Paralemnolins J—P, New Sesquiterpenoids from the Soft Coral *Paralemnalia thyrsoide*

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Six new sesquiterpenoids, paralemnolins J—O (1—6), along with one novel norsesquiterpenoid, paralemnolin P (7), have been isolated from the soft coral *Paralemnalia thyrsoides*. The structures of metabolites 1—7 were established on the basis of extensive NMR study and chemical methods. The structure of 5 was further confirmed by a single-crystal X-ray analysis. Cytotoxicity of these metabolites toward a limited panel of cancer cell lines also is described.

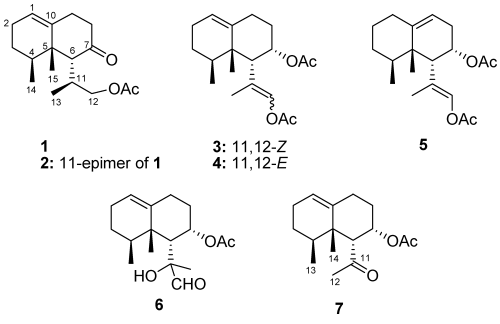
Key words sesquiterpenoid; paralemnolin; *Paralemnalia thyrsoide*; cytotoxicity

Soft coral of *Paralemnalia thyrsoides* (Alcyonaceae) has been found to be a rich sources of a variety of sesquiterpenes and norsesquiterpenes.[1—8] Our previous chemical investigation of the Formosan soft coral *P. thyrsoides* resulted in the isolation of twelve sesquiterpenoids, paralemnolins A—I,[2,3] paralemnanone,[4] isoparalemnanone,[4] and paralemnanol.[4] Our continuing search for bioactive compounds from this organism has further resulted in the isolation of seven paralemnolins J—P (**1**—**7**). Herein, we report the structural elucidation of these metabolites **1**—**7**, and the structure of **5** was unambiguously established by a single-crystal X-ray analysis. In the cytotoxicity testing, we observed that paralemnolins M, N (**4**, **5**) exhibited moderated cytotoxicity toward a human medulloblastoma cell line.

Results and Discussion

Paralrmnolin J (**1**) was isolated as a white powder with a molecular formula of $C_{17}H_{26}O_3$ requiring five degrees of unsaturation, as established by HR-electrospray ionization (ESI)-MS. The ^{13}C-NMR and distortionless enhancement by polarization transfer (DEPT) spectra of **1** showed signals of 17 carbons, including one ketone (δ_C 212.9 qC), one trisubstituted carbon–carbon double bond (δ_C 137.7 qC and 123.9 CH), one oxygenated methylene (δ_C 66.2 CH_2; δ_H 3.71, 4.56), and one acetoxy group (δ_C 170.8 qC, 20.8 CH_3; δ_H 2.05, s). The above functionalities account for three of the five degrees of unsaturation, suggesting a bicyclic skeleton for **1**. The gross structure of **1** was determined by 2D NMR spectroscopic analysis. The ^{1}H–^{1}H correlation spectroscopy (COSY) spectrum revealed three spin systems as shown in Fig. 1. Careful inspection of the heteronuclear multiple bond correlation (HMBC) spectrum led to the establishment of the planar structure of **1** (Fig. 1). The H-6, H_3-14, and H_3-15 positioned on the β face were established by the following nuclear Overhauser enhancement (NOE) cross peaks: H_3-15/H_3-14 and H_3-15/H-6. The ^{1}H-NMR spectral data and the physical properties of **1** were found to be in full agreement with those of a semisynthetic product,[9,10] of which the absolute stereochemistry was shown as in formula **1**. This compound has been isolated recently from an Indonesian soft coral *Nephthea* sp., however, the stereochemistry at C-11 was not established.[11]

Paralemnolin K (**2**) was obtained as a colorless oil. The molecular formula of **2**, deduced from HR-ESI-MS, was found to be the same as that of **1**. The ^{1}H- and ^{13}C-NMR data of **2** are very similar to those of **1** except for the chemical



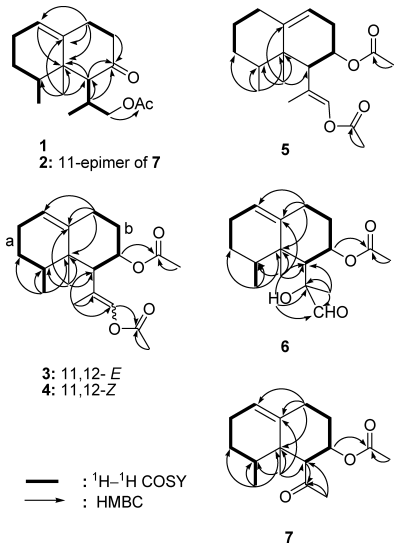


Fig. 1. Key ^{1}H–^{1}H COSY and HMBC Correlations **1**—**7**

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shifts and splitting patterns of H_2-12. Analyses of ^1H–^1H COSY and HMBC correlations led to the establishment of the same planar structure for both compounds (Fig. 1). By comparison of the NOESY interactions of **1** and **2**, it was found that the relative configurations at C-4, C-5, and C-6 of both compounds were identical. Thus, **2** was found to be an 11-epimer of **1**.

Paralemnolin L (**3**) was assigned a molecular formula of $C_{19}H_{28}O_4$ by HR-ESI-MS and ^{13}C-NMR spectral data. Thus, six degrees of unsaturation was deduced. The IR absorption (1743 cm^{-1}) and NMR spectral data (δ_H 2.09, 3H, s and 1.93, 3H, s; δ_C 170.5 qC, 168.3 qC, 21.3 CH_3, and 20.7 CH_3) revealed the presence of two acetates. Carbon resonances at δ 122.5 (CH), 139.8 (qC), 134.2 (CH), and 120.3 (qC) were deduced as two trisubstituted double bonds. Above data suggested **3** to be bicyclic. Moreover, an acetoxyl-bearing sp^3 carbon (δ_C 71.3; δ_H 5.30) was also found in the HMQC spectrum.

Two spin systems (a and b) of **3** were established by ^1H–^1H COSY spectrum (Fig. 1). The connectivity between C-11 to C-6 was indicated by the HMBC correlations from H_3-13 to C-6, C-11, and C-12. The HMBC correlations from H-7 to the carbon signal at δ 170.5 and from H-12 to the carbon resonance at δ 168.3 revealed the locations of two acetoxy groups at C-7 and C-12, respectively. The above data and the other HMBC correlations illustrated in Fig. 1 established the planar structure of **3**. The relative configuration of **3** was elucidated from a 2D NMR experiment, which showed that H_3-14, H_3-15, H-6, and H-7 are located on the β face of the molecule. The *Z* geometry of 11,12-double bond was determined by an NOE correlation between H_3-13 and H-12.

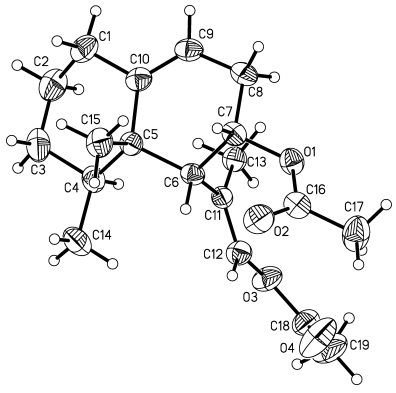

Fig. 2. X-Ray ORTEP Diagram of **5**

Compound **4** was found to possess the same molecular formula as that of **3**. Some signals in ^1H- and ^{13}C-NMR spectrum of **4** measured in $CDCl_3$ at room temperature or low temperature even at −50 °C gave mostly broad signals, suggesting the existence of slowly interconverting conformations in $CDCl_3$ solution (Tables 1 and 2). But still, the 2D NMR spectra were well resolved for the assignment of the gross structure. Inspection of the ^1H–^1H COSY and HMBC spectral data of **4** led to the establishment of the same planar structure as that of **3** (Fig. 1). By comparison of the NOESY spectra of **3** and **4**, it was found that both compounds have the same relative configurations for all chiral centers. The absence of NOE correlation between H_3-13 and H-12 and the appearance of C-13 signal of **4** at upper field (δ 13.2) relative to that of **3** (δ 17.8), suggested the *E* geometry of 11,12-double bond of **4**. Also, NOE correlations between H_3-15 with H_3-14, H-6, and H-7 suggested the β-orientation of these protons.

The same molecular formula $C_{19}H_{28}O_4$ as those of **3** and **4**, was deduced for **5** from HR-ESI-MS. The ^1H- and ^{13}C-NMR spectra data of **5** were found to exhibit broader signals than those of **4**. The carbon resonances at δ 168.0 (qC) and 171.0 (qC), coupled with two methyl protons resonating at δ 2.15 and 2.03, suggested the presence of two acetoxy groups. By comparison of the spectral data of **5** with those of **3** and **4**, it was found that **5** should be closely related to **3** and **4**. The partial 2D NMR spectral data were shown in Fig. 1, which did not provide enough information for the complete elucida-

Table 1. ^1H-NMR Spectral Data of Compounds **1**—**7**[a)]

H #	1	2	3	4	5	6	7
1	5.60 ddd (6.0, 6.0, 3.0)[b)]	5.56 ddd (5.7, 3.0, 2.7)	5.41 t (2.7)	5.46[c)]	2.08 m; 2.12 m	5.61 ddd (3.0, 2.7, 5.7)	5.51 ddd (5.1, 2.7, 2.4)
2	1.98 m; 2.15 m	2.01 m; 2.10 m	1.96 m	1.94 m; 2.05 m	1.27 m; 1.66 m	2.05 m	1.86 m; 1.98 m
3	1.49 m	1.47 m	1.37 m	1.38 m	1.35 m; 1.45 m	1.40 m	1.37 m
4	2.08 m	1.94 m	1.64 m	1.61 m	2.59 br s	1.48 m	1.52 m
6	2.37 m	2.46 m	3.54 d (6.3)	2.67 d (5.4)[b)]	2.59 br s	2.52 d (4.9)	3.35 d (5.7)
7			5.30 ddd (12.0, 6.0, 6.3)	5.26[c)]	5.33[c)]	5.51 dt (13.5, 3.9)	5.30 dt (12.0, 5.4)
8	2.31 m; 2.41 m	2.44 m	1.82 m	1.82 m	2.30 m	1.85 m; 2.19 m	1.76 m; 1.96 m
9	2.49 m	2.44 m	2.22 ddd (13.8, 3.6, 3.6)	2.24 m	5.22 br s	2.33 ddd (15.3, 5.4, 1.8)	2.24 ddd (14.7, 5.1, 2.1)
	2.67 m	2.68 m	2.51 m	2.51 m		2.63 m	2.40 m
10							
11	2.18 m	2.25 m					
12	3.71 d (10.2, 10.2) 4.56 dd (10.5, 3.0)	3.86 d (7.5)	6.92 d (1.5)	6.76[c)]	6.83[c)]	9.57 s	2.17 s
13	0.97 d (6.9)	1.03 d (7.2)	1.73 d (1.5)	1.76 br s	1.86 s	1.33 s	0.93 d (6.6)
14	0.85 d (6.9)	0.83 d (6.6)	0.75 d (6.6)	0.79 d (6.9)	0.75 d (5.7)	0.74 d (6.0)	1.07 s
15	0.94 s	0.94 s	1.13 s	1.11 s	1.17 s	1.13 s	
11-OH						3.86 s	
OAc	2.05 s	2.04 s	2.09 s	2.14 s	2.15 s	2.04 s	2.03 s
OAc			1.93 s	2.01 s	2.03 s		

a) Spectra recorded at 300 MHz in $CDCl_3$ at 25 °C. *b*) *J* values (in Hz) in parentheses. *c*) Broad signals.

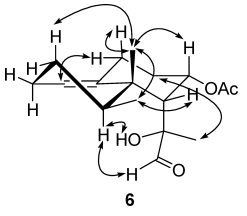

Fig. 3. Selective NOESY Correlations of **6**

tion of the gross structure. Thus, in order to resolve the structure of **5**, a single-crystal X-ray crystallographic analysis[12] (Fig. 2) was undertaken which led to the full structure elucidation and the full assignment of ^{1}H- and ^{13}C-NMR spectral data of **5**.

Paralemnolin O (**6**) was obtained as a white powder. The molecular formula of $C_{17}H_{26}O_4$ was established by HR-ESI-MS, requiring five degrees of unsaturation. The IR spectrum of **6** showed the presence of hydroxy (3497 cm^{-1}) and ester groups (1734 cm^{-1}). The NMR spectroscopic data exhibited the presence of one aldehyde (δ_C 203.5 CH; δ_H 9.57 s), one olefinic double bond (δ_C 140.3 qC and 124.9 CH), two oxygenated carbons (δ_C 71.9 CH; 80.5 qC), and one acetoxy group (δ_C 170.0 qC, 21.5 CH_3; δ_H 2.04 s). The gross structure of **6** was determined by detailed 2D NMR spectral analysis (Fig. 1). The HMBC correlations from H-7 (δ 5.51) to the carbon resonating at δ_C 170.0 disclosed the location of the acetoxy group. The hydroxy and aldehyde groups attached at C-11 were confirmed by the HMBC correlations from H_3-13 to C-6, C-11, and C-12. The planar structure of **6** was established by the inspection of the 2D NMR spectroscopic data as illustrated in Fig. 1. The position of H-6, H-7, H_3-14, and H_3-15 on the same face (β face) was established by the following NOE cross peaks: H_3-15/H_3-14, H_3-15/H-6, and H_3-15/H-7. The relative configuration of C-11 was unable to be determined due to the insufficient NOE correlations (Fig. 3).

Paralemnolin P (**7**) was isolated as a colorless oil. HR-ESI-MS, ^{13}C-NMR, and DEPT spectra established the molecular formula of $C_{16}H_{24}O_3$, implying five degrees of unsaturation. IR absorptions at 1738 cm^{-1} and 1714 cm^{-1}, as well as the carbon resonances at δ 170.2 and 210.2, indicated the presence of an acetoxyl and a ketone. By comparison of the NMR spectral data of **7** with those of a known metabolite (paralemnolin B)[3], it was found that the ketone at C-7 (δ_C 207.3) in paralemnolin B was converted to an acetoxy group (C-7, δ_C 72.0 CH; δ_H 5.30) in **7**. NOE correlations of H_3-14 with H_3-13, H-6, and H-7 revealed that these protons were located on the same face. Thus, the structure of **7** was established unambiguously.

The cytotoxicity of the compounds **1**—**7** against Hepa59T/VGH (human liver carcinoma), KB (human oral epidermoid carcinoma), Hela (human cervical epitheloid carcinoma), and Daoy (human medulloblastoma) cancer cell lines was measured. The result showed that compounds **4** and **5** exhibited moderated cytotoxicity toward Daoy cancer cell line with the ED_{50} values of 9.4, and 8.6 μg/ml, respectively. Other compounds did not show inhibitory activity against the growth of the above four cancer cell lines.

Table 2. ^{13}C-NMR Spectral Data of Compounds **1**—**7**[a]

C #	1	2	3	4	5	6	7
1	123.9	123.4	122.5	122.6	32.7	124.9	122.7
2	25.6	25.9	25.8	25.7	26.4	25.5	25.3
3	26.7	26.9	26.7	26.6	30.5	26.9	26.6
4	32.9	33.1	35.5	35.2	35.6	35.7	35.6
5	42.8	42.6	40.8	40.8	41.7	43.2	42.1
6	62.0	58.5	43.4	49.5	49.4	50.2	58.1
7	212.9	213.6	71.3	71.7	69.8	71.9	72.0
8	40.6	41.2	28.6	28.3	29.2	27.8	26.5
9	30.7	30.7	30.2	30.3	117.0	30.8	29.9
10	137.7	138.1	139.8	139.7	144.4	140.3	137.4
11	31.4	31.1	120.3	120.3	116.7	80.5	210.2
12	66.2	68.2	134.2	134.0	134.5	203.5	34.9
13	17.7	14.0	17.8	13.2	12.5	23.7	15.8
14	15.2	15.2	15.3	15.2	15.8	15.6	19.8
15	21.7	22.0	21.0	21.0	21.8	21.5	
OAc	170.8	170.9	168.3	168.0	168.0	170.0	170.2
	20.8	20.9	20.7	20.8	20.8	21.5	21.3
OAc			170.5	170.6	171.0		
			21.3	21.3	21.3		

a) Spectra recorded at 75 MHz in $CDCl_3$ at 25 °C.

Experimental

General Experimental Procedures Melting points were determined using a Fisher–Johns melting point apparatus and were uncorrected. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. IR spectra were recorded on a JASCO FT-5300 infrared spectrophotometer. NMR spectra were recorded on a Varian Mercury-Plus 300 FT-NMR at 300 MHz for ^{1}H and 75 MHz for ^{13}C in $CDCl_3$ using tetramethylsilane (TMS) as internal standard. LR-ESI-MS and HR-ESI-MS were obtained on a Bruker APEX II Mass spectrometer. Silica gel (Merck, 230—400 mesh) was used for column chromatography. Precoated silica gel plates (Merck, Kieselgel 60 F-254, 0.2 mm) were used for analytical TLC. High-performance liquid chromatography (HPLC) was performed on a Shimadzu LC-10AT apparatus equipped with the Merck Hibar Si-60 column (250×21 mm, 7 μm) or Merck Hibar RP-18e column (250×10 mm, 5 μm).

Animal Material *Paralemnalia thyrsoides* was collected by hand *via* scuba at the Green Island, which is located off the southeast coast of Taiwan, in July 2004, at a depth of 15 m, and was stored in a freezer until extraction. A voucher specimen was deposited in the Department of Marine Biotechnology and Resources, National Sun Yat-sen University (specimen no. GIPT-401).

Extraction and Isolation The soft coral (1.8 kg fresh weight) was collected and freeze-dried. The freeze-dried organism was minced and extracted exhaustively with EtOAc. The combined organic extract was evaporated to give a dark brown residue (33.0 g), which was chromatographed on a silica-gel column using solvents of increasing polarity from *n*-hexane to EtOAc to get fraction 1—20. Fraction 9 eluted with *n*-hexane–EtOAc (10 : 1) and was chromatographed by reverse phase HPLC using acetone–H_2O (3 : 1), and were further purified by normal phase HPLC, eluting with *n*-hexane–EtOAc (30 : 1), to afford compound **5** (2.9 mg). Fraction 10 eluted with *n*-hexane–EtOAc (10 : 1) and was chromatographed by reverse phase HPLC using acetone–H_2O (3 : 1), and were further purified by normal phase HPLC, eluting with *n*-hexane–EtOAc (25 : 1), to afford compounds **3** (12.5 mg), and **4** (8.6 mg). Fraction 13 eluted with *n*-hexane–EtOAc (3 : 1) were subjected to repeated normal phase HPLC column chromatography using *n*-hexane–EtOAc (8 : 1) to yield compounds **1** (3.2 mg), **2** (13.7 mg), **6** (13.8 mg) and **7** (3.4 mg).

Paralemnolin J (**1**): White powder; mp 32—33 °C; $[\alpha]_D^{25}$ −89 (c=1.56, $CHCl_3$); IR (neat) ν_{max} 2934, 1739, 1703, and 1232 cm^{-1}; ^{1}H- and ^{13}C-NMR data, see Tables 1 and 2; ESI-MS *m/z*: 301 $[M+Na]^+$; HR-ESI-MS *m/z*: 301.1782 $[M+Na]^+$ (Calcd for $C_{17}H_{26}O_3Na$, 301.1780).

Paralemnolin K (**2**): Colorless oil; $[\alpha]_D^{25}$ −130 (c=1.28, $CHCl_3$); IR (neat) ν_{max}: 2962, 1741, 1699, and 1232 cm^{-1}; ^{1}H- and ^{13}C-NMR data, see Tables 1 and 2; ESI-MS *m/z*: 301 $[M+Na]^+$; HR-ESI-MS *m/z*: 301.1781 $[M+Na]^+$ (Calcd for $C_{17}H_{26}O_3Na$, 301.1780).

Paralemnolin L (**3**): White powder; mp 90—92 °C; $[\alpha]_D^{25}$ −142 (c=1.34, $CHCl_3$); IR (neat) ν_{max}: 2974, 1743, 1637, and 1246 cm^{-1}; ^{1}H- and ^{13}C-NMR data, see Tables 1 and 2; ES-IMS *m/z*: 343 $[M+Na]^+$; HR-ESI-MS

m/z: 343.1884 [M+Na]$^+$ (Calcd for $C_{19}H_{28}O_4Na$, 343.1885).

Paralemnolin M (**4**): Colorless oil; $[\alpha]_D^{25}$ −66 (*c*=1.24, $CHCl_3$); IR (neat) ν_{max}: 2968, 1734, 1647, and 1248 cm^{-1}; ^{1}H- and ^{13}C-NMR data, see Tables 1 and 2; ESI-MS *m/z*: 343 [M+Na]$^+$; HR-ESI-MS *m/z*: 343.1884 [M+Na]$^+$ (Calcd for $C_{19}H_{28}O_4Na$, 343.1885).

Paralemnolin N (**5**): White powder; mp 85—87 °C; $[\alpha]_D^{25}$ −15 (*c*=1.72, $CHCl_3$); IR (neat) ν_{max}: 2928, 1741, 1647, and 1244 cm^{-1}; ^{1}H- and ^{13}C-NMR data, see Tables 1 and 2; ESI-MS *m/z*: 343 [M+Na]$^+$; HR-ESI-MS *m/z*: 343.1886 [M+Na]$^+$ (Calcd for $C_{19}H_{28}O_4Na$, 343.1885).

Paralemnolin O (**6**): White powder; mp 77—79 °C; $[\alpha]_D^{25}$ −94 (*c*=1.16, $CHCl_3$); IR (neat) ν_{max}: 3497, 2966, 1734, and 1236 cm^{-1}; ^{1}H- and ^{13}C-NMR data, see Tables 1 and 2; ESI-MS *m/z*: 317 [M+Na]$^+$; HR-ESI-MS *m/z*: 317.1730 [M+Na]$^+$ (Calcd for $C_{17}H_{26}O_4Na$, 317.1729).

Paralemnolin P (**7**): Colorless oil; $[\alpha]_D^{25}$ −184 (*c*=1.52, $CHCl_3$); IR (neat) ν_{max}: 2928, 1738, 1714, and 1238 cm^{-1}; ^{1}H- and ^{13}C-NMR data, see Tables 1 and 2; ESI-MS *m/z*: 287 [M+Na]$^+$; HR-ESI-MS *m/z*: 287.1625 [M+Na]$^+$ (Calcd for $C_{16}H_{24}O_3Na$, 287.1623).

X-Ray Diffraction Analysis of Paralemnolin N (5)[12] A suitable colorless crystal (0.53×0.45×0.32 mm^3) of **5** was grown by slow evaporation of the EtOAc solution. Diffraction intensity data were acquired with a Rigaku AFC7S single-crystal X-ray diffractometer with graphite-monochromated Mo$K\alpha$ radiation (λ=0.71073 Å). Crystal data for **5**: $C_{19}H_{28}O_4$ (formula weight 320.41), approximate crystal size, 0.53×0.45×0.32 mm^3, orthorhombic, space group, $P2_12_12_1$ (#4), *T*=298(2) K, *a*=8.7706(8) Å, *b*=12.3217(11) Å, *c*=16.8426(615) Å, *V*=1820.2(3) Å^3, D_c=1.169 mg/m^3, *Z*=4, *F*(000)=696, $\mu_{(MoK\alpha)}$=0.08 mm^{-1}. A total of 21811 reflections were collected in the range 2.05°<θ<28.29°, with 4450 independent reflections, completeness to θ_{max} was 99.5%; psi-scan absorption correction applied; full-matrix least-squares refinement on F^2, the number of data/restraints/parameters were 4450/0/209; goodness-of-fit on F^2=1.013; final *R* indices [$I>2\sigma(I)$], R_1=0.0533, wR_2=0.1190; *R* indices (all data), R_1=0.0940, wR_2=0.1364, largest difference peak and hole, 0.175 and −0.144 e/Å^3.

Cytotoxicity Testing Cancer cell lines were purchased from the American Type Culture Collection (ATCC). Cytotoxicity assays of the test compounds **1**—**7** were performed using the MTT [3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyltetrazolium bromide] colorimetric method.[13,14]

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12) Crystallography data of **5** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC600210. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax: +44(0)–1223–336033 or e-mail: deposit@ccdc.cam.ac.uk).
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