# Synthesis of Glycosylcurcuminoids

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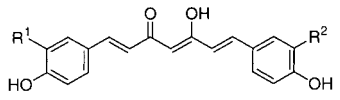
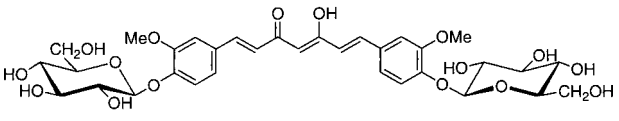
**Condensation of glycosylated arylaldehyde with acetylacetone–$B_2O_3$ complex gave a corresponding diglycosylcurcuminoid, and a similar reaction using a mixture of arylaldehyde and glycosylarylaldehyde gave an unsymmetrical monoglycosylcurcuminoid, both as boron-complexes. The boron was removed from the complexes by heating in methanol, thus achieving the synthesis of di- and mono-glycosylcurcuminoids.**

**Key words** glycosylcurcuminoid; diglucosylcurcumin; monoglucosylcurcumin; digalactosylcurcumin; monogalactosylcurcumin

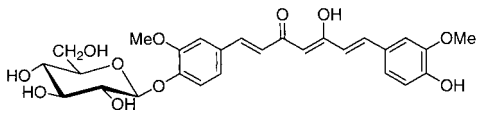
Curcumin **1**, a yellow pigment of the rhizome of *Curcuma longa* L, has been used as a dye and a cholagogue for hundreds of years. Recently, it was revealed that curcuminoids showed several significant biological activities such as the scavenging of active oxygen,[1] and antiinflammatory,[2] hypocholesterolemic,[3,4] antitumor,[5,6] and antiallergic activities.[7] The synergistic action of some curcuminoids was also reported.[8] However, most curcuminoids are hardly soluble in water, a fact which limits their use in foodstuffs. We postulated that the glycosylation of curcuminoids may increase their water solubility, which may render them as potential edible yellow dyes. The biological activities of the products are also of interest because glycosides are widely distributed in plants and play key roles in the detoxication, stabilization, and increased water solubility of aglycons. Therefore, we attempted the synthesis of glycosylcurcuminoids.



curcumin **1**: $R^1 = R^2 = OMe$
demethoxycurcumin **2** : $R^1 = OMe$, $R^2 = H$
bisdemethoxycurcumin **3** : $R^1 = R^2 = H$



diglucosylcurcumin **4**



monoglucosylcurcumin **5**

Chart 1. Common Curcuminoids and Glycosylcurcumins

Recently, Hergenhahn *et al.*[9] reported direct glucosidation of curcumin **1** by acetobromoglucose in the presence of $Et_3BnNBr$. Deacetylation with NaOMe in MeOH and treatment of the product with Amberite H50 gave diglucoside **4** and monoglucoside **5**, at yields of 3% and 8%, respectively.

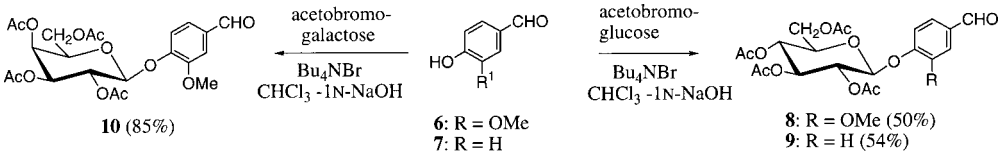
Our synthetic method is completely different from that of theirs and involves a one step condensation of an appropriately glycosylated aromatic aldehyde with acetylacetone-boric oxide complex. This method was originally reported by Pabon[10] and modified by Whiting *et al.*[11] Though the reported method removes boron compound and amine by treatment of the reaction mixture with hydrochloric acid at work-up, it can not be applied to our case because glycoside will be hydrolyzed by this treatment. Therefore, the boron compound was decomposed and removed by converting it to methyl borate on heating with MeOH. Here we describe the synthesis of curcuminoid di- and mono-glucosides and -galactosides.

## Results and Discussion

Acetobromoglucose, prepared by modification of Lemieux's method,[12] was reacted with vanillin **6** by the method reported by Kreger *et al.*[13] to yield tetra-*O*-acetyl-$\beta$-D-glucopyranosylvanillin **8**. Tetra-*O*-acetyl-$\beta$-D-glucopyranosyl-4-hydroxybenzaldehyde **9** and tetra-*O*-acetyl-$\beta$-D-galactopyranosylvanillin **10** were obtained in a similar way (see Experimental).

Condensation of glycosylvanillin **8** with acetylacetone–$B_2O_3$ complex was done by the following two methods, A and B. Method A uses two moles of the aldehyde to acetylacetone–$B_2O_3$ complex and method B a mixture of two different aldehydes. Method A gave symmetrical curcuminoids and method B produced unsymmetrical curcuminoids as major products.

The actual procedure is as follows. For method A, according to the method of Whiting,[11] tributyl borate and acetyl-



**10** (85%)

acetobromo-galactose
$Bu_4NBr$
$CHCl_3$ -1N-NaOH

**6**: R = OMe
**7**: R = H

acetobromo-glucose
$Bu_4NBr$
$CHCl_3$ -1N-NaOH

**8**: R = OMe (50%)
**9**: R = H (54%)

Chart 2. Synthesis of Glycosylated Arylaldehydes

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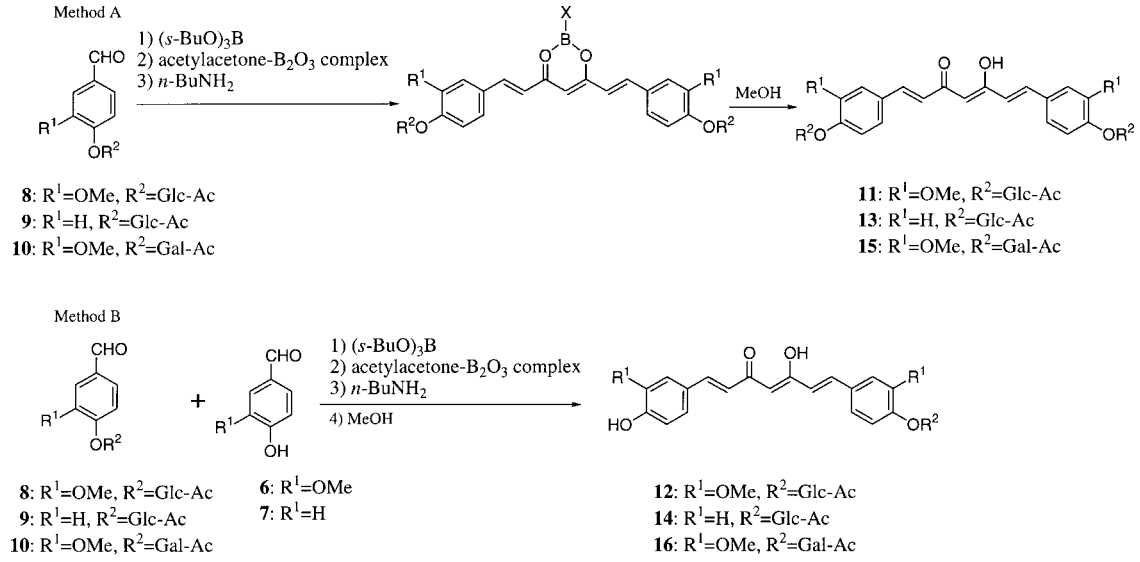



Chart 3. One Step Synthesis of Curcuminoids

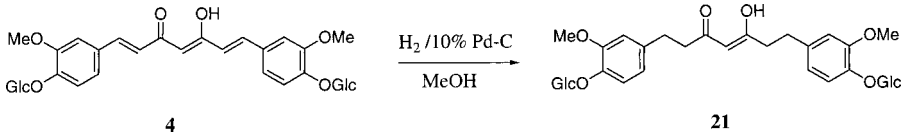



Chart 4. Hydrogenation of Diglucosylcurcumin

acetone–$B_2O_3$ complex, and then *n*-butylamine were successively added to a dry ethyl acetate solution of the aldehyde **8**, and the mixture was stirred at room temperature for 20 h. The color of the reaction mixture changed from yellow to orange when the reaction proceeded. The solvent was removed under reduced pressure, and the residue was heated with MeOH under reflux for 4 h to remove boron as $(MeO)_3B$. Chromatography of the product on silica gel gave diglucosylcurcumin octaacetate **11** in 51% yield (Table 1, Entry 1). Compound **11** is a yellow powder (mp 172—174 °C), which showed IR absorption at 3450, 1760, and 1630 $cm^{-1}$. In the $^1$H-NMR spectrum, two doublets for an olefin signal and a singlet for an enol moiety appeared instead of the aldehyde proton in **8**. The $^{13}$C-NMR spectrum supported the assigned structure **11** (Table 3).

In method B, an equivalent molar mixture of **8** and vanillin **6** was reacted with the acetylacetone–$B_2O_3$ complex in the same manner. After treatment of the product with methanol as in method A, the products were purified by silica gel chromatography to give monoglucosylcurcumin tetraacetate **12**, curcumin **1**, and diglucoside **11** in 34%, 15%, and 4% yields, respectively (Method B, Entry 2). In compound **12**, all signals (olefinic, aromatic, and methoxy groups) were observed without overlapping in the $^1$H- and $^{13}$C-NMR spectra, because of the unsymmetrical structure of the compound.

Similarly, compounds **9** and **10** were converted to diglycosides (**11**, **13**, **15**) by method A, and to monoglycosides (**12**, **14**, **16**) by method B (Table 1).

Subsequent removal of acetyl groups at the glycosyl moiety was achieved by treatment with 5% $NH_3$–MeOH at room temperature for 2 h. Diglucoside **11** gave digucosylcurcumin **4** in 79% yield after chromatography on an ODS column. Compound **4** is an orange powder (mp 155—159 °C), which is readily soluble in water, insoluble in ethyl acetate and $CHCl_3$, and slightly soluble in alcoholic solvents. The structure of **4** was determined by the IR, $^1$H-, and $^{13}$C-NMR spectra including H–H and C–H two dimensional (2D) correlated spectroscopy (COSY). Similarly, other acetates were converted to the corresponding curcuminoids by ammonolysis in good yields (Table 2).

Table 1. Synthesis of Curcumin Di- and Mono-glycosides

| Entry | Reactants | Method[a)] | Products (Yield) |
|---|---|---|---|
| 1 | **8** | A | **11** (51%) |
| 2 | **8**+**6** | B | **12** (34%)+**1** (15%)+**11** (4%) |
| 3 | **9** | A | **13** (51%) |
| 4 | **9**+**7** | B | **14** (31%)+**3** (12%)+**13** (3%) |
| 5 | **10** | A | **15** (56%) |
| 6 | **10**+**6** | B | **16** (28%)+**1** (28%)+**15** (trace) |

*a*) Method A: Single aldehyde reaction, Method B: two kinds of aldehyde reaction.

It is known that curcumin **1** is transformed *in vivo* into tetrahydrocurcumin,[14] which has higher activity than curcumin with respect to active oxygen removal capability.[15] Therefore, **4** was hydrogenated in MeOH over 10% Pd/C to yield the tetrahydro derivative **21** (80% yield). Compound **21** was a pale yellow powder (mp 92—96 °C), and showed, in the $^1$H-NMR spectrum, new triplet signals ($\delta$ 2.90 and 2.70 ppm) attributable to the methylene protons. The $^{13}$C-NMR spectrum also supported the structure of **21** (Table 3).

## Conclusion

Symmetrical and unsymmetrical glycosylcurcumins were synthesized by condensation of appropriately glycosylated arylaldehyde(s) with acetylacetone–$B_2O_3$ complex using two methods, A and B. Method A, which uses two moles of a sin-

gle arylaldehyde, produced symmetrical diglycoside and method B, which uses a mixture of glycosylated arylaldehyde and non-protected arylaldehyde, were appropriate to yield unsymmetrical mono-glycoside. Removal of the boron group from the product was achieved by refluxing with MeOH. Deacetylation from the sugar moiety was achieved in good yield by treatment with methanolic ammonia.

## Experimental

Unless otherwise stated, the following procedure was adopted. Melting points were determined on a Yanaco melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO IR-810 spectrophotometer, and data are given in $cm^{-1}$. UV spectra were recorded on a Hitachi U-2000 spectrophotometer and the absorption wavelengths are expressed in nm followed by ($\varepsilon$). $^1$H- and $^{13}$C-NMR spectra were taken with a JEOL JNM-EX90 (90 MHz for $^1$H and 22.5 MHz for $^{13}$C) or JEOL JNM-AL300 (300 MHz for $^1$H and 75 MHz for $^{13}$C) spectrometer, in $CDCl_3$ solutions with tetramethylsilane as an internal standard and the chemical shifts are given in $\delta$ values. High resolution (HR)-FAB-MS were recorded using a JEOL MStation JMS-700 spectrometer, with 3-nitrobenzylalcohol as the matrix. Elemental analyses of C and H were carried out on a Thermo Quest FlashEA 1112 microanalyzer. TLC was performed on pre-coated Kieselgel 60 $F_{254}$ plates and spots were monitored by UV (254 nm), then developed by spraying 0.5% $Ce(SO_4)_2$–0.5% $(NH_4)_6Mo_7O_{24}$ in 5% $H_2SO_4$ and heating the plates until coloration took place. Column chromatography was performed on Wakogel C-200 (silica gel). For medium-pressure liquid chromatography (MPLC), a Kusano CPS-HS-221-1 column (silica gel, 22 mm i.d.×100 mm) was used. Identification of curcumin **1** and bis-demethoxycurcumin **3** was performed by mp and TLC comparisons with the authentic specimen,[8] respectively.

**Tetra-*O*-acetyl-$\alpha$-D-glucopyranosyl Bromide** To a mixture of penta-*O*-acetyl-$\beta$-D-glucopyranose (23.4 g, 60 mmol) and red phosphorous (3.6 g, 116 mmol) in $CHCl_3$ (100 ml) was added $Br_2$ (21.6 g, 135 mmol) carefully in a dropwise manner and the resulting mixture was stirred for 30 min. Then water (4 ml) was added dropwise, and the mixture was stirred at room temperature for 2 h. After filtration of insoluble materials, the organic layer was washed with water and stirred vigorously with saturated aqueous $NaHCO_3$ solution for 10 min. The organic layer was separated, washed with water, dried over anhydrous $Na_2SO_4$, and concentrated. A solid residue was recrystallized from hexane–$Et_2O$ to afford acetobromoglucose as colorless needles (20.83 g, 84%). mp 86—88 °C (lit. mp 88—89 °C[12]).

**Tetra-*O*-acetyl-$\alpha$-D-galactopyranosyl Bromide** Penta-*O*-acetyl-$\beta$-D-galactose gave acetobromogalactose in 90% yield as a colorless gum. This was used for the next reaction without further purification.

**Glycosylation of Hydroxyarylaldehyde (Typical Example)** 1 N NaOH aq (150 ml) was added at room temperature to a stirred solution of vanillin **6** (13.6 g, 89.2 mmol), acetobromoglucose (18.3 g, 44.6 mmol) and $Bu_4NBr$ (14.6 g, 44.6 mmol) in $CHCl_3$ (150 ml). The resulting mixture was stirred vigorously at room temperature for 1 h. After dilution with AcOEt, the organic layer was washed with 1 N NaOH aq, water and brine, dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. The crude product was recrystallized from EtOH to give **8** (10.8 g, 50%) as colorless needles. The following compounds were prepared in this way.

Tetra-*O*-acetyl-$\beta$-D-glucopyranosylvanillin **8**: mp 135—137 °C (lit. mp 142 °C[16]). $^1$H-NMR: 9.90 (1H, s, CHO), 7.47—7.16 (3H, m, Ar-H), 5.35—5.06 (4H, m, Glc-H), 4.28—4.22 (2H, m, Glc-H), 3.90 (3H, s, OMe), 3.88—3.85 (1H, m, Glc-H), 2.07—2.05 (12H, OAc). $^{13}$C-NMR: 190.9 (CHO), 170.5, 170.2, 169.4, 169.2 (C=O), 151.0, 150.9, 132.8 (s, aromatic), 125.3, 118.1, 110.7 (d, aromatic), 99.7 (d), 72.3, 72.2, 70.9, 68.2 (d), 61.8 (t), 56.1 (OMe), 20.7, 20.6, 20.6×2 (OCO<u>Me</u>).

Tetra-*O*-acetyl-$\beta$-D-glucopyranosyl-4-hydroxybenzaldehyde **9**: This was obtained from 4-hydroxybenzaldehyde in 54% yield as colorless needles, mp 142—143 °C (lit. mp 145—147 °C[17]). $^1$H-NMR: 9.93 (1H, s, CHO), 7.86 (2H, d, $J$=8.6 Hz, Ar-H), 7.11 (2H, d, $J$=8.6 Hz, Ar-H), 5.34—5.16 (4H, m, Glc-H), 4.33—4.16 (2H, m, Glc-H), 3.97—3.92 (1H, m, Glc-H), 2.08—2.05 (12H, OAc). $^{13}$C-NMR: 190.7 (CHO), 170.4, 170.1, 169.3, 169.2 (C=O), 161.2, 131.8 (s, aromatic), 131.8×2, 116.7×2 (d, aromatic), 98.0 (d), 72.5, 72.2, 70.9, 68.0 (d), 61.8 (t), 20.6, 20.5, 20.5×2 (OCO<u>Me</u>).

Tetra-*O*-acetyl-$\beta$-D-galactopyranosylvanillin **10**: This was obtained by the reaction of acetobromogalactose and vanillin in 85% yield, as colorless needles, mp 124—125 °C (lit. mp 123—124 °C[18]). $^1$H-NMR: 9.90 (1H, s, CHO), 7.43—7.22 (3H, m, Ar-H), 5.59—5.46 (2H, m, Gal-H), 5.15—5.05 (2H, m, Gal-H), 4.28—4.14 (3H, m, Gal-H), 3.90 (3H, s, OMe), 2.18—2.03 (12H, OAc). $^{13}$C-NMR: 190.9 (CHO), 170.3, 170.1, 170.1, 169.3 (C=O), 151.7, 150.9, 132.7 (s, aromatic), 125.4, 117.9, 110.6 (d, aromatic), 100.3 (d), 71.2, 70.5, 68.4, 66.7 (d), 61.3 (t), 56.1 (OMe), 20.6, 20.6, 20.6, 20.5 (OCO<u>Me</u>).

**Acetylacetone–$B_2O_3$ Complex** Boric oxide ($B_2O_3$) was dried under reduced pressure at 250 °C for 3 h. The dried oxide (0.13 g, 1.8 mmol) was added to acetylacetone (0.25 g, 2.5 mmol) and the mixture was stirred at room temperature for 30 min, and then used directly.

**Synthesis of Curcuminoid Glycosides. Method A (Typical Example)** To a stirred solution of **8** (2.4 g, 5 mmol) in dry AcOEt (30 ml) was added tri-(*n*-butyl) borate $(BuO)_3B$ (2.5 ml), and the mixture was stirred for 10 min at room temperature. The above-prepared acetylacetone–$B_2O_3$ complex was then added to this solution. After stirring for 10 min at room temperature, *n*-butylamine (0.05 ml) was added to the solution, and the reaction mixture was stirred at room temperature for 20 h. The mixture was concentrated to dryness *in vacuo*. MeOH (200 ml) was added to the residue and the solution was heated under reflux for 4 h, following which the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt : hexane=3 : 2) to give **11** (1.4 g, 51%). The following compounds were prepared in this way.

Diglucosylcurcumin Octaacetate **11**: Yellow amorphous powder, mp 172—174 °C. IR (KBr): 3450, 1760, 1630. UV (MeOH): 260 (16800), 408 (47000). $^1$H-NMR: 7.59 (2H, d, $J$=15.6 Hz, H-1, 7), 7.27—7.10 (6H, m, Ar-H), 6.56 (2H, d, $J$=15.6 Hz, H-2, 6), 5.84 (1H, s, H-4), 5.26—5.06 (10H, m, Glc-H), 4.32—4.15 (4H, m, Glc-H), 3.87 (6H, s, OMe), 2.08—2.04 (24H, m, OAc). HR-FAB-MS (positive-ion mode) $m/z$: 1029.3242 $[M+H]^+$ (Calcd for $C_{49}H_{57}O_{24}$: 1029.3240). *Anal.* Calcd for $C_{49}H_{56}O_{24}\cdot 1/2H_2O$: C, 56.70; H, 5.54. Found: C, 56.97; H, 5.51.

Diglucosyl-bis-demethoxycurcumin Octaacetate **13**: Compound **9** (2.26 g, 5 mmol) was treated as described in method A with $(BuO)_3O$ (2.5 ml), acetylacetone–$B_2O_3$ complex which was prepared from acetylacetone (0.25 g, 2.5 mmol) and boric oxide (0.13 g, 1.8 mmol), and *n*-butylamine (0.05 ml) to give **13** (1.2 g, 51%), as pale yellow amorphous powder, mp 185—188 °C. IR (KBr): 1760, 1740. UV ($CHCl_3$ : MeOH=10 : 1): 407 (43700). $^1$H-NMR ($CDCl_3+CD_3OD$): 7.61 (2H, d, $J$=15.6 Hz, H-1, 7), 7.52, 7.01 (each 4H, d, $J$=8.7 Hz, Ar-H), 6.53 (2H, d, $J$=15.6 Hz, H-2, 6), 5.82 (1H, s, H-4), 5.35—3.87 (14H, m, Glc-H), 2.30—2.06 (24H, m, OAc). HR-FAB-MS (positive-ion mode) $m/z$: 969.3053 $[M+H]^+$ (Calcd for $C_{47}H_{53}O_{22}$: 969.3028). *Anal.* Calcd for $C_{47}H_{52}O_{22}\cdot 1/2H_2O$: C, 57.73; H, 5.46. Found: C, 57.73; H, 5.55.

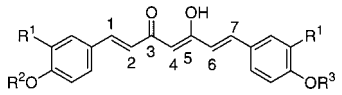
Digalactosylcurcumin Octaacetate **15**: Compound **10** (2.4 g, 5 mmol) was treated as described in method A with $(BuO)_3O$ (2.5 ml), acetylacetone–$B_2O_3$ complex which was prepared from acetylacetone (0.25 g, 2.5 mmol) and boric oxide (0.13 g, 1.8 mmol), and *n*-butylamine (0.05 ml) to give **15** (1.54 g, 56%), as yellow amorphous powder, mp 102—105 °C. IR (KBr): 1770, 1740. UV (MeOH): 260 (11900), 407 (39700). $^1$H-NMR: 7.60 (2H, d, $J$=15.8 Hz, H-1, 7), 7.12—7.08 (6H, m, Ar-H), 6.53 (2H, d, $J$=15.8 Hz, H-2, 6), 5.85 (1H, s, H-4), 5.56—5.45 (4H, m, Gal-H), 5.14—4.96 (4H, m, Gal-H), 4.25—4.02 (6H, m, Gal-H), 3.88 (6H, s, OMe), 2.18—2.02 (24H, m, OAc). HR-FAB-MS (positive-ion mode) $m/z$: 1029.3235 $[M+H]^+$ (Calcd for $C_{49}H_{57}O_{24}$: 1029.3240).

**Method B (Typical Example)** To a stirred solution of **8** (2.4 g, 5 mmol) and vanillin **6** (0.765 g, 5 mmol) in dry AcOEt (30 ml) was added $(BuO)_3B$ (5 ml) at room temperature, and the mixture was stirred for 10 min. Then acetylacetone–$B_2O_3$ complex, prepared from $B_2O_3$ (0.25 g, 3.6 mmol) and acetylacetone (0.5 g, 5 mmol), was added to the solution. After stirring for 10 min at room temperature, *n*-butylamine (0.1 ml) was added, and the reaction mixture was stirred at room temperature for a further 20 h. The resulting mixture was concentrated *in vacuo*, and the residue was heated under reflux with MeOH (200 ml) for 4 h. Evaporation of the solvent and purification of the residue by MPLC (AcOEt : hexane=3 : 2) gave curcumin **1** (281 mg, 15%), monoglucoside **12** (1.2 g, 34%), and diglucoside **11** (204 mg, 4%). The following compounds were synthesized in this way.

Monoglucosylcurcumin Tetraacetate **12**: Yellow amorphous powder, mp 86—88 °C. IR (KBr): 3420, 1750. UV (MeOH): 259 (11700), 416 (41400). $^1$H-NMR: 7.61, 7.56 (each 1H, d, $J$=15.8 Hz, H-7, H-1), 7.12—6.91 (6H, m, Ar-H), 6.52, 6.47 (each 1H, d, $J$=15.8 Hz, H-6, H-2), 5.81 (1H, s, H-4), 5.31—3.80 (7H, m, Glc-H), 3.94, 3.86 (each 3H, s, OMe), 2.09—2.05 (12H, m, OAc). HR-FAB-MS (positive-ion mode) $m/z$: 699.2311 $[M+H]^+$ (Calcd for $C_{35}H_{39}O_{15}$: 699.2289).

Monoglucosyl-bis-demethoxycurcumin Tetraacetate **14**: Compound **9** (2.26 g, 5 mmol) and 4-hydroxybenzaldehyde **7** (614 mg, 5 mmol) were treated as described in method B with $(BuO)_3O$ (2.5 ml), acetylacetone–$B_2O_3$ complex which was prepared from acetylacetone (0.25 g, 2.5 mmol) and boric oxide (0.13 g, 1.8 mmol), and *n*-butylamine (0.05 ml) to give **3**

Table 2. Glycosylcurcuminoids and Derivatives Synthesized in This Study



| Acetyl derivative | Glycosylcurcuminoid | Yield of deacetylation (%) |
|---|---|---|
| **11**: $R^1$=OMe, $R^2$=$R^3$=Glc-Ac | **4**: $R^1$=OMe, $R^2$=$R^3$=Glc | 79 |
| **12**: $R^1$=OMe, $R^2$=H, $R^3$=Glc-Ac | **5**: $R^1$=OMe, $R^2$=H, $R^3$=Glc | 63 |
| **13**: $R^1$=H, $R^2$=$R^3$=Glc-Ac | **17**: $R^1$=H, $R^2$=$R^3$=Glc | 64 |
| **14**: $R^1$=$R^2$=H, $R^3$=Glc-Ac | **18**: $R^1$=$R^2$=H, $R^3$=Glc | 68 |
| **15**: $R^1$=OMe, $R^2$=$R^3$=Gal-Ac | **19**: $R^1$=OMe, $R^2$=$R^3$=Gal | 77 |
| **16**: $R^1$=OMe, $R^2$=H, $R^3$=Gal-Ac | **20**: $R^1$=OMe, $R^2$=H, $R^3$=Gal | 85 |

Glc-Ac=tetra-*O*-acetyl-*β*-D-glucopyranosyl, Gal-Ac=tetra-*O*-acetyl-*β*-D-galactopyranosyl, Glc=*β*-D-glucopyranosyl, Gal=*β*-D-galactopyranosyl.

Table 3. $^{13}$C-NMR Data for Curcuminoid Glycosides

| | **11**[a] | **12**[a] | **13**[a] | **14**[b] | **15**[a] | **16**[a] | **4**[c] | **5**[c] | **17**[c] | **18**[c] | **19**[c] | **20**[c] | **21**[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| C-1, C-7 | 138.6 | 142.4 | 138.8 | 141.0 | 140.0 | 141.0 | 141.2 | 142.1 | 140.8 | 141.7 | 141.3 | 141.7 | 40.3 |
| | | 141.0 | | 139.0 | | 139.5 | | 140.9 | | 140.4 | | 140.6 | |
| C-2, C-6 | 122.0 | 124.9 | 121.7 | 122.9 | 121.6 | 123.4 | 123.7[d] | 122.9 | 123.3 | 123.3 | 123.8[d] | 122.6 | 31.3 |
| | | 124.4 | | 120.9 | | 123.0 | | 122.0 | | 121.8 | | 121.7 | |
| C-3, C-5 | 181.7 | 185.5 | 177.0 | 184.1 | 183.1 | 184.1 | 184.4 | 185.2 | 184.3 | 185.2 | 184.4 | 184.8 | 193.7 |
| | | 183.6 | | 181.6 | | 182.2 | | 183.7 | | 183.6 | | 183.4 | |
| C-4 | 100.2 | 102.8 | 98.5 | 101.4 | 100.8 | 100.9 | 102.4 | 102.2 | 102.3 | 102.2 | 102.7 | 102.4 | 100.2 |
| Aromatic (s) | 149.4 | 152.2 | 157.9 | 159.1 | 150.6 | 150.6 | 150.0[d] | 151.5 | 160.5 | 161.9 | 150.2[d] | 151.2[d] | 149.5 |
| | 146.3 | 149.4 | 130.3 | 157.9 | 147.9 | 148.0 | 135.7[d] | 150.5[d] | 129.6 | 160.4 | 135.9[d] | 150.2[d] | 146.4 |
| | 130.1 | 149.0 | | 130.2 | 131.4 | 147.7 | 129.9 | 149.8[d] | | 129.7 | 129.9 | 149.8[d] | 135.5[d] |
| | | 148.2 | | 126.6 | | 146.8 | | 149.3 | | 127.0 | | 149.0[d] | |
| | | 133.1 | | | | 131.5 | | 130.0 | | | | 129.5 | |
| | | 128.9 | | | | 127.5 | | 127.4 | | | | 127.2 | |
| Aromatic (d) | 120.2 | 123.1 | 129.4 | 130.0 | 123.3 | 122.9 | 123.0 | 123.5[d] | 130.6 | 131.2 | 123.0 | 123.5[d] | 120.8 |
| | 118.2 | 122.9 | 117.1 | 129.5 | 119.3 | 121.7 | 116.3 | 123.4[d] | 117.5 | 130.5 | 116.4 | 123.2[d] | 116.5 |
| | 110.3 | 121.0 | | 117.0 | 111.5 | 121.5 | 112.2 | 117.3 | | 117.5 | 112.2 | 116.9 | 113.3 |
| | | 116.2 | | 115.8 | | 119.3 | | 116.3 | | 117.3 | | 116.1 | |
| | | 113.0 | | | | 114.8 | | 112.2 | | | | 111.9 | |
| | | 111.1 | | | | 111.5 | | 112.0 | | | | 111.7 | |
| Ar-OMe | 54.7 | 57.5 | | | 56.1 | 56.1 | 56.1 | 56.2 | | | 56.1 | 55.8 | 55.9 |
| | | 57.3 | | | | 55.9 | | 56.1 | | | | | |
| Sugar (d) | 98.7 | 101.7 | 101.0 | 98.4 | 101.6 | 101.4 | 102.0 | 102.0 | 102.0 | 102.0 | 102.7 | 101.9 | 102.3 |
| | 72.8 | 73.9 | 72.6 | 72.6 | 71.0 | 71.0 | 79.3 | 79.4 | 79.4 | 79.3 | 78.0 | 77.7 | 78.8 |
| | 71.0 | 73.5 | 72.1 | 71.9 | 70.6 | 70.6 | 78.8 | 78.9 | 78.8 | 78.8 | 75.7 | 75.3 | 78.5 |
| | 70.7 | 72.5 | 71.0 | 71.0 | 68.5 | 68.5 | 75.0 | 75.1 | 75.2 | 75.2 | 72.3 | 72.0 | 74.9 |
| | 66.9 | 69.8 | 68.1 | 68.1 | 66.8 | 66.8 | 71.5 | 71.5 | 71.5 | 71.5 | 70.5 | 70.2 | 71.2 |
| Sugar (t) | 60.5 | 63.3 | 61.9 | 61.8 | 61.2 | 61.2 | 62.6 | 62.6 | 62.6 | 62.6 | 62.7 | 62.3 | 62.3 |
| OCOMe | 169.1 | 171.9 | 170.5 | 170.8 | 170.3 | 170.3 | | | | | | | |
| | 168.8 | 171.6 | 170.2 | 170.3 | 170.2 | 170.2 | | | | | | | |
| | 168.0 | 170.8 | 169.4 | 169.5 | 170.1 | 170.1 | | | | | | | |
| | 167.8 | 170.7 | 169.2 | 169.4 | 169.4 | 169.4 | | | | | | | |
| OCOMe | 19.3 | 22.0 | 20.7 | 20.6 | 20.7 | 21.0 | | | | | | | |
| | 19.2 | | 20.6 | 20.5 | 20.6 | 20.7 | | | | | | | |
| | | | 20.6 | 20.5 | 20.6 | 20.6 | | | | | | | |
| | | | | 20.4 | | 20.6 | | | | | | | |

*a*) Measured in $CDCl_3$. *b*) Measured in $CDCl_3$+$CD_3OD$. *c*) Measured in pyridine-$d_5$. *d*) Since it overlaps with that of the pyridine, the signal is not accurate.

(184 mg, 12%), monoglucoside **14** (996 mg, 31%) and diglucoside **13** (140 mg, 3%). **14**: Yellow needles, mp 232—233 °C. IR (KBr): 3400, 1750, 1740. UV ($CHCl_3$ : MeOH=10 : 1): 413 (40700). $^1$H-NMR ($CDCl_3$+$CD_3OD$): 7.61, 7.59 (each 1H, d, *J*=15.8 Hz, H-1, H-7), 7.50, 7.45, 7.00, 6.85 (each 2H, d, *J*=8.6 Hz, Ar-H), 6.52, 6.48 (each 1H, d, *J*=15.8 Hz, H-2, H-6), 5.79 (1H, s, H-4), 5.32—3.87 (7H, m, Glc-H), 2.18—2.03 (12H, m, OAc). HR-FAB-MS (positive-ion mode) *m/z*: 639.2102 $[M+H]^+$ (Calcd for $C_{33}H_{35}O_{13}$: 639.2078).

Monogalactosylcurcumin Tetraacetate **16**: Compound **10** (2.4 g, 5 mmol) and vanillin **6** (760 mg, 5 mmol) were treated as described in method B with $(BuO)_3O$ (2.5 ml), acetylacetone–$B_2O_3$ complex which was prepared from acetylacetone (0.25 g, 2.5 mmol) and boric oxide (0.13 g, 1.8 mmol), and *n*-butylamine (0.05 ml) to give **1** (525 mg, 28%), monoglucoside **16** (1.0 g, 28%) and digalactoside **15** (trace). **16**: Yellow amorphous powder, mp 98—100 °C. IR (KBr): 3400, 1750. UV (MeOH): 210 (21100), 260 (11700), 417 (47400). $^1$H-NMR: 7.60, 7.58 (each 1H, d, *J*=15.8 Hz, H-1, H-7), 7.14—6.92 (6H, m, Ar-H), 6.52, 6.48 (each 1H, d, *J*=15.8 Hz, H-2, H-6), 5.82 (1H, s, H-4), 5.56—4.03 (7H, m, Gal-H), 3.93, 3.88 (each 3H, s, OMe), 2.18—2.02 (12H, m, OAc). HR-FAB-MS (positive-ion mode) *m/z*: 699.2263 $[M+H]^+$ (Calcd for $C_{35}H_{39}O_{15}$: 699.2289).

**Ammonolysis of Acetoxy Group (Typical Example)** A solution of **11** (301 mg, 0.3 mmol) in 5% $NH_3$–MeOH (30 ml) was stirred at room temperature for 2 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by chromatography on an ODS column (MeOH : $H_2O$=1 : 1) to give deacetylated diglucoside **4** (159 mg, 79%). The following compounds were prepared in this way.

Diglucosylcurcumin **4**: Orange amorphous powder, mp 155—159 °C. IR (KBr): 3400, 1630. UV ($H_2O$): 256 (14600), 415 (26300). $^1$H-NMR (pyri-

dine-$d_5$): 7.94 (2H, d, $J$=15.7 Hz, H-1, 7), 7.41 (6H, m, Ar-H), 6.94 (2H, d, $J$=15.7 Hz, H-2, 6), 6.13 (1H, s, H-4), 5.79 (2H, d, $J$=6.8 Hz, Glc-H-1), 4.60—4.18 (12H, m, Glc-H), 3.76 (6H, s, OMe). HR-FAB-MS (positive-ion mode) $m/z$: 693.2377 $[M+H]^+$ (Calcd for $C_{33}H_{41}O_{16}$: 693.2395). *Anal.* Calcd for $C_{33}H_{40}O_{16}\cdot 5/2H_2O$: C, 53.73; H, 6.15. Found: C, 54.01; H, 5.99.

Monoglucosylcurcumin **5**: Orange amorphous powder, mp 110—113 °C. IR (KBr): 3400, 1630. UV (MeOH): 262 (13000), 417 (30400). $^1$H-NMR (pyridine-$d_5$): 7.96 (1H, d, $J$=15.8 Hz, H-1 or H-7), 7.93 (1H, d, $J$=15.8 Hz, H-7 or H-1), 7.61—7.24 (6H, m, Ar-H), 6.95 (1H, d, $J$=15.8 Hz, H-2 or H-6), 6.92 (1H, d, $J$=15.8 Hz, H-6 or H-2), 6.14 (1H, s, H-4), 5.78 (1H, d, $J$=6.8 Hz, Glc-H-1), 4.59—4.18 (6H, m, Glc-H), 3.78, 3.76 (each 3H, s, OMe). HR-FAB-MS (positive-ion mode) $m/z$: 531.1851 $[M+H]^+$ (Calcd for $C_{27}H_{31}O_{11}$: 531.1866).

Diglucosyl-bis-demethoxycurcumin **17**: Orange amorphous powder, mp 157—161 °C. IR (KBr): 3380, 1660. UV ($H_2O$): 226 (11200), 323 (15100), 403 (14400). $^1$H-NMR (pyridine-$d_5$): 7.89 (2H, d, $J$=15.7 Hz, H-1, 7), 7.57, 7.37 (each 4H, d, $J$=8.5, Ar-H), 6.81 (2H, d, $J$=15.7 Hz, H-2, 6), 6.13 (1H, s, H-4), 5.72 (2H, d, $J$=7.1 Hz, Glc-H-1), 4.61—4.18 (12H, m, Glc-H). HR-FAB-MS (positive-ion mode) $m/z$: 633.2200 $[M+H]^+$ (Calcd for $C_{31}H_{37}O_{14}$: 633.2183).

Monoglucosyl-bis-demethoxycurcumin **18**: Orange amorphous powder, mp 112—117 °C. IR (KBr): 3420, 1620. UV (MeOH): 410 (27200). $^1$H-NMR (pyridine-$d_5$): 7.96 (1H, d, $J$=15.8 Hz, H-1 or H-7), 7.93 (1H, d, $J$=15.8 Hz, H-7 or H-1), 7.69, 7.57, 7.40, 7.20 (each 2H, d, $J$=8.8 Hz, Ar-H), 6.85 (1H, d, $J$=15.8 Hz, H-2 or H-6), 6.81 (1H, d, $J$=15.8 Hz, H-6 or H-2), 6.13 (1H, s, H-4), 5.73 (1H, d, $J$=7.2 Hz, Glc-H-1), 4.61—4.18 (6H, m, Glc-H). HR-FAB-MS (positive-ion mode) $m/z$: 471.1656 $[M+H]^+$ (Calcd for $C_{25}H_{27}O_9$: 471.1655). *Anal.* Calcd for $C_{25}H_{26}O_9\cdot 5/2H_2O$: C, 58.25; H, 6.06. Found: C, 58.53; H, 6.13.

Digalactosylcurcumin **19**: Orange amorphous powder, mp 155—159 °C. IR (KBr): 3400, 1630. UV ($H_2O$): 257 (13500), 415 (21300). $^1$H-NMR (pyridine-$d_5$): 7.91 (2H, d, $J$=15.7 Hz, H-1, 7), 7.62—7.20 (6H, m, Ar-H), 6.91 (2H, d, $J$=15.7 Hz, H-2, 6), 6.13 (1H, s, H-4), 5.70 (2H, d, $J$=7.7 Hz, Gal-H-1), 4.84—4.30 (12H, m, Gal-H), 3.73 (6H, s, OMe). HR-FAB-MS (positive-ion mode) $m/z$: 693.2402 $[M+H]^+$ (Calcd for $C_{33}H_{41}O_{16}$: 693.2395). *Anal.* Calcd for $C_{33}H_{40}O_{16}\cdot 5/2H_2O$: C, 53.73; H, 6.15. Found: C, 53.98; H, 6.15.

Monogalactosylcurcumin **20**: Orange amorphous powder, mp 110—113 °C. IR (KBr): 3420, 1620. UV (MeOH): 261 (13400), 417 (33800). $^1$H-NMR (pyridine-$d_5$): 8.01 (1H, d, $J$=15.8 Hz, H-1 or H-7), 7.95 (1H, d, $J$=15.8 Hz, H-7 or H-1), 7.59—7.17 (6H, m, Ar-H), 6.95 (1H, d, $J$=15.8 Hz, H-2 or H-6), 6.91 (1H, d, $J$=15.8 Hz, H-6 or H-2), 6.14 (1H, s, H-4), 5.70 (1H, d, $J$=7.7 Hz, Gal-H-1), 4.87—4.30 (6H, m, Gal-H), 3.79, 3.73 (each 3H, s, OMe). HR-FAB-MS (positive-ion mode) $m/z$: 531.1857 $[M+H]^+$ (Calcd for $C_{27}H_{31}O_{11}$: 531.1866). *Anal.* Calcd for $C_{27}H_{30}O_{11}\cdot 3/2H_2O$: C, 58.16; H, 5.97. Found: C, 58.41; H, 5.96.

Diglucosyltetrahydrocurcumin **21**: Diglucosylcurcumin **4** (102 mg, 0.1 mmol) in MeOH (50 ml) was hydrogenated over 10% Pd/C (20 mg) under 2.5 kgf/cm$^2$ for 2 h at room temperature. After removal of the catalyst, the residue was purified by chromatography on an ODS column (MeOH : $H_2O$=1 : 1) to yield tetrahydro derivative **21** (80 mg, 80%) as a pale yellow amorphous powder. mp 92—96 °C. IR (KBr): 3370, 1700. UV ($H_2O$): 274 (8400). $^1$H-NMR (pyridine-$d_5$): 7.72—6.77 (6H, m, Ar-H), 6.80 (1H, s, H-4), 5.68 (2H, d, $J$=5.7 Hz, Glc-H-1), 4.57—4.11 (12H, m, Glc-H), 3.72 (6H, s, OMe), 2.94 (4H, t, $J$=15.2 Hz, H-1, 7), 2.66 (4H, t, $J$=15.2 Hz, H-2, 6). HR-FAB-MS (positive-ion mode) $m/z$: 697.2737 $[M+H]^+$ (Calcd for $C_{33}H_{45}O_{16}$: 697.2708). *Anal.* Calcd for $C_{33}H_{44}O_{16}\cdot 2H_2O$: C, 54.09; H, 6.60. Found: C, 54.37; H, 6.67.

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