Tetrahedron 69 (2013) 5022–5028

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of raffinose family oligosaccharides by regioselective de-O-benzylation with $Co_2(CO)_8/Et_3SiH/CO$ system

Yue-tao Zhao, Shan Niu, Lu-bai Huang, Ji-ming Wang, Zhao-jun Yin, Qing Li, Zhong-jun Li *

State Key Laboratory of Natural and Biomimetic Drugs, Department of Chemical Biology, School of Pharmaceutical Sciences, Peking University Health Science Center, Beijing 100191, PR China

ARTICLE INFO

Article history:
Received 29 January 2013
Received in revised form 18 March 2013
Accepted 25 March 2013
Available online 29 March 2013

Keywords:
Regioselective de-O-benzylation
Dicobalt octacarbonyl
Sucrose
Raffinose family oligosaccharides
Glycosylation

ABSTRACT

A convenient approach for synthesis of raffinose, stachyose, and verbascose using sucrose as the starting material is presented. The key step is the regioselective de-O-benzylation with $Co_2(CO)_8/Et_3SiH/CO$ system, followed by a high α-selective glycosylation. The newly developed de-O-benzylation system is efficient in removing the primary benzyl groups of sucrose and raffinose under mild condition and with high selectivity. Using thioglycoside as donor, NIS/AgOTf as promoter and DTBMP as additive, glycosylation of acid labile sucrose substrate is achieved in high yield.

1. Introduction

The benzyl ether protecting group is important in the chemistry of carbohydrates, because of its easy formation and stability under various conditions.[1] Despite many regioselective introduction and removal methods of the benzyl protecting group toward monosaccharides,[2] there are still limited methods for the selective de-O-benzylation of complex oligosaccharides.[3] Benzyl groups are primarily used as permanent protecting groups of complex oligosaccharides that are not removed until the last step of synthesis.

The organocobalt reagent $Co_2(CO)_8$ is an essential catalyst in many important reactions, such as the Nicholas reaction,[4] Pauson–Khand reaction,[5] and carbonylation reactions.[6] Murai et al. found that the $Co_2(CO)_8/Et_3SiH/CO$ system was efficient in catalyzing the silylformylation of olefins, alkynes, aldehydes, cyclic ethers, esters, and acetals.[7] Previous work in our laboratory showed that this system can regioselectively remove the benzyl groups protecting primary hydroxyls of carbohydrates (Fig. 1), including complex disaccharides and trisaccharides. The actual catalyst is thought to be $Co(CO)_4$-$SiEt_3$, which is generated from $Co_2(CO)_8$ and Et_3SiH in situ and sensitive to steric hindrance.[8]

Sucrose is a widely available disaccharide. Many approaches to utilize sucrose as the raw material for the preparation of different organic compounds have been attempted.[9] Because there are three primary hydroxyl groups in sucrose, the main focus of sucrose chemistry is to understand their relative reactivity and how to control their transformation. However, due to the similarity of the three hydroxyl groups, the terminal modification usually proceeds with poor regioselectivity.[10] Moreover, because of the instability of the glycoside bond in the presence of acid,[11] there are a limited number of reagents suitable for the modification of sucrose. Therefore, there is a need to develop selective and mild reagents for sucrose manipulation.

Raffinose family oligosaccharides (raffinose, stachyose, verbascose) are a group of carbohydrates with different numbers of galactose in the glucose residue of sucrose. They are called 'good Bifidus-Factors' for the ability to promote the Bifidobacterium growing in intestine and can act as anti-oxidation, anti-freeze, and anti-cancer agents.[12] Besides, stachyose is a healthcare product on sale with effect on enhancing human immunity. Though raffinose is easy to obtain from nature, it is still difficult to extract the longer oligomers stachyose and verbascose with enough purity[13a–c] and to synthesize these oligosaccharides by chemical method.[13d] Considering the chemical character of the raffinose family oligosaccharides and the good selectivity of $Co_2(CO)_8/Et_3SiH/CO$ systemin de-O-benzylation of complex oligosaccharides, we herein report a convenient synthesis of raffinose, stachyose, and verbascose using sucrose as the starting material (Fig. 2).

* Corresponding author. Tel.: +86 10 8280 1714; fax: +86 10 8280 5496; e-mail addresses: zjli@bjmu.edu.cn, zjli@mail.bjmu.edu.cn (Z.-jun Li).

0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.03.094

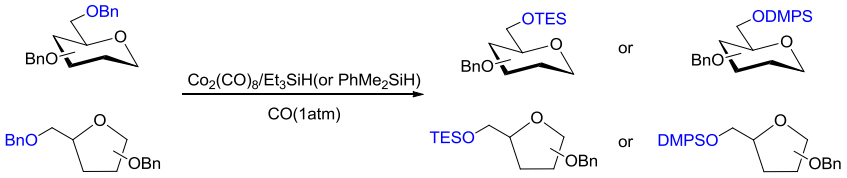


Fig. 1. Regioselective de-O-benzylation by $Co_2(CO)_8$/silane/CO system.

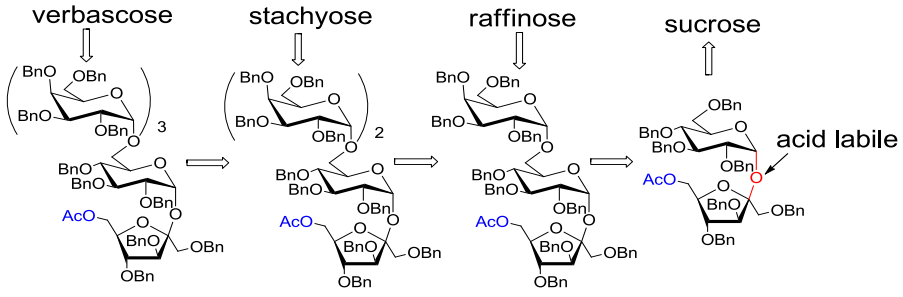
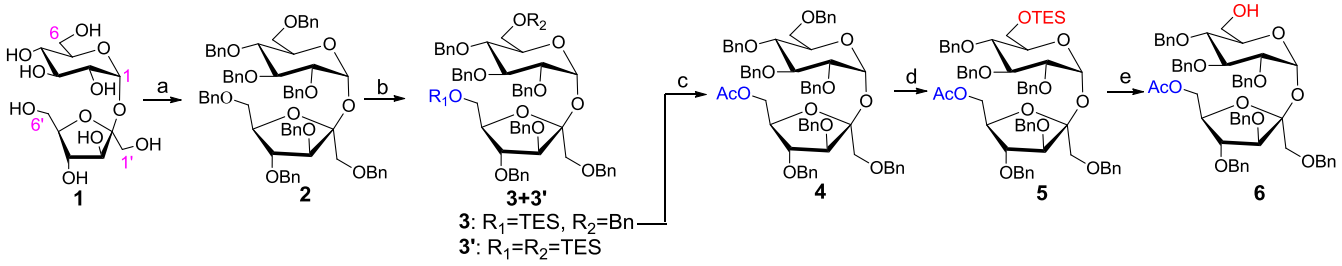


Fig. 2. Retro-synthetic strategy of raffinose family of oligosaccharides.

2. Results and discussion

Regioselective modification of the three primary hydroxyl groups of sucrose **1** is difficult to achieve, especially the selective modification of the 6′-OH and 6-OH groups. However, when sucrose is fully protected by benzyl groups **2**, the regioselective de-O-benzylation could be implemented (Scheme 1).



Scheme 1. Reagents and conditions: (a) BnBr/NaH, DMF, rt 75%; (b) $Co_2(CO)_8$ (1.5 equiv)/Et_3SiH (10 equiv)/CO, PhH, 50 °C, 85% with **3**, 15% with **3′**; (c) TBAF/THF, then Ac_2O/Py, 90% in two steps; (d) $Co_2(CO)_8$ (6 equiv)/Et_3SiH (20 equiv)/CO, PhH, 70 °C, 70%; (e) TBAF/THF, 0.5 h, quantitative.

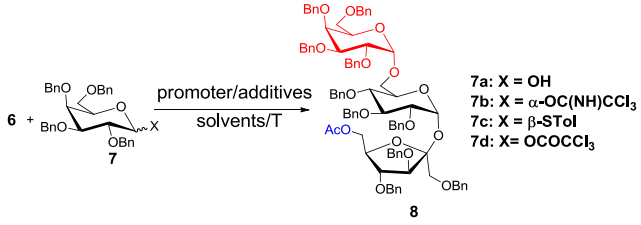
When treated with $Co_2(CO)_8$(1.5 equiv) and Et_3SiH(10 equiv) at 50 °C in benzene, the 6′-OBn was removed first and transformed to silyl ether (**3**, 85%), along with formation of a small percentage of de-6,6′-O-benzylation side-product (**3′**, 15%). These results suggested that there was a certain difference of reactivity between the 6′-OBn and 6-OBn, which could be caused by the steric hindrance difference. Because of the concern about the stability of the silyl ether in compound **3**, we converted the silyl ether to acetate **4** before further manipulation, which is stable under $Co_2(CO)_8$/Et_3SiH/CO system reported by Murai et al.[14]

The condition required for the removal of 6-OBn in **4** was harsher. We used more equivalents of $Co_2(CO)_8$ (6 equiv) and Et_3SiH (20 equiv) and higher reaction temperature (70 °C), and the yield of product **5** was moderate (70%). This result suggested that the steric hindrance of 6-OBn was higher than that of 6′-OBn. Rapid desilylation of **5** by TBAF in 0.5 h produced compound **6**, which was used directly as a glycosylation acceptor.

The glycosidic bond of sucrose is rather sensitive to acidic conditions, and it can be hydrolyzed in 0.1% HCl in MeOH in 30 min.[15] The chemical glycosylation of sucrose as substrate, either as donor or as acceptor, has rarely been reported. We screened several donors and promoters. Considering the acid labile feature of sucrose, we controlled the reaction condition to be as neutral as possible (Table 1).

Using 1-OH sugar **7a** as donor, CBr_4/PPh_3 as promoter and DMF as solvent, the monosaccharide can be glycosylated with high yield and α-selectivity.[16] But under the same condition with sucrose as the acceptor, no reaction occurred (entry 1). Using

Table 1
Screening of different glycosylation conditions



Entry	Donor	Promoter	Additives	Solvent/*T*	Yield/(α/β)
1	**7a**	CBr_4/PPh_3	—	DMF/rt	N.R.[a]
2	**7b**	TMSOTf	MS	CH_2Cl_2/0 °C	0[b]
3	**7b**	TMSOTf	DTBMP/MS	CH_2Cl_2/0 °C	75%/(1/1)
4	**7c**	NIS/AgOTf	DTBMP/MS	CH_2Cl_2/−78 °C	90%/(α only)
5	**7d**	TMSOTf	DTBMP/MS	CH_2Cl_2/0 °C	N.R.[a]

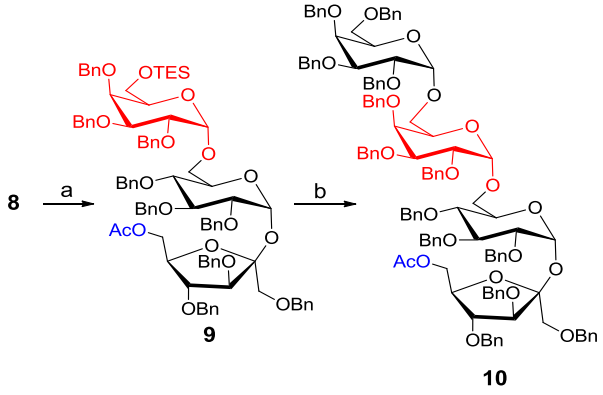
[a] No reaction.
[b] Acceptor was consumed but no product was found.

trichloroacetimidate **7b** as donor, TMSOTf as promoter and 4A MS to remove water, the sucrose acceptor was consumed but the product was complex and no trisaccharide was obtained (entry 2). This result could be attributed to the generation of TfOH acid from TMSOTf, which catalyzed hydrolysis of the glycosidic bond of sucrose. When 2,6-di-*tert*-butyl-4-methyl pyridine (DTBMP) was used as the additive to neutralize the formed TfOH, the trisaccharide product was obtained in 75% yield, but the stereoselectivity was poor (α/β=1/1, entry 3).

Using thioglycoside **7c** as the donor, NIS/AgOTf as promoter and DTBMP/4A MS as additives, we got raffinose **8** with satisfactory yield (90%) and selectivity (α only, entry 4). When using trichloroacetyl ester **7d**, which had been developed in our own group as the donor,[17] no reaction occurred (entry 5), likely because of the lower reactivity of the trichloroacetyl ester compared to the trichloroacetimidate and the thioglycosides.

For the de-O-benzylation of 6′-*O*-acetylated raffinose **8**, the distal primary benzyl was removed as expected, and the reaction went more smoothly than that of **4**. Fewer equivalent of $Co_2(CO)_8$ was needed (3 equiv) and the yield was higher (72%). Removal of the silyl group in **9** and glycosylation with **7c** gave stachyose **10** (Scheme 2).

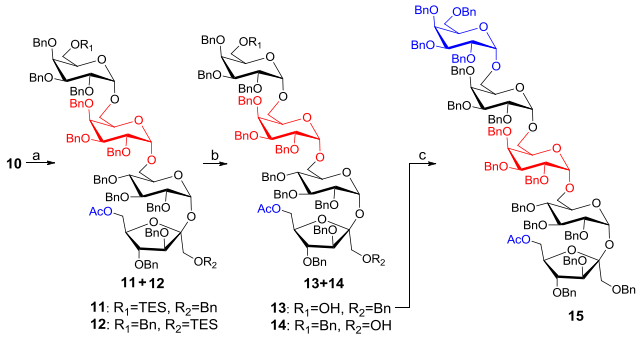
The regioselective de-O-benzylation of **10** was more complicated. Up to 12 equiv $Co_2(CO)_8$ and 40 equiv Et_3SiH could not remove the primary benzyl group completely (65% removed), and the de-1′-O-benzylation by-product **12** was formed. Compound **12** and the desired de-6‴-O-benzylation product **11** could not be separated by column chromatography. However, the two products were separated after removal of the silyl group (compound **13** and **14**). The ratio of **13**/**14** was 1.2/1.



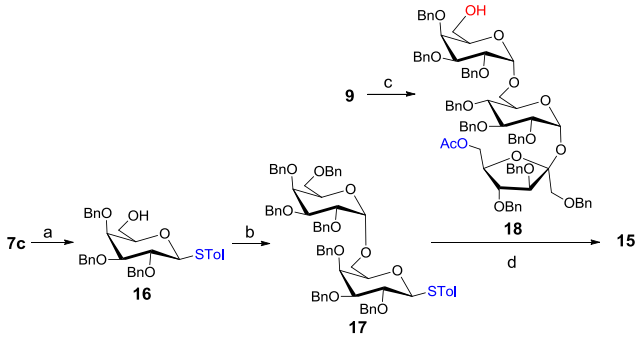
Scheme 2. Reagents and conditions: (a) $Co_2(CO)_8$ (3 equiv)/Et_3SiH (20 equiv)/CO, PhH, 70 °C, 72%; (b) i. TBAF/THF, 96%; ii. **7c**, NIS/AgOTf, DTBMP/MS, −78 °C, 88%.

We tried lower temperatures and other silanes, such as $PhMe_2SiH$ and $EtMe_2SiH$, as well as other protecting groups to replace the acetyl group (such as Bz and TBDPS) to reduce the formation of **12**. However, **12** was always formed with similar ratio to 1.2/1. This result suggested that the steric hindrance of 1′-OBn of **10** was similar to that of 6‴-OBn. Glycosylation of **13** with **7c** gave pentasaccharides **15** successfully (Scheme 3).

Because of the low selectivity of de-O-benzylation of **10**, the synthesis of verbascose was not efficient enough, so we turned to the [2+3] glycosylation strategy to prepare verbascose. The disaccharide donor **17** was synthesized from trichloroacetimidate **7b** coupling with **16**, which was prepared by de-O-benzylation of **7c** in two steps with an overall yield of 87%.[8] Glycosylation of **16** with **7b** generated **17** (82%, α/β=7/1, and the α-product was separated by carefully column chromatography). The trisaccharide acceptor **18** could be readily prepared by the removal of the silyl group of **9**. Coupling of **17** with **18** gave **15** with a yield of 74% (Scheme 4). This strategy to verbascose was more efficient than that by coupling **13** with **7c**.

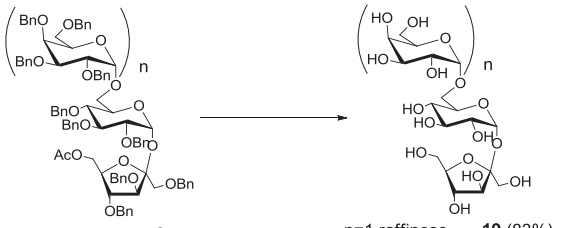


Scheme 3. Reagents and conditions: (a) $Co_2(CO)_8$ (6 equiv)/Et_3SiH (40 equiv)/CO/PhH, 50 °C, 65% for **11** and **12** (not separated); (b) TBAF/THF (94%, **13**/**14**=1.2/1); (c) **7c**/NIS/AgOTf/MS/DTBMP, CH_2Cl_2, −78 °C, 85%.



Scheme 4. Reagents and conditions: (a) i. $Co_2(CO)_8$ (3 equiv)/Et_3SiH (10 equiv)/CO, PhH, 50 °C, 90%; ii. TBAF/THF, 97%; (b) **7b**, TMSOTf, CH_2Cl_2, 0 °C, 82%; (c) TBAF/THF, 96%; (d) NIS/AgOTf/MS/DTBMP, CH_2Cl_2, −40 °C, 74%.

Using CH_3ONa to remove the acetyl group, and the catalytic hydrogenation to remove benzyl groups, the raffinose, stachyose, and verbascose were finally prepared (Scheme 5).



Scheme 5. Reagents and conditions: 1. Na/CH_3OH, overnight; 2. H_2 (0.4 MPa)/Pd−C, CH_3OH, 2 days.

3. Conclusion

In summary, we have developed a concise synthesis of the raffinose family oligosaccharides. The most important reaction is de-O-benzylation with $Co_2(CO)_8$/Et_3SiH/CO system. This system has high efficiency and regioselectivity in removing the primary benzyl group of sucrose and the raffinose family oligosaccharides under mild and neutral condition. We could expect that this de-O-benzylation procedure would be useful for the selective modification of sucrose and other complex oligosaccharides, e.g., melezitose and diglucomelezitose, and provide a short-cut for the rapid preparation of saccharides with primary hydroxyl group glycosylated. In addition, the glycosylation condition of the synthesis of raffinose family of oligosaccharides was studied. The thioglycoside/NIS/AgOTf system is mild and with high α-selectivity, and the use of bulky base DTBMP is necessary to protect the acid-sensitive glycoside bond.

4. Experimental

4.1. General

All chemicals were purchased and used without further purification, unless otherwise noted. Dichloromethane was distilled over phosphorus pentoxide. Benzene was distilled over sodium. Analytical TLC was performed on precoated aluminum sheets, with detection by fluorescence and/or by staining with 5% concentrated sulfuric acid in EtOH. Column chromatography was performed by employing silica gel (230–400 mesh, Merck). Optical rotations were measured using an Optical Activity AA-10R type polarimeter. ^{1}H NMR spectra were recorded on Advance DRX Bruker-400 spectrometers at 25 °C. High-resolution mass spectrometry was performed on a Bruker APEX IV mass spectrometer.

4.2. General procedure A for de-O-benzylation

$Co_2(CO)_8$ (1.5 equiv, 3 equiv or 6 equiv, purchased from Alfa Aesar Chemicals Co. without further purification) was added to a flask under CO atmosphere. Et_3SiH (10 equiv, 20 equiv or 40 equiv, purchased from Alfa Aesar Chemicals Co. without further purification) was then added and the mixture was stirred for 20 min at room temperature. A solution of perbenzylated carbohydrate in anhydrous benzene (1 mmol/5 ml) was degassed and then added using a syringe. The mixture was then heated in oil bath at set temperature (50 °C or 70 °C) and the reaction was monitored by TLC. After the disappearance of starting materials, the cobalt complex was precipitated by the drop-wise addition of pyridine and then bubbling oxygen through the solution for 20 min. The content of the flask was filtered through 5 cm of silica gel and eluted with ethyl acetate. The filtrate was evaporated and the residue was subjected to flash chromatography.

4.3. General procedure B for de-silylation and acylation

$TBFA\cdot 3H_2O$ (1.2 equiv) was added to a solution of the substrate in THF, and the mixture was stirred at room temperature for 30 min. Then the solvent was removed at reduced pressure and the residue was purified by flash chromatography. For acetylation, the deprotected product was dissolved in pyridine, then acetic anhydride (4 equiv) was added slowly and the mixture was stirred over 3 h. The reaction was stopped by the addition of CH_3OH in ice bath, and evaporation of the solvent afforded a residue, which was purified by flash chromatography.

4.4. General procedure C for glycosylation

To a solution of acceptor in CH_2Cl_2 (0.1 mmol/ml), the sulfur donor (1.5 equiv) was added and the mixture was stirred at room temperature with molecular sieve for 30 min. Then DTBMP (1.5 equiv), NIS (3 equiv), and AgOTf (0.5 equiv) was added successively under dark condition, and the mixture was cooled to −78 °C or −40 °C and stirred under argon. After TLC showed that the reaction was completed, the MS was filtered and the filtrate was eluted with $Na_2S_2O_3$ and saturated NaCl solution and dried by anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by flash chromatography.

4.5. General procedure D for de-protection of acetyl and benzyl groups

To a solution of the substrate in CH_3OH, Na was added and the mixture was stirred at room temperature overnight. Then H^+ cation resin was added to neutralize the solvent. After filtering the resin, CH_3OH was evaporated and the substrate was dissolved in 5 ml CH_3OH/EtOAc (1/1). Pd/C (2 equiv) was added, and the mixture was stirred under H_2 atmosphere (0.4 MPa) for 2 days. The Pd/C was filtered and the solvent was removed, the residue was solved in water and freeze-dried to get final product.

4.6. 1,3,4,6-Tetra-*O*-benzyl-β-D-fructofuranosyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (2)

To a solution of sucrose (3.42 g, 10 mmol) in DMF (200 ml), NaH (11.52 g, 3 equiv/OH) was added and the mixture was stirred in ice bath for 30 min. BnBr (25 ml, 2.5 equiv/OH) was added slowly and the mixture was moved to room temperature for 24 hours' stirring. CH_3OH was then added slowly to quench the excessive NaH and BnBr and the solvent was removed at reduced pressure. The residue was dissolved in EtOAc and the insoluble CH_3ONa was filtered by silica gel. The filtrate was concentrated and purified by flash chromatography (PE/EA=8/1) to give **2** as colorless oil (7.9 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18–7.30 (m, 40H), 7.13–7.15 (m, 2H), 5.72 (d, 1H, J=3.5 Hz), 4.87 (d, 1H, J=10.9 Hz), 4.80 (d, 1H, J=10.9 Hz), 4.70 (d, 1H, J=10.9 Hz), 4.61–4.68 (m, 2H), 4.33–4.58 (m, 13H), 4.17–4.21 (t, 1H, J=7.3 Hz), 4.06–4.14 (m, 2H), 4.91–4.96 (t, 1H, J=9.3 Hz), 3.63–3.76 (m, 4H), 3.48–3.56 (m, 3H), 3.36–3.99 (dd, 1H, J=10.5, 1.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) 139.06, 138.78, 138.49, 138.36, 138.34, 138.32, 138.20, 138.07, 128.43, 128.41, 128.11, 128.06, 128.00, 127.86, 127.85, 127.78, 127.71, 127.67, 127.63, 104.73, 90.08, 84.04, 82.51, 82.07, 79.94, 75.62, 74.91, 73.53, 73.49, 73.34, 73.11, 72.63, 72.31, 71.51, 68.59.

4.7. 1,3,4-Tri-*O*-benzyl-6-*O*-triethyl-silyl-β-D-fructofuranosyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (3)

General procedure A using **2** (770 mg, 725 μmol) as substrate, 1.5 equiv of $Co_2(CO)_8$ and 10 equiv of Et_3SiH were used and the reaction was performed at 50 °C in benzene, and **3** was isolated in 85% yield (684 mg, colorless oil). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.31 (m, 34H), 7.12–7.14 (m, 2H), 5.80 (d, 1H, J=3.6 Hz), 4.92 (d, 1H, J=10.8 Hz), 4.81 (d, 1H, J=10.9 Hz), 4.73 (d, 1H, J=10.8 Hz), 4.65 (d, 1H, J=11.5 Hz), 4.64 (d, 1H, J=11.3 Hz), 4.35–4.59 (m, 10H), 4.22 (t, 1H, J=6.9 Hz), 4.04 (d, 1H, J=10.0 Hz), 3.98 (dd, 1H, J=12.0, 5.7 Hz), 3.92 (t, 1H, J=9.3 Hz), 3.84 (d, 2H, J=5.6 Hz), 3.77 (d, 1H, J=11.0 Hz), 3.65 (t, 1H, J=9.6 Hz), 3.50–3.58 (m, 3H), 3.41 (dd, 1H, J=10.6, 1.3 Hz), 0.93 (t, 9H, J=7.9 Hz), 0.60 (q, 6H, J=8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 138.7, 138.5, 138.4, 138.2, 138.1, 138.0, 128.3, 128.2, 128.0, 127.8, 127.7, 127.6, 127.5, 127.4, 104.5, 90.0, 84.3, 83.1, 82.0, 81.6, 79.9, 77.6, 75.5, 74.8, 73.4, 73.1, 72.4, 72.1, 70.9, 70.5, 68.5, 64.1, 6.8, 4.3. HRMS (ESI) calcd for $C_{67}H_{78}O_{11}Si$ $[M+Na]^+$ 1109.5206. Found: 1109.5186. $[\alpha]_D^{25}$ +36.0 (c 1.0, $CHCl_3$).

4.8. 1,3,4-Tri-*O*-benzyl-6-*O*-triethyl-silyl-β-D-fructofuranosyl 2,3,4-tri-*O*-benzyl-6-*O*-triethyl-silyl-α-D-glucopyranoside (3′)

By-product of de-O-benzylation of **2** (123 mg, 15%, colorless oil), and it could also be prepared by General procedure A using 3 equiv of $Co_2(CO)_8$ and 10 equiv of Et_3SiH and refluxing in toluene, which was isolated in 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.35 (m, 30H), 5.87 (d, 1H, J=3.6 Hz), 4.91 (d, 1H, J=10.7 Hz), 4.85 (d, 1H, J=11.0 Hz), 4.74 (d, 1H, J=10.7 Hz), 4.70 (d, 1H, J=11.3 Hz), 4.58–4.66 (m, 5H), 4.42–4.54 (m, 4H), 4.29 (t, 1H, J=7.3 Hz), 3.81–4.00 (m, 5H), 3.74 (d, 1H, J=11.0 Hz), 3.59–3.71 (m, 2H), 3.45–3.55 (m, 3H), 0.90–0.97 (m, 18H), 0.51–0.65 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 138.6, 138.5, 138.2, 138.0, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 127.6, 127.5, 127.4, 127.3, 104.3, 89.6, 84.3, 82.4, 82.1, 81.1, 80.3, 77.2, 75.7, 74.7, 73.5, 73.2, 72.6, 72.0, 71.5, 71.4, 63.5, 61.4, 6.9, 6.8, 4.5, 4.3. HRMS (ESI) calcd for $C_{66}H_{86}O_{11}Si_2$ $[M+Na]^+$ 1133.5601. Found: 1133.5613. $[\alpha]_D^{25}$ +23.3 (c 1.2, $CHCl_3$).

4.9. 1,3,4-Tri-*O*-benzyl-6-*O*-acetyl-β-D-fructofuranosyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (4)

General procedure B using **3** (660 mg, 595 μmol) as substrate, and **4** was isolated in 90% yield (555 mg, colorless oil) in two steps. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23–7.32 (m, 34H), 7.11–7.14 (m, 2H), 5.65 (d, 1H, J=3.5 Hz), 4.92 (d, 1H, J=10.9 Hz), 4.81 (d, 1H, J=10.9 Hz), 4.78 (d, 1H, J=11.0 Hz), 4.25–4.65 (m, 14H), 4.07–4.14 (m, 3H), 3.96 (t, 1H, J=9.3 Hz), 3.72 (d, 1H, J=11.0 Hz), 3.64 (t, 1H, J=9.6 Hz), 3.58 (dd, 1H, J=10.6, 3.3 Hz), 3.51–3.55 (m, 2H), 3.46 (dd, 1H, J=10.5, 1.4 Hz), 1.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 138.8, 138.4, 138.2, 138.0, 137.9, 137.8, 137.7, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 104.5, 90.0, 83.6, 82.0, 81.8, 79.6, 78.2, 77.6, 75.4, 74.8, 73.3, 72.8, 72.5, 72.4, 70.8, 70.6, 68.3, 65.2, 20.7. HRMS (ESI) calcd for $C_{63}H_{66}O_{12}$ $[M+Na]^+$ 1037.4447. Found: 1037.4454. $[\alpha]_D^{25}$ +37.3 (*c* 1.5, $CHCl_3$).

4.10. 1,3,4-Tri-*O*-benzyl-6-*O*-acetyl-β-D-fructofuranosyl 2,3,4-tri-*O*-benzyl-6-*O*-triethyl-silyl-α-D-glucopyranoside (5)

General procedure A using **4** (600 mg, 578 μmol) as substrate, 6 equiv of $Co_2(CO)_8$ and 20 equiv of Et_3SiH were used and the reaction was performed at 70 °C in benzene, and **5** was isolated in 70% yield (430 mg, colorless oil). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23–7.33 (m, 39H), 5.66 (d, 1H, J=3.5 Hz), 4.93 (d, 1H, J=10.9 Hz), 4.86 (d, 1H, J=10.9 Hz), 4.80 (d, 1H, J=10.8 Hz), 4.67 (d, 1H, J=3.2 Hz), 4.57–4.65 (m, 6H), 4.54 (s, 1H), 4.51 (d, 2H, J=4.6 Hz), 4.49 (d, 1H, J=4.4 Hz), 4.45 (d, 1H, J=7.2 Hz), 4.37 (d, 1H, J=12.0 Hz), 4.30–4.31 (m, 2H), 4.10–4.17 (m, 2H), 3.91–4.00 (m, 3H), 3.65–3.72 (m, 3H), 3.47–3.60 (m, 4H), 1.99 (s, 3H), 0.91–0.95 (m, 9H), 0.53–0.61 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 139.0, 138.9, 138.5, 138.1, 137.9, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 104.6, 90.1, 83.8, 82.2, 82.0, 80.1, 78.2, 77.3, 75.7, 74.9, 73.5, 73.2, 73.1, 72.9, 72.6, 71.9, 71.2, 65.2, 61.5, 20.8, 6.9, 4.5. HRMS (ESI) calcd for $C_{62}H_{74}O_{12}$ Si $[M+Na]^+$ 1061.4842. Found: 1061.4858. $[\alpha]_D^{25}$ +34.7 (*c* 1.5, $CHCl_3$).

4.11. 1,3,4-Tri-*O*-benzyl-6-*O*-acetyl-β-D-fructofuranosyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (6)

General procedure B using **5** (430 mg, 405 μmol) as substrate, and **6** was isolated quantitatively as colorless oil (380 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.34 (m, 33H), 5.60 (d, 1H, J=3.6 Hz), 4.90 (d, 1H, J=10.9 Hz), 4.84 (d, 1H, J=10.9 Hz), 4.76 (d, 1H, J=10.9 Hz), 4.65 (d, 1H, J=11.4 Hz), 4.55–4.62 (m, 4H), 4.50–4.52 (t, 2H, J=4.4 Hz), 4.47 (d, 1H, J=4.1 Hz), 4.42 (d, 1H, J=7.0 Hz), 4.33–4.39 (m, 2H), 4.17–4.21 (dd, 1H, J=12.0, 3.2 Hz), 4.08–4.14 (m, 2H), 3.95–4.05 (m, 3H), 3.65–3.69 (m, 2H), 3.40–3.59 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 138.8, 138.3, 138.1, 137.9, 137.8, 137.7, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 104.7, 89.8, 83.5, 81.8, 81.5, 79.8, 78.0, 77.8, 77.2, 75.6, 75.0, 73.4, 72.9, 72.7, 72.6, 71.7, 71.2, 64.9, 62.1, 20.8. HRMS (ESI) calcd for $C_{56}H_{60}O_{12}$ $[M+NH_4]^+$ 942.4423. Found: 942.4421. $[\alpha]_D^{25}$ +48.5 (*c* 3.3, H_2O).

4.12. 1,3,4-Tri-*O*-benzyl-6-*O*-acetyl-D-fructofuranosyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-α-D-glucopyranoside (8)

General procedure C using **6** (250 mg, 265 μmol) as acceptor and **7c** (383 mg, 1.5 equiv) as donor, and **8** was isolated in 90% yield (348 mg, colorless oil). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17–7.35 (m, 62H), 5.56 (d, 1H, J=3.5 Hz), 5.07 (d, 1H, J=3.5 Hz), 4.88–4.94 (m, 2H), 4.83 (d, 1H, J=11.0 Hz), 4.75–4.79 (m, 2H), 4.71 (s, 1H), 4.67 (d, 1H, J=5.9 Hz), 4.64 (d, 1H, J=4.1 Hz), 4.61 (s, 1H), 4.32–4.58 (m, 14H), 4.26–4.27 (m, 2H), 4.01–4.09 (m, 5H), 3.89–3.97 (m, 4H), 3.67–3.81 (m, 4H), 3.47–3.57 (m, 5H), 3.31–3.34 (dd, 1H, J=9.6, 3.6 Hz), 1.91 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 139.1, 138.9, 138.8, 138.4, 138.2, 138.1, 138.0, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 104.7, 98.3, 90.3, 83.8, 82.2, 81.9, 80.1, 78.3, 77.6, 77.4, 77.1, 76.8, 75.5, 75.2, 74.9, 74.8, 73.4, 72.9, 72.7, 72.1, 71.4, 71.0, 69.4, 68.9, 66.3, 65.3, 20.8. HRMS (ESI) calcd for $C_{90}H_{94}O_{17}$ $[M+NH_4]^+$ 1464.6829. Found: 1464.6800. $[\alpha]_D^{25}$ +56.3 (*c* 2.4, CH_3CN).

4.13. 1,3,4-Tri-*O*-benzyl-6-*O*-acetyl-D-fructofuranosyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,-tri-*O*-benzyl-6-*O*-triethyl-silyl-α-D-galactopyranosyl)-α-D-glucopyranoside (9)

General procedure A using **8** (220 mg, 150 μmol) as substrate, 3 equiv of $Co_2(CO)_8$ and 20 equiv of Et_3SiH were used and the reaction was performed at 70 °C in benzene, and **9** was isolated in 72% yield (161 mg, colorless oil). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11–7.31 (m, 56H), 5.57 (s, 1H), 5.10 (s, 1H), 4.97–4.99 (d, 1H, J=11.2 Hz), 4.90–4.93 (d, 1H, J=10.8 Hz), 4.78–4.86 (m, 3H), 4.68–4.72 (m, 3H), 4.61–4.64 (d, 4H, J=10.9 Hz), 4.43–4.58 (m, 10H), 4.34–4.37 (d, 1H, J=11.9 Hz), 4.28 (s, 3H), 4.03–4.11 (m, 6H), 3.91–3.98 (m, 4H), 3.51–3.85 (m, 10H), 3.30–3.32 (d, 1H, J=9.2 Hz), 1.92 (s, 3H), 0.90–0.94 (m, 9H), 0.53–0.58 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 139.2, 139.1, 139.0, 138.8, 138.5, 138.2, 138.1, 137.9, 137.6, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 104.8, 98.4, 90.3, 83.8, 83.7, 82.3, 81.9, 81.6, 80.5, 80.2, 78.4, 75.6, 75.1, 75.0, 74.9, 73.6, 73.5, 73.0, 72.9, 72.8, 72.7, 72.1, 72.0, 71.7, 71.6, 71.3, 71.0, 68.3, 66.2, 65.4, 64.9, 61.6, 20.9, 7.0, 4.5. HRMS (ESI) calcd for $C_{89}H_{106}NO_{17}Si$ $[M+NH_4]^+$ 1488.7225. Found: 1488.7198. $[\alpha]_D^{25}$ +54.1 (*c* 3.7, CH_3CN).

4.14. 1,3,4-Tri-*O*-benzyl-6-*O*-acetyl-D-fructofuranosyl 2,3,4-tri-*O*-benzyl-6-*O*-[2,3,4,-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-α-D-galactopyranosyl]-α-D-glucopyranoside (10)

General procedure C using **9** (140 mg, 94 μmol) as substrate, and **10** was isolated in 88% yield (157 mg, colorless oil). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13–7.33 (m, 83H), 5.53 (d, 1H, J=4.0 Hz), 5.06–5.07 (d, 1H, J=4.0 Hz), 4.87–4.96 (m, 4H), 4.80–4.81 (d, 1H, J=3.2 Hz), 4.72–4.76 (m, 3H), 4.65–4.69 (m, 6H), 4.58–4.62 (m, 4H), 4.38–4.49 (m, 11H), 4.29–4.31 (dd, 1H, J=7.6, 4.3 Hz), 4.23–4.27 (m, 2H), 4.00–4.08 (m, 5H), 3.89–3.97 (m, 7H), 3.75–3.86 (m, 3H), 3.45–3.67 (m, 10H), 3.26–3.30 (dd, 1H, J=9.7, 3.5 Hz), 1.92 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 139.1, 138.9, 138.8, 138.7, 138.6, 138.5, 138.2, 138.0, 137.9, 128.5, 128.4, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 104.7, 98.5, 90.3, 83.7, 82.6, 82.1, 81.7, 80.1, 79.6, 78.4, 78.2, 77.8, 77.3, 75.5, 75.2, 75.1, 75.0, 74.7, 73.5, 73.4, 73.1, 73.0, 72.8, 72.7, 72.1, 71.4, 70.8, 69.4, 68.5, 68.4, 65.7, 28.6, 20.9. HRMS (ESI) calcd for $C_{117}H_{122}O_{22}$ $[M+Na]^+$ 1901.8320. Found: 1901.8358. $[\alpha]_D^{25}$ +51.1 (*c* 2.4, CH_3CN).

4.15. 1,3,4-Tri-*O*-benzyl-6-*O*-acetyl-D-fructofuranosyl 2,3,4-tri-*O*-benzyl-6-*O*-[2,3,4,-tri-*O*-benzyl-6-*O*-(2,3,4-tri-*O*-benzyl-6-*O*-triethyl-silyl-α-D-galactopyranosyl)-α-D-galactopyranosyl]-α-D-glucopyranoside & 1-*O*-triethyl-silyl-3,4-di-*O*-benzyl-6-*O*-acetyl-D-fructofuranosyl 2,3,4-tri-*O*-benzyl-6-*O*-[2,3,4,-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-α-D-galactopyranosyl]-α-D-glucopyranoside (11&12)

General procedure A using **10** (150 mg, 79 μmol) as substrate, 6 equiv of $Co_2(CO)_8$ and 40 equiv of Et_3SiH were used and the reaction was performed at 70 °C in benzene, and the mixture of **11** and **12** was isolated in 65% yield (98 mg, **11**/**12**=1.2/1, colorless oil). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–7.36 (m, 72H), 5.56–5.58 (dd, 1H, J=5.1, 3.7 Hz), 5.10–5.12 (dd, 1H, J=3.6, 3.5 Hz), 4.95–5.00 (m, 2H), 4.92–4.93 (d, 1H, J=1.8 Hz), 4.90 (s, 1H), 4.84–4.85 (d, 1H, J=3.2 Hz), 4.72–4.81 (m, 5H), 4.68–4.70 (m, 3H), 4.65 (s, 2H), 4.61–4.64

(m, 2H), 4.42–4.55 (m, 9H), 4.33–4.40 (m, 2H), 4.25–4.30 (m, 2H), 1.95–1.96 (d, 3H, *J*=2.4 Hz), 0.92–0.98 (m, 15H), 0.54–0.63 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 169.7, 138.3, 138.2, 138.1, 138.0, 137.9, 137.8, 137.7, 137.6, 137.4, 137.3, 137.2, 137.1, 137.0, 127.6, 127.5, 127.4, 127.3, 127.2, 127.1, 127.0, 126.9, 126.8, 126.7, 126.6, 126.5, 126.4, 104.0, 103.9, 103.1, 97.7, 97.6, 89.6, 89.5, 82.9, 81.7, 81.6, 81.3, 80.9, 79.2, 78.8, 78.6, 77.6, 77.5, 77.4, 76.9, 76.4, 75.5, 74.6, 74.4, 74.2, 74.1, 74.0, 73.9, 73.7, 72.9, 72.8, 72.7, 72.6, 72.5, 72.3, 72.1, 72.0, 71.8, 71.2, 71.1, 70.8, 70.6, 70.4, 69.9, 68.6, 68.5, 68.1, 67.7, 65.9, 65.4, 65.2, 64.9, 64.7, 60.6, 60.2, 28.9, 20.0, 6.0, 3.6. HRMS (ESI) calcd for $C_{116}H_{130}O_{22}Si$ 1/2 $[M+NH_4]^+$ 969.4750. Found: 969.4780.

4.16. 1,3,4-Tri-*O*-benzyl-6-*O*-acetyl-D-fructofuranosyl 2,3,4-tri-*O*-benzyl-6-*O*-[2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4-tri-*O*-benzyl-α-D-galactopyranosyl)-α-D-galactopyranosyl]-α-D-glucopyranoside (13)

General procedure B using the mixture of **11** and **12** (98 mg, 51 μmol) as substrate, and **13** was isolated in 55% yield (51 mg, colorless oil).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17–7.36 (m, 76H), 5.51 (d, 1H, *J*=3.1 Hz), 5.04 (d, 1H, *J*=3.3 Hz), 4.86–4.93 (m, 4H), 4.79–4.83 (m, 3H), 4.60–4.76 (m, 13H), 4.39–4.57 (m, 10H), 4.30–4.33 (d, 1H, *J*=12.0 Hz), 4.25 (d, 2H, *J*=4.3 Hz), 4.05–4.11 (m, 2H), 3.96–4.03 (m, 4H), 3.89–3.94 (m, 4H), 3.83–3.86 (m, 4H), 3.72–3.79 (m, 2H), 3.58–3.70 (m, 7H), 3.47–3.50 (d, 1H, *J*=11.1 Hz), 3.40–3.42 (d, 1H, *J*=6.3 Hz), 3.28–3.31 (dd, 1H, *J*=3.4, 9.6 Hz), 1.93 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 138.2, 138.1, 137.9, 137.8, 137.7, 137.5, 137.4, 137.3, 137.1, 137.0, 127.6, 127.5, 127.4, 127.3, 127.1, 127.0, 126.9, 126.8, 126.7, 126.6, 126.5, 103.9, 97.6, 89.6, 82.8, 81.7, 80.9, 79.2, 78.4, 77.5, 77.3, 75.5, 74.6, 74.3, 74.1, 74.0, 73.9, 73.6, 72.6, 72.5, 72.2, 71.9, 71.8, 71.3, 70.6, 70.1, 69.9, 68.3, 66.3, 65.6, 64.8, 61.4, 20.0. HRMS (ESI) calcd for $C_{110}H_{116}O_{22}$ $[M+Na]^+$1811.7850. Found: 1811.7831. $[\alpha]_D^{25}$ +54.3 (*c* 1.5, $CHCl_3$).

4.17. 3,4-Di-*O*-benzyl-6-*O*-acetyl-D-fructofuranosyl 2,3,4-tri-*O*-benzyl-6-*O*-[2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-α-D-galactopyranosyl]-α-D-glucopyranoside (14)

General procedure B using mixture of **11** and **12** (98 mg, 51 μmol) as substrate, and **14** was isolated in 45% yield (42 mg, colorless oil). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17–7.34 (m, 71H), 5.53 (d, 1H, *J*=3.3 Hz), 5.05 (d, 1H, *J*=3.4 Hz), 4.87–4.96 (m, 4H), 4.59–4.78 (m, 14H), 4.38–4.48 (m, 9H), 4.28–4.31 (m, 5H), 4.03–4.09 (m, 5H), 3.74–3.98 (m, 10H), 3.64–3.70 (m, 4H), 3.41–3.60 (m, 6H), 3.28–3.30 (m, 2H), 1.94 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 138.2, 138.0, 137.9, 137.8, 137.7, 137.6, 137.5, 137.4, 137.2, 137.0, 127.7, 127.6, 127.5, 127.4, 127.3, 127.1, 127.0, 126.80, 126.7, 126.6, 126.5, 126.4, 103.9, 103.1, 97.6, 89.5, 82.9, 81.8, 81.4, 80.9, 79.2, 78.8, 77.6, 77.4, 77.0, 76.4, 76.0, 74.6, 74.2, 74.1, 73.8, 73.4, 72.5, 72.4, 72.1, 71.9, 71.8, 71.3, 70.6, 70.0, 68.5, 67.8, 65.9, 64.9, 61.2, 20.0. HRMS (ESI) calcd for $C_{110}H_{116}O_{22}$ $[M+Na]^+$ 1811.7851. Found: 1811.7805. $[\alpha]_D^{25}$ +55.2 (*c* 1.5, $CHCl_3$).

4.18. 1,3,4-Tri-*O*-benzyl-6-*O*-acetyl-D-fructofuranosyl 2,3,4-tri-*O*-benzyl-6-*O*-{2,3,4-tri-*O*-benzyl-6-*O*-[2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-α-D-galactopyranosyl]-α-D-galactopyranosyl}-α-D-glucopyranoside (15)

General procedure C using **13** (25 mg, 14 μmol) as accepter and **7c** (3 equiv, 38 mg) as donor, and **15** was isolated in 85% yield (28 mg, colorless oil). Or by general procedure C using **17** as donor and **18** as acceptor and isolated in 74% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18–7.31 (m, 91H), 5.53–5.56 (d, *J*=1.2 Hz, 1H), 4.98–5.07 (m, 2H), 4.56–4.91 (m, 23H), 4.30–4.48 (m, 14H), 4.24–4.26 (d, 2H, *J*=5.7 Hz), 3.83–4.09 (m, 16H), 3.46–3.77 (m, 13H), 3.21–3.27 (m, 1H), 1.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 139.1, 139.0, 138.9, 138.8, 138.7, 138.6, 138.5, 138.2, 138.0, 137.9, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2, 104.8, 98.9, 98.9, 98.7, 90.6, 85.1, 84.8, 84.6, 83.9, 82.6, 81.8, 80.2, 78.5, 78.3, 77.2, 76.2, 75.3, 74.9, 74.8, 74.7, 74.6, 73.5, 73.4, 73.3, 72.9, 72.7, 72.6, 72.1, 71.9, 71.6, 70.8, 69.6, 69.1, 66.6, 66.5, 65.6, 20.7. HRMS (ESI) calcd for $C_{144}H_{150}O_{27}$ $[M+Na]^+$ 2334.0257. Found: 2334.0356. $[\alpha]_D^{25}$ +63.3 (*c* 1.3, $CHCl_3$).

4.19. *p*-Methylphenyl 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-thio-β-D-galactopyranoside (17)

4A molecular sieve was added into a solution of **16** (60 mg, 108 μmol) and **7b** (1.5 equiv, 100 mg) was dissolved in 3 ml CH_2Cl_2 and the mixture was stirred for 30 min, then TMSOTf (0.24 equiv) was added in ice bath and the reaction was moved to room temperature. After TLC showed the disappearance of **16**, filtered the molecular sieve, and the filtration was washed by saturated $NaHCO_3$ and NaCl solution and dried by Na_2SO_4. Column separation (PE/acetone=10/1) gave **17** as colorless oil in 82% yield (97 mg, colorless oil). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.46 (d, 2H, *J*=8.0 Hz), 7.36–7.39 (m, 4H), 7.21–7.34 (m, 34H), 6.95–6.97 (d, 2H, *J*=7.8 Hz), 4.91–4.93 (d, 1H, *J*=4.0 Hz), 4.89–4.90 (d, 1H, *J*=5.4 Hz), 4.75–4.80 (m, 4H), 4.67–4.73 (m, 4H), 4.55–4.61 (m, 4H), 4.43–4.46 (d, 1H, *J*=11.2 Hz), 4.35–4.38 (d, 1H, *J*=11.6 Hz), 4.00–4.03 (dd, 1H, *J*=10.1, 3.5 Hz), 3.92–3.96 (m, 2H), 3.82–3.89 (m, 4H), 3.62–3.65 (t, 1H, *J*=6.3 Hz), 3.52–3.59 (m, 5H), 2.24 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 138.9, 138,7, 138.6, 138.5, 138.1, 137.2, 132.3, 130.3, 129.7, 128.5, 128.4, 128.3, 128.1, 128.0, 127.78, 127.7, 127.6, 127.5, 98.4, 87.9, 84.1, 79.3, 77.4, 77.0, 76.5, 75.7, 74.9, 74.4, 74.1, 73.7, 73.6, 73.0, 72.9, 69.4, 68.9, 67.3, 29.8, 21.2. HRMS (ESI) calcd for $C_{68}H_{70}O_{10}S$ $[M+NH_4]^+$ 1096.5028. Found: 1096.5007. $[\alpha]_D^{25}$ +15.4 (*c* 2.6, $CHCl_3$).

4.20. 1,3,4-Tri-*O*-benzyl-6-*O*-acetyl-D-fructofuranosyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4-tri-*O*-benzyl-α-D-galactopyranosyl)-α-D-glucopyranoside (18)

General procedure B using **9** (41 mg, 28 μmol) as substrate, and **18** was isolated in 96% yield as colorless oil (36 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17–7.37 (m, 57H), 5.45 (d, 1H, *J*=3.5 Hz), 5.13 (d, 1H, *J*=3.5 Hz), 4.92 (d, 1H, *J*=11.6 Hz), 4.86–4.90 (m, 2H), 4.75–4.8 (m, 3H), 4.66–4.70 (m, 3H), 4.57–4.63 (m, 4H), 4.41–4.46 (m, 5H), 4.22–4.28 (m, 3H), 4.12–4.15 (m, 1H), 4.00–4.07 (m, 3H), 3.94 (d, 1H, *J*=9.4 Hz), 3.84–3.89 (m, 2H), 3.74–3.78 (m, 2H), 3.62–3.71 (m, 3H), 3.54–3.58 (m, 3H), 3.47–3.53 (m, 4H), 3.33–3.34 (dd, 1H, *J*=9.7, 3.4 Hz), 2.0 (s, 3H). ^{13}C NMR (100 MHz, D_2O) δ 171.1, 139.0, 138.9, 138.8, 138.7, 138.3, 138.1, 137.9, 137.8, 128.5, 128.4, 128.3, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 104.7, 97.7, 90.4, 83.5, 82.7, 81.8, 80.0, 78.2, 78.1, 77.8, 77.2, 75.4, 74.9, 74.7, 74.5, 73.3, 73.1, 72.6, 72.2, 71.6, 71.0, 70.9, 70.8, 68.9,66.0, 62.7, 20.8. MS (ESI) calcd for $C_{83}H_{88}O_{17}$ $[M+Na]^+$ 1379.5919. Found: 1379.5837. $[\alpha]_D^{25}$ +68.1 (*c* 3.5, H_2O).

4.21. *O*-α-D-Galactopyranosyl-(1→6)-*O*-α-D-glucopyranosyl-(1→2)-β-D-fructofuranoside (raffinose) (19)

General procedure D using **8** (90 mg, 61 μmol) as substrate, and **19** was isolated in 83% yield as white solid (26 mg). ^{1}H NMR (400 MHz, D_2O) δ 5.36 (d, 1H, *J*=3.8 Hz), 4.93 (d, 1H, *J*=3.7 Hz), 4.15 (d, 1H, *J*=8.8 Hz), 3.96–4.02 (m, 3H), 3.93 (d, 1H, *J*=2.9 Hz), 3.87–3.91 (t, 1H, *J*=6.3 Hz), 3.82–3.86 (m, 2H), 3.76–3.80 (m, 2H), 3.68–3.75 (m, 4H), 3.60–3.63 (m, 3H), 3.46–3.52 (m, 2H). ^{13}C NMR (100 MHz, D_2O) δ 106.4, 101.1, 94.7, 83.9, 78.9, 76.6, 75.3, 74.0, 73.6, 72.0, 71.8, 71.1, 68.5, 65.0, 64.0, 63.7. HRMS (ESI) calcd for $C_{18}H_{32}O_{16}$

$[M+NH_4]^+$ 522.2029. Found: 522.2014. $[\alpha]_D^{25}$ +80.0 (*c* 3.0, H_2O) (lit.,[18] +83.4, *c* 0.8, H_2O).

4.22. *O*-α-D-Galactopyranosyl-(1→6)-*O*-α-D-galactopyranosyl-(1→6)-*O*-α-D-glucopyranosyl-(1→2)-β-D-fructofuranoside (stachyose) (20)

General procedure D using **10** (48 mg, 25 μmol) as substrate, and **20** was isolated in 81% yield as white solid (14 mg). ^{1}H NMR (400 MHz, D_2O) δ 4.98 (s, 2H), 4.09–4.22 (m, 2H), 3.98–4.02 (m, 5H), 3.86–3.88 (m, 3H), 3.79–3.84 (m, 4H), 3.77 (s, 1H), 3.70–3.74 (m, 4H), 3.66–3.68 (m, 3H), 3.49–3.56 (m, 3H). ^{13}C NMR (100 MHz, D_2O) δ 106.6, 101.1, 100.9, 95.0, 84.1, 79.1, 76.8, 75.5, 74.1, 73.8, 73.7, 72.3, 72.2,72.1, 72.0, 71.6, 71.2, 71.1, 69.2, 68.6, 65.3, 64.2, 63.9. HRMS (ESI) calcd for $C_{24}H_{42}O_{21}$ $[M+Na]^+$ 689.2111. Found: 689.2096. $[\alpha]_D^{25}$ +133.3 (*c* 2.7, H_2O) (lit.,[19] +131.3, *c* 4.5, H_2O).

4.23. *O*-α-D-Galactopyranosyl-(1→6)-*O*-α-D-galactopyranosyl-(1→6)-*O*-α-D-galactopyranosyl-(1→6)-*O*-α-D-glucopyranosyl-(1→2)-β-D-fructofuranoside (verbascose) (21)

General procedure D using **15** (40 mg, 17 μmol) as substrate, and **21** was isolated in 79% yield as white solid (11 mg). ^{1}H NMR (400 MHz, D_2O) δ 5.42 (d, 1H, *J*=3.8 Hz), 4.98 (t, 3H), 4.16–4.23 (m, 3H), 3.97–4.10 (m, 7H), 3.80–3.92 (m, 8H), 3.78 (s, 1H), 3.62–3.75 (m, 9H), 3.47–3.58 (m, 2H). ^{13}C NMR (100 MHz, D_2O) δ 106.6, 101.1, 100.8, 100.5, 94.9, 84.1, 79.1, 76.8, 75.5, 74.2, 74.1, 73.8, 73.7, 72.3, 72.2, 72.1, 72.0, 71.9, 71.6, 71.4, 71.2, 71.1, 69.2, 68.7, 65.2, 64.1, 63.9. HRMS (ESI) calcd for $C_{30}H_{52}O_{26}$ $[M+Na]^+$ 851.2639. Found: 851.2668. $[\alpha]_D^{25}$ +152.4 (*c* 2.1, H_2O) (lit.,[20] +146, *c* 2.1, H_2O).

Acknowledgements

The National Basic Research Program of China (973 program, No. 2012CB822100), the National Natural Science Foundation of China (Nos. 20972012, 21072016) and the National Science & Technology Mega Project for Primary Drug Innovation from Ministry of Science and Technology of China (No. 2012ZX09502001-001) are gratefully acknowledged for financial support of this research.

Supplementary data

Copies of ^{1}H, ^{13}C NMR spectra of relative compounds. These data include MOL files and InChiKeys of the most important compounds described in this article. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.03.094.

References and notes

1. Greene, T. W.; Wuts, P. G. M. In *Greene's Protective Groups in Organic Synthesis*, 4th ed.; John Wiley & Sons: Hoboken, NJ, 2007; pp 102–120.
2. Selected works for selective benzylation: (a) David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643–663; (b) Classon, B.; Garegg, P. J.; Oscarson, S.; Tiden, A. K. *Carbohydr. Res.* **1991**, *216*, 187–196; (c) Bouzide, A.; Sauve, G. *Tetrahedron Lett.* **1997**, *38*, 5945–5948; (d) Grice, P.; Ley, S. V.; Pietruszka, J.; Priepke, H. W. M.; Warriner, S. L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 351–363; (e) Wang, C.-C.; Lee, J.-C.; Luo, S.-Y.; Fan, H.-F.; Pai, C.-L.; Yang, W.-C.; Lu, L.-D.; Hung, S.-C. *Angew. Chem., Int. Ed.* **2002**, *41*, 2360–2362 Selected works for selective de-O-benzylation: (a) Eby, R.; Sondheimer, S. J.; Schuerch, C. *Carbohydr. Res.* **1979**, *73*, 273–276; (b) Hori, H. i.; Nishida, Y.; Ohrui, H.; Meguro, H. *J. Org. Chem.* **1989**, *54*, 1346–1353; (c) Martin, O. R.; Kurz, K. G.; Rao, S. P. *J. Org. Chem.* **1987**, *52*, 2922–2925; (d) Xie, J.; Menand, M.; Valery, J. M. *Carbohydr. Res.* **2005**, *340*, 481–487; (e) Falck, J. R.; Barma, D. K.; Venkataraman, S. K.; Baati, R.; Mioskowski, C. *Tetrahedron Lett.* **2002**, *43*, 963–966; (f) Klemer, A.; Bieber, M.; Wilbers, H. *Liebigs Ann. Chem.* **1983**, 1416–1421; (g) Riley, G. J.; Grindley, T. B. J. *Carbohydr. Chem.* **2001**, *20*, 159–169; (h) Antonello, P.; Silvia, V.; Matteo, A.; Alfonso, I. *Chem.—Eur. J.* **2011**, *17*, 5881–5889.
3. Lecourt, T.; Herault, A.; Pearce, A. J.; Sollogoub, M.; Sinay, P. *Chem.—Eur. J.* **2004**, *10*, 2960–2971.
4. Selected works: (a) Heasley, V. L.; Shellhamer, D. F.; Gipe, R. K.; Wiese, H. C.; Oakes, M. L.; Heasley, G. E. *Tetrahedron* **2002**, *21*, 4133–4170; (b) Green, J. R. *Curr. Org. Chem.* **2001**, *5*, 809–826; (c) Diaz, D. D.; Betancort, J. M.; Martin, V. S. *Synlett* **2007**, 343–359.
5. For reviews: (a) Aubert, C.; Fensterbank, L.; Garcia, P.; Malacria, M.; Simonneau, A. *Chem. Rev.* **2011**, *3*, 1954–1993; (b) Lee, H.-W.; Yee, K.-F. *Eur. J. Org. Chem.* **2010**, *5*, 789–811; (c) Michelet, V.; Toullec, P. Y.; Pierre, G. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268–4315.
6. Selected works: (a) Ungvari, N.; Foerdos, E.; Kegl, T.; Ungvary, F. *Inorg. Chim. Aata.* **2010**, *363*, 2016–2028; (b) Hess, W.; Treutwein, J.; Hilt, G. *Synthesis-Stuttgart* **2008**, *22*, 3537–3562; (c) Ungvari, N.; Kegl, T.; Ungvary, F. *J. Mol. Catal. Chem.* **2004**, *219*, 7–11; (d) Lee, J. T.; Thomas, P. J.; Alper, H. *J. Org. Chem.* **2001**, *66*, 5424–5426; (e) Davoli, P.; Moretti, I.; Prati, F.; Alper, H. *J. Org. Chem.* **1999**, *64*, 518–521; (f) Happ, B.; Bartik, T.; Zucchi, C.; Rossi, M. C.; Ghelfi, F.; Palyi, G.; Varadi, G.; Szalontai, G.; Horvath, I. T. *Organometallics* **1995**, *14*, 809–819.
7. For reviews, see: (a) Murai, S.; Sonoda, N. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 837–846; (b) Chatani, N.; Murai, S. *Synlett* **1996**, 414–424.
8. (a) Yin, Z.-J.; Wang, B.; Li, Y.-B.; Meng, X.-B.; Li, Z.-J. *Org. Lett.* **2010**, *12*, 536–539; (b) Wang, B.; Yin, Z.-j.; Li, Y.-B.; Yang, T.-X.; Meng, X.-B.; Li, Z.-J. *J. Org. Chem.* **2011**, *76*, 9531–9535.
9. For recent reviews, see: (a) Peters, S.; Rose, T.; Moser, M. *Top. Curr. Chem.* **2010**, *294*, 1–23; (b) Queneau, Y.; Jarosz, S.; Lewandowski, B.; Fitremann, J. *Adv. Carbohydr. Chem. Biochem.* **2008**, *61*, 218–292; (c) Goodby, J. W.; Saez, I. M.; Cowling, S. J.; Gortz, V.; Draper, M.; Hall, A. W.; Sia, S.; Cozquer, G.; Lee, S. E.; Raynes, E. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 2754–2787; (d) Goodby, J. W.; Goertz, V.; Cowling, S. J.; Mackenzie, G.; Martin, P.; Plusquellec, D.; Benvegnu, T.; Boullanger, P.; Lafont, D.; Queneau, Y.; Chambert, S.; Fitremann, J. *Chem. Soc. Rev.* **2007**, *36*, 1971–2032.
10. Selected works: (a) Barros, M. T.; Petrova, K. T.; Correia-da-Silva, P.; Potewar, T. M. *Green Chem.* **2011**, *13*, 1897–1906; (b) Karl, H.; Lee, C.-K.; Khan, R. *Carbohydr. Res.* **1982**, *101*, 31–38; (c) Mach, M.; Jarosz, S.; Listkowski, A. *J. Carbohydr. Chem.* **2001**, *20*, 485–493; (d) Gagnaire, J.; Toraman, G.; Descotes, G.; Bouchu, A.; Queneau, Y. *Tetrahedron Lett.* **1999**, *40*, 2757–2760; (e) Molinier, V.; Fitremann, J.; Bouchu, A.; Queneau, Y. *Tetrahedron: Asymmetry* **2004**, *15*, 1753–1762; (f) Giry, P. N.; Descotes, G.; Bouchu, A.; Queneau, Y. *Eur. J. Org. Chem.* **1999**, 3393–3398; (g) Scherrmann, M. C.; Boutboul, A.; Estramareix, B.; Hoffmann, A. S.; Lubineau, A. *Carbohydr. Res.* **2001**, *334*, 295–307.
11. (a) Manley, H. M.; Richards, G. N. *Carbohydr. Res.* **1993**, *240*, 183–196; (b) Moreau, C.; Durand, R.; Alies, F.; Cotillon, M.; Frutz, T.; Theoleyre, M. A. *Ind. Crops Prod.* **2000**, *11*, 237–242.
12. (a) Dinoto, A.; Marques, T. M.; Sakamoto, K.; Fukiya, S.; Watanabe, J.; Ito, S.; Yokota, A. *Appl. Environ. Microbiol.* **2006**, *72*, 7739–7747; (b) Martinez, V. C.; Frias, J.; Vidal, V. C.; Gomez, R. *J. Food Prot.* **2005**, *6*, 1246–1252; (c) Mikkelsen, L. L.; Bendixen, C.; Jakobsen, M.; Jensen, B. B. *Appl. Environ. Microb.* **2003**, *69*, 654–658; (d) Hartemink, R.; Kok, B. J.; Weenk, G. H.; Rombouts, F. M. *Microbiol. Methods* **1996**, *1*, 33–44; (e) Faraji, F.; Lindsay, R. C. *J. Agric. Food Chem.* **2004**, *52*, 7164–7171; (f) Tuncer, P. B.; Bucak, M. N.; Sariozkan, S.; Sakin, F. .; Yeni, D.; Cigerci, I. H.; Atessahin, A.; Avdatek, F.; Gundogan, M.; Buyukleblebici, O. *Cryobiology* **2010**, *61*, 89–93; (g) Goun, E.; Cunningham, G.; Solodnikov, S.; Krasnykch, O.; Miles, H. *Fitoterapia* **2002**, *73*, 692–694.
13. (a) Gama, F. M.; Mota, M. *Carbohydr. Polym.* **1998**, *37*, 279–281; (b) Peterbauer, T.; Richter, A. *Plant Physiol.* **1998**, *117*, 165–172; (c) Peterbauer, T.; Mucha, J.; Mach, L.; Richter, A. *J. Biol. Chem.* **2002**, *277*, 194–200; (d) Suami, T.; Otake, T.; Nishimura, T.; Ikeda, T. *Carbohydr. Res.* **1973**, *26*, 234–239.
14. Chatani, N.; Fujii, S.; Yamasaki, Y.; Murai, S.; Sonoda, N. *J. Am. Chem. Soc.* **1986**, *108*, 7361–7373.
15. Purves, C. B.; Hudson, C. S. *J. Am. Chem. Soc.* **1934**, *56*, 1973–1977.
16. Nishida, Y.; Shingu, Y.; Dohi, H.; Kobayashi, K. *Org. Lett.* **2003**, *14*, 2377–2380.
17. Zhang, K.-Q.; Mao, J.-M.; Chen, H.-M.; Cai, M.-S. *Chin. Chem. Lett.* **1998**, *9*, 435–437.
18. Jurgen, S.; Roxana, M.; Sven, G.; Klaus, B.; Shukrallah, N.; Alice, P.; Hans-Jurgen, H. *Carbohydr. Res.* **2006**, *341*, 2335–2349.
19. Wolfromor, M. L.; Burrella, R. C.; Thompson, A.; Furst, S. S. *J. Am. Chem. Soc.* **1952**, *74*, 6299.
20. Lindberg, B.; Selleby, L. *Acta Chem. Scand.* **1958**, *12*, 1512–1515.