Communications to the Editor

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RABDOSIIN, A NEW ROSMARINIC ACID DIMER WITH A LIGNAN SKELETON, FROM RABDOSIA JAPONICA

Isao Agata,[a] Tsutomu Hatano,[b] Sansei Nishibe,[a] and Takuo Okuda*,[b]

Faculty of Pharmaceutical Sciences, Higashi Nippon Gakuen University,[a] Ishikari-Tobetsu, Hokkaido 061-02, Japan and Faculty of Pharmaceutical Sciences, Okayama University,[b] Tsushima, Okayama 700, Japan

A rosmarinic acid dimer named rabdosiin (1) was isolated from the stem of Rabdosia japonica Hara (Labiatae). Its structure was determined including the absolute configurations at four asymmetric centers.

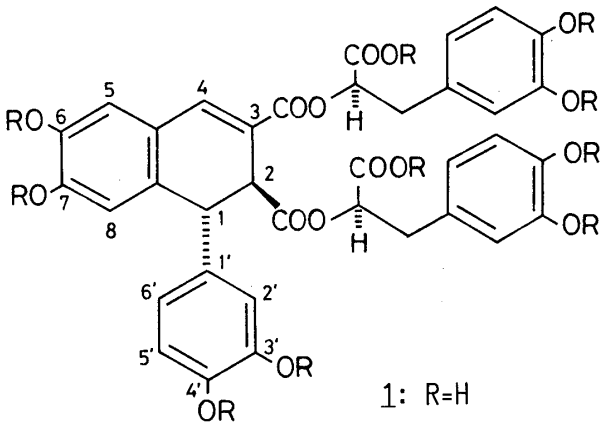
KEYWORDS — rabdosiin; caffeetannin; rosmarinic acid; rosmarinic acid dimer; caffeic acid tetramer; lignan; stereostructure; synthesis; Rabdosia japonica; Labiatae

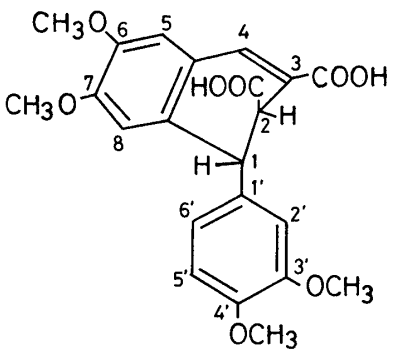
The aboveground part of Rabdosia japonica Hara (Labiatae) has been used as a common household medicine, "enmeiso," for gastrointestinal disorders in Japan, and the isolation of several diterpenoids, steroids, triterpenoids and flavonoids[1] from this plant have been reported. We have isolated from this plant a new rosmarinic acid dimer, rabdosiin (1), which has a lignan skeleton and is a tetramer of caffeic acid. Here we report the determination of the structure which has the absolute configuration of 1. We also describe the synthesis of a lignan (3) derived from rabdosiin (1).

This dimer, named rabdosiin (1) was isolated from the ethyl acetate-soluble portion obtained from the aqueous acetone homogenate of the powdered stem by column chromatography over Sephadex LH-20 and Toyopearl HW-40 (fine grade).

Rabdosiin (1), $[\alpha]_D^{25}$ -78° (c=3.5, MeOH), forms a light brown amorphous powder. The positive and negative fast atom bombardment (FAB) mass spectra of 1 showed $[M+H]^+$ and $[M-H]^-$ ions at m/z 719 and 717, and the analytical data indicate the molecular formula $C_{36}H_{30}O_{16}$ for 1. The ^{1}H-NMR spectrum [500 MHz, in $(CD_3)_2CO$] shows three protons [δ 6.38 (1H, d, J=2 Hz), 6.41 (1H, dd, J=2, 8.5 Hz) and 6.66 (1H, d, J=8.5 Hz)] of a 3,4-dihydroxyphenyl group, three singlets [δ 6.56, 6.92 and 7.62 (1H each)] in the nearby field, and two aliphatic methine protons which couple with each other [δ 3.93 (1H, d, J=1.5 Hz) and 4.56 (1H, broad s)], along with the protons of two 3-(3,4-dihydroxyphenyl)lactic acid moieties [δ 6.61 (1H, dd, J=2, 8 Hz), 6.73 (1H, d, J=8 Hz), 6.80 (1H, d, J=2 Hz)

(an ABX system), 6.64 (1H, dd, J=2, 8 Hz), 6.74 (1H, d, J=8 Hz), 6.85 (1H, d, J=2 Hz) (another ABX system), 3.01-3.05 (4H, m), 5.03 (1H, dd, J=5.5, 6 Hz), 5.07 (1H, dd, J=5.5, 7 Hz) (two $-CH_2-CH-$ systems)]. The protons at δ 6.56 and 6.92 are attributed to a 2,3,5,6-tetrasubstituted benzene moiety, and that at δ 7.62 to the β-proton of the caffeoyl group. These NMR data and UV peaks (MeOH) at 254, 284, 318 (sh) and 346 nm (log ε : 4.20, 4.00, 3.9 and 4.02) indicate the presence of the 1,2-dihydro-6,7-dihydroxy-1-(3,4-dihydroxyphenyl)-naphthalene structure.





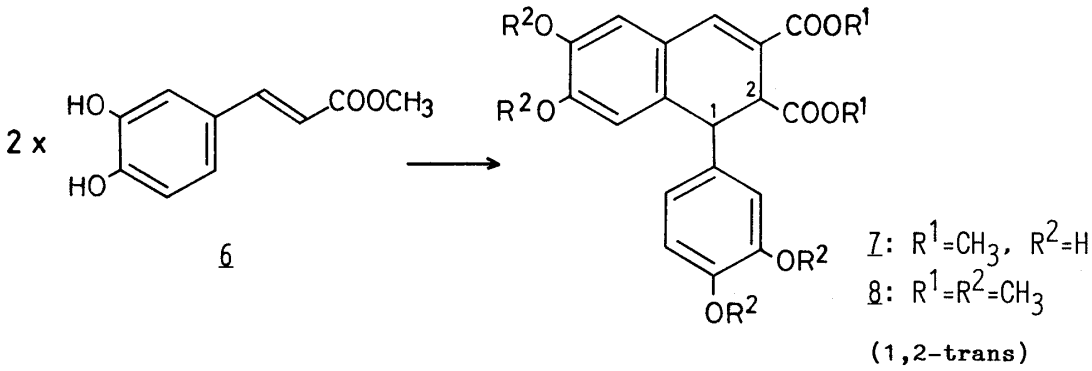
Methylation of 1 with $(CH_3)_2SO_4$ and K_2CO_3 afforded the decamethyl derivative (2) $[\alpha]_D^{25}$ -88° (c=8.9, $CHCl_3$). Treatment of 2 with 1N NaOH gave the hydrolysate (3) $[\alpha]_D^{25}$ -202° (c=1.1, $CHCl_3$), and (R)-3-(3,4-dimethoxyphenyl)lactic acid (4), $[\alpha]_D^{25}$ +31° (c=1, $CHCl_3$).

The ^{1}H-NMR spectrum [500 MHz, in $(CD_3)_2CO$] of 3 also shows the presence of a 1,2-dihydronaphthalene moiety [δ 4.68 (1H, broad s, H-1), 3.98 (1H, d, J=1.5 Hz, H-2), 7.70 (1H, s, H-4), 7.10 (1H, s, H-5), 6.88 (1H, s, H-8)], a 3,4-disubstituted phenyl group [δ 6.79 (1H, d, J=2 Hz, H-2'), 6.74 (1H, d, J=8.5 Hz, H-5'), 6.46 (1H, dd, J=2, 8.5 Hz, H-6')], and four methoxyl groups [δ 3.71, 3.72, 3.79 and 3.85 (3H each, s)]. The orientation of the bond C-2—H-2 is assigned to be quasi-equatorial on the basis of the singlet of H-4, which should be a doublet induced by the allyl coupling with H-2 if the orientation of the bond C-2—H-2 were quasi-axial. According to rotating frame Overhauser enhancement spectroscopy (ROESY) of 3, a nuclear Overhauser effect (NOE) is present between H-2 and H-2', and between H-8 and H-1. It is absent between H-8 and H-6', and between H-8 and H-2'. The coupling constant between H-1 and H-2 (1.5 Hz) indicates that the dihedral angle of the C-1—H-1 bond and the C-2—H-2 bond should be ca. 80°. This is caused by the quasi-equatorial orientation of the bond C-1—H-1.

Hydrogenation of 3 over 5% Pd-C afforded a dihydro derivative (5). The circular dichroism (CD) spectrum of 5 (in MeOH) shows the first positive couplet, [θ] +13600 (289 nm) and -7200 (273 nm), and the second positive couplet, [θ] +45900 (207 nm) and -29700 (200 nm) (lowest wavelength measured),

which are analogous to the reported data of the 1-aryltetralin lignans having 1α-substituents.[2] Therefore, the absolute configurations at C-1 and C-2 in **1** should be R and S, respectively.

The hydrolysate (**3**) was synthesized as follows. The ferric chloride-catalyzed condensation of methyl caffeate (**6**), which was carried out in a way analogous to that of condensation of ferulic acid,[3] gave the dimeric compound (**7**) which yielded the hexamethyl derivative (**8**) with dimethyl sulfate. Hydrolysis of **8** with 1N NaOH gave a product which was identified as **3** by IR, UV and NMR spectra. Therefore, the structure of rabdosiin was established to be **1**.



Rabdosiin is the first example of a caffeic acid tetramer having a lignan skeleton which is biogenetically produced from two molecules of rosmarinic acid.

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