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Alstonic acids A and B, unusual 2,3-secofernane triterpenoids from *Alstonia scholaris*

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ABSTRACT

2,3-Secofernane triterpenoids, alstonic acids A (**1**) and B (**2**), were isolated from the leaves of *Alstonia scholaris* together with an indole alkaloid, N^1-methoxymethyl picrinine (**3**). Their structures were established from MS and NMR spectroscopic analyses and confirmed by single crystal X-ray diffraction analysis.

1. Introduction

The genus *Alstonia* (Apocynaceae) is widely distributed throughout the tropical regions of Africa and Asia. The phytochemical constituents of *Alstonia* sp. have been extensively investigated; nearly 400 compounds have been isolated and characterized (Cai et al., 2008). Most of the compounds identified so far are indole and quinoline alkaloids (Abe et al., 1989; Atta-ur-Rahman et al., 1985, 1987; Cai et al., 2007, 2008; Macabeo et al., 2005; Salim et al., 2004; Yamauchi et al., 1990; Zhou et al., 2005). *Alstonia scholaris* (Linn.) R. Br. is a popular plant in Chinese medicine, where its leaves have been historically used in "Dai" ethnopharmacy to treat chronic respiratory diseases. The leaf extract, developed as a commercially available traditional Chinese medicine, has also been prescribed in hospitals and sold over-the-counter in drug stores (Cai et al., 2008).

As part of our effort to discover structurally diverse and biologically active secondary metabolites from local medicinal plants, the phytochemical investigation of the leaves of *A. scholaris* has led to the isolation of alstonic acids A and B (**1**–**2**), new 2,3-secofernane-type triterpenoids, as well as a new monoterpene indole alkaloid, N^1-methoxymethyl picrinine (**3**), together with six known alkaloids, picrinine (**4**) (Abe et al., 1989), 5α-methoxystrictamine (**5**) (Zhou et al., 2005), picralinal (**6**) (Abe et al., 1989), 19,20-(*E*)-vallesamine (**7**) (Atta-ur-Rahman et al., 1987), leuconolam (**8**) (Goh et al., 1984), and scholaricine (**9**) (Atta-ur-Rahman et al., 1985). To the best of our knowledge, this report is the first to document naturally occurring 2,3-secofernanes. The cyclization between C-3 and C-9 within alstonic acid B (**2**) is unprecedented in triterpenoids. The structural elucidation of these unique 2,3-secofernanes is described below.

2. Results and discussion

Compound **1** was isolated as colourless needles. Its molecular formula was determined to be $C_{30}H_{48}O_3$ on the basis of negative-ion HRESIMS at *m/z* 455.3512 (calcd. for $C_{30}H_{47}O_3$, 455.3525), in combination with analysis of the ^{13}C NMR (DEPT) spectrum. The IR spectrum showed absorption bands at 1727, 1699 cm^{-1}, ascribable to carbonyl groups. The ^{13}C NMR spectrum (Table 1) exhibited 30 carbon signals, including a carboxylic carbonyl and aldehyde carbonyl resonances at δ 174.6 (s), 207.3 (d), a tetra-substituted double bond at δ 136.2 (s), 131.3 (s), and eight up-field methyl signals from δ_C 14.4–23.9 ppm. The following ^1H NMR signals (Table 1) were readily distinguishable: an aldehyde singlet at δ 9.77, two AB methylene protons at δ 2.72 (d, *J* = 14.5 Hz), 2.87 (d, *J* = 14.5 Hz), a relative down-field methine proton at δ 2.90 (dd, *J* = 3.9, 3.7 Hz), six methyl singlets at δ 0.71, 0.74, 0.97, 0.99, 1.19, and 1.28, as well as two methyl doublets at δ 0.84 (d, *J* = 6.5 Hz), 0.89 (d, *J* = 6.5 Hz). The NMR spectroscopic data were similar to those of fern-8-ene (Ageta et al., 1994), except for the signals ascribed to ring A, which suggest that the compound is a *seco*-A-ring fernane triterpenoid derivative.

The following HMBC correlations (Table 1) were observed: from the above-mentioned AB methylene protons to a carboxyl carbon at δ 174.6 (s, C-2), from δ_H 0.97 (s, Me-23) and 1.19 (s, Me-24) to an aldehyde carbon at δ_C 207.3 (d, C-3), establishing that the

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Table 1
NMR spectroscopic data for alstonic acids A (**1**) and B (**2**).

No.	Alstonic acid A (**1**)[a]			Alstonic acid B (**2**)[b]		
	δ_H (J in Hz)	δ_C mult.	HMBC[c]	δ_H (J in Hz)	δ_C mult.	HMBC[c]
1	2.72 d (14.5) 2.87 d (14.5)	46.4 t	2, 5, 9, 25	2.25 d (15.4) 3.02 d (15.4)	38.5 t	2, 5, 9, 25
2		174.6 s			178.3 s	
3	9.77 s	207.3 d	5, 24		222.5 s	
4		49.5 s			46.8 s	
5	2.90 dd (3.9, 3.7)	42.3 d	1, 3, 9, 24	2.25 br s	45.6 d	3, 7
6	1.86 m, H_β 2.28 m, H_α	20.1 t	4, 8, 10	2.19 br dd (19.1, 3.1), H_β 2.55 br d (19.1), H_α	28.3 t	4, 8, 10
7	2.00, 2.05 m	23.4 t		5.58 br d (3.1)	121.0 d	5, 9, 14
8		136.2 s			143.8 s	
9		131.3 s			58.1 s	
10		41.3 s			42.7 s	
11	1.91 m, H_β 2.06 m, H_α	20.9 t		1.36 m, H_α 1.76 m, H_β	19.0 t	3, 8, 10, 13
12	1.28, 1.39 m	31.1 t		1.25, 1.65 m	29.8 t	9, 14, 27
13		37.1 s			36.9 s	
14		41.3 s			44.0 s	
15	1.25 m, H_α 1.75 m, H_β	28.3 t		1.30 m, H_α 1.69 m, H_β	29.9 t	
16	1.43 m, H_β 1.64 m, H_α	36.1 t	18, 21, 28	1.53 m, H_β 1.70 m, H_α	35.5 t	
17		43.0 s			42.9 s	
18	1.45 m	52.9 d		1.53 m	52.0 d	
19	1.37 m, H_α 1.47 m, H_β	20.7 t		1.20 m, H_α 1.39 m, H_β	20.0 t	
20	1.15 m, H_α 1.75 m, H_β	28.6 t		1.19 m, H_α 1.84 m, H_β	28.3 t	
21	0.88 m	59.7 d	16, 28	0.98 m	59.6 d	
22	1.43 m	31.0 d		1.44 m	30.7 d	
23	0.97 s	23.9 q	3, 5, 24	1.19 s[d]	28.8 q[e]	3, 5, 24
24	1.19 s	19.8 q	3, 5, 23	1.20 s[d]	29.0 q[e]	3, 5, 23
25	1.28 s	23.2 q	1, 5, 9	1.00 s	22.8 q[f]	1, 5, 9
26	0.99 s	21.4 q	8, 13, 15	0.96 s	20.9 q	8, 13, 15
27	0.71 s	16.6 q	12, 14, 18	0.71 s	15.6 q	12, 14, 18
28	0.74 s	14.4 q	16, 18, 21	0.76 s	14.9 q	16, 18, 21
29	0.89 d (6.5)	22.3 q	21, 30	0.88 d (6.6)	22.0 q	21, 30
30	0.84 d (6.5)	23.2 q	21, 29	0.82 d (6.6)	22.9 q[f]	21, 29

[a,b]Determined for C_5D_5N (δ_H 8.71 ppm, δ_C 149.9 ppm as int. standard) and $CDCl_3$ (δ_H 7.26 ppm, δ_C 77.0 ppm), respectively.
[c]Only important and discernable correlations were listed.
[d,e,f]Interchangeable.

carboxyl and aldehyde groups were positioned at C-2 and C-3, respectively. Therefore, the triterpene acid was elucidated as 2,3-*seco*-3-oxofern-8-en-2-oic acid, and named alstonic acid A. The structure of **1** was finally confirmed by single crystal X-ray diffraction, and a perspective ORTEP diagram of the molecule is shown in Fig. 2. Although 3,4-*seco*-A-ring triterpenoids have sometimes been isolated from natural sources, only a few cases of 2,3-*seco* derivatives have been reported up to now (Baas, 1985; Toriumi et al., 2003).

Compound **2**, colourless needles, possesses a molecular formula of $C_{30}H_{46}O_3$ based on the negative-ion HRESIMS at m/z 453.3359 (calcd. for $C_{30}H_{45}O_3$, 453.3368) and supported by analysis of the ^{13}C NMR (DEPT) spectrum. The IR spectrum showed the absorption bands of carbonyl (1737, 1702 cm^{-1}) and double bond (3039, 1635 cm^{-1}) groups. The NMR spectroscopic characters (Table 1) were similar to those of alstonic acid A (**1**), suggesting that **2** was also a 2,3-secofernane triterpene acid derivative. However, there were some prominent differences as follows: the resonances of the aldehyde and the tetra-substituted double bond were absent and replaced by those of a newly arisen ketone at δ_C 222.5 (s, C-3) and a tri-substituted olefin at δ_H 5.58 (1H, br d, J = 3.1 Hz), δ_C 121.0 (d, C-7), 143.8 (s, C-8), respectively, in the NMR spectrum of **2**. Considering eight degrees of unsaturation, including the contribution of five rings, the C-3 ketone group must connect with a certain carbon atom of the triterpenoid scaffolding to generate a new ring, and the linked position was determined as C-9 based on the following important HMBC correlations (Table 1): from δ_H 1.36, 1.76 (each m, H-11) to δ_C 222.5 (s, C-3), from δ_H 2.25, 3.02 (each d, J = 15.4 Hz, H-1), 5.58 (br d, J = 3.1 Hz, H-7) and 1.00 (s, Me-25) to δ_C 58.1 (s, C-9).

The configuration of H-5 was unambiguously determined to be in an α orientation (i.e., equatorial bond) based on the following evidence: (1) the proton H-5 showed a broad singlet in ^1H NMR spectrum (if axial, it should exhibit a typical double doublet, $J \approx$ 11.0, 4.0 Hz); and (2) the ROESY correlation (Fig. 3) between H-5 and H-6α was observed. Accordingly, the cyclization between C-3 and C-9 must span above the ring-B, so the relative configuration of C-9 was deduced to β. Consequently, the structure of **2** was established as shown in Fig. 1 and named alstonic acid B. The biosynthetic pathway (Fig. 4) of **2** involves an unprecedented C–C cyclization between C-3 and C-9.

Compound **3**, obtained as colourless, crystalline powder, has a molecular formula of $C_{22}H_{26}N_2O_4$ based on the positive-ion HRESIMS, showing a quasi-molecular ion peak at m/z 383.1965 (calcd. for $C_{22}H_{27}N_2O_4$, 383.1970), and the ^{13}C NMR (DEPT) spectrum. The UV spectrum showed absorptions at 238, 287 nm, typical of a modified indoline chromophore. The NMR spectrum of **3** was very similar to that of picrinine (**4**) (Abe et al., 1989), also isolated from this species. Nevertheless, there were several additional observed signals in **3**: a down-field methylene resonance at δ_H 4.74, 4.95 (each 1H, d, J = 11.0 Hz), δ_C 76.7 (t) and a methoxyl group at δ_H 3.40 (3H, s), δ_C 55.5 (q). Significant HMBC correlations (Table 2) from δ_H 4.74,

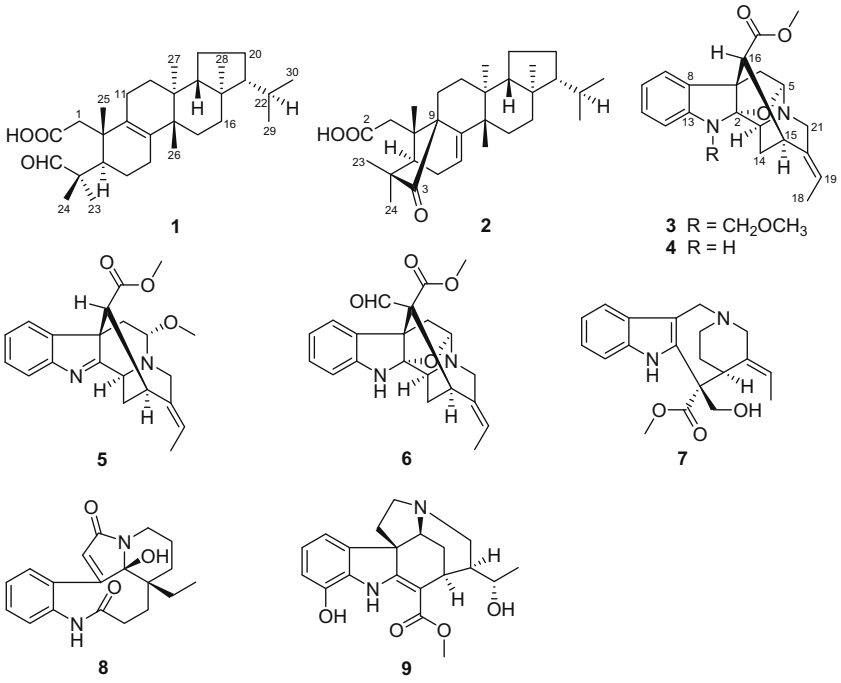

Fig. 1. Structures of **1**–**9** isolated from *A. scholaris*.

4.95 (each 1H, d, J = 11.0 Hz) to δ_C 106.8 (s, C-2), 147.8 (s, C-13) and 55.5 (q), and from δ_H 3.40 (3H, s) to δ_C 76.7 (t), were observed, indicating that a methoxymethyl group must attach to the nitrogen atom in the indoline ring. Thus, the structure of **3** was determined as N^1-methoxymethyl picrinine.

It should be mentioned that the configuration of 5-OCH_3 in **5** was wrongly assigned in the original literature (Zhou et al., 2005) and should be revised to be in an α orientation. This discrepancy was observed by comparing the NMR spectroscopic data, especially the characteristic coupling constants, with those of analogues (Abe et al., 1994, 1998). The adjustment was also supported by the observed ROESY correlations: H-5β ↔ H-6β, H-5β ↔ H-21β, and H-14α ↔ H-21α.

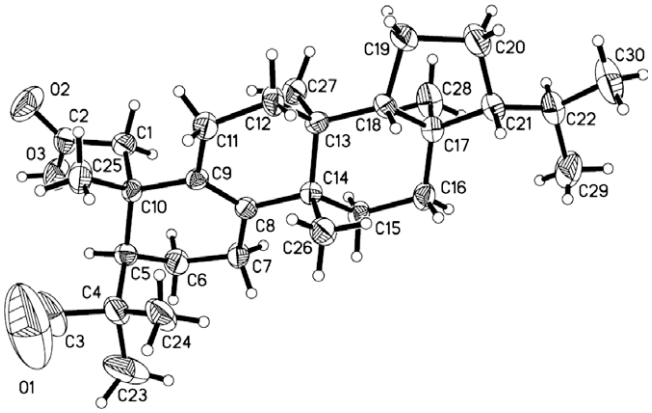

Fig. 2. Molecular structure of **1** generate by X-ray analysis.

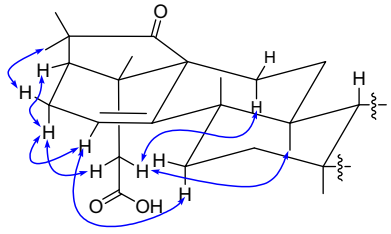

Fig. 3. Key ROESY correlation of **2**.

3. Concluding remarks

Compounds **1** and **2** have been reported as the first known examples of 2,3-secofernane triterpenoids. Their presence as markers may be helpful in chemotaxonomical classifications. Biological investigations for these compounds are underway.

4. Experimental

4.1. General experimental procedures

Melting points were measured on a PHMK 79/2289 micro-melting point apparatus and were presented as uncorrected. Optical rotations were measured on a Horiba SEPA-300 polarimeter. UV spectra were recorded on a Shimadzu UV-2401PC spectrophotometer. IR spectra were obtained using a Bruker Tensor 27 FT-IR spectrometer with KBr pellets. NMR spectra were acquired at room temperature with Bruker DRX-500 and AV-400 instruments. ESIMS and HRESIMS data were obtained with an API QSTAR Pulsar i spectrometer. X-ray crystallographic data were collected on a Bruker Smart APEX II CCD diffractometer with graphite-monochromated Mo Kα radiation. Silica gel (200–300 mesh, Qingdao Marine Chemical Inc., China) and Sephadex LH-20 (Amersham Biosciences, Sweden) were used for column chromatography. Fractions were monitored by silica gel plates immersed in vanillin-H_2SO_4 in ethanol or Dragendorff's reagent, in combination with Agilent 1200 reversed-phase HPLC (Eclipse XDB-C18 column, 5 μm, 4.6 × 150 mm, 50–100% MeOH in H_2O over 8 min followed by 100% MeOH to 15 min, 1 ml/min, 25 °C).

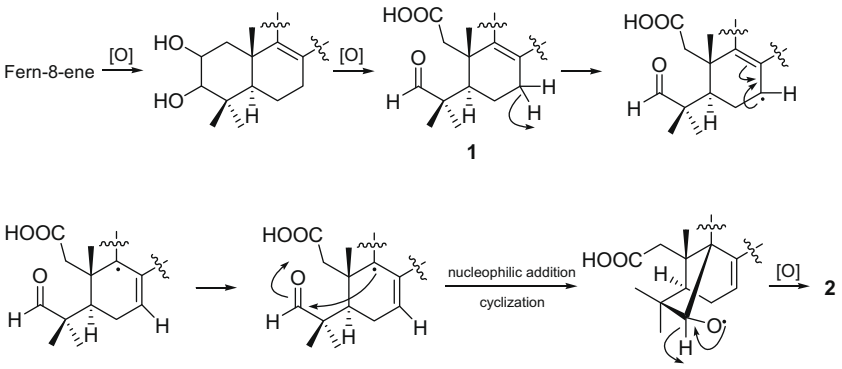

Fig. 4. The proposed biosynthetic pathway of alstonic acid (**2**).

Table 2
NMR spectroscopic data for N^1-methoxymethyl picrinine (**3**) and 5α-methoxystrictamine (**5**).

No.	N^1-Methoxymethyl picrinine (**3**)			5α-Methoxystrictamine (**5**)
	δ_H (*J* in Hz)	δ_C mult.	HMBC	δ_H (*J* in Hz)
2		106.8 s		
3	3.82 d (4.6)	50.5 d	7, 15, 21	4.48 d (5.1)
5	4.85 d (2.0)	87.2 d	2, 3, 7	3.87 d (4.0), H_β
6	2.26 dd (13.6, 2.0)	39.9 t	2, 8, 16	2.20 d (15.0), H_β
	3.43 d (13.6)			3.72 dd (15.0, 4.0), H_α
7		51.0 s		
8		134.4 s		
9	7.13 d (7.3)	124.7 d	7, 11, 13	7.61 d (7.7)
10	6.82 dd (7.9, 7.3)	121.0 d	8, 12	7.31 dd (7.7, 7.3)
11	7.15 dd (7.9, 7.9)	128.2 d	9, 13	7.12 dd (7.3, 7.3)
12	6.85 d (7.9)	109.0 d	8, 10	7.38 d (7.3)
13		147.8 s		
14	1.85 dd (14.3, 2.6)	25.7 t	2, 16, 20	1.75 dd (14.0, 3.0), H_β
	2.18 ddd (14.3, 4.6, 3.5)			2.67 ddd (14.0, 5.1, 2.1), H_α
15	3.30 br s	31.0 d	19, 21	3.43 br s
16	2.44 d (3.4)	51.9 d	2, 6, 8, 14, 20	1.90 d (3.8)
18	1.49 dd (6.9, 2.0)	12.7 q	20	1.53 dd (6.8, 1.7)
19	5.43 br q (6.9)	121.0 d	15, 21	5.49 br q (6.8)
20		135.0 s		
21	3.13 d (17.7)	46.2 t	3, 5, 15, 19	3.07 d (17.1), H_β
	3.79 br d (17.7)			4.05 br d (17.1), H_α
$COOCH_3$		172.2 s		
$COOCH_3$	3.65 s	51.5 q	$COOCH_3$	3.69 s
NCH_2O	4.74 d (11.0)	76.7 t	2, 13, OCH_3	
	4.95 d (11.0)			
CH_2OCH_3	3.40 s	55.5 q	NCH_2O	
5-OCH_3				3.21 s

Determined in $CDCl_3$ (δ_H 7.26 ppm, δ_C 77.0 ppm as int. standard).

4.2. Plant material

Leaves of *A. scholaris* were collected in Yunnan Province, China and identified by Prof. Dr. Hua Peng, Kunming Institute of Botany, CAS. A voucher specimen (BBP2008003AS) was deposited in the Herbarium of Kunming Institute of Botany.

4.3. Extraction and isolation

Air-dried, powdered leaves (8.5 kg) of *A. scholaris* were soaked with EtOH:H_2O (25 L × 3, 95:5, v/v, with each soaking for 3 days) at room temperature and filtered. The filtrate was concentrated *in vacuo* to give a residue (~500 g), which was subjected to silica gel column chromatography (CC) with a gradient elution system of petroleum ether–acetone (100:0 → 0:100) to obtain 18 fractions. Fraction-4 (3.0 g) mainly contained the triterpene acids, eluted with petroleum ether–acetone (90:10), was repeatedly separated and purified by silica gel (petroleum ether:EtOAc = 20:1) and Sephadex LH-20 CC and recrystallization to affford compounds **1** (164 mg) and **2** (13 mg). Fraction-17 (20 g) eluted with acetone was further separated and purified by silica gel ($CHCl_3$:MeOH = 100:1) and Sephadex LH-20 ($CHCl_3$:MeOH = 1:1) CC, as well as by recrystallization to yield alkaloid **3** (46 mg).

4.4. Alstonic acid A (*1*)

Colourless needles ($CHCl_3$/MeOH); m.p. 244–246 °C; R_f = 0.40 (petroleum ether:EtOAc = 1:1); $[\alpha]_D^{22}$ −4.4 (*c* 0.23, $CHCl_3$:MeOH = 1:1); IR (KBr) ν_{max} cm^{-1}: 2928, 2870, 2686, 1727, 1699, 1468, 1406, 1382, 1310, 1241; for ^1H and ^{13}C NMR spectroscopic data, see Table 1; ESIMS (neg.) *m*/*z*: 455 $[M - H]^-$; HRESIMS (neg.) *m*/*z*: 455.3512 (calcd. for $C_{30}H_{47}O_3$, 455.3525).

4.5. Alstonic acid B (*2*)

Colourless needles ($CHCl_3$); m.p. 282–284 °C; R_f = 0.60 (petroleum ether:EtOAc = 1:1); $[\alpha]_D^{23}$ +191.4 (*c* 0.43, $CHCl_3$); IR (KBr) ν_{max} cm^{-1}: 3039, 2939, 2869, 1737, 1702, 1635, 1468, 1408, 1380, 1312,

1233; for ^{1}H and ^{13}C NMR spectroscopic data, see Table 1; ESIMS (neg.) m/z: 453 $[M-H]^-$; HRESIMS (neg.) m/z: 453.3359 (calcd. for $C_{30}H_{45}O_3$, 453.3368).

4.6. N^1-Methoxymethyl picrinine (**3**)

Colourless, crystalline powder ($CHCl_3$); m.p. 181–183 °C; R_f = 0.50 ($CHCl_3$:MeOH = 20:1), t_R = 8.35 min; $[\alpha]_D^{27}$ −56.7 (*c* 0.15, $CHCl_3$); UV $\lambda_{max^{MeOH}}$ nm (log ε): 238 (3.76), 287 (3.26); IR (KBr) ν_{max} cm^{-1}: 3018, 1737, 1609, 1481, 1190, 1172, 1116, 1077; for ^{1}H and ^{13}C NMR spectroscopic data, see Table 2; ESIMS (pos.) m/z: 405 $[M+Na]^+$, 383 $[M+H]^+$, 351 $[M-OCH_3]^+$; HRESIMS (pos.) m/z: 383.1965 (calcd. for $C_{22}H_{27}N_2O_4$, 383.1970).

4.7. X-ray crystallographic analysis of alstonic acid A (**1**)

$C_{30}H_{48}O_3$, MW = 456.68, monoclinic, space group C2, with a = 29.289(7) Å, b = 7.6106(19) Å, c = 12.004(3) Å, β = 94.914(3), V = 2666.0(11) Å^3, Z = 4, D_{calcd} = 1.138 g/cm^3, λ = 0.71073 Å, μ(Mo Kα) = 0.071 mm^{-1}, and $F(000)$ = 1008, and T = 298(2) K. A colourless crystal of dimensions 0.21 × 0.13 × 0.04 mm was selected for X-ray analysis. A total of 11673 reflections, collected in the range $1.40° \leqslant \theta \leqslant 28.31°$, yielded 6024 unique reflections. The structure was solved using direct methods and was refined by full-matrix least-squares on F^2 values for 2268 $I > 2\sigma(I)$. Hydrogen atoms were fixed at calculated positions. The final indices were R_1 = 0.0820, wR_2 = 0.1779 and had a goodness-of-fit = 0.948.

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Appendix A. Supplementary data

Crystallographic data for structure **1** is deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 705372. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44 1223 336033; E-mail: deposit@ccdc.cam.ac.uk).

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.phytochem.2009.03.007.

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