Structural Studies on Stilbene Oligomers Isolated from the Seeds of Melinjo (Gnetum gnemon L.)

Hiroko Tani, Hiroyuki Koshino, Tohru Taniguchi, Maiko Yoshimatsu, Susumu Hikami, and Shunya Takahashi*

ABSTRACT: This paper describes the isolation and structural determination of a new stilbene dimer, named 7α-epi-gnetin C, from melinjo (Gnetum gnemon L.) seed extract. The relative structure was elucidated based on NMR spectroscopic evidence, while the absolute configuration was assigned by a combination of NMR and electronic circular dichroism spectroscopic analysis and chemical conversion. 7α-epi-Gnetin C was evaluated as an antioxidant and was shown to have a comparable activity to the known stilbene oligomers. In addition, the structural revision of gnetin L, a known stilbene dimer, was also discussed.

INTRODUCTION

Gnetum gnemon L. is a species of the Gnetaceae family commonly called melinjo in Indonesia, known to be rich in resveratrol derivatives. Its fruit and seeds are used as ordinary food in Indonesia and their extracts have been reported to show several pharmacological activities from in vitro to human studies.1–6 A stilbene monomer, trans-resveratrol (8) and stilbene oligomers such as gnetin C (4), gemonoside A (5), gemonoside C (6), gemonoside D (7), gnetin L, and gnetin E (9) have been isolated from the fruit and/or seeds (Figure 1).7–9 The oligomers possess a 1,2-diaryldihydrobenzofuran skeleton as a basic structural motif. The relative stereochemistry of two chiral centers in the core has been assigned by NOE experiment,1,2,7–9 whereas the absolute configuration has been traditionally elucidated by comparison of its electronic circular dichroism (ECD) spectrum with that of known structures.10–12 In our ongoing search for biologically active components from melinjo seed extract (MSE), we isolated a new minor epimer of 4, termed 7α-epi-gnetin C (1) along with known compounds as shown in Figure 1. In this paper, we report the elucidation of structure 1 and structural revision of gnetin L (2) to the regioisomer 3. In addition, a series of resveratrol derivatives shown in Figure 1 were subjected to the oxygen radical absorbance capacity (ORAC) assay and evaluated as an antioxidant.

RESULTS AND DISCUSSION

The seeds (endosperms) of melinjo (G. gnemon L.), collected in Indonesia, were powdered and extracted with 55% aqueous EtOH. MSE with enzymatic hydrolysis of glucosides was successively subjected to ODS column chromatography, silica gel column chromatography, and reversed phase HPLC to give 1. The existence of 1 in the MSE was confirmed by analytical HPLC analysis before being treated with the enzyme. The molecular formula of 1 was established as C28H22O6 by HRESI-MS spectrum (m/z: 477.1313 [M + Na]+; calcld for C28H22O6Na, 477.1314). The 1H and 13C NMR data ensured a molecule of 1 to C-11b and C-12b, which indicated that 1 possessed the same planar structure as that of 4 (Table 1). The coupling constant between H-7a and H-8a for 1 is 8.3 Hz, whereas for 4 is reported to be 4.5 Hz.7 These values were diagnostic and the same as the values reported for cis-dihydrobenzofuran and its trans isomer derived from (-)-ε-viniferin,13 and the cis- and trans-dihydrobenzofuran moieties included in suffruticosol D from Pacionia suffruticosa,14 indicating that 1 is in a cis-form on the dihydrofuran ring. In comparison between 1H NMR chemical shifts of 1 (Table 1) and those of 4 (Table S3), the cis orientation of A1 and A2 rings in 1 causes up-field shifts for aromatic ring signals of H-2a (Δ −0.22 ppm), H-3a (Δ −0.23 ppm), H-10a (Δ −0.44 ppm), and H-12a (Δ −0.22 ppm) by stacking effects. In addition, the NOESY correlations between...
vicinal H-7a and H-8a and between two aromatic groups H-2a (6a) and H-10a (14a) further supported a cis-orientation.

The absolute configuration of 1 was determined by the optical data comparison of a phenol derivative 10 derived from both 1 and 4. Namely, treatment of 1 with a Pd/C catalyst under hydrogen atmosphere at room temperature underwent a reductive opening of the tetrahydrofuran ring at C-7a to give 10 \(\{[^{\alpha}_D^{-}25-60.8 (c 0.02, MeOH)\}\) (Scheme 1). Its \(^1\)H and \(^{13}\)C NMR data were identical with those of the reduction product prepared\(^{15}\) from 4, and its optical rotation was also nearly equal in sign and magnitude\(^{16}\) to that of 10 \(\{[^{\alpha}_D^{-}25-66.8 (c 0.11, MeOH)\}\) derived from 4 \(\{[^{\alpha}_D^{-}25-18.5 (c 0.1, MeOH)\}\), indicating that the configuration of C-8a of 1 was the same as 4. Therefore, 1 was determined to be the C-7a epimer of 4.

The absolute configuration of (−)-gnetin C (shown as 4 in Figure 1) was reported to be 7aS,8aS by a vibrational circular dichroism (VCD) study.\(^{17}\) We independently ensured this assignment using a fully methylated benzaldehyde derivative, 12 prepared from 4 via 11 (Scheme 2). This compound was designed in order to suppress the effect of hydrogen bonding\(^{18}\) and the free rotation of a terminal styryl unit. As expected, the experimental ECD spectrum of 12 showed good agreement with the calculated one for (7aS,8aS)-12 at ca. 210 nm, a strong positive band at ca. 245 nm, a broad negative band at ca. 280 nm, and a broad positive band at ca. 325 nm (Figure 2).

Meanwhile, the theoretical ECD spectrum calculated for (7aR,8aS)-12 exhibited a different feature to that of the experimental one. From these results, the absolute configuration of the parent compound 4 was unambiguously assigned as 7aS,8aS, which is consistent with the previous result.\(^{17}\) Thus, the absolute configuration of the new compound 1 was determined as 7aR,8aS.

In the course of identifying other isolated compounds, we found that NMR spectral data in acetone-\(d_6\) of 3 was almost identical to those of gnetin L (2)\(^{2}\) with a 3-hydroxy-5-methoxyphenyl group. The \(^1\)H NMR spectra of the isolated 3 in acetone-\(d_6\) chemical shifts of some aromatic signals were overlapped and second order effects were observed. To clarify the substitution pattern of aromatic rings, we tried to measure \(^1\)H NMR spectra in several solvent systems. The \(^1\)H NMR

| position | \(\delta_C\) | \(\delta_H\) (J in Hz) | HMBC | NOE |
|----------|-------------|------------------------|------|-----|
| 1a       | 129.05      |                        |      |     |
| 2a (6a)  | 129.05      | 7.00 (2H, d, J = 8.7 Hz) | 1a, 4a, 6a, 7a | 3a (5a), 7a, 10a (14a) |
| 3a (5a)  | 115.1       | 6.61 (2H, d, J = 8.7 Hz) | 1a, 5a | 2a (6a) |
| 4a       | 117.4       |                        |      |     |
| 7a       | 90.3        | 5.85 (1H, d, J = 8.3 Hz) | 1a, 2a (6a), 9a | 2a (6a), 8a |
| 8a       | 51.7        | 4.56 (1H, d, J = 8.3 Hz) | 9a, 10a (14a), 11b, 12b | 7a, 10a (14a) |
| 9a       | 142.2       |                        |      |     |
| 10a (14a)| 108.6       | 5.73 (2H, d, J = 2.3 Hz) | 8a, 12a | 2a (6a), 8a |
| 11a (13a)| 158.7       |                        | 10a (14a), 12a |     |
| 12a      | 101.6       | 5.99 (1H, t, J = 2.3 Hz) | 10a (14a), 11a |      |
| 1b       | 130.0       |                        |      |     |
| 1b (6b) | 128.7       | 7.45 (2H, d, J = 8.2 Hz) | 4b, 6b, 7b | 7b, 8b |
| 3b (5b) | 116.4       | 6.86 (1H, d, J = 8.2 Hz) | 1b, 4b, 5b |     |
| 4b       | 158.3       |                        |      |     |
| 7b       | 129.13      | 7.11 (1H, d, J = 16.5 Hz) | 2b (6b), 8b, 9b | 2b (6b), 10b, 12b |
| 8b       | 126.8       | 6.99 (1H, d, J = 16.5 Hz) | 7b, 10b, 14b | 2b (6b), 10b, 14b |
| 9b       | 140.8       |                        |      |     |
| 10b      | 99.3        | 6.72 (2H, d, J = 0.9 Hz) | 8b, 11b, 12b, 14b | 7b, 8b |
| 11b      | 162.9       |                        |      |     |
| 12b      | 117.1       |                        |      |     |
| 13b      | 155.3       |                        |      |     |
| 14b      | 108.3       | 6.62 (2H, d, J = 0.9 Hz) | 8b, 10b, 12b, 13b | 7b, 8b |
| 11a (13a)| 13a-OH     | 7.85 (2H, s) | 10a (14a), 12a |     |

The absolute configuration of 1 was determined by the optical data comparison of a phenol derivative 10 derived from both 1 and 4. Namely, treatment of 1 with a Pd/C catalyst under hydrogen atmosphere at room temperature underwent a reductive opening of the tetrahydrofuran ring at C-7a to give 10 \(\{[^{\alpha}_D^{-}25-60.8 (c 0.02, MeOH)\}\) (Scheme 1). Its \(^1\)H and \(^{13}\)C NMR data were identical with those of the reduction product prepared\(^{15}\) from 4, and its optical rotation was also nearly equal in sign and magnitude\(^{16}\) to that of 10 \(\{[^{\alpha}_D^{-}25-66.8 (c 0.11, MeOH)\}\) derived from 4 \(\{[^{\alpha}_D^{-}25-18.5 (c 0.1, MeOH)\}\), indicating that the configuration of C-8a of 1 was the same as 4. Therefore, 1 was determined to be the C-7a epimer of 4.

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spectra of 3 in CD$_3$CN, the three proton signals in the A$_1$ ring were observed at 6.76, 6.80, and 6.92 ppm as doublet of doublets ($J = 7.8, 1.8$ Hz), doublet ($J = 7.8$ Hz), and doublet ($J = 1.8$ Hz), respectively (Figure 3). The ortho-coupling protons at $\delta_H$ 6.76 and 6.80 ($J = 7.8$ Hz) and meta-coupling protons at $\delta_H$ 6.76 and 6.92 ($J = 1.8$ Hz) proposed an ABX system of 4-hydroxy-3-methoxyphenyl group for the A$_1$ ring. In addition, the HMBC correlation peak from the hydroxy proton signal at $\delta_H$ 6.57 (1H, s) to $\delta_C$ 115.6 (C-5a) indicated that the hydroxy group was attached to the C-4a position (Figure 4). Thus, we concluded that the structure of natural gnetin L should be revised to be the regioisomer 3. This structural revision of gnetin L (3) revealed that gnetin L$_2$ and the later reported macrostachyol D by Sri-in et al. in 2011 were identical.$^{19}$

Finally, we have tested the antioxidant activities of the new as well as known compounds, as it is well known that polyphenols have potentially high antioxidant activities.$^{20}$ As listed in Table 2, all tested compounds showed stronger ORAC activity compared with L-ascorbic acid (Table 2). Compounds 1 and 3 were less active than 4, indicating that a change in the
Plant Material. The seeds (endosperms) of melinjo were collected in Indonesia (Desa Bangkok, Kecamatan Gurah Kabupaten Kediri, Kediri, Jawa Timur) in July 2009 and have been identified by Dr. Eishin Kato. Voucher specimens (number 090716) have been deposited at Hosoda SHC Co. Ltd., Fukui, Japan.

Extraction and Isolation. The preparation of MSE and isolation of 4–7 were performed based on the modified method reported by Kato et al. In brief, the powder of dried endosperms of melinjo was extracted with 55% aqueous ethanol, and the MSE (23.0 g) was subjected to ODS column chromatography, silica gel column chromatography, and recrystallization and/or preparative HPLC to give 4 (0.19 g), 5 (1.15 g), 6 (62 mg), and 7 (0.23 g).

The MSE (150 g) was treated with 3 g of β-glucosidase in 0.02 M citric acid (12 L) at 40 °C for 24 h. The hydrolyzed residue (120 g) was subjected to Daiso Gel column chromatography (Daiso gel IR-60, 600 mm × 80 mmID) with 9 L (each 1 L/fraction) of 6, 12, and 25% MeOH in CHCl₃ as the eluent. The fraction eluted with 25% MeOH in CHCl₃ was further purified by MPLC using ODS column chromatography (Hi-Flash Column ODS-SM, 100 mm × 26 mmID, Yamazen) using aqueous MeOH (20–80%, 54 min linear, 100%, 10 min hold) with 0.1% TFA as the eluent at a flow rate of 15 mL/min (15 mL × 64). Fraction 31–33 was then purified by preparative HPLC using aqueous MeOH (48–50%, 60 min linear, 50–55%, 60 min linear, 55%, 30 min hold) with 0.1% TFA as a flow rate of 7.5 mL/min to give 9 (tᵣ = 124 min, 1.82 mg ≥ 99% HPLC). Furthermore, the hydrolyzed residue (70 g) was subjected to ODS column chromatography (Cosmosil 75C₁₈-PREP, 400 mm × 80 mmID, Nacalai Tesque) with 6 L (each 1 L/fraction) of 20, 40, 60, and 100% aqueous MeOH. The third and fourth fractions eluted with 40% aqueous MeOH were subjected to MPLC using ultra pack silica gel column (300 mm × 37 mmID, Yamazen) with MeOH (10%, 15 min hold, 10–20%, 45 min linear, 20–50%, 45 min linear, 50%, 60 min hold) in CHCl₃ as the eluent at a flow rate of 20 mL/min (20 mL × 120). Fraction 27–30 was further purified by preparative HPLC using aqueous MeOH (43–46%, 30 min linear, 46%, 15 min hold) with 0.1% TFA as a flow rate of 7.5 mL/min to give fractions that eluted at 117 and 133 min to give 1 (1.82 mg ≥ 99% HPLC) and 3 (3.59 mg ≥ 99% HPLC), respectively.

7α-epi-Gnetin C (1): [α]₀̊ D = +26 (c 0.11, MeOH); IR (ZnSe) νₘₚₐₖ: 3235, 2932, 2840, 1670, 1595, 1509, 1448, 1429, 1251, 1194, 1142, 998, 821, and 799 cm⁻¹; ¹H and ¹³C NMR (600 and 150 MHz, acetone-d₆), see Table 1; HRERM S m/z: 477.1313 [M + Na]⁺ (calcld for C₂₃H₂₂O₅Na, 477.1314).

Gnetin L (3): ¹H and ¹³C NMR (600 and 150 MHz, CD₃CN), see Table S2.

Gnetin E (9): ¹H and ¹³C NMR (600 and 150 MHz, acetone-d₆), see Table S2.

Analysis of Resveratrol Derivatives. Analysis of resveratrol derivatives in MSE was performed by the Prominence HPLC system (Shimadzu) with a Cosmosil SC₁₈AR-II column (250 mm × 4.6 mmID, Nacalai Tesque), following the analysis conditions previously reported. The contents of dimer derivatives in MSE were as follows: 1.5 mg/g, 2.2 mg/g, 3, 28 mg/g, 4, 101 mg/g, 5, 16 mg/g, 6, 48 mg/g, 7, and 0.3 mg/g.

(5)-2-(1-(3,5-Dihydroxyphenyl)-2-(4-hydroxyphenyl)ethyl)-5-(4-hydroxyphenethyl)benzene-1,3-diol (10).
From 4. To a stirred solution of gnetin C (10.2 mg, 22.4 μmol) in ethyl acetate (2.0 mL) was added 10% Pd/C (161 mg). The mixture was stirred vigorously under a hydrogen atmosphere at room temperature (rt) for 2 h, filtered through a pad of Celite, and then concentrated. The residue was purified by preparative TLC (dichloromethane/methanol = 10:1, 3 developments) to give 10 (7.0 mg, 68%) as an amorphous solid: [α]D25 –66.8 (c 0.11, MeOH); IR (ZnSe) νmax 3200, 2920, 2843, 1590, 1510, 1423, 1240, 1219, 1142, 1000, and 818 cm−1; 1H NMR (500 MHz, CDCl3; δ 6.95 (2H, d, J = 8.6 Hz), 6.91 (2H, d, J = 8.6 Hz), 6.65 (2H, d, J = 8.6 Hz), 6.55 (2H, d, J = 8.6 Hz), 6.46 (2H, brd, J = 2.2 Hz), 6.04 (2H, s), 6.02 (1H, t, J = 2.2 Hz), 4.65 (1H, dd, J = 9.5, 6.6 Hz), 3.53 (1H, dd, J = 13.4, 9.5 Hz), 3.26 (1H, dd, J = 13.4, 6.6 Hz), 2.74–2.66 (2H, m), and 2.59–2.55 (2H, m); 13C NMR (150 MHz, CD3OD): δ 158.5, 157.6, 156.3, 155.7, 149.6, 142.2, 134.6, 134.3, 130.9, 130.4, 116.2, 116.0, 115.4, 108.34, 108.26, 100.6, 43.4, 39.3, 38.5, and 38.1; HRESIMS m/z: 481.1620 [M + Na]+ (calcld for C28H26O6Na, 481.1627).

From 1. To a stirred solution of 1 (1.10 mg, 2.42 μmol) in methanol (0.5 mL) was added 10% Pd/C (2.5 mg). The mixture was stirred vigorously under a hydrogen atmosphere at rt for 9 h, filtered through a pad of Celite, and then concentrated. The residue was purified by preparative TLC (dichloromethane/methanol = 10:1, 5 developments) to give 10 (0.61 mg, 55%) as an amorphous solid whose spectral data were identical with those of an authentic sample derived from gnetin C: [α]D25 –60.8 (c 0.02, MeOH); HRESIMS m/z: 481.1627 (calcld for C29H28O6Na [M + Na]+, 481.1627).

Permethylation of Gnetin C (11). To a stirred suspension of 4 (10.4 mg, 22.9 μmol) and potassium carbonate (61 mg, 441 μmol) in acetone (0.5 mL) was added methyl iodide (27.4 μL, 441 μmol), and the mixture was stirred under reflux for 2 h. More methyl iodide (27.4 μL, 441 μmol) and acetone (0.5 mL) were added and the reaction was further continued for 3 h. After cooling to rt, the reaction mixture was concentrated, diluted with dichloromethane/methanol (20:1), filtered through a pad of Celite, and then concentrated. The residue was purified by preparative TLC (n-hexane/ethyl acetate = 2:1, 3 developments) to give 11 (11.2 mg, 97%) as an amorphous solid: [α]D25 +1.2 (c 0.41, CHCl3); IR (ZnSe) νmax 2920, 2820, 1583, 1505, 1453, 1420, 1241, 1165, 1150, 1023, 821, and 741 cm−1; 1H NMR (500 MHz, CDCl3), see Table S3; 13C NMR (125 MHz, CDCl3): δ 191.6, 161.5, 160.9, 159.7, 157.3, 144.2, 139.1, 133.2, 126.8, 123.0, 114.1, 105.6, 105.3, 104.3, 98.7, 93.2, 55.7, 55.6, and 55.3; HRESIMS m/z: 443.1473 [M + Na]+ (calcld for C31H28O6Na, 443.1471).

ECD Calculation. ECD calculations of (7αS,8αS)-12 were initiated with a preliminary MMFF conformational search on a Spartan 10 program.23 The lower energy conformers within 2.4 kcal/mol from the most stable were optimized at the DFT/B3LYP/6-31G(d) level using a Gaussian 09 program.24 The resultant stable conformers within 2.0 kcal/mol, from the most stable ones, were further submitted to a DFT/B3LYP/6-311G(d,p) optimization considering the solvent effects. The ECD spectra of the obtained 10 conformers within 1.0 kcal/mol, from the most stable ones, were calculated at the TDDFT/B3LYP/6-311G(d,p) level. The first 55 singlet → singlet electronic transitions were considered. The calculated ECD spectra in Δε unit were obtained by using Gaussian band shapes with 0.15 eV half-width at 1/ε of peak height.

ORAC Assay. The ORAC analysis has been performed following the method25 reported by Shimizu et al. with minor modifications. In brief, a sample was dissolved directly in an ethanol/water mixture (50:50, v/v) and diluted with phosphate buffer (75 mM, pH 7.4). The sample solution (20 μL) was transferred to a 96-well microplate, and then fluorescein (200 μL, 94.4 nM) and AAPH (75 μL, 63.4 mM) were added and mixed. Phosphate buffer (75 mM, pH 7.4) was used as a blank solution, and Trolox as the standard solution. The assay was carried out on a FLUOstar OPTIMA plate reader utilizing fluorescence filters with 485 nm excitation and 520 nm emission. The antioxidant capacity of the sample was calculated as mmol Trolox equivalent per mol (mmol TE/mol).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c00910.

1H and 13C NMR spectra for 1, 3, 10, 11, and 12; FT-IR and MS spectra for 1; and NMR data for 3, 4, 9, 11, and 12 (PDF)

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Notes
The authors declare no competing financial interest.

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