C-Glycosides of Visnagin Analogues

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Glycosylation of the visnagin cleavage product **2** with *O*-acetyl-protected glycosyl donor **5a** afforded O-glycoside **6a**, which could be transformed into the *O*-benzyl-protected compound **6b**. The latter underwent Fries-type rearrangement to afford C-glycoside **4b**. The same product could be obtained directly from **2** and *O*-benzyl-protected glycosyl donor **5b**. Reaction of **4b** with benzaldehyde and anisaldehyde furnished chalcones **7A**,**B**, which, upon treatment with base, furnished flavanone C-glycosides **10A**,**B**. Selenium dioxide oxidation of **10A**,**B** or of **7A**,**B** led to the corresponding flavone C-glycosides **11A**,**B**. The same result was obtained by Baker-Venkataraman rearrangement; on treatment with base, the *O*-aroyl compounds **12A–C** gave *C*-aroyl compounds **13A–C**, which, on addition of TMSOTf, furnished flavone C-glycosides **11A–C**. Hydrogenolytic *O*-debenzylation of **11A** afforded target molecule **3A**, which was transformed into *O*-acetyl derivative **14A** for characterization. Structural assignments of all compounds were based on ^{1}H-NMR data.

Aryl C-glycosides having an electron-rich aromatic moiety, especially those derived from phloroglucinol, are widespread in nature and various physiological properties have been assigned to these compounds[1][2][3][4][5][6]. Flavone and flavanone[7] C-glycosides, which have glycosyl residues at positions 6 and/or 8, are particularly prevalent (Scheme 1, **I**, see arrows).

Commonly, aryl C-glycosides are synthesized by a Friedel−Crafts-type reaction from electrophilic glycosyl donors and electron-rich aromatic compounds as nucleophilic glycosyl acceptors[8]. However, direct *C*-glycosylation of flavanones[9] and especially of flavones is hampered by the low reactivity of these glycosyl acceptors[8][10]. Therefore, we have recently investigated an alternative strategy for the synthesis of phenol-derived C-glycosides involving *O*-glycosylation of partially *O*-unprotected phenol derivatives (for instance **II**, with R^1 or R^2 being hydrogen) using *O*-glycosyl trichloroacetimidates as glycosyl donors, followed by a Fries-type rearrangement of the *O*-glycoside intermediate[10][11]. The Fries-type rearrangement of such compounds has been found to proceed with high regio- and stereoselectivity[10][11][12]. Subsequent pyrone formation finally leads to the target molecules, for instance of type **I**. The superior glycosyl acceptor properties of **II** compared with those of **I** can be attributed to nonplanarity of the acyl group and the phloroglucinol moiety in the former, which reduces the negative influence of the −M effect of the carbonyl group on the nucleophilicity of the phloroglucinol moiety.

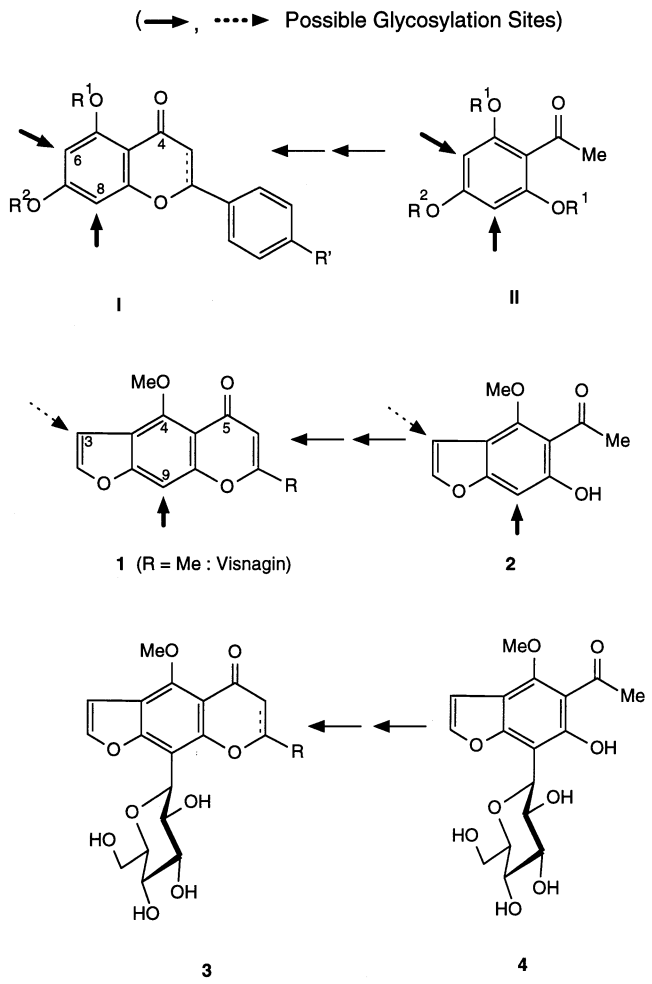
Another commonly encountered phloroglucinol-derived compound is visnagin (Scheme 1, **1**), which is isolated from various plants[13] and exhibits interesting physiological properties[14]. However, to the best of our knowledge, no C-glycoside derivatives, e.g. of type **3**, have yet been isolated, although C-9 (as well as C-3) should exhibit the required nucleophilicity for enzymatic C-glycosylations[15]. In a chemical approach to the synthesis of compounds of type **3**, cleavage product **2**[16] can be envisaged as a starting material for selective *C*-glycosylations, thus leading, for instance with a glucosyl donor, to intermediate **4**. This could then be transformed into the physiologically active compounds of type **3**.

Thus, our endeavours in this regard started with the readily available visnagin cleavage product **2**[16], which upon treatment with *O*-acetyl-protected trichloroacetimidate **5a**[17] as glycosyl donor in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) as catalyst, afforded α-linked *O*-glycoside **6a** in good yield (66%, Scheme 2). However, Fries rearrangement of **6a** by addition of further TMSOTf could not be achieved. Therefore, the *O*-acetyl groups in **6a** were removed under Zemplén conditions[18] (→ **6c**) and *O*-benzylation was carried out by treatment with benzyl bromide in the presence of sodium hydride, furnishing **6b**. This compound underwent the desired Fries-type rearrangement, affording β-linked C-glycoside **4b**, albeit only in low yield (30%). Therefore, **2** was treated with *O*-benzyl-protected trichloroacetimidate **5b**[17][19] as glycosyl donor in the presence of TMSOTf as catalyst, thereby furnishing directly (possibly via **6b**) the desired C-glycoside **4b** in 77% yield.

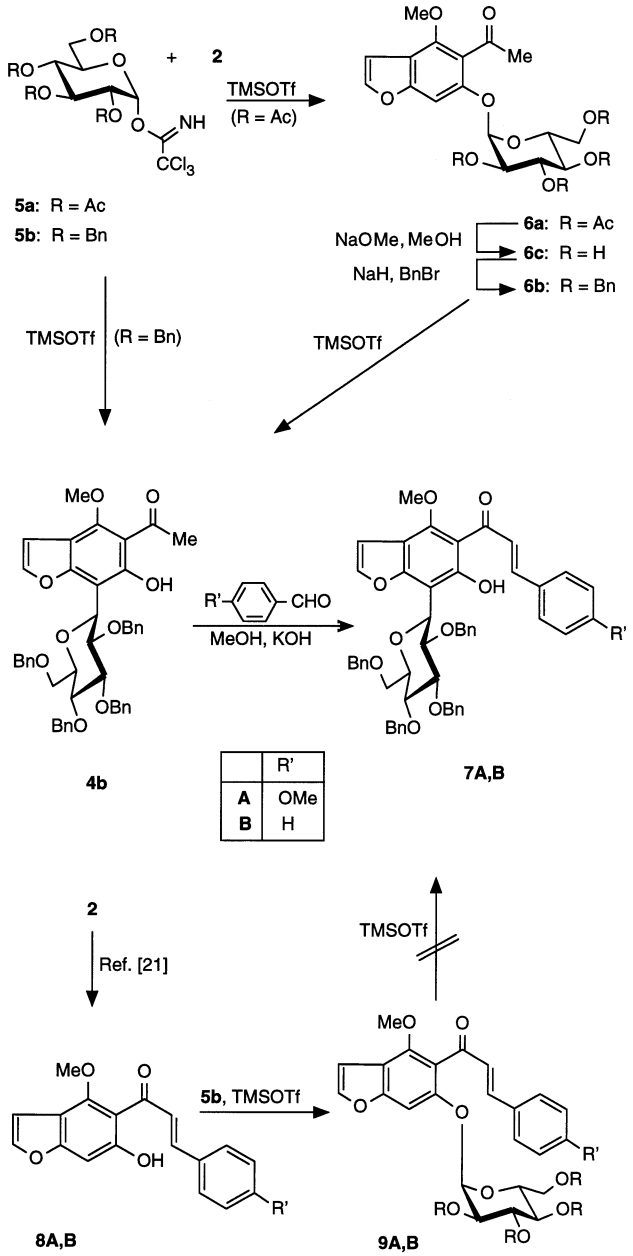
For the ring closure of **4b** to flavanones and flavones of type **3** (Scheme 1), various methods have been explored. Reaction of **4b** with aromatic aldehydes in the presence of methanolic potassium hydroxide[20] afforded chalcone de-

  1434−193X/98/1111−2317 $ 17.50+.50/0

Scheme 1



Scheme 2



rivatives **7A**,**B** in high yields (Scheme 2). However, transformation of **2** into known chalcones **8A**,**B**[21] by treatment with aromatic aldehydes, followed by glycosylation with **5b** under the aforementioned conditions did not lead to **7A**,**B**, but rather to O-glycosides **9A**,**B**. Further treatment with TMSOTf resulted in the decomposition of **9A**,**B**, and not in the formation of **7**. Treatment of **7A**,**B** with base[22] {either piperidine or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was employed} gave the desired flavanone derivatives **10A**,**B** as diastereoisomeric mixtures in good yields (Scheme 3). Oxidation with selenium dioxide in 1-butanol[20] or with dichlorodicyanobenzoquinone (DDQ) in benzene afforded the corresponding flavones **11A**,**B**. Alternatively, **11A**,**B** could be obtained in high yields directly from **7A**,**B**, since these chalcones underwent ring-closure under the oxidative conditions of selenium dioxide in 1-butanol.

The synthesis of the desired flavone intermediates **11** could also be achieved by means of the Baker-Venkataraman rearrangement[11]. To this end, **4b** was *O*-aroylated under standard conditions, affording *O*-aroyl derivatives **12A−C** (Scheme 4). Treatment of **12A−C** with sodium hydride in DMF afforded the rearranged products **13A−C**, which on treatment with TMSOTf as catalyst underwent cyclization to the desired flavone derivatives **11A−C**.

In order to demonstrate the feasibility of the deprotection step, hydrogenolytic *O*-debenzylation of **11A** was carried out in the presence of palladium on charcoal, affording **3A**. This was then treated with acetic anhydride in pyridine, furnishing the *O*-acetylated derivative **14A**. The structures were assigned with the help of NMR data. Several of the C-glycosides showed slow rotation about the C-glycosidic bond at room temperature (**11A−C**, **14A**) and hence NMR spectra had to be recorded in [D_6]DMSO at elevated temperatures in order to unequivocally assign the structures.

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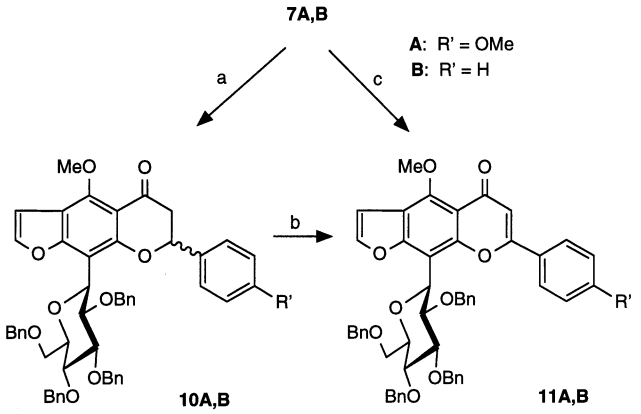
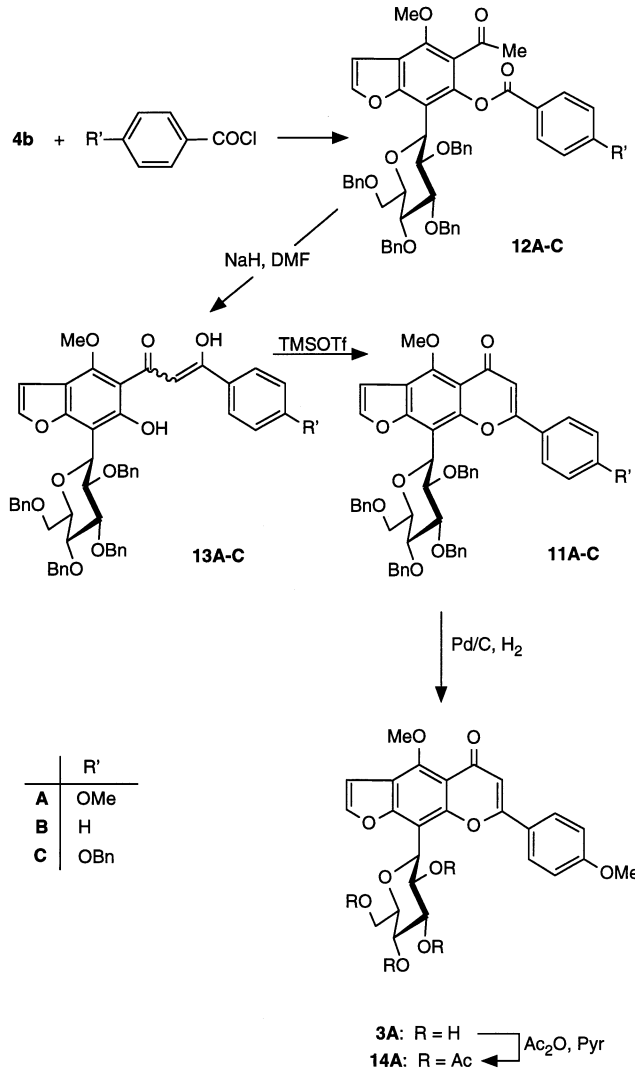
Scheme 3[a]



[a] Reaction conditions: (a) piperidine or DBU; (b) SeO_2, BuOH or DDQ, benzene; (c) SeO_2, BuOH.

Scheme 4



Experimental Section

General Methods: Solvents were purified and dried by standard procedures prior to use; petroleum ether of boiling range 35−70°C was used. − Melting points are uncorrected. − ^{1}H-NMR spectra: Avance DRX 600 and Bruker AC 250 MHz, internal standard tetramethylsilane (TMS); *J* values in Hz. − Elemental analysis: Heraeus CHN-O Rapid. − Mass spectra: Varian MAT 312/AMD 5000 FAB and MALDI-Kompact. − Flash chromatography: Silica gel 60 (Baker 0.03−0.06 mm) at a pressure of 0.3 bar. − Thin-layer chromatography (TLC): plastic foil plates, Kieselgel 60 F_{254} (Merck; layer thickness 0.2 mm); detection by treatment with a solution of 20 g of ammonium molybdate and 0.4 g of cerium(IV) sulfate in 400 ml of 10% sulfuric acid and heating at 150°C. − Optical rotations: Perkin-Elmer polarimeter 241/MS, 1-dm cell.

5-Acetyl-6-hydroxy-4-methoxy-7-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)benzofuran (**4b**)

Method A: At −30°C under nitrogen, a solution of **2**[16] (500 mg, 2.42 mmol) and **5b**[17][19] (1.6 g, 2.42 mmol) in anhydrous dichloromethane (10 ml) was treated with TMSOTf (100 µl, 0.46 mmol) for 30 min. The mixture was then gradually allowed to warm to room temp. over a period of 4 h. The reaction was quenched by the addition of satd. $NaHCO_3$ solution (5 ml), stirring was continued for a further 15 min., and then water (10 ml) was added. The mixture was extracted with dichloromethane (4 × 5 ml), and the combined organic extracts were dried with $MgSO_4$. Evaporation of the solvent in vacuo gave the crude product, which was subjected to flash chromatography (petroleum ether/ethyl acetate, 10:3), yielding **4b** (1.35 g, 77%) as pale-yellow crystals; m.p. 81°C. − TLC (petroleum ether/ethyl acetate, 10:3): R_f = 0.26. − $[\alpha]_D^{25}$ = +10.2 (*c* = 1, $CHCl_3$).

Method B: To a solution of **6b** (100 mg, 0.14 mmol) in anhydrous dichloromethane (5 ml) under nitrogen, was added TMSOTf (6 µl, 0.03 mmol). After stirring at room temp. for 24 h, satd. $NaHCO_3$ solution (2 ml) was added. The mixture was extracted with dichloromethane (3 × 4 ml), the combined extracts were dried with $MgSO_4$, and the solvent was evaporated. Column chromatography of the residue afforded **4b** (30 mg, 30%). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.69 (s, 1 H, $COCH_3$), 3.66 (m, 1 H, 5′-H), 3.68−3.90 (m, 3 H, 3′-H, 4′-H, 6′-H), 4.12 (m, 4 H, 6′′-H, OMe), 4.34 (br. s, 1 H, 2′-H), 4.48−4.98 (m, 8 H, 4 CH_2-benzylic), 5.04 (d, 1 H, $J_{1',2'}$ = 9.8 Hz, 1′-H), 6.47−7.38 (m, 22 H, 4 Ph, 2-H, 3-H), 13.6 (br., 1 H, OH). − FAB MS: *m/z* = 751 $[M + Na]^+$. − $C_{45}H_{44}O_9$ (728.83): calcd. C 74.16, H 6.08; found C 73.99, H 6.20.

5-Acetyl-4-methoxy-6-(2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyloxy)benzofuran (**6a**): At −30°C under nitrogen, a mixture of **2**[16] (500 mg, 2.42 mmol) and **5a**[17] (1.0 g, 2.42 mmol) in anhydrous dichloromethane was treated with trimethylsilyl trifluoromethanesulfonate (TMSOTf, 54 µl, 0.24 mmol) for 30 min. The mixture was gradually allowed to warm to room temp. over a period of 3 h. The reaction was quenched by the addition of satd. $NaHCO_3$ solution (5 ml), stirring was continued for a further 15 min, and then water (10 ml) was added. The organic product was extracted with dichloromethane (3 × 5 ml), the extracts were dried with $MgSO_4$, and the solvent was evaporated in vacuo. The residue was purified by flash chromatography using a mixture of toluene/ethyl acetate (8:2) as eluent, to give **6a** (850 mg, 66%) as colourless crystals; m.p. 54−55°C. − TLC (toluene/ethyl acetate, 8:2): R_f = 0.3. − $[\alpha]_D^{26}$ = +188 (*c* = 1, $CHCl_3$). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.04 (s, 3 H, OAc), 2.05 (s, 3 H, OAc), 2.1 (s, 6 H, 2 OAc), 2.59 (s, 3 H, $COCH_3$), 4.08 (s, 3 H, OMe), 4.1−4.37 (m, 3 H, 5′-H, 6′-H, 6′′-H), 5.00 (dd, 1 H, $J_{1',2'}$ = 3.7, $J_{2',3'}$ = 10.2 Hz, 2′-H), 5.14 (dd, 1 H, $J_{3',4'}$ = 9.6, $J_{4',5'}$ = 9.8 Hz, 4′-H), 5.65 (d, 1 H, $J_{1',2'}$ = 3.7 Hz, 1′-H), 6.90 (d, 1 H, $J_{2,3}$ = 2.3 Hz, 3-H), 7.12 (s, 1 H, 7-H), 7.61 (d, 1 H, $J_{2,3}$ = 2.3 Hz, 2-H). − MALDI MS:

m/z = 560 [M + Na]$^+$. − $C_{25}H_{28}O_{13}$ (536.48): calcd. C 55.97, H 5.26; found C 55.64, H 5.26.

5-Acetyl-4-methoxy-6-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyloxy)benzofuran (**6b**): To a mixture of **6c** (100 mg, 0.27 mmol) and benzyl bromide (420 µl, 2.71 mmol) in anhydrous dimethylformamide (5 ml), sodium hydride (65 mg, 2.71 mmol) was added portionwise. After stirring at room temp. for 8 h, methanol (5 ml) and then water (5 ml) were added. The mixture was extracted with ethyl acetate (4 × 5 ml), and the combined extracts were dried with $MgSO_4$. The solvent was evaporated in vacuo and the residue was subjected to flash chromatography (petroleum ether/ethyl acetate, 10:2), yielding **6b** (160 mg, 81%) as a pale-yellow oil. − TLC (petroleum ether/ethyl acetate, 10:3): R_f = 0.3. − $[\alpha]_D^{20}$ = +77 (*c* = 1, $CHCl_3$). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.55 (s, 3 H, $COCH_3$), 3.60−4.04 (m, 6 H, 2′-H to 6′′-H), 4.06 (s, 3 H, OMe), 4.44−4.98 (m, 8 H, 4 CH_2-benzylic), 5.46 (d, 1 H, $J_{1',2'}$ = 3.4 Hz, 1′-H), 6.88 (d, 1 H, $J_{2,3}$ = 2.2 Hz, 3-H), 7.08 (s, 1 H, 7-H), 7.12−7.34 (m, 20 H, 4 Ph), 7.52 (d, 1 H, $J_{2,3}$ = 2.2 Hz, 2-H).

5-Acetyl-4-methoxy-6-(α-D-glucopyranosyloxy)benzofuran (**6c**): A mixture of **6a** (1.0 g, 2.11 mmol) and sodium methoxide (10 ml, 0.1 M) was stirred at room temp for 2 h. Then, the solution was neutralized with an ion-exchange resin (Amberlite IR 120, H^+ form), filtered, and concentrated in vacuo. The residual syrup was applied to a column of flash silica gel, which was eluted with chloroform/methanol (10:1) to give **6c** (540 mg, 70%) as colourless crystals; m.p. 180−181°C. − TLC (chloroform/methanol, 10:2): R_f = 0.28. − $[\alpha]_D^{20}$ = +170 (*c* = 1, dimethyl sulfoxide). − ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 2.46 (s, 3 H, $COCH_3$), 3.13−3.20 (m, 1 H, OH), 3.36−3.61 (m, 5 H, 5′-H, 6′-H, 6′′-H, 2 OH), 4.00 (s, 3 H, OMe), 4.50 (dd, 1 H, $J_{1',2'}$ = 3.3, $J_{2',3'}$ = 5.8 Hz, 2′-H), 4.89−5.00 (m, 2 H, 3′-H, 4′-H), 5.11 (d, 1 H, *J* = 4.9 Hz, OH), 5.45 (d, 1 H, $J_{1',2'}$ = 3.3 Hz, 1′-H), 7.16 (d, 1 H, $J_{2,3}$ = 2.3 Hz, 3-H), 7.19 (s, 1 H, 7-H), 7.88 (d, 1 H, $J_{2,3}$ = 2.3 Hz, 2-H). − MALDI MS: *m/z* = 392 [M + Na]$^+$. − $C_{17}H_{20}O_9$ (368.33): calcd. C 55.43, H 5.47; found C 55.06, H 5.57.

6-Hydroxy-4-methoxy-5-[3-(4-methoxyphenyl)propenoyl]- and 6-Hydroxy-4-methoxy-5-(3-phenylpropenoyl)-7-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)benzofuran (**7A** and **7B**)

General Procedure: To a stirred mixture of **4b** (200 mg, 0.27 mmol) and the aldehyde (0.29 mmol) in methanol (5 ml) at room temperature, aq. methanolic potassium hydroxide (30 ml, 50%) was added over a period of 30 min. Stirring was continued for a further 12 h and the organic solid that separated after acidification with acetic acid was filtered off, washed with water, dried, and purified by flash chromatography (petroleum ether/ethyl acetate, 10:4) to yield **7A** and **7B**, respectively.

7A: 186 mg, 81%, orange crystals; m.p. 140−142°C. − TLC (petroleum ether/ethyl acetate; 10:4): R_f = 0.36. − $[\alpha]_D^{23}$ = +6.74 (*c* = 1, $CHCl_3$). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.68 (m, 1 H, 5′-H), 3.73 (dd, 1 H, $J_{6',6''}$ = 11.4, $J_{5',6'}$ = 10.1 Hz, 6′-H), 3.85−3.91 (m, 6 H, OMe, 3′-H, 4′-H, 6′′-H), 4.1 (m, 4 H, OMe, 0.5 CH_2-benzylic), 4.50 (br. s, 1 H, 2′-H), 4.55−4.95 (m, 7 H, 3.5 CH_2-benzylic), 5.09 (d, 1 H, $J_{1',2'}$ = 9.8 Hz, 1′-H), 6.78 (m, 2 H, 3-H, =CH), 6.95 (d, 2 H, *J* = 8.7 Hz, 3′′-, 5′′-H Ar), 7.01−7.80 (m, 25 H, 4 Ph, =CH, 2-H, 2′′-, 6′′-H Ar, OH). − FAB MS: *m/z* = 869 [M + Na]$^+$.

7B: 175 mg, 79%, orange crystals; m.p. 131−132°C. − TLC (petroleum ether/ethyl acetate, 10:4): R_f = 0.37. − $[\alpha]_D^{23}$ = +9.2 (*c* = 1, $CHCl_3$). − ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.67 (m, 1 H, 5′-H), 3.75 (m, 1 H, 6′-H), 3.87 (m, 3 H, 3′-H, 4′-H, 6′′-H), 4.09 (m, 4 H, OMe, 0.5 CH_2-benzylic), 4.33 (br. s, 1 H, 2′-H), 4.49 (d, 1 H, *J* = 12.12 Hz, 0.5 CH_2-benzylic), 4.56 (d, 1 H, *J* = 11.04 Hz, CH_2-benzylic), 4.68 (m, 2 H, CH_2-benzylic), 4.88−4.96 (m, 3 H, 1.5 CH_2-benzylic), 5.08 (d, 1 H, $J_{1',2'}$ = 9.9 Hz, 1′-H), 6.78−6.83 (m, 2 H, 3-H, =CH), 7.03−7.80 (m, 28 H, 5 Ph, =CH, 2-H, OH). − ^{13}C NMR: δ = 61.30 (MeO), 68.96 (C-6′), 72.5 (C-1′), 78.29 (C-4′), 79.71 (C-5′), 80.1 (C-2′), 87.34 (C-3′), 105.01 (C-3), 127.8 (C=), 127.9 (C=), 143.61 (C-2), 194.59 (C=O). − FAB MS: *m/z* = 839 [M + Na]$^+$. − $C_{52}H_{48}O_9$ (816.94): calcd. C 76.45, H 5.92; found C 76.45, H 6.10.

4-Methoxy-5-[3-(4-methoxyphenyl)propenoyl]- and 4-Methoxy-5-(3-phenylpropenoyl)-6-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyloxy)benzofuran (**9A** and **9B**)

General Procedure: To a mixture of **8A**[21] or **8B**[21] (1.54 mmol) and **5b**[17][19] (1.54 mmol) in anhydrous dichloromethane (10 ml) at −30°C under nitrogen, was added TMSOTf (34 µl, 0.15 mmol). The mixture was stirred at this temperature for 30 min and then was slowly allowed to warm to room temp. over a period of 3 h. The reaction was quenched in the same manner as described in the case of **6a**.

9A: 1.15 g, 88%, yellow oil. − TLC (petroleum ether/ethyl acetate; 10:4): R_f = 0.36. − $[\alpha]_D^{23}$ = +188 (*c* = 1, $CHCl_3$). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.53 (dd, $J_{5',6'}$ = 1.9 Hz, $J_{6',6''}$ = 10.6 Hz, 6′-H), 3.61−3.69 (m, 5 H, OMe, 5′-H, 6′′-H), 3.70−3.93 (m, 3 H, 2′-H to 4′-H), 4.06 (s, 3 H, OMe), 4.34−4.77 (m, 8 H, 4 CH_2-benzylic), 5.55 (d, 1 H, $J_{1',2'}$ = 3.3 Hz, 1′-H), 6.63−7.55 (m, 29 H, 4 Ph, 2-H, 3-H, 7-H, CH=CH, 2′′-, 3′′-, 5′′-, 6′′-H Ar). − FAB MS: *m/z* = 869 [M + Na]$^+$.

9B: 1.08 g, 86%, yellow oil. − TLC (petroleum ether/ethyl acetate, 10:3): R_f = 0.66. − $[\alpha]_D^{23}$ = +60.2 (*c* = 1, $CHCl_3$). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.56−3.69 (m, 4 H, 3′-H to 6′-H), 3.78−3.88 (m, 2 H, 2′-H, 6′′-H), 4.07 (s, 3 H, OMe), 4.34−4.76 (m, 8 H, 4 CH_2-benzylic), 5.54 (d, 1 H, $J_{1',2'}$ = 3.4 Hz, 1′-H), 6.54−7.56 (m, 30 H, 5 Ph, CH=CH, 2-H, 3-H, 7-H). − MALDI MS: *m/z* = 840 [M + Na]$^+$.

4-Methoxy-7-(4-methoxyphenyl)- and 4-Methoxy-7-phenyl-9-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-6,7-dihydro-5H-furo[3,2-g][1]benzopyran-5-one (**10A** and **10B**): To a solution of **7A** or **7B** (0.6 mmol) in anhydrous methanol (10 ml), two drops of piperidine and/or DBU were added and the mixture was refluxed for 10 h. Then, the mixture was neutralized with acetic acid and concentrated to dryness. Flash chromatography of the residue (petroleum ether/ethyl acetate, 5:3) yielded **10A** or **10B**.

10A: 370 mg, 72%, colourless crystals; m.p. 55−57°C. − TLC (petroleum ether/ethyl acetate, 5:3): R_f = 0.42. − $[\alpha]_D^{22}$ = −14.5 (*c* = 0.5, $CHCl_3$). − ^{1}H NMR (600 MHz, [D$_6$]DMSO, at 110°C): [racemic mixture of (*R*) and (*S*) forms]: δ = 5.32 (d, 7-H), 5.47 (dd, *J* = 4.23, 10.5 Hz, 7-H). − MALDI MS: *m/z* = 847 [M$^+$]. − $C_{53}H_{50}O_{10}$ (846.97): calcd. C 75.16, H 5.95; found C 75.16, H 6.04.

10B: 340 mg, 70%, colourless solid; m.p. 65−67°C. − TLC (petroleum ether/ethyl acetate, 5:3): R_f = 0.36. − $[\alpha]_D^{22}$ = −4.70 (*c* = 1, $CHCl_3$). − ^{1}H NMR (250 MHz, [D$_6$]DMSO at 110°C): [racemic mixture of (*R*) and (*S*) forms]: δ = 5.36 (dd, *J* = 4.3, 11.2 Hz, 7-H), 5.55 (dd, *J* = 5.9, 9.3 Hz, 7-H). − MALDI MS: *m/z* = 817 [M$^+$]. − $C_{52}H_{48}O_9$ (816.94): calcd. C 76.45, H 5.92; found C 75.96, H 6.03.

4-Methoxy-7-(4-methoxyphenyl)-, 4-Methoxy-7-phenyl- and 7-(4-Benzyloxyphenyl)-4-methoxy-9-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-5H-furo[3,2-g][1]-benzopyran-5-one (**11A−C**)

Method A: To a solution of **13A−C** (0.1 mmol) in anhydrous dichloromethane (5 ml) under nitrogen, was added TMSOTf (25

µl, 0.1 mmol). After stirring at room temp. for 1 h, satd. $NaHCO_3$ solution (2 ml) and water (5 ml) were added, and stirring was continued for a further 15 min. The mixture was extracted with dichloromethane (3 × 5 ml), the combined extracts were dried with $MgSO_4$, and the solvent was evaporated. Flash chromatography of the residue (petroleum ether/ethyl acetate, 1:1) yielded **11A−C**, respectively.

11A: 82 mg, 97%, colourless crystals; m.p. 65−66°C. − TLC (petroleum ether/ethyl acetate, 1:1): $R_f = 0.2$. − $[\alpha]_D^{24} = -5.8$ (c = 1, $CHCl_3$). − ^1H NMR (250 MHz, [D$_6$]DMSO, at 100°C): δ = 3.78−4.0 (m, 9 H, 3′-H to 6′′-H, OMe, 0.5 CH_2-benzylic), 4.07 (s, 3 H, OMe), 4.29 (dd, 1 H, $J_{1',2'}$ = 9.8, $J_{2',3'}$ = 8.7 Hz, 2′-H), 4.53 (m, 3 H, 1.5 CH_2-benzylic), 4.72−4.89 (m, 4 H, 2 CH_2-benzylic), 5.23 (d, 1 H, $J_{1',2'}$ = 9.8 Hz, 1′-H), 6.53 (d, 2 H, J = 7.3 Hz, 3′′-, 5′′-H Ar), 6.60 (s, 1 H, 6-H), 6.87−7.38 (m, 21 H, 4 Ph, 3-H), 7.95 (d, 1 H, $J_{2,3}$ = 2.3 Hz, 2-H), 8.02 (d, 2 H, J = 8.9 Hz, 2′′-, 6′′-H Ar). − FAB MS: m/z = 867 $[M + Na]^+$. − $C_{53}H_{48}O_{10}$ (844.95): calcd. C 75.33, H 5.72; found C 74.91, H 5.80.

11B: 90 mg, 92%, colourless crystals; m.p. 58−59°C. − TLC (petroleum ether/ethyl acetate; 1:1): $R_f = 0.28$. − $[\alpha]_D^{25} = -7.6$ (c = 1, $CHCl_3$). − ^1H NMR (250 MHz, [D$_6$]DMSO, at 100°C): δ = 3.76−3.96 (m, 6 H, 3′-H to 6′′-H, 0.5 CH_2-benzylic), 4.08 (s, 3 H, OMe), 4.25 (dd, 1 H, $J_{1',2'}$ = 9.7, $J_{2',3'}$ = 9.1 Hz, 2′-H), 4.37−4.52 (m, 3 H, 1.5 CH_2-benzylic), 4.71−4.88 (m, 4 H, 2 CH_2-benzylic), 5.22 (d, 1 H, $J_{1',2'}$ = 9.7 Hz, 1′-H), 6.51 (d, 2 H, J = 7.2 Hz, Ar-H), 6.71 (s, 1 H, 6-H), 6.86−7.55 (m, 22 H, 4 Ph, 3-H, Ar-H), 7.98 (d, 1 H, $J_{2,3}$ = 2.2 Hz, 2-H), 8.08 (d, 2 H, J = 7.8 Hz, Ar-H). − FAB MS: m/z = 837 $[M + Na]^+$. − $C_{52}H_{46}O_9$ (814.93): calcd. C 76.64, H 5.68; found C 76.22, H 5.71.

11C: 85 mg, 92%, colourless crystals; m.p. 61−62°C. − TLC (petroleum ether/ethyl acetate, 1:1): $R_f = 0.21$. − $[\alpha] = -14.7$ (c = 1, $CHCl_3$). − ^1H NMR (250 MHz, [D$_6$]DMSO, at 100°C): δ = 3.78−3.97 (m, 6 H, 3′-H to 6′′-H, 0.5 CH_2-benzylic), 4.08 (s, 3 H, OMe), 4.27 (dd, 1 H, $J_{1',2'}$ = 9.7, $J_{2',3'}$ = 8.8 Hz, 2′-H), 4.38−4.52 (m, 3 H, 1.5 CH_2-benzylic), 4.72−4.89 (m, 4 H, 2 CH_2-benzylic), 5.19 (s, 2 H, CH_2-benzylic), 5.25 (d, 1 H, $J_{1',2'}$ = 9.7 Hz, 1′-H), 6.52 (d, 2 H, J = 7.2 Hz, 3′′-, 5′′-H Ar), 6.63 (s, 1 H, 6-H), 6.87−7.47 (m, 26 H, 5 Ph, 3-H), 7.97 (d, 1 H, $J_{2,3}$ = 2.3 Hz, 2-H), 8.04 (d, 2 H, J = 8.8 Hz, 2′′-, 6′′-H Ar). − FAB MS: m/z = 921 $[M^+]$. − $C_{59}H_{52}O_{10}$ (921.03): calcd. C 76.94, H 5.69; found C 76.44, H 5.75.

Method B: To a solution of **10A** or **10B** (0.25 mmol) in anhydrous 1-butanol (10 ml), selenium dioxide (0.75 mmol) was added, and the mixture was refluxed overnight. The solution was then filtered through Celite, and the filtrate was concentrated to dryness. Flash chromatography of the residue yielded compound **11A** (130 mg, 61%) or **11B** (120 mg, 58%), respectively. − The same results were obtained using DDQ in benzene as the oxidizing agent.

Method C: A mixture of **7A** or **7B** (0.25 mmol) and selenium dioxide (0.75 mmol) in anhydrous 1-butanol (10 ml) was refluxed under argon for 12 h. The mixture was then filtered through Celite and the filtrate was concentrated to dryness. Flash chromatography of the residue yielded **11A** (148 mg, 70%) or **11B** (145 mg, 72%), respectively.

5-Acetyl-6-(4-methoxybenzoyloxy)- and 5-Acetyl-6-benzoyloxy-4-methoxy-7-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-benzofuran (**12A** and **12B**).

General Procedure: To a solution of **4b** (200 mg, 0.27 mmol) in anhydrous pyridine (5 ml) was added either benzoyl chloride or anisoyl chloride (0.67 mmol). After stirring at room temp for 3 h, the mixture was concentrated, treated with satd. $NaHCO_3$ solution (2 ml) and water (5 ml), and extracted with ethyl acetate (3 × 5 ml). The combined extracts were washed with water, dried with $MgSO_4$, and concentrated. Flash chromatography of the residue (petroleum ether/ethyl acetate, 10:4) yielded compound **12A** or **12B**.

12A: 510 mg, 85%, colourless crystals; m.p. 54−55°C. − TLC (petroleum ether/ethyl acetate, 10:4): $R_f = 0.33$. − $[\alpha]_D^{25} = +25.6$ (c = 1, $CHCl_3$). − ^1H NMR (250 MHz, $CDCl_3$): δ = 2.53 (s, 3 H, $COCH_3$), 3.49−3.51 (m, 2 H, 5′-H, 6′-H), 3.68 (s, 3 H, OMe), 3.74−3.81 (m, 2 H, 3′-H, 4′-H), 3.84 (s, 3 H, OMe), 4.05−4.93 (m, 11 H, 1′-H, 2′-H, 6′′-H, 4 CH_2-benzylic), 6.76−7.55 (m, 24 H, 4 Ph, 2-H, 3-H, 3′′-, 5′′-H Ar), 8.0 (d, 2 H, J = 9.6 Hz, 2′′-, 6′′-H Ar). − FAB MS: m/z = 885 $[M + Na]^+$. − $C_{53}H_{50}O_{11}$ (862.97): calcd. C 73.76, H 5.83; found C 73.37, H 5.83.

12B: 200 mg, 90%, colourless crystals; m.p. 59−60°C. − TLC (petroleum ether/ethyl acetate, 10:4): $R_f = 0.42$. − $[\alpha]_D^{25} = +67.6$ (c = 1, $CHCl_3$). − ^1H NMR (250 MHz, $CDCl_3$): δ = 2.54 (s, 3 H, $COCH_3$), 4.48−3.51 (m, 2 H, 5′-H, 6′-H), 3.69−3.81 (m, 2 H, 3′-H, 4′-H), 4.11 (m, 4 H, OMe, 6′′-H), 4.36 (br. s, 1 H, 2′-H), 4.50−4.99 (m, 9 H, 4 CH_2-benzylic, 1′-H), 6.37−7.49 (m, 23 H, 4 Ph, 2-H, 3-H, Ar-H), 7.57 (d, 2-H, J = 7.1 Hz, Ar-H), 8.1 (d, 2 H, J = 7.1 Hz, Ar-H). − FAB MS: m/z = 855 $[M + Na]^+$.

5-Acetyl-6-(4-benzyloxybenzoyloxy)-4-methoxy-7-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)benzofuran (**12C**): To a solution of **4b** (450 mg, 0.62 mmol) in anhydrous dichloromethane (10 ml), were added water-soluble carbodiimide (WSC, 346 mg, 1.8 mmol), 4-dimethylaminopyridine (DMAP, 5 mg, 0.04 mmol), and 4-(benzyloxy)benzoic acid (420 mg, 1.85 mmol). After stirring at room temp. for 36 h, the reaction mixture was poured into iced water (10 ml) and extracted with dichloromethane (3 × 10 ml). The combined extracts were dried with $MgSO_4$ and concentrated. Flash chromatography of the residue (petroleum ether/ethyl acetate, 10:4) yielded **12C** (410 mg, 71%) as colourless crystals, m.p. 56−58°C. − TLC (petroleum ether/ethyl acetate, 10:4): $R_f = 0.32$. − $[\alpha]_D^{25} = +14.8$ (c = 1, $CHCl_3$). − ^1H NMR (250 MHz, $CDCl_3$): δ = 2.53 (s, 3 H, $COCH_3$), 3.50 (m, 1 H, 5′-H), 3.74 (m, 2 H, 3′-H, 4′-H), 4.09 (m, 2 H, 6′-H, 6′′-H), 4.12 (s, 3 H, OMe), 4.36 (br. s, 1 H, 2′-H), 4.41−4.94 (m, 9 H, 4 CH_2-benzylic, 1′-H), 5.1 (s, 2 H, CH_2-benzylic), 6.80−7.55 (m, 29 H, 5 Ph, 2-H, 3-H, 3′′-, 5′′-H Ar), 8.1 (m, 2 H, 2′′-, 6′′-H Ar). − MALDI MS: m/z = 961 $[M + Na]^+$. − $C_{59}H_{54}O_{11}$ (939.05): calcd. C 75.46, H 5.79; found: C 75.00, H 5.71.

6-Hydroxy-5-[3-hydroxy-3-(4-methoxyphenyl)propenoyl]-, 6-Hydroxy-5-[3-hydroxy-3-phenylpropenoyl]-, and 6-Hydroxy-5-[3-(4-benzoyloxyphenyl)-3-hydroxypropenoyl]-4-methoxy-7-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)benzofuran (**13A−C**).

General Procedure: To a stirred solution of **12A−C** (0.24 mmol) in anhydrous dimethylformamide (5 ml), was added sodium hydride (12 mg, 0.48 mmol). The mixture was stirred at room temp. under argon for 3 h, and then the reaction was quenched by the addition of ethanol (1 ml) and water (5 ml). The mixture was extracted with ethyl acetate (3 × 5 ml), and the combined extracts were washed with water, dried with $MgSO_4$, and concentrated in vacuo. Flash chromatography of the residue (petroleum ether/ethyl acetate, 10:3) yielded **13A−C**.

13A: 170 mg, 82%, yellow solid; m.p. 59−60°C. − TLC (petroleum ether/ethyl acetate, 10:4): $R_f = 0.35$. − $[\alpha]_D^{25} = -3.6$ (c = 0.5, $CHCl_3$). − ^1H NMR (250 MHz, $CDCl_3$): δ = 3.66−3.77 (m, 2 H, 5′-H, 6′-H), 3.87−3.90 (m, 6 H, OMe, 3′-H, 4′-H, 6′′-H), 4.08 (s, 3 H, OMe), 4.33 (br. s, 1 H, 2′-H), 4.48−5.07 (m, 8 H, 4 CH_2-benzylic), 5.11 (d, 1 H, $J_{1',2'}$ = 9.8 Hz, 1′-H), 6.55−7.38 (m, 25 H, 4 Ph, 2-H, 3-H, =CH, 3′′-, 5′′-H Ar), 8.0 (m, 2 H, 2′′-, 6′′-H Ar), 13.5 (br, 1 H, OH), 15.85 (s, 1 H, OH enolic).

13B: 140 mg, 70%, yellow solid; m.p. 92−94°C. − TLC (petroleum ether/ethyl acetate; 10:3): R_f = 0.38. − $[\alpha]_D^{25}$ = −3.5 (*c* = 1, $CHCl_3$). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.66−3.89 (m, 5 H, 3′-H to 6′′-H), 4.13 (m, 4 H, OMe, 0.5 CH_2-benzylic), 4.17 (br. s, 1 H, 2′-H), 4.48−4.95 (m, 7 H, 3.5 CH_2-benzylic), 5.11 (d, 1 H, $J_{1',2'}$ = 9.7 Hz, 1′-H), 6.79−8.0 (m, 28 H, 5 Ph, 2-H, 3-H, =CH), 13.5 (br, 1 H, OH), 15.61 (s, 1 H, OH enolic). − MALDI MS: *m/z* = 857 $[M + Na]^+$.

13C: 185 mg, 82%, orange crystals; m.p. 60−61°C. − TLC (petroleum ether/ethyl acetate, 10:4): R_f = 0.42. − $[\alpha]_D^{22}$ = −2.4 (*c* = 0.5, $CHCl_3$). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.65 (m, 1 H, 5′-H), 3.67−3.87 (m, 4 H, 3′-H, 4′-H, 6′-, 6′′-H), 4.08 (s, 3 H, OMe), 4.33 (br. s, 1 H, 2′-H), 4.36−5.99 (m, 8 H, 4 CH_2-benzylic), 5.13 (m, 3 H, CH_2-benzylic, 1′-H), 6.75−7.45 (m, 30 H, 5 Ph, 2-H, 3-H, =CH, 3′′-, 5′′-H Ar), 7.98 (m, 2 H, 2′′-, 6′′-H Ar), 13.5 (br., 1 H, OH), 15.83 (s, 1 H, OH enolic). − MALDI MS: *m/z* = 963 $[M + Na]^+$. − $C_{59}H_{54}O_{11}$ (939.05): calcd. C 75.46, H 5.70; found C 75.11, H 5.60.

4-Methoxy-7-(4-methoxyphenyl)-9-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-5H-furo[3,2-g][1]benzopyran-5-one (**14A**): To a solution of **11A** (200 mg, 0.23 mmol) in ethyl acetate/methanol (10 ml, 1:1) was added palladium on charcoal (20 mg) and the reaction mixture was stirred under hydrogen for 12 h. The catalyst was then removed by filtration through Celite and the filtrate was concentrated to dryness to give **3A** (R_f = 0.29, $CHCl_3$/methanol, 10:1) as a colourless oil. The product was dissolved in anhydrous pyridine (5 ml), acetic anhydride (5 ml) and DMAP (5 mg) were added, and the mixture was stirred at room temp. for 24 h. The solvent was then removed and the residue was purified by flash chromatography (petroleum ether/ethyl acetate, 1:3), yielding **14A** (70 mg, 65%) as a colourless solid; m.p. 106−108°C; TLC (petroleum ether/ethyl acetate, 1:3): R_f = 0.42. − $[\alpha]_D^{25}$ = −5.02 (*c* = 1, $CHCl_3$). − ^{1}H NMR (250 MHz, $[D_6]$DMSO, at 80°C): δ = 1.51 (s, 3 H, OAc), 1.88 (s, 3 H, OAc), 1.93 (s, 3 H, OAc), 2.07 (s, 3 H, OAc), 3.89 (s, 3 H, OMe), 4.08 (s, 3 H, OMe), 4.19 (m, 2 H, 6′-, 6′′-H), 4.35 (m, 1 H, 5′-H), 5.32 (br. s, 1 H, 2′-H), 5.53−5.60 (m, 2 H, 3′-H, 4′-H), 5.75 (d, 1 H, $J_{1',2'}$ = 9.6 Hz, 1′-H), 6.69 (s, 1 H, 6-H), 7.16−7.23 (m, 3 H, 3-H, 3′′-, 5′′-H Ar), 8.05−8.12 (m, 3 H, 2-H, 2′′-, 6′′-H Ar). − MALDI MS: *m/z* = 651 $[M]^+$. − $C_{33}H_{32}O_{14}$ (652.60): calcd. C 60.73, H 4.94; found C 60.47, H 5.10.

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