250. Synthesis of Xanthone *O*-Glycosides

Part III[1])

Synthesis of 1- and 8-*O*-*β*-D-Glycosides of 5-*O*-Methyl- and De-*O*-methylbellidifolin

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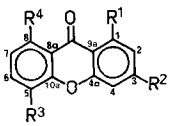
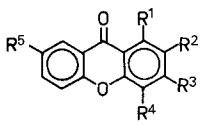
The unambiguous synthesis of three naturally occurring and biologically active xanthone 1-*O* and 8-*O*-*β*-D-glucosides of 5-*O*-methyl- and de-*O*-methylbellidifolin (**2**–**4**) was accomplished. The protected xanthone aglycones having only a single reactive OH group were prepared by selective benzylation, methylation, and debenzoylation reactions. An unexpected stability of the 1-MeO group towards demethylation was observed.

Introduction. – Earlier, we reported the synthesis of several 3-*O*- [1] and 1-*O*-*β*-D-glycosides [2] of hydroxyxanthones, which showed remarkable CNS-stimulant activity. Following this program, we synthesized the glycosides of 1,3,5,8-tetrahydroxyxanthone (= de-*O*-methylbellidifolin; **1**), which has many naturally occurring *O*-methyl derivatives and five monoglucosides [3]. The 1-(*β*-D-glucosyloxy)-3,5,8-trihydroxyxanthone (= norswertianolin; **2**) was isolated from *Swertia purpurascens* [4], *S. randaiensis* [5], and *S. racemosa* [6] and identified in the form of its permethyl ether in a mixture of xanthones isolated from *Swertia angustifolia* [7]. Isolation of 8-(*β*-D-glucosyloxy)-1,3,5-trihydroxyxanthone (**3**) was reported from *Gentiana campestris* [8], *G. germanica*, and *G. ramosa* [9]. The 1-(*β*-D-glucosyloxy)-8-hydroxy-3,5-dimethoxyxanthone (= swerchirin 1-*O*-glucoside = 5-*O*-methylbellidifolin 1-*O*-glucoside; (**4**) was isolated from *Frasera caroliniensis* [10]. Two further glucosides of bellidifolin (**5**), the 3-methyl ether of **1**, were found in





	R^1	R^2	R^3	R^4
1	OH	OH	OH	OH
2	OGlc	OH	OH	OH
3	OH	OH	OH	OGlc
4	OGlc	OMe	OMe	OH
5	OH	OMe	OH	OH
6	OH	OMe	H	OH
7	OBz	OMe	H	OH
8	OH	OMe	H	OMe
14	OMe	OH	OH	OH
15	OBz	OBz	OH	OH
16	OH	OBz	OH	OH

	R^1	R^2	R^3	R^4
17	OH	OH	OBz	OH
18	OMe	OMe	OMe	OMe
19	OH	OMe	OMe	OH
20	OH	OH	OMe	OH
21	OMe	OMe	OCOPh	OCOPh
22	OCOPh	OCOPh	OCOPh	OCOPh
23	OMe	OMe	OCOPh	OH
24	OCOPh	OCOPh	OCOPh	OH
25	OMe	OMe	OBz	OBz
26	OMe	OH	OBz	OH
27	OBz	OMe	H	OMe

	R^1	R^2	R^3	R^4	R^5
9	OH	OMe	OMe	H	OMe
10	OH	OMe	OMe	OH	Ome

Bz = benzyl

[1]) Part II, see [1].

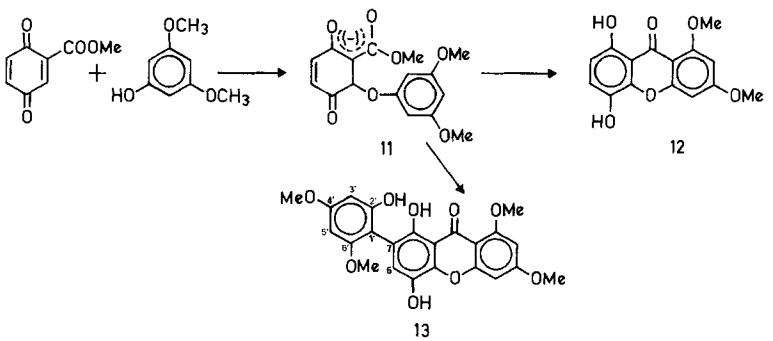
different *Swertia* and *Gentiana* species [3]. In all cases, the xanthone skeleton carries the glucose unit at C(1) or C(8). Although a large number of naturally occurring xanthone glycosides carry the sugar unit at C(8), synthesis of 8-*O*-(*β*-glycosyl) derivatives of xanthones has not been reported. In the synthesis of de-*O*-methylbellidifolin glucosides, we followed a procedure used before in the flavonoid field [11]. There, we have worked out a method for selective glucosidation which utilized differences in acidity and reactivity of the different OH groups using partially benzylated, benzoylated, or methylated compounds as aglycons.

Results and Discussion. – *Synthesis of the Aglycones.* For the synthesis of the suitable derivatives of de-*O*-methylbellidifolin (**1**) with 1,4-dihydroxyxanthone structure, our first plan was to form the *para*-dihydroxy moiety by *Elbs* oxidation. For this purpose, 1,8-dihydroxy-3-methoxyxanthone (**6**) [12] was synthesized and benzylated cautiously. It was interesting that only OH-C(1) was benzylated to give **7** in quantitative yield. The formation of the 8-benzyl ether was not observed. The structure of **7** was proved by its methylation and debenzylation which resulted in the known 1-hydroxy-3,8-dimethoxyxanthone (**8**) [12]. The *Elbs* oxidation of this compound was unsuccessful because of the alkali sensitivity of the product. *Markham* [13] reported the potassium persulfate oxidation of 1,3,8-trihydroxyxanthone on a micro scale to give **1**, but in our hands this method failed too.

The success of *Elbs* oxidation seems to depend on the oxidation pattern of the phenol. The 1-hydroxy-2,3,7-trimethoxyxanthone (**9**) [9] was successfully oxidized to 1,4-dihydroxy-2,3,7-trimethoxyxanthone (**10**). It has to be mentioned that our synthetic product was different from a naturally occurring compound isolated by *Ghosal* and coworkers [14] from *Swertia bimaculata* for which the same structure was claimed. *Simoneau* and *Brassard* [15] also came to the conclusion that the structure proposed earlier for the naturally occurring compound by Indian authors was indeed incorrect.

The successful synthesis of the 1,3,5,8-tetraoxygenated xanthones was carried out by applying to our case the method of *Müller* and coworkers [16] – namely the nucleophilic addition of phenols to alkoxycarbonyl-*p*-benzoquinones followed by reduction, methylation, hydrolysis, and finally cyclization. The addition of 3,5-dimethoxyphenol [17] to 2-methoxycarbonyl-1,4-benzoquinone [18] using 2-methoxypyridine as basic catalyst resulted in the suitable substituted diphenyl ether **11** which cyclized under our reaction conditions directly to the required 5,8-dihydroxy-1,3-dimethoxyxanthone (**12**; *Scheme*).

Scheme



From the above-described reaction, a well-defined by-product **13** was also obtained in about 5% yield. UV, HR-MS, ^{1}H- and ^{13}C-NMR spectra of this compound and its acetate showed that besides O,C addition of 3,5-dimethoxyphenol to the activated quinones, a C,C addition giving structure **13** took place too.

The next task was to transform **12** into 1,5,8-trihydroxy-3-methoxyxanthone (**5**), *i.e.* to bellidifolin [4] [5] [13] [18]. It is well known from the chemistry of flavonoids and xanthones that demethylation under controlled conditions preferentially affects the MeO group adjacent to a C = O group. Demethylation of **12** gave, however, a surprising result. Using $AlCl_3$ in Et_2O or MeCN, **12** remained unchanged. Demethylation with $AlCl_3$ in benzene at 50°, with pyridine hydrochloride at 140°C, or with $ZnCl_2$ and $POCl_3$ at 60° gave, in turn a monomethoxyxanthone which was different from bellidifolin [18]. The ^{1}H-NMR spectrum shows the presence of only one chelated OH group, and the ^{13}C-NMR spectra lack the signals characteristic of a xanthone in which the 1-position is free and the 3-position *O*-substituted [19]. Most of the δ-values are not in agreement with the principles of the shift rules postulated by *Frahm* and *Chaudhuri* [19]. So the only possible structure for our compound is 3,5,8-trihydroxy-1-methoxyxanthone (**14**). Later we will show another example of the special reactivity of the 1-OH group of this xanthone type. The desired demethylation of **12** was, finally, achieved by HI in Ac_2O or by $AlCl_3$ in benzene at 80°C and furnished 1,3,5,8-tetrahydroxyxanthone (**1**) [4] [5] [20].

In the possession of **1**, experiments were made for its selective methylation, benzylation, and debenzoylation. We have successfully used these types of reactions in the selective synthesis of flavonoid glycosides [11].

Benzylation of **1** with 3 mol of benzyl chloride gave three products, 1,3-dibenzyloxy-5,8-dihydroxy- (**15**), 3-benzyloxy-1,5,8-trihydroxy- (**16**), and as the main product 5-benzyloxy-1,3,8-trihydroxyxanthone (**17**). The structures of these compounds were proved by their ^{1}H-NMR spectra and by conversions to derivatives.

Methylation of 5-benzyloxyxanthone (**17**) with 2 mol of dimethyl sulfate and subsequent debenzylation gave the known 5,8-dihydroxy-1,3-dimethoxyxanthone (**12**). It was interesting that the methylation of **17** with diazomethane in Et_2O followed by debenzylation gave the 1-methyl ether **14**.

Methylation of the tetrahydroxyxanthone **1** with dimethyl sulfate in acetone gave the tetramethoxyxanthone **18** [4] as the main product; the formation of some **12** was also observed. On the other hand, the methylation of **1** with diazomethane in $CHCl_3$ at r.t. yielded three products: 1,8-dihydroxy-3,5-dimethoxy (**19**) [20], 5,8-dihydroxy-1,3-dimethoxy (**12**), and 1,3,8-trihydroxy-5-methoxyxanthone (**20**) [21].

Selective debenzoylation of 5,8-dibenzoyloxy-1,3-dimethoxy (**21**; obtained from **12**) and 1,3,4,8-tetra(benzoyloxy)xanthone (**22**; obtained from **1**), with $AlCl_3$ in Et_2O resulted in xanthones with a free C(8) OH group (**23** and, resp. **24**).

The experiments presented here did not give a clear picture of the reactivity order of the various OH groups in the tetrahydroxyxanthone **1**. Nevertheless, the high reactivity of the OH groups at C(5) and C(1) was a constant feature and was utilized in the synthesis of 5-*O*-methylbellidifolin 1-*O*-glucoside (**4**) [9] and de-*O*-methylbellidifolin 1-*O*-glucoside (**2**) [4–6] and 8-*O*-glucoside(**3**) [7].

Synthesis of Glucosides. For the synthesis of de-*O*-methylbellidifolin 1-*O*-glucoside (**2**), the 5-*O*-benzyl compound **17**, and for 5-*O*-methylbellidifolin 1-*O*-glucoside (**4**), 3,5-dimethoxyxanthone **19** seemed to be suitable aglucones. On coupling of **19** with

α-acetobromoglucose [22] according to *Königs* and *Knorr*, a monoglucoside fraction as main product was isolated which, after saponification, could only be the desired swerchirin 1-*O*-glucoside (**4**). In the case of **17**, the required **2** was accompanied by the 1,3-bisglucoside. For the synthesis of de-*O*-methylbellidifolin 8-*O*-glucoside (**3**), the above-mentioned 1,3,5-tribenzoyloxy-8-hydroxyxanthone (**24**) seemed to be an ideal aglycon. Coupling of this compound with α-acetobromoglucose gave, in a prolonged reaction and in a very poor yield, the acylated 8-*O*-glucoside; subsequent saponification yielded (**3**). The physical constants of our synthetic compounds and their acetates agreed with those reported for the natural products. Unfortunately, natural samples were not available.

We are indebted to Prof. *K. Hostettmann* for a sample of bellidifolin and Drs. *P. Kolonits* and *I. Balogh-Batta* for NMR spectra and microanalyses.

Experimental Part

General. Column chromatography was performed on silica gel and TLC on *Merck-GF$_{254}$* plates. Solvent systems: A = toluene/EtOH 9:1, B = toluene/EtOAc 8:1, C = toluene/EtOAc, D = EtOAc/MeOH/H_2O 200:33:27. M.p.: *Kofler* block; uncorrected. IR (cm^{-1}): KBr pellets. NMR (ppm; *J* in Hz): at 80 and 100 MHz for ^1H and 20.15 MHz for ^{13}C with TMS as internal standard.

1. *5,8-Dihydroxy-1,3-dimethoxy-9*H-*xanthen-9-one* (**12**). To a soln. of methyl 2,5-dihydroxybenzoate [23] (1.68 g, 10 mmol) in dry benzene (17 ml), K_2CO_3 (850 mg) and Ag_2O (5 g) were added. The mixture was kept at 50° for 20 min. The inorg. salts were filtered off, and to the red solution, immediately $MgSO_4$ (1.7 g) and dropwise within 10 min a soln. of 3,5-dimethoxyphenol (1.07 g, 7 mmol) and 2-methoxypyridin (2.28 g, 21 mmol) in benzene (10 ml) were added at r.t. After stirring at 25° for 2 h, $MgSO_4$ was filtered off and benzene and the excess of methoxypyridine were evaporated. The oily residue was left standing overnight with MeOH (50 ml), and the yellow precipitate was purified by column chromatography (A, R_f 0.6) to yield **12** (600 mg, 21%) as yellow plates (from MeOH), m.p. 167–169°. IR: 1680 (CO). ^1H-NMR ($CDCl_3$): 3.86, 4.05 (2 *s*, 3 H each, 2 CH_3O); 6.49 (*d*, *J* = 2.5, 1 arom. H_m); 6.57 (*d*, *J* = 2.5, 1 arom. H_m); 7.00 (*d*, *J* = 9, 1 arom. H_o); 7.31 (*d*, *J* = 9, 1 arom. H_o); 8.77 (*s*, OH–C(5)); 11.22 (*s*, OH–C(8)). ^{13}C-NMR ((D_6)DMSO): 178.5 (*s*, CO); 164.8 (*s*, C(3)); 161.0 (*s*, C(1)); 155.9, 155.1 (2*s*, C(4a), C(8)); 151.5 (*s*, C(10a)); 145.0 (*s*, C(5)); 128.5 (*d*, C(6)); 118.5 (*s*, C(8a)); 116.8 (*d*, C(7)); 105.2 (*s*, C(9a)); 97.4 (*d*, C(2)); 95.2 (*d*, C(4)); 57.6, 56.0 (2*q*, CH_3O–C(1), CH_3O–C(3)). Anal. calc. for $C_{15}H_{12}O_6$ (288.25): C 62.49, H 4.20; found: C 62.32, H 4.42.

Diacetate of **12**. Acetylation (Ac_2O pyridine) of **12** gave white plates (from MeOH), m.p. 184–188°. IR: 1750, 1620 (CO). ^1H-NMR ($CDCl_3$): 2.22, 2.35 (2*s*, 2 AcO); 3.74, 3.78 (2*s*, 2 CH_3O); 6.29 (*d*, *J* = 2, 1 arom. H_m); 6.39 (*d*, *J* = 2, 1 arom. H_m); 7.08 (*d*, *J* = 9, arom. H_o); 7.46 (*d*, *J* = 9, 1 arom. H_o). Anal. calc. for $C_{19}H_{16}O_8$ (272.32): C 61.28, H 4.33; found: C 60.97, H 4.41.

Dibenzoate **21**. Benzoylation of **12** with benzoyl chloride pyridine at 100° for 2 h gave white plates (from MeOH/$CHCl_3$ 9:1), m.p. 206–208°. IR: 1675, 1730 (CO). ^1H-NMR ($CDCl_3$): 3.25, 3.74 (2*s*, 2 CH_3O); 6.25 (*d*, *J* = 2, 1 arom H_m); 6.42 (*d*, *J* = 2, 1 arom. H_m); 7.32 (*d*, *J* = 9, 1 arom. H_o); 7.48–8.40 (*m*, 1 arom. H_o, 2 C_6H_5). Anal. calc. for $C_{29}H_{20}O_8$ (496.45): C 70.16, H 4.06; found: C 70.28, H 4.27.

*5,8-Dihydroxy-7-(2'-hydroxy-4',6'-dimethoxyphenyl)-1,3-dimethoxy-9*H-*xanthen-9-one* (**13**) is a by-product of **12** isolated by column chromatography (A, R_f 0.6). Yellow plates (180 mg, 5.5%), m.p. 259–262° (from EtOH). IR: 1680 (CO). ^1H-NMR ($(D)_6$ DMSO): 3.65, 3.77, 3.90, 4.10 (4*s*, 4 CH_3O); 6.20 (*s*, H–C(3'), H–C(5')); 6.77 (*s*, 2 arom. H_m); 7.10 (*s*, H–C(3)); 8.80 (*s*, OH–C(4)); 9.25 (*s*, OH–C(2')); 11.11 (*s*, OH–C(1)). ^{13}C-NMR ($(D)_6$ DMSO): 165.7 (*s*, C(6)); 160.9 (*s*, C(8)); 160.6, 158.7 (2*s*, C(4'), C(6')); 156.4, 155.8, 154.5 (3*s*, C(10a), C(1), C(2')); 151.5 (*s*, C(4a)); 144.0 (*s*, C(4)); 131.7 (*d*, C(3)); 124.1 (*s*, C(2)), 117.1 (*s*, C(9a)); 105.2 (*s*, C(8a)); 104.7 (*s*, C(1')); 97.5 (*d*, C(7)); 95.3 (*d*, C(5)); 94.1 (*d*, C(3')); 90.1 (*d*, C(5')); 57.6, 56.0, 55.6, 55.1 (4*q*, 4 CH_3O). MS: 440.1119 (M^+, $C_{23}H_{20}O_9$; calc. 440.1106).

Triacetate of **13**. Acetylation (Ac_2O pyridine) gave white plates (from EtOH), m.p. 159–161°. IR: 1760, 1710, 1610 (CO). ^1H-NMR ($CDCl_3$): 2.11, 2.21, 2.29 (3*s*, 3 AcO); 3.75 (*s*, CH_3O); 3.88 (*s*, 2 CH_3O); 3.91 (*s*, CH_3O); 6.42 (*m*, 4 arom. H); 7.45 (*s*, H–C(3)). MS: 556 (M^+, $C_{29}H_{26}O_{12}$).

2. *1,3,5,8-Tetramethoxy-9*H-*xanthen-9-one* (**18**). For 4 h, **12** (290 mg, 1 mmol), $NaHCO_3$ (0.5 g), and dimethyl sulfate were refluxed and stirred in 20 ml of acetone. After evaporation, the mixture was diluted with H_2O. Pale yellow plates (from EtOH), 320 mg (77%), m.p. 172–173° ([4]: 208–209°). IR: 1680 (CO). ^{1}H-NMR ($CDCl_3$): 3.87–4.05 (*m*, 4 CH_3O); 6.35 (*d*, *J* = 2, 1 arom. H_m); 6.48 (*d*, *J* = 2, 1 arom. H_m); 7.00 (*d*, *J* = 9, 1 arom. H_o); 7.40 (*d*, *J* = 9, 1 arom. H_o). Anal. calc. for $C_{17}H_{16}O_6$ (316.30): C 64.55, H 5.10; found: C 64.60, H 4.92.

3. *5,8-Dibenzyloxy-1,3-dimethoxy-9*H-*xanthen-9-one* (**25**). For 6 h **12** (290 mg, 1 mmol), $NaHCO_3$ (0.5 g), and benzyl chloride (0.26 ml, 2.2 mmol) were refluxed and stirred in 20 ml of acetone. After removal of benzyl chloride by steam destillation, extraction with EtOAc and evaporation yielded **25** (400 mg, 86%). White needles, m.p. 119–121°. IR: 1625 (CO). ^{1}H-NMR ($CDCl_3$): 3.5, 3.75 (2*s*, 2 CH_3O); 4.9, 5.1 (2*s*, 2 $PhCH_2$); 6.1–6.3 (*m*, H–C(2), H–C(4)); 6.9 (*d*, *J* = 9, 1 arom. H_o); 7.1–7.4 (*m*, 1 arom. H_o, 2 C_6H_5). Anal. calc. for $C_{29}H_{24}O_6$ (468.48): C 74.34, H 5.16; found: C 74.48, H 4.99.

4. *1,3,5,8-Tetrahydroxy-9*H-*xanthen-9-one* (**1**). *a*) For 4 h, **12** (575 mg, 2 mmol) was refluxed with anh. $AlCl_3$ (3 g, 2.25 mmol) in benzene (100 ml). The mixture was evaporated and 100 ml of H_2O followed by 20 ml of conc. HCl were added. The precipitate was filtered off to give **1** (44 mg, 85%) as yellow plates (from EtOH), m.p. 318–320° (dec.; [5]: 317°; [20]: 310–315°). *b*) For 2 h **12** (575 mg, 2 mmol) was heated with HI (2 ml) and Ac_2O (2 ml) at 140°. The mixture was poured onto 5% Na_2CO_3 soln. The product (400 mg, 78%) was identical with that prepared by *Method a*. IR: 1650 (CO). ^{1}H-NMR ((D_6)DMSO): 6.30 (*s*, 2 arom. H_m); 6.88 (*d*, *J* = 9, 1 arom H_o); 7.28 (*d*, *J* = 9, 1 arom. H_o); 11.2 (*s*, OH–C(8)); 9–11 (br. OH-Ar). ^{13}C-NMR ((D_6)DMSO): 183.4 (*s*, CO); 165.1 (*s*, C(3)); 159.6 (*s*, C(1)); 156.0 (*s*, C(4a)); 154.7 (*s*, C(8)); 151.9 (*s*, C(10a)); 142.4 (*s*, C(5)); 127.8 (*d*, C(6)); 120.6 (*s*, C(8a)); 116.0 (*d*, C(7)); 104.7 (*s*, C(9a)); 101.7 (*d*, C(2)); 96.2 (*d*, C(4)). Anal. calc. for $C_{13}H_8O_6$ (260.19): C 60.00, H 3.1; found: C 59.81, H 3.39.

Tetraacetate of **1**. Acetylation of **1** with pyridine Ac_2O gave white plates, m.p. 238–242° [20]: 242°. ^{1}H-NMR ($CDCl_3$): 2.27–2.30, 2.42 (*s*, 4 AcO); 6.94 (*d*, *J* = 2, 1 arom. H_m); 7.05 (*d*, *J* = 2, 1 arom H_m); 7.23 (*d*, *J* = 9, 1 arom. H_o); 7.55 (*d*, *J* = 9, 1 arom. H_o). Anal. calc. for $C_{21}H_{16}O_{10}$ (428.34): C 58.88, H 3.77; found: C 58.57, H 3.58.

Tetrabenzoate **22**. Benzoylation of **1** (260 mg, 1 mmol) with benzoyl chloride pyridine at 100° for 2 h gave white plates (450 mg, 67%) from EtOH/Me_2CO 9:1, m.p. 162–164°. IR: 1740, 1650 (CO). ^{1}H-NMR ($CDCl_3$): 6.95–7.1 (*m*, 2 arom. H_m); 7.2–8.3 (*m*, 2 arom. H_o, 4 C_6H_5). Anal. calc. for $C_{41}H_{24}O_{10}$ (676.6): C 72.78, H 3.58; found: C 72.91, H 3.42.

5. *3,5,8-Trihydroxy-1-methoxy-9*H-*xanthen-9-one* (**14**). *a*) For 1.5 h, **12** (290 mg, 1 mmol) was heated with pyridine hydrochloride (1.16 g, 10 mmol) at 140°. The mixture was poured onto 10% ice-cold HCl (10 ml). *b*) *Exper. 4a* was repeated at 50°. The precipitate obtained was crystallized from EtOH (210 mg, 78%). Yellow plates, m.p. 320–324° (dec.). IR: 1640 (CO). ^{1}H-NMR ((D_6)DMSO): 3.84 (*s*, CH_3O); 6.47 (*m*, 2 arom. H_m); 6.96 (*d*, *J* = 9, 1 arom. H_o); 7.29 (*d*, *J* = 9, 1 arom. H_o); 11.43 (*s*, OH–C(8)); 6.3–8.5 (br., OH–Ar). ^{13}C-NMR ((D_6)DMSO): 164.9 (*s*, C(3)); 160.9 (*s*, C(1)); 156.0, 154,9 (2*s*, C(4a), C(8)); 151.9 (*s*, C(10a)); 142.4 (*s*, C(5)); 127.7 (*d*, C(6)); 120.1 (*s*, C(8a)); 116.4 (*d*, C(7)); 104.8 (*s*, C(9a)); 100.4 (*d*, C(2)); 94.7 (*d*, C(4)); 55.6 (*q*, CH_3O). Anal. calc. for $C_{14}H_{10}O_6$ (274.22): C 61.31, H 3.68; found: C 61.47, H 3.51.

Triacetate of **14**. Acetylation of **14** with pyridine Ac_2O gave white plates from EtOH, m.p. 190–192°. IR: 1750, 1620 (CO). ^{1}H-NMR ($CDCl_3$): 2.25, 2.27, 2.38 (3*s*, 3 AcO); 3.73 (*s*, CH_3O); 6.58 (*d*, *J* = 2.5, 1 arom. H_m); 6.73 (*d*, *J* = 2.5, 1 arom. H_m); 7.12 (*d*, *J* = 9, 1 arom. H_o); 7.47 (*d*, *J* = 9, 1 arom. H_o). Anal. calc. for $C_{20}H_{16}O_9$ (400.33): C 60.00, H 4.03; found: C 60.08, H 3.97.

6. *5-Benzoyloxy-8-hydroxy-1,3-dimethoxy-9*H-*xanthen-9-one* (**23**). For 6 h, **21** (980 mg, 2 mmol) was refluxed with anh. $AlCl_3$ (4 g, 30 mmol) in anh. Et_2O. The mixture was evaporated and the residue worked up as described for **1** *(Exper. 4a)*. Pale yellow plates (500 mg, 65%) from MeOH, m.p. 206–208°. Mixed m.p. with **21** 189–195°. IR: 1730, 1670 (CO). ^{1}H-NMR ($CDCl_3$): 3.31, 3.85 (2*s*, 2 CH_3O); 6.21 (*d*, *J* = 2.5, 1 arom H_m); 6.52 (*d*, *J* = 2.5, 1 arom. H_m); 7.10 (*d*, *J* = 9, 1 arom H_o); 7.4–7.6 (*m*, 3 benzoyl H); 7.59 (*d*, *J* = 9, 1 arom. H_o); 8.16 (*m*, 2 benzoyl H); 11.28 (*s*, OH–C(8)). Anal. calc. for $C_{22}H_{16}O_7$ (392.35): C 67.34, H 4.11; found: C 67.58, H 4.00.

7. *1,3,5-Tribenzoyloxy-8-hydroxy-9*H-*xanthen-9-one* (**24**). For 3 h, **22** (680 mg, 1 mmol) was refluxed with anh. $AlCl_3$ (3 g, 22.5 mmol) in anh. Et_2O (80 ml). After evaporation, the residue was worked up as described for **1** *(Exper. 4a)*. White plates (550 mg, 96%) from EtOH/Me_2CO 8:2 m.p. 211–213°. IR: 1690, 1740 (CO). ^{1}H-NMR ($CDCl_3$): 6.75–7.1 (*m*, 2 arom. H_m); 7.2–8.3 (*m*, 2 arom. H_o, 15 benzoyl H); 11.32 (*s*, OH–C(8)). Anal. calc. for $C_{34}H_{20}O_9$ (572.50): C 71.32, H 3.52; found: C 71.57, H 3.41.

8. *1,3-Dibenzyloxy-5,8-dihydroxy-9*H-*xanthen-9-one* (**15**), *5-Benzyloxy-1,3,8-trihydroxy-9*H-*xanthen-9-one* (**17**) *and 3-Benzyloxy-1,5,8-trihydroxy-9*H-*xanthen-9-one* (**16**). For 8 h, **1** (13 g, 6.5 mmol), $NaHCO_3$ (3 g), and

benzyl chloride (1.72 ml, 15 mmol) were refluxed and stirred in acetone (50 ml). After removal of benzyl chlorid by steam destillation, extraction of the H_2O phase by EtOAc, drying, and evaporation, the product was separated by column chromatography (B). **15**: 250 mg (14%), R_f 0.8, m.p. 178–181° (from EtOH/Me_2CO). IR: 1670 (CO). ^{1}H-NMR ((D_6)DMSO): 5.1–5.16 (*s*, 2 PhCH_2); 6.68 (*m*, 2 arom. H_m); 7.00 (*d*, J = 9, 1 arom H_o); 7.21 (*d*, J = 9, 1 arom. H_o); 7.34 (*s*, 5 arom. H); 7.39 (*s*, 5 arom. H); 8.81 (*s*, OH–C(5)); 11.27 (*s*, OH–C(8)). Anal. calc. for $C_{27}H_{20}O_6$ (440.43): C 73.63, H 4.58; found: C 73.52, H 4.71.

17: 400 mg (23%), yellow needles, R_f 0.45, m.p. 203–206° (from EtOH). IR: 1660 (CO). ^{1}H-NMR ((D_6)DMSO): 5.17 (*s*, PhCH_2); 6.29–6.35 (*m*, 2 arom. H_m); 7.04 (*d*, J = 9, 1 arom. H_o); 7.37 (*s*, 5 arom. H); 7.72 (*d*, J = 9, 1 arom. H_o); 10.08 (*s*, OH–C(3)); 10.22 (*s*, OH–C(1)); 11.29 (*s*, OH–C(8)). Anal. calc. for $C_{20}H_{17}O_6$ (350.31): C 68.57, H 4.03; found: C 68.71, H 4.15.

16: 210 mg (12%), yellow plates, R_f 0.35, m.p. 211–214° (from EtOH). IR: 1660 (CO). ^{1}H-NMR ((D_6)DMSO): 5.39 (*s*, PhCH_2); 6.52 (*d*, J = 2.5, 1 arom. H_m); 6.70 (*d*, J = 2.5, 1 arom. H_m); 6.93 (*d*, J = 9, 1 arom. H_o); 7.25 (*d*, J = 9, 1 arom. H_o); 7.37–7.43 (*m*, 5 arom. H); 8.89 (*s*, OH–C(5)); 10.46 (*s*, OH–C(1)); 10.94 (*s*, OH–C(8)). Anal. calc. for $C_{20}H_{17}O_6$ (350.31): C 68.57, H 4.03; found: C 68.63, H 4.28.

9. *5-Benzyloxy-3,8-dihydroxy-1-methoxy-9*H-*xanthen-9-one* (**26**). For 20 h, **17** (350 mg, 1 mmol) was treated with 20 ml of diazomethane/Et_2O (10 mmol of CH_2N) at r.t. After evaporation, the product was separated by column chromatography (B, R_f 0.55). Pale yellow needles (120 mg, 33%) from EtOH, m.p. 213–215°. IR: 1640. ^{1}H-NMR ((D_6)DMSO): 3.51 (*s*, CH_3O); 5.32 (*s*, PhCH_2); 6.41 (*d*, J = 2.5, 1 arom. H_m); 6.60 (*d*, J = 2.5, 1 arom. H_m); 6.90 (*d*, J = 9, 1 arom. H_o); 7.15 (*d*, J = 9, 1 arom. H_o); 7.25–7.40 (*m*, 5 arom. H); 10.1 (*s*, OH–C(3)); 11.29 (*s*, OH–C(8)).

Reduction of **26** gave **14** in 85% yield.

10. *5,8-Dihydroxy-1,3-dimethoxy-9*H-*xanthen-9-one* (**12**), *1,8-Dihydroxy-3,5-dimethoxy-9*H-*xanthen-9-one* (**19**) *and 1,3,8-Trihydroxy-5-methoxy-9*H-*xanthen-9-one* (**20**). To a soln. of **1** (1.04 g, 4 mmol) in $CHCl_3$ (500 ml), diazomethane (40 mmol in 50 ml of $CHCl_3$) was added. The mixture was left overnight. After decomposition of the excess of diazomethane and evaporation, the product was separated by column chromatography (B). **19**: 205 mg (18%), pale yellow needles, R_f 0.66, m.p. 180–182° (from EtOH; [20]: 185–186°; [9]: 189–190°). IR: 1620 (CO). ^{1}H-NMR ($CDCl_3$): 3.85, 3.92 (2*s*, 2 CH_3O); 6.48 (*s*, 2 arom. H_m); 7.02 (*d*, J = 9, 1 arom. H_o); 7.44 (*d*, J = 9, 1 arom. H_o); 10.16 (*s*, OH–C(1)); 11.61 (*s*, OH–C(8)). Anal. calc. for $C_{15}H_{12}O_6$ (288.25): C 62.49, H 4.20; found: C 62.62, H 4.22.

12: 160 mg (14%), R_f 0.58, mixed m.p. with **12** from *Exper. 1* gave no depression. IR: superimposable.

20: 220 mg (20%), R_f 0.30, m.p. 221–224° (from 50% EtOH; [21]: 271°). IR: 1630 (CO). ^{1}H-NMR ((D_6)DMSO): 3.94 (*s*, CH_3O); 6.32 (*d*, J = 2.5, 1 arom. H_m); 6.35 (*d*, J = 2.5, 1 arom. H_m); 7.06 (*d*, J = 9, 1 arom. H_o); 7.68 (*d*, J = 9, 1 arom. H_o); 10.20 (*s*, OH–C(3)), 10.50 (*s*, OH–C(1)); 11.59 (*s*, OH–C(8)). Anal. calc. for $C_{14}H_{10}O_6$ (274.22): C 61.31, H 3.68; found: C 61.45, H 3.77.

11. *1-Hydroxy-2,3,7-trimethoxy-9*H-*xanthen-9-one* (**9**). For 3 h, 2-hydroxy-5-methoxybenzoic acid [25] (4.5 g, 30 mmol) and 3,4,5-trimethoxyphenol [24] (5.5 g, 30 mmol) were stirred with a mixture of freshly fused $ZnCl_2$ (12 g) and $POCl_3$ (50 ml) at 60°. The mixture was poured onto ice, and the separated solid was filtered off. The product was purified by column chromatography (B, R_f 0.7). Yellow needles (1.7 g, 56%), m.p. 183–185° (from EtOH; [9]: 177–177.5°). IR: 1644 (CO). ^{1}H-NMR ($CDCl_3$): 3.88, 3.89, 3.92 (3*s*, 3 CH_3O); 6.33 (*s*, H–C(4)); 7.26 (*d*, J = 9, H–C(5)); 7.33 (*dd*, J = 9, 2.5, H–C(6)); 7.56 (*d*, J = 2.5, H–C(8)); 12.80 (*s*, OH–C(1)). Anal. calc. for $C_{16}H_{14}O_6$ (302.29): C 63.57, H 4.67; found: C 63.97, H 4.57.

12. *1,4-Dihydroxy-2,3,7-trimethoxy-9*H-*xanthen-9-one* (**10**). A stirred soln. of **9** (910 mg, 3 mmol) in pyridine (12 ml) and NaOH (0.6 g, 15 mmol in 6 ml of H_2O) was treated with $K_2S_2O_8$ (860 mg, 3.2 mmol in 45 ml of H_2O) during 2 h. After stirring at 10–15° for 6 h, the mixture was evaporated, H_2O (45 ml) and HCl to pH 4 were added, and the precipitate of the starting material (600 mg) was filtered off. Further acidification with conc. HCl (30 ml) and treatment with Na_2SO_3 (0.6 g) for 30 min gave a second precipitate which was separated by extraction with EtOAc. After evaporation, orange needles (56 mg, 6%), m.p. 243–245° ([14]: 160–161°; [15]: 248–250°). IR: 1652 (CO). ^{1}H-NMR ((D_6)DMSO): 3.96, 4.00, 4.06 (3*s*, 3 CH_3O); 7.35 (*m*, H–C(5), H–C(6)); 7.60 (*m*, H–C(8)); 11.85 (*s*, OH–C(1)). Anal. calc. for $C_{16}H_{14}O_7$ (318.27): C 60.37, H 4.43; found: C 60.12, H 4.22.

13. *1,8-Dihydroxy-3-methoxy-9*H-*xanthen-9-one* (**6**). For 4 h, 2,6-dihydroxybenzoic acid (3.1 g, 20 mmol) and 3,5-dimethoxyphenol (3.1 g, 20 mmol) were stirred with a mixture of freshly fused $ZnCl_2$ (8 g, 58 mmol) and $POCl_3$ (35 ml) at 60°. Workup as described in *Exper. 11* yielded **6** (1.6 g, 32%). Physical constants and spectral data agreed with [12].

14. *1-Benzyloxy-8-hydroxy-3-methoxy-9*H-*xanthen-9-one* (**7**). For 4 h, **6** (1 g, 6.5 mmol), K_2CO_3 (2.5 g), KI (50 mg), and benzyl chloride (0.75 ml, 6.5 mmol) were refluxed and stirred in acetone (30 ml). After removal of benzyl chloride by steam destillation, extraction of the H_2O phase by EtOAc, drying and evaporation, pale yellow needles (1.1 g, 82%), m.p. 176–179° (from EtOH). IR: 1635 (CO). ^{1}H-NMR ($CDCl_3$): 3.84 (*s*, CH_3O); 5.23 (*s*, PhCH_2); 6.33 (*d*, *J* = 2, H–C(2)); 6.41 (*d*, *J* = 2, H–C(4)); 6.6–6.8 (*m*, H–C(5), H–C(7)); 7.33–7.55 (*m*, H–C(6), 5 arom. H); 13.88 (*s*, OH–C(8)). MS: 348 (31.9), 229 (36), 213 (23), 91 (100). Anal. calc. for $C_{21}H_{16}O_5$ (348.36): C 72.14, H 4.63; found: C 72.10, H 5.10.

Acetate of **7**. ^{1}H-NMR ($CDCl_3$): 2.53 (*s*, AcO); 3.88 (*s*, CH_3O); 5.25 (*s*, PhCH_2); 6.36 (*d*, *J* = 2, H–C(2)); 6.46 (*d*, *J* = 2, H–C(4)); 6.94 (*dd*, *J* = 9, 2, H–C(7)); 7.3–7.7 (*m*, H–C(5), H–C(6), 5 arom. H).

15. *1-Benzyloxy-3,8-dimethoxy-9*H-*xanthen-9-one* (**27**). For 16 h, **7** (210 mg, 6 mmol), dimethyl sulfate (0.29 ml, 30 mmol), and K_2CO_3 (1 g) were refluxed in acetone. The mixture was evaporated and diluted with H_2O (10 ml). The precipitate was filtered off and recrystallized from EtOH (200 mg, 92%), white needles, m.p. 193–196°. IR: 1640 (CO). ^{1}H-NMR ($CDCl_3$): 3.77, 3.94 (2*s*, $2CH_3O$); 5.22 (*s*, PhCH_2); 6.30 (*m*, H–C(2), H–C(4)); 6.58–6.93 (*m*, H–C(5), H–C(7)); 7.21–7.69 (*m*, H–C(6), 5 arom. H). Anal. calc. for $C_{22}H_{18}O_5$ (362.39): C 72.92, H 5.01; found: C 72.76, H 5.0.

16. *1-Hydroxy-3,8-dimethoxy-9*H-*xanthen-9-one* (**8**). *Method A*: Catalytic hydrogenation of **27** over Pd/C in EtOH. *Method B*: The method described in *Exper. 13* was applied using 2-hydroxy-6-methoxybenzoic acid (1 g, 6 mmol) and 3,5-dimethoxyphenol (960 mg, 6 mmol) as starting material. The products obtained with *A* (88%) and *B* (28%) were identical and their data agreed with those in [12].

17. *8-(β-*D-*Glucopyranosyloxy)-1,3,5-trihydroxy-9*H-*xanthen-9-one* (**3**). To a soln. of **24** (570 mg, 1 mmol) in pyridine (10 ml), drierite (1 g), Ag_2CO_3 (550 mg, 2 mmol), and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (1.35 g, 3 mmol) were added at 0°. After stirring for 3 h in the dark, the same amount of the sugar was added, and this was repeated twice. After 16 h, the mixture was filtered into chilled 3% aq. H_2SO_4 (200 ml), the precipitate dried and dissolved in MeOH (10 ml). The soln. was adjusted to pH 10 with 1N NaOMe and left standing overnight. After evaporation, acidification with 5% aq. HCl, extraction with EtOAc and repeated evaporation, the residue was chromatographed (D). After a fraction of **1** (R_f 0.8), **3** (R_f 0.55; 30 mg, 7.1%) was collected. Yellow plates, m.p. 244–247° (from MeOH; [8]: 241°). $[\alpha]_D^{27} = -103°$ (*c* = 0.25, MeOH). Anal. calc. for $C_{19}H_{18}O_{11}$ (422.33): C 54.03, H 4.3; found: C 54.17, H 4.15.

Heptaacetate of **3**. With pyridine/Ac_2O. Amorphous, m.p. 135° (from EtOH/$CHCl_3$; [8]: 246°). IR: 1730, 1650 (CO). ^{1}H-NMR ($CDCl_3$): 2.10 (*s*, 4 AcO); 2.28, 2.36, 2.45 (3*s*, 3 AcO); 3.98–5.38 (*m*, 6 glucose H); 6.62 (*d*, *J* = 2, 1 arom. H_m); 6.86 (*d*, *J* = 2, 1 arom. H_m); 6.96 (*d*, *J* = 9, 1 arom. H_o); 7.28 (*d*, *J* = 9, 1 arom. H_o). Anal. calc. for $C_{33}H_{32}O_{18}$ (716.08): C 55.24, H 4.42; found: C 55.62, H 4.17.

18. *1-(β-*D-*Glucopyranosyloxy)-8-hydroxy-3,5-dimethoxy-9*H-*xanthen-9-one* (**4**). To a soln. of **19** (290 mg, 1 mmol) in pyridine (16 ml), drierite (800 mg), Ag_2CO_3 (275 mg, 1 mmol), and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (470 mg, 1.1 mmol) was added at 0°. After stirring for 1.5 h at 25°, the mixture was filtered into chilled 3% aq. H_2SO_4 (100 ml) and extracted with $CHCl_3$. After the workup described in *Exper. 17*, a yellow fraction (D, R_f 0.6) was obtained (45 mg, 11%), m.p. 290–295° (dec.; from MeOH); [10]: 272°; [5]: 300° (dec.). $[\alpha]_D^{25} = -97$ (*c* = 0.25, MeOH). Anal. calc. for $C_{21}H_{22}O_{11}$ (450.39): C 55.10, H 4.50; found: C 54.95, H 4.32.

Pentaacetate of **4**. With pyridine/Ac_2O. M.p. 201–205° (from EtOH; [10]: 206–209°). IR: 1730, 1655 (CO). ^{1}H-NMR ($CDCl_3$): 1.93 (*s*, AcO); 2.00, 2.17 (2*s*, 2AcO); 2.52 (*s*, AcO); 3.86, 3.94 (2*s*, $2CH_3O$); 3.98 (*m*, 1 glucose H); 4.22–5.43 (*m*, 5 glucose H); 6.64 (*d*, *J* = 2.5, 1 arom. H_m); 6.87 (*d*, *J* = 2.5, 1 arom. H_m); 6.95 (*d*, *J* = 9, 1 arom. H_o); 7.35 (*d*, *J* = 9, 1 arom. H_o).

19. *1-(β-*D-*Glucopyranosyloxy-3,5,8-trihydroxy-9*H-*xanthen-9-one* (**2**). To a soln. of **17** (350 mg, 1 mmol) in pyridine (10 ml), drierite (800 mg), Ag_2CO_3 (275 mg, 1 mmol), and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (470 mg, 1.1 mmol) were added at 0°. After stirring for 1.5 h at r.t. the mixture was worked up as described in *Exper. 17*. The saponificated product was separated by column chromatography (D). After a fraction of **17** (R_f 0.85), **2** was collected (R_f 0.6). A diglucoside fraction was directly debenzylated in EtOH with Pd/C. After filtration and evaporation yellow needles of **2** (32 mg, 4.5%), m.p. 267–269° (from EtOH); [4]: 263–265°, [5]: 265°. $[\alpha]_D^{27} = -118°$ (*c* = 0.2, MeOH; [4]: $[\alpha]_D = -110°$). Anal. calc. for $C_{19}H_{18}O_{11}$ (422.33): C 54.03, H 4.30; found: C 53.87, H 4.41.

Heptaacetate of **2**. With pyridine/Ac_2O: M.p. 258–262° ([4]: 222–224°; [5]: 262°). IR: 1740, 1730, 1645 (CO). ^{1}H-NMR ($CDCl_3$): 2.04–2.11 (*s*, 4 AcO (sugar)); 2.30, 2.40, 2.48 (3*s*, 3 AcO); 4.02 (*m*, 1 glucose H); 4.22 (*d*, *J* = 4, CH_2O); 4.98–5.52 (*m*, 3 glucose H); 6.72 (*d*, *J* = 2.5, 1 arom H_m); 705 (*d*, *J* = 2.5, 1 arom. H_m); 7.22 (*d*, *J* = 9, 1 arom. H_o); 7.52 (*d*, *J* = 9, 1 arom. H_o).

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