Carbohydrate Research, 207 (1990) 131–137
Elsevier Science Publishers B.V., Amsterdam

Note

Phase-transfer-catalyzed synthesis of flavonoid glycosides

Costas Demetzos*, Alexios-Léandros Skaltsounis, François Tillequin, and Michel Koch†

Département de Pharmacognosie de l'Université René Descartes, U.R.A. au C.N.R.S. No 1310, Faculté des Sciences Pharmaceutiques et Biologiques, 4 avenue de l'Observatoire, F-75006 Paris (France)

(Received November 20th, 1989; accepted for publication in revised form, February 8th, 1990)

Flavonoid glycosides, particularly flavonol and flavone derivatives, are widespread ubiquitous natural compound. Some of them show interesting biological activities and are currently used for the treatment of various vascular diseases. However, only a few general, efficient methods have been so far described for their synthesis. The key-step of most syntheses involves the condensation of a flavonoid aglycon with a per-*O*-acetylglycosyl halide[1,2]. The Köenigs–Knorr reaction gives satisfactory yields, but the final workup is complicated by the presence of high concentration of silver salts in the reaction mixture[3–9]. Zemplén–Farkas synthesis, which involves the use of a per-*O*-acetylglycosyl bromide in a homogeneous alkaline medium, is more convenient from this point of view. Nevertheless, the yields remain generally low in the latter case, probably owing to a partial hydrolysis of the per-*O*-acetylglycosyl bromide in the course of the reaction[10–14]. Recent reports of the application of phase-transfer catalysis to the synthesis of simple aryl glycosides[15,16] prompted us to use this reaction in the field of flavonoid synthesis.

Condensation of 4′,7-di-*O*-benzylquercetin[17] (**1**) with either 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide or 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide was carried out in a two-phase system consisting of chloroform–1.25M aqueous potassium hydroxide solution and benzyltriethylammonium bromide as catalyst. After a simple workup, followed by column chromatography, the corresponding protected 3-β-D-glycosides **2** and **3** were isolated in 55 and 60% yield, respectively. In a similar way, condensations involving substituted per-*O*-acetylated derivatives of an α-D-glucopyranosyl bromide (such as 2,3,4,2′,3′,4′-hexa-*O*-acetyl-α-rutinosyl bromide[18,19] or 2′,3′,4′,6′,3,4,6-hepta-*O*-acetyl-α-sophorosyl bromide[20,21]) or per-*O*-acetylglycosyl bromide of pentopyranoses[22] led stereospecifically to the corresponding protected 3-glycosides in good yields (Table I).

* On leave from the Laboratory of Pharmacognosy, University of Athens, 20 Odos Hippocratous, GR-10679 Athens (Greece).
† To whom correspondence should be adressed.

0008-6215/90/$ 03.50

TABLE I

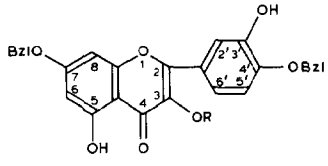
Condensation of 4',7-dibenzylquercetin (**1**) with per-*O*-acetylglycosyl bromides

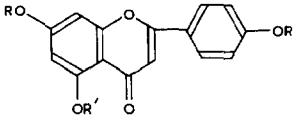
Per-O-acetylglycosyl bromide	*Compound(s) obtained*	*Yield (%)*
2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide	**2**	55
2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl bromide	**3**	60
2,3,4-Tri-*O*-acetyl-6-*O*-(2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl)-α-D-glucopyranosyl bromide	**4**	45
3,4,6-Tri-*O*-acetyl-2-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-glucopyranosyl bromide	**5**	45
2,3,4-Tri-*O*-acetyl-α-D-xylopyranosyl bromide	**6**	50
2,3,4-Tri-*O*-acetyl-α-L-arabinopyranosyl bromide	**7**	50
2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranosyl bromide	**8, 9**[a]	10
4-*O*-Acetyl-2,3-*O*-carbonyl-α-L-rhamnopyranosyl bromide	**10, 11**[b]	40

[a] Ratio 11:9 [b] Ratio 2:3.

In contrast to these results, when 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl bromide[23] was used as alkylating agent, glycosylation took place only in poor yield, and with a lack of stereospecificity. The difficulties encountered in this latter reaction can be related[24,25] to the *trans* relationship between the activated Br-1 and the participating CH_3CO_2-2. Therefore, 4-*O*-acetyl-2,3-*O*-carbonyl-α-L-rhamnopyranosyl bromide[26] was chosen as glycosylating agent, and its use increased the overall condensation yield[27], but did not overcome the lack of stereospecificity.

In order to explore further the scope of the method, unprotected apigenin (**12**) was condensed under similar conditions with an excess of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide or 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide to give the





1 R = H

2 R = 2,3,4,6-tetra-OAc-β-D-Glcp

3 R = 2,3,4,6-tetra-OAc-β-D-Galp

4 R = 2,3,4-tri-OAc-α-L-Rhap-(1→6)-2,3,4-tri-OAc-β-D-Glcp

5 R = 2,3,4,6-tetra-OAc-β-D-Glcp-(1→2)-3,4,6-tri-OAc-β-D-Glcp

6 R = 2,3,4-tri-OAc-β-D-Xylp

7 R = 2,3,4-tri-OAc-α-L-Arap

8 R = 2,3,4-tri-OAc-α-L-Rhap

9 R = 2,3,4-tri-OAc-β-L-Rhap

10 R = 4-OAc-2,3-O-carbonyl-α-L-Rhap

11 R = 4-OAc-2,3-O-carbonyl-β-L-Rhap

12 R = H R'=H

13 R = 2,3,4,6-tetra-OAc-β-D-Glcp, R' = H

14 R = 2,3,4,6-tetra-OAc-β-D-Galp, R' = H

15 R = 2,3,4,6-tetra-OAc-β-D-Galp, R' = Ac

TABLE II

Condensation of apigenin (**12**) with per-*O*-acetylglycosyl bromides

Per-O-acetylglycosyl bromide	*Compound obtained*	*Yield (%)*
2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide	**13**	20
2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl bromide	**14**	20

corresponding 4′,7-di-*O*-β-D-glycosides **13** and **14**, respectively, in 20% yield (Table II). In conclusion, phase-transfer-catalyzed glycosylation of flavonoid aglycons appears to be a facile method for flavonoid glycosides synthesis. Its value lies in an easy work-up and in yields that are generally higher than those reported for classical methods. Moreover, the stereospecificity of the reaction appears to be good, except for the L-rhamnose derivatives.

EXPERIMENTAL

General methods. — Optical rotations were measured with a Perkin–Elmer 241 polarimeter. ^{1}H-n.m.r. spectra were obtained with a Bruker HX 270 spectrometer (270 MHz) and tetramethylsilane was the internal standard. D.c.i.–m.s. were recorded with a Nermag R10-10C spectrometer using NH_3 as reagent gas.

Preparation of blocked glycosides **2–11**. — A solution of the appropriate *O*-acetylglycosyl bromide (0.3 mmol) and 4′,7-di-*O*-benzylquercetin (**1**; 120 mg, 0.25 mmol) in chloroform (5 mL) was vigorously stirred at reflux (60°) with benzyltriethylammonium bromide (55 mg, 0.2 mmol) in 1.25M aqueous KOH (2 mL) for 15 h. After dilution with water (10 mL), the two phases were separated and the organic layer was washed with 1.25M aqueous KOH (2 × 50 mL), dried (Na_2SO_4), and evaporated under reduced pressure. Purification by column chromatography (silica gel, 9:1 toluene–ethyl acetate) afforded the corresponding blocked glycosides.

Deblocking of glycosides **2–7**. — A solution of the blocked glycoside (60 mg) in methanol (10 mL) was hydrogenolyzed (Pd–C, H_2, 0.1 MPa) at 20° for 4 h. The catalyst was removed by filtration (Celite) and the solvent evaporated under reduced pressure. The residue was dissolved in M sodium methoxide in methanol (10 mL) and the mixture was stirred for 3 h at 20°. After neutralization by addition of Amberlite IR-50 (H^+) ion-exchange resin and filtration, the solvent was removed by evaporation to afford the corresponding glycoside. The quercet-3-yl glycosides obtained[28–32] from blocked glycosides **2–7** were identical with authentic natural samples (m.p., $[\alpha]_D$, t.l.c., ^{1}H-n.m.r. spectroscopy, and d.c.i.–m.s. spectrometry).

4′,7-Di-O-benzylquercet-3-yl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (**2**). — M.p. 97–98°, $[\alpha]_D^{20}$ −64° (*c* 0.4, methanol); ^{1}H-n.m.r. ($CDCl_3$): δ 12.47 (s, 1 H, OH-5), 7.65 (d, 1 H, $J_{2',6'}$, 2 Hz, H-2′), 7.62 (dd, 1 H, $J_{5',6'}$, 9 Hz, H-6′), 7.46–7.19 (m, 10 H, 2 $OCH_2C_6H_5$), 6.97 (d, 1 H, H-5′), 6.49 (d, 1 H, $J_{6,8}$ 2 Hz, H-8), 6.41 (d, 1 H, H-6), 5.86 (s, 1

H, OH-3′), 5.66 (d, 1 H, $J_{1'',2''}$ 8 Hz, H-1″), 5.28 (t, 1 H, $J_{3'',4''}$ 9 Hz, H-3″), 5.22 (dd, 1 H, H-2″), 5.20 (s, 2 H, $OCH_2C_6H_5$), 5.10 (s, 2 H, $OCH_2C_6H_5$), 5.08 (t, 1 H, $J_{4'',5''}$ 9 Hz, H-4″), 4.01 (m, 2H, H_2-6″), 3.68 (ddd, 1 H, $J_{5'',6''a}$ 7, $J_{5'',6''b}$ 3Hz, H-5), 2.11, 2.02, 2.01, and 1.91 (4 s, 12 H, 4 OAc); d.c.i.–m.s. 813 ($M+H^+$).

Anal. Calc. for $C_{43}H_{40}O_{16}$: C, 63.54; H, 4.96; O, 31.50. Found: C, 63.46; H, 4.99; O, 31.58.

4′,7-Di-O-benzylquercet-3-yl 2,3,4,6-tetra-O-acetyl-β-D-galactopyranoside (**3**). — M.p. 102–103°, $[\alpha]_D^{20}$ −32° (*c* 0.2, methanol); ^{1}H-n.m.r. ($CDCl_3$): δ 12.47 (s, 1 H, OH-5), 7.75 (d, 1 H, $J_{2',6'}$ 2 Hz, H-2′), 7.62 (dd, 1 H, $J_{5',6'}$ 9 Hz, H-6′), 7.44–7.10 (m, 10 H, 2 $OCH_2C_6H_5$), 6.95 (d, 1 H, H-5′), 6.48 (d, 1 H, $J_{6,8}$ 2 Hz, H-8), 6.39 (d, 1 H, H-6), 5.82 (s, 1 H, OH-3′), 5.66 (d, 1 H, $J_{1'',2''}$ 7 Hz, H-1″), 5.40 (dd, 1 H, $J_{2'',3''}$ 8 Hz, H-2″), 5.36 (dd, 1 H, $J_{3'',4''}$ 3, $J_{4'',5''}$ 1 Hz, H-4″), 5.18 (s, 2 H, $OCH_2C_6H_5$), 5.10 (s, 2 H, $OCH_2C_6H_5$), 5.07 (dd, 1 H, H-3″), 3.91 (m, 3 H, H-5″), 6″a,6″b), 2.14, 2.12, 2.00, and 1.91 (4 s, 12 H, 4 OAc); d.c.i.–m.s. 813 ($M+H^+$).

Anal. Calc. for $C_{43}H_{40}O_{16}$: C, 63.54; H, 4.96; O, 31.50. Found: C, 63.63; H, 4.87; O, 31.45.

4′,7-Di-O-benzylquercet-3-yl 2,3,4-tri-O-acetyl-6-O-(2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl)-β-D-glucopyranoside (**4**). — M.p. 95–96°, $[\alpha]_D^{20}$ −59° (*c* 0.3, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 12.45 (s, 1 H, OH-5), 7.63 (dd, 1 H, $J_{5',6'}$ 9, $J_{2',6'}$ 2 Hz, H-6′), 7.61 (d, 1 H, H-2′), 7.46–7.17 (m, 10 H, 2 $OCH_2C_6H_5$), 7.02 (d, 1 H, H-5′), 6.51 (d, 1 H, $J_{6,8}$ 2 Hz, H-8), 6.42 (d, 1 H, H-6), 5.96 (s, 1 H, OH-3′), 5.65 (d, 1 H, $J_{1'',2''}$ 7 Hz, H-1″), 5.27 (m, 2 H, H-2,″,3″), 5.20 (s, 2 H, $OCH_2C_6H_5$), 5.16 (m, 2 H, H-2‴,3‴), 5.12 (s, 2 H, $OCH_2C_6H_5$), 5.03 (t, 1 H, $J_{3'',4''}$ 9, $J_{4'',5''}$ 9 Hz, H-4‴), 4.95 (t, 1 H, $J_{3'',4''}$ 9, $J_{4'',5'}$, 9 Hz, H-4″), 4.60 (d, 1 H,$J_{1''',2'''}$ 1 Hz, H-1‴), 3.71 (m, 2 H, H-5″,5‴), 3.60 (dd, 1 H, $J_{5'',6''a}$ 2, $J_{6''a,6''b}$ 13 Hz, H-6″a), 3.38 (dd, 1 H, $J_{5'',6''b}$ 6 Hz, H-6″b), 2.10, 2.08, 2.04, 2.02, 1.94, 1.93 (6 s, 18 H, 6 OAc), and 1.07 (d, 3 H, $J_{5''',6'''}$ 6 Hz, CH_3-6‴); d.c.i.–m.s. 1043 ($M + H^+$).

Anal. Calc. for $C_{53}H_{54}O_{22}$: C, 61.03; H, 5.22; O, 33.75. Found: C, 60.91; H, 5.29; O, 33.67.

4′,7-Di-O-benzylquercet-3-yl 3,4,6-tri-O-acetyl-2-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-β-D-glucopyranoside (**5**). — M.p. 95–97°, $[\alpha]_D^{20}$ −38° (*c* 0.25, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 12.54 (s, 1 H, OH-5), 7.70 (d, 1 H, $J_{2',6'}$ 2 Hz, H-2′), 7.56 (dd, 1 H, $J_{5',6'}$ 9 Hz, H-6′), 7.51–7.26 (m, 10 H, 2 $OCH_2C_6H_5$), 7.02 (d, 1 H, H-5′), 6.49 (d, 1 H, $J_{6,8}$ 2 Hz, H-8), 6.40 (d, 1 H, H-6), 5.90 (s, 1 H, OH-3′), 5.56 (d, 1 H, $J_{1'',2''}$ 8 Hz, H-1″), 5.25 (t, 1 H, $J_{2'',3''}$ 8, $J_{3'',4''}$ 8 Hz, H-3″), 5.23 (s, 2 H, $OCH_2C_6H_5$), 5.17 (t, 1 H, $J_{2''',3'''}$ 8 Hz, H-3‴), 5.13 (t, 1 H, $J_{4''',5'''}$ 8 Hz, H-4‴), 5.12 (s, 2 H, $OCH_2C_6H_5$), 5.07 (t, 1 H, $J_{1''',2'''}$ 8 Hz, H-2‴), 5.03 (t, 1 H, $J_{4'',5''}$ 8 Hz, H-4″), 4.88 (1 H, d, H-1‴), 4.27 (dd, 1 H, $J_{5''',6'''a}$ 5, $J_{6'''a,6'''b}$ 13 Hz, H-6‴a), 4.07 (dd, 1 H, $J_{5''',6'''b}$ 2 Hz, H-6‴b), 4.01 (m, 3 H, H-2″,6″a,6″b), 3.66 (m, 2 H, H-5″,5‴), 2.10, 2.02, 2.01, 1.99, 1.98, 1.95, and 1.87 (7 s, 21 H, 7 OAc); d.c.i.–m.s. 1101 ($M + H^+$).

Anal. Calc. for $C_{55}H_{56}O_{24}$: C, 60.00; H, 5.13; O, 34.87. Found: C, 59.92; H, 5.07; O, 34.99.

4′,7-Di-O-benzylquercet-3-yl 2,3,4-tri-O-acetyl-β-D-xylopyranoside (**6**). — M.p. 95–96°, $[\alpha]_D^{20}$ −103° (*c* 0.2, methanol); ^{1}H-n.m.r. ($CDCl_3$): δ 12.52 (s, 1 H, OH-5), 7.63

(dd, 1 H, $J_{5',6'}$ 9, $J_{2',6'}$ 2 Hz, H-6'), 7.60 (d, 1 H, H-2'), 7.44–7.17 (m, 10 H, 2 $OCH_2C_6H_5$), 7.02 (d, 1 H, H-5'), 6.46 (d, 1 H, $J_{6,8}$ 2 Hz, H-8), 6.39 (d, 1 H, H-6), 5.85 (s, 1 H, OH-3'), 5.61 (d, 1 H, $J_{1'',2''}$ 6.5 Hz, H-1''), 5.22 (m, 2 H, H-2'',3''), 5.19 (s, 2 H, $OCH_2C_6H_5$), 5.03 (s, 2 H, $OCH_2C_6H_5$), 4.88 (ddd, 1 H, $J_{3'',4''}$ 8.5, $J_{4'',5''a}$ 7.5, $J_{4'',5''e}$ 5.5 Hz, H-4''), 3.89 (dd, 1 H, $J_{5''a,5''e}$ 13 Hz, H-5''*e*), 3.25 (dd, 1 H, H-5''*a*), 2.14, 2.08, and 2.02 (3 s, 9 H, 3 OAc); d.c.i.–m.s. 741 (M + H^+).

Anal. Calc. for $C_{40}H_{36}O_{14}$: C, 64.86; H, 4.90; O, 30.24. Found: C, 64.98; H, 4.92; O, 30.31.

4',7-Di-O-benzylquercet-3-yl 2,3,4-tri-O-acetyl-α-L-arabinopyranoside (**7**). — M.p. 104–105°, $[\alpha]_D^{20}$ +97° (*c* 0.3, chloroform); d.c.i.–m.s. 741 (M + H^+). ^{1}H-N.m.r. ($CDCl_3$): δ 12.45 (s, 1 H, OH-5), 7.80 (d, 1 H, $J_{2',6'}$ 2 Hz, H-2'), 7.65 (dd, 1 H, $J_{5',6'}$ 9 Hz, H-6'), 7.47–7.17 (m, 10 H, 2 $OCH_2C_6H_5$), 7.00 (d, 1 H, H-5'), 6.48 (d, 1 H, $J_{6,8}$ 2 Hz, H-8), 6.40 (d, 1 H, H-6), 5.87 (s, 1 H, OH-3'), 5.62 (d, 1 H, $J_{1'',2''}$ 7 Hz, H-1''), 5.45 (dd, 1 H, $J_{2'',3''}$ 8 Hz, H-2''), 5.20 (m, 2 H, H-3'', H-4''), 5.18 (s, 2 H, $OCH_2C_6H_5$), 5.10 (s, 2 H, $OCH_2C_6H_5$), 3.90 (dd, 1 H, $J_{5''a,5''e}$ 13, $J_{4'',5''e}$ 4 Hz, H-5''*e*), 3.55 (dd, 1 H, $J_{4'',5''a}$ 1 Hz, H-5''*a*), 2.20, 2.10, 2.07 (3 s, 9 H, 3 OAc).

Anal. Calc. for $C_{40}H_{36}O_{14}$: C, 64.86; H, 4.90; O, 30.24. Found: C, 64.81; H, 4.85; O, 30.32.

4',7-Di-O-benzylquercet-3-yl 2,3,4-tri-O-acetyl-α-L-rhamnopyranoside (**8**) *and 4',7-di-O-benzylquercet-3-yl- 2,3,4-tri-O-acetyl-β-L-rhamnopyranoside* (**9**). — These compounds were obtained as a 11:9 (n.m.r.) inseparable mixture; d.c.i.–m.s. 755 (M + H^+). α-L-*Anomer*. ^{1}H-n.m.r. ($CDCl_3$): δ 12.45 (s, 1 H, OH-5), 7.54 (m, 2 H, H-2', H6'), 7.52–7.15 (m, 10 H, 2 $OCH_2C_6H_5$), 7.06 (d, 1 H, $J_{5',6'}$ 9 Hz, H-5'), 6.48 (d, 1 H, $J_{6,8}$ 2 Hz, H-8), 6.41 (d, 1 H, H-6), 5.95 (s, 1 H, OH-3'), 5.60 (m, 2 H, H-1'', 2''), 5.37 (dd, 1 H, $J_{2'',3''}$ 2.5, $J_{3'',4''}$ 9 Hz, H-3''), 5.19 (s, 2 H, $OCH_2C_6H_5$), 5.11 (s, 2 H, $OCH_2C_6H_5$), 4.97 (t, 1 H, $J_{4'',5''}$ 9 Hz, H-4'') 3.49 (dq, 1 H, $J_{5'',6''}$ 6 Hz, H-5''), 2.22–1.95 (3s, 9 H, 3 OAc), and 0.97 (d, 3 H, CH_3-6'').

β-L *Anomer*. ^{1}H-n.m.r.: δ 12.42 (s, 1 H, OH-5), 7.75 (s, 1 H, $J_{2',6'}$ 2 Hz, H-2'), 7.65 (dd, 1 H, $J_{5',6'}$ 9 Hz, H-6'), 7.52–7.15 (m, 10 H, 2 $OCH_2C_6H_5$), 6.96 (d, 1 H, H-5'), 6.50 (d, 1 H, *J* 6,8 2 Hz, H-8), 6.41 (d, 1 H, H-6), 5.95 (s, 1 H, OH-3'), 5.92 (d, 1 H, $J_{1'',2''}$ 0.5 Hz, H-1'') 5.73 (dd, 1 H, $J_{2'',3''}$ 1.5 Hz, H-2''), 5.22 (dd, 1 H, $J_{3'',4''}$ 9 Hz, H-3''), 5.19 (s, 2 H, $OCH_2C_6H_5$), 5.11 (s, 2 H, $OCH_2C_6H_5$), 5.08 (t, 1 H, $J_{4'',5''}$ 9 Hz, H-4''), 3.65 (dq, 1 H, $J_{5'',6''}$ 6 Hz, H-5''), 2.22–1.95 (3s, 9 H, 3 OAc), and 1.15 (d, 3 H, CH_3-6'').

Deprotection of the mixture by hydrogenolysis, followed by saponification, led to the corresponding rhamnosides which could be separated by preparative t.l.c. (cellulose, 3:17 acetic acid–water), affording quercet-3-yl α-L-rhamnopyranoside, identical with an authentic sample ($[\alpha]_D^{20}$, t.l.c. ^{1}H-n.m.r., and d.c.i.–m.s.) and quercet-3-yl β-L-rhamnopyranoside, $[\alpha]_D^{20}$ +20° (*c* 0.1, methanol).

4',7-Di-O-benzylquercet-3-yl 4-O-acetyl-2,3-O-carbonyl-3-yl-α-L-rhamnopyranoside (**10**) *and 4',7-di-O-benzylquercet-3-yl 4-O-acetyl-2,3-O-carbonyl-β-L-rhamnopyranoside* (**11**). — These compounds were obtained as a 2:3 (n.m.r.) inseparable mixture; d.c.i.–m.s. 697 (M + H^+).

α-L *Anomer*. ^{1}H-N.m.r. ($CDCl_3$): δ 12.35 (s, 1 H, OH-5), 7.50 (m, H-2',6'),

7.48–7.15 (m, 10 H, 2 $OCH_2C_6H_5$), 7.08 (d, 1 H, $J_{5',6'}$ 9 Hz, H-5'), 6.49 (d, 1 H, $J_{6,8}$ 2 Hz, H-8), 6.43 (d, 1 H, H-6), 5.87 (s, 1 H, OH-3'), 5.55 (s, 1 H, H-1''), 5.21 (s, 2 H, $OCH_2C_6H_5$), 5.12 (s, 2 H, $OCH_2C_6H_5$), 5.10 (dd, 1 H, $J_{3'',4''}$ 7, $J_{4'',5''}$ 9 Hz, H-4''), 4.86 (t, $J_{2'',3''}$ 7 Hz, H-3''), 4.83 (d, 1 H, H-2''), 3.94 (dq, 1 H, $J_{5'',6''}$ 5 Hz, H-5''), 2.10 (s, 3 H, OAc), and 0.91 (d, 3 H, CH_3-6'').

β-L *Anomer*. ^{1}H-N.m.r.: δ 12.42 (s, 1 H, OH-5), 7.75 (dd, 1 H, $J_{5',6'}$ 9, $J_{2',6'}$ 0 Hz, H-6'), 7.65 (d, 1 H, H-2'), 7.48–7.15 (m, 10 H, 2 $OCH_2C_6H_5$), 7.08 (d, 1 H, H-5'), 6.51 (d, 1 H, $J_{6,8}$ 2 Hz, H-8), 6.41 (d, 1 H, H-6), 6.15 (s, 1 H, OH-3'), 6.06 (d, 1 H, $J_{1'',2''}$ 2 Hz, H-1''), 5.20 (s, 2 H, $OCH_2C_6H_5$), 5.12 (s, 2 H, $OCH_2C_6H_5$), 5.08 (dd, 1 H, $J_{3'',4''}$ 7, $J_{4'',5''}$ 9 Hz, H-4''), 4.91 (t, 1 H, $J_{2'',3''}$ 7 Hz, H-3''), 4.79 (dd, 1 H, H-2''), 3.81 (dq, 1 H, $J_{5'',6''}$ 6 Hz, H-5''), 2.13 (s, 3 H OAc), and 1.21 (d, 3 H, CH_3-6'').

Deprotection of the mixture led, as previously described, to the corresponding rhamnosides, separated by preparative t.l.c.

Preparation of blocked glycosides **13** *and* **14**. — Condensation of apigenin (**12**; 67.5 mg, 0.25 mmol) and the appropriate per-*O*-acetylglycosyl bromide (1 mmol), by following the general procedure described for **2**–**11**, afforded the blocked glycosides **13** and **14**.

Apigen-4',7-diyl-di(2,3,4,6-tetra-O-*acetyl-β*-D-*glucopyranoside*) (**13**). — Foam, $[\alpha]_D^{20}$ −20° (*c* 0.2, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 12.64 (s, 1 H, OH-5), 7.84 (d, 2 H, $J_{2',3'} = J_{5',6'}$ 9 Hz, H-2', 6'), 7.09 (d, 2 H, H-3',5'), 6.61 (s, 1 H, H-3), 6.57 (d, 1 H, $J_{6,8}$ 2 Hz, H-8), 6.44 (d, 1 H, H-6), 5.30–5.10 (m, 8 H, H-1'',2'',2''',3'',3''',4'',4'''), 4.28 (m, 2 H, H-6''a,6'''a), 4.18 (m, 2 H, H-6''b,6'''b), 3.94 (m, 2 H, H-5'',5'''), and 2.10–2.04 (8 s, 24 H, 8 OAc); d.c.i. –m.s. 931 ($M + H^+$).

Anal. Calc. for $C_{43}H_{46}O_{23}$: C, 55.49; H, 4.98; O, 39.53. Found: C, 55.54; H, 5.02; O, 39.48.

5-O-Acetylapigen-4',7-diyl di(2,3,4,6-tetra-O-*acetyl-β*-D-*galactopyranoside)* (**15**). — Apigen-4',7-diyl di(2,3,4,6-tetra-O-acetyl-*β*-D-galactopyranoside) (**14**) was obtained as a foam, almost insoluble in the usual solvents; d.c.i.–m.s. 931 ($M + H^+$). Acetylation (acetic anhydride–pyridine, 48 h) of **14** led, in quantitative yield, to **15**, amorphous, $[\alpha]_D^{20}$ −5° (*c* 0.1, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 7.80 (d, 2 H, $J_{2',3'} = J_{5',6'}$ 9 Hz, H-2',6'), 7.11 (d, 2 H, H-3',5'), 6.99 (d, 1 H, $J_{6,8}$ 2 Hz, H-6), 6.70 (d, 1 H, H-8), 6.53 (s, 1 H, H-3), 5.50 (m, 4 H, H-1'',1''',2'',2'''), 5.15 (m, 4 H, H-3'',3''',4'',4'''), 4.17 (m, 6H, H-5',5''',H_2-6'',6'''), 2.44 (s, 3 H, OAc-5), and 2.20–2.02 (8s, 24 H, 8 OAc); d.c.i.–m.s. 973 ($M + H^+$).

Anal. Calc. for $C_{45}H_{48}O_{24}$: C, 55.56; H, 4.97; O, 39.47. Found: C, 55.49; H, 4.91; O, 39.53.

ACKNOWLEDGMENT

The authors thank Dr. F. Hotellier, Département de Pharmacognosie, Université de Paris V, for m.s. measurements and experiments.

REFERENCES

1 H. Wagner and L. Farkas, in J. B. Harborne, T. J. Mabry, and H. Mabry (Eds.), *The Flavonoids*, Chapman and Hall, London, 1975, pp. 127–213.
2 L. Farkas and B. Vermes, *J. Indian Chem. Soc.*, 55 (1978) 1192–1197.
3 H. El Khadem and Y. S. Mohammed, *J. Chem. Soc.*, (1958) 3320–3323.
4 L. Farkas, M. Nógrádi, B. Vermes, A. Wolfner, H. Wagner, L. Hörhammer, and H. Krämer, *Chem. Ber.*, 102 (1969) 2583–2587.
5 H. Wagner, W. Budweg, L. Hörhammer, B. Vermes, and L. Farkas, *Chem. Ber.*, 104 (1971) 2118–2123.
6 L. Farkas, B. Vermes, and M. Nógrádi, *Chem. Ber.* 105 (1972) 3505–3510.
7 L. Farkas, B. Vermes, M. Nógrádi, and A Kálmán, *Phytochemistry*, 15 (1976) 215–218.
8 K. Skékely, B. Vermes, L. Farkas, and M. Nógrádi, *Acta Chim. Acad. Sci. Hung.*, 98 (1978) 241–245.
9 B. Vermes, V. M. Chari, and H. Wagner, *Helv. Chim. Acta.*, 64 (1981) 1964–1967.
10 G. Zemplén and L. Farkas, *Ber. Dtsch. Chem. Ges.*, 76 (1943) 1110–1112.
11 R. Téoule, J. Chopin and C. Mentzer, *C. R. Hebd. Seances Acad. Sci, Ser. C.*, 250 (1960) 3669–3670.
12 L. Hörhammer, L. Farkas, H. Wagner, and J. Ostermayer, *Acta Chim. Hung.*, 40 (1964) 463–469.
13 L. Farkas, L. Hörhammer, H. Wagner, H. Rösler, and R. Gurniak, *Chem. Ber.*, 97 (1964) 610–615.
14 H. Wagner, L. Hörhammer, W. Budweg, A. Major, and L. Farkas, *Chem. Ber.*, 102 (1969) 3006–3008.
15 D. Dess, H. P. Kleine, D. V. Weinberg, R. J. Kaufman, and R. S. Sidhu, *Synthesis*, (1981) 883–885.
16 H. P. Kleine, D. V. Weinberg, R. J. Kaufman, and R. S. Sidhu, *Carbohydr. Res.*, 142 (1985) 333–337.
17 L. Jurd, *J. Org. Chem.*, 27 (1962) 1294–1297.
18 G. Zémplen and Á. Gerecs, *Ber., Dtsch. Chem. Ges.*, 70 (1937) 1098–1101.
19 R. Bognár, I. Farkas Szabó, I. Farkas, and H. Gross, *Carbohydr. Res.*, 5 (1967) 241–243.
20 K. Freudenberg and K. Soff, *Ber. Dtsch. Chem. Ges.*, 69 (1936) 1245–1251.
21 B. H. Koeppen, *Carbohydr. Res.*, 7 (1968) 410–413.
22 M. Gehrke and F. X. Aichner, *Ber. Dtsch. Chem. Ges.*, 60 (1927) 918–922.
23 G. M. Bebault, G. G. S. Dutton, and C. K. Warfield, *Carbohydr. Res.*, 34 (1974) 174–179.
24 V. K. Srivastava and C. Schuerch, *Carbohydr. Res.*, 79 (1980) c13–c16.
25 T. Iversen and D. R. Bundle, *Carbohydr. Res.*, 84 (1980) c13–c15.
26 L. V. Backinowsky, N. F. Balan, A. S. Shashkov, and N. K. Kochetkov, *Carbohydr. Res.*, 84 (1980) 225–235.
27 H. P. Kleine and R. S. Sidhu, *Carbohydr. Res.*, 182 (1988) 307–312.
28 L. Hörhammer, H. Wagner, H.-G. Arndt, H. Kraemer, and L. Farkas, *Tetrahedron Lett.*, (1966) 567–571.
29 L. Hörhammer, H. Wagner, H.-G Arndt, and L. Farkas, *Chem. Ber.*, 99 (1966) 1384–1387.
30 L. Hörhammer, H. Wagner, H.-G. Arndt, R. Dirscherl, and L. Farkas, *Chem. Ber.*, 101 (1968) 450–453.
31 H. Wagner, L. Hörhammer, R. Dirscherl, L. Farkas, and M. Nógrádi, *Chem. Ber.*, 101 (1968) 1186–1189.
32 L. Hörhammer, H. Wagner, G. Hitzler, L. Farkas, A. Wolfner, and M. Nógrádi, *Chem. Ber.*, 102 (1969) 792–798.