A Pair of Epimeric Spirosesquiterpenes from the Roots of *Ligularia fischeri*

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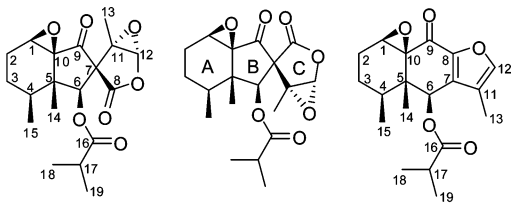
Two new highly oxygenated spirosesquiterpene lactones, ligulactones A (**1**) and B (**2**), and one known sesquiterpenoid, 1β,10β-epoxy-6β-isobutyryloxy-9-oxo-furanoeremophilane (**3**), were isolated from the roots of *Ligularia fischeri*. Their structures and relative configurations were elucidated by 1D and 2D NMR and MS data and by comparison of their NMR data with those of related compounds. Single-crystal X-ray diffraction analyses confirmed their structures. Compounds **1** and **2** are C-7 epimers. A possible biosynthetic process for their formation is proposed. Structure **3** was proposed as the likely parent compound for the two new epimeric sesquiterpenoids.

The Compositae family is a rich source of sesquiterpenes. Structurally new sesquiterpenoids belonging to this family have been the subject of our previous investigations.[1−6] The genus *Ligularia* belongs to the family Compositae, consisting of ca. 100 species distributed within China,[7] of which more than 27 species have been used as folk medicines due to their antibiotic, antiphlogistic, and antitumor activities.[8] *L. fischeri* (Ledeb.) Turcz. is widely distributed in China and has long been used as traditional folk medicine for its antiphlogistic, antitussive, and hemostatic properties.[9] Previous investigations of *L. fischeri* have reported several new eremophilane-type sesquiterpene derivatives.[10−12] Due to continued interest in the genus *Ligularia*,[13−19] we reinvestigated this species and obtained a pair of new epimeric sesquiterpene lactones, **1** and **2**, and one known furanoeremophilane (**3**). Although the first member of the bakkane class of sesquiterpenoids, bakkenolide A, was reported in 1969,[20] bakkenolide-type sesquiterpenoids, especially an epimeric pair, are rare. Herein, we describe the isolation and structural elucidation of the new natural products, along with a proposed biosynthetic pathway for their formation.



1 **2** **3**

Results and Discussion

An EtOH extract from the roots of *L. fischeri* was suspended in H_2O and partitioned successively with petroleum ether, EtOAc, and *n*-BuOH. The petroleum ether portion was subjected to repeated column chromatography over silica gel, yielding a pair of new epimeric bakkenolide-type sesquiterpenes, **1** and **2**, and one known furanoeremophilane sesquiterpene (**3**).[21]

Compound **1** was a colorless crystalline material, and its molecular formula determined as $C_{19}H_{24}O_7$ by HRESIMS at *m*/*z* 282.1856 $[M + NH_4]^+$. Its IR spectrum contained absorption bands for a ketone carbonyl (1705 cm^{-1}), an ester carbonyl (1742 cm^{-1}), and a lactone carbonyl (1809 cm^{-1}) group. The ^{13}C NMR spectrum (Table 1) of **1** indicated a structure with 19 carbons, including five methyl, two methylene, five methine, and seven quaternary carbons, as assigned by a DEPT experiment. Signals at δ_C 205.1 and 166.5 in the downfield region of the ^{13}C NMR spectrum (Table 1) were ascribed to a ketone carbonyl and a lactone carbonyl carbon, respectively. The presence of an oxymethine group was confirmed via chemical shifts at δ_C 75.6 and δ_H 5.96 (1H, s). NMR resonances at δ_C 175.2, 34.2, 18.5, 18.4 and δ_H 2.57 (1H, qq, J = 6.8, 6.8 Hz), 1.15 (6H, d, J = 6.8 Hz) indicated an isobutyryloxy component. In addition, four oxygenated carbons with associated chemical shifts δ_C 62.7(CH), 67.7(C) and δ_H 3.53 (1H, brs), and δ_C 64.4(C), 82.4(CH) and δ_H 5.45 (1H, s) were assigned to two epoxy groups.

Comparing the ^1H NMR spectrum of 1β,10β-epoxy-6β-isobutyryloxy-9-oxofuranoeremophilane (**3**)[21] with that of **1** showed some similarities including an epoxy proton at δ_H 3.53 (1H, brs) and two methyl signals at δ_H 1.26 (3H, s) and 0.81 (3H, d, J = 6.8 Hz), suggesting that **1** contains an A-ring similar to that of **3**. However, the presence of two quaternary carbons with chemical shifts δ_C 65.0 and 41.1 indicates a significant modified skeleton from that of eremophilenolide. The structure and relative configuration of **3** were unequivocally confirmed by X-ray crystallography[22] (Supporting Information, Figure 1).

The gHMQC and gHMBC data of compound **1** showed some useful structural information. The proton−carbon correlations H-1/C-2, C-3, C-9, C-10; H-3/C-1, C-5, C-15; H-4/C-2, C-6, C-14, C-15; H-6/C-5, C-14, C-7, C-8, C-11, C-16; H-12/C-8, C-7, C-11; and H-13/C-7, C-11, C-12 in gHMBC (Figure 2) led to the identification of a bakkenolide skeleton,[23,24] which is thought to be biogenetically related to eremophilenolides on the basis of their frequent concurrence in nature.[25] On the basis of the above spectroscopic data, the isobutyryloxy group was assigned to C-6, and the epoxide ring to C-11 and C-12. Consequently, the planar structure of **1** was deduced as 1,10:11,12-diepoxy-6-isobutyryloxy-9-oxobakkenolide.

The relative configuration of **1** was determined as follows. Methyl groups at C-4 and C-5 are biogenetically in a β-orientation.[26] Structurally important NOEs including H-4α (δ 1.56) to H-6 (δ 5.96), and H-2α (δ 1.82) to H-4α (δ 1.56) and H-1 (δ 3.53), observed in the NOESY spectrum acquired for **1** (Figure 3) suggest a structure with 6β-isobutyryloxy and 1β,10β-epoxy orientations. However, the configuration of the 11,12-epoxy group and the B/C ring junction could not be deduced on the basis of NMR spectra. Consequently, an X-ray crystal structure analysis was carried out for a single crystal of **1** (obtained by recrystallization from *n*-hexane−CH_2Cl_2) (Supporting Information, Figure 4)[27] to confirm the relative configuration. Compound **1** is named ligulactone A after the genus *Ligularia*.

Compound **2** was a colorless crystalline material. Its ESIMS provided a quasi-molecular ion peak $[M + H]^+$ at *m*/*z* = 365.1.

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Table 1. NMR Data of Compounds **1**−**3** in $CDCl_3$

	1		**2**		**3**	
no.	δ_H (J in Hz)[a]	δ_C mult.[b]	δ_H (J in Hz)[a]	δ_C mult. [b]	δ_H (J in Hz)[a]	δ_C mult.[b]
1	3.53 brs	62.7 CH	3.48 brs	63.6 CH	3.30 brs	62.4 CH
2β	2.18 m	26.3 CH_2	2.15 m	26.0 CH_2	2.04 m	24.7 CH_2
2α	1.82 m		1.89 m		1.42 m	
3β	1.19 m	23.3 CH_2	1.21 m	23.1 CH_2	1.51 m	18.8 CH_2
3α	1.32 m		1.30 m		2.00 m	
4	1.56 m	40.2 CH	1.68 m	39.3 CH	1.77 m	31.5 CH
5		41.1 C		40.5 C		45.2 C
6	5.96 s	75.6 CH	5.79 s	79.2 CH	6.59 s	68.6 CH
7		65.0 C		64.9 C		136.8 C
8		166.5 C		170.7 C		146.4 C
9		205.1 C		204.7 C		181.1 C
10		67.7 C		67.5 C		65.4 C
11		64.4 C		62.0 C		121.5 C
12	5.45 s	82.4 CH	5.46 s	82.0 CH	7.42 s	146.5 CH
13	1.43 s	12.5 CH_3	1.54 s	15.0 CH_3	1.90 s	8.4 CH_3
14	1.26 s	9.5 CH_3	1.09 s	10.8 CH_3	1.18 s	16.1 CH_3
15	0.81 d (6.8)	15.9 CH_3	0.86 d (6.8)	15.5 CH_3	0.99 d (6.8)	15.2 CH_3
16		175.2 C		174.9 C		176.6 C
17	2.57 qq (6.8, 6.8)	34.2 CH	2.65 qq (6.8, 6.8)	34.1 CH	2.68 qq (7.2, 7.2)	34.2 CH
18	1.153 d (6.8)	18.4 CH_3	1.22 d (6.8)	18.6 CH_3	1.22 d (7.2)	18.5 CH_3
19	1.155 d (6.8)	18.5 CH_3	1.23 d (6.8)	18.9 CH_3	1.24 d (7.2)	19.3 CH_3

[a] ^{1}H NMR (400.13 MHz, δ values, TMS) coupling constants (Hz) are in parentheses. [b] ^{13}C NMR (100.62 MHz, δ values, TMS) multiplication determined by DEPT and HMQC experiments.

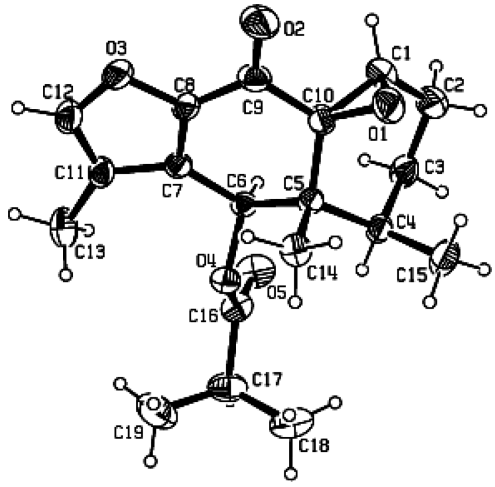

Figure 1. ORTEP diagram of the crystal structure of **3**.

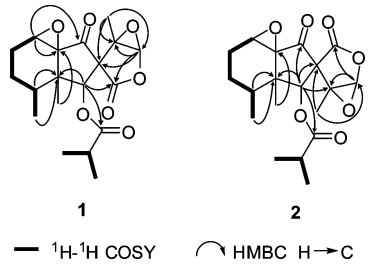

Figure 2. Key gCOSY and gHMBC correlations of **1** and **2**.

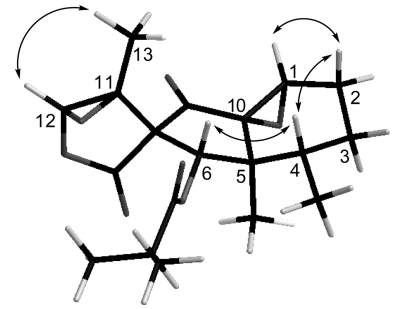

Figure 3. Conformation of **1** with minimized energy and key NOESY correlations.

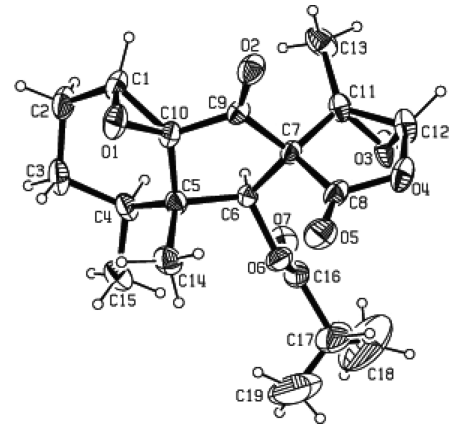

Figure 4. ORTEP diagram of the crystal structure of **1**.

This result combined with ^{13}C NMR and DEPT data suggests that **2** has a molecular formula of $C_{19}H_{24}O_7$ and eight degrees of unsaturation. Comparison of the ^{1}H and ^{13}C NMR spectra of **2** with those of **1** showed strong similarities, except that the C-6, C-8, and C-13 resonances of **2** exhibited a comparative downfield shift (Table 1). Analyses of data from gCOSY, gHMBC, and NOESY experiments (Figure 2) obtained for both ligulactones led to the conclusion that the two compounds have the same planar structure, but different stereostructures. The results of a single-crystal X-ray experiment of **2** support the above conclusion (Supporting Information, Figure 5).[28] Compounds **1** and **2** are C-7 epimeric sesquiterpenes. The new compound **2** is named ligulactone B.

Epimeric compounds **1** and **2** are highly oxygenated sesquiterpenoids and possess a rare bakkenolide-type carbon skeleton, which is thought to be biogenetically related to the eremophilane skeleton. The naturally occurring compound **3**, also obtained from *L. fischeri*, is likely the parent compound for the two new epimeric sesquiterpenoids (Figure 6). The furan ring of compound **3** is oxygenated to produce the endoperoxide **3a**,[29,30] which is transformed into **3b** as shown. The carboxylic C-9 is attacked by C-7 from both the *re*

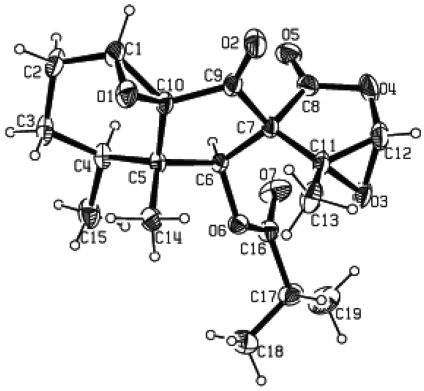

Figure 5. ORTEP diagram of the crystal structure of **2**.

and *si* faces to form the spiro junction and oxirane functionality simultaneously.

The absolute configuration of **3** was elucidated from its CD data. The Cotton effect in the 240 nm region has been linked to the C-6 configuration in 9-oxofuranoeremophilanes.[31] In adenostylone, the negative Cotton effect at 249 nm ($\Delta\varepsilon$ −4.5) is indicative of a 6*S* absolute configuration, while in the derivatives with the opposite configuration at C-6 it is positive.[31,32] Thus, the negative Cotton effect at 245 nm ($\Delta\varepsilon$ −15.8) in the CD spectrum of **3** indicated a 6*S* absolute configuration and, therefore, an absolute configuration 1*R*, 4*S*, 5*S*, 6*S*, 10*R* for compound **3**. Compounds **1** and **2** are biogenetically derived from **3**; hence their absolute configurations are likely 1*R*, 4*S*, 5*S*, 6*S*, 7*R*, 10*R*, 11*S*, 12*R* for **1** and 1*R*, 4*S*, 5*S*, 6*S*, 7*S*, 10*R*, 11*R*, 12*S* for **2**.

Experimental Section

General Experimental Procedures. Melting points were determined with an X-4 digital display micro-melting point apparatus and are uncorrected. Optical rotations were recorded on a 241 polarimeter (Perkin-Elmer) in acetone solution. UV spectra were measured on a Spect 50-UV/vis instrument (Analytic Jena AG). IR spectra were measured on an FTS165-IR instrument (Bio-Rad, USA). ^{1}H NMR (400.13 MHz) and ^{13}C NMR (100.62 MHz) spectra were recorded on a Varian INOVA-400 FT-NMR spectrometer (USA) in $CDCl_3$ with TMS as internal standard. HRESIMS were recorded on a Bruker APEX II. ESIMS were obtained on an HP-5988 MS spectrometer. Silica gel (200−300 mesh) used for column chromatography and silica gel (GF_{254}) for TLC were supplied by the Qingdao Marine Chemical Factory in China. Spots were detected on TLC by visualization under UV light or by spraying with 98% H_2SO_4−EtOH (1:19) followed by heating at 110 °C. X-ray crystallographic analysis was carried out on a Bruker Axs Smart APEX II imaging plate area detector with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). The structure was solved by direct methods (SHELXL-97) and expanded using Fourier techniques, refined by the program NOMCSDP using full-matrix least-squares calculations.

Plant Material. The roots of *L. fischeri* was collected in Nanchuan County of Chongqing, P. R. China, in October 2006 and was identified by Prof. Huan-Yang Qi, Key Laboratory for Natural Medicine of Gansu Province, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, P. R. China. A voucher specimen (No. 2006L03) was deposited at Key Laboratory for Natural Medicine of Gansu Province, Lanzhou 730000, P. R. China.

Extraction and Isolation. The air-dried roots of the plant (3.5 kg) were powdered and extracted with 95% EtOH at room temperature (10 L × 4, each extraction lasted 7 days). The residue (200 g) was suspended in H_2O (1.5 L) and extracted with petroleum ether (60−90 °C) (2.5 L), EtOAc (2.0 L), and *n*-BuOH (1.5 L), respectively. The petroleum ether extract (70 g) was subjected to column chromatography on silica gel (700 g) using petroleum ether (60−90 °C) with increasing volumes of EtOAc (50:1, 30:1, 15:1, 10:1, 7:1, 5:1, 3:1, 1:1, each about 3.0 L) as eluent. Fractions were examined by TLC and combined to afford eight pooled fractions (1A−1H). Fraction 1D (10 g) was further fractionated on a silica gel column (100 g) eluting with petroleum ether−acetone (15:1, 800 mL) to obtain compound **3** (100 mg). Fraction 1E (4.5 g) was fractionated on a silica gel column (60 g) eluting with petroleum ether−acetone (10:1, 800 mL) to give two fractions (1E1, 350 mL, and 1E2, 450 mL). Fraction 1E2 (0.35 g) was further subjected to column chromatography on silica gel (10 g) eluting with petroleum ether−EtOAc (8: 1, 100 mL) to obtain compound **2** (25 mg). Fraction 1F (6.9 g) was fractionated on a silica gel column (80 g) eluting with petroleum ether−EtOAc (6:1, 700 mL) to give colorless needles and was recrystallized from *n*-hexane−CH_2Cl_2 to yield compound **1** (48 mg).

Ligulactone A (1): colorless crystals (*n*-hexane−CH_2Cl_2); mp 159−160 °C; $[\alpha]^{20}_D$ −48 (*c* 0.14, acetone); UV (MeOH) λ_{max} 222 nm; IR (KBr) ν_{max} 2967, 2939, 2880, 1809, 1742, 1705, 1463, 1388, 1298, 1265, 1190, 1149, 1103, 1067, 1043, 921, 874, 752 cm^{-1}; ^{1}H and ^{13}C NMR, see Table 1; HRESIMS *m*/*z* 382.1856 ($[M + NH_4]^+$, cacld for $C_{19}H_{28}O_7N$ 382.1860); EIMS *m*/*z* (rel int) 293 $[M - C_4H_7O]^+$ (0.1), 249 $[M - C_4H_7O - CO_2]^+$ (0.2), 221 (5.9), 109 (5.6), 71 $[C_4H_7O]^+$ (37.1), 43 (100).

X-ray crystal data of 1: $C_{19}H_{24}O_7$, M_r = 364.38, tetragonal, space group *P*4(3)2(1)2, *a* = 10.4710(12) Å, *b* = 10.4710(12) Å, *c* = 36.304(4) Å, *V* = 3980.4(8) Å^3, *Z* = 8, D_{calc} = 1.216 g/cm^3, crystal dimensions 0.30 × 0.30 × 0.20 mm were used for measurements on a Bruker APEX II area detector diffractometer with a graphite monochromator, Mo Ka radiation (λ = 0.71073 Å). The total number of reflections measured was 33 040, of which 4870 were unique and 3504 were observed, $I > 2\sigma(I)$. Final indices: R_1 = 0.0673, wR_2 = 0.1968 for observed reflections, and R_1 = 0.0902, wR_2 = 0.2161 for all reflections. The crystal structure **1** was solved by direct methods using SHELX-97 (Sheldrick, G. M. University of Gottingen: Gottingen, Germany, 1990) and expanded using difference Fourier techniques, refined by SHELX-97 (Sheldrick, G. M., 1997).

Ligulactone B (2): colorless crystals (*n*-hexane−CH_2Cl_2); mp 88−89 °C; $[\alpha]^{20}_D$ +4 (*c* 0.24, acetone); UV (MeOH) λ_{max} 222 nm; IR (KBr) ν_{max} 2976, 2941, 2880, 1802, 1743, 1461, 1390, 1297, 1253, 1188, 1139, 1122, 1097, 1039, 1003, 894, 781, 745 cm^{-1}; ^{1}H and ^{13}C NMR, see Table 1; ESIMS *m*/*z* 365.1 $[M + H]^+$.

X-ray crystal data of 2: $C_{19}H_{24}O_7$, M_r = 364.38, orthorhombic, space group *P*2(1)2(1)2(1), *a* = 9.421(2) Å, *b* = 9.814(2) Å, *c* = 20.458(5) Å, *V* = 1891.5(8) Å^3, *Z* = 4, D_{calc} = 1.280 g/cm^3, crystal dimensions 0.30 × 0.30 × 0.20 mm were used for measurements on a Bruker APEX II area detector diffractometer with a graphite monochromator, Mo Ka radiation (λ = 0.71073 Å). The total number of reflections measured was 11 839, of which 4647 were unique and 3131 were observed, $I > 2\sigma(I)$. Final indices: R_1 = 0.0575, wR_2 = 0.1439 for observed reflections, and R_1 = 0.0882, wR_2 = 0.1618 for all reflections. The crystal structure **2** was solved by direct methods

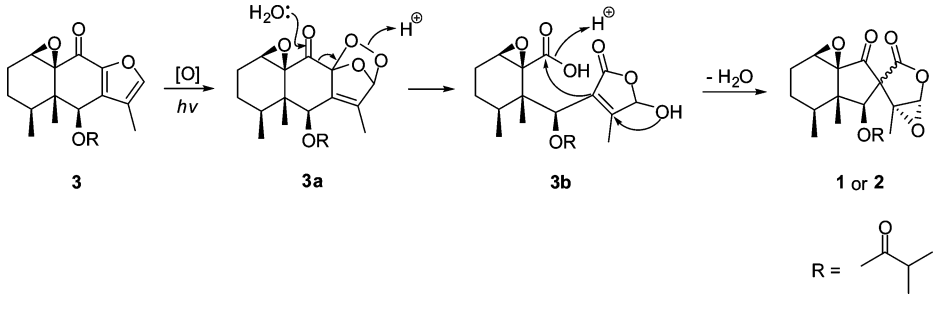

Figure 6. Plausible biosynthetic pathway for **1** and **2**.

using SHELX-97 (Sheldrick, G. M. University of Gottingen: Gottingen, Germany, 1990) and expanded using difference Fourier techniques, refined by SHELX-97 (Sheldrick, G. M., 1997).

1β,10β-Epoxy-6β-isobutyryloxy-9-oxo-furanoeremophilane (3): colorless crystals (petroleum ether−EtOAc); mp 106−107 °C; ^{1}H and ^{13}C NMR, see Table 1; HRESIMS *m/z* 355.1517 ([M + Na]$^+$, cacld for $C_{19}H_{24}O_5Na$ 355.1516); CD spectrum (*c* 0.4 mg/mL), 245 nm ($\Delta\varepsilon$ −15.8), 290 nm ($\Delta\varepsilon$ +6.3).

X-ray crystal data of 3: $C_{19}H_{24}O_5$, M_r = 332.38, orthorhombic, space group *P*2(1)2(1)2(1), a = 9.5987(2) Å, b = 15.0196(3) Å, c = 24.4517(6) Å, V = 3525.17(13) Å^3, Z = 8, D_{calc} = 1.253 g/cm^3, crystal dimensions 0.23 × 0.20 × 0.20 mm were used for measurements on a Bruker APEX II area detector diffractometer with a graphite monochromator, Mo Ka radiation (λ = 0.71073 Å). The total number of reflections measured was 20 915, of which 7457 were unique and 4316 were observed, $I > 2\sigma(I)$. Final indices: R_1 = 0.0489, wR_2 = 0.1061 for observed reflections, and R_1 = 0.0968, wR_2 = 0.1269 for all reflections. The crystal structure **3** was solved by direct methods using SHELX-97 (Sheldrick, G. M. University of Gottingen: Gottingen, Germany, 1990) and expanded using difference Fourier techniques, refined by SHELX-97 (Sheldrick, G. M., 1997).

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Supporting Information Available: 1D and 2D NMR, ESIMS, as well as IR spectra of compounds **1** and **2**, CD spectrum of compound **3**, and an ORTEP drawing and CIF file of **1**, **2**, and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Crystallographic data for the structure of **3** have been deposited with the Cambridge Crystallographic Data Centre (deposition number: CCDC 728229). Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
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