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CUMINDYSOSIDE A, A NOVEL CYTOTOXIC TRISNORTRITERPENE GLUCOSIDE WITH A 14, 18-CYCLOAPOEUPHANE-TYPE SKELETON FROM *DYSOXYLUM CUMINGIANUM*[1]

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Abstract : Cumindysoside A, a novel trisnortriterpene glucoside with a 14, 18-cycloapoeuphane-type skeleton, has been isolated from *Dysoxylum cumingianum* as a cytotoxic principle. Its structure was established from spectroscopic evidence.

As a result of our continuing investigation on novel plant cytotoxic agents against solid tumors,[2] the MeOH extract of the leaves of *Dysoxylum cumingianum* (Meliaceae)[3] were found to show significant (ED_{50} < 20 μg/ml) *in vitro* cytotoxicity against RPMI and TE-671 tissue culture cells. Subsequent bioassay-directed fractionation in these tumor cell lines has led to the isolation of cumindysoside A (**1**) as a selective cytotoxic principle.[4]

Cumindysoside A (**1**)[5] was obtained as a white amorphous powder by repeated chromatography on silica gel, MCI-gel CHP 20P, and Fuji-gel ODSQ3 prepacked column, and was positive to a Liebermann-Burchard reaction, giving a purple color. The fab-hrms established the molecular formula $C_{37}H_{56}O_{10}$. The glycosidic nature of **1** was deduced from anomeric resonances [δ 4.78 (1H, d, *J*=7.5 Hz); δ 100.4], which was confirmed by acid hydrolysis to liberate D-glucose. The ^{1}H nmr spectrum showed the presence of a cyclopropyl methylene group [δ 0.27 and 0.52 (each 1H, d, *J*=6 Hz)], four tertiary methyl groups (δ 0.89, 0.90, 1.08, and 1.13), a secondary methyl group [δ 1.07 (d, *J*=7 Hz)], and two acetoxyl groups (δ 1.96 and 2.06). This spectral evidence is analogous to that of **2**,[6] which possesses a 14, 18-cycloapoeuphane-type skeleton, such as glabretal,[7, 8] ailanthol,[9] and shimmiarepin A.[10] In the lower field, it also showed two one-proton singlets at δ 5.90 and 6.08, and a one-proton singlet at δ 9.56, indicating the presence of an exo-methylene and an aldehyde group. The carbon nmr spectrum of **1** showed the appearance of thirty-seven carbons. Among which, six carbon resonances in the

region from δ 64.9 to 100.4 indicated the presence of 6-acylglucoside moiety. In addition, the carbon resonances due to C-1 to C-19, C-28, C-29, and C-30, being in good accord with those of **2**, indicated the existence of the same partial structure in **1**, but differed only in the substituents at C-17. This was confirmed by the ^{1}H-^{1}H COSY and NOESY, as well as ^{1}H-^{13}C COSY and long-range COSY (Figure 1) spectroscopies. The remaining carbon signals, including a methyl (δ 19.8), a methine (δ 34.4), two olefinic [δ 133.9 (t) and 154.9 (s)], and an aldehyde (δ 194.9) carbons, were considered to compose the side chain group at C-17. Further examinations of the ^{1}H-^{13}C long-range COSY as well as the observation of the nOe between the aldehyde proton and one (δ 5.90) of the exo-methylene protons confirmed the structure for the side chain. On the basis of these spectral evidence described above, the structure of cumindysoside A was represented by formula **1**.

Cumindysoside A (**1**) appears to be a novel trisnortriterpene glucoside with a 14, 18-cycloapoeuphane-type skeleton. It possesses a biogenetically irregular side chain at C-17. The co-occurrence of **1** and **2** from the same plant is suggestive of the possible biogenetic pathway for **1** to be derived from **2** as shown in Scheme 1.

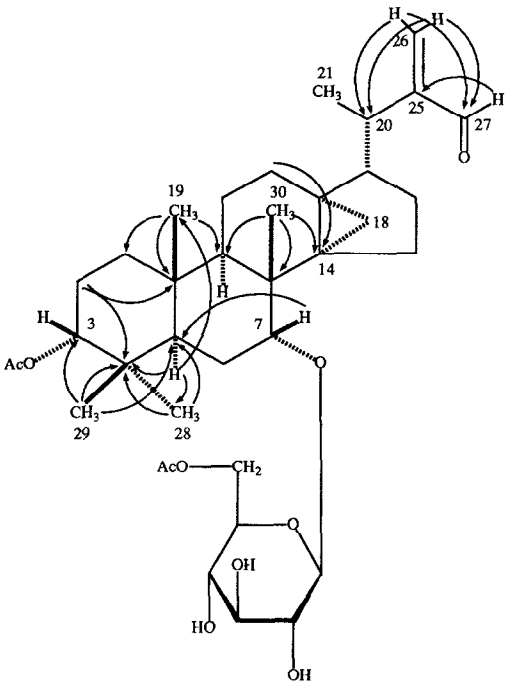
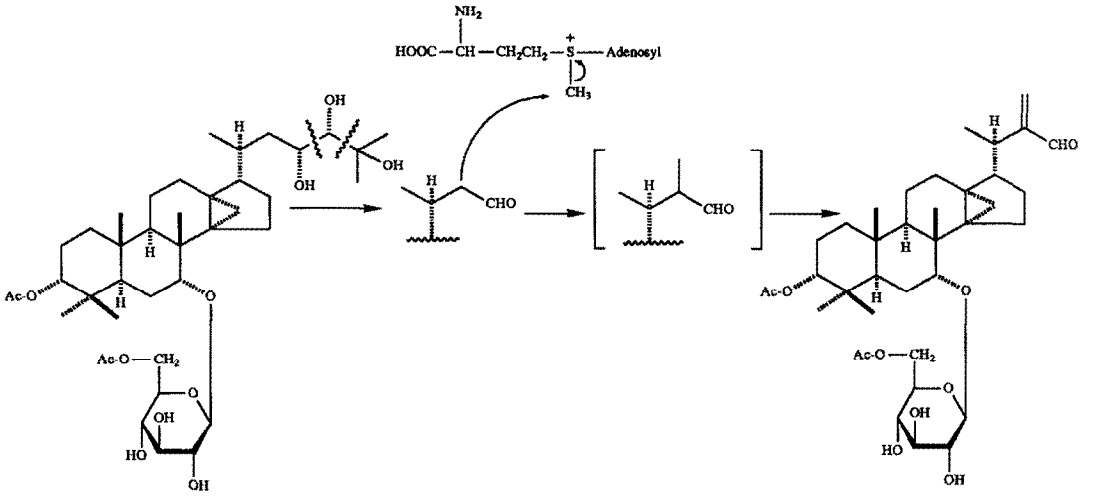


Figure 1 : ^{1}H-^{13}C Long-range Correlation in **1**

Scheme 1



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References and Notes

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3. *D. cumingianum* is an evergreen tree, known as "Lanyu Kung Mu."[11] This plant was collected in Lanyu, Taiwan in Feburary, 1990.
4. Cumindysoside A (**1**) showed selective cytotoxicity against RPMI-7951 melanoma and TE-671 medulloblastoma tumor cells with ED_{50} of 0.34 and 2.74 μg/ml, respectively. Compound **1** was not cytotoxic against A-549 lung carcinoma and HCT-8 colon carcinoma cells at 10 μg/ml. The cytotoxicity assay was carried out according to literature methods.[12,13]
5. $[\alpha]_D^{21}$ -64.5 ° (*c*=0.3, MeOH). $C_{37}H_{56}O_{10}$ [(M+Na)$^+$ *m/z* 683.3777, calc. 683.3771]. ^{1}H nmr (pyridine-d_5+D_2O, 300 MHz) : δ 0.27, 0.52 (each 1H, d, *J* 5.5 Hz, H-18), 0.88 (3H, s, 4β-CH_3), 0.90 (3H, s, 10-CH_3), 1.07 (3H, d, *J* 6 Hz, 20-CH_3), 1.8 (3H, s, 8-CH_3), 1.13 (3H, s, 4α-CH_3), 2.92 (1H, quintet, *J* 6 Hz, H-20), 2.40 (1H, d, *J* 12 Hz, H-5), 3.3 - 3.6 (4H in total,

m, glucosyl H-2 - 5), 3.99 (1H, br s, H-7), 4.69 (1H, dd, *J* 5, 11.5 Hz, glucosyl H-6), 4.71 (1H, d, *J* 7.5 Hz, anomeric H), 4.89 (1H, d, *J*=11.5 Hz, glucosyl H-6'), 4.93 (1H, br s, H-3), 5.90, 6.08 (each 1H, s, H-26), 9.56 (1H, s, H-27). ^{13}C nmr (pyridine-d_5+D_2O, 75 MHz) : δ 16.5 (C-19), 16.7 (C-18), 17.7 (C-11), 19.8 (C-21), 20.6 (C-30), 20.9 (C-6), 21.0, 21.3 (OAc), 22.4 (C-29), 23.5 (C-2), 26.8 (C-15), 26.0 (C-16), 27.9 (C-28), 28.1 (C-13), 28.4 (C-12), 34.4 (C-20), 34.6 (C-1), 36.6 (C-8), 37.1 (C-4), 37.7 (C-10), 39.5 (C-14), 41.5 (C-5), 45.3 (C-9), 52.0 (C-17), 64.9 (C-6'), 71.7 (C-4'), 74.7 (C-5'), 75.0 (C-2'), 78.3 (3C) (C-3, 7, and 3'), 100.4 (C-1'), 133.9 (C-26), 154.9 (C-25), 171.1, 171.2 (COO), 194.9 (C-27).

6. Compound **2** was also isolated from this plant. Data for **2** will be presented in detail elsewhere.
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