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Leucadenone A–D, the novel class flavanone from the leaves of *Melaleuca leucadendron* L.

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Abstract

The novel β-triketone flavanones, leucadenone A–D, have been isolated from the leaves of *M. leucadendron* L. The structures of **1–4** were determined by NMR spectral and X-ray analysis.

Keywords: natural products; β-triketones flavanone; NMR; X-ray crystal structure.

Cyclic polyketones, 'β-triketones', have a unique structure, which is rare in natural products. They are commonly found in Eucalyptus species and related members of Myrtaceas,[1] which differ in the nature of the side chain, the number of methyl groups and level of oxygenation. It is noteworthy that compounds **1–4**, if isolated, would constitute a new class of substances from *Melaleuca leucadendron* comprising a cyclic polyketone flavanone moiety. In this new class of substances, all except the flavanone moiety have the structure of asymmetric centers, which have the opposite absolute configurations between pairs of stereoisomers (Fig. 1). We now report herein the isolation and structure determination of compounds **1–4** by spectral data including X-ray analysis and chemical reaction.

The fresh leaves of the plant were extracted with acetone. The extract was concentrated under vacuum and partitioned between $CHCl_3$ and water. The organic layer (125 g) was separated by silica gel column chromatography using gradient elution of hexane–ethyl acetate. Further purification by normal phase HPLC (hexane:EtOAc:$CHCl_3$ 5:1:1) afforded a series of new cyclic polyketone flavanones **1–4**.

β-Triketone flavanones **1–4** (leucadenone A–D) are not stable compounds. These compounds kept their original structure for around ten minutes in a $CDCl_3$ solvent system. When the system was changed from *d*-acetone to *d*-methanol, the four isomers exist in solution as a mixture of equilibrating tautomers. In HPLC the analysis of each of these isomers demonstrated four peaks with similar retention times as the original separation in leucadenone A–D, they are able to interconvert during the measurement by NMR and other physical spectroscopy via the mechanism shown in Scheme 1. The possibility of such

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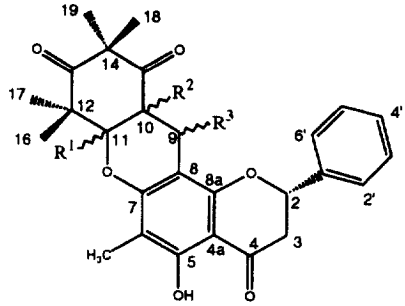
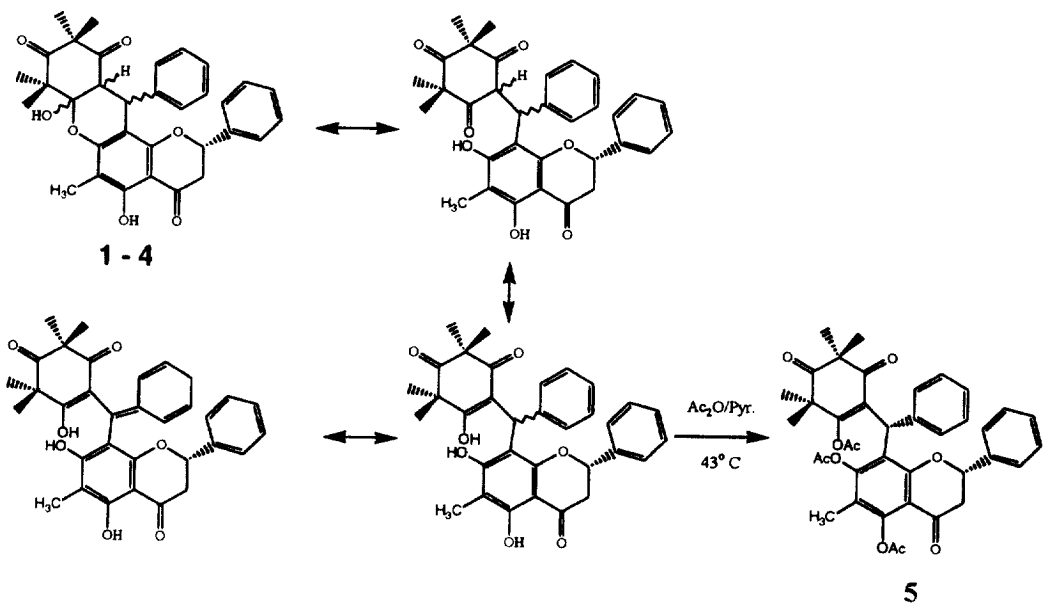


	R^1	R^2	R^3
1	β-OH	α-H	α-Ph
2	α-OH	β-H	β-Ph
3	α-OH	α-H	α-Ph
4	α-OH	β-H	α-Ph

Figure 1. Leucadenone A–D (**1–4**)

tautomerization between hemiacetal 11-hydroxy flavanones and ring-opened cyclic β-triketones has been noted previously.[2,3]



Scheme 1. Postulated conversion of **1–4** and the pathway of **5**

The molecular formula of leucadenone A obtained as crystal solid was established as $C_{33}H_{32}O_7$ by HR-EI mass spectroscopy (*m/z* 540.2144 (M^+) +0.4 mmu). The ^1H NMR spectrum of **1** showed an ABX system at δ 2.63 (1H, dd, *J*=17, 5), 2.67 (1H, dd, *J*=17, 12) and 5.25 (1H, dd, *J*=12, 5) for C-2 and C-3 protons, a strongly downfield resonance (δ_H 12.06), one methyl group δ 2.11 (3H, s) and five protons in the aromatic region [δ_H 6.80(2H), 7.26(1H) and 7.31(2H)], and that the flavanone part of **1** has a strobopinin structure.[4]

The remaining moiety ($C_{17}H_{18}O_3$), *m/z* 270 in MS fragment, includes a phenyl residue (δ 7.1–7.3, 5H), four CH_3-groups, two protons at δ 4.86 (1H, d, *J*=9), 3.67 (1H, dd, *J*=9, 2) and an exchangeable

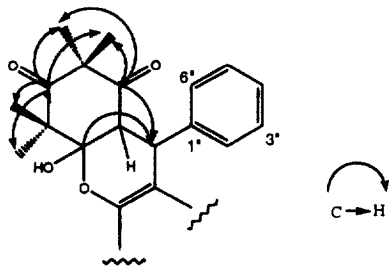


Figure 2. HMBC correlations for compound **1**

proton at δ 3.10 (1H, d, *J*=2) from the ^{1}H NMR data. The DEPT experiment of **1**, shows that except for the strobopinin moiety, the residue moiety includes four methyls, seven methines, and six quaternary carbons (including two carbonyl signals at δ_C 204.7 and 213.4). The moiety structure was also confirmed by 2D NMR experiments. In the ^{1}H–^{1}H COSY experiment, a correlation between the H-10 and H-9 and long-range coupling between H-10 and C_{11}-OH was observed. In the HMBC experiment, a correlation between C-15 and H-9, H-18 and H-19 and C-13 and H-16, H-17, H-18 and H-19 was observed (Fig. 2). The above summarized evidence the residue moiety is the 2,2,4,4-tetramethyl-1,3,5-tricyclohexanone.

The relative stereochemistry of **1** was established by a combination of observed coupling constants and NOESY spectrum. The proton of C-10 was observed as a double doublet, showing that the coupling constants (*J*=9, 2) from H-10 to the H-9 and C-11 hydroxyl proton (*w*-type) and the NOESY spectrum of the molecule showed the following connectivity C_{10}-H with C_9-H; C_{12}-$CH_{3(ax)}$;C_{14}-$CH_{3(ax)}$ and C_9-phenyl. These data support that the H-10, H-9 and C_{11}-OH are all axially oriented. The probable absolute configuration of leucadenone A was finally established by its X-ray analysis as depicted in the structure **1**.[6]

Leucadenone B (**2**) has the same molecular formula as leucadenone A. The general spectral features of compound **2** closely resemble those of its isomer **1** expect for the chemical shifts of H-2 and H-3 in the NMR spectra (Table 1). This evidence suggested that compound **2** is a stereoisomer of leucadenone A at C-2. Analysis of the observed coupling constant of H-2 (*J*=14, 3 Hz) by the Karplus relationship suggested that the dihedral angles for H-2/H-3$_\alpha$ and H-2/H-3$_\beta$ were approximately 60° and 180°, respectively, which was same as for the C-2 configuration of **1**.

From the X-ray analysis of **2**,[6] the configuration of the methylpinocembrin moiety is the same as that in **1**, but the cyclic polyketone moiety is an enantiomer of that in **1**. When comparing the 3D structures of **1** and **2**, we found the phenyl group at C-2 of **2** is inside the benzene ring at C-9. It is the reason that the C-2 protons are further up-field than in **1** (Table 1).

Leucadenone C (**3**) and D (**4**) have the same molecular formula as leucadenone A and B. A detailed analysis of the ^{1}H and ^{13}C NMR data of **3** and **4**, along with measurable ^{1}H–^{1}H coupling constants are given in Table 1. The general spectral features of **3** and **4** closely resembled those of their isomers **1** and **2** except for the chemical shifts of H-9 and H-10, and a coupling relationship of H-10 in the NMR spectrum (Table 1). This evidence suggested that compounds **3** and **4** are stereoisomers of leucadenone A and B at C-9, C-10 and C-11.

The appearance of the H-10 signal as a singlet of **3** showed that the dihedral angle for H-10/H-9 was approximately 90°. Compound **4**, with the H-10 signal being a doublet (*J*=1 Hz), implied that the proton is coupling with C_{11}-OH (*w*-type coupling). These findings allowed the assignment of the relative stereoisomers of compound **3** and **4**.

Derivatization of the **1–4** mixture (6 mg) with acetic anhydride (3 ml)–pyridine (2 ml) produced a single compound (6 mg) tentatively as the ring-opened β-triketone form of the structure **1–4** with acetyl-

Table 1
^{13}C and ^{1}H NMR data of leucadenone A (**1**), B (**2**), C (**3**) and D (**4**) in $CDCl_3$, chemical shift (δ), J in hertz

Assign-ment	^{13}C NMR at 75 MHz[a]				^{1}H NMR at 300MHz			
	A	**B**	**C**	**D**	**A**	**B**	**C**	**D**
2	79.0(d)	78.9(d)	78.1(d)	78.2(d)	5.25(dd,12,5)	4.52(dd,14,3)	5.14(dd,12,3)	5.37(dd,11,8)
3	44.1(t)	42.3(t)	41.1(t)	44.3(t)	2.63(dd,17,5)	2.54(dd,17,3)	2.92(dd,17,3)	2.73(dd,17,8)
					2.67(dd,17,12)	2.83(dd,17,14)	3.08(dd,17,12)	2.76(dd,17,11)
4	196.7(s)	197.3(s)	196.7(s)	196.1(s)				
5	159.3(s)	159.5(s)	159.8(s)	159.6(s)				
6	106.3(s)	105.8(s)	106.5(s)	106.0(s)				
7	156.3(s)	156.7(s)	157.1(s)	157.3(s)				
9	33.4(d)	33.3(d)	35.9(d)	36.2(d)	4.86(d,9)	4.82(d,9)	5.10(s)	5.05(s)
10	53.4(d)	53.1(d)	53.9(d)	53.8(d)	3.67(dd,9,2)	3.59(9,2)	3.46(s)	3.45(d,1)
11	98.4(s)	98.4(s)	99.5(s)	99.5(s)				
12	53.9(s)	53.9(s)	54.0(s)	53.9(s)				
13	213.4(s)	213.4(s)	211.4(s)	211.4(s)				
14	58.0(s)	57.9(s)	55.1(s)	55.1(s)				
15	204.7(s)	204.9(s)	209.0(s)	209.1(s)				
16	24.4(q)	24.4(q)	24.6(q)	24.6(q)	1.50(s)	1.48(s)	1.39(s)	1.36(s)
17	17.7(q)	17.7(q)	15.7(q)	15.7(q)	1.56(s)	1.50(s)	1.44(s)	1.44(s)
18	27.1(q)	27.1(q)	26.4(q)	26.4(q)	1.21(s)	1.17(s)	0.98(s)	1.02(s)
19	21.7(q)	21.7(q)	21.5(q)	21.5(q)	1.29(s)	1.25(s)	1.20(s)	1.21(s)
1'	138.4(s)	137.3(s)	137.1(s)	138.8(s)				
2'and 6'	125.6(d)	125.9(d)	125.9(d)	125.7(d)	6.80(dd,7,2)	6.91(dd,8,2)	6.78(dd,7,2)	6.72(dd,7,4)
8a	157.7(s)	158.0(s)	158.0(s)	157.7(s)				
6-Me	7.1(q)	7.1(q)	7.0(q)	6.9(q)	2.11(s)	2.06(s)	1.97(s)	1.97(s)
-OH					3.10(d,2)	3.18(d,2)	3.46(s)	3.37(s)
					12.06(s)	11.92(s)	12.01(s)	11.96(s)

[a] Multiplicities are assigned by the DEPT spectrum.

ation at all hydroxyl groups.[5] The structure and probable absolute configuration of **5** was established by its X-ray analysis.[6]

Because of the apparently easy interconversion of **1–4** via a ring-opened β-triketone intermediate, it is not known whether only one isomer or the **1–4** are originally present in the plant. Nevertheless, this is the first report of naturally occurring cyclic β-triketone flavanone.

Acknowledgements

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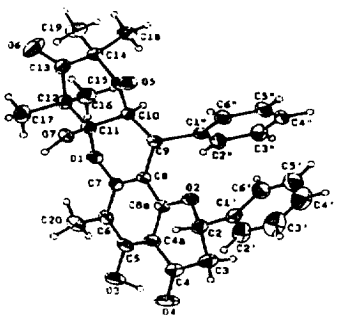
5. Spectral data for **5**: ^{1}H NMR ($CDCl_3$) δ 7.05–7.29 (m, 10H), 5.85 (s, 1H), 5.37 (br d, J=12 Hz, 1H), 2.93 (dd, J=17,12 Hz, 1H), 2.70 (dd, J=17,3 Hz, 1H), 2.39 (s, 6H), 1.80 (s, 3H), 1.77 (s, 6H), 1.30 (s, 3H), 1.13 (s, 3H), 1.05 (s, 3H); MS (EI) *m/z* 623 (M^+–Ac, 2), 606(9), 582(31), 271(100).

6. The crystal structure of compounds **1**, **2** and **5** is shown below.



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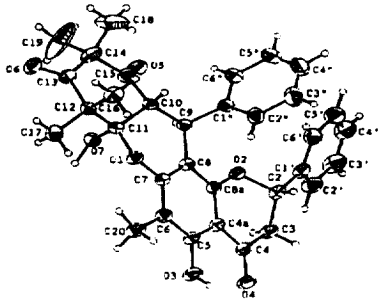

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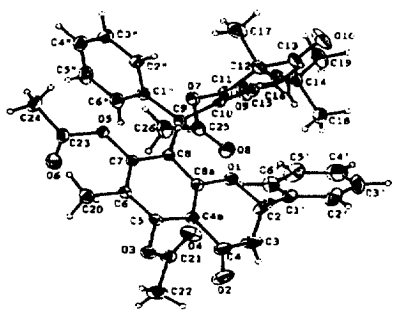

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