Pergamon

Tetrahedron Letters 40 (1999) 157–160

TETRAHEDRON LETTERS

Lateriflorone, a cytotoxic spiroxalactone with a novel skeleton, from *Garcinia lateriflora Bl.*

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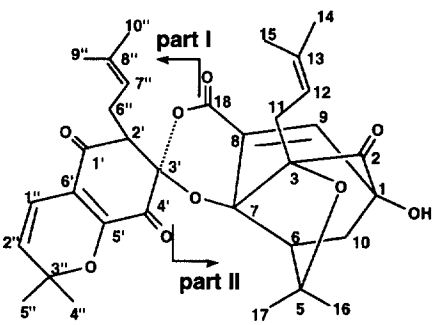
Received 6 October 1998; accepted 19 October 1998

Abstract:: Lateriflorone (1), a cytotoxic natural product with an unprecedented spiroxalactone skeleton isolated from *Garcinia lateriflora*, has been characterized by NMR and X-ray crystallography studies as 6,21-bis(3-methylbut-2-enyl)-19-hydroxy-2,2,23,23-tetramethyl-13,15,22-trioxaspiro[6,7-dihydro-2H-chromene-7,4'-tetracyclo[7.4.1.0^{2,7}.0^{2,11}]tetradecane]-17-ene-5,8,16,20-tetraone.

Keywords: Garcinia, lateriflorone, cytotoxicity, NMR

In continuation of our studies on bioactive secondary metabolites of the South-east Asian plants,[1-6] we have examined the species *Garcinia lateriflora Bl.* (Guttiferae) collected from Indonesia and present herein the isolation and structural elucidation of a novel bioactive natural product, with an unprecedented trioxatetracyclo[7.4.1.0^{2,7}.0^{2,11}]tetradecane system, by a study of its spectral data and single crystal X-ray analysis.



1

Silica gel chromatography of the hexane extract of the stem bark of *Garcinia lateriflora Bl.* (Guttiferae) furnished lateriflorone (1) (0.002%), which was active against the P388 cancer cell line with ED_{50} value of 5.4 μg/ml. Lateriflorone (1), light yellow needles had the molecular formula of $C_{33}H_{38}O_9$ [*m/z* calc. 578.2516; found

PII: S0040-4039(98)02255-2

(HR EIMS) 578.2535]. **7** The IR [ν_{max} cm^{-1} (KBr)] spectrum exhibited absorption bands, 3432 (OH), 1739 (α,β-unsaturated lactone), 1706 (C=O), 1688 (C=O), 1638 (C=O).

Table 1. ^{1}H NMR, ^{13}C NMR, HMBC and NOESY data for **1** (^{1}H: 500 MHz and ^{13}C: 125 MHz in $CDCl_3$)[a]

No.[b]	^{13}C[c]	^{1}H[d]	HMBC (H to C)	NOESY (cross peaks)
1	78.2			
2	202.5			
3	84.3			
5	83.1			
6	48.7 d[e]	1.90 d (9.6)[f]	1, 3, 7, 10, 17	H-17, Hb-10
7	85.9			
8	124.4			
9	142.2 d	7.29 s	2, 7, 18	
10	35.0 t	Ha: 1.98 d (12.8)	Ha: 1, 5, 6, 7, 9	Ha:H-16,Hb-10
		Hb: 1.80 dd (12.8, 9.6)	Hb: 1, 2, 5, 6, 9	
11	28.1	Ha: 2.44 dd (14.6, 7.1)	Ha,b: 2, 3, 7, 12, 13	Hb: H-15, Ha-11
		Hb: 2.81 m		
12	115.6 d	4.68 tm (7.1)	11, 14, 15	H-14, Ha-11
13	136.6			
14	25.7 q	1.58 3H, s	12, 13, 15	
15	17.9 q	1.49 3H, s	12, 13, 14	
16	28.3 q	1.11 3H, s	5, 6, 17	
17	29.8 q	1.18 3H, s	5, 6, 16	
18	157.6			
1'	188.9			
2'	57.3 d	3.21 dd (8.4, 3.2)	1', 3', 6', 7'	
3'	101.2			
4'	186.4			
5'	150.8			
6'	122.9			
1''	115.3 d	6.50 d (10.1)	1', 5', 3''	H-2''
2''	133.4 d	5.78 d (10.1)	6', 3'', 5''	H-1'', H-4''
3''	81.2			
4''	27.7 q	1.46 3H, s	2'', 3'', 5''	
5''	29.0 q	1.57 3H, s	2'', 3'', 4''	
6''	21.5 t	Ha: 2.85 m	Ha,b: 1', 2', 7', 8''	
		Hb: 2.58 m		
7''	121.5 d	5.32 tm (7.2)	6', 9'', 10''	H-10''
8''	133.9			
9''	17.8 q	1.68 3H, s	7'', 8'', 10''	
10''	25.8 q	1.70 3H, s	7'', 8'', 9''	
OH		3.68 s		

[a] All assignments were confirmed by HMQC, HMBC and NOESY spectral data.
[b] The compound is numbered for convenience; for systematic name, see Abstract.
[c,d] Chemical shifts (δ) in ppm from TMS.
[e] Multiplicity was determined from DEPT spectrum. The others which were not indicated were s carbons.
[f] One proton unless otherwise stated; s: singlet, d: doublet, m: multiplet; coupling constants in Hz in parentheses.

The ^{1}H, ^{13}C NMR and DEPT spectra (Table 1) of **1** indicated the presence of 8 methyls, 3 methylenes, 2 methines, 5 olefinic protons and 15 quaternary carbons. The HMQC and HMBC spectra (Table 1) revealed that the structure of **1** consisted of two parts. Part I was deduced to be a prenylated dimethylpyranodihydrobenzoquinone nucleus. The prenyl group attached to C-2' since H-6" showed correlations with C-1' and C-2' and the dimethylpyran was fused to the dihydrobenzoquinone nucleus at C-5'/C-6' as H-1" exhibited HMBC correlations with C-1' and C-5'.

Part II of the structure was more difficult to establish unambiguously from the spectral data. ^{1}H-^{1}H COSY, HMBC and NOESY spectra showed the presence of a prenyl group, a *gem*-dimethyl-$C_{(s)}$-methine-methylene group and an isolated olefinic proton. H-coupled connectivities could be observed to the following quaternary oxygenated carbons in part II, C-1, 3, 5, 7, and 18, which were suggestive of a bicyclic or tricyclic system, but these still precluded the connectivity of parts I and II of the molecule. Suitable crystals were obtained for an X-ray crystallographic study (Figure 1) and the structure of lateriflorone was determined as **1**, which is compatible with the ^{1}H, ^{13}C NMR, HMBC and NOESY data assigned in Table 1.

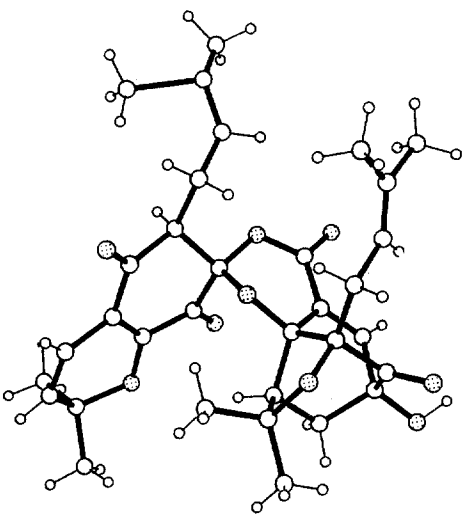
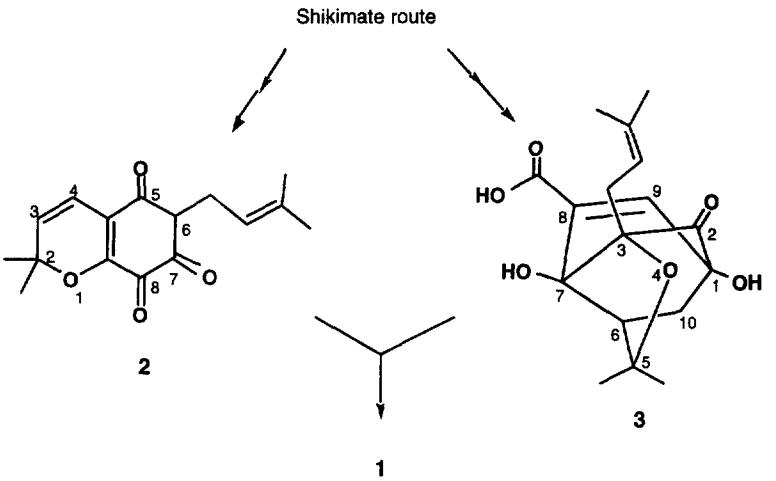


Figure 1. X-ray structure of **1**

The biosynthetic origin of the unusual spiroxalactone structure of lateriflorone is intriguing. The prenylpyranodihydroquinone moiety (part I) could be regarded as related to prenylquinone,[8] helinudichromenequinone,[9] and the prenylated dihydroquinone part of a coumarin isolated by Corey and Wu.[10] It is possible that the biosynthesis of this moiety and the 4-oxatricyclo[4.3.1.$0^{3,7}$]decane ring system (part II) could originate from a common shikimate pathway through gallic and shikimic acids, each with incorporation of two mevalonate-derived prenyl units *via* appropriate cyclizations, oxidation and dehydration steps to furnish two intermediates **2** and **3**. The 7-keto group of **2** could react with the 7-hydroxyl of **3** to form a hemiketal with subsequent lactonization of the carboxylic acid to yield the novel spiroxalactone **1** (Scheme 1). However, as the moiety (part II) is similar to that present in the complex prenylated xanthonoid, gaudichaudione H,[6] recently isolated from *Garcinia gaudichaudii Bl.*, we cannot exclude the possibility of its being derived from the cleavage

of such a complex xanthonoid. The possibility that **1** could be an artefact formed by the reaction of the two moieties can be ruled out as the isolation conditions were very mild and, as far as we are aware, caged alicyclic compounds with structures of the type **3** have not been isolated as natural products.

Acknowledgement: The research work was supported by the National University of Singapore (NUS). SGC thanks NUS for a research scholarship.



Scheme 1. A proposed biogenetic pathway to 1

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[7] **1**: light yellow needles (EtOH), m.p. 220-222 °C; $[\alpha]_D^{29}$ –173.6 (*c* 0.1, EtOH); UV λ_{max} nm (log ε) (EtOH): 220 (4.57), 372 (3.98); EIMS *m/z* (rel. int.): 578 $[M]^+$ (1.2), 560 [M - H_2O] (7), 545 [M - H_2O - Me] (15), 519 [M - $HOCMe_2$] (5), 503 [M - $OCMe_2$ - OH] (8), 481 [M - Me_2CCHCH_2CO] (10), 304 [part II] (15), 275 [part I + H] (60), 259 [part I - Me] (70), 207 [part II - Me_2CCHCH_2CO] (76), 69 [C_5H_9] (100), 55 [C_4H_7] (55), 44 [CO_2] (87), and 28 [C=O] (88); *Crystal data* for **1**: $C_{33}H_{38}O_9$, M = 578, orthorhombic, space group $P2_12_12_1$, a = 10.3580 (2) Å, b = 11.3540 (1), c = 26.7954 (5), β = 90°, V = 3151.27 (9) $Å^3$ (λ = 0.71073 Å), Z = 4, D_{calc} = 1.218 Mg/m^3, $F(000)$ = 1228, μ(Mo-Kα) = 0.088 mm^{-1}. Crystal size (mm) was 0.25 × 0.15 × 0.05. Frame data were collected at 293(2) K in the range 1.95 to 24.99 ($-10 \le h \le 14$; $-15 \le k \le 15$; $-30 \le l \le 35$) on a Siemens SMART CCD system and processed. The processed *hkl* data were absorption corrected using the program SADABS. Anisotropic thermal parameters were refined for all the non-hydrogen atoms. All the hydrogen atoms were located in the difference Fourier routines. The positional and isotropic thermal parameters of the hydroxyl H-atom were refined. Riding models were used to place the rest of the H-atoms in their idealized positions. In the final least-squares refinement cycles on F^2, the model converged at R_1 = 6.62 %, wR_2 = 12.01 % and GOF = 1.114 for 5470 reflections with $F_o > 4\sigma(F_o)$ and 410 parameters. In the final difference Fourier synthesis, the electron density fluctuated in the range 0.193 to -0.221 $eÅ^{-3}$. Atomic coordinates bond lengths and angles, and thermal parameters will be deposited at the Cambridge Crystallographic Data Centre (CCDC).
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