Faculty of Pharmaceutical Sciences,
Chiba University
1-33, Yayoi-cho, Chiba, 260,
Japan

KEIICHI YAMAGUCHI
HISASHI ISHII

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Novel Type Secoiridoid Glucosides, Hydrangenosides B, C and D from *Hydrangea macrophylla*

Along with the known hydrangenoside A (**4**), new glucosides of the same series, hydrangenosides B (**1**), C (**2**) and D (**3**), have been isolated from *Hydrangea macrophylla* and their absolute structures have been established. These substances are considered to be formed by an aldol-type condensation of secologanin (**5**) with a shikimate–malonate derived moiety followed by decarboxylation. Hydrangenoside A (**4**) and B (**1**) are stereoisomers, while hydrangenoside C (**2**) and D (**3**) are their homologues containing one fewer acetate unit and also are stereoisomers.

Keywords——*Hydrangea macrophylla*; Saxifragaceae; secoiridoid glucosides with shikimate–malonate derived side chain; Hydrangenosides B, C and D; structure elucidation

We have previously isolated hydrangenoside A from *Hydrangea macrophylla* (Thunb.) Ser. var. *macrophylla* (Japanese name, Ajisai) and established[1] that it has the novel structure **4** consisting of secologanin (**5**) and a unit formed by the shikimate–malonate route, which are joined through a C–C bond.

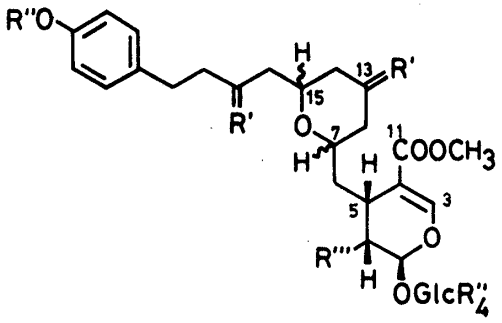
In this paper we describe the structure elucidation of three new glucosides, hydrangenosides B (**1**), C (**2**) and D (**3**), isolated as the minor components from the same plant.

The ethyl acetate soluble portion of the aqueous extract of the overground parts of *Hydrangea macrophylla* was fractionated by sequential silica gel column chromatography, droplet counter current chromatography and high performance liquid chromatography, affording hydrangenosides B (**1**), C (**2**) and D (**3**), along with hydrangenoside A (**4**).

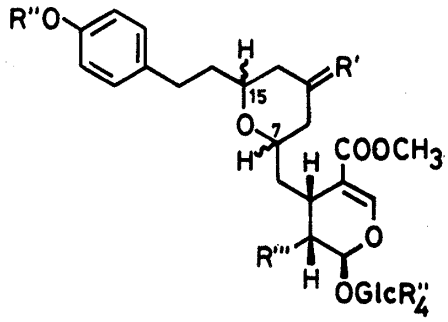
Hydrangenoside B (**1**) was obtained as a white powder, $C_{31}H_{40}O_{13}\cdot H_2O$, $[\alpha]_D$ −80.9° (MeOH). Its spectral data (infrared (IR), ultraviolet (UV) and ^1H nuclear magnetic resonance (NMR)) are in good accordance with those of hydrangenoside A (**4**), suggesting that **1** is closely related in structure to **4**. Acetylation of **1** gave a pentaacetate (**6**) whose ^1H NMR spectrum is similar to that of hydrangenoside A pentaacetate (**7**), except that the C-7 and C-15 protons of **6** resonate at higher field (δ 3.75 and 4.05) than those of **7** (δ 4.20 and 4.60, respectively). Additionally, the ^{13}C NMR signals of **6** are in agreement with those of **7**, except for the chemical shifts of C-7 and C-15 (δ 72.8 and 73.7). Thus, hydrangenoside B (**1**) is assumed to be a C-7 and/or C-15 stereoisomer of hydrangenoside A (**4**). In order to verify this assumption, **6** was subjected to the same chemical degradation as was **7**. Thus, **6** was converted, through $NaBH_4$ reduction, mesylation and 2,6-lutidine-induced elimination, into an olefinic mixture, which was hydrogenated over 10% Pd-C in AcOH to give the lactone (**8**), the 7-alcohol (**9**) and the tetrahydropyran (**10**).

The lactone (**8**) was identical to the 7*S*-isomer (whose ^1H NMR showed 11% nuclear Overhauser effect (NOE) between the C-5 and C-7 protons) of the two lactones[1] which had been synthesized by Grignard reaction of *p*-benzyloxyphenyloctanyl bromide (**11**) and secologanin tetraacetate (**12**). Since the conversion of **6** into **8** (*vide supra*) is expected to occur with

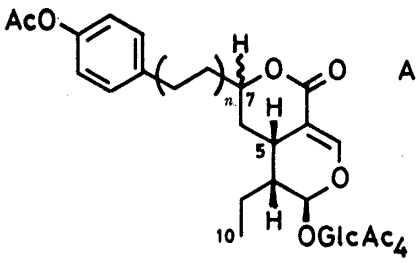
retention of configuration at all asymmetric centers except C-15, the C-7 configuration in hydrangenoide B (**1**), thus, must be *R*. Determination of the C-15 stereochemistry in **1**, the only remaining problem, was accomplished by comparison of ^{1}H- and ^{13}C NMR spectra of the aforementioned tetrahydropyran (**10**) and the *trans*-tetrahydropyran (**13**)[1] obtained from **7**. Maurer *et al.*[2] reported that in the ^{1}H NMR spectrum, both oxymethine protons of (*cis*-6-methyltetrahydropyran-2-yl)acetic acid (**14**) resonated *ca.* 0.5 ppm upfield relative to the



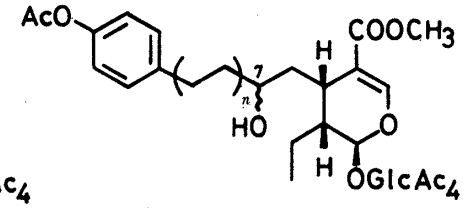
1: R'=O ; R''=H ; R'''= -CH=CH$_2$
7 ····H, 15 ····H
4: R'=O ; R''=H ; R'''= -CH=CH$_2$
7 ——H, 15 ····H
6: R'=O ; R''=Ac ; R'''= -CH=CH$_2$
7 ····H, 15 ····H
7: R'=O ; R''=Ac ; R'''= -CH=CH$_2$
7 ——H, 15 ····H
10: R'=H$_2$; R''=Ac ; R'''= -CH$_2$CH$_3$
7 ····H 15 ····H
13: R'=H$_2$; R''=Ac ; R'''= -CH$_2$CH$_3$
7 ——H, 15 ····H



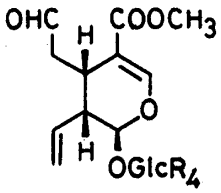
2: R'=O ; R''=H ; R'''= -CH=CH$_2$
7 ——H, 15 ····H
3: R'=O ; R''=H ; R'''= -CH=CH$_2$
7 ····H, 15 ····H
16: R'=O ; R''=Ac ; R'''= -CH=CH$_2$
7 ——H, 15 ····H
17: R'=H$_2$; R''=Ac ; R'''= -CH$_2$CH$_3$
7 ——H, 15 ····H
22: R'=O ; R''=Ac ; R'''= -CH=CH$_2$
7 ····H, 15 ····H
23: R'=H$_2$; R''=Ac ; R'''= -CH$_2$CH$_3$
7 ····H, 15 ····H



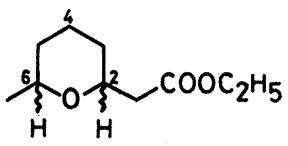
8: n = 4, 7 ——H
19: n = 3, 7 ····H
20: n = 3, 7 ——H



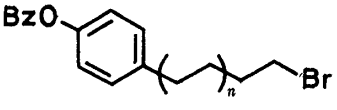
9: n = 4, 7 ——OH
18: n = 3, 7 ····OH
24: n = 3, 7 ——OH



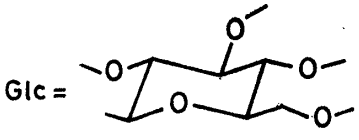
5: R = H
12: R = Ac



14: 2,6-*cis*
15: 2,6-*trans*



11: n = 3
21: n = 2



Bz = benzyl

corresponding protons of the *trans* isomer (**15**), and in the ^{13}C NMR spectrum, the signals for C-2, C-4 and C-6 in **15** appeared 5—6 ppm upfield compared with the corresponding resonances in **14**, this difference being due to the shielding induced by the γ-effect. On the other hand, the ^{1}H NMR spectrum of **10** showed signals for the C-7 and C-15 protons at δ 3.22, whereas that of the *trans* isomer (**13**) showed these resonances at δ 3.72. Furthermore, in the ^{13}C NMR spectrum of **10** the signals for carbons 7, 13 and 15 appeared *ca.* 5 ppm downfield relative to the corresponding resonances of **13**. Thus, based on the view-point of Maurer *et al.*, the C-7 and C-15 protons in **10** are assumed to be *cis*. Since the C-7 configuration in **1** is *R* (*vide supra*), that at C-15 is deduced to be *S*. From the evidence mentioned so far, the structure **1** is assigned to hydrangenoside B.

Hydrangenoside C (**2**) was obtained as a white powder, $C_{29}H_{38}O_{12}\cdot H_2O$, $[\alpha]_D$ $-94.7°$ (MeOH). Its spectral data (IR, UV, Mass and ^{1}H NMR) are similar to those of **1** and **4**. Acetylation of **2** gave a pentaacetate (**16**), whose ^{1}H NMR spectrum lacked the signals due to the ethyl moiety of the *p*-acetoxyphenylethylcarbonyl group appearing in **6** and **7**. The ^{13}C NMR spectrum of **16** is similar to those of **6** and **7**, the only difference being the absence of the three signals due to one keto-carbonyl carbon and the two methylene carbons linked to it. From these facts hydrangenoside C is presumed to have the structure **2** containing one fewer acetate unit than hydrangenoside A (**4**) or B (**1**), though there remain stereochemical uncertainties. Thus, **16** was subjected to chemical degradation in the same way as were **6** and **7**, giving the tetrahydropyran (**17**), the 7-alcohol (**18**) and the lactone (**19**). Compound (**18**) was further converted through mesylation into the 7-epilactone (**20**). Both compounds (**19**) and (**20**) were synthesized by condensation of secologanin tetraacetate (**12**) with the magnesium complex of *p*-benzyloxyphenylhexyl bromide (**21**), which was prepared from 5-bromopentan-1-ol tetrahydropyranyl ether and *p*-benzyloxybenzaldehyde through several steps. Thus, except for the configuration at C-7 and C-15, the stereostructure of hydrangenoside C (**2**) was elucidated. Furthermore, about 11% NOE was detected between the C-5 and C-7 protons of **20**, whereas no enhancement was observed between the corresponding protons of **19**. Thus, it became evident that **19** and **20** have C-7 configurations *R* and *S*, respectively, and hence that of hydrangenoside C (**2**) is *S*. The C-15 configuration of **2** was established in the following way. The ^{1}H- and ^{13}C NMR spectra of the tetrahydropyran (**17**) derived from **16** are similar to those of the *trans*-tetrahydropyran (**13**) formed from **7**, especially in terms of the signals of the C-7 and C-15 protons and the frequencies of the C-7, C-13 and C-15 carbons. Accordingly, the C-7 and C-15 protons of **17** are assumed to be *trans*. On the basis of the C-7 configuration of hydrangenoside C (**2**) being *S* (*vide supra*), that at C-15 is deduced to be *S* and the structure **2** is assigned to hydrangenoside C.

Hydrangenoside D (**3**) was obtained as colorless needles, $C_{29}H_{38}O_{12}\cdot H_2O$, mp 186—187°C, $[\alpha]_D$ $-126.3°$ (MeOH). Its spectral data (IR, UV, ^{1}H- and ^{13}C NMR) are in accordance with those of hydrangenoside C (**2**), suggesting that **3** is a congener of **2**. The ^{1}H NMR spectrum of the pentaacetate (**22**) of **3** is similar to that of **16**, except for the signals of the C-7 and C-15 protons, which appeared 0.6 ppm upfield relative to those (δ 4.06) of **16**. Furthermore, the ^{13}C NMR spectrum of **22** is similar to that of **16**, except for the signals of C-7 and C-15 (δ 75.2 and 77.0). As hydrangenoside D (**3**) is thus assumed to be a C-7 and/or C-15 stereoisomer of hydrangenoside C (**2**), **22** was subjected to chemical degradation in the same way as **16**, giving rise to the tetrahydropyran (**23**), the 7-alcohol (**24**), and the lactone (**20**). The formation of the latter (**20**) indicates *R*-chirality for C-7 in **3**. The ^{1}H- and ^{13}C NMR spectra of the tetrahydropyran (**23**) derived from **22** are similar to those of the *cis*-tetrahydropyran (**10**) arising from **6**, suggesting the *cis* orientation of the C-7 and C-15 protons of **3**. Since the C-7 configuration of **3** is *R* (*vide supra*), that at C-15 must be *S*. Thus the structure **3** is assigned to hydrangenoside D.

Hydrangenosides A (**4**) and B (**1**) are thought to be biosynthesized through an aldol-type condensation of secologanin (**5**) with a C-15 unit (C_6-C_3+3$\times$acetyl) formed by the shikimate–

malonate route, followed by decarboxylation and ether ring formation. Similarly, hydrangenosides C (2) and D (4) are presumed to be formed from 5 and a C-13 unit (C_6-C_3+2×acetyl).

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Faculty of Pharmaceutical Sciences,
Kyoto University,
Sakyo-ku, Kyoto 606, Japan

Shinichi Uesato
Toshihiro Hashimoto
Yoshio Takeda
Kenichi Uobe
Hiroyuki Inouye*

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A Highly Stereoselective Synthesis of *rel*[1*R*, 3*R*, 7*R*, 9*S*]9-Acetoxy-8,8-dimethyltricyclo[5.4.0.0^{1,3}]undecan-4-one, a Versatile Intermediate to Terpenoids. Synthesis of α-Onocerin

Hydrogenation of the tricyclic acetal **4**, which was prepared from the octalone **3** by 2 steps, yielded the *trans*-dihydro product **5** with high stereoselectivity, while hydrogenation of the dimethyloctalones, **8** and **9**, showed low stereoselectivity. **5** was converted to the cyclopropyl-decalone **2** in high yield. Reductive alkylation of **2** gave regioselectively the C_1 alkylated trimethyldecalone **12**, which was converted to the key intermediate to α-onocerin **16**, thus illustrating potential utility of **2** in terpenoid synthesis.

Keywords——Li–liq. ammonia reduction; reductive alkylation; stereoselectivity in hydrogenation; terpenoid synthesis; 8,8-dimethyl-tricyclo[5.4.0.0^{1,3}]undecane; cyclopropylketone; triterpenoid; α-onocerin

Although the trimethyl-*trans*-decalone-2 **1**[1] has been regarded as an attractive precursor of many terpenoid frameworks, its alkylation does not yield the 1-alkyl derivative but produces the 3-alkyl isomer.[2] For achieving selective C_1-alkylation in that system we have noticed to a 8,8-dimethyltricyclo[5.4.0.0^{1,3}]undecan-4-one, since there are several precedents of regiospecific reductive alkylation of a cyclopropylketone.[3] This communication describes efficient and highly stereoselective synthesis of its 9β-acetoxy derivative **2**, which would be a potential intermediate to a number of 3β-hydroxylated terpenoids.

The dimethyloctalone **3**, which is easily derivable from 2-ethoxycarbonyl-4,4-ethylenedioxycyclohexanone by Robinson annelation followed by methylation,[4] on reduction with $LiAlH_4$ followed by treatment with 1% *p*-TsOH in ethanol (90°C, 15 min) gave the cyclic ethylacetal **4**, mp 114—116°C,[5] [^{1}H-NMR δ: 1.22 (3H, t, J=7 Hz), 3.68 (2H, dq, J=7 and 2 Hz), and 5.64 (1H, t, J=3.4 Hz)]. Hydrogenation of **4** in ethanol over 20% Pd–C (3.6 kg/cm^2, 4 h) afforded the *trans*-isomer **5**, mp 123—125°C, [^{1}H-NMR δ: 0.89 and 1.01 (each 3H, s)], practically as a single product, which was most conveniently purified as the keto-monoacetate **7**,[6] mp 136—137°C, (67% yield from **3**) [IR cm^{-1}: 3350 and 1720, ^{1}H-NMR δ: 0.93, 0.95, and 2.01 (each 3H, s)], by acetylation (Ac_2O–pyr., r.t., overnight) and deacetalization with 1% HCl–acetone (60°C, 5 min) of the resulting acetate **6**, mp 108.5—110°C [IR cm^{-1}: 1725, ^{1}H-NMR δ: 2.03 (3H, s)].