Tetrahedron Letters 53 (2012) 1183–1185

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Dysoxylentin A, the first 21-nortriterpenoid bearing a 2-(propan-2-ylidenyl)furan-3(*2H*)-one, from *Dysoxylum lenticellatum*

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ARTICLE INFO

Article history:
Received 30 July 2011
Revised 26 December 2011
Accepted 27 December 2011
Available online 2 January 2012

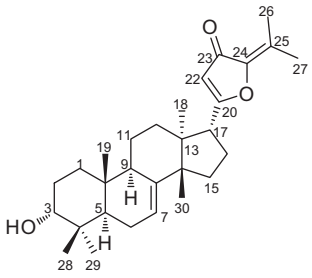
Keywords:
Dysoxylum lenticellatum
Dysoxylentin A
21-Nortriterpenoid
Cytotoxicity

ABSTRACT

Dysoxylentin A (**1**), the first 21-nortriterpenoid bearing a 2-(propan-2-ylidenyl)furan-3(*2H*)-one functional group was isolated from the stem of *Dysoxylum lenticellatum*. Its structure was elucidated by extensive spectroscopic analysis. A plausible biosynthetic pathway was postulated. Dysoxylentin A exhibited selective cytotoxicity against HL-60 tumor cell line.

Introduction

The genus *Dysoxylum* (Meliaceae) comprises about 200 species, which are mainly distributed in India, Southeast Asia, and Polynesia. Among these species, fourteen are distributed in China and ten have been found to grow in Yunnan Province.[1] Many species have been traditionally used as medicines by the indigenous people in Fiji, Papua New Guinea, and New Zealand to relieve fever, convulsions, hemorrhage, rigid limbs, and facial distortion in children.[2] Phytochemical investigations of more than twenty species in this genus have led to the isolation of a number of structurally diverse and biologically active compounds including cytotoxic alkaloids,[3] antifeeding limonoids,[4] cytotoxic diterpenoids,[5] antileukemic triterpenoid glucosides,[6] antibacterial and cytotoxic triterpenoids,[7] sesquiterpenoids,[2b,8] oxyneolignans,[9] bioflavonoids,[10] and a sulfur-containing compound.[11] *Dysoxylum lenticellatum* is a plant endemic to southwest Yunanan province. Previous investigation of the twigs and leaves of *D. lenticellatum* has revealed the presence of triterpenoids, diterpenoids, and ceramids in this plant.[12] As part of our ongoing project aiming at structurally diverse natural products, the stems of *D. lenticellatum* have been chemically investigated. As a result, dysoxylentin A, a new 21-nortriterpenoid with a 2-(propan-2-ylidenyl)furan-3(*2H*)-one unit, was isolated. In this Letter, we report the isolation, structural elucidation, and biological activity of the new compound. A plausible biosynthetic pathway was also postulated.



Dysoxylentin A (**1**)

Dysoxylentin A (**1**)[13] was isolated as a white amorphous powder. Its molecular formula was determined to be $C_{29}H_{42}O_3$ by the HREIMS ion at *m*/*z* 438.3138 (calcd 438.3134) showing 9° of unsaturation. The UV spectrum of dysoxylentin A (**1**) showed absorption maxima at 204, 260, and 307 nm, suggesting the presence of a conjugated system. The IR spectrum indicated the presence of hydroxyl (3440 cm^{-1}), conjugated carbonyl (1707 cm^{-1}) and double bond (1641, 1591 cm^{-1}) groups. In the ^1H spectrum (Table 1), signals for seven quaternary methyls [δ_H 0.79 (s, 6H), 0.91, 0.93, 1.06, 1.98, 2.26], two olefinic protons [δ_H 5.30 (t-like) and δ_H 5.63 (s)], one oxygenated methine proton [δ_H 3.47 (br s)], and one methine

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doi:10.1016/j.tetlet.2011.12.109

Table 1
^{1}H-(400 MHz) and ^{13}C-(100 MHz) NMR data of **1** in $CDCl_3$

No.	δ_H (mult, *J*, in Hz)	δ_C
1α	1.48[NR]	31.1
1β	1.39[NR]	
2α	1.91[NR]	25.3
2β	1.62[NR]	
3	3.47 (br s)	76.2
4		37.4
5	1.78[NR]	44.5
6α	1.93[NR]	23.7
6β	2.04[NR]	
7	5.30 (t-like)	119.0
8		144.6
9	2.35 (m)	48.3
10		34.8
11α	1.66[NR]	17.2
11β	1.60[NR]	
12α	1.96[NR]	31.3
12β	1.70[NR]	
13		46.2
14		50.8
15α	1.75[NR]	34.0
15β	1.64[NR]	
16α	2.07[NR]	23.9
16β	1.89[NR]	
17	2.91 (t, 9.0 Hz)	48.5
18	0.79 (3H, s)	23.1
19	0.79 (3H, s)	12.9
20		184.0
22	5.63 (s)	107.3
23		187.2
24		144.9
25		130.2
26	1.98 (3H, s)	19.9
27	2.26 (3H, s)	17.0
28	0.91 (3H, s)	21.7
29	0.93 (3H, s)	27.7
30	1.06 (3H, s)	27.1

[NR] Indicates that the proton signal was either partially overlapped or unresolved.

[δ_H 2.91 (t, *J* = 9.0 Hz)] adjacent to a methylene were easily identified. The ^{13}C NMR (Table 1) and DEPT spectra exhibited 29 carbon resonances, which corresponded to seven methyls, seven methylenes, six methines (one oxygenated and two olefinic), and nine quaternary carbons (one ketone and four olefinic). The above functionalities accounted for 4° of unsaturation, the remaining 5° of unsaturation suggested the presence of a pentacyclic system in dysoxylentin A. The aforementioned data were very different from those of the compounds isolated from the same plant,[12] suggesting that dysoxylentin A (**1**) possibly possessed a new structural skeleton. Extensive 2D NMR experiments (^{1}H–^{1}H COSY, HSQC, HMBC, and ROESY) were thus performed and the structure of **1** was established. All proton signals were unambiguously assigned to their respective carbon atoms by using HSQC experiment. Four spin systems drawn with bold bonds were established on the basis of ^{1}H–^{1}H COSY spectrum (Fig. 1). Further HMBC correlation analysis (Fig. 1) led to the assembly of the four subunits with the quaternary carbons and other functionalities. In particular, HMBC correlations of H_3-19 to C-1, C-5, C-9, and C-10, of H_3-18 to C-12, C-13, C-14, and C-17, of H_3-28/H_3-29 to C-3, C-4, and C-5, of H_3-30 to C-8, C-13, C-14, and C-15, and of H-7 to C-14 indicated that dysoxylentin A (**1**) possessed a carbon skeleton with an ABCD-ring system same as that of a 3-hydroxy tirucallane-type triterpenoid.[12b,14] The tetracyclic feature of the above structure required the presence of an additional ring in the rest part of dysoxylentin A. The remaining ^{1}H- and ^{13}C-NMR data for one ketone (δ_C 187.2), one trisubstituted double bond (δ_H 5.63, δ_C 107.3; δ_C 130.2, 144.9, 184.0), and two olefinic methyls (δ_H 1.98, 2.26, δ_C 17.0, 19.9) suggested the presence of a 2-(propan-2-ylidenyl)furan-3(*2H*)-one-5-yl group in dysoxylentin A.[15] HMBC correlations from H-22 to C-17, C-20, C-23, and C-24, and from H_3-26/27 to C-23, C-24, and C-25 further confirmed this conclusion, while correlations from H-17 to C-20 and C-22 indicated that the group was located at C-17. Thus, the planar structure of dysoxylentin A was established as shown in Figure 1.

The relative configuration of dysoxylentin A (**1**) was determined by the coupling patterns and ROESY correlations. The broad singlet of H-3 suggested the β-orientation of H-3,[3a] which was further confirmed by the ROESY correlation of H-3 with H_3-28. The α-orientations of H-5 and H-9 were deduced from

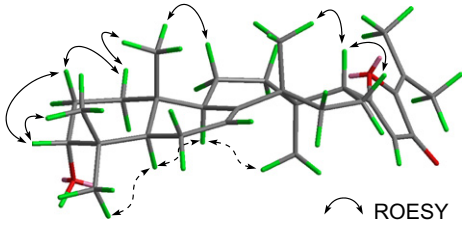


Figure 2. Key ROESY correlations of **1**.

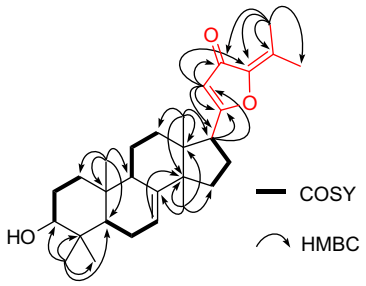
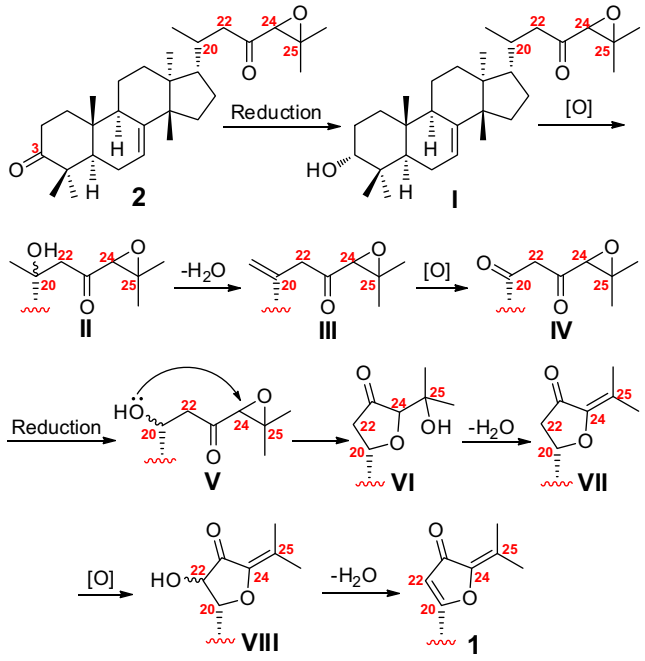


Figure 1. Key HMBC and ^{1}H–^{1}H COSY correlations of **1**.



Scheme 1. Plalusible biosynthetic pathway proposed for **1**.

the correlations of H-5/H_3-29, H-9/H_3-18. The β-orientation of H-17 was determined by the correlations of H-17/H_3-30. Consequently, the relative stereochemistry of dysoxylentin A was determined as depicted (Fig. 2).

To the best of our knowledge, this is the first 21-nortirucallane triterpenoid that bears a 2-(propan-2-ylidenyl)furan-3(*2H*)-one-5-yl group, which has never been reported to be present in nature. Although two endophytic fungi[15] and one plant[16] were reported to produce natural products with such a structural unit, this unit was only present as a part of benzofuranone[15] or as a simple aglycone.[16] The biogenetic origin of dysoxylentin A (**1**) could be traced back to 24,25-epoxytirucall-7-ene-3,23-dione (**2**),[3a] a tirucallane triterpenoid also isolated in this investigation (Scheme 1). Reduction of the 3-ketone group of **2** to a α-hydroxyl would yield **I**, subsequent dehydration between H-21 and OH-20 of the hydroxylated product of which would afford **III**. Oxidative cleavage of the $\Delta^{20(21)}$ double bond followed by reduction of the newly generated ketone group would give **V**, nucleophilic attack of the 21-OH of which on C-24 of the 24,25-epoxide would furnish the dihydrofuranone derivative **VI**. Dehydration between H-24 and OH-25 of **VI** followed by hydroxylation of H-22 would yield **VIII**. In the last step, dehydration would occur between the OH-22 and H-20 to give **1**.

Dysoxylentin A (**1**) was assayed for its cytotoxicity against five human tumor cell lines (human myeloid leukemia HL-60, hepatocellular carcinoma SMMC-7721, lung cancer A-549, breast cancer MCF-7, and colon cancer SW480) by using MTT method[17] with cisplatin as the positive control (IC_{50} 1.94 μM against HL-60). Dysoxylentin A showed selective activity (IC_{50} 34.61 μM) against the HL-60 cell line but did not show any obvious cytotoxicity (IC_{50} >100 μM) against the other cell lines.

Acknowledgment

Financial support from the Chinese Academy of Sciences (KSCX2-YW-R-172) is gratefully acknowledged.

Supplementary data

Supplementary data (experimental details, NMR spectrum, MS data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.12.109.

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13. Dysoxylentin A (**1**): white amorphous powder; $[\alpha]_D^{25.8}$ −2.42 (*c* 0.0015, CH_3OH); UV (CH_3OH) λ_{max} (log ε) 307 (3.53), 260 (3.86), 204 (3.89) nm; CD (CH_3OH) λ_{max} ($\delta\varepsilon$) 213 (−6.07), 259 (+11.68), 290 (−0.92), 340 (+1.19); IR (KBr) ν_{max} 3440, 2950, 1707, 1641, 1591, 1459, 1384, 1135 cm^{-1}; ^1H and ^{13}C NMR data, see Table 1; EIMS *m*/*z* (relative intensity) 438 $[M]^+$ (58), 423 (36), 405 (49), 321 (20), 298 (45), 255 (20), 187 (23), 150 (100), 83 (71), 69 (59), 55 (49); HREIMS *m*/*z* 438.3138 (calcd for $C_{29}H_{42}O_3$, 438.3134).
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