[Chem. Pharm. Bull.
33(8)3293—3298(1985)]

Tannins and Related Compounds. XXXIII.[1] Isolation and Characterization of Procyanidins in *Dioscorea cirrhosa* LOUR.

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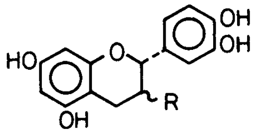
(Received December 10, 1984)

Dimeric, trimeric and tetrameric procyanidins have been isolated, together with (+)-catechin (**1**) and (−)-epicatechin (**2**), from the tubers of *Dioscorea cirrhosa* LOUR. (Dioscoreaceae). By comparisons of the physical and spectral data, the dimers (**3**—**5**), trimers (**6**—**8**) and tetramer (**9**) were identified as procyanidins obtained previously. The structures of two other trimers (**10** and **11**) were established by acid-catalyzed thiolytic degradation, while the formation of the tetramer (**12**) by condensation of the 4-carbocation of **1** with **6**, in conjunction with ^{1}H- and ^{13}C-nuclear magnetic resonance examinations, established the structure of **12**.

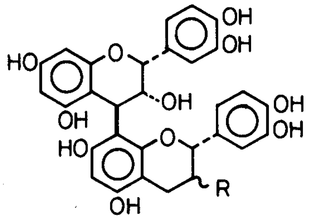
Keywords——*Dioscorea cirrhosa*; Dioscoreaceae; yam tuber; flavan-3-ol; procyanidin; condensed tannin; thiolytic degradation; syntheis

In some species of yam (Dioscorea) tubers, rapid browning reactions occur when the tissues are injured and exposed to air.[2] This type of browning has generally been interpreted in terms of the oxidation of phenolic constituents, especially that of *o*-dihydroxy or *vic*-trihydroxyphenolics, by a phenol oxidase present in the tissues.[3] Earlier work on yam tubers showed the occurrence of several phenolic compounds, *i.e.*, anthocyanidins[4] and highly conjugated diarylheptanoids.[5] However, these compounds are deeply colored in themselves and may not be responsible for the browning reactions. More recently, in the edible yam, *Dioscorea alata* L., (+)-catechin and accompanying procyanidins, together with catecholamine, have been reported to be the main substances involved in the enzymatic browning, although the constitution of the procyanidins remains to be clarified except for the dimers.[6] As part of our chemical studies on tannins and related compounds, we have examined the polyphenolic constituents of *Dioscorea cirrhosa* LOUR., which is the most sensitive to browning among yam species distributed in Japan and Taiwan; the tubers have been reported to possess hemostatic and antibacterial activities[7] and are utilized for dyeing fishing nets.[8] This work has resulted in the isolation of several procyanidin dimers, trimers and tetramers, in addition to (+)-catechin and (−)-epicatechin. We now wish to report the isolation and characterization of these compounds.

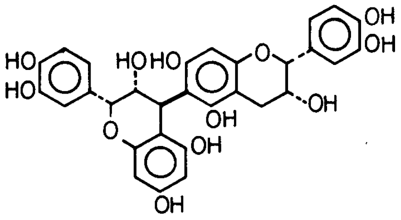
Initial fractionation of the phenolic constituents obtained by acetone extraction of the fresh tubers of *D. cirrhosa* (collected in Taiwan) was achieved by chromatography over Sephadex LH-20 with water containing increasing proportions of methanol. From the fraction eluted earlier, some simple phenolic glycosides such as a 3,4-dihydroxyphenethyl alcohol glucoside and a phloroglucinol glucoside were obtained. A mixture of (+)-catechin (**1**) and (−)-epicatechin (**2**) was eluted in the next fraction, and clear-cut separation of these compounds was accomplished by MCI-gel CHP-20P chromatography. Application of similar chromatography to the separation of dimeric procyanidins yielded the known procyanidins B-1 (**3**),[9] B-2 (**4**)[9] and B-5 (**5**),[10] whose structures were confirmed by direct comparisons of their physical and spectral data with those of authentic specimens obtained previously. Procyanidin trimers and tetramers, which were less mobile on Sephadex LH-20 chromatography, were separated by using chromatographic techniques similar to those outlined in previous papers.[1,11] Of the seven oligomeric procyanidins isolated, the chromatographic properties and the ^{1}H-nuclear magnetic resonance (^{1}H-NMR) data of the trimer (**6**) coincided with those of procyanidin C-1[10] [epicatechin-(4β-8)-epicatechin-(4β-8)-epicatechin],[12] while the trimers (**7** and **8**) were found to be identical with catechin-(4α-6)-epicatechin-(4β-8)-epicatechin and epicatechin-(4β-6)-epicatechin-(4β-8)-catechin obtained previously from *Rhaphiolepis umbellata*[13] and *Kandelia candel*,[11] respectively. In addition, one of the tetramers was identified as the procyanidin (**9**), consisting entirely of 4,8-linked epicatechin units, isolated from *Cinnamomum cassia* bark.[14]



R
1 : —OH
2 : ---OH



R
3 : —OH
4 : ---OH



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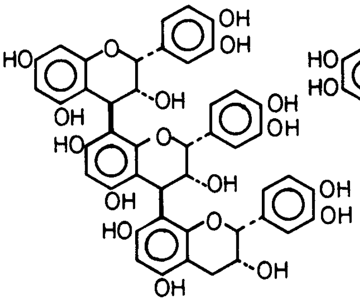

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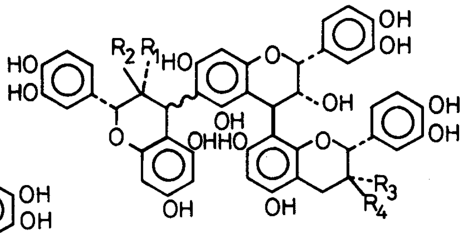
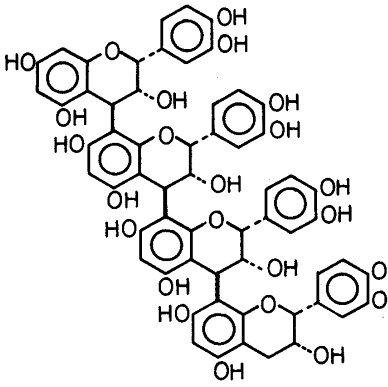


	R1	R2	R3	R4	∼
7 :	H	OH	OH	H	---
8 :	OH	H	H	OH	—



9

Whereas most of the linearly linked procyanidins so far obtained were off-white amorphous powders, the trimer (**10**) was isolated in a crystalline form, mp 215 °C (dec.). The ^{1}H-NMR spectrum of **10** was complicated by conformational isomerism,[15] and provided no information on the structure. However, owing to the existence of unequal proportions of conformers, the ^{13}C-nuclear magnetic resonance (^{13}C-NMR) signals arising from the major conformer could be assigned. The appearance of six major peaks (see Experimental) attributable to flavan C-2 and C-3 confirmed its triflavanoid constitution. The chemical shift (δ 81.7) of one of the C-2 signals was consistent with that (δ 82.3) found in **1**, suggesting the presence of a flavan unit with 2,3-*trans* configuration.[15b] Furthermore, at least one epicatechin unit was shown to be located in the molecule by the C-2 resonance (δ 78.1), which is analogous to that (δ 79.3) of **2**.

A definitive structural assignment of **10** was made by acid-catalyzed degradation with benzylmercaptan.[15a] Complete degradation afforded **2** and three benzylthioethers (**13**, **14** and **15**). The structures of these benzylsulfides were corroborated by comparisons of their physical and ^{1}H-NMR data with those of authentic samples.[11] Thus, **10** was shown to possess (+)-catechin and (−)-epicatechin units in the upper procyanidin units, and (−)-epicatechin as the

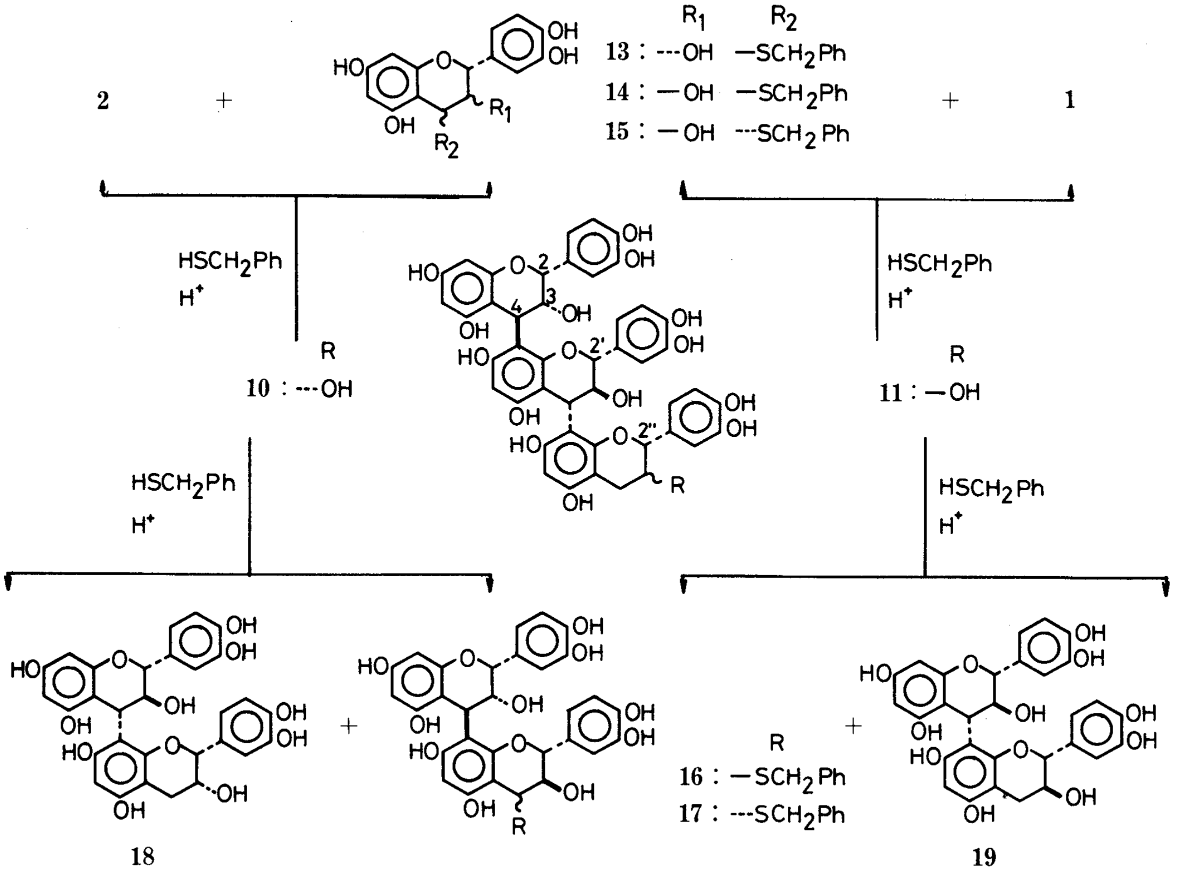


Chart 1

terminal unit. Partial thiolytic degradation yielded, in addition to the above products, two dimeric benzylsulfides (**16** and **17**) and procyanidin B-4 (**18**),[16] the structures of the former two compounds being confirmed by ^{1}H-NMR examinations and by their conversion with Raney nickel to **3**. On the basis of this chemical evidence, the structure of **10** was established unequivocally as epicatechin-(4β→8)-catechin-(4α→8)-epicatechin.

Application of similar thiolytic degradation to another trimer (**11**) (see Chart 1) enabled the constitution and the mode of interflavanoid linkages to be established as epicatechin-(4β→8)-catechin-(4α→8)-catechin. Compound **11** has also been isolated from *Areca catechu*, *Quercus miyagii* and *Eucalyptus* species in our laboratory.[17]

In contrast to the above-mentioned trimers, compound **12** provided interpretable ^{1}H- and ^{13}C-NMR spectra showing straightforward signal patterns. The lowfield flavan H-2 signals [δ 5.28 (2H), br s and δ 5.07 (1H) br s] were readily distinguished from other C-ring signals, the chemical shifts being similar to those [δ 5.15 (2H), br s and δ 5.05 (1H), br s] found in **6**. Another H-2 signal appeared at δ 4.62 as a doublet ($J = 8$ Hz), suggesting the presence of a flavan-3-ol unit with 2,3-*trans* configuration. Besides the presence of additional signals due to an epicatechin moiety, the ^{1}H-NMR spectrum resembled that of **7**. In particular, the chemical shifts [δ 5.90 (2H), s; δ 6.05 (2H), s and δ 6.12 (1H), s] of the A-ring protons agreed with those [δ 5.89 (2H), s; δ 6.02 (1H), s and δ 6.09 (1H), s] of **7**. The ^{13}C-NMR spectrum was also closely related to those of **6** and **7**. Two sets of four signals (see Experimental) due to C-2 and C-3 reconfirmed its tetrameric constitution. The observation of the relatively lowfield signal (δ 82.9) is consistent with the presence of a catechin unit,[15b] while the chemical shifts (δ 79.1, 76.8 and 76.6) of other C-2 resonances were similar to those [δ 78.7 and 76.3 (2C)] of **6**, suggesting the presence of three epicatechin units linked through C-4, C-8 bonds. The absence of rotational isomerism, as seen from the ^{1}H- and ^{13}C-NMR spectra, suggested that the catechin unit is attached to the C-6 position of another flavan unit, since 4,8-linked procyanidins containing catechin unit(s) in the upper unit(s) almost invariably display isomerism due to restricted rotation about the interflavanoid bond(s).[15a)]

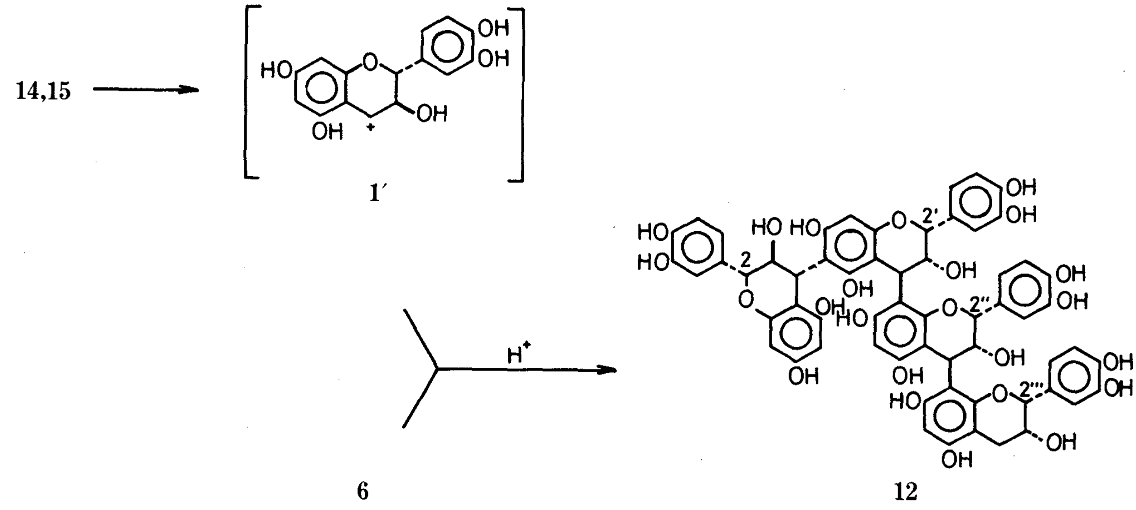


Chart 2

To confirm the structure of **12**, condensation of the 4-carbocation (**1′**) of **1** with **6** was attempted. The carbocation (**1′**) was easily generated, with retention of the configurations at C-2 and C-3, by acid treatment of 4-benzylthiocatechins (a mixture of **14** and **15**).[18)] In the presence of **6**, the carbocation was captured regio- and stereospecifically by its phloroglucinol ring, and chromatographic purification finally yielded, among others, a product found to be identical with **12**. Based on these observations, **12** was concluded to be catechin-(4α→6)-epicatechin-(4β→8)-epicatechin-(4β→8)-epicatechin.

The isolation of various dimeric, trimeric and tetrameric procyanidins from *Dioscorea cirrhosa* has clarified the nature of the heterogeneity of interflavanoid linkages in condensed tannins of this plant, and may assist in developing an understanding of the darkening in yams caused by enzymatic oxidation.

Experimental

Melting points are uncorrected. Most of the instruments and chromatographic conditions used in this study were the same as described in a previous paper.[11)]

Isolation of Procyanidins——Fresh tubers (28.2 kg) of *Dioscorea cirrhosa* Lour., collected in Taiwan, were extracted with acetone at room temperature. The acetone was removed by evaporation under reduced pressure, and the resulting aqueous solution was shaken with *n*-butanol. The *n*-butanol-soluble portion was mixed with Celite 545 and the solvent was evaporated off. The brown powder thus obtained was packed in a glass column. Elution with acetone and concentration afforded a gum, which was subjected to Sephadex LH-20 chromatography with increasing amounts of methanol in water to furnish five fractions (Frs. 1—5). Rechromatography of fraction 1 over Sephadex LH-20 with ethanol afforded 3,4-dihydroxyphenethyl alcohol (0.7 g) and its glucoside (0.3 g). Fraction 2 consisting of monomeric flavan-3-ols was separated by chromatography over MCI-gel CHP-20P with water–methanol (1 : 1) to yield (+)-catechin (**1**) (*ca.* 5 g) and (−)-epicatechin (**2**) (*ca.* 10 g). 4,8-Linked dimeric procyanidins B-1 (**3**) (0.2 g) and B-2 (**4**) (1.7 g), and the trimer (**11**) (1.8 g) were obtained from fraction 3 by chromatographic separation on Sephadex LH-20 (ethanol) and MCI-gel (water–methanol). The isolation of **11** from the earlier eluted fraction was rather unusual. Repeated chromatography of fraction 4 over Sephadex LH-20 (ethanol, water–methanol), MCI-gel (water–methanol) and LiChroprep RP-8 (water–methanol) afforded procyanidins B-5 (**5**) (0.51 g) and C-1 (**6**) (0.47 g), the trimers (**8**) (0.77 g) and (**10**) (1.3 g), and the tetramer (**9**) (0.21 g). Similar chromatographic separation (Sephadex LH-20, MCI-gel, LiChroprep RP-8) of fraction 5 furnished the trimer (**7**) (0.52 g) and the tetramer (**12**) (0.07 g).

Compounds **1**—**9** were identified by comparisons of physical and spectral data with those of authentic samples (**1**,[11] **2**,[11] **3**,[9] **4**,[9] **5**,[10] **6**,[10] **7**,[13] **8**,[11] **9**[14]).

Epicatechin-(4β→8)-catechin-(4α→8)-epicatechin (10)——Colorless needles (H_2O), mp 215 °C (dec.), $[\alpha]_D^{27}$ −97.6° ($c=1.0$, MeOH). *Anal.* Calcd for $C_{45}H_{38}O_{18}\cdot 2H_2O$: C, 59.87; H, 4.66. Found: C, 59.43; H, 4.70. The ^{1}H-NMR spectrum was complicated by rotational isomerism. ^{13}C-NMR (DMSO-d_6 + D_2O) ppm: 64.7 (C-3′′), 71.1, 71.4 (C-3, C-3′), 75.0 (C-2), 78.1 (C-2′′), 81.7 (C-2′).

Thiolytic Degradation of 10——a) Complete degradation: A mixture of **10** (150 mg), benzylmercaptan (2 ml) and acetic acid (1 ml) in ethanol (5 ml) was refluxed for 4 h. The solvent was evaporated off under reduced pressure, and the residue was subjected to Sephadex LH-20 chromatography with chloroform–methanol (4 : 1—1 : 1) to yield **13** (30 mg), **14** (33 mg), **15** (7 mg) and **2** (32 mg).

4β-Benzylthioepicatechin (**13**): A tan amorphous powder, $[\alpha]_D^{25}$ −28.0° ($c=0.9$, acetone). ^{1}H-NMR (acetone-d_6) ppm: 3.96 (1H, m, H-3), 4.01 (2H, s, $-SCH_2-$), 4.08 (1H, d, $J=2$ Hz, H-4), 5.28 (1H, s, H-2), 5.90 (1H, d, $J=2$ Hz, H-6), 6.04 (1H, d, $J=2$ Hz, H-8), 6.74 (1H, dd, $J=8$, 2 Hz, H-6′), 6.83 (1H, d, $J=8$ Hz, H-5′), 7.03 (1H, d, $J=2$ Hz, H-2′), 7.16—7.54 (5H in total, aromatic H).

4β-Benzylthiocatechin (**14**): A tan amorphous powder, $[\alpha]_D^{20}$ +25.4° ($c=0.8$, acetone). ^{1}H-NMR (acetone-d_6) ppm: 4.09 (2H, s, $-SCH_2-$), 4.00—4.24 (1H, m, H-3), 4.38 (1H, d, $J=4$ Hz, H-4), 4.94 (1H, d, $J=10$ Hz, H-2), 5.82 (1H, d, $J=2$ Hz, H-6), 6.03 (1H, d, $J=2$ Hz, H-8), 6.76 (1H, dd, $J=8$, 2 Hz, H-6′), 6.84 (1H, d, $J=8$ Hz, H-5′), 6.93 (1H, br s, H-2′), 7.16—7.46 (5H in total, aromatic H).

4α-Benzylthiocatechin (**15**): A tan amorphous powder, $[\alpha]_D^{17}$ +31.2° ($c=0.5$, acetone). ^{1}H-NMR (acetone-d_6) ppm: 3.76, 3.95 (each 1H, d, $J=12$ Hz, $-SCH_2-$), 4.00 (1H, d, $J=7$ Hz, H-4), 4.15 (1H, m, H-3), 4.49 (1H, d, $J=8$ Hz, H-2), 5.96 (1H, d, $J=2$ Hz, H-6), 6.07 (1H, d, $J=2$ Hz, H-8), 6.73 (1H, dd, $J=8$, 2 Hz, H-6′), 6.82 (1H, d, $J=8$ Hz, H-5′), 6.90 (1H, d, $J=2$ Hz, H-2′).

b) Partial Degradation: A mixture of **10** (290 mg), benzylmercaptan (4 ml), acetic acid (2 ml) and ethanol (10 ml) was heated under reflux for 1 h. Work-up as described above gave partial degradation products, **16** (95 mg), **17** (17 mg) and **18** (9 mg). Compound **18** was identified as procyanidin B-4 by comparison of the physical and spectroscopic data with those of an authentic sample.[10]

4′β-Benzylthioprocyanidin B-1 (**16**): A tan amorphous powder, $[\alpha]_D^{15}$ +90.5° ($c=1.4$, acetone). *Anal.* Calcd for $C_{37}H_{32}O_{12}S\cdot H_2O$: C, 60.03; H, 4.89. Found: C, 60.30; H, 5.26. The fast atom bombardment mass spectrum (FAB-MS) *m/z*: 701 $(M+H)^+$. ^{1}H-NMR (acetone-d_6 + D_2O) ppm: 3.84 (1H, m, H-3), 4.05 (2H, br s, $-SCH_2-$), 4.11 (1H, m, H-3′), 4.48 (1H, d, $J=4$ Hz, H-4′), 4.56 (1H, br s, H-4), 4.98 (1H, d, $J=8$ Hz, H-2′), 5.06 (1H, br s, H-2), 5.90 (1H, br s, H-6), 6.01 (1H, d, $J=2$ Hz, H-8), 6.03 (1H, s, H-6′), 6.52—7.12 (6H in total, B-ring H), 7.16—7.52 (5H in total, aromatic H). ^{13}C-NMR (acetone-d_6 + D_2O) ppm: 36.5 (C-4), 38.6 (C-4′), 45.0 ($-SCH_2-$), 71.6 (C-3′), 72.5 (C-3), 76.6 (C-2), 78.9 (C-2′), 95.4, 96.0, 97.0 (C-6, C-6′, C-8), 102.4 (C-4a, C-4a′), 107.3 (C-8′), 115.2, 115.5, 116.0, 116.1 (B-ring C-2, C-2′, C-5, C-5′), 119.1, 120.5 (B-ring C-6, C-6′), 127.5 (aromatic C-4), 129.1 (aromatic C-3, C-5), 129.8 (aromatic C-2, C-6), 132.2 (B-ring C-1, C-1′), 139.8 (aromatic C-1), 145.0, 145.2, 145.5 (B-ring C-3, C-3′, C-4, C-4′), 152.7, 155.0, 157.1, 157.3, 157.6, 157.8 (C-5, C-5′, C-7, C-7′, C-8a, C-8a′).

4′α-Benzylthioprocyanidin B-1 (**17**): A tan amorphous powder, $[\alpha]_D^{15}$ +75.5° ($c=0.5$, acetone). *Anal.* Calcd for $C_{37}H_{32}O_{12}S\cdot 3H_2O$: C, 58.89; H, 5.04. Found: C, 58.84; H, 4.98. FAB-MS *m/z*: 701 $(M+H)^+$. ^{1}H-NMR (acetone-d_6 + D_2O) ppm: 3.81 (2H, br s, $-SCH_2-$), 3.88 (1H, m, H-3), 4.11 (1H, d, $J=7$ Hz, H-4′), 4.15 (1H, m, H-3′), 4.56 (1H, m, H-2′), 4.65 (1H, m, H-4), 5.12 (1H, br s, H-2), 5.85—5.99 (2H, H-6, H-8), 6.07 (1H, br s, H-6′), 6.56—7.04 (6H in total, B-ring H), 7.28 (5H in total, aromatic H). ^{13}C-NMR (acetone-d_6 + D_2O) ppm: 36.6 (C-4), 38.7 (C-4′), 45.1 ($-SCH_2-$), 71.7 (C-3′), 72.6 (C-3), 76.7 (C-2), 79.0 (C-2′), 95.5, 96.0, 97.1 (C-6, C-6′, C-8), 102.5 (C-4a, C-4a′), 107.4 (C-8′), 115.3, 115.5, 115.8, 116.2 (B-ring C-2, C-2′, C-5, C-5′), 119.1, 120.5 (B-ring C-6, C-6′), 127.5 (aromatic C-4), 129.1 (aromatic C-3, C-5), 130.0 (aromatic C-2, C-6), 132.2 (B-ring C-1, C-1′), 140.0 (aromatic C-1), 145.1, 145.3, 145.6 (B-ring C-3, C-3′, C-4, C-4′), 153.6, 155.1, 155.4, 157.4, 157.8, 158.0 (C-5, C-5′, C-7, C-7′, C-8a, C-8a′).

Epicatechin-(4β→8)-catechin-(4α→8)-catechin (11)——An off-white amorphous powder, $[\alpha]_D^{20}$ −97.4° ($c=1.4$, acetone). *Anal.* Calcd for $C_{45}H_{38}O_{18}\cdot 3/2H_2O$: C, 60.47; H, 4.59. Found: C, 60.73; H, 5.03. FAB-MS *m/z*: 867 $(M+H)^+$. ^{13}C-NMR (acetone-d_6 + D_2O) ppm: 36.4 (C-4), 37.9 (C-4′), 67.9 (C-3′′), 72.0 (C-3′), 72.8 (C-3), 76.1 (C-2), 82.4 (C-2′′), 83.4 (C-2′).

Thiolytic Degradation of 11——Complete degradation of **11** (80 mg) as describes for **10**, followed by similar chromatographic separation, afforded **13** (17 mg), **14** (7 mg) and **1** (14 mg), while partial thiolysis of **11** (150 mg) yielded **16** (18 mg), **17** (5 mg) and **19** (6 mg). Compound **19** was identified as procyanidin B-3[19] by physical and spectral comparisons.

Catechin-(4α→6)-epicatechin-(4β→8)-epicatechin-(4β→8)-epicatechin (12)——An off-white amorphous powder, $[\alpha]_D^{24}$ −2.2° ($c=0.9$, acetone). *Anal.* Calcd for $C_{60}H_{50}O_{24}\cdot 3H_2O$: C, 59.60; H, 4.66. Found: C, 59.81; H, 4.91. ^{1}H-NMR (acetone-d_6 + D_2O) ppm: 2.90 (2H, m, H-4′′′), 4.08 (1H, br s, H-3′), 4.14 (1H, br s, H-3′′), 4.44 (1H, m, H-3), 4.58 (1H, br s, H-3′′′), 4.62 (1H, d, $J=8$ Hz, H-2), 4.80 (1H, d, $J=7$ Hz, H-4), 4.84 (2H, m, H-4′, H-4′′), 5.07 (1H, br s, H-2′′′), 5.28 (2H, br s, H-2′, H-2′′), 5.90 (2H, s, H-6, H-8), 6.05 (2H, s, H-6′′, H-6′′′), 6.12 (1H, s, H-8′), 6.56—7.40 (12H in total, B-ring H). ^{13}C-NMR (acetone-d_6 + D_2O) ppm: 29.3 (C-4′′′), 36.9 (C-4′, C-4′′), 38.4 (C-4), 66.2 (C-3′′′), 71.7 (C-3′′), 72.6, 72.8 (C-3, C-3′), 76.6, 76.8 (C-2′, C-2′′), 79.1 (C-2′′′), 82.9 (C-2), 96.1, 97.1 (C-6, C-8, C-

8′, C-6″, C-6‴), 100.3 (C-4a‴), 100.5 (C-4a′, C-4a″), 101.5 (C-4a), 106.3, 106.8, 107.1 (C-6′, C-8″, C-8‴).

Preparation of 12——A mixture of 4-benzylthiocatechins (a mixture of **14** and **15**) (200 mg), **6** (460 mg), acetic acid (1.5 ml) and acetonitrile (8 ml) was heated at 50 °C for 16 h. After removal of the solvent by evaporation under reduced pressure, the residue was subjected to chromatography over Sephadex LH-20. Elution with ethanol yielded a crude product, which was further purified by chromatography over MCI-gel (water–methanol) to furnish a product (20 mg) which was shown to be identical with **12** by physical and spectral comparisons.

Acknowledgement The authors wish to express their gratitude to Mr. Y. Tanaka, Miss K. Soeda and Mr. K. Isobe for measurements of ^{13}C-NMR, ^{1}H-NMR and MS, respectively. This work was supported by a grant (No. 59570897) from the Ministry of Education, Science and Culture, Japan, which is gratefully acknowledged.

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