CHEMISTRY LETTERS, pp. 1461-1464, 1980. © The Chemical Society of Japan 1980

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

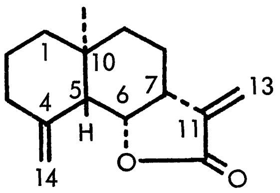
Reiji TAKEDA,* Yoshimoto OHTA, and Yoshio HIROSE
Suntory Institute for Bioorganic Research
Wakayamadai, Shimamoto-cho, Mishima-gun, Osaka 618

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

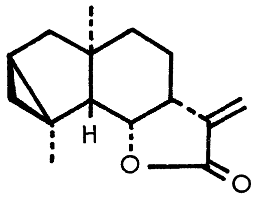
The absolute structures of these lactones have been established.

A number of novel sesquiterpene lactones[1)] 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.



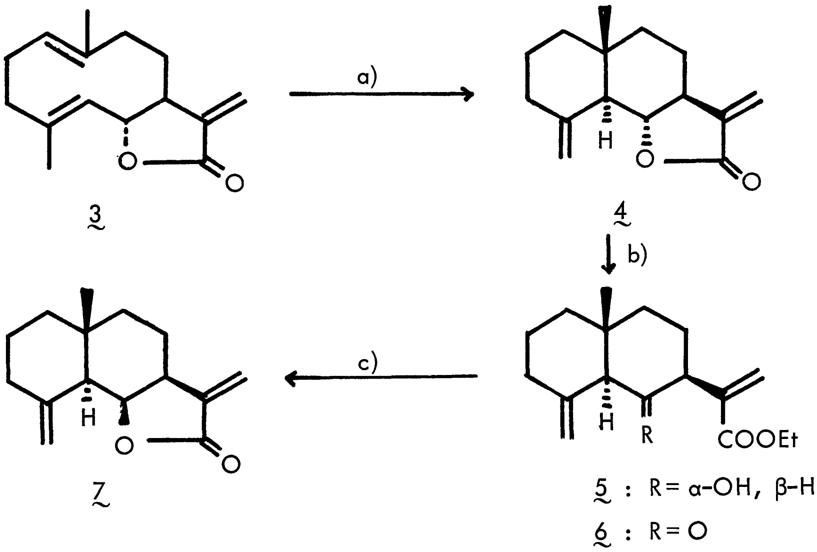
1



2

The physical constants of (+)-β-frullanolide are as follows: $C_{15}H_{20}O_2$ (M^+, m/e 232); Mp. 165-7°C; $[\alpha]_D$ +178° (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); ^1H-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}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 =CH_2 (109.7 and 119.0), O-CH (77.8), two =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 cyclized[2)] with thionyl chloride to give the cyclocostunolide mixture from which was separated β-cyclocostunolide 4 in 50% yield after passage through a 10% $AgNO_3$-SiO_2 column. Ethanolysis of the lactone 4 with Na_2CO_3 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 ($CHCl_3$) 1718 cm^{-1} (ketone and ester).[3)] Reduction of the ester 6 with $NaBH_4$ in MeOH and work-up gave in 50% yield the *cis*-lactone 7: $[\alpha]_D$ -162° (c=0.64, $CHCl_3$).



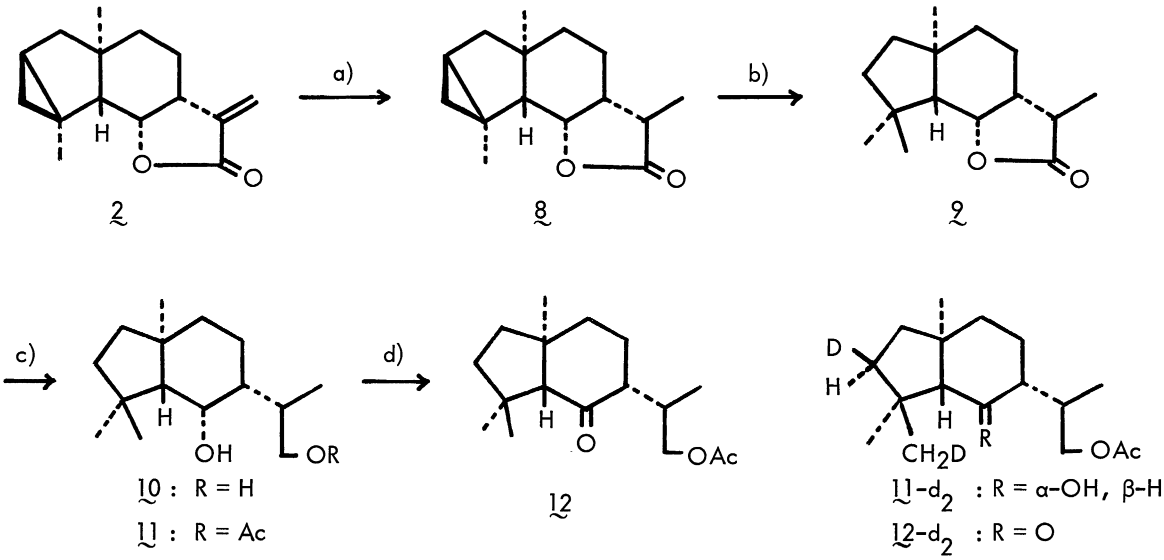
a) $SOCl_2$/ pyridine
b) i. $NaHCO_3$/EtOH
ii. Jones reagent
c) $NaBH_4$/MeOH

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: $C_{15}H_{20}O_2$ (M^+, m/e 232); Mp. 113-4°C; $[\alpha]_D$ +153° (c=1.14, $CHCl_3$); CD, $\Delta\epsilon_{255}$ -1.6 (c=0.012, MeOH); IR ($CHCl_3$), 3040 (cyclopropane ring), 1660, 1760 cm^{-1} (α,β-unsaturated γ-lactone); ^1H-NMR ($CDCl_3$), 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); ^{13}C-NMR ($CDCl_3$) two CH_3 (20.4 and 20.9), four CH_2 (25.5, 34.1, 35.7, and 46.3), three CH (25.9, 40.5, and 56.5), C=O (171.3), =CH_2 (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 8α- and 8β-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 PtO_2 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 2 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 Ac_2O-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).



2

8

9

10 : R = H

11 : R = Ac

12

11-d_2 : R = α-OH, β-H

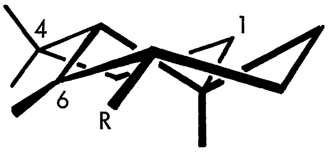
12-d_2 : R = O

a) H_2/Pd-C/EtOH

b) H_2/PtO_2/EtOH-AcOH

c) LAH/Et_2O

d) Jones reagent



12a

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-d_2 (the d_2-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 CH_2D signal in 11-d_2 Oxidation of 11-d_2 gave 12-d_2 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 **11**-d_2 to 4β-Me and 10-Me groups, respectively.

Molecular models **12**a 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 CH_2D group in **11**-d_2 is thus β-oriented, and therefore, the cyclopropane methylene group is also β-oriented in brothenolide.

Acknowledgment. We wish to thank Dr. Tsutomu Kodama of Ottemon Gakuin high school for identification of *Frullania brotheri*, to Prof. Tetsuro Fujita of Tokushima Univ. for bioassay of brothenolide, to Mr. Hiroshi Nii of Nagaoka Perfumery Co. Ltd., for providing the Costus root oil, and to Dr. Yoshinori Asakawa of Tokushima-Bunri Univ. for supply of costunolide.

References and Note.

1) H. Knoche, G. Ourisson, G.W. Perold, J. Foussereau, and J. Maleville, *Science* ,**166**, 239 (1969).
J.D. Connolly and I.M.S. Thornton, *Phytochemistry* ,**12**, 631 (1973).
Y. Asakawa, J.C. Muller, G. Ourisson, J. Foussereau, and G. Ducombs, *Bull. Soc. Chim. France*, 1465 (1976).
Y. Asakawa, G. Ourisson, and T. Aratani, *Tetrahedron Letters*, 3957 (1976).

2) R.W. Doskotch and F.S. El-Feraly, *J. Org. Chem.* , **35**, 1928 (1970).

3) Spectroscopic data were in agreement with the respective structures.

4) K. Takeda, M. Ikuta, and M. Miyawaki, *Tetrahedron* , **20**, 2991 (1964).

(Received September 8, 1980)