Note

Synthesis and Taste of Naringenin 7-*O*-(2-*O*- α -L-lyxopyranosyl- β -D-galactopyranoside) and Its Dihydrochalcone Derivative[†]

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Naringin (**I**), whose structure is naringenin 7-*O*-(2-*O*- α -L-rhamnopyranosyl- β -D-glucopyranoside), is an intensely bitter constituent of grapefruit and pummelo, while naringin dihydrochalcone (DHC) (**II**),¹⁾ obtainable by reduction of **I**, has been reported to be an intensely sweet compound comparable to saccharine. Niekerk and Koeppen²⁾ have synthesized naringenin 7-*O*-(2-*O*- α -L-rhamnopyranosyl- β -D-galactopyranoside) (**III**) and its DHC derivative (**IV**) and revealed them to be as bitter as **I** and as sweet as **II**. We³⁾ have already reported the synthesis and taste of many isomers and analogs of **I** and **II** and discussed the structure-taste relationships between them. Among these discussions, we pointed out that one of the essential factors required for intense bitterness and sweetness in the sugar component of **I** and **II** is the presence of the methyl group of L-rhamnose. If this observation is valid, naringenin 7-*O*-(2-*O*- α -L-lyxopyranosyl- β -D-galactopyranoside), **V** and its DHC derivative (**VI**) will be less bitter than **I** and **III**, and less sweet than **II** and **IV**. From this viewpoint, an attempt was made to synthesize **V** and **VI** according to this paper. L-Lyxopyranose (α - β =3:7) was acetylated with a mixture of acetic anhydride and pyridine to give 1,2,3,4-tetra-*O*-acetyl- α -L-lyxopyranose (**VII**) stereoselectively, which was further converted to 2,3,4-tri-*O*-acetyl- α -L-lyxopyranosyl chloride (**VIII**) with titanium tetrachloride. Coupling of

VIII with 1,3,4,6-tetra-*O*-acetyl- α -D-galactopyranose (**IX**)⁴⁾ in the presence of silver triflate and tetramethylurea according to the method of Hanessian *et al.*⁵⁾ afforded two new crystalline products, hepta-*O*-acetyl-2-*O*- α -L-lyxopyranosyl- α -D-galactopyranose (**X**) and hepta-*O*-acetyl-2-*O*- β -L-lyxopyranosyl- α -D-galactopyranose (**XI**), in a 10:6.6 ratio. The configuration of interlinkage of the disaccharides were judged from their optical rotation values and *R_f* values. The α -1 $\rightarrow$ 2 linkage of **X** was also confirmed from the NMR spectral data of the trimethylsilyl ethers of **V** (lyxosyl α -H-1, δ , 4.76, doublet, *J*=2 Hz) and **VI** (lyxosyl α -H-1, δ , 4.80, doublet, *J*=2 Hz). Silver triflate-promoted disaccharide syntheses have been reported always to form 1,2-*trans*-linked configurations, but stereospecificity was not observed in the above case. The compound **X** was brominated with hydrogen bromide to furnish hexa-*O*-acetyl-2-*O*- α -L-lyxopyranosyl- α -D-galactopyranosyl bromide (**XII**). Coupling **XII** with naringenin in the presence of silver carbonate in quinoline gave the condensing product which was deacetylated with methanolic sodium methoxide to yield **V**. Reduction of **V** with hydrogen under palladium-carbon (10%) gave **VI**. The structures of **V** and **VI** were confirmed by UV and NMR spectral data.

Organoleptic studies⁶⁾ have revealed that **V** is 0.12 times less bitter than **I** and **II** on a weight basis, while **VI** tastes rather bitter. The presence of the methyl group of L-rhamnose in the molecules of **I** and **II** was reconfirmed to be important for the emergence of their intense bitter and sweet tastes, respectively.

EXPERIMENTAL

Thin-layer chromatographic analyses were carried out using silica gel plates and the following solvents: solvent A, benzene-ethyl acetate (7:3); solvent B, benzene-ethyl acetate (3:2); solvent C, benzene-ether (1:1); solvent D, chloroform-acetone (9:1); solvent E, ethyl acetate-methanol-water (80:14:10).

1,2,3,4-Tetra-*O*-acetyl- α -L-lyxopyranose (**VII**). L-Lyxopyranose (Sigma Co. Ltd., 25 g) was acetylated with a mixture of acetic anhydride (25 ml) and pyridine (25 ml) at room temperature for 48 hr. The reaction mixture was

I, II, $R_1 = \text{OH}$, $R_2 = \text{H}$, $R_3 = \text{CH}_3$; **III, IV**, $R_1 = \text{H}$, $R_2 = \text{OH}$, $R_3 = \text{CH}_3$; **V, VI**, $R_1 = \text{H}$, $R_2 = \text{OH}$, $R_3 = \text{H}$.

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poured into ice-cooled water and left for 24 hr in a refrigerator. A white precipitated solid was collected, washed with water and crystallized from ethanol to give **VII** (27 g, 50.94%) as plates, mp 96~97°C (EtOH), $[\alpha]_D^{10} -27.5^\circ$ ($c=2.0$, CHCl_3). Lit.⁷⁾ mp 95~96°C, lit.⁷⁾ $[\alpha]_D^{10} -24^\circ$ ($c=1.0$, CHCl_3).

2,3,4-Tri-O-acetyl- α -L-lyxopyranosyl chloride (VIII). To a solution of **VII** (25 g) in dry chloroform (175 ml), a solution of titanium tetrachloride (16.5 g) in chloroform (175 g) was added dropwise and the mixture was boiled for 3 hr. The reaction mixture was poured into ice-cooled water with stirring. After a short period, the mixture was extracted with chloroform and the organic layer washed successively with water, aq. sodium hydrogen carbonate and water, and finally dried over calcium chloride. After filtration, the filtrate was evaporated to afford **VIII** (20.5 g, 88.40%) as a colorless syrup which did not crystallize but was homogeneous on TLC (R_f 0.71, solvent A), $[\alpha]_D^{30} -78^\circ$ ($c=2.5$, CH_2Cl_2). Anal. Found: C, 44.70; H, 4.98. Calcd. for $\text{C}_{11}\text{H}_{15}\text{O}_7\text{Cl}$: C, 44.75; H, 5.08%. NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 2.04 (3H), 2.07 (3H), 2.17 (3H) (each singlet, sugar-OCOCH₃); 3.60~4.30 (2H, broad multiplet, H-5); 4.95~5.70 (3H, broad multiplet, H-2, H-3, H-4); 5.84 (1H, doublet, $J=2$ Hz, H-1).

Hepta-O-acetyl-2-O- α -L-lyxopyranosyl- α -D-galactopyranose (X) and hepta-O-acetyl-2-O- β -L-lyxopyranosyl- α -D-galactopyranose (XI). To a solution of **IX** (20.26 g), **VIII** (20.5 g) and tetramethylurea (20 ml) in dry dichloromethane (500 ml) was added silver triflate (22.4 g) and the suspension was stirred for 2 hr in the dark at room temperature. After the reaction was completed, the filtrate was processed as described in the literature⁸⁾ and then chromatographed over silica gel (1.8 kg). On elution with benzene-ether (1:1), a colorless product (**X**) migrated and was crystallized from ether as needles in a yield of 5 g (15.35%), mp 215°C, $[\alpha]_D^{28} +60^\circ$ ($c=1.0$, CHCl_3). TLC, R_f 0.65 (B), 0.48 (C). NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 2.03 (12H), 2.10 (3H), 2.13 (3H), 2.20 (3H, each singlet, sugar-OCOCH₃); 3.33~4.36 (6H, broad multiplet, H-2,5,6,6',5',5'); 4.82~5.52 (6H, broad multiplet, H-3,4, H-1',2',3',4'); 6.35 (1H, doublet, $J=2$ Hz, H-1). Anal. Found: C, 49.85; H, 5.68. Calcd. for $\text{C}_{25}\text{H}_{34}\text{O}_{17}$: C, 49.50; H, 5.61%. Subsequent elution with the same solvent afforded a syrupy product (**XI**, 5 g) which crystallized from the alcohol as plates (3.3 g, 9.35%). mp 161°C, $[\alpha]_D^{28} +172^\circ$ ($c=1.0$, CHCl_3). TLC, R_f 0.55 (B), 0.39 (C). NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 2.07 (9H), 2.13 (3H), 2.17 (9H, each singlet, sugar-OCOCH₃); 3.33~4.44 (6H, broad multiplet, H-2,5,6,6', H-5',5'); 4.73~5.53 (6H, broad multiplet, H-3,4, H-1',2',3',4'); 6.37 (1H, doublet, $J=3$ Hz, H-1). Anal. Found: C, 49.47; H, 5.66. Calcd. for $\text{C}_{25}\text{H}_{34}\text{O}_{17}$: C, 49.50; H, 5.61%.

Hexa-O-acetyl-2-O- α -L-lyxopyranosyl- α -D-galactopyranosyl bromide (XII). To a solution of **X** (5 g) in dichloromethane (8 ml) was added 30% hydrogen bromide

in acetic acid (30 ml) and the mixture was allowed to stand at 0°C for 3 hr. The reaction mixture was diluted with chloroform and washed with water, aq. sodium hydrogen carbonate and water, and dried over calcium chloride. The filtrate was evaporated and **XII** was obtained as an amorphous powder which did not crystallize from any solvent, although it appeared homogeneous on TLC. Yield, 4.7 g (78.90%), $[\alpha]_D^{30} +128^\circ$ ($c=1.0$, CHCl_3). R_f 0.86 (D). NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 2.0 (3H), 2.03 (9H), 2.13 (6H, each singlet, sugar-OCOCH₃); 3.6~4.6 (6H, broad multiplet, H-2,5,6,6',5',5'); 4.76~5.5 (6H, broad multiplet, H-3,4,1',2',3',4'); 6.36 (1H, doublet, $J=3$ Hz, α -H-1). Anal. Found: C, 43.58; H, 4.83. Calcd. for $\text{C}_{23}\text{H}_{31}\text{O}_{15}\text{Br}$: C, 44.10; H, 4.95%.

Naringenin 7-O-(2-O- α -L-lyxopyranosyl- β -D-galactopyranoside) (V). According to the literature³⁾ naringenin (2.04 g) was coupled with **XII** (4.7 g) in the presence of silver carbonate (2.1 g) and Drierite (2.4 g) in quinoline (30 ml). The condensing product, after deacetylation with methanolic sodium methoxide, was purified on silica gel and polyamide columns and **V** was obtained as a white powder (0.81 g, 18.21%), $[\alpha]_D^{25} -60^\circ$ ($c=1.0$, CH_3OH). UV⁹⁾: $\lambda_{\text{max}}^{\text{MeOH}}$ (nm) 282,320; $\lambda_{\text{max}}^{\text{MeOH-AlCl}_3}$ (nm) 309,382; $\lambda_{\text{max}}^{\text{MeOH-AlCl}_3\text{-HCl}}$ (nm) 307,381; $\lambda_{\text{max}}^{\text{MeOH-AcONa}}$ (nm) 284,331; $\lambda_{\text{max}}^{\text{MeOH-NaOH}}$ (nm) 284, 414~420. TMS ether⁹⁾ of **V**, NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 2.5~2.86 (2H, multiplet, H-3); 3.1~4.03 (11H, multiplet, sugar-H); 4.70 (1H, doublet, $J=8$ Hz, galactosyl H-1); 4.76 (1H, doublet, $J=2$ Hz, lyxosyl H-1); 4.93~5.36 (1H, multiplet, H-2); 6.76 (2H, doublet, $J=8$ Hz, H-3',5'); 7.20 (2H, doublet, $J=8$ Hz, H-2',6'). Anal. Found: C, 52.42; H, 5.55. Calcd. for $\text{C}_{26}\text{H}_{30}\text{O}_{14} \cdot 11/2\text{H}_2\text{O}$: C, 52.61; H, 5.56%. R_f 0.43 (E).

Naringenin DHC 4'-(2-O- α -L-lyxopyranosyl- β -D-galactopyranoside) (VI). A solution of **V** (0.4 g) in 10% aq. potassium hydroxide (10 ml) was reduced under hydrogen (3 kg/cm²) in the presence of Pd-C (10%, 0.15 g) for 6 hr. After filtration, the filtrate was evaporated to a syrup which was crystallized from water to give **VI** as needles (0.26 g, 63.88%), mp 172~176°C (H_2O), $[\alpha]_D^{25} 0^\circ$ ($c=1.0$, MeOH). UV $\lambda_{\text{max}}^{\text{MeOH}}$ (nm) 282. R_f 0.45 (E). TMS ether⁹⁾ of **VI**, NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 2.73~3.0 (4H, multiplet, $-\text{CH}_2-\text{CH}_2-$); 3.3~4.33 (11H, multiplet, sugar-H); 4.76 (1H, doublet, $J=8$ Hz, galactosyl H-1); 4.80 (1H, doublet, $J=2$ Hz, lyxosyl α -H-1); 6.04 (2H, singlet, H-3',5'); 6.6 (2H, doublet, $J=8$ Hz, H-2,6); 7.02 (2H, doublet, $J=8$ Hz, H-3,5). Anal. Found: C, 51.63; H, 5.62. Calcd. for $\text{C}_{26}\text{H}_{32}\text{O}_{14} \cdot 2\text{H}_2\text{O}$: C, 51.66; H, 5.96%.

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