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Synthesis and Absolute Configuration of Lepidimoide, a High Potent Allelopathic Substance from Mucilage of Germinated Cress Seeds

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Key Words: Lepidimoide; 1,2-cis-linked disaccharide; allelopathic substance; cress; *Lepidium sativum* L; synthesis; absolute configuration

Summary: Lepidimoide (**1**), 1,2-cis-linked disaccharide, was synthesized from D-glucose and α-L-rhamnose for determination of the absolute configuration.

Lepidimoide (**1**) was isolated as a novel allelopathic substance, which promoted the shoot growth of different plant species but inhibited the root growth, from mucilage of germinated cress (*Lepidium sativum* L.) seeds.[1] For example, lepidimoide (**1**) promoted the hypocotyl growth of etiolated *Amaranthus caudatus* L. at concentrations higher than 3 μM and inhibited the root growth at concentrations higher than 100 μM. The growth-promoting activity in hypocotyls was 20 or 30 times as much as that of gibberellic acid. The structural study of lepidimoide, with spectral analyses and some chemical evidence, has showed that lepidimoide **1** is regarded as the uronic acid derivative bearing an α,β-unsaturated carboxylate bonded to rhamnose *via* α-glucoside linkage.[1] Thus, the intriguing structure as well as its unique biological activity prompted us to determine the absolute configuration of lepidimoide (**1**), by total synthesis. In this communication we wish to report a total synthesis and the absolute configuration of lepidimoide **1**.

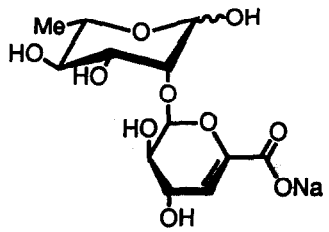

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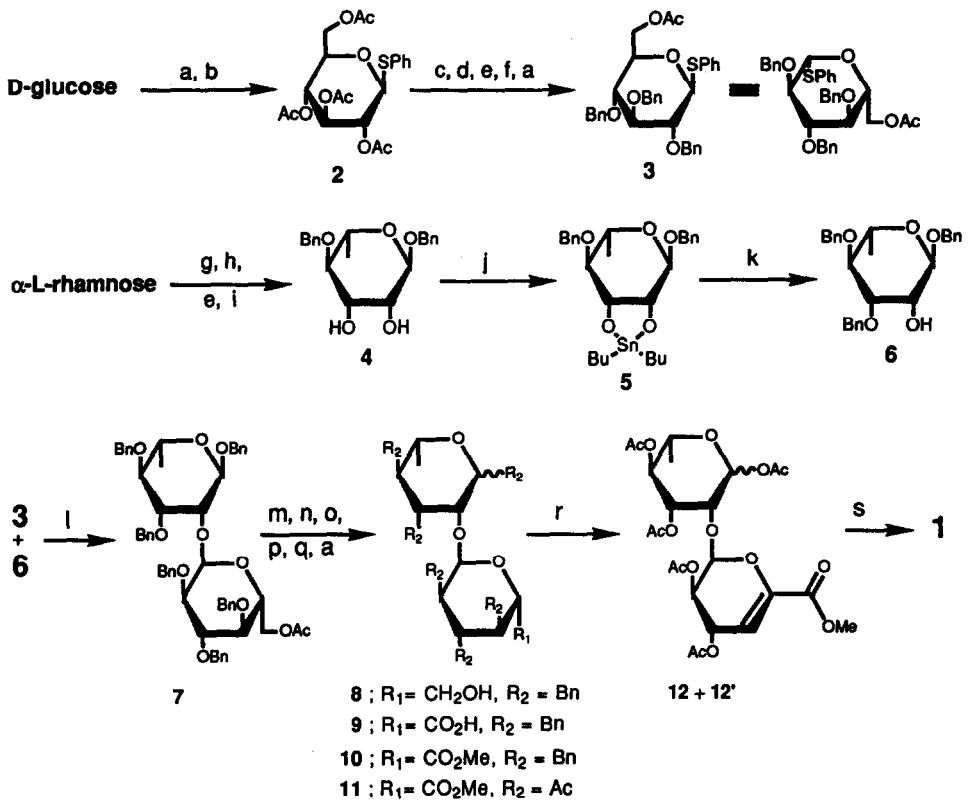
Fig.1 Absolute configuration of lepidimoide 1



a) Ac_2O, Pyr., quant. ; b) PhSH, $SnCl_4$, PhH, 87% ; c) MeONa, MeOH, quant. ; d) TrCl, Pyr., 70°C, 5 h, 94% ; e) BnBr, NaH, DMF, 76% ; f) AcOH, H_2O, 95% ; g) BnOH, H_2SO_4(cat), PhH, 93% ; h) 2,2-dimethoxypropane, p-Ts OH, acetone, 89% ; i) AcOH-H_2O-dioxane (1:1:1), 70% ; j) Bu_2SnO, PhH, reflux ; k) BnBr, CsF, DMF, room temp., 15 h, 88% in two steps ; l) MSB, MS4A, dichloromethane, 1,2-dichloroethane, room temp., 37.5% ; m) K_2CO_3, MeOH, quant. ; n) SO_3-Pyr., DMSO, Et_3N ; o) t-BuOH-H_2O-2-methyl-2-butene (3:2:1), NaH_2PO_4, $NaClO_2$, 79% in two steps ; p) $TMSCHN_2$, PhH-MeOH, quant. ; q) 10% Pd-C, H_2, MeOH-AcOEt , 98% ; r) DBU, Pyr., room temp., 12:12' (54% : 43%); s) NaOH, H_2O-MeOH (1:1), quant.

Lepidimoide is a 1,2-cis-linked disaccharide. Therefore, phenyl 1- thio-β-D-glucopyranoside (**3**) having non-participating protecting group at C_2-position was prefered as one of the two sugars, which was readily obtained through the intermediate **2** by successive deacetylation, tritylation, benzylation, detritylation, and acetylation of phenyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside derived from D-glucose in 2 steps.[2, 3] Oxidation of the primary hydroxyl group of the D-glucose moiety in the disaccharide followed by formation of the unsaturated uronoside (**8** → **12** +**12'**)was desired in later stage close to the final step of synthesis. The remaining sugar as a candidate for the present study is **6**, which must be conveniently synthesized from α-L-rhamnose in 6 steps. Thus, α-L-rhamnose was subjected to successive benzylglucosidation, isopropylydenation, benzylation, and deisopropylydenation to afford a compound **4** and consequently the resulting diol **4** was heated under reflux with Bu_2SnO in benzene with azeotropic removal of water to afford the dibutylstannane **5**, which was immediately treated with BnBr in the presence of CsF at room temperature in DMF,[4] wherein the alkylation occured at the equatorial 3-OH group giving **6** in 88 % yield. Stereocontrolled glycosylation[5] of the thio-glucoside **3** with 2.5 equivalents of **6** was carried out at room temperature in 1,2-dichloroethane-dichloromethane (1:4) using the activator, methyl sulfenyl bromide (MSB)[6] and powdered molecular sieves 4A to afford the disaccharide **7** in 40% yield (based on **3**) as a mixture of the anomers (α:β = 14.9: 1). When treated with K_2CO_3 in MeOH at room temperature, the desired 1,2-cis-linked disaccharide was almost quantitatively converted into the corresponding primary alcohol **8**. Crucial oxidation of **8** into **9** was successively achieved in 2 steps (1, SO_3-Pyridine, DMSO, Et_3N. 2, $NaClO_2$, NaH_2PO_4 in t-BuOH - H_2O - 2-methylbutene[7] (3:2:1), 79 % overall yield) followed by methylation with $TMSCHN_2$ in benzene - MeOH (5:1) to give the methyl ester **10**. Debenzylation of **10** with 10% Pd-C and H_2 in MeOH - AcOEt followed by acetylation with Ac_2O - pyridine to give the corresponding hexaacetates **11** as a nonseparable mixture of two anomers. Elimimation of acetic acid proceeded cleanly, when the hexaacetates **11** were treated with 1,5-diazabicyclo (5.4.0)-undec-5-ene (DBU)[8] in pyridine at room temperature, to afford two separable alkenes **12** and **12'**, in 54 and 43 % yields, respectively.[9] Finally, the mixture of **12** and **12'** were hydrolyzed with NaOH in MeOH - H_2O to give rise to lepidimoide **1** in quantitative yield. The spectral (^1H NMR, IR)[1] and physical properties{$[\alpha]_D^{21}$ +65.2° (c 0.025, D_2O)} of the synthetic compound were compatible with those of natural lepidimoide {$[\alpha]_D^{19}$ +87.8° (c 0.033, D_2O)}.

In the present study, the absolute configulation of lepidimoide was unambiguously determined to be 2-O-L-rhamnopyranosyl 4-deoxy-α-L-threo-hex-4-enopyranosiduronate as depicted in Fig. 1.

Biological studies on lepidimoide and related synthetic compounds are in progress and the result will be reported in due course.

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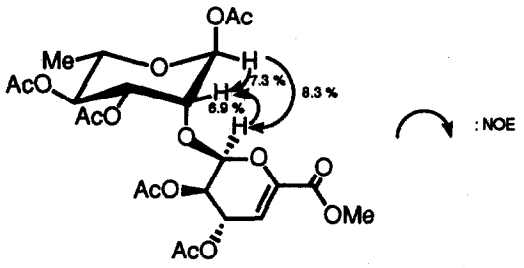
9. The spectral data (by resulting mass, ^1H NMR and ^{13}C NMR) for the new compounds cited here are in accord with the structures assigned.

Compound **12** as a colorless oil : $C_{23}H_{30}O_{15}$ [m/z 546.1564(M+)]; IR(film) 1740 cm^{-1}; $\delta_H(CDCl_3)$ 6.14(1H, d, J=3.3Hz), 6.04(1H, d, J=2.0Hz), 5.59(1H, dd, J=7.5, 3.3Hz), 5.31(1H, d, J=2.4Hz), 5.18(1H, dd, J=7.5, 2.4Hz), 5.16(1H, dd, J=9.8, 3.4Hz), 5.06(1H, dd, J=9.8, 9.3Hz), 4.27(1H, dd, J=3.4, 2.0Hz), 3.88(1H, dq, J=9.3, 6.0Hz), 3.80(3H, s), 2.14(6H, s), 2.10(3H, s), 2.05(3H, s), 2.00(3H, s), 1.22(3H, d, J=6.0Hz); $\delta_C(CDCl_3)$ 170.4(s), 170.1(s), 169.9(s), 169.5(s), 168.8(s), 161.6(s), 141.6(s), 108.6(d), 95.6(d), 90.2(d), 73.3(d), 70.4(d), 69.4(d), 69.0(d), 68.3(d), 66.2(d), 52.5(q), 20.94(q), 20.90(q), 20.7(q), 20.6(q), 20.5(q), and 17.5(q).



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Compound **12'** as a colorless oil : $C_{23}H_{30}O_{15}$ [m/z 546.1609(M+)]; IR(film) 1740 cm^{-1}; $\delta_H(CDCl_3)$ 6.15(1H, d, J=2.9Hz), 5.72(1H, s), 5.71(1H, d, J=2.9Hz), 5.64(1H, dd, J=7.8, 2.9Hz), 5.10(1H, dd, J=7.8, 2.9Hz), 5.02(1H, dd, J=9.8, 9.8Hz), 4.91(1H, dd, J=9.8, 3.2Hz), 4.43(1H, d, J=3.2Hz), 3.59(1H, dq, J=9.8, 6.1Hz), 3.80(3H, s), 2.13(3H, s), 2.12(3H, s), 2.10(3H,s), 2.04(3H, s), 1.95(3H, s), and 1.25(3H, d, J=6.1Hz).

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