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ACYLATED FLAVANOLS AND PROCYANIDINS FROM *SALIX SIEBOLDIANA**

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Key Word Index—*Salix sieboldiana*; Salicaceae; bark; acylated flavan-3-ols; acylated procyanidins; 1-hydroxy-6-oxo-2-cyclohexene-1-carboxylic acid; 1,6-dihydroxy-2-cyclohexene-1-carboxylic acid.

Abstract—An homologous series of acylated flavan-3-ols and procyanidins have been isolated, together with the known procyanidins B-1, B-3 and trimer, from the bark of *Salix sieboldiana*. Chemical and spectroscopic evidence led to the assignments of their structures as the 3-*O*-(1,6-dihydroxy-2-cyclohexene-1-carboxylic acid ester) of (+)-catechin and the 1-hydroxy-6-oxo-2-cyclohexene carboxylic acid esters of (+)-catechin and procyanidins B-1, B-3 and trimer.

INTRODUCTION

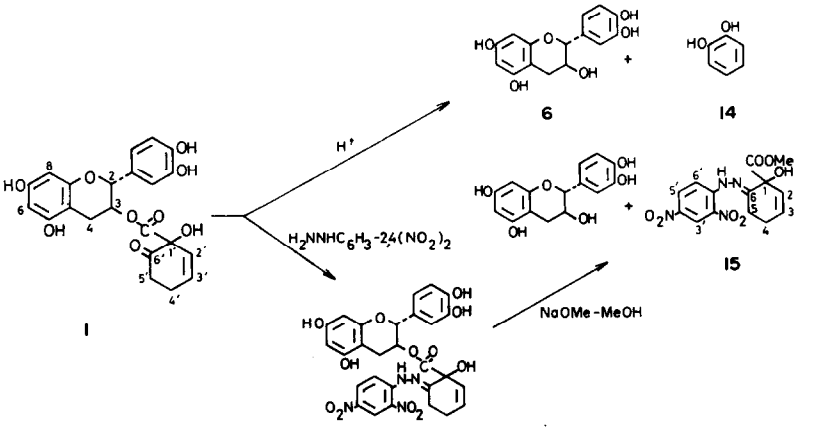
Some of members of the large genus *Salix* (Salicaceae) contain proanthocyanidins which on acid treatment yield cyanidin, accompanied in same cases by delphinidin [1, 2]. During a systematic study of proanthocyanidins in *Salix* species, we have encountered the occurrence of a series of acylated flavan-3-ols and procyanidins, in addition to the prevalent dimeric and trimeric procyanidins, in *Salix sieboldiana*, a shrub common in Japan. In this paper we report the isolation and structures of these acylated compounds.

RESULTS AND DISCUSSION

Extraction of the fresh bark of *S. sieboldiana* with acetone, followed by repeated CC over Sephadex LH-20 (EtOH, H_2O–MeOH, etc.) and MCI-gel CHP-2OP (H_2O–MeOH), afforded the new acylated flavan-3-ols **1** and **2**, and procyanidins **3**, **4** and **5**, together with the known compounds (+)-catechin (**6**), (−)-epicatechin (**7**) and procyanidins B-1 (**8**) [3, 4], B-3 (**9**) [3, 5], B-6 (**10**) [6] and B-7 (**11**) [4, 6], and trimeric procyanidins **12** and **13** [4].

The FD-mass spectrum of compound **1** gave $[M]^+$ at m/z 428 consistent with a molecular formula of $C_{22}H_{20}O_9$. The presence of a flavan-3-ol skeleton with a 2,3-*trans* configuration was clearly shown by ^1H and ^{13}C NMR spectra which were similar to those of catechin (**6**). The lowfield shift (δ5.25, *m*) of the flavan H-3, as well as an IR absorption band at 1740 cm^{-1}, indicated the presence of an ester carbonyl group at the C-3 position. The ^{13}C NMR spectrum revealed the presence of two olefinic carbons (δ128.2, *d*; δ132.8, *d*), a hydroxy-bearing quarternary carbon (δ78.6, *s*) and two methylenes (δ24.6, *t*; δ36.6, *t*). A carbonyl signal appeared at δ206.5, the chemical shift of which indicated it to be nonconjugated, in agreement with an IR absorption at 1715 cm^{-1}. Appropriate resonances for the olefinic group were also found in the ^1H NMR spectrum (δ5.57, *d*, J = 11 Hz; δ6.00, *m*). From the J-values, they were shown to be coupled with each other and one of these to be further coupled to methylene protons. The methylenes were found to be adjacent to each other by ^1H NMR examination in pyridine-d_5 showing separate methylene signals coupled with each other.

*Part 32 in the series "Tannins and Related Compounds". For Part 31 see ref. [10].



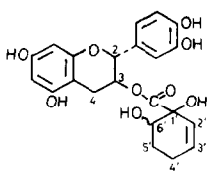
Hydrolysis of **1** with dilute hydrochloric acid or silica gel in H_2O yielded (+)-catechin (**6**) and catechol (**14**). The production of the latter compound is rather unusual but is consistent with a characteristic property of β-ketonic acids which easily release carbon dioxide when heated. All attempts to obtain the ester were unsuccessful owing to its facile decarboxylation and/or aromatization. However, protection of the carbonyl group with 2,4-dinitrophenylhydrazine, followed by methanolysis in a weak alkaline medium, afforded, together with **6**, the expected 2,4-dinitrophenylhydrazone of the methyl ester (**15**). The structure of **15** was confirmed by EI-mass spectrometry ($[M]^+$ m/z 350) and ^1H NMR (see Experimental) examinations. Thus, **1** was characterized as the 3-*O*-(1-hydroxy-6-oxo-2-cyclohexene-1-carboxylic acid ester) of (+)-catechin. The unique carboxylic acid is also reported to occur as esters of the characteristic salicin derivatives, salicortin and tremulacin [7, 8].

The ^{13}C NMR spectrum of compound **2** was almost identical to that of **1** except for the presence of a hydroxy-bearing methine signal (δ74.5, *d*) in place of the carbonyl signal, suggesting that the carbonyl group is replaced by a hydroxyl group. The ^{13}C NMR observation was consistent with that of the FD-MS which showed an $[M]^+$ peak at m/z 430, two amu more than that of **1**. Methylation of **2** with diazomethane and subsequent alkaline methanolysis yielded (+)-catechin tetramethyl ether and a methyl ester (**16**). The ^1H NMR spectrum of the ester **16** exhibited signals due to a methoxyl (δ3.71), olefinic protons (δ5.48, *dt*, J = 10, 2 Hz; δ5.85, *dt*, J = 10, 4 Hz) and two methylenes (δ1.82–2.01, 2H, *m*; δ2.12–2.29, *m*). In addition, the signal of a methine with a hydroxyl group appeared as a multiplet at δ3.80. These observations, combined with EI-mass spectral data ($[M]^+$ m/z 172), confirmed the structure of **16**. Since the ^1H NMR spectrum of **2** exhibited the flavan H-3 signal shifted considerably downfield (δ5.32), the ester group was shown to be attached to this position. Accordingly, the structure of **2** was established as the 3-*O*-(1,6-dihydroxy-2-cyclohexene-1-carboxylic acid ester) of (+)-catechin. The absolute configurations of the hydroxy-bearing carbon atoms in the ester moiety still remain to be determined.

The FAB-mass spectrum of compound **3** and the FD-mass spectrum of **4** with the same $[M+H]^+$ ion at m/z 717 agreed with a molecular formula of $C_{37}H_{32}O_{15}$. The ^1H NMR spectrum of **3** was related to those of **1** and procyanidin B-1 (**8**), while that of **4** was complicated due to conformational isomerism caused by steric interaction between flavan units [6, 9]. The presence of the above-mentioned cyclohexene carboxylic acid ester in **3** was indicated from its ^{13}C NMR spectrum showing signals similar to those found in **1**. Upon hydrolysis with dilute ammonia, **3** and **4** yielded, together with **14**, procyanidins B-1 (**8**) and B-3 (**9**), respectively. The location of the ester moiety in **3** was established to be at the C-3 position in the lower unit by lowfield shifts of the corresponding ^1H and ^{13}C signals (H-3, δ5.37, *m*; C-3, δ71.8) as compared with those of **8** (δ4.05, *m*; δ67.7). The ^{13}C NMR spectrum of **4** was duplicated like the ^1H NMR spectrum. However, comparison of the spectrum of **4** with that of **9** permitted the allocation of the ester group to the C-3 position in the lower unit. The major conformer exhibited two flavan C-3 signals at δ72.0 and 73.2. Whereas the latter signal was in good agreement with the signal (δ73.4) attributable to the upper C-3 in **9**, the former was shifted downfield as compared with that (δ68.9) of **9**. Furthermore, the signal of C-2 in the lower unit appeared in the upper field (δ78.6) than that (δ82.5) of **9**, in contrast to the same chemical shift (δ83.5) of C-2 in the upper unit in **4** and **9**. On the basis of these observations, **3** and **4** were concluded to be the 3′-*O*-(1-hydroxy-6-oxo-2-cyclohexene-1-carboxylic acid ester) of procyanidins B-1 and B-3, respectively.

The trimeric constitution of compound **5** was confirmed by FAB-mass spectrometry ($[M+H]^+$ m/z 1005). The ^1H and ^{13}C NMR spectra showed complex signal patterns owing to rotational isomerism analogous to that observed in **4**. However, ^{13}C NMR resonances (see Experimental) arising from the major rotamer confirmed the presence of the cyclohexene carboxylic acid ester in **5**. When treated with dilute ammonia, **5** afforded **14** and a trimeric procyanidin which was found to be identical with **12**.

Earlier work showed that in the ^{13}C NMR spectrum the signal due to C-3 in the lower terminal unit appears at a higher field than those of C-3 in the extension units and it is therefore easily discernible [9–11]. Actually, the lower C-3 in **12** resonated at higher field (δ67.9) than others



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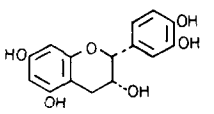

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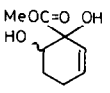

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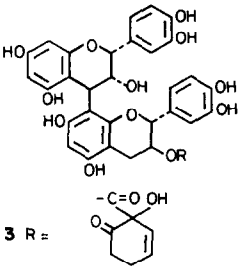

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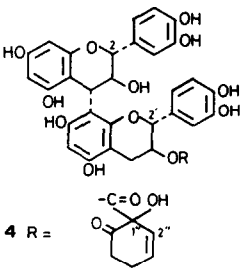

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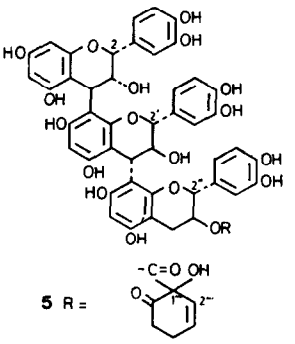
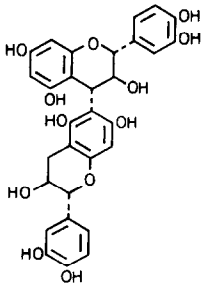


5 R = 12 R = H



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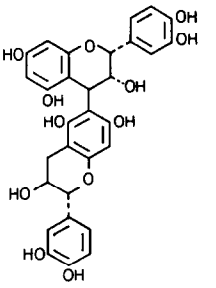

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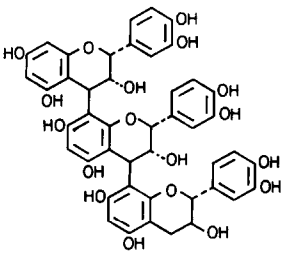

13

(δ72.0–72.8). However, in the spectrum of **5** this upfield signal was absent; instead the signal appeared shifted downfield (δ72.2), thus establishing the location of the ester group at the C-3 position in the lower terminal unit. Consequently, the structure of this compound was represented by formula **5**.

In conclusion, it is shown that *S. sieboldiana* contains proanthocyanidins consisting entirely of either (+)-catechin unit or the unit of the cyclohexene carboxylic acid ester of (+)-catechin as the lower terminal. 1-Hydroxy-6-oxo-2-cyclohexene-1-carboxylic acid is structurally related to *o*-hydroxybenzyl alcohol (saligenin), and therefore seems to be a biosynthetic precursor of salicin and populin which are common constituents in the Salicaceae.

EXPERIMENTAL

General. Mps are uncorr. ^{1}H and ^{13}C NMR spectra [δ (ppm), J (Hz)] were obtained at 100 MHz and 25.05 MHz, respectively, with TMS as int. standard. TLC was conducted on precoated silica gel (Merck) with C_6H_6–Et formate–HCO_2H (5:4:1 or 2:7:1), and spots were detected under UV or by spraying ethanolic $FeCl_3$. CC was performed on Sephadex LH-20 (25–100 μm, Pharmacia), MCI-gel CHP-20P (75–100 μm, Mitsubishi) and Bondapak C_{18}/Porasil B (Waters).

Plant material. S. sieboldiana was collected at Mt. Seburi, Fukuoka Pref., in May 1983. A voucher specimen has been deposited in the Herbarium of the Faculty of Pharmaceutical Sciences, Kyushu University.

Isolation. Fresh bark (3.5 kg) of *S. sieboldiana* was extracted × 3 with Me_2CO. After concn, the aq. soln was shaken with Et_2O to remove fats, chlorophylls, etc. The aq. layer, after concn, was applied to a Sephadex LH-20 column. Elution with increasing proportions of MeOH in H_2O yielded four fractions (fr. I–IV). Fr. I contained very hygroscopic compounds negative to the $FeCl_3$ reagent, while fr. II consisted mainly of flavonoids. These fractions were not examined further. Rechromatography of fr. III over Sephadex LH-20 with EtOH yielded three fractions (fr. III-1, III-2 and III-3). Fr. III-1 was chromatographed over MCI-gel with H_2O containing increasing amounts of MeOH to give (+)-catechin (**6**; 7.5 g) and (−)-epicatechin (**7**; 2.5 g). Further chromatography of fr. III-2 over MCI-gel with H_2O–MeOH (3:2) afforded compounds **1** (1.9 g) and **2** (0.34 g), and a mixture of **3** and **4**. Separation of this mixture was achieved by chromatography over Bondapak C_{18} using H_2O with increasing proportions of MeOH to furnish pure **3** (79 mg) and **4** (83 mg). Fr. IV, which contained 4,6-linked procyanidins and trimeric proanthocyanidins, was separated on Sephadex LH-20 with EtOH, followed by purification on MCI-gel, giving compound **5** (51 mg) and procyanidins B-6 (**10**; 66 mg) and B-7 (**11**; 62 mg), together with the trimers **12** (190 mg) and **13** (86 mg). Compounds **6**–**13** were identified by comparison of their physical and spectral data with those of authentic specimens (**6** [4], **7** [4], **8** [3, 4], **9** [3, 5], **11** [4, 6], **12** [4], **13** [4]) and with the lit. (**10** [6]).

3-O-(1-*Hydroxy*-6-*oxo*-2-*cyclohexene*-1-*carboxylic acid ester*) *of* (+)-*catechin* (**1**). White amorphous powder, $[\alpha]_D^{27}$ −102.9° (Me_2CO; *c* 0.9). FD-MS *m/z* 428 $[M]^+$. IR ν_{max}^{KBr} cm^{-1}: 1740, 1715. ^{1}H NMR (Me_2CO-d_6–D_2O): δ2.18–2.50 (4H, *m*, H-4′ and H-5′), 2.60 (1H, *dd*, *J* = 16, 8 Hz, H-4), 2.90 (1H, *dd*, *J* = 16, 6 Hz, H-4), 4.90 (1H, *d*, *J* = 7 Hz, H-2), 5.24 (1H, *m*, H-3), 5.57 (1H, *d*, *J* = 11 Hz, H-2′), 6.00 (1H, *m*, H-3′), 5.92 (1H, *d*, *J* = 2 Hz, H-6), 6.08 (1H, *d*, *J* = 2 Hz, H-8). ^{13}C NMR (Me_2CO-d_6–D_2O): δ24.6 (C-4′), 26.5 (C-4), 35.6 (C-5′), 72.3 (C-3), 78.5 (C-2), 78.6 (C-1′), 95.2 (C-6), 96.5 (C-8), 98.8 (C-4a), 128.2 (C-3′), 132.8 (C-2′), 170.0 (COO), 206.5 (C-6′). (Found: C, 61.3; H, 5.0. $C_{22}H_{20}O_9$ requires: C, 61.7; H, 4.7%.)

Hydrolysis of **1**. A soln of **1** (0.1 g) in H_2O was heated under reflux for 4 hr with silica gel (2 g). After filtration, the filtrate was subjected to Sephadex LH-20 CC with EtOH and then to silica gel CC with C_6H_6–Me_2CO (4:1) yielding **6** (24 mg) and **14** (3 mg), both being identified by comparison of the physical and spectral data with those of authentic samples.

Formation of phenylhydrazone of **1**, *followed by methanolysis.* A mixture of **1** (0.22 g), 2,4-DNPH (0.1 g) and 3 drops of conc HCl in MeOH (2 ml) was kept at room temp for 40 min. Evapn of solvent *in vacuo* left a residue, which was purified by chromatography over Sephadex LH-20 using EtOH. The 2,4-DNPH (169 mg) thus obtained was treated with 0.05% NaOMe in MeOH (10 ml) at 60° for 6 hr. Neutralization with Amberlite IR 120B (H^+ form) and purification by silica gel CC with $CHCl_3$–MeOH (49:1) afforded **6** (49 mg) and the hydrazone **15** (20 mg), orange needles (EtOH), mp 203–205°, $[\alpha]_D^{26}$ −331.8° [$CHCl_3$–MeOH (1:1); *c* 0.6]. EI-MS *m/z*: 350 $[M]^+$. ^{1}H NMR ($CDCl_3$–CD_3OD): δ2.30–2.60 (2H, *m*, H-4), 2.70–3.00 (2H, *m*, H-5), 3.76 (3H, *s*, COOMe), 5.66 (1H, *dt*, *J* = 10, 2 Hz, H-2), 6.22 (1H, *dt*, *J* = 10, 4 Hz, H-3), 7.96 (1H, *d*, *J* = 10 Hz, H-6′), 8.26 (1H, *dd*, *J* = 10, 2 Hz, H-5′), 9.08 (1H, *d*, *J* = 2 Hz, H-3′). ^{13}C NMR ($CDCl_3$–MeOH): δ25.3 (C-4′), 32.3 (C-5), 53.5 (OMe), 75.5 (C-1), 116.5 (C-3′), 123.7 (C-6′), 128.1 (C-3), 130.0 (C-5′), 132.8 (C-2), 137.8, 137.9 (C-1′ and C-2′), 145.4 (C-4′), 152.9 (C-6), 175.9 (COO). (Found: C, 47.9; H, 4.1; N, 15.9. $C_{14}H_{14}O_7N_4$ requires: C, 48.0; H, 4.0; N, 16.0%.)

3-O-(1,6-*Dihydroxy*-2-*cyclohexene*-1-*carboxylic acid ester*) *of* (+)-*catechin* (**2**). White amorphous powder, $[\alpha]_D^{26}$ −87.1° (Me_2CO; *c* 0.9). FD-MS *m/z*: 430 $[M]^+$. ^{1}H NMR (Me_2CO-d_6–D_2O): δ1.56–2.24 (4H, *m*, H-4′ and H-5′), 2.60 (1H, *dd*, *J* = 16, 8 Hz, H-4), 2.86 (1H, *dd*, *J* = 16, 6 Hz, H-4), 3.76 (1H, *m*, H-6′), 5.04 (1H, *d*, *J* = 7 Hz, H-2), 5.34 (1H, *d*, *J* = 10 Hz, H-2′), 5.32 (1H, *m*, H-3), 5.74 (1H, *dt*, *J* = 10, 4 Hz, H-3′), 5.94 (1H, *d*, *J* = 2 Hz, H-6), 6.06 (1H, *d*, *J* = 2 Hz, H-8), 6.64–6.96 (3H, *m*, B-ring H). ^{13}C NMR (Me_2CO-d_6–D_2O): δ23.8 (C-5′), 24.3 (C-4′),

26.8 (C-4), 71.5 (C-3), 74.5 (C-6'), 77.9 (C-1'), 78.9 (C-2), 95.2 (C-6), 96.4 (C-8), 98.9 (C-4a), 127.1 (C-3'), 131.6 (C-2'), 173.1 (COO). (Found: C, 59.9; H, 5.7. $C_{22}H_{22}O_9 \cdot 1/2H_2O$ requires: C, 60.1; H, 5.2%.)

Methylation of **2** *followed by methanolysis.* A soln of **2** (0.12 m) in MeOH was treated with CH_2N_2–Et_2O under cooling for 6 hr. Evapn of solvent and purification by silica gel CC with C_6H_6–Me_2CO (4:1) gave the tetraMe ether as a white amorphous powder (71 mg), $[\alpha]_D^{17}$ −87.8° ($CHCl_3$; *c* 0.7). ^{1}H NMR ($CDCl_3$): δ1.70 (2H, *m*, H-4'), 2.04 (2H, *m*, H-5'), 2.66 (1H, *dd*, *J* = 16, 8 Hz, H-4), 2.98 (1H, *dd*, *J* = 16, 6 Hz, H-4), 3.66 (1H, *m*, H-6'), 5.08 (1H, *d*, *J* = 7 Hz, H-2), 5.31 (1H, *dt*, *J* = 10, 2 Hz, H-2'), 5.46 (1H, *m*, H-3), 6.08 (1H, *d*, *J* = 2 Hz, H-6), 6.16 (1H, *d*, *J* = 2 Hz, H-8), 6.87 (3H, *m*, B-ring H). Methanolysis of the Me ether (30 mg) with 0.1% NaOMe in MeOH (2 ml) at room temp for 6 hr, followed by separation by silica gel CC with C_6H_6–Me_2CO (5:1), yielded (+)-catechin tetraMe ether (16 mg) and the ester **16** (4 mg) as a white amorphous powder, $[\alpha]_D^{17}$ +3.1° (Me_2CO; *c* 0.2). EI-MS *m/z*: 172 $[M]^+$. ^{1}H NMR (Me_2CO-d_6): δ1.82–2.01 (2H, *m*, H-5), 2.12–2.29 (2H, *m*, H-4), 3.71 (1H, *s*, COOMe), 3.77–3.91 (1H, *m*, H-6), 5.48 (1H, *dt*, *J* = 10, 2 Hz, H-2), 5.85 (1H, *dt*, *J* = 10, 4 Hz, H-3).

3'-O-(1-*Hydroxy-6-oxo-2-cyclohexene-1-carboxylic acid ester*) *of procyanidin B-1* (**3**). Off-white amorphous powder, $[\alpha]_D^{18}$ −62.6° (Me_2CO; *c* 1.0). FAB-MS *m/z*: 717 $[M+H]^+$. ^{1}H NMR (Me_2CO-d_6–D_2O): δ2.18–2.54 (4H, *m*, H-4'' and H-5''), 2.70 (2H, *m*, H-4'), 3.94 (1H, *br s*, H-3), 4.70 (1H, *br s*, H-4), 5.12 (1H, *br s*, H-2). 5.16 (1H, *m*, H-2'), 5.37 (1H, *m*, H-3'), 5.59 (1H, *d*, *J* = 10 Hz, H-2''), 5.92 (1H, *m*, H-3''), 5.98 (1H, *d*, *J* = 2 Hz, H-6), 6.04 (1H, *d*, *J* = 2 Hz, H-8), 6.6–7.1 (6H total, B-ring H). ^{13}C NMR (Me_2CO-d_6–D_2O): δ22.7 (C-4''), 26.3 (C-4'), 35.8 (C-5''), 36.7 (C-4), 71.8 (C-3'), 72.6 (C-3), 76.8 (C-2), 77.5 (C-1''), 78.6 (C-2'), 95.2, 95.9, 96.9 (C-6, C-6' and C-8), 99.0 (C-4a'), 101.0 (C-4a), 107.6 (C-8'), 128.0 (C-3''), 133.0 (C-2''), 170.3 (COO), 207.0 (CO). (Found: C, 59.2; H, 5.1. $C_{37}H_{32}O_{15} \cdot 2H_2O$ requires: C, 59.0; H, 4.8%.) Hydrolysis of **3** (75 mg) with 1% aq. NH_4OH at room temp for 7 hr, followed by neutralization with 2% HOAc afforded a mixture of products. Separation by MCI-gel CC with H_2O–MeOH (7:3) yielded procyanidin B-1 (**8**; 33 mg) and **14** (7 mg).

3'-O-(1-*Hydroxy-6-oxo-2-cyclohexene-1-carboxylic acid ester*) *of procyanidin B-3* (**4**). Off-white amorphous powder, $[\alpha]_D^{16}$ −291.6° (Me_2CO; *c* 0.9). FD-MS *m/z*: 717 $[M+H]^+$. The ^{1}H NMR spectrum was so complicated due to rotational isomerism that assignments of the signals could not be made. ^{13}C NMR (Me_2CO–D_2O): δ23.7 (C-4''), 26.4 (C-4'), 35.8 (C-5''), 37.9 (C-4), 72.0 (C-3'), 73.2 (C-3), 77.6 (C-1''), 78.6 (C-2'), 83.5 (C-2), 170.1 (COO), 207.3 (CO). (Found: C, 58.9; H, 5.0. $C_{37}H_{32}O_{15} \cdot 2H_2O$ requires: C, 59.0; H, 4.8%.) **4** (80 mg) yielded procyanidin B-3 (**9**) (45 mg) and **14** (6 mg) on similar hydrolysis with 1% aq. NH_4OH (5 ml).

3''-O-(1-*Hydroxy-6-oxo-2-cyclohexene-1-carboxylic acid ester*) *of procyanidin trimer* (**5**). Off-white amorphous powder, $[\alpha]_D^{17}$ −160.4° (Me_2CO; *c* 0.5). FAB-MS *m/z*: 1005 $[M+H]^+$. The ^{1}H NMR spectrum, like that of **4**, gave a complex signal pattern. ^{13}C NMR (Me_2CO-d_6–D_2O): δ22.2 (C-4'''), 26.2 (C-4''), 36.4 (C-4'), 38.1 (C-4), 72.2 (C-3''), 73.2 (C-3'), 76.5 (C-2), 78.5 (C-1'''), 79.1 (C-2'''), 83.9 (C-2'), 170.4 (COO), 208.8 (CO). (Found: C, 58.6; H, 4.7. $C_{52}H_{44}O_{21} \cdot 3H_2O$ requires: C, 59.0; H, 4.7%.) Similar alkaline hydrolysis of **5** (32 mg) with 1% aq. NH_4OH (3 ml) furnished the trimer **12** (9 mg) and **14** (2 mg).

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