NEW REARRANGED *ENT*-EUDESMANE- AND *ENT*-EREMOPHILANE-TYPE SESQUITERPENE LACTONES FROM THE LIVERWORT *FRULLANIA DILATATA* (L.) DUM. VAR. *ANOMALA* CORB.

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Three new rearranged *ent*-eudesmane-type sesquiterpene lactones, spirodilatanolides A (**1**), B (**2**) and C (**3**), and two new *ent*-eremophilane-type sesquiterpene lactones, dilatanolides A (**4**) and B (**5**), have been isolated and their absolute structures determined by extensive spectroscopic and X-ray crystallographic analyses.

KEYWORDS *Frullania dilatata* var. *anomala* ; spirodilatanolide A ; spirodilatanolide B ; spirodilatanolide C ; dilatanolide A ; dilatanolide B

We are continuing to study the chemical constituents of liverworts.[1] The epiphytic liverworts *Frullania* species are rich sources of eudesmane- and eremophilane-type sesquiterpene lactones and/or bibenzyl derivatives.[1] We have investigated *F. dilatata* (L.) Dum. var. *anomala* Corb. collected in Bulgaria and isolated three new rearranged *ent*-eudesmane-type spirosesquiterpene lactones **1** - **3** and two new *ent*-eremophilane-type sesquiterpene lactones **4** and **5**, and established their absolute structures on the basis of spectral evidence and X-ray crystallographic analysis.

The ether extract of *F. dilatata* var. *anomala* (5.20g) was subjected to column chromatography on silica gel and Sephadex LH-20 and prep. HPLC to give three new spirosesquiterpene lactones, spirodilatanolides A (**1**, 200mg), B (**2**, 42mg) and C (**3**, 10mg), and two new *ent*-eremophilane-type sesquiterpene lactones, dilatanolides A (**4**, 47 mg) and B (**5**, 77 mg).

The molecular formula of **1**[2] was revealed to be $C_{15}H_{20}O_2$ (anal. 232.1460) by the high-resolution mass spectrum (HRMS). The ^{13}C NMR and IR spectra showed the presence of a γ-lactone group (1757 cm^{-1} ; δ 170.3 s). The ^1H NMR spectrum contained the signals of a secondary methyl (δ 1.08 d, *J*=7.3), an exomethylenic protons (δ 4.90, 4.96 each s), a methine proton bearing an oxygen (δ 4.39 d, *J*=5.4) and an α-exomethylenic protons (δ 5.53, 6.10 each d, *J*=1.5) on the γ-lactone. The ^{13}C NMR spectrum displayed 15 carbon signals : a methyl, five methylenes, two methines, a quaternary carbon, a methine carbon bearing an oxygen (δ 82.3), two pairs of exomethylene carbons (δ 110.6 t, 146.1 s and 119.2 t, 141.2 s) and a carbonyl carbon (δ 170.3) on the γ-lactone. The analysis of the ^1H-^1H, ^{13}C-^1H COSYs and the HMBC spectra suggested that **1** was the rearranged eudesmane-type spirosesquiterpene lactone. As useful information for stereochemistry of **1** was not obtained by the NOE spectrometry, the X-ray crystallographic analysis[3] of **1** was carried out and gave the ORTEP drawing as shown in Fig. 1. The absolute configuration of **1** was established by the negative Cotton effect (Δε -0.40 (294 nm)) of a ketone **6** derived from **1** (reduction, acetylation and ozonolysis). The structures of **2**[4] and **3**[5] were established by a combination of spectral data (the ^1H-^1H, ^{13}C-^1H COSYs and the HMBC spectra) and spectroscopic comparison with those of **1**.

The molecular formula, $C_{15}H_{22}O_2$ (anal. 234.1611), of **4**[6] was determined by HRMS. The ^{13}C NMR and IR spectra showed the presence of a γ-lactone group (1775 cm^{-1} ; δ 180.4 s). The ^1H and ^{13}C NMR spectra indicated the presence of a tertiary methyl (δ 1.14 s), two secondary methyls (δ 1.84, 1.03 each d, *J*=7.1), an olefinic proton (δ 5.61 br. s) and a methine proton bearing an oxygen (δ 4.47 d, *J*=8.1), together with four methylene carbons, three methine carbons and a quaternary carbon. Moreover, ^1H-^1H, ^{13}C-^1H COSYs and HMBC spectra led to the eremophilane-type sesquiterpene lactone and its stereochemistry was clarified by the difference NOE spectrum. The CD spectrum of **4** indicated the negative Cotton effect (Δε -4.46 (214 nm)), which was very similar to those of **1** - **3** and (+)-frullanolide (**7**)[1, 7] co-occurring in the same species. Thus, the absolute structure of dilatanolide A was established to be **4**. The structure of **5**[8] was also established by a combination of spectral data (the ^1H-^1H, ^{13}C-^1H COSYs and the HMBC spectra) and spectroscopic comparison with those of **4**.

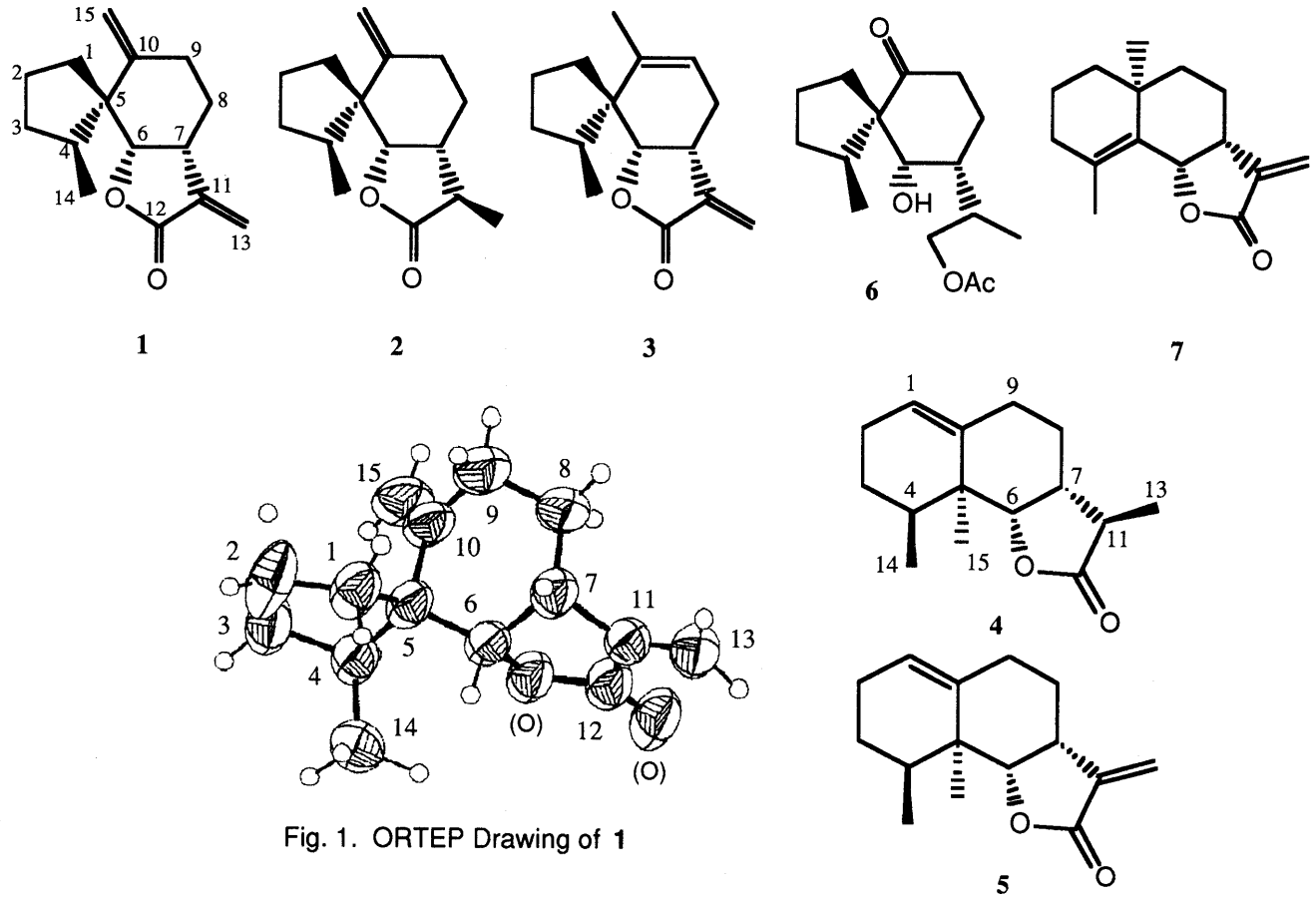

Fig. 1. ORTEP Drawing of **1**

The liverworts belonging to the family Frullaniaceae biosynthesize many sesquiterpene lactones.[1] *F. dilatata* var. *anomala* is one of the characteristic liverworts, because it produces both *ent*-eudesmane- and *ent*-eremophilane-type sesquiterpene lactones which cause the intense allergenic contact dermatitis.[1] This is the first report of the isolation of the rearranged *ent*-eudesmane-type spirosesquiterpene lactones and C_{12}, C_6-eremophilanolide from the bryophytes. The spirolactones **1**, **2** and **3** might be biosynthesized[9] from costunolide-like sesquiterpene lactone *via* (+)-frullanolide (**7**).

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2) mp 65-67°C; $[\alpha]_D^{20}$ +241.5° (c 1.92, $CHCl_3$); HRMS; *m/z* 232.1460 $C_{15}H_{20}O_2$ requires 232.1463; UV(MeOH) λ_{max} 210nm (ε 7719); CD (MeOH) Δε : -0.51 (265) (negative maximum), Δε : +8.93 (206) (positive maximum) ; IR; 1760cm^{-1}; δ_H ($CDCl_3$) 6.10(1H, d, *J*=1.5 Hz, H-13), 5.53(1H, d, *J*=1.5 Hz, H-13), 4.96(1H, s, H-15), 4.90(1H, s, H-15), 4.39(1H, d, *J*=5.4 Hz, H-6), 3.10(1H, like br. q, H-7), 2.52(1H, m, H-4), 2.38(1H, m, H-9), 2.22(1H, dt, *J*=14.7, 5.9, 5.9 Hz, H-9), 2.05-1.91(2H, m, H-3, 8), 1.79-1.66(2H, m, H-1, 2), 1.67-1.54(2H, m, H-1, 2), 1.49(1H, m, H-8), 1.36(1H, m, H-3), 1.08(3H, d, *J*=7.3 Hz, H-14); δ_C ($CDCl_3$) 170.3(C-12), 146.1(C-10), 141.2(C-11), 119.2(C-13), 110.6(C-15), 82.3(C-6), 51.8(C-5), 38.7 (C-7), 38.0(C-4), 33.4(C-2), 31.5(C-3), 29.6(C-9), 28.5(C-8), 21.2(C-1), 17.0(C-14).

3) Recrystallized from *n*-hexane as single crystal. Crystal data for **1**; monoclinic, a=7.785(3), b=13.476(5), c=6.365(2) Å, β=98.04 (3) °, space group $P2_1$, Dcalc=1.16, Cu-Kα radiation, λ=1.54178, μ=5.22cm^{-1}. Diffraction measurements were made on a Mac Sciences MXC 18. The structure was solved by direct methods using MONTECALRO and refined by full-matrix least-squares. Final R=0.044, R_W=0.058, S=2.40. The supplementary material has been deposited at the Cambridge Data Centre.

4) mp 48-50°C; $[\alpha]_D^{20}$ +164.0° (c 2.75, $CHCl_3$); HRMS; *m/z* 234.1614, $C_{15}H_{22}O_2$ requires 234.1619; CD (MeOH) Δε : -1.52 (217) (negative maximum) ; IR; 1770cm^{-1}; δ_H ($CDCl_3$) 4.96(1H, s, H-15), 4.86(1H, s, H-15), 4.46(1H, d, *J*=4.4Hz, H-6), 2.51(1H, m, H-4), 2.31(1H, m, H-9), 2.28(1H, dd, *J*=7.6, 7.1 Hz, H-11), 2.19-2.13(2H, m, H-7, 9), 2.03(1H, m, H-3), 1.87(1H, m, H-8), 1.76-1.67(2H, m, H-1, 2), 1.62-1.54(2H, m, H-1, 2), 1.36(1H, m, H-3), 1.28(3H, d, *J*=7.6 Hz, H-13), 1.27(1H, m, H-8), 1.06(3H, d, *J*=7.1 Hz, H-14); δ_C ($CDCl_3$) 180.1(C-12), 146.9(C-10), 110.8(C-15), 83.2(C-6), 52.0(C-5), 44.2(C-11), 40.9(C-7), 38.0(C-4), 33.2(C-2), 31.8(C-3), 31.1(C-9), 29.0(C-8), 21.3(C-1), 17.4(C-14), 14.0(C-13).

5) Amorphous; $[\alpha]_D^{20}$ +314.8° (c 0.88, $CHCl_3$); HRMS; *m/z* 232.1474 $C_{15}H_{20}O_2$ requires 232.1464; UV(MeOH) λ_{max} 212 nm (ε 12529.9); CD (MeOH) Δε : -0.36 (264) (negative maximum), Δε : +1.91 (218) (positive maximum), Δε : +2.11 (212) (positive maximum) ; IR; 1760cm^{-1}; δ_H ($CDCl_3$) 6.19(1H, d, *J*=2.0 Hz, H-13), 5.59(1H, d, *J*=2.0 Hz, H-13), 5.53(1H, m, H-9), 4.72(1H, d, *J*=6.8 Hz, H-6), 3.33(1H, m, H-7), 2.52(1H, m, H-8), 2.47(1H, m, H-4), 2.02-1.94(2H, m, H-3, 8), 1.77(3H, d, *J*=2.0 Hz, H-15), 1.76-1.67(2H, m, H-1, 2), 1.65-1.55(2H, m, H-1, 2), 1.11(3H, d, *J*=6.8 Hz, H-14); δ_C ($CDCl_3$) 171.2(C-12), 142.9(C-11), 141.4(C-10), 121.3(C-13), 121.1(C-9), 82.3(C-6), 51.6(C-5), 38.7 (C-4), 37.3(C-7), 33.4(C-1, 3), 30.8(C-8), 22.4(C-2), 21.0(C-15), 17.9(C-14).

6) mp 58-60°C; $[\alpha]_D^{20}$ -2.1° (c 0.94, $CHCl_3$); HRMS; *m/z* 234.1620, $C_{15}H_{22}O_2$ requires 234.1611; CD (MeOH) Δε : -4.46 (214) (negative maximum) ; IR; 1775cm^{-1}; δ_H ($CDCl_3$) 5.61(1H, br. s, H-1),, 4.47(1H, d, *J*=8.1 Hz, H-6), 2.50(1H, m, H-11), 2.35(1H, m, H-9), 2.29(1H, m, H-7), 1.83(1H, m, H-8), 1.68(1H, m, H-8), 1.24(3H, d, *J*=7.1 Hz, H-13), 1.14(3H, s, H-15), 1.03(3H, d, *J*=7.1 Hz, H-14); δ_C ($CDCl_3$) 180.4(C-12), 139.9(C-10), 124.2(C-1), 79.9(C-6), 42.5(C-7), 42.3(C-5), 40.1(C-4), 39.5(C-11), 27.6(C-3), 27.3(C-9), 26.7(C-8), 25.0(C-2), 21.3(C-15), 16.8(C-14), 15.3(C-13).

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8) mp. 57-59°C; $[\alpha]_D^{20}$ +1.7° (c 1.73, $CHCl_3$); HRMS; *m/z* 232.1464, $C_{15}H_{20}O_2$ requires 232.1463; CD (MeOH) Δε : -0.30 (262) (negative maximum), Δε : +1.13 (229) (positive maximum) ; IR; 1765cm^{-1}; δ_H ($CDCl_3$) 6.21(1H, d, *J*=3.2 Hz, H-13), 5.60(1H, br. t, H-1), 5.50(1H, d, *J*=3.2 Hz, H-13), 4.56(1H, d, *J*=8.3 Hz, H-6), 3.13(1H, m, H-7), 2.36(1H, m, H-9), 1.96(2H, m, H-2), 1.06(3H, s, H-15), 1.05(3H, d, *J*=4.6 Hz, H-14); δ_C ($CDCl_3$) 171.3(C-12), 139.6(C-10), 139.1(C-11), 124.2(C-1), 118.8(C-13), 79.6(C-6), 42.3(C-5), 39.5(C-4), 38.9(C-7), 27.3(C-3), 27.2(C-9), 26.6(C-8), 24.7(C-2), 20.8(C-15), 16.7(C-14).

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(Received April 18, 1994; accepted May 12, 1994)