Prenylated Xanthones from the Root Bark of *Cudrania tricuspidata*

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Four new prenylated xanthones, cudratricusxanthones J−M (**1**−**4**), were isolated from the CH_2Cl_2-soluble extract of the root bark of *Cudrania tricuspidata*, along with four known prenylated xanthones, isocudraxanthone K (**5**), cudraxanthone C (**6**), cudratricusxanthone A (**7**), and cudraxanthone L (**8**), and three known prenylated flavonoids, cudraflavone A (**9**), cudraflavanone A (**10**), and cudraflavone B (**11**). The structures of compounds **1**−**4** were elucidated using spectroscopic methods. Cudratricusxanthone A (**7**), cudraflavanone A (**10**), and cudraflavone B (**11**) showed moderate inhibitory effects on mouse brain monoamine oxidase (MAO) with IC_{50} values of 88.3, 89.7, and 80.0 μM, respectively.

The genus *Cudrania* belongs to the Moraceae family and is widely distributed in Korea, mainland China, and Japan. The roots of *C. tricuspidata* (Carr.) Bur. have been used for the treatment of gonorrhea, rheumatism, jaundice, hepatitis, boils, scabies, bruising, and dysmenorrhea.[1] Isoprenylated xanthones[2−9] and flavonoids[10−14] are the major compound classes in *C. tricuspidata*. Previous biological studies have shown that the constituents of *C. tricuspidata* are cytotoxic,[4,5] antioxidant,[3] antiatherosclerotic, anti-inflammatory,[15] and hepatoprotective.[16,17] Recently, we have described three known prenylated isoflavonoids and their monoamine oxidase (MAO) inhibitory activities from the fruits of this plant.[18] In the course of our studies to search for MAO inhibitors from higher plants, the CH_2Cl_2-soluble extract of the fruits of *C. tricuspidata* was found to inhibit mouse brain MAO significantly. We report herein the isolation, structure determination, and MAO inhibitory activity of four new prenylated xanthones along with four known prenylated xanthones and three known prenylated flavonoids.

Compound **1**, a yellow and amorphous powder, showed a molecular ion peak $[M]^+$ at *m/z* 396 in the EIMS, consistent with the formula $C_{23}H_{24}O_6$, as deduced from HRFABMS (*m/z* 397.1672 $[M + H]^+$; calcd 397.1651). The UV spectrum of **1** resembled the spectra of 1,3,6,7-tetrahydroxyxanthone derivatives.[2−6] The ^1H and ^{13}C NMR spectra revealed the presence of two aromatic protons [δ_H 6.71 (1H, s, H-5) and 6.02 (1H, s, H-2); δ_C 100.6 (C-5) and 92.8 (C-2)] and a 3,3-dimethylallyl (prenyl) group [δ_H 5.37 (1H, m), 4.15 (2H, br d, $J = 6.5$ Hz), and 1.83, 1.62 (each 3H, s); δ_C 26.3 (C-16), 125.1 (C-17), 130.2 (C-18), 25.8 (C-19), 18.1 (C-20)]. Moreover, the ^1H and ^{13}C NMR spectra provided evidence of the presence of a 2,3-dihydro-2,3,3-trimethylfuran ring with characteristic signals at δ_H 4.47 (1H, q, $J = 6.5$ Hz), 1.50, 1.22 (each 3H, s), and 1.36 (3H, d, $J = 6.5$ Hz) and at δ_C 44.1 (C-11), 21.4 (C-12), 25.8 (C-13), 90.9 (C-14), and 14.6 (C-15). Furthermore, the ^{13}C NMR spectrum of **1** revealed the presence of 23 carbons, including one conjugated carbonyl carbon at δ 182.4 and two aromatic rings with six oxygenated quaternary carbons at δ 165.0, 164.6, 158.6, 154.2, 152.8, and 143.7. The above observations indicated that compound **1** has a tetrahydroxylated xanthone with two C_5 units in the molecule. The obviously downfield benzylic methylene proton signal at δ 4.15 suggested that the prenyl group was located at C-8, *peri* to the carbonyl group.[5] This finding was confirmed by the HMBC correlations between the benzylic methylene protons at δ_H 4.15 and δ_C 143.7 (C-7), 130.2 (C-8), and 108.7 (C-8a). In the HMBC spectrum, cross-peaks between the chelated hydroxyl group at δ_H 14.35 and δ_C 164.6 (C-1), 104.0 (C-9a), and 92.8 (C-2) suggested that the single aromatic proton was located at C-2. Further HMBC cross-peaks of two methyl protons at δ_H 1.22 and 1.50 (H-12 and H-13, respectively) with C-4 at δ_C 111.8 indicated that the 2,3-dihydro-2,3,3-trimethylfuran ring was fused at C-3 and C-4. Thus, the structure of compound **1** was identified as 1,6,7-trihydroxy-8-(3-methylbut-2-enyl)-4′,5′-dihydro-4′,4′,5′-trimethylfurano-(3,4:2′,3′)-xanthone, and it was named cudratricusxanthone J.

Compound **2**, obtained as a yellow and amorphous powder, was assigned the molecular formula of $C_{24}H_{26}O_6$ by HRFABMS (*m/z* 411.1785 $[M + H]^+$; calcd 411.1808). The ^1H NMR spectrum of **2** exhibited two aromatic proton singlets at δ_H 7.56 (1H, s, H-8) and 6.99 (1H, s, H-5), a methoxyl group at δ_H 3.83 (3H, s, OCH_3-3), and two prenyl groups, one with a pair of *gem*-dimethyl protons at δ_H 1.79 (3H, s, CH_3-15) and 1.67 (3H, s, CH_3-14), a methine proton at δ_H 5.25 (1H, t, $J = 6.8$ Hz, H-12), and a methylene proton at δ_H 3.38 (2H, d, $J = 6.8$ Hz, H-11) and the other with a pair of *gem*-dimethyl protons at δ_H 1.89 (3H, s, CH_3-20) and 1.66 (3H, s, CH_3-19), a methine proton at δ_H 5.24 (1H, t, $J = 7.0$ Hz, H-17), and a methylene proton at δ_H 3.52 (2H, d, $J = 7.0$ Hz, H-16). The two prenyl groups were located at the C-2 and C-4 positions by the HMBC correlations between the benzylic methylene protons at δ_H 3.38 (H-11) and δ_C 162.9 (C-3), 158.6 (C-1), and 116.3 (C-2) as well as between the other benzylic methylene protons at δ_H 3.52 (H-16) and δ_C 162.9 (C-3), 153.1 (C-4a), and 112.6 (C-4). Futhemore, cross-peaks between the chelated hydroxyl group at δ_H 13.35 (1H, s, OH-1) and δ_C 158.6 (C-1), 116.3 (C-2), and 105.1 (C-9a) and between the methoxyl group at δ_H 3.83 and δ_C 162.9 (C-3) clearly suggested that a hydroxyl group and a methoxyl group were located at C-1 and C-3, respectively. Thus, the structure of compound **2** was identified as 1,6,7-trihydroxy-3-methoxy-2,4-di-(3-methylbut-2-enyl)xanthone, and it was named cudratricusxanthone K.

Compound **3**, obtained as a yellow and amorphous powder, had a molecular formula of $C_{18}H_{16}O_6$ as deduced from HRFABMS (*m/z* 351.0857 $[M + Na]^+$; calcd 351.0845). The ^1H NMR spectrum of **3** showed signals assignable to one chelated hydroxyl proton at δ_H 13.43, three aromatic proton singlets at δ_H 7.52 (1H, s, H-8), 6.92 (1H, s, H-5), and 6.27 (1H, s, H-2), and protons of a 1,1-dimethylallyl group at δ_H 6.37 (1H, dd, $J = 17.4$, 10.6 Hz, H-14), 5.02 (1H, dd, $J = 17.4$, 1.2 Hz, H-15a), 4.91 (1H, dd, $J = 10.6$, 1.2 Hz, H-15b), and 1.68 (6H, s, CH_3-12 and CH_3-13). The ^{13}C NMR spectrum of **3** showed signals assignable to one conjugated carbonyl carbon and six oxygenated quaternary carbons, together

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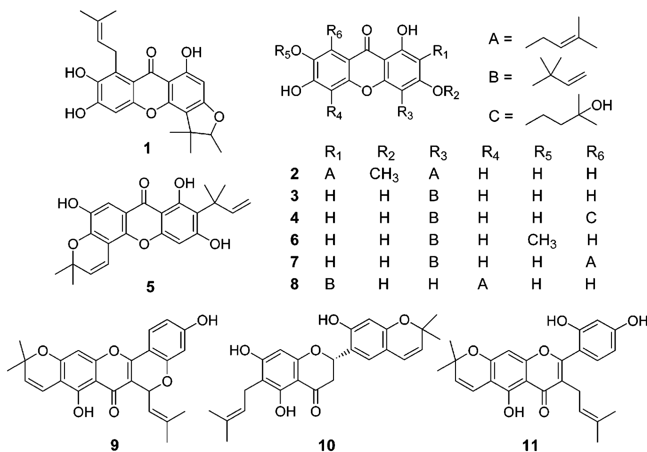

with signals belong to a 1,1-dimethylallyl group. The location of the 1,1-dimethylallyl side chain was assigned at C-4 on the basis of the HMBC correlations of C-4 with H-2, H-14, and the two tertiary methyls at CH_3-12 and CH_3-13. Thus, the structure of compound **3** was identified as 1,3,6,7-tetrahydroxy-4-(1,1-dimethylallyl)xanthone, and it was named cudratricusxanthone L.

Compound **4**, obtained as a yellow and amorphous powder, showed a molecular formula of $C_{23}H_{26}O_7$ by HRFABMS (*m/z* 437.1590 $[M + Na]^+$; calcd 437.1576). The ^1H NMR spectrum of **4** was almost identical to that of **3** except that an aromatic proton at δ_H 7.52 (H-8) of **3** was replaced in **4** by a 3-hydroxy-3-methylbutyl group [δ_H 3.45 (2H, m, CH_2-16), 1.88 (2H, m, CH_2-17), and 1.20 (6H, s, CH_3-19 and CH_3-20)]. In the HMBC spectrum, the long-range correlations of CH_2-16 (δ_H 3.45) with C-7 (δ_C 141.1), C-8 (δ_C130.4), and C-8a (δ_C 111.0) showed that the 3-hydroxy-3-methylbutyl group was attached to C-8. Thus, the structure of compound **4** was identified as 1,3,6,7-tetrahydroxy-4-(1,1-dimethylallyl)-8-(3-hydroxy-3-methylbutyl)xanthone, and it was named cudratricusxanthone M.

Seven compounds with previously known structures were also isolated from the CH_2Cl_2 extract of the stem bark of *C. tricuspidata*, as described in the Experimental Section. These were identified as isocudraxanthone K (**5**),[15] cudraxanthone C (**6**),[9] cudratricusxanthone A (**7**),[4,5] cudraxanthone L (**8**),[6] cudraflavone A (**9**),[13] cudraflavanone A (**10**),[14] and cudraflavone B (**11**)[13] by comparison of their physical and spectroscopic data with reported values.

Compounds **1**−**11** were evaluated for their potential to inhibit mouse brain MAO activity. The results demonstrated that cudratricusxanthone A (**7**), cudraflavanone A (**10**), and cudraflavone B (**11**) exhibited weak inhibitory activity, with IC_{50} values of 88.3, 89.7, and 80.0 μM, respectively, while the other compounds were inactive (IC_{50} values > 150 μM).

Experimental Section

General Experimental Procedures. Optical rotations were measured with a JASCO DIP-1000 polarimeter using MeOH as the solvent. The UV and IR spectra were recorded on JASCO UV-550 and Perkin-Elmer model LE599 spectrometers, respectively. HRFABMS and EIMS were obtained on JMS-HX110/110A and JMS 700 Mstation (JEOL, Tokyo, Japan) mass spectrometers, respectively. The ^1H, ^{13}C, and 2D NMR spectra were recorded on a Bruker AMX 500 MHz NMR spectrometer using acetone-d_6 as a solvent. Open column chromatography (CC) was performed using silica gel (Kieselgel 60, 70−230 mesh, Merck), Lichroprep RP-18 (40−63 μM, Merck), and Sephadex LH-20 (Pharmacia, Sweden). Thin-layer chromatography (TLC) was performed using precoated silica gel 60 F_{254} (0.25 mm, Merck) plates. Preparative HPLC was carried out using two Waters 515 pumps, a 2996 photodiode array detector, and a YMC J'sphere ODS-H80 column (4 μm, 150 × 20 mm i.d., YMC Co., Ltd.). The column was eluted with a mixed solvent system of ACN−H_2O at a flow rate of 6.5 mL/min.

Plant Material. The root bark of *Cudrania tricuspidata* was collected in the herb garden of the College of Pharmacy, Chungbuk National University, Cheongju, Korea, in October 2005, and the plant was identified by Emeritus Professor Kyong Soon Lee. A voucher specimen (CBNU-0502) was deposited at the Herbarium of the College of Pharmacy, Chungbuk National University, Korea.

Extraction and Isolation. The milled, air-dried root bark of *C. tricuspidata* (1.5 kg) was extracted with MeOH (10 L × 3) at room temperature, and the solution was evaporated in vacuo. The dried MeOH extract (150 g) was suspended in 90% MeOH and then partitioned with CH_2Cl_2 (2 L × 3) and EtOAc (2 L × 3). The CH_2Cl_2 extract (11 g), with 50% inhibitory activity at a concentration of 10 μg/mL in the MAO inhibition assay, was subjected to silica gel CC and eluted with a CH_2Cl_2−MeOH gradient system (100:0 to 1:1, v/v) to give four fractions (CT-A to CT−D). Fraction CT-A (3.1 g) was chromatographed over silica gel, using a hexane−acetone gradient system (100:0 to 0:100, v/v), and was fractionated into five subfractions (CT-A1 to CT-A5). Fraction CT-A4 (300 mg) was further chromatographed over silica gel with a CH_2Cl_2−MeOH gradient (100:0 to 1:1, v/v) and yielded the additional fractions CT-A41 to CT-A44. Fraction CT-A43 was further purified by preparative HPLC and eluted with ACN−H_2O (75:25) to yield isocudraxanthone K (**5**, t_R = 7.3 min, 8 mg) and cudraxanthone C (**6**, t_R = 11.2 min, 11 mg). Fraction CT-A5 (500 mg) was further separated by silica gel CC using a CH_2Cl_2−MeOH gradient (100:0 to 5:1, v/v), yielding fractions CT-A51 to CT-A53. Preparative HPLC of fraction CT-A52 (180 mg) using ACN−H_2O (70:30) yielded compound **1** (t_R = 14.4 min, 6 mg) and cudratricusxanthone A (**7**, t_R = 21.3 min, 71 mg). Fraction CT-C (4.3 g) was subjected to silica gel CC with a hexane−acetone gradient system (100:0 to 1:1, v/v) and afforded four subfractions (CT-C1 to CT-C4). Fraction CT-C1 (500 mg) was subjected to flash column chromatography on RP-18 and eluted with ACN−H_2O (1:1 to 100:0, v/v) to give cudraflavone A (**9**, 9.2 mg) and cudraflavanone A (**10**, 64.3 mg). Fraction CT-C3 (1.1 g) was further purified through a RP-18 column and eluted with ACN−H_2O (1:1 to 100:0, v/v) to yield three fractions (CT-C31 to CT-C33). Fraction CT-C32 was repeatedly chromatographed over Sephadex LH-20, eluted with MeOH−H_2O (1:1 to 100:1, v/v), affording cudraxanthone L (**8**, 150 mg) and cudraflavone B (**11**, 210 mg). Fraction CT-D (4.1 g) was further chromatographed over silica gel with a hexane−acetone gradient system (5:1 to 1:1, v/v) and yielded four combined fractions (CT-D1 to CT-D4). Fraction CT-D2 was subjected to flash column chromatography on RP-18 and eluted with ACN−H_2O (1:1 to 100:0, v/v) to give compound **2** (10.5 mg). Fraction CT-D4 was further chromatographed over Sephadex LH-20 and eluted with MeOH−H_2O (60:40 to 100:0, v/v) to yield six subfractions (CT-D41 to CT-D46). Fraction CT-D44 and CT-D46 were further purified by preparative HPLC and eluted with ACN−H_2O (45:55) to yield compounds **3** (t_R = 37.1 min, 10.2 mg) and **4** (t_R = 49.5 min, 8.6 mg).

Cudratricusxanthone J (1): yellow, amorphous powder; $[\alpha]^{25}_D$ −13.6 (*c* 0.012, MeOH); UV (MeOH) λ_{max} (log ϵ) 239 (4.2), 259 (4.3), 317 (4.1), 365 (3.7) nm; ^1H NMR (acetone-d_6, 500 MHz) δ 14.35 (1H, s, OH-1), 6.71 (1H, s, H-5), 6.02 (1H, s, H-2), 5.37 (1H, m, H-17), 4.47 (1H, q, J = 6.5 Hz, H-14), 4.15 (2H, br d, J = 6.5 Hz, CH_2-16), 1.83 (3H, s, CH_3-20), 1.62 (3H, br s, CH_3-19), 1.50 (3H, s, CH_3-13), 1.36 (3H, d, J = 6.5 Hz, CH_3-15), 1.22 (3H, s, CH_3-12); ^{13}C NMR (acetone-d_6, 125 MHz), see Table 1; EIMS *m/z* 396 (90), 381 (83), 353 (100), 341 (49), 325 (68), 285 (73); HRFABMS *m/z* 397.1672 $[M + H]^+$ (calcd for $C_{23}H_{25}O_6$, 397.1651).

Cudratricusxanthone K (2): yellow, amorphous powder; UV (MeOH) λ_{max} (log ϵ) 232 (4.0), 258 (4.3), 303 (3.8), 380 (3.7) nm; IR (KBr) ν_{max} 3464, 1634, 1595, 1514 cm^{-1}; ^1H NMR (acetone-d_6, 500 MHz) δ 13.35 (1H, s, OH-1), 7.56 (1H, s, H-8), 6.99 (1H, s, H-5), 5.25 (1H, t, J = 6.8 Hz, H-12), 5.24 (1H, t, J = 7.0 Hz, H-17), 3.83 (3H, s, OCH_3-3), 3.52 (2H, d, J = 7.0 Hz, CH_2-16), 3.38 (2H, d, J = 6.8 Hz, CH_2-11), 1.89 (3H, s, CH_3-20), 1.79 (3H, s, CH_3-15), 1.67 (3H, s, CH_3-14), 1.66 (3H, s, CH_3-19); ^{13}C NMR (acetone-d_6, 125 MHz), see Table 1; HRFABMS *m/z* 411.1785 $[M + H]^+$ (calcd for $C_{24}H_{27}O_6$, 411.1808).

Cudratricusxanthone L (3): yellow, amorphous powder; UV (MeOH) λ_{max} (log ϵ) 240 (4.1), 258 (4.3), 319 (3.9), 368 (3.7) nm; IR (KBr) ν_{max} 3435, 1633, 1592, 1510 cm^{-1}; ^1H NMR (acetone-d_6, 500 MHz) δ 13.43 (1H, s, OH-1), 7.52 (1H, s, H-8), 6.92 (1H, s, H-5), 6.37 (1H, dd, J = 17.4 and 10.6 Hz, H-14), 6.27 (1H, s, H-2), 5.02 (1H, dd, J = 17.4 and 1.2 Hz, H-15a), 4.91 (1H, dd, J = 10.6 and 1.2 Hz, H-15b), 1.68 (6H, s, CH_3-12 and 13); ^{13}C NMR (acetone-d_6, 125 MHz), see Table 1; HRFABMS *m/z* 351.0857 $[M + Na]^+$ (calcd for $C_{18}H_{16}O_6Na$, 351.0845).

Table 1. ^{13}C NMR Spectroscopic Data for Compounds **1**−**4**[a]

position	**1**	**2**	**3**	**4**
1	164.6	158.6	162.0	162.2
2	92.8	116.3	99.4	99.2
3	165.0	162.9	163.8	163.4
4	111.8	112.6	111.5	110.7
4a	158.6	153.1	163.8	155.8
4b	152.8	152.1	152.1	153.5
5	100.6	102.7	103.0	100.6
6	154.2	153.8	154.1	153.0
7	143.7	143.3	143.9	141.1
8	130.2	108.3	108.6	130.4
8a	108.7	112.7	113.1	111.0
9	182.4	180.5	180.8	183.2
9a	104.0	105.1	103.5	104.2
11	44.1	22.2	41.6	41.4
12	21.4	122.9	30.3	30.3
13	25.8	131.1	30.3	30.3
14	90.9	24.9	151.3	151.3
15	14.6	17.2	107.8	107.7
16	26.3	22.4		22.2
17	125.1	122.9		43.8
18	130.2	130.8		70.9
19	25.8	24.9		30.0
20	18.1	17.1		30.0
OCH$_3$-3		61.4		

[a] Carbon chemical shifts (ppm) were recorded at 125 MHz using acetone-d_6 as a solvent. Assignments were based on COSY, HMQC, and HMBC experiments.

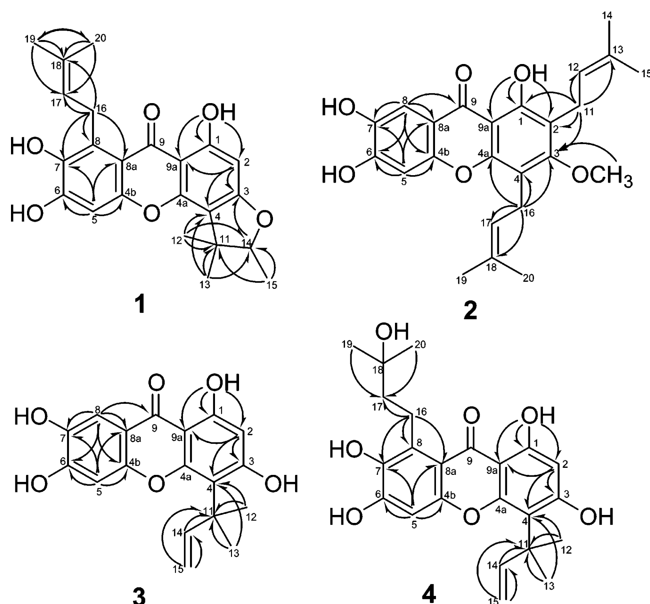

Figure 1. HMBC correlations for compounds **1**−**4**.

Cudratricusxanthone M (4): yellow, amorphous powder; UV (MeOH) λ_{max} (log ϵ) 239 (4.1), 260 (4.3), 318 (3.9), 365 (3.7) nm; IR (KBr) ν_{max} 3432, 1635, 1590, 1504 cm^{-1}; ^{1}H NMR (acetone-d_6, 500 MHz) δ 13.77 (1H, s, OH-1), 6.80 (1H, s, H-5), 6.24 (1H, s, H-2), 6.36 (1H, dd, J = 17.4 and 10.6 Hz, H-14), 5.01 (1H, dd, J = 17.4 and 1.2 Hz, H-15a), 4.90 (1H, dd, J = 10.6 and 1.2 Hz, H-15b), 3.45 (2H, t, J = 7.3 Hz, CH$_2$-16), 1.88 (2H, t, J = 7.3 Hz, CH$_2$-17), 1.66 (6H, s, CH$_3$-12 and 13), 1.20 (6H, s, CH$_3$-19 and 20); ^{13}C NMR (acetone-d_6, 125 MHz), see Table 1; HRFABMS m/z 437.1590 [M + Na]$^+$ (calcd for $C_{23}H_{26}O_7Na$, 437.1576).

MAO Preparation and Assay for MAO Inhibitory Activity. Mouse brain mitochondrial fraction was prepared as a source of MAO activity following the procedure described previously.[19,20] MAO activity was measured fluorometrically using kynuramine as a substrate according to the method of Kraml with a slight modification.[20,21] The fluorescence intensity of 4-hydroxyquinoline, which was formed from kynuramine by MAO, was measured at an emission wavelength of 380 nm and an excitation wavelength of 315 nm using a Perkin-Elmer LS 50B fluorescence spectrometer. The tested compounds were dissolved in dimethyl sulfoxide (DMSO), which was found to have no effect on MAO activity at below 3% concentration. Iproniazid was used as a positive control (IC$_{50}$ value 19.7 μM).

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