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Nepalensolide A, Novel Sesquiterpene Lactone from the Liverwort *Frullania nepalensis*. Compound Breaking the Samek Rule. A Study by NOE and X-Ray

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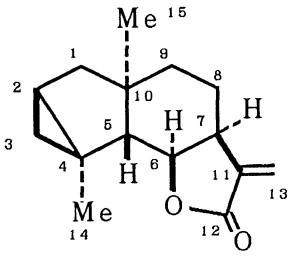
The structure of a new sesquiterpene lactone, nepalensolide A, from the liverwort *Frullania nepalensis* has been determined by spectroscopic considerations and X-ray analysis. Since the compound does not obey the Samek rule, the conformation has to be considered when we use this rule.

Liverworts produce various kinds of terpenoids and aromatic compounds, which frequently show interesting biological activities. *Frullania* species are divided into six chemotypes.[1,2] In connection with our study on chemical constituents and chemosystematics of the liverwort, we collected *Frullania nepalensis* in Taiwan and have isolated a new sesquiterpene lactone, nepalensolide A (1), which does not follow the Samek rule.

The dichloromethane extract (0.67 g) of *F. nepalensis* (193 g) was purified by silica-gel column chromatography to give a new sesquiterpene, nepalensolide A (1), $C_{15}H_{22}O_2$ (high-resolution MS spectrum), mp 99°C, $[\alpha]_D$ +98.5° (*c* 0.12 in $CHCl_3$), showing the presence of a lactone (1760 cm^{-1}, δ_C 170.8), an exomethylene [980 cm^{-1}; δ_H 5.47 (1H, d, *J*=3.3 Hz) and 6.26 (1H, d, *J*=3.3 Hz); δ_C 119.6 (C) and 137.9 (CH_2)], a cyclopropane [δ_H 0.34 (1H, t, *J*=4.3 Hz), 0.91 (1H, dd, *J*=8.3 and 4.3 Hz), 1.14 (1H, m)], and two *tertiary*-methyl groups (δ_H 1.00 and 1.30).[3] From the H-H COSY, C/H COSY, and HMBC spectra, the structure of an eudesmane-type skeleton having the cyclopropane and α-methylene-γ-lactone is suggested. Since the value of the coupling constant ($J_{7,13}$=3.3 Hz) of the exo-methylene proton is larger than 3 Hz, the lactone ring is deduced to be *trans* if the Samek rule[4] is applied. Contrary to this assumption, the NOE experiments showed that both protons H-6 and H-7 were on the same side as the methyl group at the C-10 position. The stereochemistry of the H-5 was clearly assigned to be β axial from the value of the coupling constants of the H-6 [δ_H 4.80 (dd, *J*=11.6 and 7.6 Hz)] and H-5 [δ_H 0.78 (d, *J*=11.6 Hz)].[5] These results are contrary to each other.

Therefore the X-ray analysis was next undertaken.[6] The result is shown in the Fig. 1. The proton H-6 and H-7 are on the same side as the methyl group at the C-10 position, which is consistent with the results from the NOE measurements. The Samek rule could not be applied in this case at all. This is presumably because the most stable conformation of 1 is different from that considered in the Samek rule. As we are interested in this phenomenon, further study is following.[7]

The absolute configuration was determined by CD spectrum ($[\theta]_{223nm}$ +1412 and $[\theta]_{245nm}$ +1157) of 1 as depicted in the formula.[8] This is the first example of the eudesmanolides having the *cis*-fused lactone showing the large coupling constant between H-13 and H-7. It is interesting to isolate the compound having the methyl group at the C-10 position and the substituent at the C-7 position in the *trans* arrangement from the point of chemosystematics of Frullaniaceae.[1]



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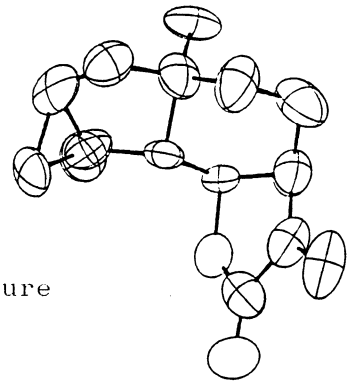

Fig.1. Crystal structure of 1.

References

1)Y. Asakawa, "Chemical Constituents of the Hepaticae," in "Progress in the Chemistry of Organic Natural Products," ed by W. Herz, H. Grisebach, and G. W. Kirby, Springer-Verlag, Wien, New York (1982), Vol. 42, pp. 1-285.

2)M. Toyota, F. Nagashima, and Y. Asakawa, *Phytochemistry*, **27**, 1789 (1988).

3)^{13}C NMR data (100 MHz) of 1: δ_C 18.9 (CH_3), 19.0 (CH_3), 22.0 (CH_2), 25.4 (CH), 26.3 (C), 31.9 (CH_2), 33.5 (CH_2), 39.1 (CH), 45.5 (CH_2), 52.9 (C), 58.2 (CH), 78.9 (CH), 119.6 (CH_2), 137.9 (C), 170.8 (C).

4)Z. Samek, *Collect. Czech. Chem. Commun.*, **35**, 3818 (1970); *Tetrahedron Lett.*, **1970**, 671; *Collect. Czech. Chem. Commun.*, **43**, 3210 (1978).

5)The cyclopropane ring was assigned to be β, since the NOE between the proton H-3 and H-5 was observed.

6)The crystal of 1 belongs to orthorhombic, space group $P2_12_12_1$, and the lattice parameters are a=12.672(4), b=9.399(3), and c=9.093(3) A. The final R value was 0.775 for 1181 reflections.

7)Refer to the following paper.

8)T. G. Waddell, W. Stocklin, and T. A. Geissman, *Tetrahedron Lett.*, **1969**, 1313.

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