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The Constituents of Cinnamomi Cortex. I. Structures of Cinncassiol A and Its Glucoside

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Compounds I—X were isolated from the water extractive of Cinnamomi Cortex, which shows anti-complement activity. Among them, the structures of I—VI were clarified on the basis of chemical and spectral studies. Compounds I and II were identified as cinnzeylanine and cinnzeylanol, respectively. Compounds III and IV were proved to be dehydrated products of I and II, respectively. Compound V was shown to be 19-hydroxylated IV and was named cinncassiol A. VI was identified as cinncassiol A 19-O-β-D-glucopyranoside.

Keywords——Cinnamomi Cortex; diterpenoids; anti-complement activity; cinncassiol A; cinncassiol A 19-O-β-D-glucopyranoside

Cinnamomi Cortex is one of the most widely used Chinese drugs. Recently, Koda *et al.*[2] have reported that the water extractives of Cinnamomi Cortex (*Cinnamomum cassia* Blume; Kannan Keihi in Japanese) exhibit potent anti-complement activity. Thus, we designed experiments to identify the substance possessing this activity. As shown in Chart 1, compounds I—X have been isolated from the acetone fraction, which shows anti-complement activity.

This paper deals with the structure elucidation of compounds I—VI.

Compound I, $C_{22}H_{34}O_8$, mp 278—279°. $[\alpha]_D$ +60.8° (MeOH), whose molecular formula was determined by high resolution mass spectrometry and elementary analysis, showed the presence of hydroxyl (3440 cm^{-1}) and acetoxyl (1685 cm^{-1})[3] functions in the infrared (IR) spectrum. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of I showed signals due to three secondary methyls (δ 0.83, 0.93, 1.00), two tertiary methyls (δ 0.86, 1.33), one acetoxyl (δ 2.07) and one acetoxy-methine (d of J=10 Hz, δ 5.27). In addition, its carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum showed the presence of five tertiary carbons (δ 83.1, 86.0, 86.4, 89.8 and 97.1) each bearing a tertiary hydroxyl group. The above spectroscopic data are reminiscent of those of cinnzeylanine,[4] a novel type of pentacyclic diterpenoid isolated from *Cinnamomum zeylanicum* Nees as an insecticidal substance. By direct comparison (mp, TLC and ^{1}H-NMR) with an authentic specimen, I was identified as cinnzeylanine.

Compound II, $C_{20}H_{32}O_7$, mp 139—142°, $[\alpha]_D$ +30.6° (MeOH), showed hydroxyl absorption (3440 cm^{-1}) in its IR spectrum. The ^{1}H-NMR spectrum of II resembled that of I except for the absence of the acetoxyl signal. II was thus supposed to be a deacetylated compound of I, that is, cinnzeylanol.[4] This was substantiated by direct comparison (mp, IR and ^{1}H-NMR) with cinnzeylanol derived from I by alkaline hydrolysis.

1) Location: *a) 3-1-1, Maedashi, Higashi-ku, Fukuoka 812, Japan; b) 6-1, Higashi-5-chome, Mitahora, Gifu 502, Japan.*
2) A. Koda, E. Katsuta, and S. Watanabe, *Nippon Yakurigaku Zasshi*, **66**, 366 (1970); A. Koda and H. Nagai, *Proc. Symp. Wakan-Yaku*, **8**, 13 (1974); H. Nagai, M. Ichikawa, S. Watanabe, and A. Koda, *Proc. Symp. Wakan-Yaku*, **11**, 51 (1978).
3) Shifted towards lower wave number owing to intermolecular hydrogen bonding.
4) A. Isogai, A. Suzuki, S. Tamura, S. Murakoshi, Y. Ohashi, and Y. Sasada, *Agrc. Biol. Chem.*, **40**, 2305 (1976); A. Isogai, S. Murakoshi, A. Suzuki, and S. Tamura, *Agrc. Biol. Chem.*, **41**, 1779 (1977).

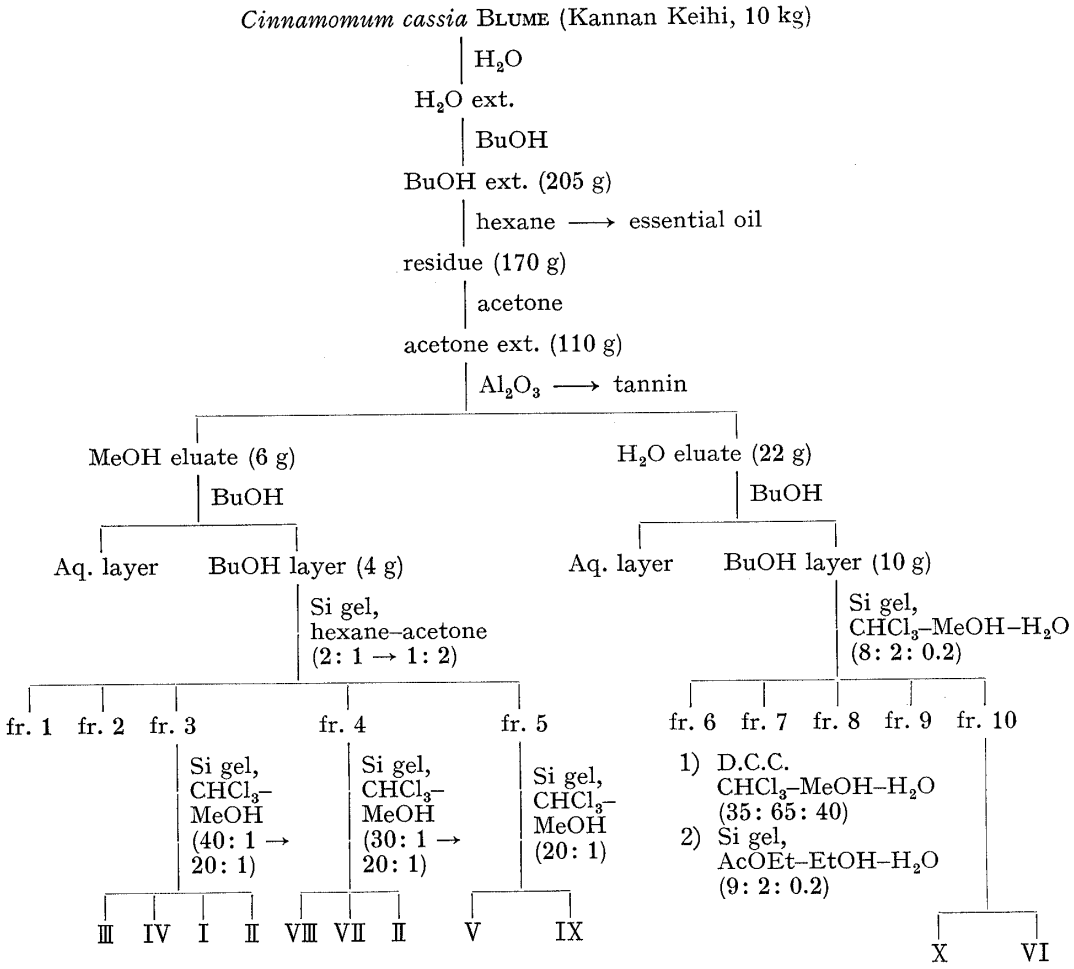


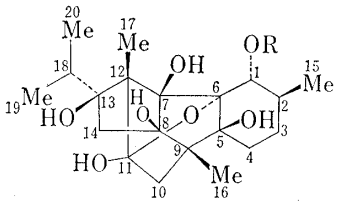
Chart 1

Compound III, $C_{22}H_{32}O_7$, mp 195—199°, $[\alpha]_D$ +88.7° (MeOH), showed the presence of hydroxyl (3440 cm^{-1}), acetoxyl (1720 cm^{-1}) and δ-lactone (1750 cm^{-1})[5] in the IR spectrum. The ^{1}H-NMR spectrum of III, in comparison with that of I, exhibited a signal due to a vinyl methyl (3H, br s, δ 1.65) instead of one tertiary methyl at C-12 on the skeleton of I. Irradiation of an allylic proton (1H, m) around δ 2.64 changed two doublet signals at δ 0.94 and 0.96, ascribable to two secondary methyls attached to C-18, into two singlets. Therefore, this allylic proton is assignable as 18-H, and the double bond should be located at C-12 (13). On the basis of the above spectroscopic data III seems likely to be anhydrocinnzeylanine[4] which was artificially obtained by Tamura *et al.* upon acid treatment of cinnzeylanine (I). Acid hydrolysis (1N HCl–MeOH, under reflux for 15 min) of I gave a product identical with III.

Compound IV, $C_{20}H_{30}O_6$, mp 205—207°, $[\alpha]_D$ +56.4° (MeOH), showed hydroxyl (3400 cm^{-1}) and δ-lactone (1740 cm^{-1}), but no acetyl absorptions in the IR spectrum. Since the ^{1}H-NMR spectrum revealed a pattern similar to that of III except for the acetyl signal, IV is assumed to be anhydrocinnzeylanol[4] which was obtained by acid treatment of II. Alkali treatment of III gave a product identical with IV.

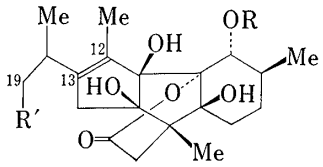
Compound V, $C_{20}H_{30}O_7$, mp 172—174°, $[\alpha]_D$ +30.2° (MeOH), whose molecular formula includes one more oxygen atom than that of IV, showed the presence of hydroxyl (3440 cm^{-1}) and δ-lactone (1725 cm^{-1}) groups in the IR spectrum. The ^{1}H-NMR spectrum showed signals due to two secondary methyls (δ 1.12 and 1.23). one tertiary methyl (δ 1.22), one vinyl methyl

5) These assignments were based on a comparison with those for IV. The presence of lactone and acetoxyl groups was also supported by the ^{13}C-NMR evidence (δ 171.6 and 170.6).



I: R=Ac
II: R=H

Formula 1



III: R=Ac, R′=H
IV: R=R′=H
V: R=H, R′=OH
V′: R=H, R′=OTs
VI: R=H, R′=O-β-D-glc·pyr
VI′: R=Ac, R′=O-2′,3′,4′,6′-tetra-O-acetyl-β-D-glc·pyr

Formula 2

(δ 2.15), one methylene (2H, br s, δ 2.58) adjacent to a carbonyl, one hydroxymethyl (2H, d, J=7 Hz, δ 3.59) and one proton (d, J=10 Hz, δ 4.56) of a secondary hydroxyl group. Comparison of the ^{1}H-NMR spectra of V and IV revealed that V possesses a $-CH_2-O-$ function instead of a secondary methyl, with no significant difference in other signals. When a signal around δ 3.0, attributable to one allylic proton at C-18 was irradiated, the doublet signal of the hydroxymethyl changed into a singlet together with a change of the doublet signal (δ 1.12) due to secondary methyl at C-18 into a singlet. Thus, it was concluded that the new hydroxymethyl is at C-18. This structure, including the stereochemistry in regard to the asymmetric cabons except for C-18, was substantiated by chemical correlation between V and IV. The monotosylate (V′) of V on lithium aluminum hydride reduction gave a product identical with IV. The structure of V, named cinncassiol A, is shown above.

Compound VI, $C_{26}H_{40}O_{12}$, amorphous, $[\alpha]_D$ +5.6° (MeOH), showed strong OH absorption (3440 cm^{-1}), probably glycosidic, together with δ-lactone (1720 cm^{-1}) absorption in the IR spectrum. Enzymatic hydrolysis of VI with crude hesperidinase afforded an aglycone identical with cinncassiol A (V) and D-glucose. Therefore, VI is a glucoside of V. In order to determine the location of the glycosyl linkage, VI was acetylated to yield an acetate (VI′), mp 112—115°, whose ^{1}H-NMR spectrum (Fig. 1). showed five acetoxy signals (δ 2.02, 2.04, 2.06, 2.10, 2.19). By assignment of the corresponding protons as shown in Fig. 1, the acetate was proved to be the 1,2′,3′,4′,6′-pentaacetate.

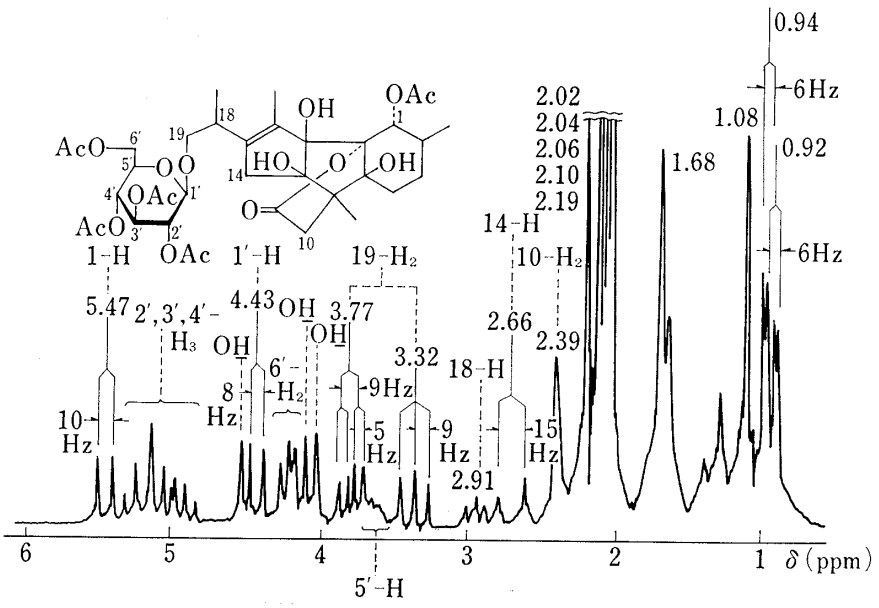
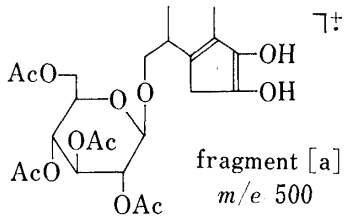


Fig. 1. ^{1}H-NMR Spectrum of VI′ ($CDCl_3$).

A triplet signal at δ 3.32 and a quartet at δ 3.77, both of which are coupled with each other and with 18-H (as determined by spin decoupling experiments), are assignable to the hydroxymethyl attached to C-18 on cinncassiol A (V). Taking into account these chemical shifts and their relationships, it is rationalized that the glucosyl moiety should be bound with C-19-OH in VI. In addition, a prominent peak of *m/e* 500 in the mass spectrum of VI', which is probably due to the fragment [a], provides support for this 19-O-glucoside structure. The glucosyl linkage was concluded to be a β-one on the basis of the coupling constant value[6] (1H, d, J=8 Hz, δ 4.43) of the glucosyl anomeric proton and the difference[7] of molecular rotation between V and VI (ΔM_D=−84°). Consequently, VI was concluded to be cinncassiol A 19-O-β-D-glucopyranoside.



Formula 3

Experimental

The following instruments were used to obtain physical data: mp (Yanagimoto micro-melting apparatus; data are recorded uncorrected); specific rotations (JASCO DIP-SL); IR spectra (JASCO DS-701 G); MS and high resolution MS (JEOL 01SG and JEOL 01SG-2); ^{1}H-NMR and ^{13}C-NMR spectra (JEOL XL-100 (100 MHz) and PS-100, respectively, with tetramethylsilane as an internal standard). Silica gel (Merck, 70—230 mesh) and alumina (Merck, 70—230 mesh) were used for column chromatography, and Kieselgel 60 (Merck, DC-Fertigplatten) was used for TLC. Detection was done by spraying 10% H_2SO_4 and heating.

Isolation of Diterpenoids——Commercial Cinnamomi Cortex (Kannan Keihi, 10 kg) was extracted three times with dist. water (8 l each) at 60°. The combined extract was shaken with *n*-BuOH (total volume: 40 l). The organic layer was concentrated under reduced pressure to give a residue (205 g), which was refluxed with *n*-hexane (1 l) for 1 hr to remove essential oil (30 g). The insoluble residue (170 g) was then refluxed with acetone (1 l) for 30 min. The acetone solution obtained by filtration was evaporated down to give a brown resinous syrup (110 g), which was subjected to alumina (*ca.* 2 kg) column chromatography eluting first with MeOH (3 l) and then with water (3 l). The eluates were concentrated to give a yellow syrup (6 g) and a light brown resin (22 g), respectively. The former was partitioned between *n*-BuOH and water. The *n*-BuOH layer was taken up and evaporated to dryness *in vacuo* to give a residue (4 g), which was subjected to silica gel chromatography. Repeated silica gel chromatography using *n*-hexane–acetone (2: 1→1: 1→1: 2) and $CHCl_3$–MeOH (40: 1→30: 1→20: 1) as solvents furnished compounds I (200 mg), II (230 mg), III (100 mg), IV (150 mg), V (250 mg), VII (50 mg), VIII (45 mg) and IX (30 mg). The latter eluate from the alumina column was concentrated under reduced pressure to give a residue (22 g), which was shaken with *n*-BuOH and water as mentioned above. The organic layer was concentrated to give a residue (10 g), which was purified by silica gel column chromatography (solv. $CHCl_3$–MeOH–H_2O=8: 2: 0.2 and AcOEt–EtOH–H_2O=9: 2: 0.2) and droplet counter-current chromatography (D.C.C.; moving phase= lower layer of $CHCl_3$–MeOH–H_2O=35: 65: 40; stationary phase=the upper layer) to furnish compounds X (50 mg) and VI (300 mg).

Identity of Compound I with Cinnzeylanine——Colorless plates from benzene–AcOEt, mp 278—279°, $[\alpha]_D^{26}$ +60.8° (c=1.28, MeOH). *Anal.* Calcd for $C_{22}H_{34}O_8$: C, 61.95; H, 8.04. Found: C, 61.94; H, 8.01. IR ν_{max}^{KBr} cm^{-1}: 3440 (OH), 1685 (ester). High resolution MS: Found (%) 366.206 (base peak), 348.194(39), 223.134(37), 177.095(30). Calcd for $C_{20}H_{30}O_6$(M^+−AcOH)=366.204, $C_{20}H_{28}O_5$=348.194, $C_{13}H_{19}O_3$=223.134, $C_{11}H_{13}O_2$=177.092. ^{1}H-NMR (CD_3OD) δ: 0.83, 0.93, 1.00 (3H each, all d of J=6 Hz, 3×*sec.*CH_3), 0.86 (3H, s, *tert.*CH_3), 1.33 (3H, s, *tert.*CH_3), 1.74 (1H, d, J=15 Hz), 2.07 (3H, s, $-OCOCH_3$), 2.41 (1H, d, J=15 Hz), 5.27 (1H, d, J=10 Hz, >C<u>H</u>–OAc). ^{13}C-NMR (CD_3OD) δ: 9.6, 11.1, 18.3, 18.7, 19.0, 21.4 (6×$-CH_3$), 26.9, 28.9, 43.0, 49.3 (4×$-CH_2-$), 33.8, 33.9 (2×⩾CH), 48.3, 66.0 (2×⩾C–), 74.1 (>CH–O–), 83.1, 86.0, 86.4, 89.8, 97.1 (5×–<u>C</u>–O–), 102.0 (–O–<u>C</u>–O–), 172.4 (C=O).

Identity of Compound II with Cinnzeylanol——Colorless plates from benzene–AcOEt. mp 139—142°, $[\alpha]_D^{26}$ +30.6° (c=0.53, MeOH). *Anal.* Calcd for $C_{20}H_{32}O_7\cdot H_2O$: C, 59.68; H, 8.51. Found: C, 59.26; H, 8.46. IR ν_{max}^{KBr} cm^{-1}: 3440 (OH). High resolution MS: Found (%) 384.215(9), 349.197(10), 348.194(38), 341.162(19), 331.188(18), 330.182(73), 324.159(19), 323.151 (base peak). Calcd for $C_{20}H_{32}O_7$(M^+)=384.215, $C_{20}H_{29}O_5$=349.201, $C_{20}H_{28}O_5$=348.194, $C_{17}H_{25}O_7$=341.160, $C_{20}H_{27}O_4$=331.191, $C_{20}H_{26}O_4$=330.183, $C_{17}H_{24}O_6$=324.157, $C_{17}H_{23}O_6$=323.150. ^{1}H-NMR (CD_3OD) δ: 0.95, 1.00, 1.00 (3H each, all d of J=6 Hz, 3×*sec.*CH_3), 0.86, (3H, s, *tert.*CH_3), 1.32 (3H, s, *tert.*CH_3), 1.76 (1H, d, J=15 Hz), 2.41 (1H, d, J=15 Hz), 3.78

6) R.U. Lemiux, R.K. Kullnig, H.J. Bernstein, and W.G. Schreider, *J. Am. Chem. Soc.*, **80**, 6 (1958).
7) W. Klyne, *Biochem. J.*, **47**, xii (1950).

(1H, d, J=10 Hz, -CH-OH). (d_5-Py) δ: 1.22 (3H, s, *tert.*CH_3), 1.23 (3H, d, J=6 Hz, *sec.*CH_3), 1.29, 1.45 (3H each, both d of J=7 Hz, 2×*sec.*CH_3), 2.12 (3H, s, *tert.*CH_3), 2.46, 2.86 (1H each, both d of J=15 Hz), 4.54 (1H, d, J=10 Hz).

Alkali Treatment of I to give II——Compound I (30 mg) was dissolved in 3% KOH–MeOH (2 ml) and kept for twenty minutes at room temperature. After addition of water, the reaction mixture was extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate and evaporated to dryness *in vacuo*. The residue was purified by silica gel column chromatography using $CHCl_3$–MeOH (10: 1) as an eluent to afford crystals (5 mg, mp 138—140°), identical with those of II.

Compound III (Anhydrocinnzeylanine)——Colorless plates from benzene–AcOEt. mp 195—199°, $[\alpha]_D^{26}$ +88.7° (c=1.0, MeOH). *Anal.* Calcd for $C_{22}H_{32}O_7 \cdot C_6H_6$: C, 69.11; H, 7.87. Found: C, 68.92; H, 7.85. IR ν_{max}^{KBr} cm^{-1}: 3440 (OH), 1750 (lactone), 1720 (OAc). High resolution MS: Found (%) 390.205(22), 331.190(13), 237.112(44), 178.102(28), 177.093(base peak), 154.099(28). Calcd for $C_{22}H_{30}O_6$ (M^+-H_2O)= 390.204, $C_{20}H_{27}O_4$=331.191, $C_{13}H_{17}O_4$=237.113, $C_{11}H_{14}O_2$=178.099, $C_{11}H_{13}O_2$=177.092, $C_9H_{14}O_2$=154.099. ^{1}H-NMR ($CDCl_3$) δ: 0.92, 0.94, 0.96 (3H each, all d of J=6 Hz, 3×*sec.*CH_3), 1.08 (3H, s, *tert.*CH_3), 1.65 (3H, br s, vinyl CH_3), 2.15 (3H, s, -OCOCH$_3$), 2.32 (2H, br s, 10-H$_2$), 2.61 (1H, d, J=15 Hz), 2.64 (1H, m, 18-H), 3.67, 4.27, 4.80 (1H each, all s, 3×OH), 5.42 (1H, d, J=10 Hz, >CH-OAc). ^{13}C-NMR (CD_3OD) δ (off reson.): 11.9(q), 13.5(q), 18.2(q), 20.3(q), 20.6(q), 21.4(q), 26.5(t), 28.2(t), 28.7(t), 34.0, 37.2(t), 40.5(t), 48.0(t), 74.6(d), 84.5(s), 88.9(s), 92.3(s), 96.3(s), 134.2(s), 146.2(s), 170.6(s), 171.6(s).

Acid Treatment of I to give III——After refluxing compound I (30 mg) with 1 N HCl–MeOH (2 ml) on a hot bath for 15 minutes, the reaction mixture was neutralized with 3% KOH–MeOH. The resulting salts were filtered off and the filtrate was passed through Sephadex LH-20 with methanol as an eluent to give III (9 mg), mp 194—196°, $[\alpha]_D^{27}$ +87.8° (c=0.32, MeOH), which was identical with anhydrocinnzeylanine.

Compound IV (Anhydrocinnzeylanol)——Colorless plates from benzene–AcOEt. mp 205—207°, $[\alpha]_D^{28}$ +56.4° (c=0.51, MeOH). *Anal.* Calcd for $C_{20}H_{30}O_6$: C, 65.55; H, 8.25. Found: C, 65.07; H, 8.24. IR ν_{max}^{KBr} cm^{-1}: 3440 (OH), 1740 (lactone). High resolution MS: Found (%) 348.195(4), 196.108(30), 195.102 (base peak). Calcd for $C_{20}H_{28}O_5$(M^+-H_2O)=348.194, $C_{11}H_{16}O_3$=196.110, $C_{11}H_{15}O_3$=195.102. ^{1}H-NMR ($CDCl_3$) δ: 0.94, 0.98, 1.10 (3H each, all d of J=6 Hz, 3×*sec.*CH_3), 1.08 (3H, s, *tert.*CH_3), 1.72 (3H, br s, vinyl CH_3), 2.38 (2H, s, 10-H$_2$), 3.56, 4.17, 4.67 (1H each, all s), 4.03 (1H, d, J=10 Hz, >CH-OH). (d_5-Py) δ: 0.79, 1.07, 1.29 (3H each, all d of J=6 Hz, 3×*sec.*CH_3), 1.31 (3H, s, *tert.*CH_3), 2.27 (3H, br s, vinyl CH_3), 2.68 (2H, s, 10-H$_2$), 4.76 (1H, d, J=10 Hz).

Compound V (Cinncassiol A)——Colorless plates from dil.methanol. mp 172—174°, $[\alpha]_D^{32}$ +30.2° (c=1.1, MeOH); $[M]_D$ +115°. *Anal.* Calcd for $C_{20}H_{30}O_7$: C, 62.81; H, 7.91. Found: C, 62.88; H, 7.90. IR ν_{max}^{KBr} cm^{-1}: 3440 (OH), 1725 (lactone). MS m/e: 364 (M^+-H_2O, $C_{20}H_{28}O_6^+$), 195, 177, 170. ^{1}H-NMR (d_5-Py) δ: 1.12 (3H, d, J=7 Hz, *sec.*CH_3), 1.22 (3H, s, *tert.*CH_3), 1.23 (3H, d, J=6 Hz, *sec.*CH_3), 2.15 (3H, br s, vinyl CH_3), 2.58 (2H, br s), 3.59 (2H, d, J=7 Hz, -CH$_2$-OH), 4.56 (1H, d, J=10 Hz).

Transformation of V into IV——A mixture of V (60 mg) and *p*-toluenesulfonyl chloride (20 mg) in pyridine (5 ml) was left to stand for one day at room temperature. Ice-water was added to the reaction mixture and the whole was extracted with AcOEt. The organic layer was evaporated to dryness *in vacuo* to give a residue, which was chromatographed on silica gel (20 g), eluting with $CHCl_3$–MeOH (30: 1), to afford the monotosylate (35 mg). Rf 0.77 ($CHCl_3$–MeOH=10: 1), MS m/e: 500 (M^+-2H_2O), 195, 177, 172, 152, 149, 91. The monotosylate (30 mg) was reduced with $LiAlH_4$ (20 mg) in dry tetrahydrofuran (4 ml) under reflux for 3.5 hr. The usual work-up of the reaction mixture and the subsequent purification by conventional silica gel column chromatography (15 g, solv. $CHCl_3$–MeOH=30: 1) gave the product (20 mg), mp 206—207° (from benzene–AcOEt), $[\alpha]_D^{14}$ +52.9° (c=0.61, MeOH), which was identical with IV.

Compound VI (Cinncassiol A 19-O-β-D-glucopyranoside)——Colorless powder (mp 95—99°), $[\alpha]_D^{25}$ +5.6° (c=2.82, MeOH); $[M]_D$ +31°. *Anal.* Calcd for $C_{26}H_{40}O_{12}$: C, 57.34; H, 7.40. Found: C, 57.77; H, 7.38. IR ν_{max}^{KBr} cm^{-1}: 3440 (OH), 1720 (lactone).

Enzymatic Hydrolysis of VI——Cinncassiol A 19-O-β-D-glucopyranoside (VI, 110 mg) was incubated with crude hesperidinase (40 mg) in dist. water (6 ml) at 40° for 4 hr. The reaction mixture was evaporated to dryness, giving a residue to which methanol was added. After filtration, the filtrate was subjected to Sephadex LH-20 column chromatography with methanol as a solvent. The early eluate gave the aglycone (35 mg), mp 171—174°, $[\alpha]_D^{28}$ +33.4° (c=0.62, MeOH), which was identified as cinncassiol A (V). The later eluate gave D-glucose, $[\alpha]_D^{23}$ +48.2° (c=0.36, water), Rf 0.37 (on PPC with Toyo Roshi No. 50 paper: visualizing agent, aniline hydrogene phthalate; solvent, the upper layer of *n*-BuOH–Py–water=6: 2: 3+py (1)).

VI-Pentaacetate (VI′)——VI (40 mg) was acetylated with acetic anhydride (2 ml) and pyridine (2 ml) for 14 hr at room temperature, giving the pentaacetate (VI′), 16 mg, mp 112—115° (colorless needles from dil. MeOH). MS m/e: 736 (M^+-H_2O), 500 (found 500.186. Calcd for $C_{23}H_{32}O_{12}$=500.188), 331 ($C_{14}H_{19}O_9^+$), 239, 229, 177, 169, 139, 109. ^{1}H-NMR ($CDCl_3$): see Fig. 1.

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