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Novel Lactone Chamigrene-Derived Metabolites from *Laurencia majuscula*

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Gomerolactones A–D along with the known majusculone, obtusol, and elatol were isolated from *Laurencia majuscula*, and their structures were determined spectroscopically. With the aid of Pirkle's reagent at low temperature, NMR spectroscopy was used to determine the absolute configuration at the ring closure carbon atom of a α-alkylidene-γ-lactone and an α-alkylidene-δ-lactone unit embedded in the chamigrene network of compounds **1** and **2**, respectively. The absolute stereochemistry of compounds **3** and **4** was determined by X-ray analysis.

Introduction

Studies on natural products chemistry reveal that specific compounds are only produced by certain species, therefore conferring upon them a chemical signature. Examples include over 120 naturally occurring sesquiterpene metabolites with the chamigrene skeleton in *Laurencia*. Notwithstanding the intensive research on the genus *Laurencia*, new chemical studies of *Laurencia* species from different latitudes have always resulted in the discovery of interesting and novel structures[1–5] as well as biologically active metabolites.[6,7] The widespread and prolific production of secondary metabolites observed in *Laurencia* species may be interpreted as an ecological adaptive response.

In this work we report on the discovery of compounds **1**–**4** that render three new structural types of tricyclic polyoxygenated chamigrenes that contain a five-, six-, or seven-membered ring lactone moiety. These compounds constitute all possible ring-size lactones that can be formed along ring B of the chamigrene framework.

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Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

Results and Discussion

Gomerolactones A-D (**1**–**4**), along with the known majusculone,[8] obtusol,[9] and elatol[10] were isolated from *Laurencia majuscula* (Ceramiales, Rhodomelaceae), a red alga common in the southern coast of La Gomera (Canary Islands). Vacuum flash chromatography of the acetone extract of *L. majuscula* gave three fractions, from which tricyclic keto–lactones **1**–**4** were obtained by standard chromatographic procedures involving gel filtration, silica-gel chromatography, and HPLC (Figure 1).

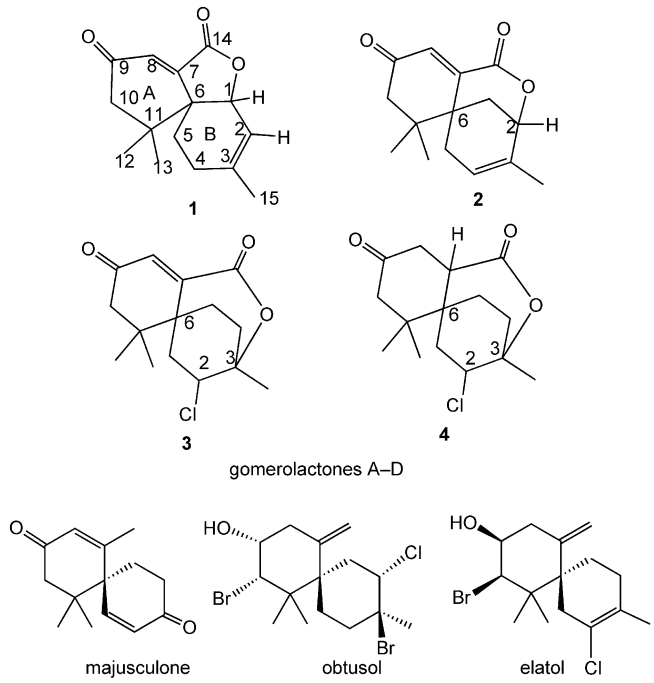

Figure 1. Metabolites isolated from *L. majuscula*.

Gomerolactone A (**1**) is a colorless oil. The EI-MS spectrum showed a peak at m/z = 246 $[M]^+$, which corresponds to the empirical formula $C_{15}H_{18}O_3$ $[M]^+$ (HRMS), indicative of seven sites of unsaturation. Absorptions for the α,β-unsaturated carbonyl and carbonyl ester groups at 1680 and 1757 cm^{-1}, respectively, were observed in the IR spectrum. The ^{13}C NMR spectrum of **1** (Table 1) showed signals for 15 carbon atoms. Multiplicities of the carbon signals were determined from the DEPT spectrum: three methyl groups, three methylene groups, three methine groups (two olefinic), and six nonprotonated carbon atoms (two carbonyl groups). The ^1H NMR spectrum of **1** displayed signals at δ = 6.56 ppm and δ = 5.82 ppm due to olefinic protons. A doublet at δ = 4.87 ppm was assigned to a proton geminal to the oxygen atom, whereas six well-resolved signals, each attributed to one of the remaining aliphatic protons, appeared at δ = 1.70–2.75 ppm. Three methyl groups at δ = 1.82, 1.14, 1.07 ppm accounted for all the protons of the molecule (Table 1). According to the spectroscopic data and the molecular formula, compound **1** has to be tricyclic. Because no IR absorption for a free acid was observed, two of the oxygen atoms given by the molecular formula must be involved in a lactone ring. Thus, the remaining oxygen atom should be involved in a trisubstituted enone system. Both oxygenated functionalities are consistent with the observed IR absorptions. The lack of one additional methyl group expected for a sesquiterpene skeleton suggested that it was oxidized to form part of the lactone ring.

All C–H correlations for **1** were inferred from the HSQC spectrum. A ^1H–^1H COSY experiment showed coupling between two methine protons (H-1 and H-2) and between two methylene groups (H_2-4–H_2-5). The HMBC mutual correlations of H_3-12/C-13 and H_3-13/C-12 and their long-range correlations with an isolated C-10 methylene unit and with the quaternary carbon atoms C-6 and C-11 secured a *gem* dimethyl group. The correlations of H-8 with C-6 and C-14 as well as those of H-10 with C-6, C-8, and C-9 determined ring A. On the other hand, the H_3-15/C-2, C-3, and C-4 correlations placed Me-15 at C-3, and the connectivity of both carbocyclic rings through the spiro C-6 carbon atom was deduced from the H-1/C-2,C-3, C-5, C-6, and C-7 correlations. The nature of the third ring of the molecule was confirmed to be a γ-lactone by the long-range correlation of H-1 with C-7, thus configuring the tricyclic structure as depicted in **1**.

Gomerolactone B (**2**) has an identical molecular formula and carbon pattern as those of **1**. The difference between both compounds lies on the site of the lactone ring closure. The HMBC long-range correlation of H-2 with C-15 and C-4 secured that the compound contains a δ-lactone core, as shown in **2**.

An NMR spectroscopic based method with the use of Pirkle's reagent at low temperature has proved to be useful to establish the absolute configuration of structurally diverse butenolide-containing compounds; for example, diterpenes,[11] fatty acid di-γ-lactones,[12] and annonaceous butenolides.[13] Now for the first time we apply this method with success to determine the absolute configuration at the ring closure carbon atom of a γ- and δ-lactone embedded in the chamigrene network of compounds **1** and **2**, respectively. In this work we examine the selective shielding effects that the geometry of the chiral solvating agent (CSA)–substrate complex produce on the corresponding H-1 and H-2 of the lactone ring closure of compounds **1** and **2**.

(*R*)- and (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE) were used to form complexes with the γ-lactone unit of gomerolactone A. It can be predicted that the H-1 signal for (*S*,*S*) or (*R*,*R*) solvates appears upfield relative to that of the (*R*,*S*) or (*S*,*R*) solvate. Therefore, if $\Delta[\delta_{H\text{-}1(R)} - \delta_{H\text{-}1(S)}]$ is positive, the absolute configuration at C-1 is (*S*). *R*-TFAE

Table 1. ^1H and ^{13}C NMR spectroscopic data [δ / ppm, multiplicity (J / Hz)] of compounds **1**–**4** (500 MHz, $CDCl_3$).

	1		**2**		**3**		**4**	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1	4.87 d (5.1)	75.8	1.88 ddd (0.9, 2.7, 13.5) 2.28 ddd (1.8, 3.3, 13.5)	27.7	2.56 m 2.56 m	36.4	α: 2.61 dd (9.0, 14.5) β:1.67 ddd (2.0, 9.0, 14.5)	38.5
2	5.82 dd (1.5, 5.4)	116.9	4.66 dd (3.0, 3.0)	74.7	4.16 br. s	61.1	4.11 dd (9.0, 9.0)	61.6
3	–	144.0	–	134.2	–	81.2	–	79.8
4	2.33 m 2.13 m	28.8	5.59 ddd (1.8, 1.8, 5.4)	124.2	1.85 m 2.19 m	34.0	2.10 m 2.10 m	34.1
5	1.70 m 2.10 m	24.7	2.17 dddd (1.8, 1.8, 5.4, 17.4) 2.74 ddd (2.7, 2.7, 17.4)	35.9	1.85 m 1.85 m	25.6	α: 1.77 m β: 1.98 m	20.7
6	–	45.9	–	40.4	–	42.5	–	39.8
7	–	155.0	–	150.2	–	153.6	3.15 ddd (1.1, 4.0, 14.3)	50.1
8	6.56 s	126.3	6.98 s	133.9	6.80 s	133.5	2.44 m 2.83 ddd (2.1, 4.0, 15.1)	41.5
9	–	198.1	–	198.2	–	197.7	–	206.1
10	2.18 d (17.7) 2.75 d (17.7)	49.2	2.68 d (18.3) 2.24 dd (1.2, 18.3)	48.9	2.19 m 2.56 m	48.7	1.98 dd (2.4, 15.4) 2.41 m	51.7
11	–	39.5	–	39.1	–	39.2	–	39.3
12	1.14 s	25.6	1.08 (s)	24.1	1.02 s	23.7	0.93 s	24.7
13	1.07 s	25.6	1.04 (s)	23.7	0.96 s	23.0	0.84 s	22.9
14	–	168.1	–	164.9	–	167.1	–	172.3
15	1.82 s	23.5	1.84 (br. s)	20.6	1.54 s	27.1	1.41 s	27.2

and *S*-TFAE were used to form complexes with the α-alkenyl-substituted γ-lactone moiety of **1**. NMR spectroscopic analysis of $\Delta\delta$ of H-1 of the two complexes (Table 2) gave clear evidence to establish the absolute stereochemistry at C-1 as *S*. Hence, the absolute stereochemistry of gomerolactone A is (1*S*,6*R*) (Figure 2).

Table 2. $\Delta\delta_{H\text{-}1}$ of **1** with 6 equiv. of (*R*)- and (*S*)-TFAE.

T [K]	$\delta_{H\text{-}1(R)}$	$\delta_{H\text{-}1(S)}$	$\Delta[\delta_{H(R)} - \delta_{H(S)}]$
293	4.84446	4.84067	0.00379
253	4.81546	4.80663	0.00883
240	4.81861	4.80915	0.00946

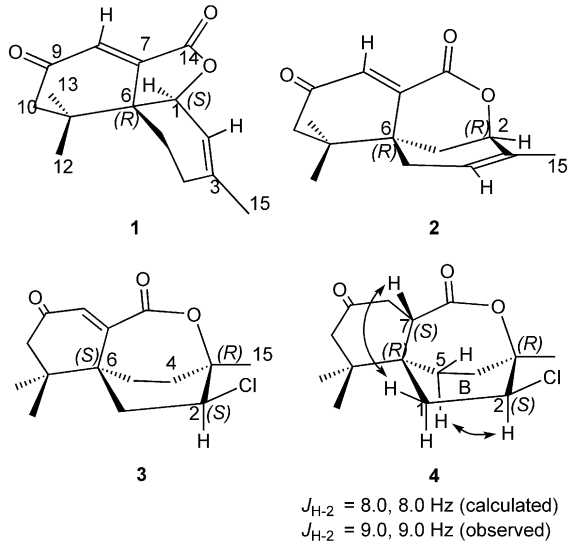

Figure 2. Minimized structures of **1**–**4** and selected NOEs of **4**.

To determine the absolute stereochemistry of gomerolactone B we used (*R*)- and (*S*)-TFAE to form complexes with its δ-lactone unit. NMR spectroscopic analysis of $\Delta\delta$ of H-2 of the two complexes (Table 3) gave clear evidence to establish the absolute stereochemistry at C-2 as *R*. Hence, the absolute stereochemistry of gomerolactone A is (2*R*,6*R*) (Figure 2).

Table 3. $\Delta\ \delta_{H\text{-}2}$ of **2** with 6 equiv. of (*R*)- and (*S*)-TFAE.

T [K]	$\delta_{H\text{-}2(R)}$	$\delta_{H\text{-}2(S)}$	$\Delta[\delta_{H(R)} - \delta_{H(S)}]$
293	4.65219	4.65786	–0.00567
253	4.64210	4.65093	–0.00830
240	4.63391	4.64904	–0.01513

Gomerolactone C (**3**) is a colorless oil. The EI-MS spectrum showed peaks at *m*/*z* = 282/284 $[M]^+$, with relative intensities for one chlorine atom, which correspond to the empirical formula $C_{15}H_{19}ClO_3$ $[M]^+$ (HRMS) indicative of six sites of unsaturation. Two absorptions for the carbonyl groups at 1676 and 1701 cm^{-1} were observed in the IR spectrum. The NMR spectroscopic data of **3** resemble those of compounds **1** and **2**. The carbon atoms involved in the trisubstituted olefinic bond of ring B of **1** and **2** become saturated carbon atoms in **3**. The chemical shift of H_3-15 at δ = 1.54 ppm, typical for a methyl group geminal to an oxygen atom, suggested that C-3 bears the ring closure atom of a seven-membered ring lactone. Hence, a chlorine atom is the adjacent heteroatom. Therefore, the structure of gomerolactone C is that depicted in **3**.

Gomerolactone D (**4**) is a colorless oil. The EI-MS spectrum showed peaks at *m*/*z* = 284/286 $[M]^+$, with relative intensities for one chlorine atom, which correspond to the empirical formula $C_{15}H_{21}ClO_3$ $[M]^+$ (HRMS) indicative of five sites of unsaturation. The absorption for the carbonyl group at 1710 cm^{-1} was observed in the IR spectrum. From comparison of the spectroscopic data of **3** and **4** it was deduced that the double bond of the dicarbonylic conjugated system of **3** is saturated in **4**, which was also corroborated by their MS spectra. Because the spectral characteristics of the corresponding ring B were very similar in both compounds, gomerolactone D has to be the hydrogenated derivative of **3** at C-7–C-8, which is consistent with the lack of IR absorption for an enone system. The structure shown in **4** was confirmed by the HMBC correlations of H-7 with C-9 and C-14.

The relative configuration of compound **4** was established by a combination of NOESY experiments, molecular mechanic calculations, and a study of the coupling constants. A clear NOE observed between H-7 and one of the protons of the well-resolved H_2-1 methylene unit allowed us to identify H-1β and to assign the relative configuration at C-6 and C-7. The configuration at C-2 was established by the NOE effect observed between H-2 and H-5α. Molecular mechanic calculations[14] were carried out on compound **4**. The minimized-energy structure is illustrated in Figure 2. The pseudoaxial disposition of H-2 of **4** in a twisted-boat conformation of ring B is in good agreement with the NOE observed. Also, the calculated coupling constants of H-2 with the protons of the adjacent methylene H_2-1 (J = 8.0 Hz and J = 8.0 Hz) fit well with the experimental values (J = 9.0 Hz and J = 9.0 Hz).

Similar analysis was used to establish the relative stereochemistry for compound **3**. However, its relative stereochemistry at C-2 could not be confidently assigned due to the fact that H-2 appears as a broad singlet in the ^1H NMR spectrum. Compounds **3** and **4** were crystallized and an X-ray diffraction experiment was undertaken that solved their structures in an unambiguous manner along with their absolute stereochemistries (Figure 2). The ORTEP representation of the crystallographically independent unit of **3** and **4** showing the atom numbering can be found in the Supporting Information.

Gomerolactones A–D (**1**–**4**) and chamigrenelactone[15] are the only compounds oxidized at C-14 among all naturally occurring chamigrene metabolites known today. Because naturally occurring compounds **1**–**4** have been isolated from the same algae specimens collected in a reduced area it should be expected that all these compounds originate from a common chamigrene precursor with a fixed configuration at C-6. The unusual high degree of oxidation and oxygen content of **1**–**4** may reflect an ecological adaptive response to enhance the fitness of the alga.

Conclusions

Gomerolactones A–D represent three new structural types of tricyclic polyoxygenated chamigrenes that contain a five-, six- or, seven-membered ring lactone moiety and constitute all possible ring size lactones that can be formed along ring B of the chamigrene framework. To the best of our knowledge, they are, together with chamigrenelactone,[15] the only compounds oxidized at C-14 among all naturally occurring chamigrene metabolites. An NMR spectroscopic based method with the use of Pirkle's reagent at low temperature allowed us to determine the absolute configuration at the carbon ring closure of a γ-butanolide and a δ-lactone embedded in the chamigrene network of compound **1** and **2**, respectively. The absolute stereochemistry of compounds **3** and **4** was determined by X-ray analysis.

Experimental Section

General Procedures: Optical rotations were measured with a Perkin–Elmer model 343 Plus polarimeter by using a Na lamp at 25 °C. IR spectra were obtained with a Perkin–Elmer 1650/FTIR spectrometer. ^{1}H NMR and ^{13}C NMR, HSQC, HMBC, NOESY, and COSY spectra were measured with a Bruker AMX 500 instrument operating at 500 MHz for ^{1}H and at 125 MHz for ^{13}C nuclei. Two-dimensional NMR spectra were obtained with the standard Bruker software. EI-MS and HRMS data were measured with a Micromass Autospec spectrometer. HPLC separations were performed with a Hewlett Packard 1050 (Jaigel-Sil semipreparative column, 10 μ, 20 × 250 mm) with hexane/EtOAc mixtures at a flow of 3.5 mL min^{-1}. The gel filtration column (Sephadex LH-20) used hexane/MeOH/CH_2Cl_2 (3:1:1) as solvent. The spray reagent for TLC was H_2SO_4/H_2O/AcOH (1:4:20).

Biological Material: *Laurencia majuscula* was collected by scuba diving off La Gomera (Canary Islands) at –1.5 m. A voucher specimen was deposited at the Department of Vegetal Biology, Universidad de La Laguna, Tenerife, Canary Islands, Spain (TFC Phyc 13091).

Extraction and Isolation: Dry samples (2.0 kg) were extracted with acetone at room temperature and were concentrated to give a dark residue (89.8 g). The extract was chromatographed by flash chromatography on silica gel. From the fraction eluted with hexane/EtOAc (9:1), obtusol (1.5 g), and elatol (5.5 mg) were obtained. The fraction eluted with hexane/EtOAc (8:2) (8.7 mg) was further separated by gel filtration and HPLC (hexane/EtOAc, 8:2) to give compounds **1** (6.6 mg), **2** (34.8 mg), and **3** (224.4 mg). The fraction eluted with hexane/EtOAc (1:1) (2.3 g) was further separated by gel filtration and HPLC (hexane/EtOAc, 1:1) to give compound **4** (152.0 mg) and majusculone (81.3 mg).

Compound 1: Colorless oil. $[\alpha]_D^{20}$ = –30 (c = 0.33, $CHCl_3$). IR (film): $\tilde{\nu}$ = 1757, 1680, 1452 cm^{-1}. ^{1}H and ^{13}C NMR see Table 1. EI-MS: m/z (%) = 246 (11) $[M]^+$, 228 (25); 190 (53), 162 (100). EI-HRMS: calcd. for $C_{15}H_{18}O_3$ $[M]^+$ 246.1256, found 246.1252.

Compound 2: Colorless oil. $[\alpha]_D^{20}$ = +11 (c = 1.74, $CHCl_3$). IR (film): $\tilde{\nu}$ = 1717, 1681, 1471 cm^{-1}. ^{1}H and ^{13}C NMR see Table 1. EI-MS: m/z (%) = 246 (62) $[M]^+$, 218 (8) $[M - CO]^+$, 202 (4), 192 (57), 163 (100). EI-HRMS: calcd. for $C_{15}H_{18}O_3$ $[M]^+$ 246.1256, found 246.1268; calcd. for $C_{14}H_{18}O_2$ $[M - CO]^+$ 218.1307, found 218.1299.

Compound 3: Colorless oil. $[\alpha]_D^{20}$ = –14 (c = 3.6, $CHCl_3$). IR (film): $\tilde{\nu}$ = 1701, 1676, 1475 cm^{-1}. ^{1}H and ^{13}C NMR see Table 1. EI-MS: m/z (%) = 282/284 (20, 8) $[M]^+$, 247 (8) $[M - Cl]^+$, 238/240 (24, 11) $[M - CO_2]^+$, 203 (55) $[M - CO_2 - Cl]^+$, 183 (100). EI-HRMS: calcd. for $C_{15}H_{19}{}^{37}ClO_3$ $[M]^+$ 284.0993, found 284.0986; calcd. for $C_{15}H_{19}{}^{35}ClO_3$ 282.1023, found 282.1030.

Compound 4: Colorless oil. $[\alpha]_D^{20}$ = +0.76 (c = 2.65, $CHCl_3$). IR (film): $\tilde{\nu}$ = 1710 cm^{-1}. ^{1}H and ^{13}C NMR see Table 1. EI-MS: m/z (%) = 284/286 (9, 3) $[M]^+$, 269/271 (5, 1) $[M - CH_3]^+$, 266/268 (4, 1) $[M - H_2O]^+$, 249 (12) $[M - Cl]^+$, 231 (10) $[M - H_2O - Cl]^+$, 213 (10) $[M - H_2O - H_2O - Cl]^+$, 205 (36) $[M - CO_2 - Cl]^+$, 121 (100). EI-HRMS: calcd. for $C_{15}H_{21}{}^{37}ClO_3$ $[M]^+$ 286.1150, found 286.1137; calcd. for $C_{15}H_2{}^{35}ClO_3$ $[M - CH_3]^+$ 284.1179, found 284.1180; calcd. for $C_{14}H_{18}{}^{35}ClO_3$ 269.0944, found 269.0948; calcd. for $C_{15}H_{21}O_3$ $[M - Cl]^+$ 249.1491, found 249.1500; calcd. for $C_{15}H_{19}O_2$ $[M - H_2O - Cl]^+$ 231.1385, found 231.1393; calcd. for $C_{14}H_{21}O$ $[M - CO_2 - Cl]^+$ 205.1592, found 205.1592.

Preparation of the 2,2,2-Trifluoro-1-(9-anthryl)ethanol Complexes of 1 and 2: Compound **1** (1.0 mg, 4.06 μmol) and $CDCl_3$ (0.5 mL) were placed in a 5-mm NMR tube with (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol (6 equiv.). The same experimental procedure was followed for the production of the corresponding (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol complexes. The ^{1}H NMR spectrum for each complex was recorded at 293, 253, and 240 K. The same experimental procedure was followed for the production of the complex with compound **2**.

X-ray Data: X-ray diffraction data on single crystals of **3** and **4** were collected at room temperature with a Nonius Kappa CCD diffractometer by using graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å). Orientation matrix and lattice parameters were determined by least-squares refinement of the reflections obtained by a θ-χ scan (Dirac/lsq method). Data collection and data reduction of **3** and **4** were indexed, integrated, and scaled by using the EVALCCD[16] program. All the measured independent reflections were used in the analysis. The structures of **3** and **4** were solved by direct methods by using the SHELXS97 computational program. The absolute configuration was performed with SHELXL97.[17] The Flack factor[18] was refined without restriction to allow the complete data convergence, giving rise in the final refinement the values of 0.00(8) and –0.06(8) for **3** and **4**, respectively, values which led to the enantiomer form showing in Figure 2. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares technique on F^2 by using the SHELXL97[17] program. The hydrogen atoms in **3** and **4** were located in the calculated positions by using the riding model. The final geometrical calculations and the graphical manipulations were carried out with PARST97[19] and PLATON[20] programs. CCDC-692916 (for **3**) and -692917 (for **4**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of gomerolactones A–D (**1**–**4**); ORTEP representation of the crystallographically independent unit of **3** and **4**.

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