Three Syntheses of Lacticolorin

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Lacticolorin (15) [2-hydroxy-4-(hydroxymethyl)phenyl 6-*O*-benzoyl-β-D-glucopyranoside], a metabolite from the leaves of *Protea lacticolor* Salisb., has been synthesized by three different routes. These comprise four- to six-step procedures and apply extended use of blocking groups, selective reactions, and chromatographic separations.

RECENTLY lacticolorin (15), the main metabolite of the leaves of *Protea lacticolor* Salisb., has been isolated, and identified from degradation results and spectroscopic data.[1] In addition to providing further structural proof, its synthesis appeared of interest in connection with approaches to the preparation of certain polyfunctional aromatic glycosides. Three alternative routes explored all turned out to be feasible.

In lacticolorin the benzylic hydroxy-group at C-4 and the phenolic group at C-2 are reactive. For removal of potential blocking groups neither acidic conditions (causing rupture of the glycosidic linkage) nor basic conditions (causing saponification of the benzoic ester group) could be employed. The first synthesis makes use of blocking groups which can be released by reductive methods.

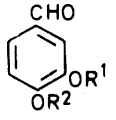
It was thought that 3-benzyloxy-4-hydroxybenzaldehyde (3) would be particularly suitable for a Koenigs–Knorr reaction with tetra-*O*-acetyl-α-D-glucopyranosyl bromide. However benzylation of 3,4-dihydroxybenzaldehyde (1) in the presence of 1 mol. equiv. of alkali gives predominantly 4-benzyloxy-3-hydroxybenzaldehyde (2).[2] According to a patent,[3] reaction of the aldehyde (1) in the presence of 2 mol. equiv. of alkali with 1 mol. equiv. of methyl iodide gives 4-hydroxy-3-methoxybenzaldehyde (7) preferentially.

[1] G. W. Perold, P. Beylis, and A. S. Howard, *J.C.S. Perkin I*, 1973, 638.

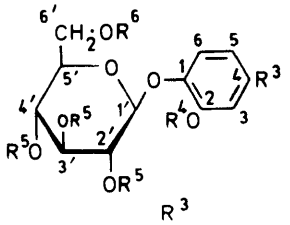
[2] Chem. Fabr. Schering, D.R.P. 82,816/1895; *Fortschr. d. Teerfarbenfabr. P. Friedländer*, 1899, **4**, 1238.

[3] J. Bertram, D.R.P. 63,007/1892; *Fortschr. d. Teerfarbenfabr. P. Friedländer*, 1896, **3**, 895.

By a similar procedure the monobenzyl ether (3) was prepared in 43% yield. Comparison of the n.m.r. spectrum of its acetate (6) with the spectra of the isomeric acetates (4) and (5) confirmed its structure.



	R^1	R^2
(1)	H	H
(2)	H	CH_2Ph
(3)	CH_2Ph	H
(4)	Ac	Me
(5)	Me	Ac
(6)	CH_2Ph	Ac
(7)	Me	H



	R^3	R^4	R^5	R^6
(8)	CHO	CH_2Ph	Ac	Ac
(9)	CH_2OH	CH_2Ph	Ac	Ac
(10)	Me	H	Ac	Ac
(11)	CH_2OH	H	Ac	Ac
(12)	CHO	CH_2Ph	H	H
(13)	CHO	CH_2Ph	H	Bz
(14)	Me	H	H	Bz
(15)	CH_2OH	H	H	Bz
(16)	CH_2OAc	Ac	Ac	Bz
(17)	CH_2OH	CH_2Ph	H	Bz
(18)	CHO	Me	Ac	Ac
(19)	CHO	Me	H	H
(20)	CHO	Me	H	Bz
(21)	CH_2OH	Me	H	Bz
(22)	CHO	H	Ac	Ac
(23)	CHO	H	H	H
(24)	CHO	Bz	H	Bz
(25)	CHO	H	H	Bz
(26)	CHO	Bz	H	H

In analogy to the reaction of vanillin (see later) with tetra-*O*-acetyl-α-D-glucopyranosyl bromide according to Mann [4] and Fischer and Raske [5] in the presence of 1 mol. equiv. of alkali in ethanol–chloroform, the selectively blocked benzaldehyde (3) gave 2-benzyloxy-4-formylphenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (8) in 60% yield. By reduction of the aldehyde (8) with sodium borohydride the benzyl alcohol (9) was obtained quantitatively. Catalytical hydrogenation over palladium–charcoal in ethanol resulted not only in debenzylation, but also in reduction of the aldehyde function to a methyl group. However, when tetrahydrofuran was used as solvent, as well as compound (10) the desired 2-hydroxy-4-hydroxymethylphenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (11) was isolated, in 34% yield. As a model for the other compounds of this series n.m.r. analysis of the product (11) was performed at 270 MHz, and the structure was deduced unequivocally by a full assignment (see Table).

[4] R. M. Mann, *J. Amer. Chem. Soc.*, 1934, **56**, 1631.
[5] E. Fischer and K. Raske, *Ber.*, 1909, **42**, 1465.

^{1}H N.m.r. data for the glucoside (11) (270 MHz; $CDCl_3$)

	δ	*J*/Hz		δ	
1'H	4.94 (d)	1',2'	7.6	ArOH [a]	6.20 (s)
2'H	5.14 (dd)	2',3'	9.6	CH_2·O*H* [a]	2.24 (s)
3'-H	5.30 (t)	3',4'	9.6	CH_2O	4.60 (s)
3'-H	5.25 (t)	4',5'	9.6	OAc	2.01 (s)
5'-H	3.84 (ddd)	4',6'a	2.2		2.02 (s)
6'-H_a	4.29 (dd)	5',6'b	5.4		2.06 (s)
6'-H_b	4.16 (dd)	6'a,6'b	12.4		2.07 (s)
3-H	6.95 (d)	3,5	1.8		
5-H	6.81 (dd)	5,6	8.2		
6-H	6.94 (d)				

[a] Removed by D_2O.

Zémplen deacetylation of the aldehyde (8) with sodium methoxide in methanol gave the glycoside (12) in quantitative yield. By benzoylation with 1 mol. equiv. of benzoyl chloride in pyridine at 4 °C the 6'-monobenzoate (13) was obtained in 70% yield. By hydrogenation of (13) in alcoholic solvents over palladium–charcoal again the over-reduced compound (14) was formed. Even by reaction in tetrahydrofuran no more than 5% of lacticolorin (15) could be isolated. Various additives such as pyridine, triethylamine, or quinoline did not improve the results.

Finally the exclusive formation of lacticolorin was attained by reduction of the aldehyde function and hydrogenolysis of the benzyl ether in a two-step procedure. Treatment of the aldehyde (13) with sodium borohydride in tetrahydrofuran gave the crystalline benzyl alcohol (17) in high yield. In the subsequent debenzylation lacticolorin (15) was obtained as a single clean product. In accord with Perold's report [6] on the natural compound, it was difficult to crystallize the synthetic product. Lacticolorin (15) was finally obtained as colourless needles from water. Chromatography, spectroscopic data, optical rotation, and mixed m.p. proved the identity of synthetic and natural products. In addition data for lacticolorin pentaacetate (16) corresponded with those reported.[1]

In the second approach vanillin (7) was condensed with tetra-*O*-acetyl-α-D-glucosyl bromide to yield the β-glucoside (18).[4,5] By deacetylation to (19) and subsequent monobenzoylation 4-formyl-2-methoxyphenyl 6-*O*-benzoyl-β-D-glucopyranoside (20) was obtained pure after chromatography. Reduction of (20) with sodium borohydride is a clean reaction. The product, 2-methoxylacticolorin (21), was treated with boron tribromide in dichloromethane.[7] By small-scale experiments it was demonstrated that demethylation could be achieved without influencing the glycosidic linkage. Lacticolorin (15) obtained by this procedure was chromatographically identical with natural material.[6]

[6] G. W. Perold, personal communication.
[7] J. F. W. McOmie, M. L. Watts, and D. E. West, *Tetrahedron*, 1968, **24**, 2289.

The third synthesis makes use of our experience with the preparation of monobenzylated isomers [(2) and (3)] of 3,4-dihydroxybenzaldehyde. Treatment of the diphenol (1) with tetra-*O*-acetyl-α-D-glucopyranosyl bromide in ethanol–chloroform in the presence of 1 mol. equiv. of base (KOH) resulted in preferential formation of 2-hydroxy-4-formylphenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (22), which was isolated crystalline. Reduction of (22) with sodium borohydride gave the benzyl alcohol (11) obtained previously; this proves the structure of (22).

Deacetylation of (22) gave a quantitative yield of (23), which was benzoylated (1 mol equiv. of benzoyl chloride) gently at room temperature. Chromatography showed the presence of three benzoylated compounds in addition to starting material (23). By column chromatography 6% of the dibenzoate (14), 22% of the monobenzoate (15), and 16% of the isomeric monobenzoate (26) were isolated. The attachment of a benzoyloxy-group to C-2 of the aromatic ring in the dibenzoate (24) and the monobenzoate (26) is evident from the downfield shift of the 1′-H doublet to δ *ca.* 5.0, whereas in the monobenzoate (25) the 1′-H signal is within the multiplet due to the other sugar ring protons. Furthermore, compounds (24) and (26) show a positive optical rotation, whereas that of (25), as expected for a β-D-*gluco*-compound, is negative. In accord with similar results, this can probably be explained by a failure of Hudson's isorotation rule [8] because of the influence of the 2-benzoyloxy-group on the anomeric centre.

Treatment of the monobenzoate (25) with sodium borohydride gave lacticolorin (15) in good yields.

Of the three syntheses the first seems the most valuable because of the high selectivity in every step. Nevertheless, the others are useful, although they include separations of isomers and a not yet quantified demethylation procedure. The essential steps of these syntheses may be useful in the preparation of phenyl glycosides related to lacticolorin.

EXPERIMENTAL

M.p.s were taken with a Kofler hot-stage apparatus. I.r. spectra (KBr discs) were taken with a Perkin-Elmer 257 spectrophotometer. Optical rotations were measured with a Perkin-Elmer 141 or 241 polarimeter. For n.m.r. spectra Varian T 60, EM-360 (60 MHz), and HA-100 (100 MHz), Perkin-Elmer R-32 (90 MHz), and Bruker WH-270 (270 MHz) instruments were used (internal standard Me_4Si). For t.l.c. silica gel 60 F_{254} on aluminium foil (Merck) was used; for column chromatography silica gel 60 (Merck); and for preparative t.l.c. 20 × 20 cm plates, 2 mm thick, of silica gel 60 (Merck); detection was performed by u.v. illumination and spraying with conc. sulphuric acid or ethanolic 0.15% naphthoresorcinol–2N-sulphuric acid (1 : 1 v/v) and heating to 150 °C.

3-*Benzyloxy*-4-*hydroxybenzaldehyde* (3).—Benzyl chloride (12.60 g, 0.1 mol) was slowly added to a solution of 3,4-dihydroxybenzaldehyde (1) (13.80 g, 0.1 mol) in ethanolic 2N-potassium hydroxide (100 ml). The mixture was stirred overnight under nitrogen. Most of the alcohol was distilled off *in vacuo* and the remaining solution treated with iced water. For removal of the dibenzyl ether the alkaline solution was extracted twice with ether, then acidified with concentrated hydrochloric acid and again extracted thrice with methylene chloride. The dried organic phase was concentrated to 50 ml and light petroleum (20 ml) added. Starting material (1) (5.01 g) crystallized out overnight and was filtered off. Concentration of the mother liquor gave the monobenzyl ether (3) (6.30 g, 43.4%), m.p. (from ethanol) 110—113° (lit.,[2] 113—114°), δ (60 MHz; $CHCl_3$) 5.06 (2 H, s, OCH_2), 6.39 (1 H, s, OH), 6.95 (1 H, d, 5-H, $J_{5,6}$ 8 Hz), 7.1—7.4 (7 H, m, C_6H_5, 2-H, and 6-H), and 9.57 (1 H, s, CHO).

3-*Acetoxy*-4-*methoxybenzaldehyde* (4).[9]—The acetate (4) had m.p. 64° (lit.,[4] 64°), δ (60 MHz; $CDCl_3$) 2.27 (3 H, s, OAc), 3.87 (3 H, s, OCH_3), 6.95 (1 H, d, 5-H, $J_{5,6}$ 8 Hz), 7.50 (1 H, d, 2-H, $J_{2,6}$ 2.5 Hz), 7.63 (1 H, dd, 6-H, $J_{2,6}$ 2.5, $J_{5,6}$ 8 Hz), and 9.73 (1 H, s, CHO).

4-*Acetoxy*-3-*methoxybenzaldehyde* (5).[10]—The acetate (5) had m.p. 76—77° (lit.,[10] 77°), δ (60 MHz; $CDCl_3$) 2.28 (3 H, s, OAc), 3.77 (3 H, s, OCH_3), 7.08 (1 H, d, 5-H, $J_{5,6}$ 8 Hz), 7.2—7.5 (2 H, m, 2-H and 6-H), and 9.77 (1 H, s, CHO).

4-*Acetoxy*-3-*benzyloxybenzaldehyde* (6).—The phenol (3) (212 mg, 1 mmol) was treated with acetic anhydride–pyridine to give the *acetate* (6) (220 mg, 85%), m.p. 83—85° (from ethanol) (Found: C, 70.15; H, 5.2. $C_{15}H_{14}O_4$ requires C, 69.75; H, 5.45%), δ (60 MHz; $CDCl_3$) 2.20 (3 H, s, OAc), 5.03 (2 H, s, OCH_2), 7.10 (1 H, d, 5-H, $J_{5,6}$ 8 Hz), 7.17—7.57 (7 H, m, C_6H_5, 2-H, and 6-H), and 9.90 (1 H, s, CHO).

2-*Benzyloxy*-4-*formylphenyl* 2,3,4,6-*Tetra*-O-*acetyl*-β-D-*glucopyranoside* (8).—The monobenzyl ether (3) (1.15 g, 5.4 mmol) in ethanolic N-potassium hydroxide (5 ml) was treated with tetra-*O*-acetyl-α-D-glucopyranosyl bromide (2 g) in chloroform (10 ml) and heated under reflux for 1 h. The solution was poured into iced water, and the chloroform layer was separated, washed with water, dried (Na_2SO_4), and evaporated *in vacuo*. The β-D-*glucopyranoside* (8) (1.70 g, 60.4%) crystallized from ethanol; m.p. 143—145°; $[\alpha]_D^{20}$ −46.6° (*c* 0.97 in $CHCl_3$) (Found: C, 60.05; H, 5.45. $C_{28}H_{30}O_{12}$ requires C, 60.2; H, 5.4%), δ (60 MHz; $CDCl_3$) 1.77 (3 H, s, OAc), 1.97 (3 H, s, OAc), 2.03 (6 H, s, 2 × OAc), 3.6—3.9 (1 H, m, 5′-H), 4.07—4.23 (2 H, m, 6′-H_2), 5.07 (2 H, s, OCH_2), 4.87—5.43 (4 H, m, 1′-, 2′- 3′-, and 4′-H), and 6.97—7.43 (8 H, m, C_6H_5 and 3-, 5-, and 6-H).

2-*Benzyloxy*-4-*hydroxymethylphenyl* 2,3,4,6-*Tetra*-O-*acetyl*-β-D-*glucopyranoside* (9).—The aldehyde (8) (280 mg, 0.5 mmol) was suspended in propan-2-ol (10 ml) and stirred with sodium borohydride (40 mg) for 30 min. The mixture was poured into iced water, neutralized with little dilute hydrochloric acid, and extracted three times with dichloromethane. The organic phase was dried (Na_2SO_4); the *benzyl alcohol* (9) crystallized from a little ethanol; yield 260 mg (92%), m.p. 130—132°, $[\alpha]_D^{20}$ −69.5° (*c* 0.66 in $CHCl_3$) (Found: C, 59.85; H, 5.85. $C_{28}H_{32}O_{12}$ requires C, 60.0; H, 5.75%), δ (60 MHz; $CDCl_3$) 1.73 (3 H, s, OAc), 1.97 (3 H, s, OAc), 2.00 (6 H, s, 2 × OAc), 3.5—3.8 (1 H, m, 5′-H), 4.03—4.20 (2 H, m, 6′-H_2), 4.50 (1 H, s, $HO{\cdot}CH_2$), 4.97 (2 H, s, CH_2O), 4.83—5.33 (4 H, m, 1′-, 2′-, 3′-, and 4′-H), 6.6—6.97 (3 H, m, 3-, 5-, and 6-H), and 7.27 (5 H, m, C_6H_5).

[8] C. S. Hudson, *J. Amer. Chem. Soc.*, 1909, **31**, 66.
[9] R. Pschorr and W. Stöhrer, *Ber.*, 1903, **35**, 4397.
[10] F. Tiemann and W. Nagai, *Ber.*, 1878, **11**, 647.

2-Hydroxy-4-methylphenyl 2,3,4,6-*Tetra*-O-*acetyl*-β-D-*glucopyranoside* (10).—Compound (8) (110 mg, 0.2 mmol) was suspended in ethanol (30 ml) and hydrogenated over 10% palladium–charcoal (uptake 9 ml, 0.4 mmol). The solution was filtered; on evaporation the methyl compound (10) crystallized (85 mg, 94%); m.p. 131—132.5°; $[\alpha]_D^{20}$ −52.5° (*c* 1.13 in $CHCl_3$) (Found: C, 55.3; H, 5.7. $C_{21}H_{26}O_{11}$ requires C, 55.5; H, 5.75%), δ (60 MHz; $CDCl_3$) 2.03 (6 H, s, 2 × OAc), 2.13 (6 H, s, 2 × OAc), 2.27 (3 H, s, CH_3), 3.7—3.97 (1 H, m, 5′-H), 4.17—4.33 (2 H, m, 6′-H_2), 4.8—5.4 (4 H, m, 1′-, 2′-, 3′- and 4′-H), 6.03 (1 H, s, OH), and 6.43—6.74 (3 H, m, 3-, 5-, and 6-H).

2-Hydroxy-4-hydroxymethylphenyl 2,3,4,6-*Tetra*-O-*acetyl*-β-D-*glucopyranoside* (11).—(*a*) The aldehyde (8) (250 mg, 0.44 mmol) was dissolved in tetrahydrofuran (30 ml) and hydrogenated over 10% palladium–charcoal (uptake 32 ml). T.l.c. showed two well separated spots. From ether the less soluble diol (11) crystallized, and was completely separated by five-fold recrystallization from the methyl compound (10); yield of (11) 70 mg (34%).

(*b*) The aldehyde (21) (300 mg, 0.64 mmol) was suspended in propan-2-ol (20 ml), a few drops of acetic acid and sodium borohydride (100 mg) were added, and the mixture was stirred at room temperature for 1 h. The solution was taken up in water (50 ml) and extracted with dichloromethane; the extract was dried (Na_2SO_4) and evaporated and the residue crystallized from ether to give the *product* (11) (280 mg, 93%), m.p. 142—144°, $[\alpha]_D^{20}$ −9.4° (*c* 0.925 in $CHCl_3$) (Found: C, 53.45; H, 5.9. $C_{21}H_{26}O_{12}$ requires C, 53.6; H, 5.55%) (for n.m.r. see Table).

2-Benzyloxy-4-formylphenyl β-D-*Glucopyranoside* (12).—Compound (8) (700 mg, 1.25 mmol) was suspended in absolute methanol (30 ml), treated with sodium methoxide (50 mg), and stirred at room temperature for 4 h. The solution was neutralized with an excess of Amberlite IR 120 (H^+) resin, filtered, and evaporated. The *glucoside* (12) crystallized from little methanol (yield 460 mg, 94%); m.p. 156—158°, $[\alpha]_D^{20}$ −48.8° (*c* 0.87 in Me_2CO) (Found: C, 59.85; H, 5.8. $C_{20}H_{22}O_3$,0.5H_2O requires C, 60.15; H, 5.8%).

2-Benzyloxy-4-formylphenyl 6-O-*Benzoyl*-β-D-*glycopyranoside* (13).—The glucoside (12) (1.57 g, 4.1 mmol) was dissolved in absolute pyridine (10 ml) and treated in the cold with benzoyl chloride (0.65 g, 4.5 mmol). The mixture was left overnight at room temperature. The reaction was followed by t.l.c. After 12 h more benzoyl chloride (0.6 g) was added. The pyridine was removed *in vacuo* and the residue dissolved in saturated sodium chloride solution (30 ml) and extracted with dichloromethane (7 × 20 ml). The extracts were washed twice with water (10 ml). Extraction of the combined water phase with ethyl acetate yielded starting material (230 mg). The dried (Na_2SO_4) dichloromethane layer was evaporated, and the remaining oil extracted with ether–10% light petroleum (3 × 10 ml) to remove over-benzoylated material. The *product* (3) was obtained crystalline from methanol–ether; yield 1.20 g (70%), m.p. 145—147.5°, $[\alpha]_D^{20}$ −51.0° (*c* 1.77 in Me_2CO) (Found: C, 64.9; H, 5.4. $C_{27}H_{26}O_9$ requires C, 65.6; H, 5.3%), $\nu_{max.}$ (KBr) 3 360br (OH), 1 725, 1 705, and 1 693 (C=O), 1 601, 1 588, and 1 505 (arom.), 1 280, 1 130, and 1 020 (C–O), and 715 cm^{-1}.

2-Hydroxy-4-methylphenyl 6-O-*Benzoyl*-β-D-*glucopyranoside* (14).—The monobenzoate (13) (100 mg, 0.2 mmol) was hydrogenated over 10% palladium–charcoal in absolute tetrahydrofuran (10 ml). By preparative t.l.c. on silica gel lacticolorin (15) (5 mg) and the *methyl compound* (14) (70 mg) were obtained. The latter (14) crystallized from little methanol–ether; yield 51 mg (64.6%), m.p. 67.5—70.5°, $[\alpha]_D^{20}$ −53.5° (*c* 0.65 in Me_2CO) (Found: C, 58.85; H, 5.8. $C_{20}H_{22}O_8$,0.5H_2O requires C, 58.8; H, 5.9%).

Lacticolorin (15).—(*a*) The benzyl alcohol (16) (200 mg, 0.4 mmol) dissolved in tetrahydrofuran (20 ml) was hydrogenated over 10% palladium–charcoal (uptake 90 ml). The product was identical (t.l.c.) with the authentic natural product;[6] yield 151 mg (92%), m.p. 195—197° (lit.,[1] 192—195°), mixed m.p. 194—197°, $[\alpha]_D^{20}$ −52.9° (*c* 0.894 in CH_3OH) (lit.,[1] −58°).

(*b*) The aldehyde (21) (13.4 mg, 0.032 mmol) was dissolved in dichloromethane (5 ml) at room temperature. With strict exclusion of moisture a solution of boron tribromide (0.05 ml, 0.53 mmol) in dichloromethane (2 ml) was added and the mixture kept at room temperature for 20 min. The solution was quenched with iced water and extracted quickly with dichloromethane; this phase was washed with water and dried (Na_2SO_4). T.l.c. ($CHCl_3$–CH_3OH, 20 : 3) showed the presence of material running concurrently with natural lacticolorin.[6] Quantitative isolation was not performed.

(*c*) The aldehyde (25) (85 mg, 0.21 mmol) was dissolved in warm propan-2-ol (10 ml) containing a few drops of acetic acid. Reduction was performed with sodium borohydride (12.2 mg, 0.31 mmol) at room temperature. The mixture was poured into water and continuously extracted with dichloromethane to afford lacticolorin (15) (71 mg, 83%), $[\alpha]_D^{20}$ −50.2° (*c* 0.71 in CH_3OH) [Found for amorphous (15): C, 59.05; H, 5.6. Calc. for $C_{20}H_{22}O_9$: C, 59.1; H, 5.45. Found for (15) crystallized from water and dried under high vacuum at 100 °C for 4 h: C, 58.4; H, 5.45. Calc. for $C_{20}H_{22}O_9$,0.5H_2O: C, 57.85; H, 5.6%], $\nu_{max.}$ (KBr) 3 320—3 350br (OH), 1 719 (C=O), 1 603 and 1 510 (arom.), 1 282, 1 120, and 1 070 (C–O), and 710 cm^{-1}.

2-Acetoxy-4-acetoxymethylphenyl 2,3,4-*Tri*-O-*acetyl*-6-O-*benzoyl*-β-D-*glucopyranoside* (*Lacticolorin Penta-acetate*) (16).[1] —Lacticolorin (15) (45 mg, 0.11 mmol) was acetylated in dry pyridine with acetic anhydride; yield 63 mg (91%), m.p. 134—135° (lit.,[1] 134—136°) (Found: C, 58.5; H, 5.25. Calc. for $C_{30}H_{32}O_{14}$: C, 58.45; H, 5.25%), $\nu_{max.}$ (KBr) 1 750—1 710br (C=O), 1 603 and 1 512 (arom.), 1 370, 1 280, 1 230br, and 710 cm^{-1}, δ (90 MHz; $CDCl_3$) 2.04, 2.06, 2.07, and 2.08 (12 H, 4 × s, 2′-, 3′-, 4′-, and CH_2–OAc), 2.23 (3 H, s, 2-OAc), 4.06 (1 H, ddd, 5′-H, $J_{4',5'}$ 9.0, $J_{5',6'a}$ 3.0, $J_{5',6'b}$ 6.0 Hz), 4.38 (1 H, dd, 6′-H_b, $J_{5',6'b}$ 6.0, $J_{6'a,6'b}$ 12.3 Hz), 4.60 (1 H, dd, 6′-H_a, $J_{5',6'a}$ 3.0, $J_{6'a,6'b}$ 12.3 Hz), 5.01 (2 H, s, CH_2), 5.00—5.44 (4 H, m, 1′-, 2′-, 3′-, and 4′-H), 7.03 (3 H, m, 3-, 5-, and 6-H), 7.35—7.69 (3 H, m, *m*- and *p*-H of Bz), and 8.06 (2 H, dd, *o*-H of Bz, J_o 7.7, J_m 2.0 Hz).

2-Benzyloxy-4-hydroxymethylphenyl 6-O-*Benzoyl*-β-D-*glucopyranoside* (17).—The chromatographically pure but oily monobenzoate (13) (1.20 g, 2.43 mmol) was dissolved in tetrahydrofuran (50 ml) and stirred (30 min) with sodium borohydride (100 mg). The mixture was poured into water (100 ml), neutralized with little dilute hydrochloric acid, and extracted with dichloromethane (10 × 10 ml). The dried extracts (Na_2SO_4) were evaporated *in vacuo* and the residue crystallized. The crystals were washed thoroughly with ether–10% light petroleum to give the alcohol (17) (800 mg). By chromatography of the mother liquor another 190 mg was isolated (total 960 mg, 80%); m.p. 132—134°, $[\alpha]_D^{20}$ −32.6° (*c* 0.645 in CH_3OH) (Found: C, 64.7; H, 5.75. $C_{27}H_{28}O_9$ requires C, 65.3; H, 5.7%),

δ (100 MHz; $CDCl_3$–CD_3OD) 3.4—4.0 (4 H, m, 2′-, 3′-, 4′-, and 5′-H, and 3 × OH), 4.51 (2 H, s, CH_2O), 4.63—4.75 (1 H, m, 1′-H), 4.75—4.90 (2 H, m, 6′-H_2), 5.07 (2 H, s, CH_2Ph), 6.73 (1 H, dd, 5-H, $J_{3,5}$ 2.5, $J_{5,6}$ 8 Hz), 6.95—7.12 (2 H, m, 3- and 6-H), and 7.2—8.5 (10 H, m, Bz and Ph).

4-Formyl-2-methoxyphenyl 2,3,4,6-Tetra-O-acetyl-β-D-glucopyranoside (18).[4]—Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (4.11 g, 10 mmol) in chloroform (50 ml) was refluxed (14 h) with vanillin (7) 1.65 g, 10.9 mmol) and potassium hydroxide (530 mg) in ethanol (10.3 ml). The mixture was poured into iced water and extracted with chloroform; the extract was dried ($MgSO_4$), filtered, and evaporated. The product (18) crystallized from ethanol–water (95 : 5); yield 3.2 g (66.3%) (lit.,[4] 50%), m.p. 135—137° (lit.,[5] 143—144°), δ (90 MHz; $CDCl_3$) 2.09 (12 H, m, 4 × OAc), 3.93 (3 H, s, OCH_3), 3.93 (1 H, m, 5′-H), 4.27 (2 H, m, 6′-H_2), 5.06—5.44 (4 H, m, 1′-, 2′-, 3′-, and 4′-H), 7.20—7.56 (3 H, m, 3-, 5-, and 6-H), and 9.91 (1 H, s, CHO).

4-Formyl-2-methoxyphenyl β-D-Glucopyranoside (19).—Compound (18) (1.3 g, 2.7 mmol) was dissolved in N-sodium methoxide (20 ml) and left at room temperature (14 h). The solution was neutralized with Amberlite IR 120 (H^+) resin, filtered, and evaporated. The product (19) crystallized from methanol (760 mg, 90%), m.p. 180—183° (lit.,[5] 185—186°).

4-Formyl-2-methoxyphenyl 6-O-Benzoyl-β-D-glucopyranoside (20).—Compound (19) (610 mg, 1.95 mmol) dissolved in dry pyridine (20 ml) was treated with benzoyl chloride (0.26 ml, 2.24 mmol) at 0 °C. The mixture was warmed to room temperature and then kept at 35 °C for 4 days. Following normal work-up separation was carried out by column chromatography on silica gel G 60 (45 g) (Merck) with toluene–ethanol (4 : 1) (plus 3% triethylamine); yield of microcrystalline *product* (20) 280 mg (34.3%), m.p. 180—182°, $[\alpha]_D^{20}$ −45.5° (*c* 0.52 in Me_2CO) (Found: C, 59.7; H, 5.55. $C_{21}H_{22}O_9$ requires C, 60.3; H, 5.3%), δ (60 MHz; $CDCl_3$–CD_3OD) 3.93 (3 H, s, OCH_3), 3.47—4.03 (3 H, m, 5′- and 6′-H_2), 4.37—5.30 (7 H, m, 1′-, 2′-, 3′-, and 4′-H and 3 × OH), 7.25—7.70 (6 H, m, *m*- and *p*-H of Bz and 3-, 5-, and 6-H), 7.92—8.10 (2 H, m, *o*-H of Bz), and 9.93 (1 H, s, CHO).

4-Hydroxymethyl-2-methoxyphenyl 6-O-Benzoyl-β-D-glucopyranoside (21).—Compound (20) (230 mg, 0.55 mmol) dissolved in warm propan-2-ol (20 ml) containing a few drops of acetic acid was treated with sodium borohydride (25.2 mg, 0.66 mmol) at 10 °C and stirred. After reduction was complete (t.l.c.) the mixture was poured into water (20 ml) and continuously extracted with dichloromethane. Evaporation of the extract gave the *product* (21) (140 mg, 60.6%), which was crystallized from propan-2-ol; m.p. 165—168.5°, $[\alpha]_D^{20}$ −14.5° (*c* 0.44 in Me_2CO) (Found: C, 60.05; H, 6.0. $C_{21}H_{24}O_9$ requires C, 60.0; H, 5.75%), δ (60 MHz; $CDCl_3$–CD_3OD) 3.40—4.00 (3 H, m, 5′- and 6′-H_2), 3.83 (3 H, s, OCH_3), 4.2—5.4 (9 H, m, 1′-, 2′-, 3′-, and 4′-H, 3 × OH, and CH_2O), and 6.8—8.1 (8 H, m, 3-, 5-, and 6-H and Bz).

4-Formyl-2-hydroxyphenyl 2,3,4,6-Tetra-O-acetyl-β-D-glucopyranoside (22).—A solution prepared from potassium hydroxide (950 mg, 24.4 mmol) and 3,4-dihydroxybenzaldehyde (1) (3.024 g, 24 mmol) in dry ethanol (120 ml) and a solution of tetra-*O*-acetyl-α-D-glucopyranosyl bromide (8.22 g, 20 mmol) in chloroform (80 ml) was heated under reflux for 3 h. The mixture was poured into iced water and extracted with chloroform (5 × 50 ml); the extract was dried ($MgSO_4$), treated with charcoal, filtered, and evaporated *in vacuo*. The residue was crystallized from ethanol with addition of a little water to give the *product* (22) (6.01 g, 64.2%), m.p. 179—183.5°, $[\alpha]_D^{20}$ −49.2° (*c* 0.903 in $CHCl_3$) (Found: C, 53.85; H, 5.2. $C_{21}H_{24}O_{12}$ requires C, 53.85; H, 5.15%), δ (90 MHz; $CDCl_3$) 2.04 (6 H, s, 2 × OAc), 2.08 (6 H, s, 2 × OAc), 3.93 (1 H, ddd, 5′-H, $J_{4',5'}$ 9.0, $J_{5',6'a}$ 2.4, $J_{5',6'b}$ 5.6 Hz), 4.25 (2 H, m, 6′-H_2), 5.03—5.40 (4 H, m, 1′-, 2′-, 3′-, and 4′-H), 6.15 (1 H, s, phenolic OH), 7.09 (1 H, d, 6-H, $J_{5,6}$ 7.85 Hz), 7.39 (1 H, dd, 5-H, $J_{3,5}$ 1.74, $J_{5,6}$ 7.85 Hz), 7.45 (1 H, d, 3-H, $J_{3,5}$ 1.74 Hz), and 9.86 (1 H, s, CHO).

4-Formyl-2-hydroxyphenyl β-D-Glucopyranoside (23).—Compound (22) (3.4 g, 7.47 mmol) was suspended in dry methanol (100 ml) and treated with N-sodium methoxide solution (8 ml) for 15 min at room temperature. The mixture was neutralized with Amberlite IR 120 (H^+) resin, filtered, and evaporated, and the residue crystallized from hot methanol to give the *product* (23) (2.13 g, 95%), m.p. 173.5—175°, $[\alpha]_D^{20}$ −126.7° (*c* 0.84 in CH_3OH) (Found: C, 50.15; H, 5.45. $C_{13}H_{16}O_8$,0.5H_2O requires C, 50.5; H, 5.55%).

2-Benzoyloxy-4-formylphenyl 6-O-Benzoyl-β-D-glucopyranoside (24), *4-Formyl-2-hydroxyphenyl 6-O-Benzoyl-β-D-glucopyranoside* (25), *and 2-Benzoyloxy-4-formylphenyl β-D-Glucopyranoside* (26).—Compound (23) (530 mg, 1.77 mmol) was dissolved in dry pyridine (50 ml) at room temperature and cooled to −15 °C. Benzoyl chloride (0.21 ml, 1.8 mmol) was added and the mixture allowed to warm to room temperature. After 7 days t.l.c. ($CHCl_3$–CH_3OH, 20 : 3) showed three new spots in addition to starting material (23). The mixture was poured into water and extracted with chloroform. Compound (23) remained in the water phase. The mixture of benzoates (420 mg) was chromatographed on silica gel G 60 (150 g) with toluene–ethanol (4 : 1) to give the *dibenzoate* (24) (60.5 mg, 6.7%), amorphous material, $[\alpha]_D^{20}$ +19.3° (*c* 1.006 in CH_3OH) (Found: C, 63.4; H, 4.85. $C_{27}H_{24}O_{10}$ requires C, 63.8; H, 4.75%), δ (60 MHz; $CDCl_3$) 3.33—3.93 (6 H, m, 5′-H, 6′-H_2, and 3 × OH), 4.4—4.67 (3 H, m, 2′-, 3′-, and 4′-H), 5.00 (1 H, d, 1′-H, $J_{1',2'}$ 7.0 Hz), 7.17—7.72 (6 H, m, *m*- and *p*-H of Bz and 3-, 5-, and 6-H), 7.90—8.27 (2 H, m, *o*-H of Bz), and 9.83 (1 H, s, CHO); the *monobenzoate* (25) (156.5 mg, 21.9%), m.p. 143—146° (from methanol), $[\alpha]_D^{20}$ −53.9° (*c* 1.565 in CH_3OH) (Found: C, 59.3; H, 5.1. $C_{20}H_{20}O_9$ requires C, 59.4; H, 5.0%), δ (60 MHz; $CDCl_3$–CD_3OD) 3.27—3.77 (3 H, m, 5′-H and 6′-H_2), 4.03—5.03 (7 H, m, 1′-, 2′-, 3′-, and 4′-H and 3 × OH), 6.33 (1 H, s, phenolic OH), 7.05—7.65 (6 H, m, *m*- and *p*-H of Bz and 3-, 5-, and 6-H), 7.92—8.18 (2 H, m, *o*-H of Bz), and 9.72 (1 H, s, CHO); and the *monobenzoate* (26) (115.7 mg, 16.2%), amorphous material, $[\alpha]_D^{20}$ +47.7° (*c* 1.157 in CH_3OH) (Found: C, 59.2; H, 5.15%), δ (60 MHz; $CDCl_3$–CD_3OD) 3.25—4.22 (10 H, m, 2′-, 3′-, 4′-, and 5′-H, 6′-H_2, and 4 × OH), 5.08 (1 H, d, 1′-H, $J_{1',2'}$ 7.0 Hz), 7.25—7.78 (6 H, m, *m*- and *p*-H of Bz and 3-, 5-, and 6-H), 8.05—8.28 (2 H, m, *o*-H of Bz), and 9.87 (1 H, s, CHO).

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