react for 15 min. It was then quenched with Et_3N and stirring was continued for additional 10 min. The mixture was then diluted, filtered and concentrated. The residue was subjected to silica gel column chromatography (R_f=0.54; 3% MeOH in CH_2Cl_2) to yield **1** (30%) as a syrup. $[\alpha]_D^{24}$ +124.01 (*c* 0.68, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.96 (s, 3H, $COCH_3$), 1.97 (s, 3H, $COCH_3$), 1.99 (3H, s, $COCH_3$), 2.01 (3H, s, $COCH_3$), 2.02 (3H, s, $COCH_3$), 2.03 (3H, s, $COCH_3$), 2.05 (s, 3H, $COCH_3$), 2.08 (s, 3H, $COCH_3$), 2.11 (s, 3H, $COCH_3$), 2.11 (s, 3H, $COCH_3$), 2.13 (s, 3H, $COCH_3$), 2.14 (s, 3H, $COCH_3$), 3.6–3.63 (m, 3H), 3.92–4.31 (m, 14H), 4.58 (t, *J*=10.62 Hz, 1H), 4.64–4.67 (m, 1H), 4.7 (d, *J*=11.64 Hz, 1H), 4.84 (s, 1H), 4.92 (s, 1H), 4.98 (s, 1H), 5.2–5.44 (m, 10H), 5.58 (m, 1H), 5.76–5.79 (m, 1H), 5.85–5.88 (m, 1H), 7.24–8.09 (m, 20H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 20.57, 20.69, 20.76, 20.82, 20.85, 20.91, 20.97, 62.20, 62.28, 62.51, 62.54, 65.90, 65.95, 65.98, 66.34, 66.61, 67.67, 68.38, 68.68, 68.84, 68.89, 69.30, 69.38, 69.58, 69.78, 69.86, 69.88, 70.31, 70.66, 70.94, 74.63, 80.03, 80.27, 97.27, 97.61, 98.78, 98.90, 98.99, 127.89, 127.95, 128.03, 128.27, 128.43, 128.46, 128.52, 128.65, 128.69, 128.75, 129.02, 129.08, 129.70, 129.86, 129.91, 133.14, 133.64, 133.67, 137.03, 165.15, 165.62, 165.64, 169.51, 169.62, 169.72, 169.85, 169.96, 170.02, 170.46, 170.56, 170.83; HRMS (ESI) calcd for $C_{82}H_{94}O_{41}Na$ 1757.5168 and found 1757.5136.

*4.1.7. Ethyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside-(1→6)-2,3,4-tri-O-benzoyl-1-thio-α-D-mannopyranoside (**13**).* Thick glass. $[\alpha]_D^{24}$ −1.32 (*c* 1.26, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.4 (t, *J*=7.2 Hz, 3H, S–CH_2–CH_3), 1.94 (s, 3H, $COCH_3$), 2.0 (s, 3H, $COCH_3$), 2.05 (s, 3H, $COCH_3$), 2.13 (s, 3H, $COCH_3$), 2.72–2.82 (m, 2H, S–CH_2–CH_3), 3.65 (dd, *J*=10.8, 1.8 Hz, 1H), 3.98–4.0 (m, 3H), 4.1–4.12 (m, 1H), 4.72–4.75 (m, 1H), 4.84 (d, *J*=1.8 Hz, 1H), 5.25 (t, *J*=10.2 Hz, 1H), 5.29–5.3 (m, 1H), 5.37 (dd, *J*=3.6, 10.2 Hz, 1H), 5.56 (s, 1H), 5.79 (dd, *J*=1.2, 3.0 Hz, 1H), 5.83 (dd, *J*=3.3, 9.9 Hz, 1H), 5.9 (t, *J*=10.2 Hz, 1H), 7.24–8.12 (m, 15H, aromatic protons); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 14.66, 20.58, 20.70, 20.74, 20.85, 25.27, 62.24, 65.89, 66.47, 67.23, 68.54, 68.94, 69.32, 69.72, 70.45, 72.11, 81.78, 97.31, 128.31, 128.53, 128.74, 128.88, 129.26, 129.71, 129.84, 129.91, 133.22, 133.56, 133.64, 165.36, 165.52, 165.54, 169.59, 169.73, 169.93, 170.55 ppm; HRMS (ESI) calcd for $C_{43}H_{46}O_{17}SNa$ 889.2353 and found 889.2423.

*4.1.8. Benzyl 3-O-(2,3,4-tri-O-benzoyl-6-O-(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)-α-D-mannopyranosyl)-4-O-acetyl-6-O-tert-butyldiphenylsilyl-α-D-mannopyranoside (**14**).* Yellow syrup. $[\alpha]_D^{24.0}$ −4.37 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.08 [s, 9H, $Ph_2SiC(CH_3)_3$], 1.95 (s, 3H, $COCH_3$), 1.97 (s, 3H, $COCH_3$), 2.0 (s, 3H, $COCH_3$), 2.09 (s, 3H, $COCH_3$), 2.12 (s, 3H, $COCH_3$), 3.63 (dd, *J*=1.8, 10.8 Hz, 1H), 3.71 (dd, *J*=5.55, 11.10 Hz, 1H), 3.85–3.97 (m, 5H), 4.12–4.15 (m, 2H), 4.26 (s, 1H), 4.57 (d, *J*=12.0 Hz, 1H, O–CH_2Ph), 4.64–4.67 (m, 1H), 4.8 (d, *J*=11.4 Hz, 1H, O–CH_2Ph), 4.85 (s, 1H), 5.1 (s, 1H), 5.22–5.30 (m, 3H), 5.36 (t, *J*=9.9 Hz, 1H), 5.4 (dd, *J*=3.3, 10.2 Hz, 1H), 5.56–5.57 (m, 1H), 5.76 (dd, *J*=3.3, 9.9 Hz, 1H), 5.87 (t, *J*=5.1 Hz, 1H), 7.26–8.09 (m, 30H, aromatic protons); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 19.19, 20.54, 20.68, 20.81, 26.77, 26.83, 62.20, 63.49, 65.98, 66.64, 66.66, 66.80, 68.62, 68.87, 68.90, 69.30, 69.78, 69.82, 69.90, 70.64, 71.97, 80.38, 97.53, 98.48, 98.61, 127.64, 127.68, 127.79, 127.96, 128.22, 128.38, 128.49, 128.67, 128.71, 128.80, 128.86, 128.92, 129.05, 129.10, 129.65, 129.67, 129.84, 129.89, 133.05, 133.26, 133.32, 133.58, 133.61, 135.65, 135.68, 137.14, 165.07, 165.57, 165.64, 169.52, 169.72, 169.84, 170.05, 170.54 ppm; HRMS (ESI) calcd for $C_{72}H_{78}O_{24}SiNa$ 1377.4550 and found 1377.4514.

*4.1.9. Benzyl 3-O-(2,3,4-tri-O-benzoyl-6-O-(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)-α-D-mannopyranosyl)-4-O-acetyl-6-O-trimethylsilyl-α-D-mannopyranoside (**15**).* Colourless syrup. $[\alpha]_D^{24}$ −5.37 (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 0.26 (s, 9H, $Si(CH_3)_3$), 1.9 (s, 3H, $COCH_3$), 1.98 (s, 3H, $COCH_3$), 2.03 (s, 3H, $COCH_3$), 2.13 (s, 3H, $COCH_3$), 2.22 (s, 3H, $COCH_3$), 3.55–3.59 (m, 3H), 3.64 (dd, *J*=1.8, 10.8 Hz, 1H), 3.86 (dd, *J*=1.8, 12.6 Hz, 1H), 3.92 (ddd, *J*=1.8, 5.1 and 4.95 Hz, 1H), 3.96 (dd, *J*=4.8, 11.1 Hz, 1H), 4.09 (d, *J*=5.4 Hz, 1H), 4.1–4.11 (m, 1H), 4.26 (dd, *J*=2.4, 3.0 Hz, 1H), 4.4–4.42 (m, 1H), 4.57 (d, *J*=8.4 Hz, 1H), 4.67 (d, *J*=12.0 Hz, 1H), 4.85 (s, 1H), 4.87 (s, 1H), 5.28 (t, *J*=10.2 Hz, 1H), 5.35–5.41 (m, 3H), 5.45 (dd, *J*=10.2, 3.0 Hz, 1H), 5.57–5.58 (m, 1H), 5.92 (dd, *J*=10.2, 3.0 Hz, 1H), 6.07 (t, *J*=10.2 Hz, 1H), 7.24–8.14 (m, 20H, aromatic protons); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 0.52, 20.50, 20.69, 20.75, 20.84, 20.88, 61.38, 62.08, 65.76, 66.44, 66.72, 68.66, 68.82, 69.15, 69.30, 69.39, 69.48, 69.68, 70.57, 71.67, 71.86, 76.08, 98.13, 98.91, 99.62, 127.93, 127.95, 128.28, 128.50, 128.52, 128.83, 128.88, 129.03, 129.14, 129.74, 129.93, 133.11, 133.55, 133.59, 137.24, 165.22, 165.28, 165.57, 169.37, 169.74, 169.78, 170.49, 171.61 ppm; HRMS (ESI) calcd for $C_{59}H_{68}O_{24}SiNa$ 1211.3767 and found 1211.3767.

*4.1.10. Benzyl α-D-mannopyranosyl-(1→3)-α-D-mannopyranosyl-(1→6)-[α-D-mannopyranosyl-(1→6)-α-D-mannopyranosyl-(1→3)]-α-D-mannopyranoside (**17**).* A solution of **1** (20 mg, 0.01 mmol) in MeOH (2 ml) was added to a saturated solution of ammonia in MeOH (2 ml). After 6 days at room temperature the solution was

concentrated, and the residue was purified by Biogel P-2 (F) column (1.0 cm I.D×90 cm; water as eluent) to produce **17** (80%). $[\alpha]_D^{24}$ +37.24 (*c* 0.1, MeOH); ^{1}H NMR (D_2O, 600 MHz): δ 3.53–4.02 (m, 30H, ring protons), 4.57 (d, *J*=11.6 Hz, 1H), 4.63 (d, *J*=11.6 Hz, 1H), 4.75 (s, 1H), 4.77 (s, 1H), 4.84 (s, 1H), 4.94 (s, 1H), 5.03 (s, 1H), 7.3–7.37 (m, 5H, aromatic protons); ^{13}C NMR (D_2O, Me_2O, 150 MHz): δ 61.66, 61.73, 61.76, 66.64, 67.40, 67.52, 67.64, 70.42, 70.73, 70.79, 70.86, 70.89, 71.18, 71.39, 71.51, 72.05, 72.40, 73.47, 73.65, 74.06, 74.08, 79.52, 80.09, 100.45, 100.49, 103.03, 103.14, 103.48, 129.38, 129.43, 129.63, 129.66, 137.67 ppm; HRMS (ESI) calcd for $C_{37}H_{58}O_{26}Na$ 941.3114 and found 941.3121.

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Supplementary data

Spectroscopic characterization data, ^{1}H, ^{13}C NMR spectra for all new compounds are included in the supplementary data. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.03.109. These data include MOL files and InChiKey of the most important compounds described in this article.

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