Daphnipaxianines A–D, Alkaloids from *Daphniphyllum paxianum*

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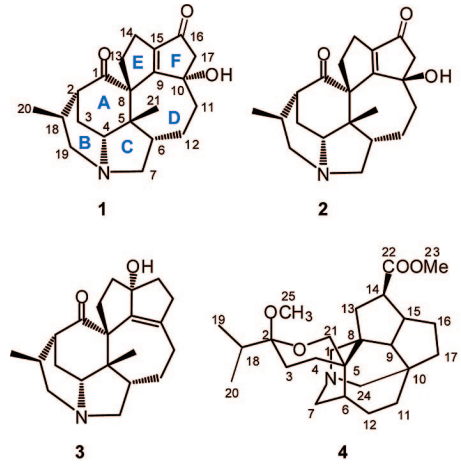
Four new *Daphniphyllum* alkaloids, daphnipaxianines A–D (**1**–**4**), along with six known ones, have been isolated from the leaves and fruits of *Daphniphyllum paxianum*. Daphnipaxianines A and B (**1**, **2**), a pair of epimers differing at C-10, are the first caliciphylline A type *Daphniphyllum* alkaloids with a $\Delta^{9(15)}$-unsaturated cyclic ketone unit, and daphnipaxianine D (**4**) is the first yuzurine-type *Daphniphyllum* alkaloid containing a hexacyclic ring system. The structures of these alkaloids were characterized by spectroscopic methods, especially 2D NMR techniques. A single-crystal X-ray diffraction analysis was used to confirm the structure of **1**.

Daphniphyllum alkaloids with unusual polycyclic ring systems have attracted great interest from a biogenetic and synthetic point of view.[1] In a search for structurally unique and biogenetically interesting *Daphiphyllum* alkaloids, our group has isolated novel alkaloids such as calycilactone A,[2] daphnioldhanins A–C,[3] longeracinphyllines A and B,[4] daphnilongerine,[5] daphnilongertone,[6] daphlongeramine A,[7] calydaphninone,[8] and daphlongeranines A and B.[9]

Our investigation on extracts of the leaves and fruits of *Daphniphyllum paxianum* has led to the isolation of four new *Daphniphyllum* alkaloids, daphnipaxianines A–D (**1**–**4**), together with six known ones, daphniyunnine A,[10] daphniyunnine C,[10] daphniyunnine E,[10] daphniyunnine D,[10] longistylumphylline A,[11] and methyl longistylumphylline B.[11] Daphnipaxianines A and B (**1**, **2**), a pair of epimers differing at C-10, are the first caliciphylline A type *Daphniphyllum* alkaloids[10] with a $\Delta^{9,15}$-unsaturated cyclic ketone unit. Daphnipaxianine D (**4**) is the first yuzurine-type *Daphniphyllum* alkaloid possessing a hexacyclic ring system. This paper describes the isolation and structural elucidation of these new compounds.

Daphnipaxianine A (**1**) was obtained as a colorless, columnar crystal. Its molecular formula was established as $C_{21}H_{27}NO_3$ with nine degrees of unsaturation by positive HRESIMS (*m/z* 342.2070, $[M + H]^+$, calcd 342.2069). The IR absorption spectrum showed the presence of OH (3395 cm^{-1}), ketone (1707 cm^{-1}), and α,β-unsaturated ketone (1674 cm^{-1}) groups. Its UV absorption bands at 208 (3.411) and 243 (3.883) nm further indicated the presence of an α,β-unsaturated ketone unit. In accordance with the molecular formula, ^{13}C NMR and DEPT data (Table 1) revealed 21 carbon signals assigned to two ketone carbonyls (δ_C 221.2 and 202.2), one tetrasubstituted double bond (δ_C 180.1 and 152.8), three quaternary carbons, four methines, eight methylenes, and two methyls. Of these, two methylenes (δ_C 53.4, δ_H 2.90; δ_C 49.2, δ_H 2.88 and 2.56) and one methine (δ_C 64.7, δ_H 3.53) were typical of carbons attached to nitrogen, similar to those in longistylumphylline A[11]and daphniyunnine D.[10] Two carbonyls and one double bond accounted for three degrees of unsaturation, and the remaining six degrees of unsaturation were ascribed to the existence of a hexacyclic ring system in **1**.



Comparison of the ^1H and ^{13}C NMR data of **1** with those of daphniyunnine D[10] indicated that both compounds were very similar, especially at the A, B, and C rings. The main structural changes occurred at the F ring, which affected some chemical shifts of both proton and carbon signals in the D and E rings. Analysis of 2D NMR spectra (HSQC, ^1H–^1H COSY, and HMBC) showed that alkaloid **1** shared the same carbon backbone and structure as that of daphniyunnine D,[10] except for different locations of the α,β-unsaturated ketone and the OH groups. The location of the α,β-unsaturated ketone was determined by HMBC correlations of H_2-14 (δ_H 2.41) with C-9 (δ_C 180.1), C-15 (δ_C 152.8), and C-16 (δ_C 202.2), as well as H_2-17 (δ_H 2.93 and 2.68) with C-16. The hydroxyl group was linked to C-10 at δ_C 75.1, which was judged by the HMBC cross-peaks of H_2-17 and H_2-11 (δ_H 2.03 and 1.75) with C-10.

The relative configuration of **1** was assigned by analyzing the ROESY spectrum and modeled by CS Chem 3D Pro version 9.0 using MM2 field calculations for energy minimization. The configurations at C-2, C-4, C-5, C-6, C-8, and C-18 of **1** were consistent with daphniyunnine D.[10] Furthermore, the configuration of the OH group at C-10 in **1** was deduced to be α-oriented by a single-crystal X-ray diffraction study. In its crystal structure (Figure 1), the A and B rings both took twist-boat conformations, the C, E, and F rings all took envelope conformations, and the D ring took a twist-chair conformation.

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Table 1. ^{1}H (δ_H, in ppm) and ^{13}C (δ_C, in ppm) NMR Data of Daphnipaxianines A–C (**1**–**3**)

	1[a]		**2**[b]		**3**[c]	
no.	δ_H mult., J (Hz)	δ_C	δ_H mult., J(Hz)	δ_C	δ_H mult., J (Hz)	δ_C
1		221.2		214.7		225.4
2	2.16 (1H, d, 4.5)	44.1	2.06 (1H, m)	45.3	2.21 (1H, m)	45.1
3a	2.31 (1H, m)	20.0	2.21 (1H, m)	21.6	2.36 (1H, m)	20.1
3b	2.09 (1H, m)		2.04 (1H, m)		2.08 (1H, m)	
4	3.53 (1H, d, 4.4)	64.7	3.45 (1H, br. s)	66.1	3.43 (1H, d, 4.5)	66.0
5		54.0		51.1		53.9
6	2.26 (1H, m)	49.5	2.37 (1H, m)	50.9	2.09 (1H, m)	51.2
7a	2.90 (1H, m)	53.4	2.79 (1H, m)	55.7	2.85 (1H, m)	54.7
7b			2.85 (1H, m)		2.78 (1H, m)	
8		69.6		69.5		68.3
9		180.1		187.2		159.0
10		75.1		76.3		147.3
11a	2.03 (1H, m)	33.6	1.79 (1H, m)	30.0	1.82 (1H, m)	35.9
11b	1.75 (1H, m)				1.59 (1H, m)	
12a	1.78 (1H, m)	20.4	2.46 (1H, m)	20.7	1.66 (1H, m)	21.3
12b	1.37 (1H, m)		1.68 (1H, m)		1.54 (1H, m)	
13a	2.92 (1H, m)	38.5	2.50 (1H, m)	39.4	2.92 (1H, m)	40.4
13b	2.25 (1H, m)		2.61 (1H, m)		2.16 (1H, m)	
14a	2.41 (2H, m)	24.5	2.22 (1H, m)	22.4	2.35 (1H, m)	30.7
14b			1.99 (1H, m)		2.22 (1H, m)	
15		152.8		149.8		82.3
16a		202.2		201.3	2.49 (1H, m)	28.2
16b					2.13 (1H, m)	
17a	2.93 (1H, m)	55.5	2.93 (1H, d, 16.0)	57.6	2.23 (2H, m)	44.2
17b	2.68 (1H, m)		2.67 (1H, d, 16.0)			
18	2.92 (1H, m)	33.5	2.87 (1H, m)	33.4	2.76 (1H, m)	33.3
19a	2.88 (1H, m)	49.2	2.78 (1H, m)	49.3	2.88 (1H, m)	50.3
19b	2.56 (1H, dd, 11.2, 8.0)		2.50 (1H, m)		2.57 (1H, dd, 11.2, 8.4)	
20	1.04 (1H, d, 6.5)	18.5	0.98 (1H, d, 6.8)	18.6	1.03 (1H, d, 6.8)	19.3
21	1.16 (3H, s)	20.9	1.31 (3H, s)	23.2	1.20 (3H, s)	21.7

[a] ^{1}H, ^{13}C NMR data measured at 500 and 125 MHz, respectively in $CDCl_3$. [b] ^{1}H, ^{13}C NMR data measured at 400 and 100 MHz, respectively in $CDCl_3$. [c] ^{1}H, ^{13}C NMR data measured at 500 and 125 MHz, respectively in CD_3OD.

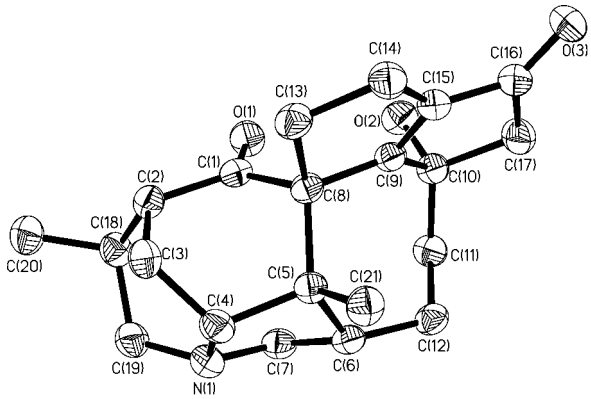

Figure 1. X-ray crystal structure of **1** (ORTEP drawing).

Daphnipaxianine B (**2**) had the same molecular formula as **1** ($C_{21}H_{27}NO_3$), as determined by positive HRESIMS (*m/z* 342.2061, $[M + H]^+$, calcd 342.2069). The ^{1}H and ^{13}C NMR data (Table 1) of **2** were closely related to those of **1**, implying that they likely shared the same planar structure, confirmed by 2D NMR (HSQC, ^{1}H–^{1}H COSY, and HMBC) spectra. The key ROESY correlations of **2** indicated that its relative configuration was identical to that of compound **1**, except for C-10, implying that the two alkaloids (**1**, **2**) were a pair of epimers differing at C-10. Both the A and B rings adopted boat conformations deduced by the ROESY cross-peaks of H-13a/H-3b and H-3a/H-19b. The hydroxyl group at C-10 in **2** was assigned as β-orientated, since **2** was the epimer of **1**. Thus, the structure of daphnipaxianine B was established as **2**.

Daphnipaxianine C (**3**) was isolated as a colorless, amorphous powder, and its molecular formula was determined to be $C_{21}H_{29}NO_2$, with eight degrees of unsaturation, by positive HRESIMS (*m/z* 328.2281, $[M + H]^+$, calcd 328.2276). An IR absorption band at 1680 cm^{-1} indicated the presence of a carbonyl group. Its ^{13}C NMR spectrum (Table 1) showed 21 carbon signals including one ketone group (δ_C 225.4), one tetrasubstituted double bond (δ_C 159.0 and 147.3), three quaternary carbons, four methines, nine methylenes, and two methyls. In addition to one ketone and one double bond, the remaining six degrees of unsaturation required a hexacyclic ring system for **3**. Analysis of the NMR spectra suggested that **3** was a caliciphylline A type *Daphniphyllum* alkaloid. Extensive analysis of the HSQC, ^{1}H–^{1}H COSY, and HMBC spectra of **3** indicated that it had the same basic skeleton as daphniyunnine D.[10] By comparison with daphniyunnine D,[10] the only difference in **3** was the lack of the ketone group on the F ring. In the HMBC spectrum, the correlations of H-4 (δ_H 3.43) with C-7 (δ_C 54.7) and H_2-19 (δ_H 2.88 and 2.57) with C-4 (δ_C 66.0) and C-7 indicated the connection of C-4, C-7, and C-19 via the nitrogen atom. The ketone group was assigned to C-1 on the basis of the HMBC correlations of H-2, H-3a, and H-18 with C-1. The HMBC correlations of H_2-11 and H-16a with C-9 and H-11b, H_2-12, and H-16a with C-10 indicated the location of a $\Delta^{9(10)}$ double bond in **3**.

The relative configuration of **3** was demonstrated by the ROESY spectrum, which was identical to daphniyunnine D.[10] ROESY correlations of H_3-21/H-6, H_3-21/H-13b, H-6/H-4, H-6/H-7b, H-4/H-19b, and H-19b/H_3-20 suggested that H_3-21, H-4, H-6, and H_3-20 were β-oriented. The presence of an α-oriented OH at C-10 was determined by ROESY cross-peaks of H_3-21/H-13b, H-13b/H-14b, and H-14b/ H-16b.

Daphnipaxianine D (**4**) was obtained as a colorless solid, and its positive HRESIMS signal at *m/z* 418.2960 ($[M + H]^+$, calcd 418.2957) established the molecular formula $C_{25}H_{39}NO_4$ with seven degrees of unsaturation. The IR spectrum implied the presence of an ester carbonyl (1736 cm^{-1}). The ^{13}C NMR and DEPT spectral data (Table 2) of **4** gave 25 carbon signals including one ester carbonyl, four quaternary carbons, five methines, 11 methylenes, and four methyls. One ester carbonyl group accounted for one out of the seven degrees of unsaturation, then the remaining six ones required the presence of six rings in **4**. All of the above suggested

Table 2. ^{1}H (δ_H, in ppm) and ^{13}C (δ_C, ppm) NMR[a] Data of Daphnipaxianine D (**4**) in $CDCl_3$

no.	δ_H mult., *J* (Hz)	δ_C	no.	δ_H mult., *J* (Hz)	δ_C
1a	3.81 (1H, d, 12.5)	61.1	14	2.80 (1H, m)	41.9
1b	3.85 (1H, d, 12.5)				
2		100.5	15	3.38 (1H, m)	54.5
3a	1.56 (1H, m)	21.6	16a	1.78 (1H, m)	27.9
3b	1.27 (1H, m)		16b	1.19 (1H, m)	
4a	1.83 (1H, m)	21.9	17a	2.60 (1H, m)	42.4
4b	1.52 (1H, m)		17b	2.22 (1H, m)	
5		36.0	18	1.96 (1H, m)	31.2
6	2.20 (1H, m)	32.5	19	0.77 (1H, d, 7.0)	16.3
7a	3.40 (1H, m)	57.4	20	0.86 (1H, d, 7.0)	17.3
7b	3.57 (1H, m)				
8		46.7	21a	3.86 (1H, dd, 12.0, 3.0)	62.6
		21b	4.11 (1H, m)		
9	2.79 (1H, m)	54.5	22		175.0
10		55.7	23	3.56 (3H, s)	50.8
11a	1.59 (1H, m)	26.8	24a	3.82 (1H, d, 14.0)	60.7
11b	2.20 (1H, m)		24b	3.86 (1H, d, 14.0)	
12a	2.20 (1H, m)	27.5	25	3.09 (3H, s)	46.2
12b	1.99 (1H, m)				
13a	1.52 (1H, m)	39.3			
13b	2.60 (1H, m)				

[a] ^{1}H, ^{13}C NMR data measured at 400 and 100 MHz, respectively.

that **4** was a yuzurine-type *Daphniphyllum* alkaloid containing a hexacyclic ring system and that its structure was closely related to daphnezomine R.[12] Compared with daphnezomine R, the main difference was the carbon–carbon bond between C-10 and C-24 to form a new nitrogen-containing six-membered ring in **4**. Analysis of 2D NMR, including HSQC, ^{1}H–^{1}H COSY, and HMBC spectra, finally confirmed the backbone of **4**, which was consistent with the above deduction. In the HMBC spectrum, the cross-peaks of H-24a (δ_H 3.82) with C-10 (δ_C 55.7), C-11 (δ_C 26.8), and C-17 (δ_C 42.4) suggested the connections among C-11, C-17, and C-24 via C-10, indicating the presence of a nitrogen-containing hexacyclic skeleton in **4**, just like daphtenidine B.[13]

The relative configuration of **4** was closely similar to that of daphnezomine R[12] deduced by ROESY correlations of H-21b/H-4b, H-7b/H-1b, H-21b/H-13b, H-13b/H-4b, H_3-20/H-3b, H-3b/H-6, H-13a/H-14, H-14/H-15, and H-15/H-16a. Furthermore, the correlations of H-24a/H-9, H-9/H-15, and H-15/H-14 implied H-24a was α-oriented.

Daphnipaxianines A–D (**1**–**4**) were evaluated in a cytotoxicity bioassay against three cell lines, HCT116, HCT116 Bax−/−, and MEF Bax−/− Bak−/−, respectively. The results indicated that none of them were active.

Experimental Section

General Experimental Procedures. Melting points were obtained on an X-4 apparatus and are uncorrected. Optical rotations were measured on a Horiba SEPA-300 high sensitive polarimeter. IR spectra were recorded on a Bio-Rad FTS-135 spectrometer as KBr discs. NMR spectra were obtained on a Bruker AM-400 or DPX-500 NMR spectrometer with TMS as an internal standard. ESIMS were measured on a Waters 2695 HPLC-Thermo Finnigan LCQ Advantage ion trap mass spectrometer. HRESIMS was measured by a VG Auto Spec 3000 spectrometer. Column chromatography was carried out on (amino) silica gel (200–300 mesh; Qingdao Marine Chemical Factory, Qingdao, People's Republic of China), silica gel H (10–40 μm; Qingdao), and Sephadex LH-20 (40–70 μm; Amersham Pharmacia Biotech AB, Uppsala, Sweden). TLC was performed with glass precoated with silica gel GF_{254}. Solvents used for extraction and isolation were distilled prior to use.

Plant Material. The leaves and fruits of *D. paxianum* were collected from Gaoli Mountain inYunnan Province, People's Republic of China, in September 2006, and the plant sample was identified by Prof. Heng Li of Kunming Institute of Botany, Chinese Academy of Sciences (CAS). A voucher specimen (KIB 06090411) was deposited at State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences (CAS).

Extraction and Isolation. The air-dried and powdered leaves and fruits (6.2 kg) of *D. paxianum* were extracted three times with 95% EtOH. The extract was concentrated under reduced pressure, followed by partitioning between EtOAc and 3% tartaric acid. The aqueous phase was adjusted to pH 9–10 with saturated Na_2CO_3 and extracted with $CHCl_3$ to give crude alkaloids (17.0 g). The crude alkaloids were subjected to a silica gel column, using $CHCl_3$–MeOH (1:0 to 0:1) as eluent, to obtain four fractions (Fr.1–Fr.4). Fr.2 eluted with $CHCl_3$–MeOH (100:1 to 40:1) was further separated using Sephadex LH-20 column chromatography with $CHCl_3$–CH_3OH (1:1) and repeated column chromatography over silica gel with petroleum ether–Et_2NH (40:1) and petroleum ether–acetone (10:1) to obtain **1** (9.2 mg), **2** (4.8 mg), daphniyunnine A (30 mg), and daphniyunnine E (20 mg). Fr.3 eluted with $CHCl_3$–MeOH (50:1 to 20:1) was subjected to repeated column chromatography over silica gel H with petroleum ether–Et_2NH (80:1 to 10:1) solvent systems, purified by Sephadex LH-20 column chromatography using $CHCl_3$–MeOH (1:1) and MeOH, alternately, to yield **4** (10 mg), longistylumphylline A (30 mg), methyl longistylumphylline B (6 mg), and daphniyunnine D (8 mg). Fr.4 eluted with $CHCl_3$–MeOH (10:1 to 0:1) was separated and purified by repeated column chromatography on silica gel with $CHCl_3$–MeOH (40:1) and petroleum ether–Et_2NH (20:1 to 4:1), followed by Sephadex LH-20 column chromatography with MeOH to afford **3** (5.3 mg) and daphniyunnine C (8 mg), consecutively.

Daphnipaxianine A (1): colorless, columnar crystals (acetone); mp 175 °C; $[\alpha]^{22.1}_D$ −93.8 (*c* 0.32, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ε) 208 (3.411), 243 (3.883); IR (KBr) ν_{max} 3395, 2938, 1707, 1674, 1639, 1450, 1408, 1381, and 1272 cm^{-1}; ^{1}H and ^{13}C NMR, see Table 1; ESIMS (positive) *m/z* 342 $[M + H]^+$; HRESIMS (positive) *m/z* 342.2070 $[M + H]^+$ (calcd for $C_{21}H_{28}NO_3^+$, 342.2069).

Daphnipaxianine B (2): colorless solid; $[\alpha]^{22.3}_D$ −99.7 (*c* 0.30, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ε) 205 (3.484), 251 (3.818); IR (KBr) ν_{max} 3435, 2955, 1702, 1668, 1626, 1445, 1378, and 1269 cm^{-1}; ^{1}H and ^{13}C NMR, see Table 1; ESIMS (positive) *m/z* 342 $[M + H]^+$; HRESIMS (positive) *m/z* 342.2061 $[M + H]^+$ (calcd for $C_{21}H_{28}NO_3^+$, 342.2069).

Daphnipaxianine C (3): colorless, amorphous powder; $[\alpha]^{22.5}_D$ −153.2 (*c* 0.26, $CHCl_3$); IR (KBr) ν_{max} 3447, 2922, 1680, 1638, 1450, and 1385 cm^{-1}; ^{1}H and ^{13}C NMR, see Table 1; ESIMS (positive) *m/z* 328 $[M + H]^+$; HRESIMS (positive) *m/z* 328.2281 $[M + H]^+$ (calcd for $C_{21}H_{30}NO_2^+$, 328.2276).

Daphnipaxianine D (4): colorless solid; $[\alpha]^{25.4}_D$ −23.0 (*c* 1.00, MeOH); IR (KBr) ν_{max} 3425, 2960, 1736, 1642, and 1460, 1375, and 1347 cm^{-1}; ^{1}H and ^{13}C NMR, see Table 2; ESIMS (positive) *m/z* 418 $[M + H]^+$; HRESIMS (positive) *m/z* 418.2960 $[M + H]^+$ (calcd for $C_{25}H_{40}NO_4^+$, 418.2957).

X-Ray Diffraction of 1.[14] Crystal data: $C_{21}H_{27}NO_3$, MW = 341.4, orthorhombic system, space group $P2_12_12_1$, crystal cell parameters: *a* = 8.056(1) Å, *b* = 13.046(1) Å, *c* = 16.798(1) Å, *V* = 1765.4(6) Å^3,

$Z = 4$, $d = 1.285$ g/cm$^{3.}$ A colorless, columnar crystal of dimensions $0.20 \times 0.20 \times 0.40$ mm was used for X-ray measurements on a MAC DIP-2030K diffractometer with graphite-monochromated Mo Kα radiation, and the $2\theta_{max}$ value was set at 50.0°. The total number of independent reflections measured was 1834, of which 1622 were considered to be observed ($F^2 \geq 2\sigma F^2$). The crystal structure of **1** was solved by the direct method SHELXS-97[15] and expanded using difference Fourier techniques, refined by the program and method NOMCSDP,[16] and the full-matrix least-squares calculations. H atoms were fixed at calculated positions. The final indices were $R_1 = 0.0458$, $wR_2 = 0.1155$, $S = 1.109$, $(\Delta/\sigma)_{max} = 0.021$, $(\Delta/\rho)_{min} = -0.197$ e/Å^3, $(\Delta/\rho)_{max} = 0.308$ e/Å^3.

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Supporting Information Available: The 1D and 2D NMR, HRESIMS, and IR spectra and crystal data of **1** and 1D and 2D NMR spectra of **2** and **3** are supplied in the supplementary data, figures of ^{1}H–^{1}H COSY, key HMBC, and ROESY correlations for compounds **1**–**4**. This information is available free of charge via the Internet at http://pubs.acs.org.

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(14) Crystallographic data for daphnipaxianine A (**1**) reported in this paper have been deposited at the Cambridge Crystallographic Data Centre, CCDC 653194. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: +44-(0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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