JOURNAL OF NATURAL PRODUCTS

pubs.acs.org/jnp

Article

Synthesis of *Salicaceae* Acetyl Salicins Using Selective Deacetylation and Acetyl Group Migration

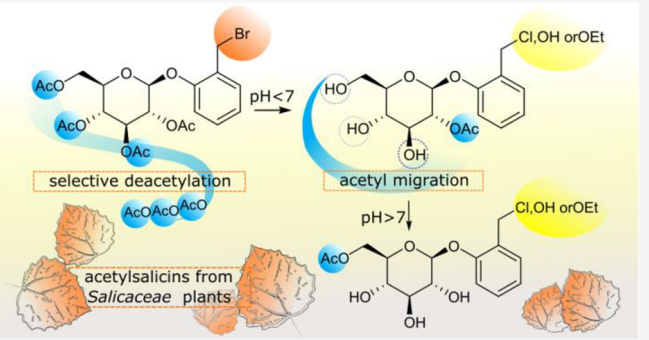
Dariya A. Romanova, David L. Avetyan, Maxim L. Belyanin, and Elena V. Stepanova*

Cite This: https://dx.doi.org/10.1021/acs.jnatprod.9b00570

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: In the present work, the synthesis of acetylated salicins, which occur naturally in many *Salicaceae* species, is reported. The preparation of 2-*O*-acetylsalicin, 2-*O*-acetylchlorosalicin, and 2-*O*-acetylethylsalicin from peracetylated bromosalicin with selective acid-catalyzed deacetylation and one-pot nucleophilic substitution of bromine as the key steps is described. The base-catalyzed O-2 → O-6 acetyl migration afforded 6-*O*-acetylsalicin derivatives in good yields. Thus, the first synthesis of 6-*O*-acetylsalicin (fragilin) using acetyl group migration is reported as well as the synthesis of 6-*O*-acetylchlorosalicin and 6-*O*-acetylethylsalicin. The NaOMe-catalyzed deacetylation of acetylated glycosides gave salicin, chlorosalicin, and ethylsalicin recently reported from *Alangium chinense*.



Salicin is the glucoside of salicylic alcohol and the first isolated and well-studied natural arylglycoside.[1] It is one of the most abundant secondary metabolites of *Salicaceae* and other plants[2] and is a valuable human resource in both native form[3−5] and as the precursor of aspirin.[6−8] Many partially acetylated salicin-like glycosides bearing different aglycones have been isolated from natural sources.[9−12] Fragilin was isolated from *Salix fragilis* L. in the 1960s[13,14] and identified as 6-*O*-acetylsalicin (also referred to as 6′-*O*-acetylsalicin), although the position of the acetyl group was not unequivocally known. The isolation of fragilin in the early studies was likely enabled by a process of acetyl group migration in the 2-*O*- and 3-*O*-acetylsalicins during plant material treatment.[15] For instance, the migration of the benzoyl group occurred readily during the isolation of benzoylated salicins from aspen leaves.[16] 2-*O*-Acetylsalicin (also referred to as 2′-*O*-acetylsalicin) was first described in 1991 and[17] 3-*O*-acetylsalicin was described in 2013,[11] and since then, both were found in *Salicaceae* plants, as a rule, along with other partially acetylated salicins including fragilin.[18−26] Therefore, the possibility for acetyl migration should be considered during the isolation of the acetylated glucosides from plants. Thus, acetyl group migration should not only be seen as an unwanted side process but also as a preparative reaction to yield value-added products.[27,28]

It was demonstrated that the acetyl groups at different positions of the sugar moiety may have a significant effect on the biological activity.[29,30] As an example, 2-acylated glycosides are not decomposed by β-glucosidase and are more stable in acidic medium[9] and at elevated temperatures[31] compared to the nonacylated analogues.

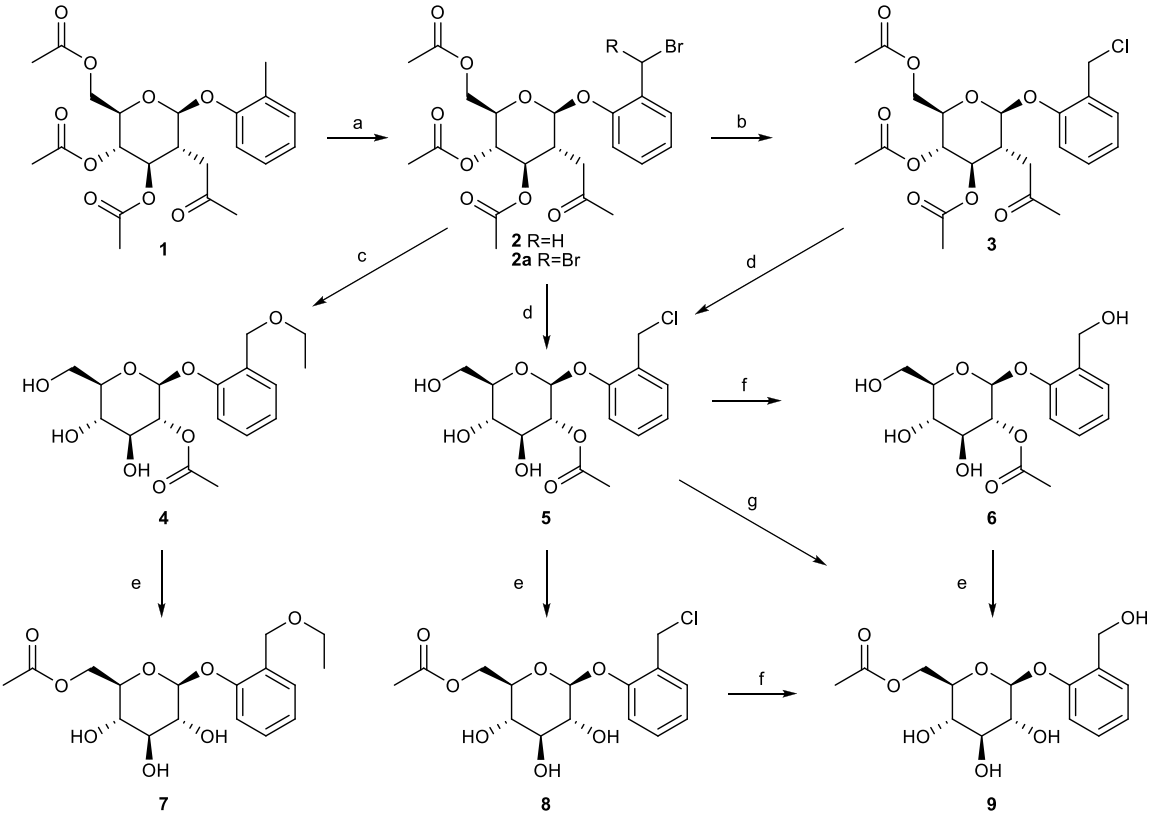
The semisynthesis of 2-*O*- and 3-*O*-acetylsalicins was recently performed *via* the organotin-mediated acetylation of 4,6-benzylidene-ω-tritylsalicin.[32] Herein the synthesis of 2-*O*-acetylsalicins using peracetylated bromosalicin as the key intermediate is described. An additional acetyl group migration is the key step for the preparation of 6-*O*-acetylsalicins from 2-*O*-acetylsalicins.

RESULTS AND DISCUSSION

The starting material for the transformations was the known 2-methylphenyl-(2,3,4,6-tetra-*O*-acetyl)-β-D-glucopyranoside (**1**),[33] which was converted to bromide **2** using photogenerated bromine radicals (Scheme 1). A small amount of dibromide **2a** (∼5%) was also produced but could be removed by recrystallization of the product mixture from EtOH. We and others have found that bromide **2** is highly labile due to its reactive benzylic C−Br bond.[34,35] Thus, recrystallization of the **2**/**2a** mixture from EtOH permitted the isolation of **2a**; however, partial substitution of the bromo substituent with an ethoxy group occurred. To decrease the reactivity of **2**, it was converted to chloride **3** using a halogen-exchange reaction.[36] However, the high reactivity of bromide **2** indicated that deacetylation and the bromo-substitution may be carried out in

Received: June 20, 2019

Scheme 1. Preparation of Acetylated Salicins[A]



[A]Reagents and conditions: (a) Br_2 (equimolar), $CHCl_3$, $h\nu$, 2 h, 95%; (b) Me_4NCl, MeCN, reflux, 4 h, 85%; (c) HBr 36%, $CHCl_3$, EtOH, 30°C, 8 h, 68%; (d) HCl 36%, $CHCl_3$, EtOH, 30°C 8 h; (e) MeCN, H_2O, $NaHCO_3$, room temperature (RT), 3−3.5 h; (f) Ag_2O, acetone, H_2O, HOAc, RT, 48 h; (g) Ag_2O, acetone, H_2O, RT, 24 h, 35%.

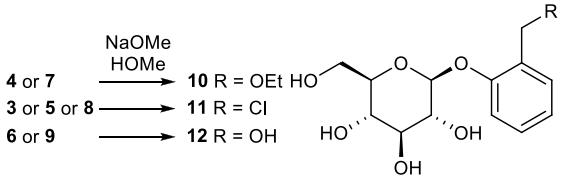
a one-pot reaction. Indeed, HCl-catalyzed deacetylation[37−39] of **2** (HCl, $CHCl_3$, EtOH: 1 M HCl concentration) led to a bromo/chloro exchange with 2-*O*-acetyl chloride **5** as the main product (48%). The same product was obtained from chloride **3** under the same reaction conditions, albeit with a higher yield (67%). By substituting HBr for HCl in the acidic deacetylation of **2**, only insignificant amounts of the deacetylated bromide could be detected using HRMS and NMR data, and this product could not be isolated from the reaction mixture. Instead, the 2-*O*-acetylated ethoxymethyl product **4** was formed. This is the first report of the formation of **4** and the 2-*O*-acetylated chloromethyl derivative **5**.

The conversion of the chloromethyl group in compound **5** to a hydroxymethyl group using Ag_2O in acetone−water led to acetyl group migration to afford 6-*O*-acetylsalicin (fragilin) (**9**) in a mixture with other monoacetates. The unwanted acetyl group migration was suppressed by adding HOAc to the reaction mixture and afforded 2-*O*-acetylsalicin (**6**) in excellent yield (95%). This simple procedure may presumably also be employed to suppress acyl group migration during syntheses of carbohydrates. Thus, using chloro- and/or bromosalicins as synthetic intermediates can be considered as a new (compared with ref 32) method for the preparation of 2-*O*-acetylsalicin (**6**).

However, the migration of acetyl groups is not always an unwanted process that requires suppression. We made use of acetyl group migration for target synthetic transformations. The moderate basification (to pH 7.5−8)[40] of the solutions of 2-*O*-acetylglycosides in a MeCN−water mixture caused rapid acetyl migration instead of hydrolysis and provided 6-*O*-acetylated glucosides in good yields. Thus, we converted 2-*O*-acetylglucosides **4**, **5**, and **6** to 6-*O*-acetylated glucosides **7**, **8**, and **9**, respectively, in 79−88% yields. Compound **9** was also obtained from chloromethyl derivative **8** by the chloro/hydroxy exchange using Ag_2O. The 6-*O*-acetyl derivatives **7**−**9** were synthesized for the first time.

The deacetylated glucosides **10**, **11**, and **12** were obtained by transesterification of compounds **4**, **7**, **3**, **5**, **8**, and **6**, and **9**, respectively, in NaOMe-MeOH (Scheme 2). Small amounts of

Scheme 2. Preparation of *O*-Ethylsalicin (10), Chlorosalicin (11), and Salicin (12)



compounds **10** and **11** were also obtained during selective deacetylation of **2** and **3** (Scheme 1, conditions c and d) as side products. Although the 2-*O*-acetyl group is the most stable among the acetyl groups of peracetates, it can still be cleaved under prolonged reaction times.[38] Therefore, chromatographic monitoring of the reaction progress is necessary during acid-catalyzed deacetylation reactions.

O-Ethylsalicin (**10**) was recently isolated from *Alangium chinense*,[41] an herb that is used in traditional Chinese medicine.

https://dx.doi.org/10.1021/acs.jnatprod.9b00570
J. Nat. Prod. XXXX, XXX, XXX−XXX

Table 1. ^{1}H NMR (400 MHz, DMSO-d_6) Data for Compounds 4−12: δH, mult (J in Hz)[a]

	2-*O*-acetylglucosides			6-*O*-acetylglucosides			deacetylated glucosides		
proton	**4**	**5**	**6**	**7**	**8**[b]	**9**	**10**[b]	**11**[b]	**12**[c]
1	5.09, d (8.0)	5.17, d (8.1)	5.04, d (8.1)	4.82, d (6.8)	4.89, d (7.5)[d]	4.81, d (7.0)	4.88, d (7.4)	4.91, d (7.8)[d]	5.04−5.15, m
2	4.81, dd (8.0, 9.3)	4.86, dd (8.1, 9.5)	4.72, dd, (8.1, 9.1)	3.23−3.30, m	3.53, dd (7.5, 8.9)	3.25−3.32, m	3.35−3.53, m	3.53, dd (7.8, 8.5)	3.55−3.64, m
3	3.48−3.54, m	3.46−3.56, m	3.38−3.56, m	3.23−3.30, m	3.47, dd∼t (8.9)	3.25−3.32, m	3.35−3.53, m	3.39−3.50, m	3.55−3.64, m
4	3.28, dd (5.7, 9.1)	3.29, dd∼t (8.7)	3.26, dd∼t (9.4)	3.18, ddd (5.3, 8.9, 9.1)	3.39, dd (8.9, 9.3)	3.14−3.22, m	3.35−3.53, m	3.39−3.50, m	3.44−3.52, m
5	3.48−3.54, m	3.46−3.56, m;	3.38−3.56, m	3.58, dd (6.8, 8.9)	3.63, ddd (2.2, 6.4, 9.3)	3.59, br dd∼t (8.1)	3.35−3.53, m	3.39−3.50, m	3.55−3.64, m
6	3.48−3.54, m; 3.73, dd (5.5, 11.0)	3.46−3.56, m; 3.74, d (10.3)	3.38−3.56, m; 3.72, dd (5.0, 11.6)	4.09, dd (6.8, 11.8); 4.27, d (11.8)	4.25, dd (6.4, 11.9); 4.40, dd (2.2, 11.9)	4.10, dd (6.8, 11.7); 4.28, d (11.7)	3.70, dd (5.0, 12.0); 3.89, d (12.0)	3.71, dd (5.1, 12.1); 3.90, dd (1.6, 12.1)	3.73, dd (5.6, 12.4); 3.90, dd (2.2, 12.4)
CH_2X	4.32, s	4.57, d (10.7); 4.64, d (10.7)	4.34, dd (5.0, 14.9); 4.40, dd (5.0, 14.9)	4.49, d (13.1); 4.54, d (13.1)	4.74, d (11.4); 4.81, d (11.4)	4.46, d (14.4); 4.63, d (14.4)	4.53, d (12.3); 4.73, d (12.3)	4.72, d (11.4); 4.85, d (11.4)	4.66, d (12.6); 4.71, d (12.6)
CH_2CH_3	3.46, q (7.0)			3.50,q (7.0)			3.57, q (7.0)		
CH_2CH_3	1.15, t (7.0)			1.16, t (7.0)			1.22, t (7.0)		
$COOCH_3$	2.05, s	2.05, s	2.04, s	2.00, s	2.04, s	2.02, s			
aglycone	7.02, dd∼t (7.3); 7.11, d (8.3); 7.24, dd∼t (7.9); 7.31, d (7.7)	7.03, dd∼t (J 7.4); 7.15, d (8.3); 7.33, dd∼t (7.7); 7.40, d (7.4)	7.02, dd∼t (7.4); 7.06, d (8.1); 7.18, dd∼t (7.6); 7.39, d (7.5)	7.01, dd∼t (7.4); 7.05, d (8.3); 7.23, dd∼t (7.6); 7.32, d (7.4)	7.06, dd∼t (7.5); 7.16, d (8.0); 7.24−7.34, m; 7.40, dd (1.5, 7.6)	6.94−7.08, m (2H); 7.20, dd∼t (7.1); 7.38, d (7.4)	7.03, dd∼t (7.3); 7.21, d (8.2); 7.27, dd∼t (7.7); 7.34, d (7.5)	7.03, ddd∼td (1.0, 7.5); 7.21, d (7.6); 7.26−7.34, m; 7.39, dd (1.4, 7.6)	7.13, ddd∼td (1.1, 7.5); 7.19, dd (0.8, 8.3); 7.32−7.42, m (2H)

[a]Spectra of compounds **4**, **6**, and **7** also displayed OH signals, which are not included in the Table. See the Supporting Information file for the complete peak assignments. [b]Spectra were recorded in methanol-d_4 [c]Spectra were recorded in D_2O [d]Signal is partially overlapped with H_2O peak

https://dx.doi.org/10.1021/acs.jnatprod.9b00570
J. Nat. Prod. XXXX, XXX, XXX−XXX

We trust that the chemical synthesis of such compounds will contribute to their phytochemical study.

The NMR data of monoacetylated and deacetylated compounds are summarized in Tables 1 (for ^{1}H NMR) and 2 (for ^{13}C NMR). Notably, the acetylation of HO-2 leads to a downfield shift of the H-2 signal in the ^{1}H NMR spectra but does not significantly affect the ^{13}C NMR chemical shift of C-2. Acetylation of HO-6 shifts both H-6 and C-6 resonances downfield.

In conclusion, acetyl groups in glucosides behave differently depending on the pH of the reaction medium. Acidic catalysis prompted selective deacetylation, providing several 2-*O*-acetylsalicin derivatives from peracetylated bromosalicin. The moderately basic conditions favored O-2 → O-6 acetyl group migration, providing 6-*O*-acetylsalicins from 2-*O*-acetylsalicins. Finally, the classic methanolysis with a strong base (NaOMe) caused complete acetyl group cleavage to yield deacetylated products.

EXPERIMENTAL SECTION

General Experimental Procedures. The reactions were performed in commercial reagents (Aldrich, Fluka, Acros Organics). Anhydrous solvents were purified and dried according to standard procedures. Melting points, which are uncorrected, were determined using an MP50 melting point system (Mettler Toledo). UV spectra were recorded on an Evolution 600 UV−visible spectrophotometer. Optical rotations were measured on an automatic compact polarimeter POP-1/2. IR spectra were recorded on an Agilent Cary 630 FTIR spectrometer equipped with a diamond ATR. ^{1}H and ^{13}C NMR spectra were acquired for solutions in $CDCl_3$, DMSO-d_6, or methanol-d_4 on a Bruker AVANCE III HD instrument (400 and 101 MHz for ^{1}H and ^{13}C, respectively). The ^{1}H NMR chemical shifts are referred to the residual signal of $CHCl_3$ (δ_H 7.26), DMSO-d_5 (δ_H 2.50), methanol-d_3 (δ_H 3.31), or HDO (δ_H 4.79), and the ^{13}C NMR shifts, to the central line of $CDCl_3$ signal (δ_C 77.00), DMSO-d_6 signal (δ_C 39.52), and methanol-d_4 signal (δ_C 49.00). Assignments of the signals in the NMR spectra were performed using 2D-spectroscopy (COSY, HSQC, and HMBC) experiments. High resolution mass spectra (electrospray ionization, ESI-HRMS) were recorded in a positive ion mode on a Bruker micrOTOF II mass spectrometer for 2×10^{-5} M solutions in MeCN. Column chromatography was performed on silica gel 60 (40−63 μm, Merck). Flash chromatography was carried out on Reveleris X2 Büchi chromatographer using FlashPure Select C_{18} 30 μm columns. Thin-layer chromatography was carried out on silica gel 60 F_{254} plates on aluminum foil (Merck). Spots of compounds were visualized under UV light (254 nm) and by heating the plates (at ca. 150 °C) after immersion in a 1:10 (v/v) mixture of 85% aqueous H_3PO_4 and 95% EtOH.

2-(Bromomethyl)phenyl-2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (2). To a stirred suspension of 2-methylphenyl-(2,3,4,6-tetra-*O*-acetyl)-β-D-glucopyranose (**1**) (1 g, 2.28 mmol) and $NaHCO_3$ (3 g, 35.70 mmol) in $CHCl_3$ (120 mL), the solution of bromine (118 μL, 2.28 mmol) in $CHCl_3$ (5.8 mL) was added dropwise, and the reaction mixture was irradiated with an incandescent lamp (200 W) until all bromine reacted (red color disappeared). Solids were filtered off and washed with $CHCl_3$ (100 mL). The filtrate was concentrated under reduced pressure, and the residue was purified by flash-chromatography on a C_{18} column to give 1.12 g (95%) of the title compound as colorless crystals, R_f 0.33 (toluene−acetone 10:1). Mp: 150−151 °C. $[\alpha]^{20}_D$ +7 (*c* 1, CH_2Cl_2). UV (EtOH): λ_{max} 277 nm. FTIR (ATR): ν_{max} 2960, 1749, 1602, 1488, 1368, 1225, 1038, 908, 731 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm, *J*, Hz): 2.05 (s, 3H), 2.06 (s, 3H), 2.08 (s, 3H), 2.12 (s, 3H, $COOCH_3$), 3.91 (ddd, 1H, *J* 2.4, *J* 5.4, *J* 9.8, H-5), 4.19 (dd, 1H, *J* 2.4, *J* 12.3, H-6a), 4.30 (dd, 1H, *J* 5.4, *J* 12.3, H-6b), 4.35 (d, 1H, *J* 9.8, CH_2Br), 4.64 (d, 1H, *J* 9.8, CH_2Br), 5.16 (d, 1H, *J* 7.6, H-1), 5.19 (dd, 1H, *J* 9.2, *J* 9.8, H-4), 5.33 (dd~t, 1H, *J* 9.2, H-3), 5.39 (dd, 1H, *J* 7.6, *J* 9.2, H-2), 7.01 (d, 1H, *J* 8.3, C_6H_4), 7.06

Table 2. ^{13}C NMR (101 MHz, DMSO-d_6) Data for Compounds 4−12

	2-*O*-acetylglucosides			6-*O*-acetylglucosides			deacetylated glucosides		
carbon	**4**	**5**	**6**	**7**	**8**[a]	**9**	**10**[a]	**11**[a]	**12**[b]
1	98.2	97.9	98.3	101.1	103.1	101.1	103.2	102.9	100.4
2	73.5	73.4	73.5	73.3	74.9	73.3	75.1	75.0	72.9
3	73.8	73.7	73.8	76.2	77.9	76.2	78.0 or 78.2	78.1 or 78.2	75.5 or 76.0
4	69.8	69.7	69.8	69.9	71.5	69.9	71.3	71.3	69.3
5	77.2	77.2	77.2	73.6	75.4	73.6	78.0 or 78.2	78.1 or 78.2	75.5 or 76.0
6	60.6	60.5	60.5	63.5	64.7	63.4	62.5	62.5	60.4
CH_2X	66.0	41.0	57.4	66.3	41.9	58.1	68.7	42.0	59.2
CH_2CH_3	65.2			65.2			66.8		
CH_2CH_3	15.1			15.2			15.4		
$COOCH_3$	20.9	21.1	20.9	20.7	20.7	20.7			
$COOCH_3$	169.4	169.5	169.5	170.3	172.7	170.3			
aglycone	114.5, 122.0, 127.3, 128.3, 128.5, 154.2	114.9, 122.3, 126.0, 130.3, 130.9, 154.7	114.2, 122.0, 126.7, 127.5, 131.2, 153.6	115.0, 122.0, 127.9, 128.0, 128.2, 154.3	117.3, 123.9, 129.1, 120.9, 131.5, 156.7	114.7, 121.9, 127.2, 127.6, 131.6, 154.4	116.8, 123.4, 129.0, 130.2, 130.4, 157.2	116.9, 123.6, 128.7, 131.0, 131.5, 156.9	115.2, 123.3, 129.3, 129.61, 129.64, 154.5

[a]Spectra were recorded in methanol-d_4. [b]Spectra were recorded in D_2O

https://dx.doi.org/10.1021/acs.jnatprod.9b00570
J. Nat. Prod. XXXX, XXX, XXX−XXX

(t, 1H, *J* 7.5, C_6H_4), 7.24−7.30 (m, 1H, C_6H_4), 7.37 (dd, 1H, *J* 1.3, *J* 7.5, C_6H_4). ^{13}C NMR (101 MHz, $CDCl_3$, *δ*, ppm): 20.6, 20.6, 20.7, 21.0 (4 × $COOCH_3$), 27.9 (CH_2Br), 61.9 (C-6), 68.3 (C-4), 70.7 (C-2), 72.0 (C-5), 72.6 (C-3), 98.5 (C-1), 115.0, 123.5, 127.5, 130.1, 131.3, 154.2 (6 × C_6H_4), 169.4, 169.5, 170.2, 170.6 (4 × $COOCH_3$). HRESIMS: *m*/*z* 539.0531 $[M + Na]^+$ (calcd for $C_{21}H_{25}BrO_{10}Na$, 539.0529).

*2-(Chloromethyl)phenyl-2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (**3**).* Bromide **2** (200 mg, 0.35 mmol) and Me_4NCl (423 mg, 3.86 mmol) were dissolved in dry MeCN (20 mL) and refluxed under stirring for 4 h. MeCN was distilled off *in vacuo*, and the residue was dissolved in $CHCl_3$ (30 mL), washed with 5% aq HCl (3 × 30 mL), water (2 × 30 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The solid residue was recrystallized from EtOH (4 mL) to give 185 mg (85%) of the title compound as white crystals, R_f 0.33 (toluene−acetone 10:1). Mp: 148−149 °C. $[\alpha]^{20}_D$ +7 (*c* 1, CH_2Cl_2). UV (EtOH): λ_{max} 219, 275 nm. FTIR (ATR): ν_{max} 2958, 2877, 1742, 1605, 1494, 1366, 1227, 1209, 1035, 908, 752 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, *δ*, ppm, *J*, Hz): 2.05 (s, 3H), 2.05 (s, 3H), 2.08 (s, 3H), 2.09 (s, 3H, $COOCH_3$), 3.90 (ddd, 1H, *J* 2.0, *J* 5.3, *J* 9.3, H-5), 4.19 (dd, 1H, *J* 2.0, *J* 12.3, H-6a), 4.30 (dd, 1H, *J* 5.3, *J* 12.3, H-6b), 4.43 (d, 1H, *J* 11.2, CH_2Cl), 4.73 (d, 1H, *J* 11.2, CH_2Cl), 5.12 (d, 1H, *J* 7.9, H-1), 5.19 (dd∼t, 1H, *J* 9.3, H-4), 5.32 (dd∼t, 1H, *J* 9.3, H-3), 5.37 (dd, 1H, *J* 7.8, *J* 9.3, H-2), 7.03 (d, 1H, *J* 8.3), 7.08 (t, 1H, *J* 7.5), 7.29 (t, 1H, *J* 7.9), 7.38 (d, 1H, *J* 7.5, C_6H_4). ^{13}C NMR (101 MHz, $CDCl_3$, *δ*, ppm): 20.6, 20.6, 20.7, 20.8 (4 × $COOCH_3$), 40.8 (CH_2Cl), 61.9 (C-6), 68.3 (C-4), 70.7 (C-2), 72.0 (C-5), 72.6 (C-3), 98.9 (C-1), 115.1, 123.5, 127.2, 130.0, 131.0, 154.4 (6 × C_6H_4), 169.4, 169.4, 170.2, 170.6 (4 × $COOCH_3$). HRESIMS: *m*/*z* 495.1041 $[M + Na]^+$ (calcd for $C_{21}H_{25}ClO_{10}Na$, 495.1034).

*2-(Ethoxymethyl)phenyl-2-O-acetyl-β-D-glucopyranoside (**4**).* Peracetylated bromide **2** (330 mg,0.64 mmol) was dissolved in a mixture of $CHCl_3$ (1.5 mL) and EtOH (3 mL), and 36% aqueous HBr (1 mL) was added. The reaction mixture was kept at 30 °C for 8 h (TLC showed the formation of the major component and one lower-running spot), and anion-exchange resin AB-17 (OH^- form) was added until pH ∼ 7, then was filtered off, and the mixture was thoroughly washed with EtOH (80 mL). The solvents were combined and evaporated under reduced pressure. The residue was purified on silica gel column chromatography $CHCl_3$−EtOH 13% and recrystallized from EtOH (4 mL) to give 0.155 g (68%) of the title compound as a white solid, R_f 0.66 ($CHCl_3$−EtOH 8:1). Mp: 141−143 °C. $[\alpha]^{28}_D$ −40 (*c* 2, MeOH). UV (EtOH): λ_{max} 218, 269 nm. FTIR (ATR): ν_{max} 3405 (br), 2970, 2923, 2875, 1743, 1492, 1228, 1075, 1031, 756 cm^{-1}. ^{1}H and ^{13}C NMR data are given in Tables 1 and 2, respectively. HRESIMS: *m*/*z* 379.1361 $[M + Na]^+$ (calcd for $C_{17}H_{24}O_8Na$, 379.1369).

*2-(Chloromethyl)phenyl-2-O-acetyl-β-D-glucopyranoside (**5**).* Peracetylated bromide **2** (2 g, 3.80 mmol) or chloride **3** (1.83 g, 3.80 mmol) was dissolved in a mixture of $CHCl_3$ (4 mL) and EtOH (6 mL), and 36% aqueous HCl (1.5 mL) was added. The reaction mixture was kept at 30 °C for 8 h (TLC showed the formation of major component and one lower-running spot), and anion-exchange resin AB-17 (OH^- form) was added until pH ∼ 7, then was filtered off, and the mixture was thoroughly washed with EtOH (130 mL). The solvents were combined and evaporated under reduced pressure. The residue was purified on silica gel column chromatography $CHCl_3$−EtOH 20:1 → 4:1 and recrystallized from EtOH (7 mL) to give the title compound as a white solid. The yield was 0.640 g (48%) from **2** and 0.898 g (67%) from **3**, R_f 0.67 ($CHCl_3$−EtOH 4:1). Mp: 187−188 °C. $[\alpha]^{20}_D$ −12 (*c* 0.6, Me_2CO). UV (EtOH): λ_{max} 212, 275 nm. FTIR (ATR): ν_{max} 3515, 3240 (br), 2972, 2902, 1726, 1605, 1497, 1259, 1236, 1077, 1035, 748 cm^{-1}. ^{1}H and ^{13}C NMR data are given in Tables 1 and 2, respectively. HRESIMS: *m*/*z* 369.0726 $[M + Na]^+$ (calcd for $C_{15}H_{19}ClO_7Na$, 369.0712).

*2-(Hydroxymethyl)phenyl-2-O-acetyl-β-D-glucopyranoside (2-O-acetylsalicin) (**6**).* Chloride **5** (20 mg, 57.80 μmol) was dissolved in a mixture of acetone (2 mL) and water (2 mL), and grounded Ag_2O (20 mg, 86.60 μmol) was added followed by HOAc (0.5 mL). Whereupon the black Ag_2O suspension changed color to gray. The reaction mixture was stirred at RT (∼20 °C) for 48 h and concentrated *in vacuo*, and the residue was directly purified by silica gel column chromatography $CHCl_3$−EtOH 14% to give 18 mg (95%) of the title compound as a white solid, R_f 0.45 ($CHCl_3$−EtOH 3:1). Mp: 191−193 °C (lit. 189−191 °C).[18] $[\alpha]^{20}_D$ −34 (*c* 1 MeOH). UV (EtOH): λ_{max} 215, 267 nm. FTIR (ATR): ν_{max} 3307 (br), 2919, 1735, 1637, 1491, 1374, 1230, 1072, 1022, 991, 759 cm^{-1}. ^{1}H and ^{13}C NMR data are given in Tables 1 and 2, respectively. HRESIMS: *m*/*z* 351.1038 $[M + Na]^+$ (calcd for $C_{15}H_{20}O_8Na$, 351.1050). The spectroscopic data are in agreement with the literature.[18]

General Procedure For O-2 → O-6 Acetyl Group Migration. 2-*O*-Acetylglucoside **4**, **5**, or **6** (0.06 mmol) was dissolved in a mixture of CH_3CN (1.5 mL) and H_2O (1 mL), and saturated aqueous $NaHCO_3$ (100 μL) was added. The reaction mixture was stirred at RT (∼20 °C) for 3−3.5 h (TLC control), HOAc (100 μL) was added, and solvents were distilled under reduced pressure. The residue was dissolved in water (3 mL), and extracted with EtOAc (3 × 3 mL). The EtOAc extracts were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified on silica gel column chromatography using $CHCl_3$−EtOH 20:1 → 10:1.

*2-(Ethoxymethyl)phenyl-6-O-acetyl-β-D-glucopyranoside (**7**).* The title compound was obtained from compound **4** as an amorphous powder. Yield: 88%. R_f 0.69 ($CHCl_3$−EtOH 8:1). $[\alpha]^{20}_D$ −94 (*c* 0.4, MeOH). UV (EtOH): λ_{max} 215, 269 nm. FTIR (ATR): ν_{max} 3428 (br), 3092, 1735, 1654, 1624, 1458 1235, 1000, 821, 759 cm^{-1}. ^{1}H and ^{13}C NMR data are given in Tables 1 and 2, respectively. HRESIMS: *m*/*z* 379.1359 $[M + Na]^+$ (calcd for $C_{17}H_{24}O_8Na$, 379.1369).

*2-(Chloromethyl)phenyl-6-O-acetyl-β-D-glucopyranoside (**8**).* The title compound was obtained from compound **6** as an amorphous powder. Yield: 85%. R_f 0.70 ($CHCl_3$−EtOH 4:1). $[\alpha]^{20}_D$ −52 (*c* 0.2, MeOH). UV (EtOH): λ_{max} 220, 275 nm. FTIR (ATR): ν_{max} 3367 (br), 2917, 1718, 1603, 1492, 1368, 1235, 1068, 1035, 749 cm^{-1}. ^{1}H and ^{13}C NMR data are given in Tables 1 and 2, respectively. HRESIMS: *m*/*z* 369.0720 $[M + Na]^+$ (calcd for $C_{15}H_{19}ClO_7Na$, 369.0712).

*2-(Hydroxymethyl)phenyl-6-O-acetyl-β-D-glucopyranoside (Fragilin) (**9**).* The title compound wasobtained from compound **5** as colorless crystals. Yield: 79%; R_f 0.47 ($CHCl_3$−EtOH 4:1). Mp: 179−180 °C (lit. 177−179 °C,[14] 178−180 °C).[29] $[\alpha]^{20}_D$ −57 (*c* 0.6, MeOH). UV (EtOH): λ_{max} 212, 268 nm. FTIR (ATR): ν_{max} 3429 (br), 3099, 3074, 2970, 1701, 1654, 1161, 1358, 1182, 1000, 763 cm^{-1}. ^{1}H and ^{13}C NMR data are given in Tables 1 and 2, respectively. HRESIMS: *m*/*z* 351.1044 $[M + Na]^+$ (calcd for $C_{15}H_{20}O_8Na$, 351.1050). The spectroscopic data are in agreement with the literature.[29]

General Procedure For Nonselective Deacetylation. Acetylated glucosides **3**, **4**, **5**, **6**, **7**, **8**, or **9** (0.120 mmol) were separately dissolved or suspended in MeOH (6 mL), and solid NaOMe (5 mg) was added. The reaction mixture was stirred at RT (∼20 °C) for 2 h, neutralized by adding cation-exchange resin KU-2-8, which was filtered off, and washed with MeOH (30 mL). The methanolic solution was concentrated under reduced pressure and dried *in vacuo* to produce deacetylated glucosides.

*2-(Ethoxymethyl)phenyl-β-D-glucopyranoside (Ethylsalicin) (**10**).* The title compound was obtained from compounds **4** or **7** as an amorphous powder. Yield: 99% in both cases. R_f 0.70 ($CHCl_3$−EtOH 4:1). $[\alpha]^{20}_D$ −35 (*c* 0.8, MeOH). UV (EtOH): λ_{max} 211, 269 nm. FTIR (ATR): ν_{max} 3449 (br), 2974, 2872, 1603, 1491, 1389, 1232, 1020, 751 cm^{-1}. ^{1}H and ^{13}C NMR data are given in Tables 1 and 2, respectively. HRESIMS: *m*/*z* 337.1255 $[M + Na]^+$ (calcd for $C_{15}H_{22}O_7Na$,337.1263). The spectroscopic data are in agreement with the published data.[41]

*2-(Chloromethyl)phenyl-β-D-glucopyranoside (Chlorosalicin) (**11**).* The title compound was obtained from compounds **5**, **8**, or **3** as colorless crystals. Yield: 99% in both cases. R_f 0.34 ($CHCl_3$−EtOH 4:1). Mp: 120 °C (decomp). $[\alpha]^{20}_D$ −82 (*c* 0.3, MeOH). UV (EtOH): λ_{max} 221, 275 nm. FTIR (ATR): ν_{max} 3380 (br), 2921, 2877, 1604, 1492, 1241, 1072, 1043, 751 cm^{-1}. ^{1}H and ^{13}C NMR data are

https://dx.doi.org/10.1021/acs.jnatprod.9b00570
J. Nat. Prod. XXXX, XXX, XXX−XXX

given in Tables 1 and 2, respectively. HRESIMS: m/z 327.0609 $[M + Na]^+$ (calcd for $C_{13}H_{17}ClO_6Na$, 327.0611).

2-(Hydroxymethyl)phenyl-β-D-glucopyranoside (Salicin) (12). The title compound was obtained from compounds **6** and **9** as colorless crystals. Yield: 99% in both cases. R_f 0.25 ($CHCl_3$−EtOH 4:1). Mp: 201−202 °C (lit. 198−200 °C).[42,43] $[\alpha]^{20}_D$ −58 (*c* 1, MeOH). UV (EtOH): λ_{max} 213, 268 nm. FTIR (ATR): ν_{max} 3345 (br), 3077, 2972, 2932, 1603, 1494, 1238, 1079, 1038, 1012, 755 cm^{-1}. ^1H and ^{13}C NMR data are given in Tables 1 and 2, respectively. The spectroscopic data are in agreement with the published data.[42,44]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jnatprod.9b00570.

Assignments of all protons and figures of 1D and 2D NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Elena V. Stepanova − *Tomsk Polytechnic University, Tomsk 634050, Russian Federation; N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences, Moscow 119991, Russian Federation;* orcid.org/0000-0001-9617-9110; Phone: +7 (3822) 563861; Email: eline_m@mail.ru, glycoside.m@gmail.com

Authors

Dariya A. Romanova − *Tomsk Polytechnic University, Tomsk 634050, Russian Federation*

David L. Avetyan − *Tomsk Polytechnic University, Tomsk 634050, Russian Federation; Siberian State Medical University, Tomsk 634050, Russian Federation*

Maxim L. Belyanin − *Tomsk Polytechnic University, Tomsk 634050, Russian Federation*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.jnatprod.9b00570

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by the Tomsk Polytechnic University Competitiveness Enhancement Program grant. The authors would like to thank TPU Shared Knowledge Center − Physical and Chemical Methods and Aleksey Ivanov for the help with UV experiments.

■ REFERENCES

(1) Pelouze; Gay-Lussac, J. *Ann. Phys.* **1830**, *95*, 304−304.
(2) Boeckler, G. A.; Gershenzon, J.; Unsicker, S. B. *Phytochemistry* **2011**, *72*, 1497−1509.
(3) Schmid, B.; Kötter, I.; Heide, L. *Eur. J. Clin. Pharmacol.* **2001**, *57*, 387−391.
(4) Turner, E. B. *Lancet* **1891**, *138*, 121−122.
(5) Maclagan, T. *Lancet* **1876**, *107*, 383−384.
(6) Lévesque, H.; Lafont, O. *Rev. Méd. Interne* **2000**, *21*, S8−S17.
(7) Lafont, O. *Rev. Hist. Pharm.* **2007**, *55*, 209−216.
(8) Weissmann, G. *Sci. Am.* **1991**, *264*, 84−91.
(9) Julkunen-Tiitto, R.; Meier, B. *J. Nat. Prod.* **1992**, *55*, 1204−1212.
(10) Kammerer, B.; Kahlich, R.; Biegert, C.; Gleiter, C. H.; Heide, L. *Phytochem. Anal.* **2005**, *16*, 470−478.
(11) Yang, H.; Lee, S. H.; Sung, S. H.; Kim, J.; Kim, Y. C. *Planta Med.* **2013**, *79*, 78−82.
(12) Keefover-Ring, K.; Ahnlund, M.; Abreu, I. N.; Jansson, S.; Moritz, T.; Albrectsen, B. R. *PLoS One* **2014**, *9*, No. e107189.
(13) Thieme, H. *Naturwissenschaften* **1964**, *51*, 310−310.
(14) Thieme, H. *Naturwissenschaften* **1963**, *50*, 477−477.
(15) Julkunen-Tiitto, R.; Tahvanainen, J. *Planta Med.* **1989**, *55*, 55−58.
(16) Pearl, I. A.; Darling, S. F. *Arch. Biochem. Biophys.* **1963**, *102*, 33−38.
(17) Shao, Y. *Phytochemischer Atlas der Schweizer Weiden*; ETH: Zurich, 1991.
(18) Reichardt, P. B.; Merken, H. M.; Clausen, T. P.; Wu, J. *J. Nat. Prod.* **1992**, *55*, 970−973.
(19) Ruuhola, T.; Tikkanen, O.-P.; Tahvanainen, J. *J. Chem. Ecol.* **2001**, *27*, 1595−1615.
(20) Ruuhola, T.; Julkunen-Tiitto, R.; Vainiotalo, P. *J. Chem. Ecol.* **2003**, *29*, 1083−1097.
(21) Ruuhola, T.; Julkunen-Tiitto, R. *J. Chem. Ecol.* **2003**, *29*, 1565−1588.
(22) Iqbal, K.; Malik, A.; Mehmood, A.; Mukhtar, N.; Tareen, R. *J. Chem. Soc. Pak.* **2004**, *26*, 392−394.
(23) Foerster, N.; Ulrichs, C.; Zander, M.; Kätzel, R.; Mewis, I. *Gesunde Pflanz.* **2009**, *61*, 129−134.
(24) Dagvadorj, E.; Shaker, K. H.; Windsor, D.; Schneider, B.; Boland, W. *Phytochemistry* **2010**, *71*, 1900−1907.
(25) Abreu, I. N.; Ahnlund, M.; Moritz, T.; Albrectsen, B. R. *J. Chem. Ecol.* **2011**, *37*, 857−870.
(26) Nybakken, L.; Julkunen-Tiitto, R. *Physiol. Plant.* **2013**, *147*, 465−476.
(27) Lassfolk, R.; Rahkila, J.; Johansson, M. P.; Ekholm, F. S.; Warna, J.; Leino, R. *J. Am. Chem. Soc.* **2019**, *141*, 1646−1654.
(28) Terreni, M.; Salvetti, R.; Linati, L.; Fernandez-Lafuente, R.; Fernández-Lorente, G.; Bastida, A.; Guisan, J. M. *Carbohydr. Res.* **2002**, *337*, 1615−1621.
(29) Kim, C. S.; Subedi, L.; Park, K. J.; Kim, S. Y.; Choi, S. U.; Kim, K. H.; Lee, K. R. *Fitoterapia* **2015**, *106*, 147−152.
(30) Hongu, M.; Funami, N.; Takahashi, Y.; Saito, K.; Arakawa, K.; Matsumoto, M.; Yamakita, H.; Tsujihara, K. *Chem. Pharm. Bull.* **1998**, *46*, 1545−1555.
(31) Julkunen-Tiitto, R.; Gebhardt, K. *Planta Med.* **1992**, *58*, 385−386.
(32) Shao, C.; Pei, Y.; Borg-Karlson, A.-K.; Pei, Z. *Chem. Res. Chin. Univ.* **2014**, *30*, 774−777.
(33) Stepanova, E.; Nagornaya, M.; Belyanin, M.; Filimonov, V. *Curr. Org. Synth.* **2017**, *14*, 394−397.
(34) Briggs, J. C.; Haines, A. H.; Taylor, R. J. K. *J. Chem. Soc., Chem. Commun.* **1992**, *0*, 1039−1041.
(35) Stepanova, E. V.; Belyanin, M. L.; Filimonov, V. D. *Carbohydr. Res.* **2014**, *388*, 105−111.
(36) Briggs, J. C.; Haines, A. H.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1995**, 27−32.
(37) Stepanova, E. V.; Nagornaya, M. O.; Filimonov, V. D.; Valiev, R. R.; Belyanin, M. L.; Drozdova, A. K.; Cherepanov, V. N. *Carbohydr. Res.* **2018**, *458−459*, 60−66.
(38) Nasibullin, R. T.; Valiev, R. R.; Faiskanova, K. M.; Stepanova, E. V.; Cherepanov, V. N.; Filimonov, V. D.; Sundholm, D. *Chem. Phys. Lett.* **2019**, *723*, 123−127.
(39) Stepanova, E. V.; Belyanin, M. L.; Filimonov, V. D.; Valiev, R. R.; Gruner, M.; Rogachev, V. *Carbohydr. Res.* **2015**, *409*, 36−40.
(40) Roslund, M. U.; Aitio, O.; Warna, J.; Maaheimo, H.; Murzin, D. Y.; Leino, R. *J. Am. Chem. Soc.* **2008**, *130* (27), 8769−8772.
(41) Zhang, Y.; Liu, Y.-B.; Li, Y.; Ma, S.-G.; Li, L.; Qu, J.; Zhang, D.; Jiang, J.-D.; Yu, S.-S. *Chin. Chem. Lett.* **2017**, *28*, 32−36.
(42) Zapesochnaya, G. G.; Kurkin, V. A.; Braslavskii, V. B.; Filatova, N. V. *Chem. Nat. Compd.* **2002**, *38*, 314−318.
(43) Diogo, H. P.; Pinto, S. S.; Moura Ramos, J. J. *Int. J. Pharm.* **2008**, *358*, 192−197.
(44) Itoh, A.; Tanahashi, T.; Ikejima, S.; Inoue, M.; Nagakura, N.; Inoue, K.; Kuwajima, H.; Wu, H.-X. *J. Nat. Prod.* **2000**, *63*, 95−98.