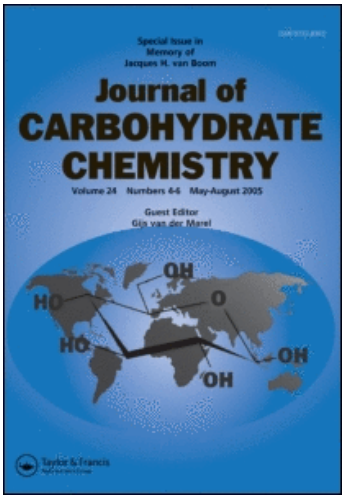

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Synthesis of a Trisaccharide Related to the Triterpenoid Saponin Kalopanaxsaponin I Isolated from *Nigella sativa*

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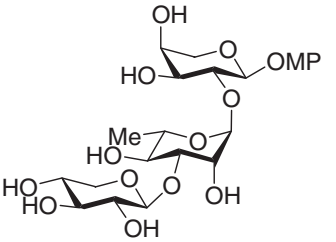

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Graphical Abstract

Saponins are plant secondary metabolites important for growth and development, and they have immense potential as drug candidates for various diseases. Synthesis of the glycone part of the triterpenoid saponin kalopanaxsaponin I isolated from *Nigella sativa* is reported as its *p*-methoxyphenyl glycoside. The synthesis of the target trisaccharide has been accomplished by following concise protecting group manipulations on commercially available L-arabinose, L-rhamnose, and D-xylose. Stereoselective glycosylations are achieved through activation of thioglycoside by *N*-iodosuccinimide in conjunction with H_2SO_4 silica.

Keywords Triterpenoid saponin; Glycosylation; H_2SO_4 silica

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INTRODUCTION

Triterpenoid saponins are synthesized by plants during their regular program of growth and development. Many of them are exploited as a source of drugs, for example, ginseng and liquorice, and also crop plants like legumes and oats.[1] This class of molecules is important because of their antifungal properties through preformed barriers in the healthy plants.[2] Despite the commercial interest associated with this class of natural products, the genetic machinery involved in the biosynthesis of these glycosylated secondary metabolites are yet to be discovered completely. Glycosylation at the C-3 position of the triterpenoid backbone is a common feature shared by this class of molecules. Since the C-3 position of the triterpenoid is important for saponin bioactivity, the glycosylation pattern at this site is worthy of exploration.[3] To obtain a better understanding of the glycosyltransferases involved and to establish the order of events in saponin biosynthesis, synthetic saccharide fragments would be very useful.[4]

In this communication, we report a concise route for the synthesis of the glycone part of the triterpenoid saponin kalopanaxsaponin I isolated from *Nigella sativa*[5] in the form of its *p*-methoxyphenyl glycoside (Fig. 1).

RESULT AND DISCUSSION

The glycone part of the triterpenoid saponin kalopanaxsaponin I isolated from *N. sativa* consists of L-arabinose, L-rhamnose, and D-xylose units. The choice of *p*-methoxyphenyl group as the reducing end glycoside was driven by the fact that after the total synthesis, this glycoside can be hydrolyzed selectively and coupled to suitable aglycon to generate biologically relevant glycoconjugate.

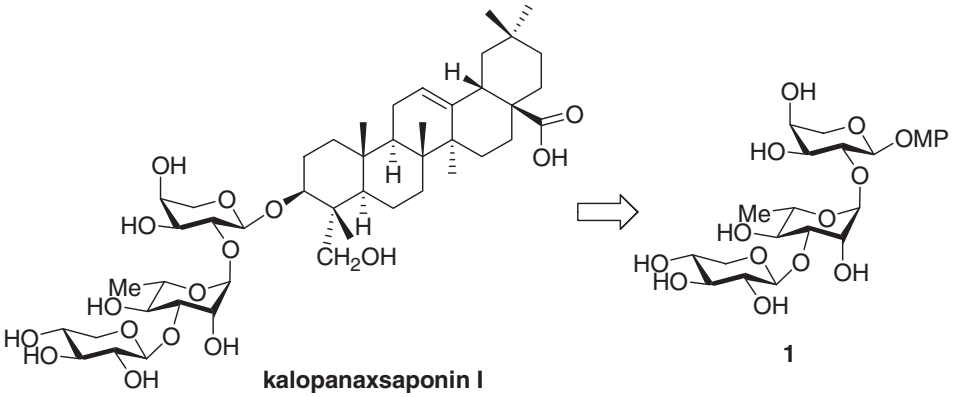


Figure 1: Structure of kalopanaxsaponin I and the synthetic target.

The axial OH group of the known *p*-tolyl 4-*O*-benzyl-1-thio-α-L-rhamnopyranoside (**2**)[6] was selectively benzylated by phase-transfer technique using BnBr and 10% NaOH in the presence of Bu_4NBr[7] to afford the dibenzyl derivative **3** in 78% yield. Acetylation of the remaining OH group with Ac_2O and pyridine[8] furnished the rhamnosyl donor *p*-tolyl 3-*O*-acetyl-2,4-di-*O*-benzyl-1-thio-α-L-rhamnopyranoside (**4**) in 92% yield.

Further, glycosylation of compound **4** with known *p*-methoxyphenyl 3,4-*O*-isopropylidene-β-L-arabinopyranoside (**5**)[9] was accomplished by using *N*-iodosuccinimide (NIS) in the presence of H_2SO_4 immobilized on silica (H_2SO_4-silica)[10] to furnish the disaccharide **6** in 86% yield. The required α-linkage has been confirmed by the $J_{C,H}$ coupling constant 172 Hz, which is normal for α-Rha linkage.[11] Removal of the acetyl group using NaOMe in MeOH afforded the disaccharide acceptor **7** in 89% yield. Finally, the disaccharide acceptor was coupled with the known donor *p*-tolyl 2,3,4-tri-*O*-acetyl-1-thio-β-D-xylopyranoside (**8**) following the same glycosylation strategy as above to afford the protected trisaccharide **9** in 81% yield. Next, hydrolysis of the isopropylidene acetal with 80% AcOH at 80°C[12] and catalytic hydrogenation using Pd-C followed by Zemplén de-*O*-acylation furnished the target trisaccharide *p*-methoxyphenyl β-D-xylopyranosyl-(1→3)-α-L-rhamnopyranosyl-(1→2)-β-L-arabinopyranoside (**1**) in 73% yield over three steps (Sch. 1).

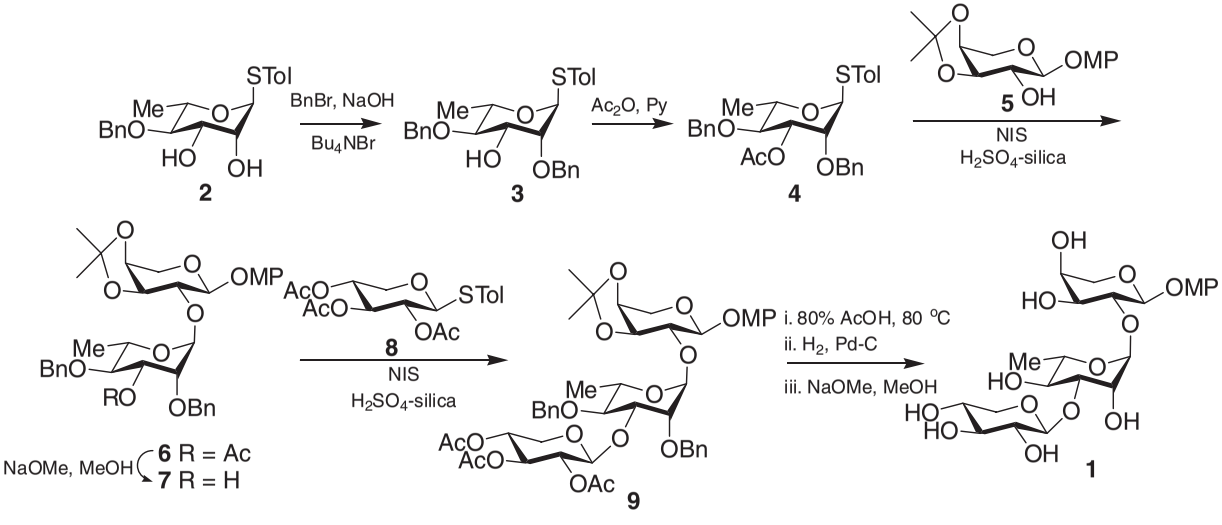
CONCLUSION

In conclusion, we have developed an efficient synthetic strategy for the trisaccharide fragment related to the glycone part of the triterpenoid saponin kalopanaxsaponin I isolated from *N. sativa*. The trisaccharide will be evaluated for its biological activity in due course.

EXPERIMENTAL

General Methods

All reagents and solvents were dried prior to use according to standard methods.[13] Commercial reagents were used without further purification unless otherwise stated. Analytical TLC was performed on silica gel 60-F_{254} with detection by fluorescence and/or by charring following immersion in a 10% ethanolic solution of sulfuric acid. An orcinol dip, prepared by the careful addition of concentrated sulfuric acid (20 mL) to an ice-cold solution of 3,5-dihydroxytoluene (360 mg) in EtOH (150 mL) and H_2O (10 mL), was used to detect deprotected compounds by charring. Flash chromatography was performed with silica gel 60. Optical rotations were measured at the sodium D-line at ambient temperature. ^1H NMR and ^{13}C NMR spectra were recorded



Scheme 1: Synthesis of the target trisaccharide **1**.

on a spectrometer at 500 MHz and 125 MHz, respectively. Mass spectra were recorded on a Micromass Q-TOF Micro TM spectrometer.

p-Tolyl 3-*O*-acetyl-2,4-di-*O*-benzyl-1-thio-α-L-rhamnopyranoside (4)

Compound **2** (2.2 g, 6.2 mmol) was dissolved in CH_2Cl_2 (40 mL); 10% aq. NaOH (7 mL) was added followed by Bu_4NBr (2.9 g, 8.9 mmol) and BnBr (1.1 mL, 9.8 mmol), and the biphasic mixture was vigorously stirred at rt for 16 h. Then the mixture was washed with H_2O (3 × 50 mL) and the organic layer was collected, dried (Na_2SO_4), filtered, and evaporated. The crude product was purified by flash chromatography using *n*-hexane-EtOAc (3:1) to afford pure compound **3** (2.2 g, 78%) as a colorless gel. To a solution of compound **3** (2.0 g, 4.4 mmol) in dry pyridine (15 mL), Ac_2O (10 mL) was added and the solution was stirred at rt for 2 h. After evaporating the solvents in vacuo, the residue was purified by flash chromatography using *n*-hexane-EtOAc (4:1) to afford pure compound **4** (2.0g, 92%) as a colorless gel. $[\alpha]_D^{25}$ +78 (*c* 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.36–7.10 (m, 14H, ArH), 5.39 (d, 1H, $J_{1,2}$ = 1.5 Hz, H-1), 5.17 (dd, 1H, $J_{2,3}$ = 3.5 Hz, $J_{3,4}$ = 9.0 Hz, H-3), 4.73, 4.66, 4.64, 4.47 (4d, AB system, 4H, J = 12.5 Hz, 2 × CH_2Ph), 4.23 (m, 1H, H-5), 4.08 (dd, 1H, $J_{1,2}$ = 1.5 Hz, $J_{2,3}$ = 3.5 Hz, H-2), 3.69 (t, 1H, $J_{3,4}$, $J_{4,5}$ = 9.0 Hz, H-4), 2.32 (s, 3H, S-C$_6$H$_4$-CH_3), 1.97 (s, 3H, COCH_3), 1.34 (d, 3H, J = 6.5 Hz, C-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.2 (*C*OCH_3), 138.2, 137.7, 132.2(2), 130.5, 129.8(2), 128.4(3), 128.0(2), 127.9(2), 127.8(2), 127.7(2) (ArC), 85.6, 79.2, 75.0, 73.7, 72.4, 69.0, 21.1 (CO*C*H$_3$), 21.0 (S-C$_6$H$_4$-*C*H$_3$), 18.0 (C-*C*H$_3$). HRMS calcd. for $C_{29}H_{32}O_5SNa$ $(M+Na)^+$: 515.1868, found: 515.1866.

p-Methoxyphenyl 3-*O*-acetyl-2,4-di-*O*-benzyl-1-thio-α-L-rhamnopyranosyl-(1→2)-3,4-*O*-isopropylidene-β-L-arabinopyranoside (6)

A mixture of compound **4** (1.9 g, 3.9 mmol), compound **5** (1.0 g, 3.4 mmol), and MS 4Å (1.5 g) in dry CH_2CI_2 (20 mL) was stirred under nitrogen atmosphere for 1 h. NIS (1.1 g, 4.7 mmol) was added and the mixture was cooled to 10°C using ice-water bath. After stirring for 15 min, TMSOTf (20 μL, 1.2 mmol) was added and the mixture was allowed to stir at 10°C until complete conversion of acceptor **5** was evident by TLC (45 min). The mixture was immediately filtered through a pad of Celite and the filtrate was washed successively with $Na_2S_2O_3$ (2 × 30 mL), $NaHCO_3$ (2 × 30 mL), and brine (30 mL). The organic phase was collected, dried (Na_2SO_4), and evaporated to a syrup. The crude product thus obtained was purified by flash chromatography using *n*-hexane-EtOAc (3:1) to afford pure compound **6** (1.9 g, 86%) as white foam. $[\alpha]_D^{25}$ +134 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.36–7.24 (m, 12H, ArH), 6.96, 6.77 (2d, 4H, O-C$_6H_4$-OCH$_3$), 5.30 (d, 1H, $J_{1',2'}$ = 1.5 Hz, H-1′), 5.13

(dd, 1H, $J_{2',3'} = 3.5$ Hz, $J_{3',4'} = 9.5$ Hz, H-3′), 4.91 (d, 1H, $J_{1,2} = 7.5$ Hz, H-1), 4.70, 4.67, 4.62, 4.57 (4d, AB system, 4H, $J = 12.0$ Hz, 2 × CH_2Ph), 4.34 (m, 1H, H-4), 4.19 (t, 1H, $J_{1,2}$, $J_{2,3} = 7.5$ Hz, H-2), 4.12–4.01 (m, 3H, H-3, H-5a, H-5′), 3.93 (dd, 1H, $J_{1',2'} = 1.5$ Hz, $J_{2',3'} = 3.5$ Hz, H-2′), 3.89 (dd, 1H, $J_{4,5a} = 5.0$ Hz, $J_{5a,5b} = 12.5$ Hz, H-5b), 3.74 (s, 3H, O-C_6H_4-OCH_3), 3.64 (t, 1H, $J_{3',4'}$, $J_{4',5'} = 9.5$ Hz, H-4′), 1.92 (s, 3H, COCH_3), 1.54, 1.37 (2s, 6H, isopropylidene-CH_3), 1.35 (d, 3H, $J = 6.5$ Hz, C-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.3 (*C*OCH$_3$), 155.2, 151.1, 138.5, 138.0, 128.4(2), 128.3(2), 128.0, 127.8, 127.5(2), 127.4(2), 118.4(2), 114.6(2) (ArC), 110.6 (isopropylidene-*C*), 99.9 (C-1), 97.2 (C-1′), 79.0, 78.3, 76.4, 76.2, 74.5, 73.6, 73.0, 72.5, 67.9, 62.5 (C-5), 55.7 (O-C_6H_4-O*C*H$_3$), 27.7, 25.9 (2 × isopropylidene-*C*H$_3$), 21.1 (CO*C*H$_3$), 18.0 (C-*C*H$_3$). HRMS calcd. for $C_{37}H_{44}O_{11}Na$ $(M+Na)^+$: 687.2781, found: 687.2778.

p-Methoxyphenyl 2,4-di-*O*-benzyl -α-L-rhamnopyranosyl-(1→2)-3,4-*O*-isopropylidene-β-L-arabinopyranoside (7)

To a solution of compound **6** (1.8 g, 2.7 mmol) in dry MeOH (20 mL), 0.5N NaOMe in MeOH (2 mL) was added and the solution was allowed to stir at rt for 2 h. Then the solution was neutralized by DOWEX 50W H^+ resin and filtered. The filtrate was evaporated in vacuo and coevaporated with toluene to remove residual MeOH. Flash chromatography using *n*-hexane-EtOAc (3:1) afforded pure compound **7** (1.3 g, 89%) as white foam. $[\alpha]_D^{25}$ +96 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.38–7.24 (ArH), 6.95, 6.77 (2d, 4H, O-C_6H_4-OCH$_3$), 5.36 (s, 1H, H-1′), 4.87 (d, 1H, $J_{1,2} = 7.0$ Hz, H-1), 4.85, 4.77, 4.64, 4.60 (4d, AB system, 4H, $J = 12.0$ Hz, 2 × CH_2Ph), 4.34 (m, 1H, H-4), 4.15 (t, 1H, $J_{1,2}$, $J_{2,3} = 7.0$ Hz, H-2), 4.03–4.00 (m, 3H, H-3, H-3′, H-5a), 3.92 (m, 1H, H-5′), 3.89 (dd, 1H, $J_{4,5a} = 5.0$ Hz, $J_{5a,5b}$ 12.5 Hz, H-5b), 3.78 (bd, 1H, $J_{2',3'} = 3.5$ Hz, H-2′), 3.73 (s, 3H, O-C_6H_4-OCH_3), 3.34 (t, 1H, $J_{3',4'}$, $J_{4',5'} = 9.0$ Hz, H-4′), 2.39 (bs, 1H, O*H*), 1.54, 1.37 (2s, 6H, isopropylidene-CH_3), 1.32 (d, 3H, $J = 6.5$ Hz, C-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 155.2, 151.2, 138.7, 137.8, 128.6(2), 128.4(2), 128.1(2), 128.0, 127.8(2), 127.6, 118.3(2), 114.6(2) (ArC), 110.7 (isopropylidene-*C*), 99.9 (C-1), 96.5 (C-1′), 82.2, 78.5, 78.2, 76.2, 74.7, 72.9, 72.4, 71.3, 67.5, 62.4 (C-5), 55.7 (O-C_6H_4-O*C*H$_3$), 27.8, 25.9 (2 × isopropylidene-*C*H$_3$), 18.1 (C-*C*H$_3$). HRMS calcd. for $C_{35}H_{42}O_{10}Na$ $(M+Na)^+$: 645.2676, found: 645.2673.

p-Methoxyphenyl 2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl-(1→3)-2,4-di-O-benzyl -α-L-rhamnopyranosyl-(1→2)-3,4-O-isopropylidene-β-L-arabinopyranoside (9)

A mixture of compound **7** (1.2 g, 1.9 mmol), compound **8** (950 mg, 2.5 mmol), and dried MS 4Å (2 g) in dry CH_2CI_2 (20 mL) was stirred under nitrogen atmosphere for 1 h. NIS (672 mg, 3.0 mmol) was added and the mixture was

cooled to 10°C using ice-water bath. After stirring for 15 min, TMSOTf (10 μL, 0.8 mmol) was added and the mixture was allowed to stir at 10°C until complete conversion of acceptor **7** was evident by TLC (45 min). The mixture was immediately filtered through a pad of Celite and the filtrate was washed successively with $Na_2S_2O_3$ (2 × 25 mL), $NaHCO_3$ (2 × 25 mL), and brine (25 mL). The organic phase was collected, dried (Na_2SO_4), and evaporated to a syrup. The crude product thus obtained was purified by flash chromatography using *n*-hexane-EtOAc (3:1) to afford pure compound **9** (1.4 g, 81%) as white foam. $[\alpha]_D^{25}$ +107 (*c* 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.43–7.26 (ArH), 6.95, 6.78 (2d, 4H, O-C$_6H_4$-OCH$_3$), 5.22 (d, 1H, $J_{1',2'}$ = 2.0 Hz, H-1′), 5.15 (t, 1H, $J_{2'',3''}$, $J_{3'',4''}$ = 9.0 Hz, H-3″), 5.03 (dd, 1H, $J_{1'',2''}$ = 7.0 Hz, $J_{2'',3''}$ = 9.0 Hz, H-2″), 4.92 (m, 1H, H-4″), 4.90 (d, 1H, $J_{1'',2''}$ = 7.0 Hz, H-1″), 4.81 (d, 1H, $J_{1,2}$ = 7.5 Hz, H-1), 4.79, 4.77, 4.72, 4.55 (4d, 4H, J = 12.0 Hz, AB system, 2 × CH_2Ph), 4.33 (m, 1H, H-4), 4.15 (t, 1H, $J_{1,2}$, $J_{2,3}$ = 7.5 Hz, H-2), 4.03–4.00 (m, 3H, H-3, H-3′, H-5′, H-5a, H-5a″), 3.90 (dd, 1H, $J_{4,5a}$ = 5.0 Hz, $J_{5a,5b}$ = 12.5 Hz, H-5b), 3.78 (dd, 1H, $J_{1',2'}$ = 2.0 Hz, $J_{2',3'}$ = 3.5 Hz, H-2′), 3.76 (s, 3H, O-C$_6$H$_4$-OCH_3), 3.58 (t, 1H, $J_{3',4'}$, $J_{4',5'}$ = 9.0 Hz, H-4′), 3.24 (dd, 1H, $J_{4'',5b''}$ = 9.5 Hz, $J_{5a'',5b''}$ = 11.0 Hz, H-5b″), 2.04, 2.01, 1.83 (3s, 9H, 3 × COCH_3), 1.52, 1.36 (2s, 6H, isopropylidene-CH_3), 1.28 (d, 3H, J = 6.5 Hz, C-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.2, 169.9, 169.3 (3 × *C*OCH$_3$), 155.0, 151.1, 138.5, 138.3, 128.5(2), 128.3(2), 128.1(2), 127.7, 127.4(2), 127.3, 118.0(2), 114.5(2) (ArC), 110.6 (isopropylidene-*C*), 101.6 (C-1″), 99.6 (C-1), 97.7 (C-1′), 80.3, 79.1, 78.0, 75.7, 74.6, 73.3, 72.3, 72.0, 71.5, 69.2, 68.1, 62.3 (C-5), 62.1 (C-5″), 55.7 (O-C$_6$H$_4$-OCH_3), 27.7, 25.8 (2 × isopropylidene-*C*H$_3$), 20.7, 20.6, 20.5 (3 × CO*C*H$_3$), 17.8 (C-*C*H$_3$). HRMS calcd. for $C_{46}H_{56}O_{17}Na$ $(M+Na)^+$: 903.3415, found: 903.3416.

p-Methoxyphenyl β-D-xylopyranosyl-(1→3)-α-L-rhamnopyranosyl-(1→2)-β-L-arabinopyranoside (1)

A solution of compound **9** (1.0 g, 1.1 mmol) in 80% AcOH (10 mL) was stirred at 80°C for 2 h when the TLC showed complete conversion of the starting material. Solvents were evaporated in vacuo and the syrupy mass was dissolved in MeOH (100 mL). The dilute methanolic solution was then passed through the flow hydrogenation assembly (H-cube, Thales Nano, Hungary) that contained the Pd-C (10% Pd) cartridge. Complete hydrogenation was achieved after three cycles at rt and 40 psi hydrogen pressure. Solvents were evaporated and the residue was redissolved in dry MeOH (10 mL); 0.5N NaOMe in MeOH (1 mL) was added and the solution was stirred at rt for 12 h. The solution was neutralized with DOWEX 50W H^+ resin, filtered, and evaporated in vacuo to afford pure trisaccharide **1** (440 mg, 73%) as amorphous white solid. $[\alpha]_D^{25}$ +68 (*c* 0.8, H_2O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.92, 6.80 (2d, 4H, O-C$_6H_4$-OCH$_3$), 4.95 (bs, 1H, H-1′), 4.89 (d, 1H,

J = 6.0 Hz, H-1), 4.40 (d, 1H, $J_{1'',2''}$ = 7.6 Hz, H-1″), 3.67 (s, 3H, $C_6H_4OCH_3$), 1.04 (d, 3H, J = 6.0 Hz, C-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 154.6, 150.3, 117.9(2), 115.1(2) (ArC), 104.5 (C-1″), 101.0 (C-1), 99.8 (C-1′), 79.6, 77.2, 75.5, 73.2, 72.6, 71.0, 70.1, 69.2, 68.9, 68.4, 65.1, 65.0, 55.7 (O-C_6H_4-OCH_3), 16.6 (C-CH_3). HRMS calcd. for $C_{23}H_{34}O_{14}Na$ $(M+Na)^+$: 557.1846, found: 557.1844.

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