Tetrahedron 91 (2021) 132216

Contents lists available at ScienceDirect

Tetrahedron

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

Effective total synthesis of schaftoside

Chengxiang Shang [a, b], Chuanfang Zhao [a, b], Pengpeng Nie [a, b], Jun Liu [a, b, *], Yuguo Du [a, b, c, **]

[a] State Key Laboratory of Environmental Chemistry and Eco-toxicology, Research Center for Eco-Environmental Sciences, Chinese Academy of Science, Beijing, 100085, China
[b] School of Chemical Sciences, University of Chinese Academy of Sciences, Beijing, 100049, China
[c] National Engineering Research Center for Carbohydrate Synthesis, Jiangxi Normal University, Nanchang, 330022, Jiangxi, China

ARTICLE INFO

Article history:
Received 19 March 2021
Received in revised form
29 April 2021
Accepted 5 May 2021
Available online 24 May 2021

Keywords:
Schaftoside
Total synthesis
C-glycosylflavones
C-glycosylation

ABSTRACT

A short and scalable approach toward the total synthesis of schaftoside, a naturally occurring bioactive *C*-glycosylflavone, has been developed from readily available (±)-naringenin. The highlights of this work are double Lewis acid promoted O→C rearrangement to form C-glycoside, oxidative dehydrogenation to construct flavone ring, and easy operational process to make the target product in multigram-scale.

1. Introduction

C-glycosylflavones are a class of important natural products with promising druggability due to their potent bioactivities and high stability against gastrointestinal hydrolysis metabolism (Fig. 1). Some of them are major components of well-known folk medicines for treating acute and chronicle hepatitis, and cholecystitis diseases in China [1]. Herbs containing flavonyl C-glycosides have long been applied in cooking soup and herbal tea in Guangxi and Guangdong provinces of China [2]. In a joint-project with Guangxi local research institute, we were assigned to investigate the potential bioactivities of schaftoside (apigenin 6-*C*-*β*-D-glucopyranosyl-8-*C*-*α*-L-arabino pyranoside) possessing in sugarcane (*saccharum*) leafs. Since there was no well-established method in our hand to get pure di-*C*-glycosyl flavonoids from nature sources [3], we thus launched an alternative and effective organic synthesis to obtain sufficient quantities of schaftoside for the in vivo and in vitro bioactivity screening and pharmacological exploration. Based on our previous work [4], we were expecting to investigate the anti-obesity and anti-diabetic potentials of this synthetic schaftoside through inhibition of pancreatic lipase and promotion of glucose-induced insulin secretion [5], as well as its hepatoprotective and antiallergenic properties [6].

2. Results and discussion

According to our previous synthetic experiences [4], direct C-glycosylation between an aromatic ring and two glycosyl donors seems to be the most straightforward approach to the synthesis of the target *C*-glycosyl flavonoid. Initially we envisaged that thermodynamically favored β-C-glycosylflavone could be prepared through glycosylation of 2,4,6-trihydroxyacetophenone with armed perbenzylated sugar donor, followed by $Sc(OTf)_3$-catalyzed O→C rearrangement (Fries rearrangement) [7]. However, the low overall yield and the tedious global debenzylation and purification turned this strategy into a cost-ineffective process. Attempted direct C-glycosylation on dihydroxyacetonphenone of apigenin (I) never got success, and the direct C-glycosylation on unprotected naringenin (II) in the presence of lewis acid $Sc(OTf)_3$ was also problematic. Results from both Sato's [8] and our preliminary synthetic efforts revealed that $Sc(OTf)_3$-promoted C-glycosylation of naringenin only led to the formation of an inseparable mixture of 6-*C* and 8-*C*-glucosylnaringenin in very low yield (<20%), along

* Corresponding author. State Key Laboratory of Environmental Chemistry and Eco-toxicology, Research Center for Eco-Environmental Sciences, Chinese Academy of Science, Beijing, 100085, China.
** Corresponding author. School of Chemical Sciences, University of Chinese Academy of Sciences, Beijing, 100049, China.
E-mail address: junliu@rcees.ac.cn (J. Liu).

https://doi.org/10.1016/j.tet.2021.132216
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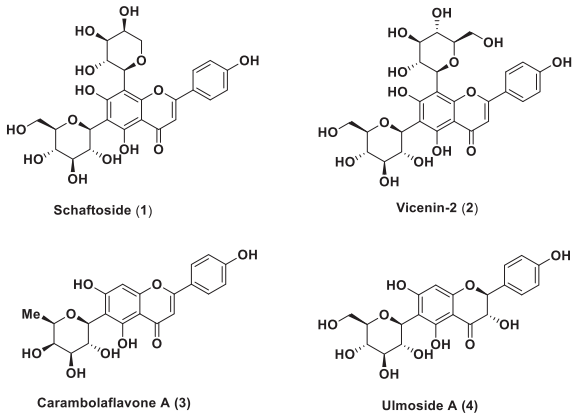


Fig. 1. Structures of representative natural flavonoid C-glycosides.

with di-*C*-glucosylnaringenin as by-product.

NBO (Natural Bond Orbital) charge population analysis indicated that the total atomic charges on phenol part (A-ring) of **I**, **II**, and **III** are −0.200, −0.298, and −0.438, respectively, suggesting that A-ring of flavan (**III**) is more electron rich than that of **I** and **II** [9]. (Fig. 2) This might be due to the electron withdrawing effect of the carbonyl group (C-4) on the C-ring of apigenin (**I**) and naringenin (**II**), as well as the strong hydrogen bonding between 5-OH and C-4 carbonyl group. This information suggested that transformation of electron-deficient naringenin (**II**) into an electron-rich flavan structure (**III**) should be necessary for the effective C-glycosylation. Accordingly, we designed and actually practiced the following approach towards the total synthesis of schaftoside in tens' gram scale using flavan (**III**) as the starting material.

Retrosynthetically, the synthetic plan for schaftoside makes the obvious disconnection at the 6-*C*-*β*-D-glucopyranoside and 8-*C*-*α*-L-arabinopyranoside linkage to A-ring of apigenin (Scheme 1). The conjugated system of C-ring in the flavone **5** would be reconstructed in a two-step process involving oxidative dehydrogenation of *C*-glycosylflavan **6** followed by halogenation and elimination with the corresponding *C*-glycosylflavanone at a late stage. Thus, we envisioned that the regio- and stereoselective C-glycosylations between flavan (**7**) and the corresponding peracetylglycosyl trichloroacetimidates (**8**, **9**) could be fashioned via a Lewis acid promoted O→C rearrangement glycosylation (in which the *O*-glycoside were formed initially and then followed by Fries-type rearrangement to give the *ortho* *C*-glycoside) [7]. In general, O→C rearrangement type C-glycosylation depends on the electron density and steric hindrance on the aromatic ring [10]. The C-glycosylation of aromatic ring with electron donating groups proceeds smoothly, while it is suppressed by the electron withdrawing substituted groups and steric hindrance on the aromatic ring. Based on our previous experiences and NBO-supported charge population analysis, the electron-rich flavan derivative **7** emerged as the best glycosyl acceptor for this rearrangement. Therefore, readily available natural flavone (±)-naringenin was chosen as the starting material which allowed an expeditious entry to the flavan precursor (**7**) on 100 g scale. D-Glucose and L-arabinose were elaborated to the corresponding peracetylglycosyl trichloroacetimidates (**8**, **9**) to act as the glycosyl donors (Scheme 1). The synthetic details are thus undertaken as described below.

Accordingly, the synthesis of the key *C*-glycosyl flavan **6** started from naringenin and is outlined in Scheme 2. Regioselective silyl-protection of the commercially available (±)-naringenin (**10**) with *tert*-butyldimethylsilyl chloride (TBSCl) in the presence of triethylamine occurred selectively at the most acidic 7-OH group at A-ring. Acetylation of the remaining free 5-OH at A-ring and 4″-OH at B-ring with acetic chloride in one-pot sequence afforded diacetate flavanone derivative **11** from (±)-naringenin with 70% yield. To our delight, these reactions gave repeatable results over 180 g scale and the crude product could be used directly in the next step without chromatographic separation. Subsequently, in order to eliminate the electron-withdrawing effect of the carbonyl group at C-4, electron-deficient flavanone **11** was transformed into electron-rich glycosyl acceptor **7**. Removal of the carbonyl group at C-4 along with deacetylation at 5-OH was carried out by reduction of **11** with excess sodium borohydride in a THF/H_2O (1:1) solution at 0 °C to give flavan **7** as a racemate (67−82% isolated yield from tens' to over one hundred gram reaction scale) [11]. Gratifyingly, C-glycosylation of flavan **7** with glycosyl donor **8** in the presence of catalytic amounts of TMSOTf [12] gave the desired 6-*C*-*β*-D-glucopyranosyl flavan **12** as a major product, along with a small amount of **13** generated by the loss of the TBS at the 7-OH group. It was noteworthy that the desired 6-*C*-*β*-D-glucopyranosyl flavan **12** was obtained as a single *β*-anomer (5.10 ppm, d, J = 10.0 Hz, H-1″). The positional selectivity for this glycosylation on the aromatic ring was evident by the absence of C-6 aromatic signal around at 6.04 ppm (s, H-6). Selective removal of the TBS group of **12** with hydrogen fluoride-pyridine (HF•Py) complex afforded phenolic compound **13** in 60% yield over two steps. Similarly, the second C-glycosylation with another glycosyl donor **9** proceeded smoothly at C-8 to give the desired 6-*C*-*β*-D-glucopyranosyl-8-*C*-*α*-L-arabinopyranosyl flavan **6** in a moderate yield of 51% over 40 g scale. The excellent stereo- and regioselectivity for C-glycosylation was rationalized by free 5-OH or 7-OH group directed *ortho*-C-glycosylation and anchimeric assistance of the C-2 acetyl group of the glycosyl donors [7a]. The appearance of several sets of peaks in the ^{1}H and ^{13}C NMR spectra suggests that all the C-glycosides intermediates exist as rotational isomers at ambient temperature on the NMR time-scale [13].

With the key *C*-glycosylflavan **6** (>40 g) in hand, we then focused our attention on the construction of the conjugated system of C-ring in the flavone **5** (Scheme 3). However, the envisaged oxidative dehydrogenation of *C*-glycosylflavan **6** turned out to be more difficult than we expected. Initially, the attempted direct oxidation of *C*-glycosylflavan **6** without protective groups on phenols failed to give any desired products and led to undesired benzoquinone product along with unidentified decomposition products. We reasoned that the oxidation of phenol A-ring

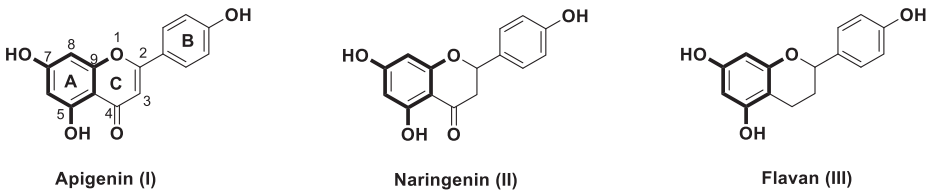
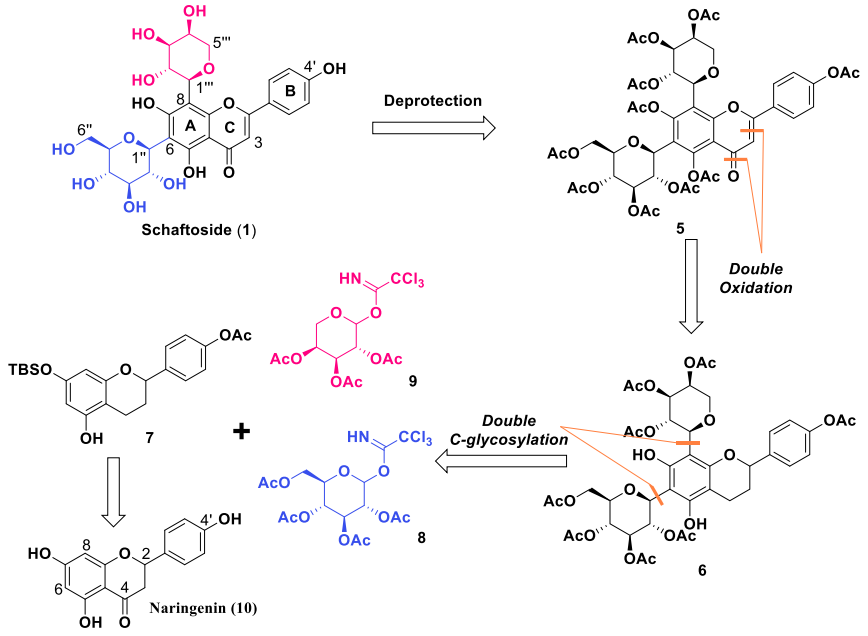
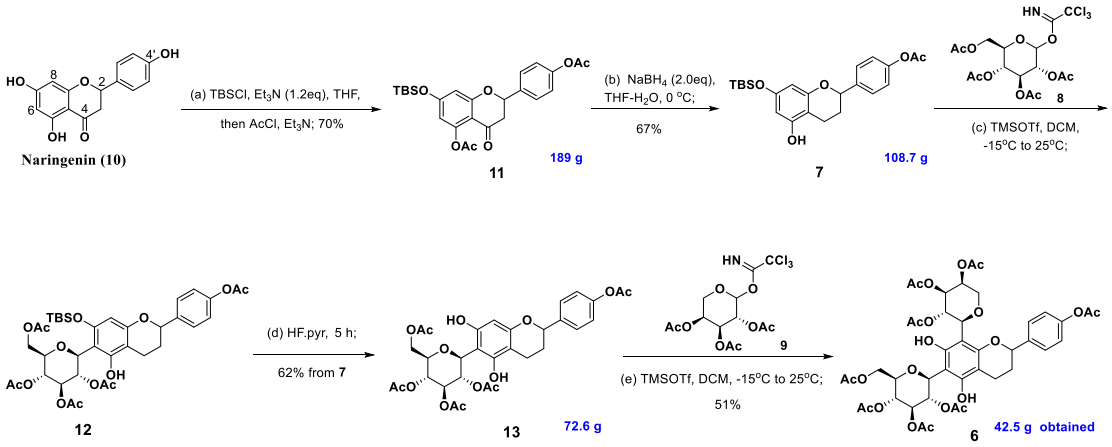


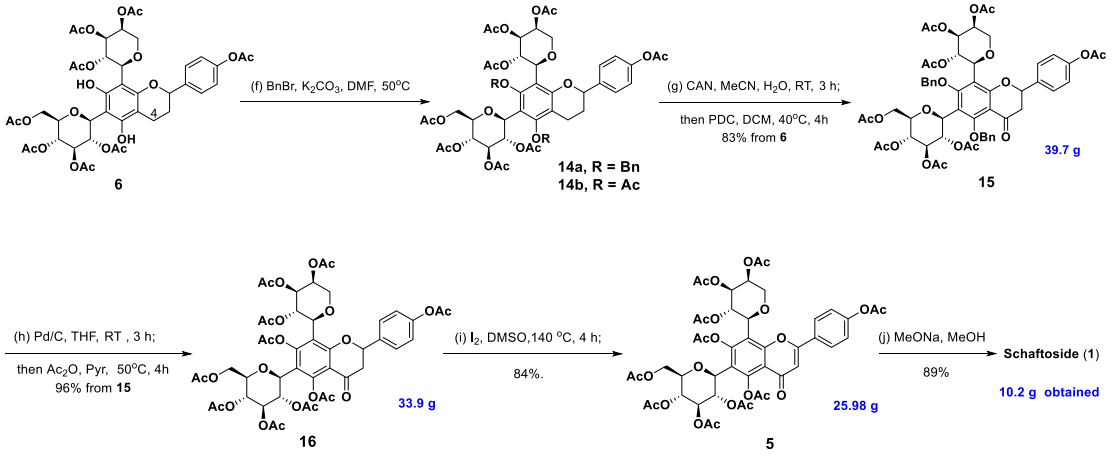
Fig. 2. Structures and NBO charge population analysis of **I-III**



Scheme 1. Retrosynthetic analysis of schaftoside (**1**).



Scheme 2. Synthesis of *C*-glycosyl flavan **6**.



Scheme 3. Gram-scale synthesis of schaftoside (**1**).

probably preceded to the oxidative dehydrogenation of the C-4 position [14]. Thus, to tackle this problem, blocking of the phenolic hydroxyl groups in **6** with benzyl groups in the presence of potassium carbonate in DMF gave the bis-benzylation product **14** in almost quantitative yield. Subsequently, oxidative dehydrogenation of *C*-glycosylflavan **14** was carried out successfully by a two-step procedure following a modified procedure from Wong [15a] and Suzuki [15b], while the other reported one-pot methods (for example, cerium (IV) ammonium nitrate (CAN) in AcOH/H_2O/CH_3CN [10b]) were fruitless in our efforts. The bis-benzylation derivative **14a** was smoothly oxidized by cerium (IV) ammonium nitrate to give the corresponding *C*-glycosylflavanols, which was further oxidized by pyridinium dichromate (PDC) to give the di-*C*-glycosylflavanone **15** in 83% yield over three steps. The same oxidation conditions were also subjected to the peracetylated *C*-glycosylflavan **14b**, generating complicated results in our hands (<30% yield). The low yield for bis-acetylation derivative was due to the electron-withdrawing acyl groups in the phenolic hydroxyl group, which decreased the oxidative reactivity of C-4 position. Hydrogenolysis of **15** with 10% Pd/C catalyst under H_2 atmosphere obtained the corresponding phenol and subsequent treatment with acetic anhydride in pyridine delivered the flavanone acetates **16** in a yield of 96% over two steps. The halogenation and elimination of *C*-glycosylflavanone **16** proceeded smoothly in the presence of catalytic amounts of iodine following a heating in dimethyl sulfoxide (DMSO) at 140 °C for 4 h to give the desired 6-*C*-glucosylflavone **5** in a good yield (84%) [16]. Global deacetylation of **5** with sodium methoxide in dry methanol successfully achieved the desired schaftoside (**1**) in 89% yield on a 10.2 g scale. The spectroscopic data (^{1}H, ^{13}C NMR, and HRMS) of the synthetic schaftoside (**1**) were in good agreement with those of the natural products [17].

3. Conclusion

In summary, we have accomplished the first and a scalable total synthesis of schaftoside (**1**) in 11 linear steps and in 8.83% overall yield. Taking advantages of the relatively electron-rich flavan significantly facilitated the synthesis of C-glycosylflavone, and also make the scale-up preparation possible. With tens' grams of synthetic schaftoside (**1**) in hand, we are now undergoing the investigation of biological activities, such as in-depth assessment of the anti-obesity, anti-diabetic activity, as well as its hepatoprotective and antiallergenic properties both in vitro and in vivo. The related results will be disclosed in due course.

4. Experimental

4.1. General Experimental

Unless noted otherwise, commercially available materials were used without further purification. All solvents were dried according to the established procedures ahead of use. Flash chromatography (FC) was performed using silica gel (100–200 meshes) according to the standard protocol. All reactions under standard conditions were monitored by thin-layer chromatography (TLC) on gel F254 plates. High-resolution mass spectrometry data (HRMS) were acquired using a Q-TOF analyzer in methanol as solvent. ^{1}H NMR, ^{13}C NMR were measured on 400 or 600 MHz, 100 or 150 MHz spectrometers. Chemicals shifts (δ) were expressed in ppm relative to residual $CDCl_3$, MeOD or DMSO-d_6. Multiplicity is tabulated as *s* for singlet, *d* for doublet, *t* for triplet, q for quadruplet, and m for multiplet and *br* when the signal in question is broadened. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials.

5. Experimental procedures for the synthesis of compounds

5.1. Synthesis of compound 11

TBSCl (112.93 g, 0.749 mol) in dry THF (500 mL) was added dropwise to the solution of (±) naringenin (170.00 g, 0.624 mol) and Et_3N (104.15 mL, 0.749 mol) in dry THF (1200 mL) at 0 °C. The cooling bath was removed and the mixture was stirred for 2 h. After consumption of the starting materials, Et_3N (260 mL, 1.87 mol) was added to the solution. The reaction mixture was cooled to 0 °C and acetic chloride (110.8 mL, 1.56 mol) in THF (300 mL) was added dropwise to the mixture. After the intermediate was consumed, the mixure was quenched with saturated solution of $NaHCO_3$ (1200 mL, Caution!) at 0 °C. The aqueous layer was separated and extracted with EtOAc (3 × 1200 mL), and the combined organic phase were washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash column chromatography (Petroleum -EtOAc, 2:1) to give compound **11** as racemate mixture (205.7 g, 70%, colorless oil). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.45 (m, 2H), 7.16–7.14 (d, J = 8.7 Hz, 2H), 6.37–6.36 (d, J = 2.4 Hz, 1H), 6.22–6.21 (d, J = 2.3 Hz, 1H), 5.46–5.42 (dd, J = 13.5, 2.7 Hz, 1H), 3.02–2.95 (dd, J = 16.7, 13.6 Hz, 1H), 2.73–2.68 (dd, J = 16.7, 2.8 Hz, 1H), 2.37 (s, 3H), 2.30 (s, 3H), 0.97 (s, 9H), 0.25 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.74, 169.47, 169.34, 163.83, 162.45, 151.84, 150.91, 136.04, 127.42, 122.06, 109.70, 108.54, 106.12, 78.89, 45.14, 25.48, 21.16, 21.14, 18.18, −4.37. HRMS (Maldi) for C25H30O7SiNa [M+Na]+: calcd. 493.1653; found 493.1666.

5.2. Synthesis of compound 7

Sodium borohydride (30.3 g, 0.80 mol) was added by portions to the solution of **11** (189 g, 0.40 mol) in THF/H_2O (1:1, 2 L) at −5 °C. The temperature of the reaction should be controlled rigorously below 0 °C. After completion, the mixture was quenched by the addition of saturated aq. NH_4Cl (200 mL). The aqueous layer was separated and extracted with EtOAc (3 × 1000 mL) and the combined organic phase were washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by column chromatography (Petroleum -EtOAc, 3:1) to give compound **7** as a white amorphous powder (111.4 g, 67%, racemate mixture). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.40 (dd, J = 8.6, 2.8 Hz, 2H), 7.10–7.08 (dd, J = 8.6, 2.4 Hz, 2H), 6.05 (s, 1H), 5.93 (s, 1H), 4.98–4.95 (dd, J = 10.3, 2.2 Hz, 1H), 2.73–2.60 (m, 1H), 2.30 (s, 1H), 2.27–2.16 (dtd, J = 11.5, 3.5, 1.3 Hz, 1H), 2.05–1.95 (ddt, J = 9.9, 6.6, 3.6 Hz, 0H), 0.96–0.90 (s, 9H), 0.18 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.73, 156.36, 155.03, 154.30, 150.17, 139.19, 127.21, 121.61, 102.54, 101.12, 100.04, 29.45, 25.69, 21.19, 19.01, 18.19. HRMS (Maldi) for C23H30O5SiNa [M+Na]+: calcd. 437.1755; found 437.1766.

5.3. Synthesis of compound 12 and 13

To a mixture of compound **7** (72.84 g, 0.176 mol), 2, 3, 4, 6-tetra-O-acetyl-D-glucopyranosyl trichloroacetimidate (104 g, 0.21 mmol) and molecular sieves (4 Å, 20 g) in anhydrous CH_2Cl_2 (2000 mL) was added TMSOTf (5.3 mL, in 20 mL anhydrous CH_2Cl_2, 29 mmol) via syringe at - 20 °C under N_2 protection. The solution was stirred for 30 min at - 20 °C and then warmed to room temperature for another 2 h. After completion, hydrogen fluoride-pyridine (HF.Py, 120 mL) was added to the mixture at 0 °C. The mixture was quenched with saturated solution of $NaHCO_3$ (1200 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 1000 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (Petroleum -EtOAc,

2:1) to afford compound **13** (68.7 g, 62%, white foam) as mixtures of C-2 epimers (Rotamers observed by ^{1}H NMR and ^{13}C NMR). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.38 (d, J = 5.8 Hz, 1H), 7.10–7.07 (m, 1H), 5.89–5.89 (s, 1H), 5.41–5.27 (m, 3H), 5.14–5.12 (d, J = 3.3 Hz,1H), 4.95–4.87 (m, 1H), 4.34–4.29 (m, 1H), 4.18–4.14 (m, 1H), 3.91–3.87 (m, 1H), 2.77–2.72 (m, 1H), 2.67–2.58 (tt, J = 10.7, 5.4 Hz, 1H), 2.31 (s, 2H), 2.34–1.86 (m, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.80, 170.51, 169.71, 169.48, 156.66, 139.10, 127.29, 127.24, 121.59, 77.24, 77.16, 76.17, 76.11, 74.27, 73.84, 73.78, 70.83, 70.77, 67.88, 61.48, 61.45, 29.46, 29.30, 21.17, 20.69, 20.59, 20.39, 20.36,19.11,19.01. HRMS (Maldi) for C31H34O14Na [M+Na]+: calcd. 653.1841; found 653.1855. In our original procedure, the crude intermediate **12** was purified on a silica gel column to get the physical spectra data. (Rotamers observed by ^{1}H NMR and ^{13}C NMR): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.42 (d, 2H), 7.38 (s, 1H),7.12–7.09 (dd, J = 8.6, 2.4 Hz, 2H), 5.92–5.91 (d, 1H), 5.45–5.39 (d, J = 9.1 Hz, 1H), 5.33–5.26 (m, 2H), 5.10–5.07 (d, J = 10.0 Hz, 1H), 4.99–4.89 (m, 1H), 4.36–4.32 (m, 1H), 4.19–4.16 (d, J = 10.3 Hz, 1H), 3.85–3.77 (dt, J = 9.4, 2.9 Hz, 1H), 2.84–2.79 (m, 1H), 2.71–2.61 (m, 1H), 2.39–1.84 (m, 19H), 1.06 (s, 9H), 0.30–0.18 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.63, 170.29, 169.45, 169.40, 169.05, 169.02, 156.62, 156.60, 155.04, 155.01, 152.00, 151.90, 150.28, 150.26, 139.12, 139.08, 127.33, 121.62, 104.54, 104.50, 103.89, 103.76, 98.63, 98.52, 77.56, 77.42, 77.31, 76.43, 76.35, 74.87, 74.05, 74.00, 70.22, 70.18, 68.02, 61.45, 29.63, 29.33, 25.75, 25.71, 21.14, 20.68, 20.66, 20.58, 20.41, 20.39, 19.23, 19.15, 18.22, −4.09, −4.14, −4.79, −4.85.

5.4. Synthesis of compound 6

To a mixture of compound **13** (57.25 g, 0.09 mol), 2, 3, 4-tri-O-acetyl-L-Arabinopyranosyl trichloroacetimidate (41.9 g, 0.1 mol) and molecular sieves (4 Å, 10 g) in anhydrous CH_2Cl_2 (1000 mL) was added TMSOTf (1.65 mL, in 8 mL anhydrous CH_2Cl_2, 9 mmol) via syringe at - 20 °C under N_2 protection. The solution was stirred for 30 min at - 20 °C and then warmed to room temperature for another 4 h. After completion, the mixture was quenched with saturated solution of $NaHCO_3$ (1200 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 600 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (Petroleum -EtOAc, 1:1) to afford compound **6** (41.15 g, 51%, white amorphous foam) as mixtures of C-2 epimers (Rotamers observed by ^{1}H NMR and ^{13}C NMR). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.68 (s, 1H), 7.46–7.38 (m, 3H), 7.16–7.13 (m, 2H), 5.53–5.24 (m, 6H), 5.13–5.02 (m, 2H), 4.89–4.86 (d, J = 7.5 Hz, 1H), 4.33–4.28 (m, 1H), 4.16–4.07 (m, 2H), 3.89–3.78 (m, 2H), 2.85–2.58 (m, 2H), 2.32–1.68 (m, 26H)· ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.66, 170.37, 170.33, 170.22, 170.02, 169.79, 169.60, 169.46, 168.58, 155.25, 155.18, 153.40, 153.10, 153.04, 150.25, 150.06, 139.36, 138.73, 127.26, 127.00, 126.41, 121.77, 121.75, 121.61, 103.08, 102.22, 101.55, 76.19, 76.09, 74.30, 73.71, 72.04, 71.96, 70.27, 68.66, 68.37, 68.06, 67.89, 61.55, 30.85, 28.72, 21.17, 21.14, 20.94, 20.79, 20.73, 20.71, 20.62, 20.55, 20.50, 19.82, 18.89. HRMS (Maldi) for C42H48O21Na [M+Na]$^+$: calcd. 911.2580; found 911.2597.

5.5. Synthesis of compound 15

To a mixture of **6** (32.92 g, 37.1 mmol) and K_2CO_3 (25.6 g, 0.184 mol) in dry DMF (500 mL) was added BnBr (11 mL, 92 mmol) via syringe at room temperature. The solution was warmed to 50 °C for another 5 h. After completion, the mixture was cooled to room temperature and diluted with H_2O (600 mL). The aqueous layer was extracted with EtOAc (3 × 600 mL) and the combined organic phase were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford crude **14** as a reddish syrup. The crude bis-benzylation product could be used for next step without further purification.

Cerium ammonium nitrate (225.3 g, 0.368 mol) was added by portions to the solution of crude **14** in CH_3CN/H_2O (5:1, 800 mL) at room temperature. After completion, the mixture was diluted with H_2O (300 mL) and the aqueous layer was separated and extracted with EtOAc (3 × 400 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to afford crude *C*-glycosylflavanol as a brown syrup. The crude *C*-glycosylflavanol could be used for next step without further purification. Pyridinium dichromate (PDC) (69.6 g, 0.184 mol) was added by portions to the solution of the above residue in CH_2Cl_2 (500 mL) and the mixture was heated to reflux for 4 h. After completion, the mixture was filtered with Celite and the filter cake was washed with CH_2Cl_2 (200 mL). The combined organic layers were concentrated and purified by flash column chromatography (Petroleum -EtOAc, 1:1) to afford compound **15** (33.29 g, 83%, white amorphous solid) as mixtures of C-2 epimers (Rotamers observed by ^{1}H NMR and ^{13}C NMR). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.39 (m, 9H), 7.20–7.16 (m, 2H), 6.15–5.99 (m, J = 42.6, 9.8 Hz, 1H), 5.62–5.40 (m, 1H), 5.27–4.66 (m, 3H), 4.16–4.10 (m, J = 12.4, 4.5 Hz, 3H), 3.54–3.47 (dq, J = 8.1, 2.4 Hz, 1H), 2.31 (s, 1H), 2.02–1.53 (m, 17H), 1.31 (s, 1H)· ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.54, 188.81, 170.69, 170.63, 170.61, 170.59, 170.39, 170.34, 170.07, 169.98, 169.34, 169.08, 169.03, 168.89, 168.61, 166.32, 166.27, 164.47, 164.36, 160.46, 160.38, 151.18, 151.10, 137.31, 137.18, 136.72, 136.56, 136.33, 135.87, 129.23, 129.02, 128.93, 128.88, 128.81, 128.72, 128.66, 128.57, 128.49, 128.42, 128.14, 128.07, 128.01, 127.87, 127.54, 125.93, 125.91, 122.11, 121.99, 121.95, 118.21, 117.52, 115.41, 114.94, 112.67, 111.49, 79.48, 79.30, 79.14, 78.91, 77.59, 77.30, 75.69, 74.95, 74.71, 73.51, 73.08, 72.65, 72.49, 70.42, 70.31, 68.36, 68.23, 68.18, 68.14, 67.93, 67.10, 66.59, 61.91, 61.78, 46.32, 45.16, 21.12, 20.74, 20.71, 20.66, 20.58, 20.56, 20.51, 20.43, 20.34, 20.31, 20.17, 20.08, 19.79. HRMS (Maldi) for C56H58O22Na [M+Na]$^+$: calcd. 1105.3312; found 1105.3325.

5.6. Synthesis of compound 16

A solution of **15** (33.28 g, 30.8 mmol) in THF (500 mL) was hydrogenated over palladium-loaded activated carbon (Pd/C, 10%, 3.0 g) under hydrogen atmosphere. After completion, the Pd/C catalyst was filtered and the filtrate was concentrated to afford crude phenol as colorless syrup. The crude phenol could be used for next step without further purification. Acetic anhydride (25 mL) was added to the solution of crude phenol in pyridine (200 mL) at room temperature. The solution was warmed to 50 °C for 2 h. After completion, the mixture was concentrated and purified by flash column chromatography (Petroleum -EtOAc, 1:1) to afford compound **16** (29.1 g, 96% white amorphous solid) as mixtures of C-2 epimers (Rotamers observed by ^{1}H NMR and ^{13}C NMR). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.64 (m, 2H), 7.43–7.36 (m, 1H), 7.19–7.14 (m, 2H), 6.02–5.91 (m, 1H), 5.74–5.61 (m, 2H), 5.29–4.93 (m, 5H), 4.49–3.70 (m, 5H), 3.68–3.38 (m, 3H), 3.20–2.51 (m, 3H),2.49–1.12 (m, 43H)· ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.95, 170.71, 170.44, 170.29, 170.24, 169.54, 169.09, 169.03, 168.22, 168.07, 167.38, 167.27, 163.10, 155.28, 151.17, 150.04, 150.01, 135.96, 128.01, 128.01, 127.79, 126.80, 122.47, 122.17, 122.03, 116.95, 115.41, 112.27, 79.42, 74.75, 74.50, 74.01, 72.52, 72.40, 72.01, 69.40, 68.93, 68.48, 68.34, 68.18, 66.17, 61.85, 45.26, 21.38, 21.23, 21.12, 20.76, 20.70, 20.67, 20.64, 20.60, 20.37, 20.28, 20.25, 19.83. HRMS (Maldi) for C46H50O24Na [M+Na]$^+$: calcd. 1009.2584; found 1009.2606.

5.7. Synthesis of compound 5

A solution of **16** (18.0 g, 18.26 mmol) in dry DMSO (400 mL) was

heated to 140 °C with iodine (465 mg, 1.8 mmol). After completion, the mixture was quenched with solution of $Na_2S_2O_3$ (400 mL) at 0 °C. The aqueous layer was separated and extracted with EtOAc (3 × 300 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (Petroleum -EtOAc, 2:3) to afford compound **5** (15.09 g, 84%) as a white amorphous solid. (Rotamers observed by ^{1}H NMR and ^{13}C NMR). $[\alpha]_D^{20}$ − 12.01 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.03–8.01 (d, *J* = 8.3 Hz, 2H), 7.86–7.84 (d, *J* = 8.3 Hz, 1H), 7.34–7.32 (d, *J* = 8.4 Hz, 1H), 7.25–7.23 (s, 1H), 6.58–6.50 (d, 1H), 6.07–6.02 (s, 1H), 5.76–5.67 (d, *J* = 13.1 Hz, 2H), 5.54–5.45 (m, 1H), 5.35–5.14 (m, 5H), 4.46–4.33 (dd, 10.0 Hz, 2H), 4.26–4.11 (m, 2H), 3.98–3.64 (ddd, *J* = 86.4, 31.7, 11.4 Hz, 4H), 2.56–1.58 (m, 46H)·^{13}C NMR (100 MHz, $CDCl_3$) *δ* 175.80, 175.54, 170.75, 170.61, 170.49, 170.41, 170.22, 170.10, 169.86, 169.67, 169.59, 169.46, 168.99, 168.78, 168.55, 168.21, 167.68, 167.58, 163.02, 161.14, 157.22, 154.90, 153.48, 153.13, 150.81, 149.36, 129.59, 128.59, 127.52, 122.95, 122.39, 121.55, 118.89, 117.29, 115.83, 115.66, 115.36, 110.54, 109.03, 74.93, 74.67, 74.44, 73.45, 72.62, 72.30, 72.09, 70.32, 70.10, 69.71, 69.35, 68.70, 68.62, 68.13, 67.95, 67.03, 61.84, 21.39, 21.30, 21.23, 21.15, 21.05, 20.96, 20.77, 20.71, 20.69, 20.65, 20.62, 20.50, 20.30, 20.20, 20.13. HRMS (Maldi) for C46H50O22Na $[M+Na]^+$: calcd. 1007.2428; found 1007.2451.

5.8. Synthesis of schaftoside (1)

To a solution of **5** (14.58 g, 14.8 mmol) in dry CH_3OH (300 mL, freshly distilled) was added sodium methoxide (1 M, freshly made) at room temperature. **T**he pH of the solution was controlled around 9–10 with sodium methoxide. After completion, the mixture was neutralized with Dowex 50W × 8 (H+) resin. The mixture was filtered and the organic layers were concentrated to afford Schaftoside **(1)** (7.44 g, 89%) as a yellowish solid. (Rotamers observed by ^{1}H NMR and ^{13}C NMR). $[\alpha]_D^{20}$ +77.8 (*c* 1.0, MeOH), ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) *δ* 13.77 (1H, brs, OH-5), 10.13 (1H, brs, OH-7), 9.24 (1H, brs, OH-4′), 8.08 (2H, br d, H-2′,6′), 6.94–6.92 (2H, d, *J* = 8 Hz, H-3′,5′), 6.76 (1H, s, H-3); *6-C-ß -Glc*: 4.74 (1H, d, *J* = 9.8 Hz, H-1″), 3.92 (1H, m, H-2″), 3.28 (1H, m, H-3″), 3.28 (1H, m, H-4″), 3.28 (1H,m, H-5″), 3.70, 3.54 (2 × 1H, 2 × m, 6″-CH2); *8-C-α-Ara:* 4.81 (1H, d, *J* = 9.6 Hz, H-1‴), 4.09 (1H, br m, H-2‴), 3.53 (1H, m, H-3‴), 3.88 (1H, m, H-4‴), 3.93, 3.69 (2 × 1H, 2 × m, 5‴-CH2); ^{13}C NMR (125 MHz, DMSO-d_6, 60 °C) *δ*101.9 (C-2),102.0 (C-3), 181.8 (C-4), 160.7 (C-5), 108.0 (C-6), 159.0 (C-7), 104.0 (C-8), 153.9 (C-9), 103.0 (C-10), 120.9 (C-1′), 161.0 (C-4′), 128.6 (C-2′,6′), 115.6 (C-3′,5′); 6-C-ß-Glc: 73.1 (C-1″),70.6(C-2″), 78.2 (C-3″), 69.7(C-4″), 80.9 (C-5″), 60.5 (C-6″); 8-C-α-Ara: 74.6(C-1‴), 68.7 (C-2‴), 74.1 (C-3‴), 68.3 (C-4‴), 70.3 (C-5‴). HRMS (ESI) for C26H28O14Na $[M+Na]^+$: calcd. 587.1371; found 587.1362.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Jun Liu reports financial support and administrative support were provided by Chinese Academy of Science.

Acknowledgements

This work was supported by the STS Project of Chinese Academy of Sciences (KFJ-STS-QYZD-201-5-1) and the National Key Research and Development Program of China (2016YFA0203102).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.132216.

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[17] See *Supplementary Information* for the detailed comparisons of ^{1}H and ^{13}C NMR of natural and synthetic schaftoside. The observed optical rotation values for our synthetic schaftoside was $[\alpha]_D^{20}$ +77.8 (*c* 1.0, MeOH). However, the optical rotation for natural schaftoside was not recorded in literature.[3] the rotational isomerism of synthetic schaftoside was confirmed by variable-temperature ^{1}H NMR in DMSO-d_6 from 60°C to 100 °C. The full characterized details (^{1}H, ^{13}C NMR, COSY, HSQC, HSBC, HPLC, and HRMS) of synthetic schaftoside can be found in the Supporting Information.