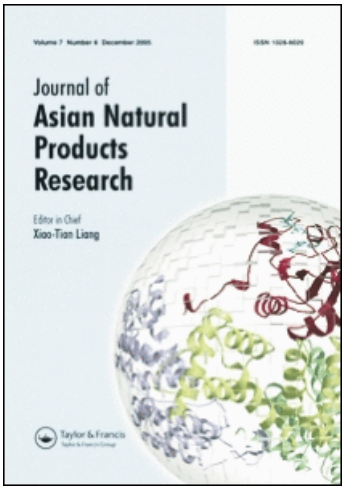


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# Three new norlignans from *Curculigo capitulata*

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# Three new norlignans from *Curculigo capitulata*

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From the ethanolic extract of the rhizomes of *Curculigo capitulata* have been isolated, and structurally elucidated by spectral evidences and chemical methods, three new norlignans, capituloside (**1**), a mixture of curculigenin (**2**) and isocurculigenin (**3**), along with four known compounds (**4**–**7**), a mixture of 1-*O*-methylcurculigine (**4**) and 1-*O*-methylisocurculigine (**5**) and a mixture of curculigine (**6**) and isocurculigine (**7**).

*Keywords*: *Curculigo capitulata*; Hypoxidaceae; Capituloside; Norlignan; Norlignan glucosides

## 1. Introduction

Our previous studies on the rhizomes of *Curculigo capitulata* (Hypoxidaceae), used as a tonic and a medicine to treat dysmenorrhea and rheumatism [1], resulted in the isolation of capitulatin A [2]. In continuation of our studies on the rhizomes of *C. capitulata*, this paper reports the isolation and structural elucidation of capituloside (**1**), a mixture of curculigenin (**2**) and isocurculigenin (**3**) along with four known compounds, a mixture of 1-*O*-methylcurculigine (**4**) [3] and 1-*O*-methylisocurculigine (**5**) [3] and a mixture of curculigine (**6**) [3] and isocurculigine (**7**) [3], which were identified by comparison of their spectral data (FABMS, $^{1}$H and $^{13}$C) with those reported in the literature and 2D NMR spectra. These compounds are norlignans and their glucosides with skeletons of ph-$C_5$-ph. They can be considered as norlignans generated by the coupling of two ph-$C_3$ units (cinnamic acid and cinnamyl alcohol) at the position β-γ′ and loss of a terminal carbon atom in the side chain [4].

## 2. Results and discussion

Compound **1** was assigned a molecular formula of $C_{23}H_{26}O_{11}$ on the basis of the HRFAB-MS (−) (*m*/*z* 477.1377 $[M-1]^-$, calcd. 477.1397). The $^{1}$H NMR spectrum shows two 3,4-disubstituted aromatic rings, in one of which H-2 and H-6 were shifted downfield ($\delta_H$ 7.24 and 7.23, respectively) due to an ortho carbonyl group (IR: $\nu_{CO}$ 1651 and $\delta_{CO}$

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201.2 $cm^{-1}$). By a selective $^1$H-decoupling experiment, the norlignan sequence ph–CH (O)–CH (O)–$CH_2$–$CH_2$–CO–ph was established. The remaining carbons presumably belong to a hexose unit (anomeric carbon at $\delta$93.9). An anomeric proton signal doublet at $\delta_H$ 4.44 ($J = 7.80$ Hz) in the $^1$H NMR spectrum indicates a glucose unit in **1**. From the coupling constant of the anomeric proton and $^{13}$C NMR chemical shifts, the glucose unit should be in the β-form. The other linkages of the glucose unit were confirmed by $^1$H–$^1$H COSY, HMBC, HMQC–TOCSY and NOE spectra. In the HMBC spectrum of **1**, the anomeric proton signal is correlated with that of C-2 at $\delta_C$ 79.2; the signal of glucose H-2 at $\delta_H$ 3.03 is correlated with that of C-1 at $\delta_C$ 80.4, which suggests that the glucose is connected with the norlignan at C-2 and C-1, respectively. The stereochemical configuration of **1** was revealed by a NOESY experiment. There are clear correlations between H-1 and H-2, H-1 and H-2 (Glc.) but not between H-2 and H-1 (Glc.). Thus, H-1 is at an axial orientation and H-2 at an equatorial orientation. Following acetylation of **1** with acetic anhydride in pyridine, the acetate was subjected to FAB-MS (+) analysis, and showed *m/z* 479 + 7 × 42 ($[M + 1]^+ + 7Ac$) (773), indicating that the glucose unit has only three free hydroxy groups, the other four acetyl groups were due to the phenolic hydroxy groups. On the basis of the above evidence, compound **1** was determined as a glucosyl-fused norlignan (figure 1). This structure was confirmed by a Mitsunobu reaction [5], employing a mixture of triphenylphosphine ($Ph_3P$) and a diethyl azodicarboxylate (DEAD), which is a very useful reaction in the refunctionalization of alcohols and, in particular, inversion of this moiety (scheme 1). By applying this condition, compounds **6** and **7** were successfully converted into compound **1**, suggesting that compound **1** has the proposed structure.

Compounds **2** and **3** were assigned to curculigenin (**2**) and isocurculigenin (**3**), and had the same molecular formula of $C_{18}H_{20}O_7$ on the basis of HRFAB-MS (−) (*m/z* 347.1135 $[M - 1]^-$, calcd. 347.1130). They were obtained as an irresolvable 2:1 mixture by TLC and HPLC (see Experimental section). Most of the NMR signals of the mixture are in pairs. H-1, $\delta_H$ 4.29, d, $J = 3.80$ Hz in **2** and $\delta_H$ 4.21, d, $J = 7.08$ Hz in 3, where the former predominates. The $^1$H NMR spectrum shows two 3,4-disubstituted aromatic rings, in one of which H-2 and H-6 are shifted downfield ($\delta_H$ 8.14 and 7.72, respectively) due to an ortho carbonyl group (IR $\nu_{CO}$ 1651 $cm^{-1}$ and $\delta_{CO}$ 199.6 and 199.3 $cm^{-1}$). By selective $^1$H-decoupling experiment, the norlignans sequence ph–CH (O)–CH (O)–$CH_2$–$CH_2$–CO–ph was established. The 1D and 2D NMR spectra show that **2** and **3** are aglycones of the known compounds **4** and **5** [3], respectively. The $\delta$ at C-2 in **2** and **3** are shifted upfield 8–10 ppm compared with those of **4** and

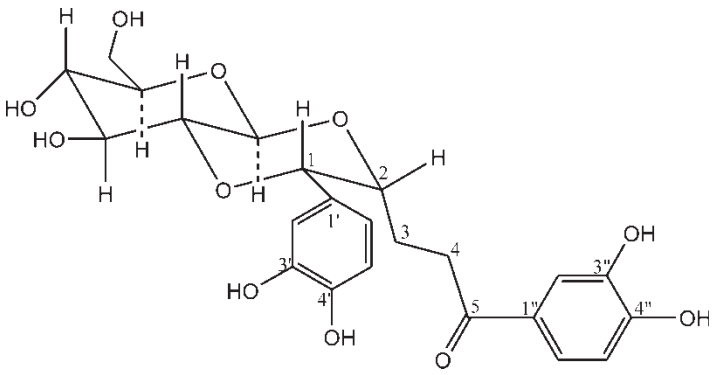
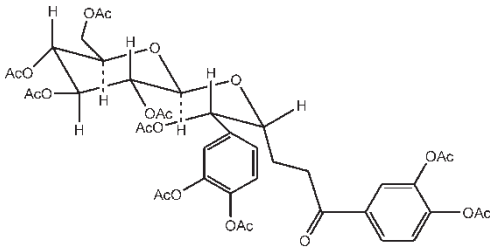
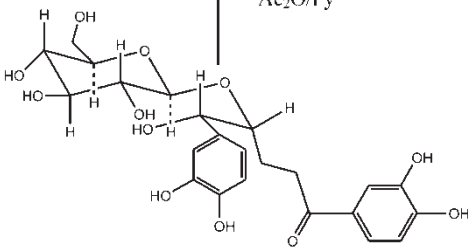



Figure 1. Structure of compound **1**.



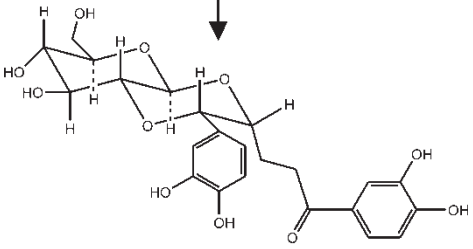
A nonacetyl derivative

$Ac_2O/Py$



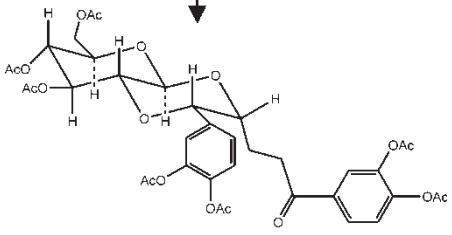
A mixture of compounds **6** and **7**

$PPh_3$
DEA
D
TH
F



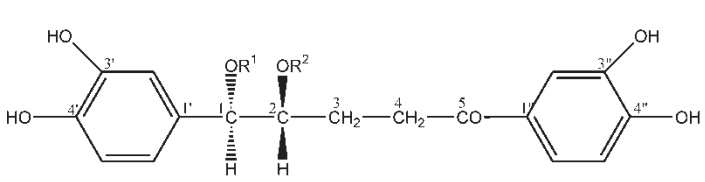
Compound **1**

$Ac_2O/Py$

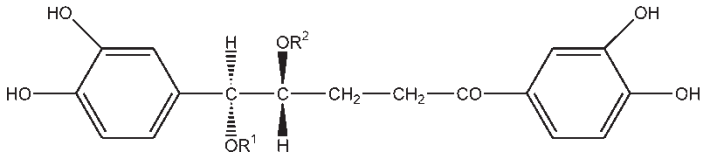


A heptacetyl derivative

Scheme 1. Structures of Mitsunobu reaction and acetylation derivatives of **1**, **6** and **7**.




| | $R^1$ | $R^2$ |
|---|---|---|
| **2** | Me | H |
| **4** | Me | β -D-glucose |
| **6** | H | β-D-glucose |




| | $R^1$ | $R^2$ |
|---|---|---|
| **3** | Me | H |
| **5** | Me | β -D-glucose |
| **7** | H | β-D-glucose |

Figure 2. Structures of compounds **2**–**7**.

**5**, while the $\delta$ at C-1 and C-3 in **2** and **3** is downfield shifted, due to the absence of a β-D-glucose unit at C-2. The $\delta$ of remaining carbons in **2** and **3** are similar to the corresponding positions of **4** and **5**. The correlation peak between C-1 and protons of $OCH_3$ in the HMBC spectra of **2** and **3** confirms that $OCH_3$ is linked at C-1. The coupling constant between H-1 and H-2 in the *threo*-isomer is larger (6–8 Hz) than that in the *erythro*-isomer (2–4 Hz) [6–8]. Hence, the coupling constant of H-1 and H-2 shows that **2** and **3** are *erythro*- and *threo*-isomers, respectively. From the above results, and by comparison with those of the two known compounds **4** and **5**, the structures of curculigenin (**2**) and isocurculigenin (**3**) have been established as aglycones of compounds **4** and **5** (figure 2).

Conversely, $\delta$s at C-1 and C-2 in compounds **4**–**7** are contrary to the literature [3]. The $\delta$ at C-1 should be shifted downfield, with those at C-2 upfield, which was confirmed by $^1H-^1H$ COSY, HMQC and HMBC spectra. Thus, the chemical shifts of C-1 and C-2 were assigned (table 2 below).

## 3. Experimental

### *3.1 General experimental procedures*

The melting point was determined on an XRC-1 micro melting point apparatus and is uncorrected; $[\alpha]_D$ was determined with a JASCO-20. IR spectra were recorded on a Bio-Rad FTS-135 spectrometer with KBr pellets. UV spectra were recorded on an UV 210A spectrometer using MeOH as solvent. 1D- and 2D-NMR spectra were run on a Bruker AM-400 instrument with TMS as internal standard, using $CD_3OD$ and $C_5D_5N$ as solvent. FAB-MS was carried out on a VG Auto Spec-3000 spectrometer. TLC was performed on silica gel G (MEIJING) precoated plates. Spots were detected by spraying 5% sulfuric acid-ethanol solution followed by heating.

### *3.2 Plant material*

Rhizomes of *Curculigo capitulata* were collected from the west garden of Xi Shuang Ban Na Tropical Botanical Garden, Chinese Academy of Sciences and identified by Professor Xu Zai Fu of Xi Shuang Ban Na Tropical Botanical Garden, Chinese Academy of Sciences. A voucher specimen has been deposited in Xi Shuang Ban Na Tropical Botanical Garden.

Table 1. $^{1}$H NMR spectral data of compounds **1**–**7**[a] (400 MHz).

| *H* | *1* | *2* | *3* | *4* | *5* | *6* | *7* |
|---|---|---|---|---|---|---|---|
| 1 | 4.71 d (2.52) | 4.29 d (3.80) | 4.21 d (7.08) | 4.55 d (3.28) | 4.33 d (7.32) | 4.46 d (3.76) | 4.73 d (7.02) |
| 2 | 4.00 ddd (11.08, 7.32, 2.04) | 4.23 m | 4.23 m | 3.78 m | 3.99 m | 3.86 m | 3.86 m |
| 3 | 1.98 m, 1.31 m | 2.57 m | 2.25 m | 1.90 m | 1.54 m | 1.58–1.79 m | 1.58–1.79 m |
| 4 | 2.71 m | 3.49 m | 3.33 m | 3.22 m | 2.97 m | 2.96 m, 3.01 m | 2.96 m, 3.01 m |
| 2′ | 6.72 d (1.50) | 7.56 d (1.68) | 7.56 d (1.68) | 6.82 d (2.00) | 6.82 d (2.00) | 6.88 d (2.01) | 6.88 d (2.01) |
| 5′ | 6.63 d (8.15) | 7.23 d (7.80) | 7.23 d (7.80) | 6.78 d (8.28) | 6.74 d(8.04) | 6.78 d (8.04) | 6.78 d (8.04) |
| 6′ | 6.58 dd (1.50, 8.15) | 7.05 dd (1.68, 7.80) | 6.96 dd (1.68, 7.80) | 6.67 dd (2.00, 8.28) | 6.68 dd (2.00, 8.04) | 6.70 dd (2.01, 8.04) | 6.70 dd (2.01, 8.04) |
| 2″ | 7.24 d (1.70) | 8.14 d (1.80) | 8.14 d (1.80) | 7.41 d (2.24) | 7.41 d (2.24) | 7.38 d (2.04) | 7.38 d (2.04) |
| 5″ | 6.67 d (8.95) | 7.52 d (7.82) | 7.52 d (7.82) | 6.77 d (8.28) | 6.77 d (8.28) | 6.82 d (8.00) | 6.82 d (8.00) |
| 6″ | 7.23 dd (1.70, 8.95) | 7.72 dd (1.80, 7.82) | 7.72 dd (1.80, 7.82) | 7.38 dd (2.24, 8.28) | 7.38 dd (2.24, 8.28) | 7.37 dd (2.04, 8.00) | 7.37 dd (2.04, 8.00) |
| Glucose | | | | | | | |
| 1 | 4.44 d (7.80) | | | 4.40 d (7.52) | 4.48 d (7.56) | 4.47 d (7.08) | 4.44 d (7.12) |
| 2 | 3.03 m | | | 3.29–3.34 m | 3.29–3.34 m | 3.41–3.62 m | 3.41–3.62 m |
| 3 | 3.49 m | | | 3.29–3.34 m | 3.29–3.34 m | 3.41–3.62 m | 3.41–3.62 m |
| 4 | 3.25 m | | | 3.29–3.34 m | 3.29–3.34 m | 3.41–3.62 m | 3.41–3.62 m |
| 5 | 3.28 m | | | 3.29–3.34 m | 3.29–3.34 m | 3.41–3.62 m | 3.41–3.62 m |
| 6 | 3.55 dd (5.04, 11.84) | | | 3.71 dd (5.28, 12.00) | 3.71 dd (5.28, 12.00) | 3.76 dd (4.52, 12.00) | 3.76 dd (4.52, 12.00) |
| | 3.74 dd (1.42, 11.84) | | | 3.89 dd (2.04, 12.00) | 3.89 dd (2.04, 12.00) | 3.92 dd (2.03, 12.00) | 3.92 dd (2.03, 12.00) |
| OMe | | 3.26 s | 3.27 s | 3.28 s | 3.21 s | | |

[a] Compounds **2** and **3** in $C_5D_5N$; **1**, **4**–**7** in $CD_3OD$.

Table 2. $^{13}C$ NMR spectral data of compounds **1**–**7** (100 MHz).

| *C* | *1* | *2* | *3* | *4* | *5* | *6* | *7* |
|---|---|---|---|---|---|---|---|
| 1 | 80.4 d | 88.4 d | 89.2 d | 86.9 d | 86.4 d | 86.0 d | 85.8 d |
| 2 | 79.2 d | 74.3 d | 74.6 d | 85.0 d | 81.8 d | 77.4 d | 76.1 d |
| 3 | 21.3 t | 29.4 t | 28.9 t | 24.8 t | 26.6 t | 27.5 t | 26.0 t |
| 4 | 34.7 t | 35.4 t | 35.2 t | 35.4 t | 34.7 t | 34.7 t | 35.4 t |
| 5 | 201.2 s | 199.6 s | 199.3 s | 202.2 s | 201.9 s | 201.7 s | o.l. |
| 1′ | 130.5 s | 131.7 s | 131.3 s | 131.5 s | 130.7 s | 133.2 s | 133.5 s |
| 2′ | 115.8 d | 116.5 d[a] | o.l. | 116.2 d[a] | o.l. | 116.3 d | o.l. |
| 3′ | 146.3 s | 146.9 s[b] | o.l. | 145.7 s[b] | o.l. | 146.0 s | 145.8 s |
| 4′ | 145.7 s | 147.4 s[b] | o.l. | 146.3 s[b] | o.l. | 146.0 s | 145.8 s |
| 5′ | 116.2 d | 116.0 d[a] | o.l. | 115.4 d[a] | 115.8 d[a] | 115.8 d | o.l. |
| 6′ | 118.4 d | 120.3 d | 120.1 d | 120.2 d | 120.9 d | 120.4 d | 120.2 d |
| 1″ | 130.4 s | 130.3 s | o.l. | 130.4 s | o.l. | 130.3 s | 130.0 s |
| 2″ | 114.2 d | 116.2 d[a] | o.l. | 116.0 d[a] | o.l. | 115.9 d | o.l. |
| 3″ | 146.2 s | 147.2 s[b] | o.l. | 146.2 s[b] | o.l. | 146.0 s | 145.2 s |
| 4″ | 152.1 s | 152.6 s | o.l. | 152.0 s | o.l. | 152.0 s | o.l. |
| 5″ | 115.9 d | 116.4 d[a] | o.l. | 116.1 d[a] | o.l. | 115.5 d | o.l. |
| 6″ | 123.0 d | 122.3 d | o.l. | 123.2 d | o.l. | 123.1 d | o.l. |
| Glucose | | | | | | | |
| 1 | 93.9 d | | | 105.4 d | 104.0 d | 103.8 d | 104.5 d |
| 2 | 81.9 d | | | 75.2 d | o.l. | 75.0 d | o.l. |
| 3 | 75.0 d | | | 78.00 d[c] | o.l. | 77.6 d | o.l. |
| 4 | 72.0 d | | | 71.6 d | o.l. | 71.2 d | o.l. |
| 5 | 79.9 d | | | 77.94 d[c] | o.l. | 77.5 d | o.l. |
| 6 | 62.5 t | | | 62.8 t | o.l. | 62.5 t | o.l. |
| OMe | | 56.7 q | 56.6 q | 57.6 q | 57.0 q | | |

Compounds **2** and **3** in $C_5D_5N$; **1**, **4**, **5**, **6** and **7** in $CD_3OD$.
[a–c] These values may be interchangeable in the same column. o.l., overlapping $^{13}C$ NMR signals.



### 3.3 Extraction and isolation

The air-dried and powered rhizomes of *C. capitulata* (3 kg) were extracted with 85% EtOH (3 × 20 L) at room temperature, and the combined extracts were evaporated *in vacuo*. The residue was suspended in $H_2O$ and then passed through a D101 resin column to eliminate sugars; the column was then eluted with 95% EtOH. The EtOH eluent was concentrated *in vacuo* to give a residue (240 g), which was chromatographed on silica gel column (200–300 mesh) with $CHCl_3$–MeOH (7:2) to give 8 fractions. Fraction 5 was subjected to column chromatography over silica gel eluted with $CHCl_3$–MeOH (5.5:1) to afford **1** (18 mg, yield 0.0075%). Fraction 6 was submitted to column chromatography over silica gel eluted with $CHCl_3$–MeOH (10:1) and a 2:1 mixture (120 mg, yield 0.05%) of **2** and **3** (inseparable by HPLC and TLC) was obtained. Fraction 7 was submitted to column chromatography over silica gel eluted with $CHCl_3$–MeOH (4.5:1); on recycling, a 2:3 mixture (63 mg, yield 0.026%) of **4** and **5** (inseparable by HPLC and TLC) and a 1:1 mixture (24 mg, yield 0.01%) of **6** and **7** (likewise inseparable by HPLC and TLC) were obtained.

### 3.4 Acetylation of 1 and a mixture of 6 and 7

Each sample (1 mg) was dissolved in $Ac_2O$-pyridine (1:0.5) in a sealed micro-tube. After reacting at 60–70°C for 6 h, each acetate was subjected to FAB-MS (+) analysis, and showed *m/z* $479 + 7 \times 42$ ($[M + 1]^+ + 7Ac$) (773) for **1** and $497 + 9 \times 42$ ($[M + 1]^+ + 9Ac$) (875) for the mixture of **6** and **7**. They were a heptacetyl derivative of **1** and a nonacetyl derivative of **6** and **7** (Scheme 1).

### *3.5 Mitsunobu reaction*

To a solution of a mixture of **6** and **7** (4.4 mg, 8.8 μmol) and $Ph_3P$ (2.3 mg, 8.8 μmol) in THF (2 ml) at 0°C was slowly added DEAD (2.3 mg, 13 μmol) under $N_2$. The solution was then warmed to room temperature and stirred for 2.5 h. The solvent was evaporated *in vacuo* and the residue extracted with EtOAc. The EtOAc solution was then washed with brine, and dried over $MgSO_4$. After filtration, the organic solution was concentrated *in vacuo* to provide the crude product (3.9 mg). By TLC and FAB-MS (−) analyses, compound 1 was dotted on the same silica gel G plate ($CHCl_3$–MeOH, 3:1) from the crude product and an *m/z* 477 $[M - H]^-$ corresponding to $C_{23}H_{26}O_{11}$ was observed.

**3.5.1 Capituloside (1)**. Colorless needles (EtOH), mp 185–187°C; $[\alpha]_D^{21} + 50$ (*c* 0.05, MeOH); IR (KBr) $\nu_{max}$ ($cm^{-1}$): 3428, 2924, 1651, 1442, 1288, 1054; UV (MeOH) $\lambda_{max}$ (nm): 229, 277, 309. Molecular formula $C_{23}H_{26}O_{11}$, HRFAB-MS (−), *m/z*: 477.1377 $[M - 1]^-$, calcd. for $C_{23}H_{25}O_{11}$ 477.1397. $^1H$ ($CD_3OD$, 400 MHz) and $^{13}C$ ($CD_3OD$, 100 MHz) NMR data are shown in tables 1 and 2, respectively.

**3.5.2 Curculigenin (2) and isocurculigenin (3)**. White amorphous powder; IR (KBr) $\nu_{max}$ ($cm^{-1}$): 3438, 2924, 1651, 1456, 1287, 878; UV (MeOH) $\lambda_{max}$ (nm): 204, 281, 311. Molecular formula $C_{18}H_{20}O_7$, HRFAB-MS (−), *m/z*: 347.1135 $[M - 1]^-$, calcd. for $C_{18}H_{19}O_7$ 347.1130. $^1H$ ($C_5D_5N$, 400 MHz) and $^{13}C$ ($C_5D_5N$, 100 MHz) NMR data are shown in tables 1 and 2, respectively.

**3.5.3 Mixture of 1-*O*-methylcurculigine (4) and 1-*O*-methylisocurculigine (5)**. White amorphous powder; IR (KBr) $\nu_{max}$ ($cm^{-1}$) 1659; UV (MeOH) $\lambda_{max}$ (nm): 274, 303. FAB-MS (−), *m/z*: 509 $[M - H]^-$, $C_{24}H_{30}O_{12}$. $^1H$ ($CD_3OD$, 400 MHz) and $^{13}C$ ($CD_3OD$, 100 MHz) NMR data are shown in tables 1 and 2, respectively.

**3.5.4 Mixture of curculigine (6) and isocurculigine (7)**. White amorphous powder. IR (KBr) $\nu_{max}$ ($cm^{-1}$) 1670; UV (MeOH) $\lambda_{max}$ (nm) 274, 303. FAB-MS, *m/z*: 495 $[M - H]^-$, $C_{23}H_{28}O_{12}$. $^1H$ ($CD_3OD$, 400 MHz) and $^{13}C$ ($CD_3OD$, 100 MHz) NMR data are shown in tables 1 and 2, respectively.

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