

(+)- β -FRULLANOLIDE AND (+)-BROTHENOLIDE, TWO NEW SESQUITERPENE LACTONES
FROM THE LIVERWORT *FRULLANIA BROTHERI* STEPH.

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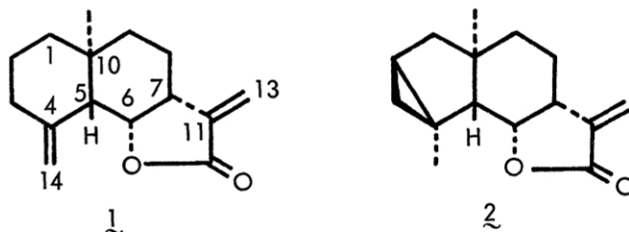
Wakayamadai, Shimamoto-cho, Mishima-gun, Osaka 618

Two new sesquiterpene lactones, named (+)- β -frullanolide and (+)-brothenolide, were isolated from liverwort *Frullania brotheri* Steph.

The absolute structures of these lactones have been established.

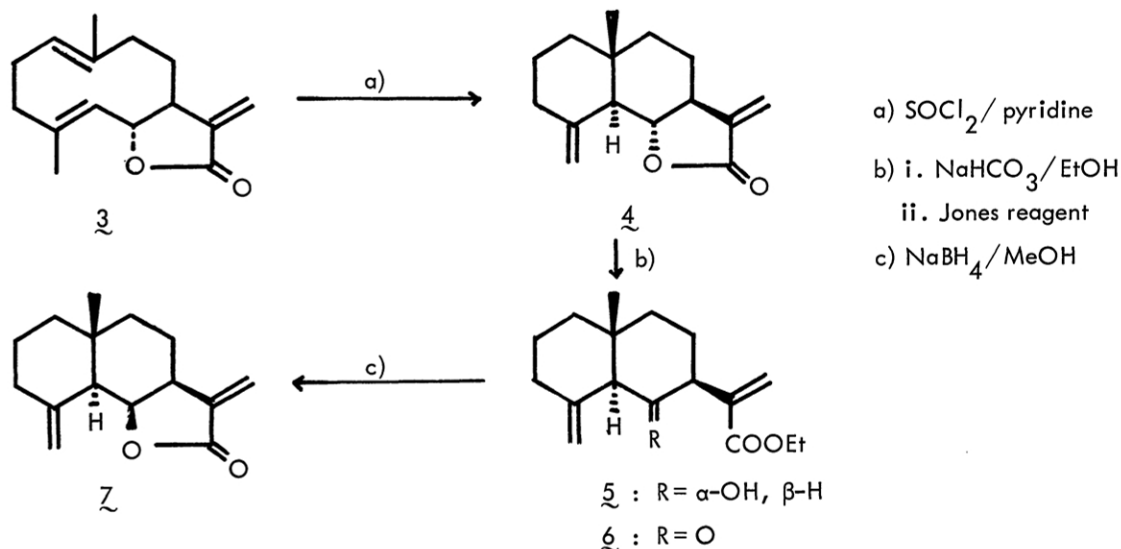
A number of novel sesquiterpene lactones¹⁾ were isolated from the liverwort *Frullania* species and some of them have intense allergenic properties.

We report the isolation and structural determination of (+)- β -frullanolide (**1**) and (+)-brothenolide (**2**) (allergenic agent) from the liverwort *Frullania brotheri* (Japanese name: Kamimurayasudegoke) collected in Wakayama Pref. around Mt. Ohto in June, 1976. Column chromatographic separation on SiO_2 using CHCl_3 and AgNO_3 - SiO_2 using hexane-EtOAc (10:1) of the ether extract of the fresh material (100 g) gave 40 mg of lactone **1** and 270 mg of lactone **2**.



The physical constants of (+)- β -frullanolide are as follows: $\text{C}_{15}\text{H}_{20}\text{O}_2$ (M^+ , m/e 232); Mp. 165-7°C; $[\alpha]_D^{25} +178^\circ$ ($c=1.17$, CHCl_3); CD, $\Delta\epsilon_{254} -1.5$ ($c=0.012$, MeOH); IR (CHCl_3), 1670, 1760 cm^{-1} (α,β -unsaturated γ -lactone), 910 cm^{-1} (exocyclic methylene); $^1\text{H-NMR}$ (CDCl_3), δ 0.92 (3H, s, 10-Me), 4.58 (1H, dd, $J=4.5$, 3 Hz, 6-H), 4.92 (1H, br s, 14- H_A), 5.09 (1H, br s, 14- H_B), 5.52 (1H, d, $J=0.6$ Hz, 13- H_A), 6.07 (1H, d, $J=0.6$ Hz, 13- H_B); $^{13}\text{C-NMR}$ (CDCl_3), CH_3 (18.3), five CH_2 (23.0, 24.6, 37.5, 38.8, and 43.0), two CH (41.4 and 50.9), C=O (170.8), two $=\text{CH}_2$ (109.7 and 119.0), O-CH (77.8), two $=\text{C}$ (141.7 and 145.3), and C (34.7). These results suggested that the lactone has the eudesmanolide structure **1**, an assumption which was confirmed by partial synthesis.

Costunolide **3** (from Costus root oil) was cyclized²⁾ with thionyl chloride to give the cyclocostunolide mixture from which was separated β -cyclocostunolide **4** in 50% yield after passage through a 10% AgNO₃-SiO₂ column. Ethanolysis of the lactone **4** with Na₂CO₃ in EtOH gave in quantitative yield the hydroxy ester **5**: IR (film) 3460 (OH), 1718 cm⁻¹ (ester), which was oxidized with Jones reagent to the keto-ester **6** in 70% yield: IR (CHCl₃) 1718 cm⁻¹ (ketone and ester).³⁾ Reduction of the ester **6** with NaBH₄ in MeOH and work-up gave in 50% yield the *cis*-lactone **7**: [α]_D -162° (c=0.64, CHCl₃).

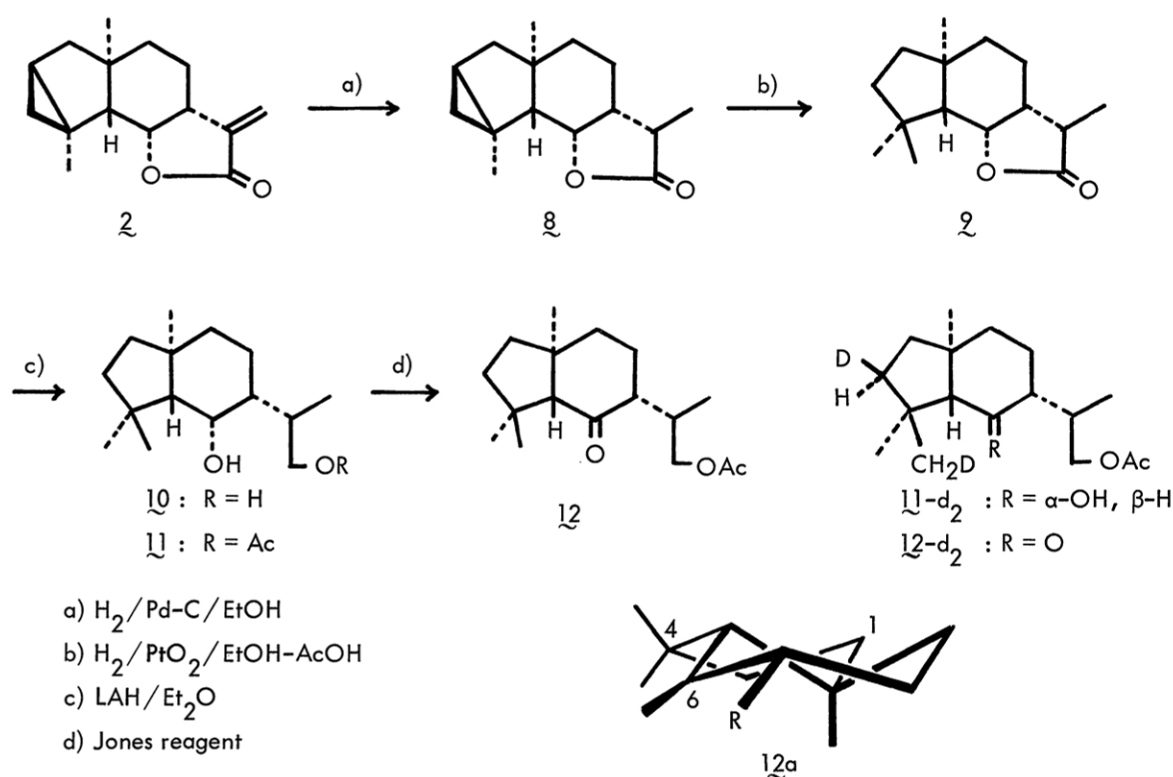


Compound **7** was identified in every respects with (+)- β -frullanolide except for chiroptical properties, CD (in MeOH) $\Delta\epsilon_{254} +1.5$ for **7** vs. $\Delta\epsilon_{254} -1.5$ for **1**. (+)- β -Frullanolide is fully represented by structure **1**.

(+)-Brothenolide **2** exhibits the following constants: C₁₅H₂₀O₂ (M⁺, m/e 232); Mp. 113-4°C; [α]_D +153° (c=1.14, CHCl₃); CD, $\Delta\epsilon_{255} -1.6$ (c=0.012, MeOH); IR (CHCl₃), 3040 (cyclopropane ring), 1660, 1760 cm⁻¹ (α,β -unsaturated γ -lactone); ¹H-NMR (CDCl₃), δ 0.38 (1H, t-like, J=3.6 Hz, 3-H_A), 0.85 ~ 0.95 (1H, m, 3-H_B), 1.11 and 1.36 (each 3H, s, 10-Me and 4-Me), 2.80 (1H, m, W_{1/2} 23.4 Hz, 7-H), 4.75 (1H, dd, J_{5,6} = 3 Hz, J_{6,7} = 4.8 Hz, 6-H), 5.52 (1H, d, J=0.6 Hz, 13-H_A), and 6.09 (1H, d, J=0.6 Hz, 13-H_B); ¹³C-NMR (CDCl₃) two CH₃ (20.4 and 20.9), four CH₂ (25.5, 34.1, 35.7, and 46.3), three CH (25.9, 40.5, and 56.5), C=O (171.3), =CH₂ (119.5), O-CH (77.8), =C (141.8), and two C (26.6 and 50.4).

The proton system comprising carbons 4, 5, 6, 7, 10, 11, 13, and 8 was elucidated by ¹H-NMR with the aid of shift reagent. The fact that 7-H is coupled to 8 α - and 8 β -H's with J=7.0, 10.2 Hz indicates that it is axial; this together with the J_{6,7} value of 4.8 Hz shows that 6-H is equatorial, i.e. the *cis*-fused. The 5-H signal appeared at the high field of 1.08 ppm as a result of the ring current of the cyclopropane moiety.

Hydrogenation of (+)-brothenolide **2** with Pd/C in EtOH yielded the dihydro compound **8**, which was further reduced⁴⁾ with PtO₂ in EtOH-AcOH to give the compound **9** having four methyl groups. Disappearance of cyclopropane proton signals and appearance of a new tertiary Me signal in the ¹H-NMR spectrum of **9** and the presence of its IR bands at 1380 and 1370 cm⁻¹ (gem-dimethyl) could most reasonably be explained by the formula **9** in which one of the two tertiary Me groups is attached to the cyclopropane ring. LAH reduction of the tetra methyl compound **9** afforded the diol **10**, which gave the mono acetate **11** upon treatment with Ac₂O-pyridine at room temp.; **11** was oxidized with Jones reagent to give the ketone **12**: IR (film) 1720 cm⁻¹ (ketone). All these data, together with biogenetic considerations show that the new sesquiterpene lactone **2** is most favourably represented by formula **2** (planer).



The fact that the CD Cotton effects of lactones **1** and **2** have the same signs (see above) shows that they belong to the same chiroptical series. The β-configuration of the cyclopropane ring was determined as follows. Reduction of dihydro brothenolide **8** with deuterium instead of hydrogen (see above), followed by LAH treatment and acetylation gave **11-d₂** (the d₂-derivative of **11**). The ¹H-NMR spectrum of **11** showed three tertiary Me signals at 1.17, 1.20 and 1.03 ppm, one of which at 1.03 ppm appeared as a CH₂D signal in **11-d₂**. Oxidation of **11-d₂** gave **12-d₂** in which one Me peak at 1.20 ppm had undergone a low field shift to 1.34 ppm whereas the other at 1.17 ppm shifted to 1.07 ppm. Analysis of these shifts of Me peaks caused by the difference of anisotropic effects between 6α-OH and 6-keto functions led to the assigning of the methyl signals at 1.17 and 1.20 ppm

in $\underline{11}$ -d₂ to 4 β -Me and 10-Me groups, respectively.

Molecular models $\underline{12a}$ clearly show that the 4-Me group (δ 1.34) should have the α -configuration since it is in-plane of the carbonyl group. The CH₂D group in $\underline{11}$ -d₂ is thus β -oriented, and therefore, the cyclopropane methylene group is also β -oriented in brothenolide.

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References and Note.

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