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Tannins and Related Compounds. XXXVIII.[1] Isolation and Characterization of Flavan-3-ol Glucosides and Procyanidin Oligomers from Cassia Bark (*Cinnamomum cassia* BLUME)

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A chemical examination of the bark of *Cinnamomum cassia* (広南桂皮: Lauraceae) has led to the isolation of three flavan-3-ol glucosides (**1**—**3**) and three oligomeric procyanidins (**4**—**6**) named cinnamtannins A_2–A_4, together with (−)-epicatechin(**7**), procyanidins B-2 (**8**), B-5 (**9**) and C-1 (**11**), and a doubly-linked proanthocyanidin (**10**). On the basis of chemical and spectroscopic evidence, compounds **1**—**3** were characterized as (−)-epicatechin 3-*O*-, 8-*C*- and 6-*C*-β-D-glucopyranosides, respectively, while compounds **4**—**6** were shown to be tetrameric, pentameric and hexameric procyanidins, respectively, consisting exclusively of (−)-epicatechin units linked linearly through C(4β)–C(8) bonds.

Keywords——*Cinnamomum cassia*; Lauraceae; flavan-3-ol glucoside; procyanidin; tannin; thiolytic degradation

Various sorts of cinnamon barks have been used, either alone or in combination, in many Chinese traditional medicines. Among cinnamons of commerce, cassia bark (広南桂皮: the bark of *Cinnamomum cassia* BLUME) produced in the southeastern regions of China has been commonly utilized in Japan and China. With regard to the constituents of cassia bark, detailed examinations on essential oils[2] and diterpenes[3] have been reported. In addition, the occurrence of tannins has been suggested because of the astrigency of the bark, although their chemical nature has remained unclear. As part of our chemical studies on tannins and related compounds in *Cinnamomum* plants, we previously reported the isolation of oligomeric proanthocyanidins containing a doubly-linked (proanthocyanidin A-2) unit in the molecule, from the bark of *C. zeylanicum* NEES (セイロン桂皮)[4] and the root bark of *C. sieboldii* MEISNER (日本桂皮).[5] We have now investigated cassia bark, and have isolated three flavan-3-ol glucosides (**1**—**3**) and three oligomeric procyanidins (**4**—**6**), the latter compounds being named cinnamtannins A_2—A_4, together with (−)-epicatechin (**7**) and several known proanthocyanidins (**8**—**11**). This paper deals with the isolation and structure elucidation of these compounds.

The aqueous extract of commercial cassia bark was subjected to a combination of Sephadex LH-20, MCI-gel CHP 20P and Bondapak C_{18} chromatographies with various solvent systems to yield compounds **1**—**11**. Compounds **7**—**11** were identified as (−)-epicatechin and proanthocyanidins B-2, B-5, A-2 and C-1, respectively, by comparisons of their physical and spectral data with those of authentic samples.[4]

Compound **1** was positive to the ferric chloride (dark green) and the anisaldehyde–sulfuric acid (orange) reagents. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **1** showed aliphatic signals at δ 5.15 (d, J=2 Hz), 4.41 (m), and 2.50—2.96 (2H) ascribable to the flavan H-2, H-3 and H-4, respectively. Aromatic proton signals appeared as an ABX-type pattern at δ 6.72 (dd, J=2, 8 Hz), 6.84 (d, J=8 Hz) and 7.15 (d, J=2 Hz), and as a pair of

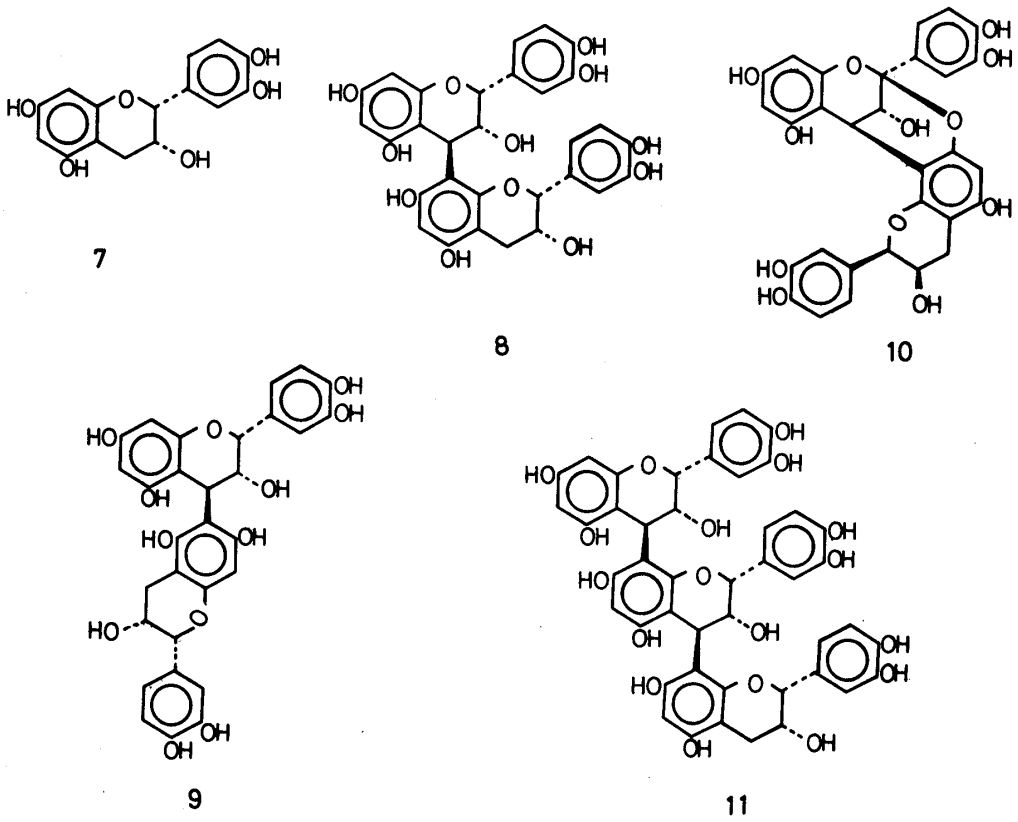

Chart 1

TABLE I. ^{13}C-NMR Spectral Data for Flavan-3-ol Derivatives[a]

		1	2	2a	3	3a	7
	C-2	78.2	79.2	79.3	79.2	79.6	79.3
	C-3	73.3	66.7	66.8	66.3	66.5	66.9
	C-4	24.2	29.2	28.5	28.1	29.5	28.4
	C-6	95.4	97.2	89.7	105.0	114.2	95.7
	C-8	96.3	103.8	111.5	96.5	96.7	96.2
Sugar	C-1	102.3	76.0	75.0	76.6	75.2	
	C-2	74.4	73.2	72.0	74.1	72.3	
	C-3	77.0	78.9	80.6	79.2	80.6	
	C-4	70.9	70.5	71.6	70.3	72.3	
	C-5	77.2	81.2	81.7	81.1	81.6	
	C-6	62.3	61.6	63.2	61.4	61.8	

a) Spectra were run in acetone-d_6 + D_2O at 25.05 MHz.

meta-coupled doublets (J=2 Hz) at δ 5.94 and 6.04. The former ABX-type signals were assigned to the flavan B-ring protons, and the latter doublets to the A-ring protons. These ^{1}H-NMR observations suggested the occurrence of an epicatechin moiety in the molecule. In addition, the existence of a carbohydrate residue was shown by the anomeric proton resonance at δ 4.55 (d, J=7 Hz) and also by carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectroscopy (Table I). On enzymatic hydrolysis with crude hesperidinase, **1** gave glucose and an aglycone which was identical with (−)-epicatechin (**7**). Glucose was presumed to be linked at the C-3 position, since the ^{13}C-NMR spectrum of **1** showed a downfield shift of the C-3 signal (δ 73.3) as compared with that in compound **7** (δ 66.9). This presumption was

supported by the following results. Methylation of **1** with dimethyl sulfate and anhydrous potassium carbonate in dry acetone gave a tetramethylether (**1a**), which, on subsequent methanolysis with 0.5 N HCl–MeOH, afforded 5,7,3′,4′-tetra-*O*-methyl-(−)-epicatechin (**7a**). Thus, the location of the glucose moiety was established to be at the C-3 position of the (−)-epicatechin moiety. The configuration of the anomeric center was determined to be *β* on the basis of the coupling constant ($J=7$ Hz) of the above-mentioned anomeric proton signal. Thus, **1** was characterized as (−)-epicatechin 3-*O*-*β*-D-glucopyranoside.

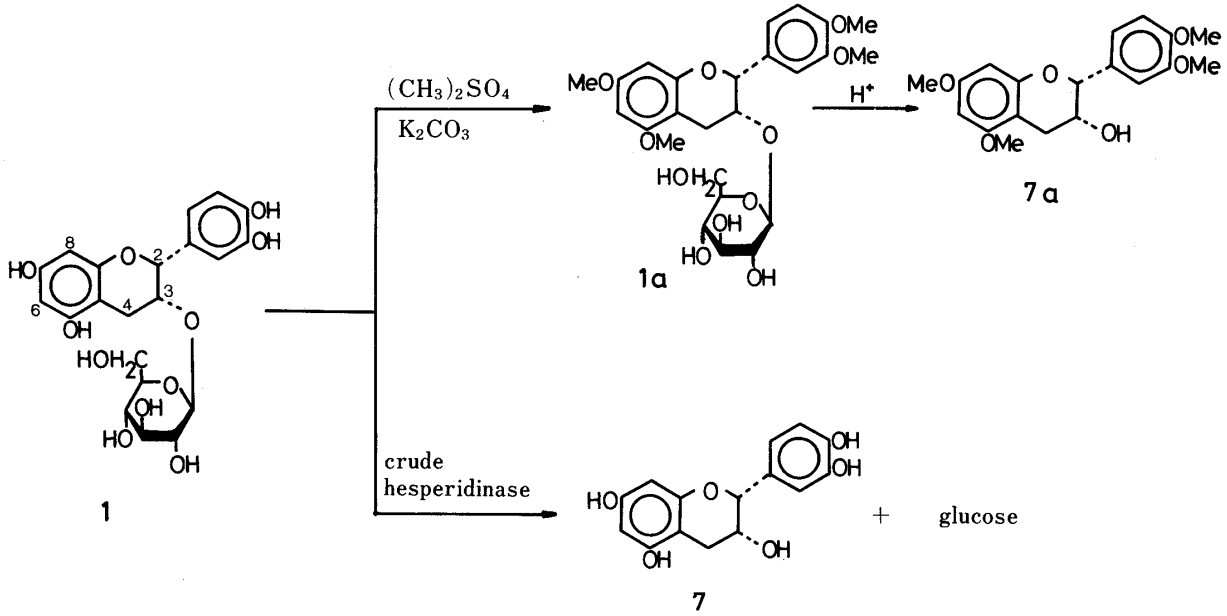

Chart 2

Compounds **2** and **3** exhibited in the fast atom bombardment mass spectra (FAB-MS) the same $(M+H)^+$ ion peak at *m/z* 453, which also corresponded to that of compound **1**. The ^{1}H-NMR spectra of both compounds were almost indistinguishable, and were closely correlated with that of compound **1**, showing the presence of an epicatechin nucleus and a sugar moiety in each molecule. However, the ^{1}H-NMR spectra of **2** and **3** differed markedly from that of **1** in that each A-ring signal appeared as a singlet instead of two *meta*-coupled doublets. In the ^{13}C-NMR spectra of **2** and **3**, the sugar C-1 signal appeared at *δ* 76.0 and 76.6, respectively, together with five other sugar-carbon signals. From these spectroscopic data, in conjunction with the fact that **2** and **3** were resistant to hydrolysis with crude hesperidinase, these compounds were concluded to possess a C-glucosidic bond located in the A-ring of the epicatechin moiety.

Oxidative degradation of **2** and **3** with ferric chloride,[6] producing glucose and arabinose in each case, confirmed the sugar residue to be glucose, and the configuration at the glucose C-1 position was concluded to be *β* on the basis of the *J*-value ($J=7$ Hz) found in each ^{1}H-NMR spectrum.

Previously, we reported that the position of the substituent in the A-ring in 5,7,3′,4′-tetrahydroxyflavan-3-ol derivatives could be determined by comparison of the C-6 and C-8 chemical shifts in their methyl ethers.[7-9] In the case of the methyl ether (**2a**) prepared from **2** by methylation with dimethyl sulfate and anhydrous potassium carbonate in dry acetone, the ^{13}C-NMR spectrum showed a signal at *δ* 89.7 (d), consistent with those of C-6 in C-8 substituted compounds [*e.g.* gambiriin A_1 nonamethyl ether (**12**)[7]: *δ* 88.6 (C-6)], indicating that the substituent was located at the C-8 position. On the other hand, the spectrum of the methyl ether (**3a**) formed from **3** exhibited the signal at *δ* 96.7 (d), which is in good agreement

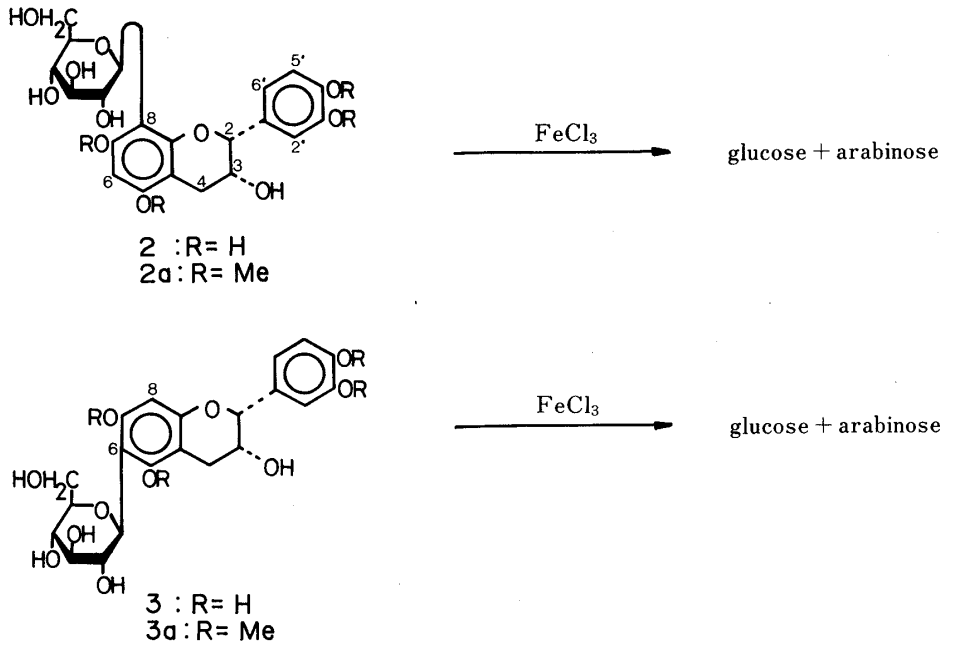

Chart 3

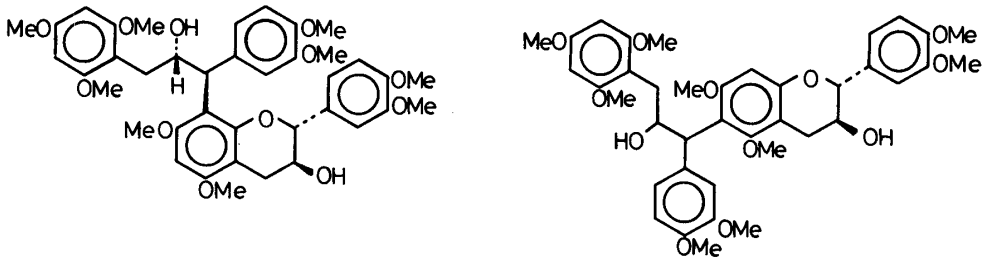

Chart 4

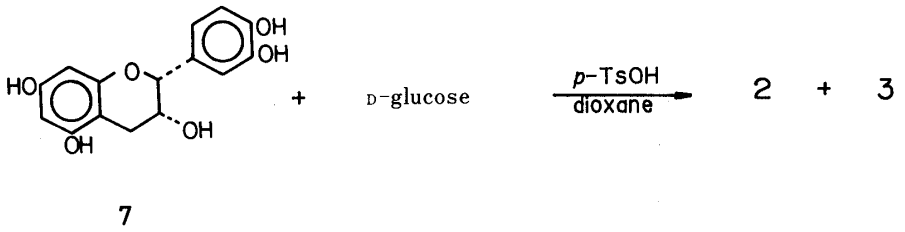

Chart 5

with those of C-8 in C-6 substituted compounds [*e.g.* gambiriin A_3 nonamethyl ether (**13**)[7]: δ 96.2 (C-8)]. On the basis of these spectral data, the positions of the sugar residue in **2** and **3** were concluded to be at C-8 and C-6, respectively.

To establish the absolute stereochemistry of compounds **2** and **3**, an attempt was made to prepare **2** and **3**. Acid-catalyzed condensation[8,9] of (−)-epicatechin (**7**) and D-glucose afforded two major products, which, after separation, were shown to be identical with **2** and **3**. Thus, compounds **2** and **3** were characterized unequivocally as (−)-epicatechin 8-*C*- and 6-*C*-β-D-glucopyranosides, respectively.

Compound **4** (cinnamtannin A_2), obtained as a pale brown amorphous powder, gave with the anisaldehyde-sulfuric acid reagent an orange-red coloration characteristic of procyanidins. The FAB-MS of **4** exhibited the $(M+H)^+$ ion peak at *m/z* 1155, consistent with a

TABLE II. ^{13}C-NMR Spectral Data for Procyanidins[a]

	8	11	4	5	6
C-2	76.5	76.3	76.6	76.2	76.7
C-3	72.7	71.5	72.0	71.5	72.1
C-4	36.4	36.6	36.8	36.9	36.8
C-2′	78.8	76.3	76.6	76.2	76.7
C-3′	66.2	72.7	72.0	71.5	72.1
C-4′	—[b]	36.6	36.8	36.9	36.8
C-2″		78.8	76.6	76.2	76.7
C-3″		65.9	72.3	72.0	72.1
C-4″		—[b]	36.8	36.9	36.8
C-2‴			78.9	76.2	76.7
C-3‴			66.0	72.2	72.1
C-4‴			—[b]	36.9	36.8
C-2⁗				78.6	76.0
C-3⁗				66.2	72.1
C-4⁗				—[b]	36.8
C-2⁗′					79.0
C-3⁗′					66.3
C-4⁗′					—[b]

a) Spectra were run in acetone-d_6+D_2O at 25.05 MHz. *b*) These signals were overlapped with solvent signals.

tetraflavanoid constitution. In the ^{1}H-NMR spectrum, the coupling patterns of the flavan H-2 signals [δ 5.08, 5.16, 5.20 and 5.22 (each s)] suggested that compound **4** consists entirely of flavan-3-ol units with epicatechin (2,3-*cis*) stereochemistry, and this was supported by the ^{13}C-NMR chemical shifts of the C-2 signals [δ 76.6 (3C) and 78.9].[10] Acid-catalyzed thiolytic degradation[11] of **4** gave (−)-epicatechin (**7**) (formed from the lower terminal unit) and epicatechin 4-benzylthioether (**14**)[4] (formed from the upper units), confirming that all component units possess (−)-epicatechin stereochemistry. The configurations and the points of the interflavanoid linkages between the component units were determined as follows. On partial thiolytic degradation, **4** afforded, in addition to **7** and **14**, procyanidins B-2 (**8**) and C-1 (**11**), and the benzylsulfides (**15**)[4] and (**16**). The sulfide (**16**) was characterized as procyanidin C-1 4″-benzylthioether by analysis of the ^{1}H-NMR spectrum and by conversion with Raney nickel to procyanidin C-1 (**11**). Among these degradation products, the formation of **11** and **16** established the configurations and locations of the interflavanoid linkages to be C(4β)–C(8). Accordingly, compound **4** was characterized as epicatechin-(4β→8)-epicatechin-(4β→8)-epicatechin-(4β→8)-epicatechin.[12]

Compound **5** (cinnamtannin A_3) exhibited in the FAB-MS the $(M+K)^+$ ion peak, at *m/z* 1481, corresponding to a pentaflavanoid constitution. The appearance of ^{1}H-NMR singlets at δ 4.96 (2H), 5.04, 5.20 and 5.27 due to H-2 as well as the ^{13}C-NMR chemical shifts [δ 76.2 (4C) and 78.6] of the C-2 carbons,[10] suggested that compound **5** consists entirely of epicatechin units. The constitution of **5** was definitively established by similar thiolytic degradation. Namely, complete thiolytic degradation of **5** afforded (−)-epicatechin (**7**) and the benzylsulfide (**14**), establishing that each component unit possesses (−)-epicatechin stereochemistry, while partial degradation yielded procyanidins B-2 (**8**) and C-1 (**11**), and compound **4**, together with procyanidin B-2 4′-benzyl thioether (**15**). Among these degradation products, the formation of **4** indicated that the configurations and locations of the interflavanoid linkages between the lower four units are C(4β)–C(8). Furthermore, on detailed examination of the partial degradation products by means of high-performance liquid chromatography (HPLC) and thin-layer chromatography (TLC), the absence of the 4,6-

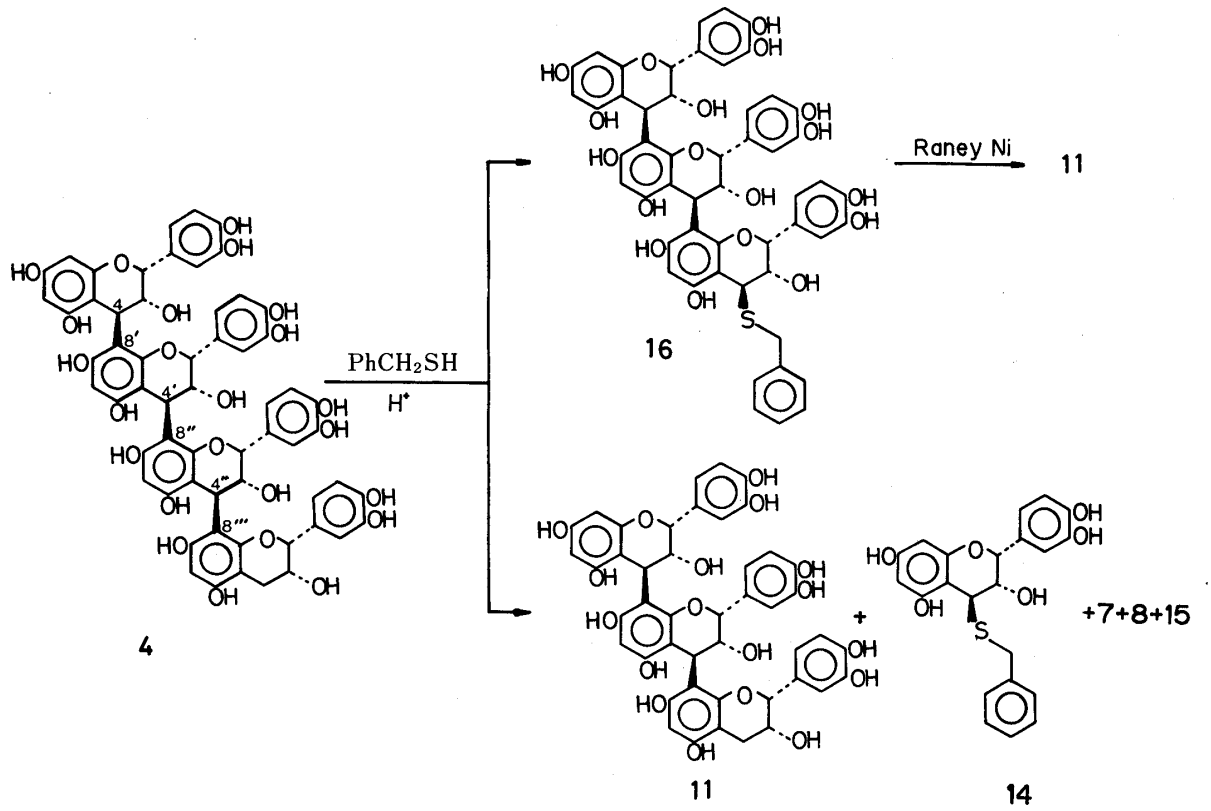

Chart 6

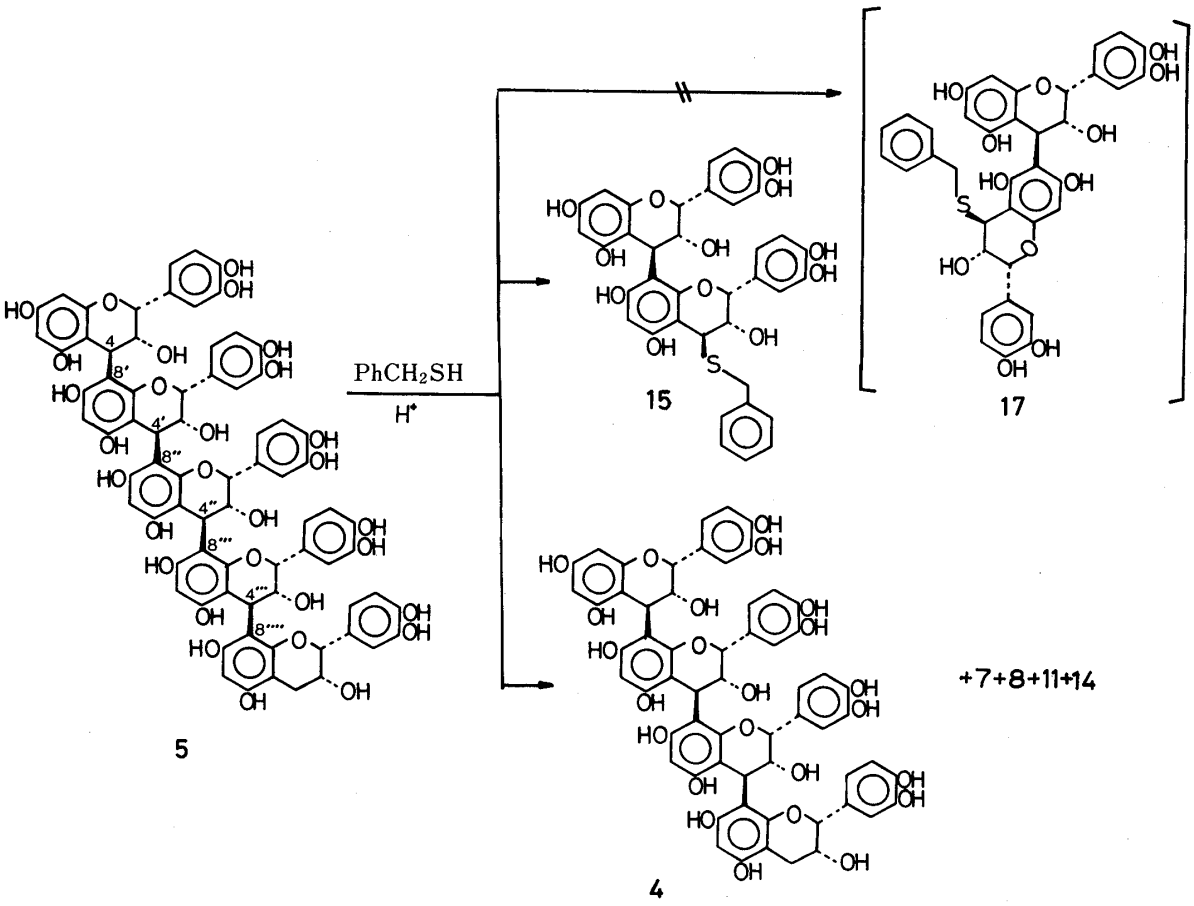

Chart 7

linked procyanidin benzylthioether (**17**) was demonstrated, indicating that all components are connected through C(4)–C(8) bonds. From these chemical and spectroscopic data, **5** was concluded to be epicatechin-(4β→8)-epicatechin-(4β→8)-epicatechin-(4β→8)-epicatechin-(4β→8)-epicatechin.

Compound **6** (cinnamtannin A_4) formed the tetracosamethyl ether (**6a**) on methylation with dimethyl sulfate and anhydrous potassium carbonate in dry acetone. The field-desorption mass spectrum (FD-MS) of the methyl ether (**6a**) showed the $(M+H)^+$ ion peak at *m/z* 2067, which is consistent with a hexaflavanoid constitution. The ^{1}H-NMR spectra of **6** and **6a** showed broad signal patterns, probably because of slow rotations about the interflavanoid bonds, and provided little information on its structure. However, examination of the ^{13}C-NMR spectrum of **6** suggested that it consists exclusively of epicatechin units. In the spectrum, the flavan C-2 signals appeared at δ 76.7 (5C) and 79.0, the former signals being attributed to C-2 in the upper units and the latter to that in the lower terminal unit. In addition, the chemical shifts of these signals were in good agreement with those found in compounds possessing epicatechin units.[10]

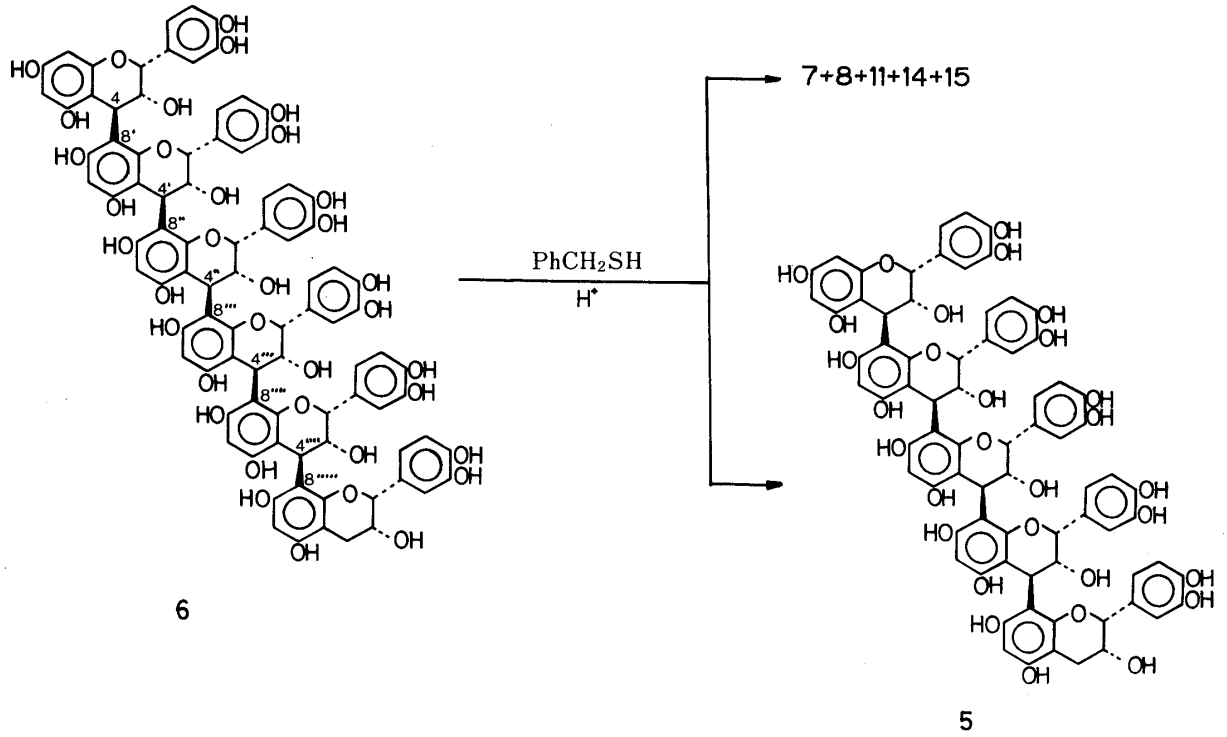

Chart 8

In order to establish the constitution of **6**, similar thiolytic degradation was attempted. On complete degradation, **6** afforded (−)-epicatechin (**7**) and the benzylthioether (**14**), while partial thiolysis yielded, together with the above products, procyanidins B-2 (**8**) and C-1 (**11**), compounds **4** and **5**, and the benzylsulfide (**15**) as isolable products, among which the production of **5** and **15** was of particular importance. In addition, TLC and HPLC analyses of the partial degradation products demonstrated the absence of the thioether **17**. Accordingly, compound **6** was shown to be a hexameric procyanidin possessing (−)-epicatechin units linked through C(4β)–C(8) bonds.

In conclusion, the procyanidins isolated from the bark of *C. cassia* were found to consist entirely of (−)-epicatechin units linked through C(4β)–C(8) bonds. It is interesting from the biosynthetic point of view that the bark of *C. cassia* predominantly contains the linearly-linked procyanidins, whereas the bark of *C. zeylanicum* and the root bark of *C. sieboldii*

contain large amounts of procyanidins with a doubly-linked unit (proanthocyanidin A-2 unit). Compounds **2** and **3** represent the first examples of C-glycosyl flavan-3-ols. It is also interesting that the glycosides of flavan-3-ols are rarely found in nature, although flavan-3-ols are regarded as metabolites derived from flavones,[13] which mostly occur as the glycosides.

Experimental

Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Optical rotations were taken with a JASCO DIP-4 digital polarimeter. FD- and FAB-MS were obtained with a JEOL JMS DX-300 instrument. ^{1}H- and ^{13}C-NMR spectra were recorded on JEOL PS-100 and JEOL FX-100 spectrometers, respectively, using tetramethylsilane as an internal standard, and chemical shifts are given in δ. Column chromatography was carried out with Sephadex LH-20 (25—100 μ, Pharmacia Fine Chemical Co., Ltd.), MCI-gel CHP 20P (75—150 μ, Mitsubishi Chemical Industries, Ltd.), Bondapak C_{18}/Porasil B (37—75 μ, Waters Associates, Inc.) and Kieselgel 60 (70—230 mesh, Merck). TLC was conducted on precoated Kieselgel 60 F_{254} plates (0.2 mm, Merck) and precoated cellulose F_{254} plates (0.1 mm, Merck), and spots were located by ultraviolet illumination and by spraying $FeCl_3$, anisaldehyde–sulfuric acid (for phenolics) and aniline–hydrogen–phtalate (for sugars) reagents. HPLC was conducted on a Toyo Soda apparatus equipped with an SP 8700 solvent delivery system and a UV-8 model II spectrophotometer.

Isolation——The powdered cassia bark (広南桂皮, 29.5 kg) was extracted five times with water at room temperature. The extract was concentrated under reduced pressure, and the brown residue was chromatographed over MCI-gel CHP 20P with water and then with MeOH. The MeOH eluate (212 g) was subjected to Sephadex LH-20 chromatography. Elution with EtOH afforded fractions 1 (21 g), 2 (89 g) and 3 (61 g). Fraction 1 was chromatographed over Sephadex LH-20 with acetone to give fractions 1-a (3.5 g) and 1-b (4.5 g). Fraction 1-a was repeatedly chromatographed over Sephadex LH-20 (80% aqueous MeOH) and Bondapak C_{18} (20% aqueous MeOH) to yield compounds **1** (82 mg), **2** (67 mg) and **3** (52 mg). Fraction 1-b was chromatographed over Sephadex LH-20 with 60% aqueous MeOH. Elution with the same solvent, followed by crystallization from H_2O, afforded compound **7** (215 mg). Fraction 2 was further divided by Sephadex LH-20 chromatography with 60% aqueous MeOH into two fractions; fractions 2-a (61 g) and 2-b (2.1 g). Chromatography of fraction 2-a on Sephadex LH-20 (EtOH) and MCI-gel CHP 20P (30% aqueous MeOH) columns gave compounds **8** (12 g) and **11** (35 g). Fraction 2-b was chromatographed over Sephadex LH-20 (60% aqueous MeOH) to afford compounds **9** (38 mg) and **10** (25 mg). Fraction 3 was repeatedly chromatographed over Sephadex LH-20 (EtOH) and MCI-gel CHP 20P (30% aqueous MeOH) to afford compounds **4** (1.1 g), **5** (215 mg) and **6** (173 mg).

Compound 1——An off-white amorphous powder, $[\alpha]_D^{19}$ −71.5° (c=1.0, MeOH). *Anal.* Calcd for $C_{21}H_{24}O_{11}\cdot H_2O$: C, 53.61; H, 5.57. Found: C, 53.51; H, 5.40. FAB-MS m/z: 453 $(M+H)^+$. ^{1}H-NMR (acetone-d_6) δ: 2.58 (1H, dd, J=7, 16 Hz, H-4), 2.83 (1H, dd, J=5, 16 Hz, H-4), 4.41 (1H, m, H-3), 4.55 (1H, d, J=7 Hz, anomeric H), 5.15 (1H, d, J=2 Hz, H-2), 5.94 (1H, d, J=2 Hz, H-6), 6.04 (1H, d, J=2 Hz, H-8), 6.72 (1H, dd, J=2, 8 Hz, H-6′), 6.84 (1H, d, J=8 Hz, H-5′), 7.15 (1H, d, J=2 Hz, H-2′). ^{13}C-NMR; Table I.

Enzymatic Hydrolysis of 1 with Crude Hesperidinase——A solution of **1** (25 mg) in H_2O (2 ml) was incubated overnight with crude hesperidinase at 37 °C. The solvent was evaporated off under reduced pressure, and the residue was treated with MeOH. The MeOH-soluble portion was subjected to Sephadex LH-20 chromatography. Elution with MeOH afforded glucose, which was identified by cellulose TLC [*Rf*: 0.38; solvent: *n*-BuOH–pyridine–H_2O (6:4:3)], and (−)-epicatechin (**7**) (11 mg), colorless prisms, mp 240 °C, $[\alpha]_D^{20}$ −60.0° (c=1.1, acetone).

Methylation of 1——A mixture of **1** (25 mg), dimethyl sulfate (0.6 ml) and anhydrous potassium carbonate (1 g) in dry acetone (10 ml) was refluxed for 3 h with stirring. After removal of the inorganic salts by filtration, the filtrate was concentrated under reduced pressure. The oily residue was applied to a silica gel column with EtOAc–MeOH–H_2O (20:2:1) to give the tetramethylether (**1a**) (20 mg) as a white amorphous powder, $[\alpha]_D^{19}$ −51.3° (c=1.0, acetone). *Anal.* Calcd for $C_{25}H_{32}O_{11}$: C, 59.05; H, 6.34. Found: C, 59.41; H, 6.12. ^{1}H-NMR ($CDCl_3$) δ: 2.83 (2H, m, H-4), 3.72 (6H, s, OMe × 2), 3.80, 3.84 (each 3H, s, OMe), 4.19 (1H, m, H-3), 4.64 (1H, d, J=7 Hz, anomeric H), 4.99 (1H, s, H-2), 6.06 (1H, d, J=2 Hz, H-6), 6.13 (1H, d, J=2 Hz, H-8), 6.70—7.20 (3H in total, m, H-2′,5′,6′).

Acid Hydrolysis of 1a——A mixture of **1a** (15 mg) and 0.5 N methanolic HCl (5 ml) was refluxed for 1 h. Neutralization with Amberlite IRA-400 (OH^- form) and evaporation of the solvent gave a syrup, which was chromatographed on silica gel [benzene–acetone (4:1)] to give 5,7,3′,4′-tetra-*O*-methyl-(−)-epicatechin (**7a**) (7 mg) as colorless needles (MeOH), mp 188 °C, $[\alpha]_D^{20}$ −34.2° (c=0.5, acetone).

Compound 2——An off-white amorphous powder, $[\alpha]_D^{19}$ −37.5° (c=0.9, acetone). *Anal.* Calcd for $C_{21}H_{24}O_{11}\cdot H_2O$: C, 53.61; H, 5.57. Found: C, 53.50; H, 5.95. FAB-MS m/z: 453 $(M+H)^+$. ^{1}H-NMR (acetone-d_6) δ: 2.85 (2H, m, H-4), 4.20 (1H, m, H-3), 4.92 (1H, d, J=7 Hz, anomeric H), 4.93 (1H, s, H-2), 6.08 (1H, s, H-6), 6.77 (1H, dd, J=2, 7 Hz, H-6′), 6.88 (1H, d, J=7 Hz, H-5′), 7.19 (1H, d, J=2 Hz, H-2′). ^{13}C-NMR: Table I.

Methylation of 2——A mixture of **2** (15 mg), anhydrous potassium carbonate (1 g) and dimethyl sulfate (0.6 ml) in dry acetone (10 ml) was refluxed for 2 h with stirring. The reaction mixture was worked up as before, yielding a

tetramethylether (**2a**) (10 mg) as a white amorphous powder, $[\alpha]_D^{19}$ −18.2° (c=0.9, acetone). *Anal.* Calcd for $C_{25}H_{32}O_{16}\cdot H_2O$: C, 57.03; H, 6.51. Found: C, 57.41; H, 6.32. FD-MS m/z: 509 $(M+H)^+$. ^{1}H-NMR (acetone-d_6) δ: 2.84 (2H, m, H-4), 3.80, 3.84 (12H, each s, OMe × 4), 4.23 (1H, m, H-3), 4.82 (1H, d, J=7 Hz, anomeric H), 5.01 (1H, s, H-2), 6.31 (1H, s, H-6), 6.80—7.30 (3H in total, m, H-2′,5′,6′). ^{13}C-NMR: Table I.

Degradation of 2 with $FeCl_3$——A mixture of **2** (10 mg) and $FeCl_3$ (50 mg) in H_2O (2 ml) was refluxed for 5 h. The reaction mixture was passed through an Amberlite MB-3 column, and the eluate was concentrated under reduced pressure. The syrupy residue thus obtained was subjected to Avicel cellulose TLC [*n*-BuOH–pyridine–H_2O (6 : 4 : 3)]. Spots corresponding to glucose (Rf 0.38) and arabinose (Rf 0.35) were detected on the chromatogram.

Compound 3——An off-white amorphous powder, $[\alpha]_D^{19}$ +8.85° (c=1.1, MeOH). *Anal.* Calcd for $C_{21}H_{24}O_{12}\cdot H_2O$: C, 53.61; H, 5.57. Found: C, 53.97; H, 5.60. FAB-MS m/z: 453 $(M+H)^+$. ^{1}H-NMR (acetone-d_6) δ: 2.80 (2H, m, H-4), 4.23 (1H, m, H-3), 4.87 (1H, s, H-2), 4.95 (1H, d, J=7 Hz, anomeric H), 6.04 (1H, s, H-8), 6.90—7.10 (3H in total, m, H-2′,5′,6′). ^{13}C-NMR: Table I.

Methylation of 3——A mixture of **3** (15 mg), anhydrous potassium carbonate (1 g) and dimethyl sulfate (0.6 ml) in dry acetone (10 ml) was refluxed for 3 h with stirring. The reaction mixture was worked up as before, yielding a tetramethyl ether (**3a**) (8 mg) as a white amorphous powder, $[\alpha]_D^{19}$ +11.3° (c=1.1, acetone). *Anal.* Calcd for $C_{25}H_{32}O_{11}\cdot H_2O$: C, 57.03; H, 6.51. Found: C, 57.33; H, 6.81. FAB-MS m/z: 509 $(M+H)^+$. ^{1}H-NMR (acetone-d_6) δ: 2.84 (2H, m, H-4), 3.73, 3.80 (12H, each s, OMe × 4), 4.26 (1H, m, H-3), 4.68 (1H, d, J=7 Hz, anomeric H), 5.04 (1H, s, H-2), 6.30 (1H, s, H-8), 6.80—7.20 (3H in total, m, H-2′,5′,6′). ^{13}C-NMR: Table I.

Degradation of 3 with $FeCl_3$——A mixture of **3** (10 mg) and $FeCl_3$ (50 mg) in H_2O (2 ml) was refluxed for 5 h. The reaction mixture was worked up as before to afford a syrup, which was examined by Avicel cellulose TLC [*n*-BuOH–pyridine–H_2O (6 : 4 : 3)], and spots corresponding to glucose (Rf 0.38) and arabinose (Rf 0.35) were detected.

Preparation of 2 and 3——A mixture of (−)-epicatechin (**7**) (2.7 g), D-glucose (0.8 g) and *p*-toluenesulfonic acid (50 mg) in dry dioxane (70 ml) was refluxed for 12 h. The reaction mixture was concentrated under reduced pressure. The residue was repeatedly chromatographed over Sephadex LH-20 (60% aqueous MeOH) and MCI-gel CHP 20P (20% aqueous MeOH) to yield compounds **2** (78 mg) and **3** (62 mg).

Compound 4——A pale brown amorphous powder, $[\alpha]_D^{23}$ +89.2° (c=0.9, acetone). *Anal.* Calcd for $C_{60}H_{50}O_{24}\cdot 3H_2O$: C, 59.60; H, 4.67. Found: C, 60.00; H, 4.50. FAB-MS m/z: 1155 $(M+H)^+$. ^{1}H-NMR (acetone-d_6) δ: 2.84 (2H, m, H-4‴), 4.12 (3H, br s, H-3,3′,3″), 4.32 (1H, br s, H-3‴), 4.79 (3H, br s, H-4,4′,4″), 5.08, 5.16, 5.20, 5.22 (each 1H, s, H-2,2′,2″,2‴), 5.80—6.20 (5H in total, m, A-ring H), 6.40—7.40 (12H in total, m, B-ring H). ^{13}C-NMR: Table II.

Complete Thiolytic Degradation of 4——A mixture of **4** (100 mg), benzylmercaptan (2 ml) and acetic acid (3 ml) in EtOH (10 ml) was refluxed for 24 h with stirring. The reaction mixture was concentrated under reduced pressure, and the oily residue was subjected to Sephadex LH-20 chromatography. Elution with 80% aqueous MeOH afforded compound **7** (25 mg). Further elution with the same solvent yielded compound **14** (31 mg) as a white amorphous powder, $[\alpha]_D^{24}$ −34.5° (c=1.0, acetone). ^{1}H-NMR (acetone-d_6) δ: 3.96 (1H, br s, H-3), 4.01 (2H, s, $-SCH_2-$), 4.08 (1H, d, J=3 Hz, H-4), 5.24 (1H, s, H-2), 5.90 (1H, d, J=2 Hz, H-6), 6.07 (1H, d, J=2 Hz, H-8), 6.70—7.60 (8H in total, m, aromatic H).

Partial Thiolytic Degradation of 4——A mixture of **4** (800 mg), benzylmercaptan (4 ml) and acetic acid (3 ml) in EtOH (20 ml) was refluxed for 6 h. The reaction mixture was worked up as before to give compounds **7** (34 mg), **8** (78 mg), **11** (66 mg), **14** (56 mg) and **15** (33 mg), and the trimeric procyanidin benzylthioether **16** (7 mg). **16**: An off-white amorphous powder, $[\alpha]_D^{24}$ +51.2° (c=1.1, acetone). *Anal.* Calcd for $C_{52}H_{44}O_{18}S\cdot 3H_2O$: C, 59.88; H, 4.83. Found: C, 60.12; H, 4.49. ^{1}H-NMR (acetone-d_6) δ: 3.90—4.20 (6H in total, m, $-SCH_2-$, H-3,3′,3″,4″), 4.58, 4.68 (each 1H, s, H-4,4′), 4.95 (1H, s, H-2″), 5.28 (2H, br s, H-2,2′), 5.80—6.40 (4H in total, m, A-ring H), 6.60—7.60 (14H in total, m, aromatic H).

Desulfurization of 16——A solution of **16** (6 mg) in acetic acid–EtOH (1 : 9) (1 mg) was treated with Raney nickel (W-4) at room temperature for 1 h. Removal of the catalyst by filtration and chromatography over Sephadex LH-20 with EtOH afforded procyanidin C-1 (**11**) (3 mg).

Compound 5——A pale brown amorphous powder, $[\alpha]_D^{24}$ +102.1° (c=1.0, acetone). *Anal.* Calcd for $C_{75}H_{62}O_{30}\cdot 3H_2O$: C, 60.16; H, 4.58. Found: C, 60.00; H, 4.50. FAB-MS m/z: 1481 $(M+K)^+$. ^{1}H-NMR (acetone-d_6) δ: 2.83 (2H, m, H-4⁗), 4.10 (4H, br s, H-3,3′,3″,3‴), 4.36 (1H, br s, H-3⁗), 4.63, 4.68, 4.80 (4H, each s, H-4,4′,4″,4‴), 4.96, 5.04, 5.20, 5.27 (5H, each s, H-2,2′,2″,2‴,2⁗), 5.80—6.20 (6H in total, m, A-ring H), 6.50—7.20 (15H in total, m, B-ring H). ^{13}C-NMR: Table II.

Complete Thiolytic Degradation of 5——A mixture of **5** (30 mg), benzylmercaptan (1.5 ml) and acetic acid (2 ml) in EtOH (10 ml) was heated under reflux for 24 h with stirring. Work-up as described for compound **4** afforded compounds **7** (7 mg) and **14** (13 mg).

Partial Thiolytic Degradation of 5——A mixture of **5** (150 mg), benzylmercaptan (3 ml) and acetic acid (2 ml) in EtOH (15 ml) was refluxed for 6 h. Work-up as before afforded compounds **7** (6 mg), **8** (29 mg), **11** (19 mg), **14** (11 mg) and **15** (13 mg).

Compound 6——A pale brown amorphous powder, $[\alpha]_D^{22}$ +112.5° (c=0.9, acetone). *Anal.* Calcd for $C_{90}H_{74}O_{36}\cdot 3H_2O$: C, 60.54; H, 4.52. Found: C, 60.92; H, 4.81. ^{13}C-NMR: Table II.

Methylation of 6——A mixture of **6** (16 mg), anhydrous potassium carbonate (0.8 g) and dimethyl sulfate (0.5 ml) in dry acetone (8 ml) was heated under reflux for 3 h. The reaction mixture was treated as before to afford the tetracosamethyl ether (**6a**) (5.5 mg) as a white amorphous powder, $[\alpha]_D^{22}$ +110.5° (c=0.3, acetone). *Anal.* Calcd for $C_{114}H_{122}O_{36}\cdot H_2O$: C, 65.63; H, 5.99. Found: C, 66.05; H, 6.32. FD-MS m/z: 2067 $(M+H)^+$.

Complete Thiolytic Degradation of 6——A mixture of **6** (30 mg), benzylmercaptan (1 ml) and acetic acid (2 ml) in EtOH (10 ml) was treated as described for compound **4** to give compounds **7** (5 mg) and **14** (10 mg).

Partial Thiolytic Degradation of 6——A mixture of **6** (100 mg), benzylmercaptan (3 ml) and acetic acid (2 ml) in EtOH (20 ml) was refluxed for 5 h with stirring. The reaction mixture was treated as described for compound **4** to give compounds **4** (5 mg), **5** (14 mg), **7** (6 mg), **8** (15 mg), **11** (12 mg), **14** (9 mg) and **15** (7 mg).

HPLC Analyses of Thiolytic Degradation Products of 5 and 6——A mixture of **5** (5 mg), benzylmercaptan (0.2 ml) and acetic acid (0.3 ml) in EtOH (2 ml) was refluxed for 4 h. The reaction mixture was concentrated under reduced pressure, and the oily residue thus obtained was analyzed by HPLC (TSK-gel LS 410 K; solvent, 25% aqueous acetonitrile; flow rate, 0.75 ml/min), which showed peaks due to compounds **4** (t_R 7.7 min), **7** (t_R 6.2 min), **8** (t_R 5.5 min), **11** (t_R 6.2 min), **14** (t_R 31.0 min), **15** (t_R 24.2 min) and **16** (t_R 24.6 min). Similar thiolytic degradation of **6** and HPLC analysis confirmed the production of compounds **5** (t_R 7.9 min), **4**, **7**, **8**, **11**, **14** and **15**.

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