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NEW SECOIRIDOID GLUCOSIDES, HYDRANGENOSIDES E, F AND G FROM HYDRANGEA SCANDENS

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Along with the known hydrangenosides C and D, new glucosides of the same series, hydrangenosides E, F, and G, have been isolated from Hydrangea scandens and their absolute structures have been established. These glucosides were found to consist of secologanin and a shikimate-malonate derived C-13 unit. Hydrangenoside G is considered to be a biogenetic intermediate of the other glucosides.

KEYWORDS —— Hydrangea scandens; Saxifragaceae; Secoiridoid glucosides; Hydrangenosides E, F, G; structure elucidation

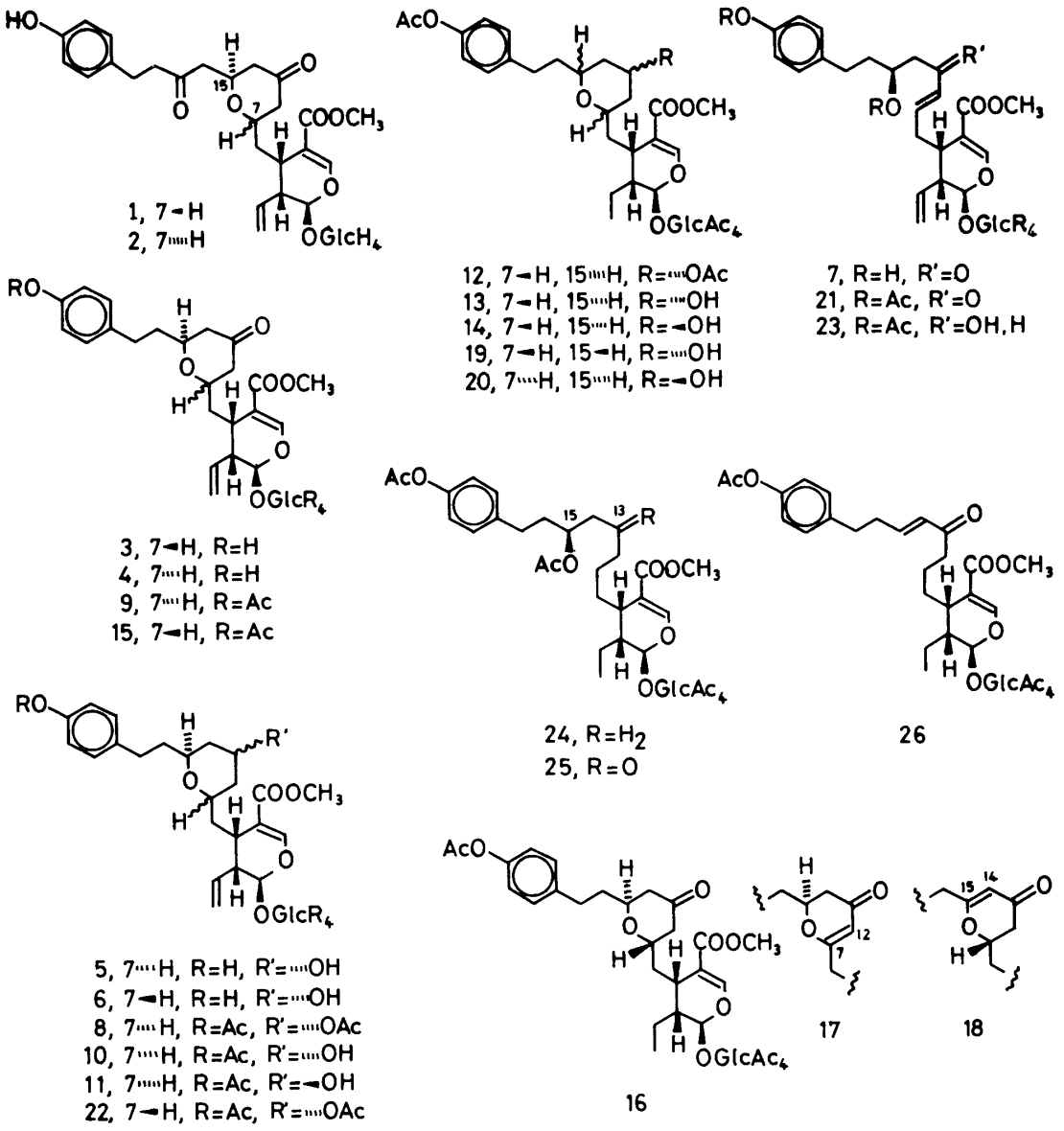
Previously, we isolated a novel type of secoiridoid glucosides, hydrangenosides A (**1**), B (**2**), C (**3**) and D (**4**) from Hydrangea macrophylla (Thunb.) Ser. var. macrophylla (Japanese name, Ajisai) and elucidated their absolute structures.[1,2] This paper describes the structure elucidation of three new related secoiridoid glucosides isolated from a congeneric plant, Hydrangea scandens (Linn, fil.) Seringe (Japanese name, Gakuutsugi).

The n-butanol-soluble portion of the methanolic extract of the leaves of H. scandens was fractionated by silica gel column chromatography and preparative thick layer chromatography, giving new iridoid glucosides, hydrangenosides E (**5**), F (**6**) and G (**7**), along with hydrangenosides C (**3**) and D (**4**).

Hydrangenoside E (**5**), $C_{29}H_{40}O_{12}\cdot H_2O$, a white powder, $[\alpha]_D$ -108.7° (MeOH), showed spectral data similar to those of hydrangenoside D (**4**). The ^{13}C- and ^{1}H NMR spectra of **5**, however, differed from those of **4** on the following points: i) Instead of signals due to the keto-carbonyl ($_C$ 209.7) and the two methylenes (δ_C 48.5 and 50.9) adjacent to it in the ^{13}C NMR spectrum of **4**, signals due to a hydroxymethine (δ_C 65.4) and the two methylenes (δ_C 39.2 and 39.7) linked to it were observed in the spectrum of **5**. ii) In place of signals due to the two methylenes (δ_H 2.70) adjacent to a keto group in the ^{1}H NMR spectrum of **4**, signals due to the two methylenes (δ_H 1.48) linked to a hydroxymethine appeared in the spectrum of **5**. The hexaacetate (**8**) of **5** also showed spectral data similar to those of the pentaacetate (**9**) of **4**. Therefore, hydrangenoside E (**5**) is assumed to be a 13-alcoholic congener of hydrangenoside D (**4**). This was verified by the identifi-

fication of **8** with the 13-acetate of the minor product **10** of both 13-alcoholic epimers **10** and **11** derived from **9** by $NaBH_4$ reduction. The remaining problem, the C-13 configuration of **5**, was solved by comparison of the ^{13}C NMR spectra of **10** and **11**. In the ^{13}C NMR spectra of alkylcyclohexanols, Roberts et al. observed 2-5 ppm upfield shifts of all the carbon signals except C-4 in each compound on going from an equatorial to an axial hydroxy group.[3] On the other hand, the ^{13}C NMR-signals due to carbons 7, 12, 13, 14 and 15 of **10** appeared about 3 ppm upfield relative to the corresponding frequencies of **11**. Application of the above-mentioned regularity to hydroxytetrahydropyrans **10** and **11** led us to deduce that the C-13 hydroxy group of **10** is axial and that of **11**, equatorial. In view of the cis-orientation of the C-7 and C-15 substituents in both compounds, which is the same as in **4**,[2] the substituents on these centers should assume the more stable equatorial position. Furthermore, since C-7 and C-15 of both **10** and **11** are R- and S-configurated, respectively, the configuration at the 13-position possessing an axial hydroxy group should be S, whereas that at the 13-position having an equatorial hydroxy group should be R. Thus, it is concluded that hydrangenoside E has the S-configuration at C-13 and is, therefore, represented by the structure **5**.

Hydrangenoside F (**6**), a stereoisomer of **5**, was obtained as a white powder, $[\alpha]_D$ -87.0° (MeOH). It showed spectral data similar to those of hydrangenoside C (**3**). The ^{13}C NMR spectrum of **6**, however, lacked the signals of a keto-carbonyl (δ_C 210.2) and the two methylenes (δ_C 47.4 and 50.9) linked to it appearing in the spectrum of **3**, but it showed the frequencies appropriate to a hydroxymethine (δ_C 64.9) and the two methylenes (δ_C 39.0 and 41.7) adjacent to it. These findings led us to the assumption that hydrangenoside F is a 13-alcoholic congener of hydrangenoside C (**3**) though there remains an uncertainty regarding the C-13 chirality. In fact, the dihydrohexaacetate (**12**) of **6** was identified with the acetate of the less polar alcohol (**13**) of both 13-alcoholic epimers **13** and **14**, which were derived from hydrangenoside C pentaacetate (**15**) through $NaBH_4$ reduction and Pd-C-catalyzed reduction. The C-13 configuration of **6** was elucidated in the following way. The dihydro compound (**16**), obtained by catalytic reduction of **15**, was treated with bromine to give a mixture consisting of four isomeric α-keto monobromides. Dehydrobromination of this mixture with MgO yielded the 7,12- and 14,15-dehydro compounds **17** and **18**, of which the major one, **18**, was reduced with $NaBH_4$ and hydrogenated over Pt to afford dihydrohydrangenoside F pentaacetate (**13**) and its stereoisomer **19**. The ^{13}C- and ^{1}H NMR spectra of **19** were quite similar to those of the dihydro derivative **20** of 13-epihydrangenoside E pentaacetate (**11**), especially in the signals due to the C-7, 13 and 15 positions. This observation suggested that the tetrahydropyran moiety of **19** has a cis-orientation between C-7 and 15 but is antipodal to that of **20**. Thus the C-13 configuration of **19** was deduced to be S, the opposite of the R-chirality for **20**. Since **13**, having been established as the 7,8-dihydropentaacetate of hydrangenoside F (vide supra), should possess the same chirality at C-13 as does **19**, hydrangenoside F is concluded to have the S-con-



figuration on C-13 and is represented by the structure **6**.

Hydrangenoside G (**7**), $C_{29}H_{38}O_{12}.H_2O$, a white powder, $[\alpha]_D$ -104.1° (MeOH), showed UV and IR data similar to those of **3**, **4**, **5** and **6**. The ^1H NMR spectrum of the hexaacetate (**21**) of **7** showed signals due to protons of the trans-olefin conjugated to a ketone at δ_H 5.96 (d, J=16 Hz) and 6.72 (m), but did not show any signals attributed to the protons of C-7 and C-15 oxymethines which were observed in the respective acetates **15**, **9**, **8** and **22** of **3**, **4**, **5** and **6**. In keeping with this observation, the ^{13}C NMR spectrum of **21** showed, besides signals arising from a sugar moiety, frequencies due to a keto-carbonyl (δ_C 196.8), olefinic carbons (δ_C 132.1 and 145.7) conjugated to it, a methine (δ_C 70.3) bearing an acetoxy group, etc. Based on the above spectral evidence and

the consideration of the biogenesis of the above-mentioned glucosides, hydrangenoside G is presumed to have the structure **7** comprising a straight side chain, though there remains a stereochemical uncertainty at C-15.

Thus, compound **21** was reduced with $NaBH_4$ to alcohol **23**, which on hydrogenation over Pd-C gave deoxytetrahydro compound (**24**). This compound was identified with the 15-alcohol acetate[2] obtained by the chemical modification of hydrangenoside C (**3**). Thus, the carbon-framework of **7** and the presence of a hydroxy group at the S-configurated C-15 were established. Next, catalytic reduction of **21** over Pd-C followed by the treatment of the resultant tetrahydro compound (**25**) with alumina yielded another conjugated ketone **26**. Its ^{13}C- and ^{1}H NMR spectra showed the presence of trans-olefin conjugated to the ketone (δ_C 130.8 and 145.7; δ_H 6.08 (d, J=16 Hz) and 6.76 (m)), indicating that **26** is formed through the elimination of an acetic acid from **25**. Thus, it was deduced that hydrangenoside G comprises a keto group at C-13, -- β-position to the hydroxy-bearing C-15 -- as well as a trans-olefin at the 7,12-position. From the findings mentioned so far, the structure **7** was assigned to hydrangenoside G. This was confirmed through the synthesis of **24** from secologanin with the defined structure, which will be reported elsewhere.[4]

All the glucosides of this plant described so far consist of secologanin and a shikimate-malonate derived C-13 unit. It is noteworthy that hydrangenoside G (**7**) has the same S-chirality at C-15 as the other glucosides with the tetrahydropyran ring. This fact strongly suggests that **7** is the biosynthetic intermediate of the other compounds.

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