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DIMERIC ELLAGITANNINS IN PLANTS OF MELASTOMATACEAE

Takashi Yoshida,[a] Yoshitaka Ikeda,[a] Hideyuki Ohbayashi,[a] Koukichi Ishihara,[a] Wakayo Ohwashi,[a] Tetsuro Shingu,[b] and Takuo Okuda*,[a]

Faculty of Pharmaceutical Sciences, Okayama University,[a] Tsushima, Okayama 700, Japan and Faculty of Pharmaceutical Sciences, Kobe-Gakuin Univesity,[b] Ikawadani, Nishi-ku, Kobe 673, Japan

Six novel ellagitannins, four of which are dimers mutually correlated in their structures, have been isolated from Tibouchina semidecandra, and Medinilla magnifica. Their structures were elucidated based on spectral and chemical evidence.

KEYWORDS — Tibouchina semidecandra; Medinilla magnifica; Melastomataceae; ellagitannin; nobotanin A; nobotanin B; nobotanin D; nobotanin F; medinillin A; medinillin B

Some plants of Melastomataceae have been used traditionally as astringents, antidiarrheics and hemostatics in diverse areas of southeast Asia.[1] Although tannin is presumably responsible for these medicinal applications, no chemical study on tannins of this family has yet been reported. We have found that the leaves of Tibouchina semidecandra Cogn. and Medinilla magnifica Lindle. are rich in tannins, and have isolated new ellagitannin oligomers named nobotanin A, B and F, and monomeric nobotanin D from the former plant. We have also isolated medinillin A (monomer) and medinillin B (dimer) from the latter. Here we report on the structures of these new tannins.[2]

Nobotanin A (**1**), B (**2**), F (**3**) and medinillin B (**4**) are ellagitannin dimers as evidenced by the characteristic color with $NaNO_2$-AcOH reagent and high-performance gel permeation chromatography. On acid hydrolysis, all of these tannins gave glucose, and gallic acid, ellagic acid and valoneic acid dilactone which were characterized as the methyl derivatives.

Nobotanin F (**3**), an off-white amorphous powder, $C_{82}H_{56}O_{52}\cdot 8H_2O$, $[\alpha]_D$ +60° (MeOH), showed a $[M+Na]^+$ peak at m/z 1895 in the FAB-mass spectrum. The ^{1}H-NMR spectrum of **3** indicates the presence of three galloyl groups (δ 7.19, 7.17, 7.16), two hexahydroxydiphenoyl (HHDP) groups and a valoneoyl group [δ 7.04, 6.48, 6.46, 6.45, 6.42, 6.39, 6.21 (1H each, s)], and two anomeric protons (δ 6.17, 6.18). The β-orientation of the acyloxy groups on the anomeric centers in both glucose cores of the $^4C_1$ conformation is shown by the large coupling constants, $J_{1,2}$=8.4 Hz, $J_{2,3}=J_{3,4}=J_{4,5}$=10 Hz. The ^{13}C-NMR spectrum has peaks at δ 92.4

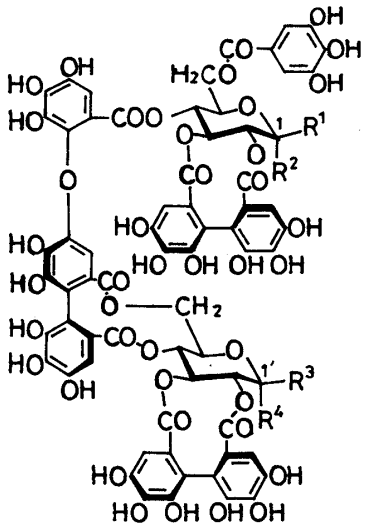
and 92.3 due to the anomeric carbons characteristic of ellagitannins having a galloyl group or galloyl as part of the valoneoyl group at O-1, and an HHDP or a valoneoyl group at O-2～O-3 of the glucose core.[3] Methylation of **3** with dimethyl sulfate and potassium carbonate in acetone gave a product of partial degradation, which was identical with the octadecamethyl derivative (**6**) of rugosin C,[4] together with the permethylated derivative, methyl tri-O-methylgallate and dimethyl hexamethoxydiphenate. Upon hydrolysis in boiling water for 15 h, **3** furnished five partial hydrolysates, **7**～**11**, among which two were identified as 2,3-O-(S)-hexahydroxydiphenoyl-D-glucose (**7**) and isostrictinin (**8**).[5] All of the remaining hydrolysates **9**～**11** possess a galloyl and a dilactonized valoneoyl group as common components, as demostrated by the UV (220, ～265 and ～365 nm) and the ^{1}H-NMR spectra.[6] Compound **10**, which is a mixture of α- and β-anomers as revealed by the double signals in its ^{1}H-NMR spectrum, was obtained also by degalloylation with tannase of the fully acylated compound **9**. This finding and ^{1}H-NMR spectral comparison of **9** and **11** allow the assignments of one of two galloyl groups and the HHDP group to be at O-1 and O-2～O-3 in **9**, respectively. Locations of the additional galloyl group and the lactonized valoneoyl group in **9** were determined to be at O-6 and O-4 respectively as follows. Medinillin B (**4**), which was chemically correlated with **3** as described later, provided 6-O-galloyl-2,3-O-HHDP-D-glucose (**12**)[7] upon hydrolysis in boiling water. Furthermore, in the ^{1}H-NMR spectrum, the second galloyl group in **9** absorbs significantly more upfield (δ 6.89) than the galloyl group at O-1 (δ 7.09). This unusual upfield shift of one of the galloyl groups can be most reasonably explained by the magnetic anisotropy of the lactonized valoneoyl group at O-4. Therefore, the structures of these hydrolysates are represented by **9**, **10** and **11**. The S-configuration of the HHDP and valoneoyl groups in **3** was evidenced by a strong positive Cotton effect at 235 nm ([θ] +32.4 x 10^4) and a negative one at 261 nm ([θ] -10.2 x 10^4) in the CD spectrum.[8] Based on these data, nobotanin F is formulated as **3**.

Nobotanin B (**2**), an off-white amorphous powder, $C_{82}H_{56}O_{52}\cdot 15H_2O$, $[\alpha]_D$ +54° (MeOH), was shown to be an isomer of nobotanin F, by its CD ($[\theta]_{236}$ +39.8 x 10^4), $[\theta]_{262}$ -13.9 x 10^4) and NMR spectra [^{1}H-NMR δ: 7.30, 7.12, 6.99 (2H each, s, galloyl x 3), 7.15, 6.65, 6.56, 6.48, 6.46, 6.41, 6.12 (1H each, s, HHDP x 2, valoneoyl x 1), 6.21, 6.04 (1H each, d, J=8.4 Hz, glucose H-1). ^{13}C-NMR δ: 92.4 (2C, glucose C-1)]. Hydrolysis of **2** in boiling water yielded partial hydrolysates, **8**, **9** and **11**. HPLC analysis showed the formation of **8** and **9** in a ratio approximately 1:1 in the early stage of the reaction, indicating that nobotanin B (**2**) differs from **3** only in the orientation of the valoneoyl group at O-4 and O-6 of one of the glucose residues. This assignment was confirmed by production of an octadecamethyl derivative (**13**) [^{1}H-NMR δ: 7.23 (2H, s), 7.15, 6.95, 6.87, 6.66, 6.50 (1H each, s, HHDP and valoneoyl), 6.18 (1H, d, J=8.4 Hz, glucose H-1), 4.01-3.65 (18 x OMe)], which is isomeric to **6**, upon methylation with dimethyl sulfate and potassium carbonate in acetone. Based on the above evidence, structure **2** was assigned to nobotanin B.

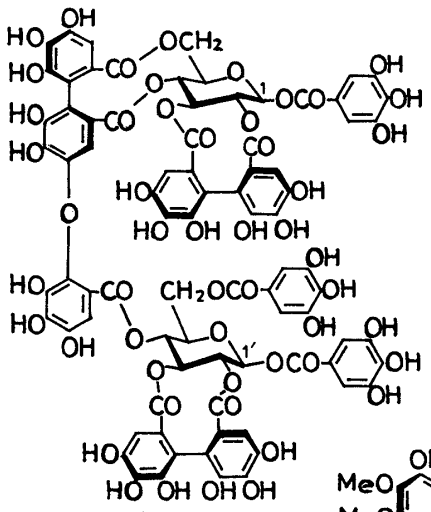
Nobotanin A (**1**), $C_{75}H_{52}O_{48}\cdot 8H_2O$, $[\alpha]_D$ +88° (MeOH), displays the ^{1}H-NMR peaks due to a valoneoyl, two galloyl and two HHDP groups, each of which appears as double peaks [δ 7.19, 7.17 (1H total 4H, galloyl), 6.98, 6.92, 6.75, 6.65, 6.53, 6.50, 6.47, 6.45, 6.44, 6.43, 6.41, 6.33, 6.31, 6.22 (HHDP x 2, valoneoyl x 1)].

In addition, a paired-doublet assignable to an anomeric proton of glucose appears at δ 6.20 and 6.17 (in total 1H, J=8.5 Hz), while signals of another anomeric proton appear at δ 5.50 (J=3.2 Hz) and 5.17 (J=8.5 Hz). These signals indicate that 1 has a free anomeric hydroxyl group in the molecule to form an equilibrium mixture of α- and β-anomers. Upon the partial hydrolysis with boiling water, 1 afforded isostrictinin (8) and 10. These data suggest that 1 is a derivative of nobotanin F (3) or nobotanin B (2) degalloylated at C-1, and the structure (1) from the former was verified by degalloylation of 3 with tannase to give nobotanin A.

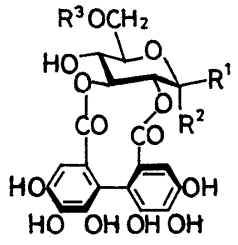
Medinillin B (4), a light brown amorphous powder, $C_{68}H_{48}O_{44}.10H_2O$, $[\alpha]_D$ +35° (MeOH), FAB-MS, m/z 1591 $[M+Na]^+$, exhibits signals for a valoneoyl, a galloyl and two HHDP groups in the ^{1}H-NMR spectrum. Formation of four lines by each proton signal, combined with absence of an anomeric proton signal in the region δ 6.00-6.50, indicates that both anomeric hydroxyl groups of the glucose residues are not acylated, and that 4 exists as a mixture of four tautomers. Partial hydrolysis of medinillin B gave 7, 10 and 12. Based on these data and the formation of medinillin B upon hydrolysis of 1 and 3 with tannase, medinillin B was characterized as degalloylnobotanin A (4).



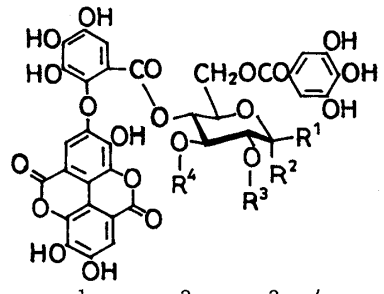
1: R^1,R^2=H,OH, R^3=OG, R^4=H
3: R^1=R^3=OG, R^2=R^4=H
4: R^1,R^2=H,OH, R^3,R^4=H,OH



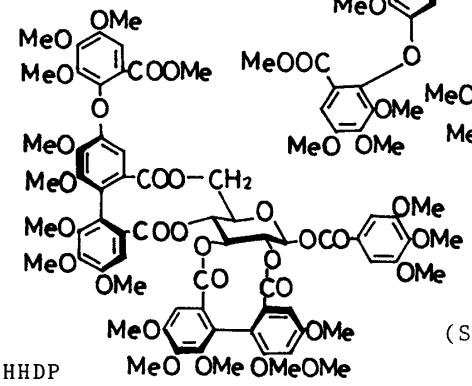
2



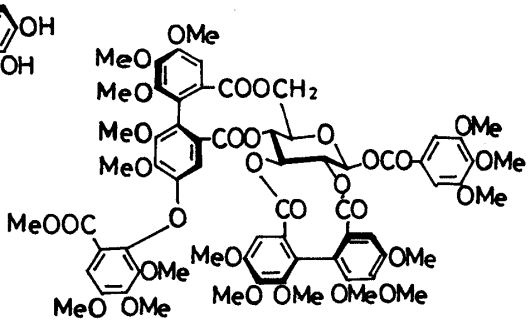
5: R^1=OG, R^2=H, R^3=G
7: R^1,R^2=H,OH, R^3=H
8: R^1=OG, R^2=R^3=H
12: R^1,R^2=H,OH, R^3=G



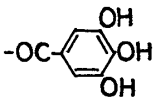
9: R^1=OG, R^2=H, R^3~R^4=(S)-HHDP
10: R^1,R^2=H,OH, R^3~R^4=(S)-HHDP
11: R^1=OG, R^2=R^3=R^4=H

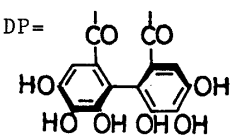


6



13

G= 

(S)-HHDP= 

Nobotanin D (**5**), $C_{34}H_{26}O_{22}\cdot 7H_2O$, $[\alpha]_D$ -68° (MeOH), is a monomeric ellagitannin with an HHDP group and two galloyl groups, as shown by two 2H-singlets at δ 7.16 and 7.14, and two 1H-singlets at δ 6.72 and 6.44 in the ^{1}H-NMR spectrum. Sugar proton signals of **5** are very similar to those of 1,2,3,6-tetra-O-galloyl-β-D-glucose. Hydrolysis of nobotanin D with tannase gave **12** which was further hydrolysed to **7** upon prolonged hydrolysis. Therefore nobotanin D was established as 1,6-di-O-galloyl-2,3-O-(S)-hexahydroxydiphenoyl-β-D-glucose (**5**).

Medinillin A, $C_{48}H_{30}O_{30}\cdot 5H_2O$, $[\alpha]_D$ +65° (MeOH), was found by direct comparison of their physico-chemical properties to be identical with compound **10**.

Nobotanin A, B, F and medinillin B are the first examples of dimeric ellagitannins which are biogenetically regarded as the product of intermolecular C-O oxidative coupling[9] between the galloyl group at O-4 of a monomer and the HHDP group at O-4∼O-6 of another monomer.

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6) ^{1}H-NMR (400 MHz, acetone-d_6) **9**:δ 7.54, 7.20, 7.16 (valoneoyl), 7.09, 6.89 (galloyl x 2), 6.43,6.40 (HHDP), 6.18 (d, J=8.6 Hz, H-1), 5.53 (t, J=9.8 Hz, H-4), 5.41 (dd,J=9.8,9.4 Hz, H-3), 5.08 (dd, J=8.6, 9.4 Hz, H-2), 4.27 (ddd, J=9.8, 4.4, 1.5 Hz,H-5), 4.33 (dd, J=1.5, 13 Hz, H-6), 4.09 (dd, J=4.4, 13 Hz, H-6'). **10**: δ 7.53,7.52, 7.19, 7.16, 7.13, 7.12 (in total 3H, valoneoyl), 6.89, 6.87 (in total 2H, galloyl), 6.55, 6.54,6.39,6.38 (in total 2H, HHDP), glucose H: α-anomer; δ 5.38 (d,J=3.6 Hz, H-1), 4.95 (dd, J=3.6, 9.2 Hz, H-2), 5.43 (t, J=9.2 Hz,H-3), 5.38 (t, J=9.2 Hz, H-4), 4.25 (H-5), 4.15, 3.94 (H-6, 6'). β-anomer; δ 5.02 (d, J=8 Hz, H-1), 4.77 (dd, J=8,9.2 Hz, H-2), 5.19 (t, J=9.2 Hz, H-3), 5.37 (t, J=9.2 Hz, H-4), H-5 and H-6, 6' are overlaped by those of α-anomer. **11**: δ 7.53,7.24,7.15 (valoneoyl), 7.11,6.88 (galloyl x 2), 5.66 (d,J=8 Hz, H-1), 3.58 (dd, J=8, 9.6 Hz, H-2), 3.68 (t, J=9.6 Hz, H-3), 5.14 (t, J=9.6 Hz, H-4), 3.84 (ddd, J=9.6, 5, 1.2 Hz, H-5), 4.07 (dd, J=1.2, 12 Hz, H-6), 3.90 (dd, J=5, 12 Hz, H-6').
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