

Anthelmintic flavonoids and other compounds from *Combretum glutinosum* Perr. ex DC (Combretaceae) leaves

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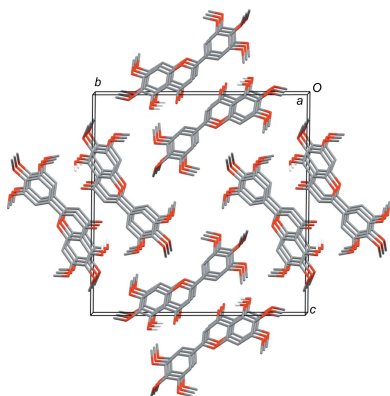
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A chemical study of the hydro-ethanol extract of the leaves of *Combretum glutinosum* resulted in the isolation of nine compounds, including 5-demethylsinensetin (**1**), umuhengerin (**2**), (2*S*,24*R*)-ocotillone (**3**), lupeol (**4**), β -sitosterol (**5**), oleanolic acid (**6**), betulinic acid (**7**), corymbosin (**8**) and β -sitosterol glucoside (**9**). Four compounds have been isolated for the first time from the genus *Combretum* [*viz.* (**1**), (**2**), (**3**) and (**8**)]. The crystal structures of flavonoid (**2**), C₂₀H₂₀O₈, *Z'* = 2, and triterpene (**3**), C₃₀H₅₀O₃, *Z'* = 1, have been determined for the first time; the latter confirmed the absolute configuration of native (2*S*,24*R*)-ocotillone previously derived from the crystal structures of related derivatives. The molecules of (**3**) are linked into supramolecular chains by intermolecular O—H...O hydrogen bonds. The crude extracts obtained by aqueous decoction and hydro-ethanolic maceration, as well as the nine isolated compounds, were tested for their anthelmintic activity on the larvae and adult worms of *Haemonchus contortus*, a hematophage that causes parasitic disorders in small ruminants. The evaluated anthelmintic activity showed that the extracts at different doses, as well as all the compounds tested at 150 $\mu\text{g ml}^{-1}$, inhibited the migration of the larvae and the motility of the adult worms of the parasite compared with the phosphate buffer solution negative reference control. The best activity was obtained with flavonoids (**1**), (**2**) and (**8**) on both stages of the parasite. The flavones that showed good activity can be used for the further development of other derivatives, which could increase the anthelmintic efficacy.

1. Introduction

Combretaceae are trees, shrubs or often lianas widely distributed in subtropical to tropical regions. This family consists of 18 genera, including 370 species of *Combretum* (Malgras, 1992; McGaw *et al.*, 2001, Amadou, 2004). These species are widely used in traditional medicine for their numerous pharmacological properties (Komlan, 2002). *C. glutinosum* is a tree of the genus *Combretum* belonging to the family Combretaceae. This plant is most often present in tree savannas, normally on shallow soils (Akoègninou *et al.*, 2006). It is distributed in tropical Africa from Mauritania to Uganda, passing through, for example, Senegal, Cameroon and Chad. In Bénin, the plant is spread in the North in Kandi, Kétou, Toukountouna, south of Malanville, Bessassi and Porga, and in the Pendrari Park (Akoègninou *et al.*, 2006). This species is among the most widely used of the medicinal plants in West Africa (Kerharo & Adam, 1974). It has been reported by Toklo *et al.* (2021) that it is used in the treatment of malaria,



dysentery, diarrhea, bronchitis and hypertension. The traditional uses of this plant have led to numerous pharmacological studies, including antibacterial, antifungal, anthelmintic, anti-malarial and antidrepanosite properties (Baba-Moussa *et al.*, 1999; Ouattara *et al.*, 2006; Usman *et al.*, 2017; Sall *et al.*, 2017; Alowanou *et al.*, 2019). Previous phytochemical studies of the genus *Combretum* led to the isolation of tannins, flavonoids, triterpenoids and steroids (Jossang *et al.*, 1994; Dawe *et al.*, 2013; Roy *et al.*, 2014, Amako *et al.*, 2016; Sene *et al.*, 2018; N'Diaye *et al.*, 2017; Balde *et al.*, 2019). In the search for a new active ingredient effective against increasing biological resistance to synthetic anthelmintics, the study reported here was undertaken on the leaves of *C. glutinosum*, which were obtained from plants in Bénin. The search for bioactive secondary metabolites from the leaves revealed nine known compounds (Scheme 1), of which the crystal structures of two, one flavonoid and one triterpene, have been determined for the first time. The biological activity of these compounds on the larvae and adult worms of *H. contortus*, a hematophage that causes parasitic disorders in small ruminants, has also been investigated.

2. Experimental

2.1. Chromatographic and spectroscopic analysis

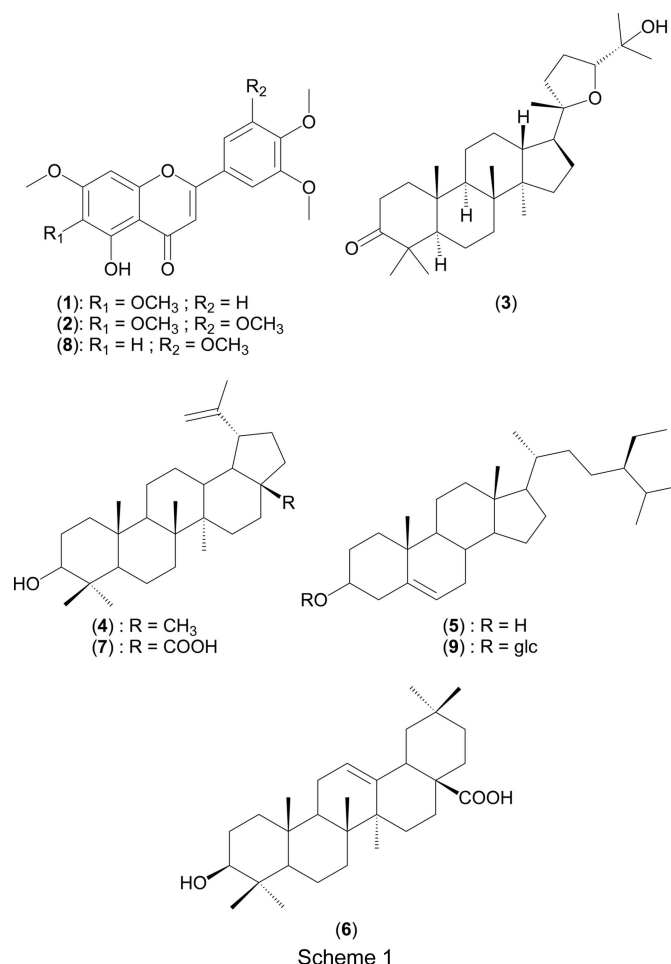
Column chromatography was performed using 230–400 mesh silica gel (Merck, Darmstadt, Germany), 70–230 mesh silica gel (Merck) and sephadex LH-20 (Sigma–Aldrich). Thin-layer chromatography (TLC) was performed on a pre-coated aluminium sheet of silica gel 60 F254 (Merck). The spots of compounds were detected using UV lamps at two wavelengths (254 and 365 nm) and then fixed using a 10% sulfuric acid spray reagent, followed by heating to 373 K. The high-resolution mass spectra were recorded in positive mode using a QTOF mass spectrometer (Bruker, Germany) equipped with an HESI source. The spectrometer operates in positive mode (mass range 100–1500, with a scan rate of 1.00 Hz), with automatic gain control to provide high accuracy mass measurements within the mass range. NMR spectra were recorded in deuterated chloroform (CDCl₃) and/or deuterated methanol (MeOD) using a Bruker DRX 500 NMR spectrometer (Bruker, Rheinstetten, Germany); the chemical shifts (δ) are given in ppm relative to tetramethylsilane (TMS) (Sigma–Aldrich, Germany) as the internal standard.

2.2. Collection of plant material, extraction and isolation of compounds

The leaves of *C. glutinosum* were collected in April 2018 in Kandi (in northern Bénin) and identified at the national herbarium of the University of Abomey–Calavi. A reference specimen was stored under the accession number YH 241/HNB after authentication.

The leaves were dried in the shade for two weeks before pulverization. The leaf powder (500 g) was macerated three times in 10 l of an ethanol/water (7:3 v/v) mixture at room temperature for 72 h. After filtration, the crude extract (67 g)

was obtained by evaporation of the solvent under reduced pressure using a rotary evaporator equipped with a vacuum pump. Different systems were used for TLC of the extract in order to find the best separation system. The extract was separated directly by silica-gel column chromatography. The column was eluted with mixtures of hexane–ethyl acetate (hex/EtOAc) and methanol with increasing polarity to give 92 fractions of 200 ml each. They were grouped on the basis of their TLC profile into five main fractions, *i.e.* FCG1 (Hex/EtOAc 10%, 5.3 g), FCG2 (Hex/EtOAc 20%, 12.9 g), FCG3 (Hex/EtOAc 30%, 5.6 g), FCG4 (Hex/EtOAc 40–50%, 5 g) and FCG5 (MeOH, 21.6 g), with one pure compound, lupeol [(4); 13 mg], obtained in the hex/EtOAc 10% system.



The FCG2 fraction was purified by silica-gel column chromatography using an isocratic system of hex/EtOAc (17:3 v/v) to give betulinic acid [(7); 35 mg], oleanolic acid [(6); 12 mg], β -sitosterol [(5); 26 mg], and (20*S*,24*R*)-ocotillone [(3); 55 mg], as well as two subfractions, FCG2-1 and FCG2-2. The FCG2-1 subfraction (2.1 g) was separated on a Sephadex LH-20 column by eluting with dichloromethane–methanol (4:6 v/v) to yield corymbosin [(8); 6 mg].

Based on the TLC profiles, the FCG2-2 subfraction was combined with the FCG3 fraction and subjected to silica-gel column chromatography using a gradient elution of hex/EtOAc with increasing polarity to obtain the compounds 5-demethylsinensetin [(1); 17 mg] and umhengerin [(2)

Table 1
Experimental details.

For both structures: $Z = 4$. Experiments were carried out at 160 K with Cu $K\alpha$ radiation. H atoms were treated by a mixture of independent and constrained refinement. The absorption correction was numerical based on Gaussian integration over a multifaceted crystal model (Coppens *et al.*, 1965) plus empirical (using intensity measurements) using spherical harmonics (*CrysAlis PRO*; Rigaku Oxford Diffraction, 2021).

	(2)	(3)
Crystal data		
Chemical formula	$C_{20}H_{20}O_8$	$C_{30}H_{50}O_3$
M_r	388.36	458.70
Crystal system, space group	Triclinic, $P\bar{1}$	Orthorhombic, $P2_12_12_1$
a, b, c (Å)	4.97902 (15), 18.5654 (5), 19.1368 (3)	6.37386 (6), 12.10746 (11), 33.8928 (3)
α, β, γ (°)	89.5065 (18), 84.322 (2), 89.375 (2)	90, 90, 90
V (Å ³)	1760.12 (8)	2615.55 (4)
μ (mm ⁻¹)	0.96	0.56
Crystal size (mm)	0.17 × 0.03 × 0.01	0.24 × 0.19 × 0.05
Data collection		
Diffractometer	Rigaku Oxford Diffraction XtaLAB Synergy dual radiation	Oxford Diffraction SuperNova dual radiation
T_{\min} – T_{\max}	0.694, 1.000	0.614, 1.000
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	34916, 6662, 5215	26797, 5424, 5324
R_{int}	0.060	0.018
$(\sin \theta/\lambda)_{\text{max}}$ (Å ⁻¹)	0.610	0.630
Refinement		
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.047, 0.113, 1.05	0.032, 0.089, 1.03
No. of reflections	6661	5424
No. of parameters	524	310
$\Delta\rho_{\text{max}}$, $\Delta\rho_{\text{min}}$ (e Å ⁻³)	0.44, -0.23	0.23, -0.14
Absolute structure	–	Flack x determined using 2226 quotients $[(I^+) - (I^-)]/[I^+ + (I^-)]$ (Parsons <i>et al.</i> , 2013)
Absolute structure parameter	–	-0.07 (4)

Computer programs: *CrysAlis PRO* (Rigaku Oxford Diffraction, 2021), *SHELXT2018* (Sheldrick, 2015a), *OLEX2* (Dolomanov *et al.*, 2009), *Mercury* (Macrae *et al.*, 2020), *SHELXL2018* (Sheldrick, 2015b) and *PLATON* (Spek, 2020).

22 mg]. The FCG4 fraction was also eluted with a mixture of ethyl acetate and 5% methanol to give eight subfractions (FCG4 1–8), which all contained an impure compound (CCG20). The FCG4-2 fraction was passed through a Sephadex LH-20 column and eluted with methanol to give solely pure CCG20, which was identified as β -sitosterol glucoside [(9); 48 mg].

Colourless needle-like crystals of (2) and colourless plate-like crystals of (3) were obtained by slow diffusion of dichloromethane into their solutions in methanol. Selected crystals were mounted on cryo loops.

2.3. Aqueous extract

An aqueous extract was obtained by boiling 100 g of *C. glutinosum* leaf powder in 1000 ml of distilled water brought to the boil for 30 min. After decantation, the mixture was filtered on Whatman paper and the filtrate obtained was evaporated under vacuum to obtain the dry extract.

2.4. Anthelmintic tests

2.4.1. Test for inhibition of larval migration and motility of adult worms. The test of larval migration and motility of adult worms in the presence of the samples was evaluated following the procedure of Hounzangbe-Adote *et al.* (2005). The observation of the worms in the presence of the extracts was done every 6 h and every 3 h in the presence of the com-

pounds. The concentration of the tested compounds was 150 $\mu\text{g ml}^{-1}$ in phosphate buffer solution (PBS, pH 7 and 0.15 M), analogous to that used by Brunet & Hoste (2006). Levamisole and PBS were used as positive and negative reference controls, respectively.

2.4.2. Statistical analysis. The different values were included in a two-criteria repeated measures analysis of variance model. The comparison of means for the different tests was done using the SNK procedure, which runs the Student–Newman–Keuls test in the R software. Differences were considered significant at the 5% level.

2.5. Refinement

Crystal data, data collection and structure refinement details for (2) and (3) are summarized in Table 1. For both structures, the hydroxy H atoms were located in a difference Fourier map and their positions were refined freely along with individual isotropic displacement parameters. The methyl H atoms were constrained to an ideal geometry ($C-H = 0.98$ Å), with $U_{\text{iso}}(H) = 1.5U_{\text{eq}}(C)$, but were allowed to rotate freely about the $C-C$ bonds. All other H atoms were placed in geometrically idealized positions and constrained to ride on their parent atoms, with $C-H$ distances of 0.95 (aromatic), 0.99 (methylene) or 1.00 Å (methine) and with $U_{\text{iso}}(H) = 1.2U_{\text{eq}}(C)$. The absolute configuration of (3) was determined confidently from the diffraction experiment by refinement of

the absolute structure parameter using the intensity quotients method (Parsons *et al.*, 2013). For (2), one reflection was omitted from the final cycles of refinement because its observed intensity was much lower than the calculated value as a result of being partially obscured by the beam stop; a correction for secondary extinction was also applied.

3. Results and discussion

3.1. Identification of compounds

Repeated column chromatography of *C. glutinosum* leaf hydro-ethanol extract followed by silica-gel and sephadex LH-20 column purification yielded nine known compounds: 5-demethylsinensetin, (1) (Khazneh *et al.*, 2016), umuhengerin, (2) (Rwangabo *et al.*, 1988; Imbenzi *et al.*, 2014), (2*S*,24*R*)-ocotillone, (3) (Aalbersberg *et al.*, 1991), lupeol, (4) (Sholichin *et al.*, 1980; Banskota *et al.*, 2000; Balde *et al.*, 2019), β -sitosterol, (5) (Rubinstein *et al.*, 1976; Banskota *et al.*, 2000), oleanolic acid, (6) (Mahato & Kundu, 1994), betulinic acid, (7) (Sholichin *et al.*, 1980; Banskota *et al.*, 2000), corymbosin, (8) (Çitoğlu *et al.*, 2003), and β -sitosterol glucoside, (9) (Adnyana *et al.*, 2000) (Scheme 1). The structures of the compounds were

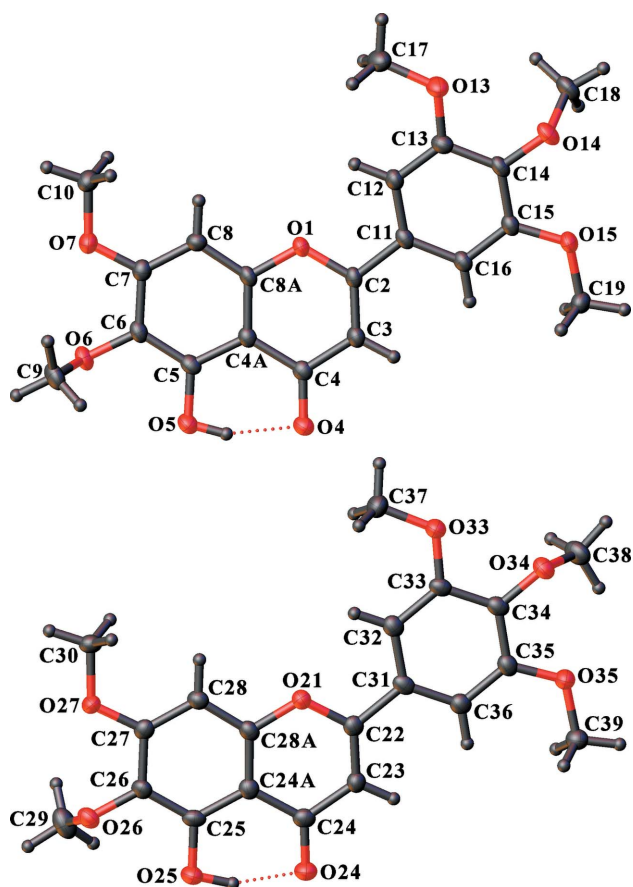


Figure 1
Separate views of the two symmetry-independent molecules of (2), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level. H atoms are represented by spheres of arbitrary size.

Table 2
Hydrogen-bond geometry (Å, °) for (2).

<i>D</i> –H··· <i>A</i>	<i>D</i> –H	H··· <i>A</i>	<i>D</i> ··· <i>A</i>	<i>D</i> –H··· <i>A</i>
O5–H5···O4	0.89 (3)	1.75 (3)	2.595 (2)	159 (3)
O25–H25···O24	0.96 (3)	1.68 (3)	2.591 (2)	155 (3)

established by interpretation of their spectroscopic data, mainly 1D NMR [^1H , ^{13}C and DEPT (distortionless enhancement by polarization transfer)], 2D NMR [COSY (correlated spectroscopy), HSQC (heteronuclear single quantum coherence) and HMBC (heteronuclear multiple bond correlation)] and mass spectrometry, and by comparison with literature data. Although all of these compounds are known, compounds (1), (2), (3) and (8) have been isolated for the first time from the genus *Combretum* and the crystal structures of compounds (2) and (3), previously undetermined, have been established.

3.2. The crystal structures of (2) and (3)

The flavonoid umuhengerin, (2), was originally isolated from the leaves of *Lantana trifolia* L. (Verbenaceae) and found to display *in vitro* antibacterial and antifungal properties (Rwangabo *et al.*, 1988). In the crystal structure of (2), there are two symmetry-independent molecules in the asymmetric unit (Fig. 1). The conformations of these molecules differ primarily in the orientations of the C6/C26 and C14/C34 methoxy groups, which are the substituents adjacent to the hydroxy group and at the 4-position of the trimethoxyphenyl ring, respectively. In the former case, these methoxy C–O torsion angles differ by 15.7 (3)°, while the rotation is 164.81 (3)° in the latter case (calculated when one molecule is overlaid with the inverted form of the other molecule, as allowed by the space-group symmetry). Apart from the methyl groups of these methoxy substituents, both flavonoid molecules are essentially planar, with r.m.s. deviations of all ring C and O atoms of 0.27 and 0.14 Å for the molecules containing atoms O1 and O21, respectively, although there may be a little bowing along the axis of the three-ring system. The dihedral angles between the individual planes of the phenyl and fused rings are 7.18 (8) and 3.05 (8)°, respectively.

The hydroxy group in each independent flavonoid molecule forms an intramolecular hydrogen bond with the adjacent carbonyl O atom (Table 2). In the crystal packing, the molecules form stacks, each of which consists of repeats of just one of the independent molecules. The molecules containing atom O1 lie tilted within an otherwise uniform column that runs parallel to the [100] direction. The molecular plane is tilted by approximately 45° with respect to the stacking direction. Nonetheless, there are no significant π – π interactions, because the ring offsets resulting from the tilting preclude significant overlap of the ring systems. The molecules containing atom O21 also stack parallel to the [100] direction in a similar 45°-tilted fashion, but the orientation of the tilted planes differs from that in the O1-containing stacks (Fig. 2); the normals to the molecular planes in the two independent stacks point in

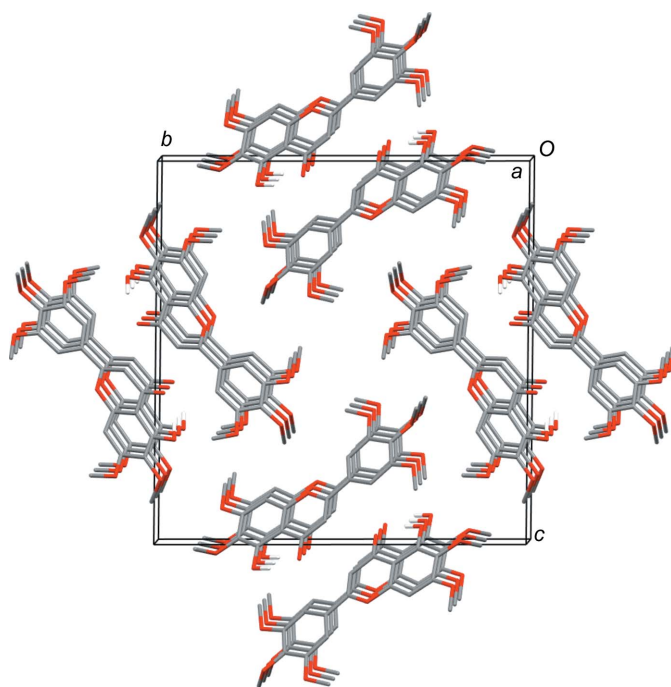


Figure 2

The crystal packing of (2), viewed down the *a* axis, showing the centrosymmetric double-stack columns of molecules, with the columns at the top and bottom being composed solely of one of the symmetry-independent types of molecules and the columns on the left and right being composed solely of the other independent type.

different directions. Each type of stack runs parallel to another stack of the same kind related by a centre of inversion to give a centrosymmetric double-stack pair. As the planes of the molecules in the two independent types of pairs of stacks are oriented differently, π - π interactions between the stacks are precluded and the stacks are not intertwined with one another.

The Cambridge Structural Database (CSD, Version 2020.3.0 with May 2021 update; Groom *et al.*, 2016) contains data for six closely related flavones with hydroxy or methoxy substituents at least at the 5-, 6-, 7-, 3'- and 4'-positions. The ring systems in four of these structures are planar, with perhaps a tendency towards a slight bowing along the axis of the three-ring system, similar to that observed in (2), as seen solely from visual inspection. These structures are 5,7,4'-trihydroxy-6,3',5'-trimethoxyflavone ethyl acetate solvate (Martinez-Vazquez *et al.*, 1993), 5,3'-dihydroxy-6,7,4'-trimethoxyflavone (Parvez *et al.*, 2001), 5,7-dihydroxy-6,3',4'-trimethoxyflavone (Suleimenov *et al.*, 2005) and 5,7,3'-trihydroxy-6,4',5'-trimethoxyflavone (Adizov *et al.*, 2013; Turdybekov *et al.*, 2014). In the structure of 5,6,7,2',3',4'-hexamethoxyflavone (Butler *et al.*, 2018), the bowing within the fused rings appears to be more prominent. In the structure of 5,3'-dihydroxy-6,7,2',4',5'-pentamethoxyflavone (Al-Yahya *et al.*, 1987), the individual planes of the phenyl and fused rings are significantly tilted from one another, with a dihedral angle of 12.23 (14)°; this is the only example with four substituents on the phenyl ring (three methoxy and one hydroxy).

The crystal structure of the triterpene (2*S*,24*R*)-ocotillone, (3), has one molecule in the asymmetric unit (Fig. 3). In the

Table 3

Hydrogen-bond geometry (Å, °) for (3).

<i>D</i> —H... <i>A</i>	<i>D</i> —H	H... <i>A</i>	<i>D</i> ... <i>A</i>	<i>D</i> —H... <i>A</i>
O25—H25...O3 ⁱ	0.90 (3)	2.03 (3)	2.9325 (18)	172 (3)

Symmetry code: (i) $-x + \frac{1}{2}, -y + 1, z - \frac{1}{2}$.

chosen crystal, the compound is enantiomerically pure and the absolute configuration of the molecule was determined independently by the diffraction experiment; the value of the absolute structure parameter (Parsons *et al.*, 2013) was -0.07 (4). According to the numbering of the atoms used in the refinement model, the absolute configuration of the stereogenic C atoms of the molecule is established as follows: 5*R*,8*R*,9*R*,10*R*,13*R*,14*R*,17*S*,20*S*,24*R*. The isolation and identification of 20*S*- and 20*R*-ocotillones have been reported on several occasions (Bisset *et al.*, 1966, 1967; Betancor *et al.*, 1983; Aalbersberg *et al.*, 1991). The isolation of the corresponding alcohol, ocotillol, appears to be mentioned for the first time by Warnhoff & Halls (1965). The absolute configuration of (20*S*,24*R*)-ocotillone was deduced from an X-ray crystal structure of a bromobenzoyl derivative of the corresponding ocotillol (Yamauchi *et al.*, 1969). The crystal structure determination of (3) is the first time the absolute configuration has been confirmed crystallographically for the native (20*S*,24*R*)-ocotillone.

The core of the molecule of (3) consists of five rings, including four fused rings, cyclohexane rings *A* (atoms C1–C5/C10), *B* (C5–C10) and *C* (C8/C9/C11–C14), and cyclopentane ring *D* (C13–C17), plus furan ring *E* (O18/C20–C24) attached to the fused rings at atom C17. An isopropanol substituent is present at atom C24 of the furan ring. Thus, compound (3) is (5*R*,8*R*,9*R*,10*R*,13*R*,14*R*,17*S*)-17-[(2*S*,5*R*)-5-(2-hydroxypropan-2-yl)-2-methyloxolan-2-yl]-4,4,8,10,14-pentamethyl-1,2,5,6,7,9-,11,12,13,15,16,17-dodecahydrocyclopenta[*a*]phenanthren-3-one. Rings *A*, *B* and *C* adopt a chair conformation, with ring *A* being the most distorted because of the presence of the sp^2 -hybridized keto C atom. The puckering parameters (Cremer

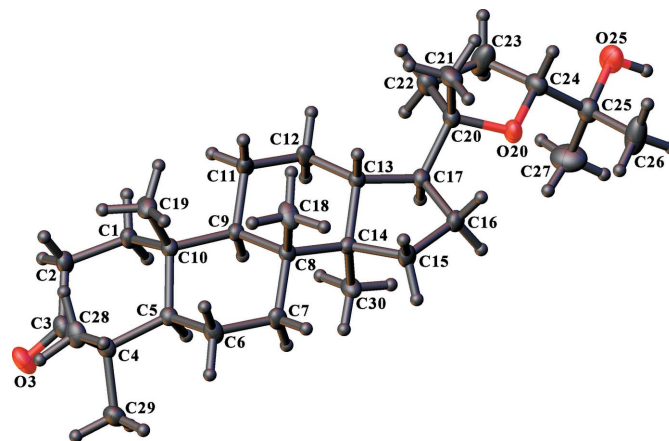


Figure 3

View of the molecule of (3), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level. H atoms are represented by spheres of arbitrary size.

& Pople, 1975) for ring *A* are $\theta = 15.82$ (18°) and $\varphi = 322.1$ (7°) for the atom sequence C1–C2–C3–C4–C5–C10. For ring *B*, $\theta = 11.01$ (15°) and $\varphi = 17.2$ (8°) for the atom sequence C5–C6–C7–C8–C9–C10 and for ring *C*, $\theta = 6.30$ (15°) and $\varphi = 8.5$ (13°) for the atom sequence C8–C9–C11–C12–C13–C14. Ring *D* has a near-ideal half-chair conformation twisted on C13–C14 [$\varphi_2 = 197.8$ (4°) for the atom sequence C13–C14–C15–C16–C17], while ring *E* has a slightly distorted envelope conformation with atom O20 as the envelope flap [$\varphi_2 = 188.6$ (4°) for the atom sequence O20–C21–C22–C23–C24]. The *A/B*, *B/C* and *C/D* ring junctions are all *trans*-fused to each other along the C5–C10, C8–C9 and C13–C14 bonds, respectively. This brings the methyl groups at C8 and C10 into *cis* positions, while the methyl groups at C8 and C14 are *trans* to one another. The furan substituent at the cyclopropane ring lies *trans* to the C14 methyl group.

Intermolecular O–H...O hydrogen bonds involving the hydroxy group and the ketone O atom link the molecules into extended wave-like chains (Table 3 and Fig. 4), which run parallel to the [001] direction and can be described by a graph-set motif (Bernstein *et al.*, 1995) of *C*(16).

3.3. Anthelmintic activity

3.3.1. About the extracts. The crude extracts obtained by aqueous decoction and hydro-ethanolic maceration, as well as the nine isolated compounds, were tested for their anthelmintic activity on the larvae and adult worms of *H. contortus*. The larval migration inhibition technique applied is based on the measurement of the migration rate of parasite larvae through a membrane after contact with the tested extract. At different doses, aqueous and hydro-ethanol extracts of *C. glutinosum* significantly inhibited *in vitro* larval migration of *H. contortus* ($p < 0.001$) (Fig. 5). This effect is independent of the dose and does not vary with the extraction solvent ($p > 0.05$). However, the aqueous extract appeared to be more effective than the hydro-ethanolic extract (Fig. 5). Similarly, both extracts significantly reduced the motility of adult *H. contortus* worms ($p < 0.001$). Although the inhibition effect did not vary with dose and extraction solvent ($p > 0.05$), it did vary with time ($p < 0.001$) and, paradoxically, the hydro-ethanolic

Table 4

The motility (%) of adult *H. contortus* worms in the presence of different concentrations of *C. glutinosum* extracts and reference control media.

Sample	Concentration (dose, $\mu\text{g ml}^{-1}$)	Time				
		6 h	12 h	18 h	24 h	30 h
PBS	d0	100	100	66.7	33.3	0
Levamisol	d500	50	50	0	0	0
	d250	66.7	0	0	0	0
	d125	0	0	0	0	0
	d2400	100	25	0	0	0
	d1200	100	75	25	0	0
Aqueous extract	d600	100	100	0	0	0
	d300	100	66.7	0	0	0
	d150	100	33.3	25	0	0
	d75	100	75	50	0	0
	d2400	100	0	0	0	0
Ethanol/water extract	d1200	100	33.3	0	0	0
	d600	100	75	25	0	0
	d300	66.67	66.7	0	0	0
	d150	100	50	0	0	0
	d75	100	33.3	0	0	0

extract appeared to inhibit adult worm motility more (Table 4). In order to know the chemical composition of these two extracts for the identification of the active principle, the present work was continued with the hydro-ethanolic extract and the compounds isolated therefrom were tested on *H. contortus* larvae and worms.

3.3.2. On the compounds. *In vitro*, the effect of the compounds was evaluated on *H. contortus* larvae and adult worms. All the compounds inhibited the migration of *H. contortus* larvae (Fig. 6) and the three isolated flavonoids seem to present the best results with inhibition percentages of 75.37, 53.26 and 47.73%, respectively, for compounds **(1)**, **(2)** and **(8)**, although they are all less active than the reference drug levamisol (95.97%). For the adult worms observed every 3 h with a magnifying glass after their contact with the tested compounds, the total inhibition of their motility was observed with the positive reference control (levamisol) after just 3 h of exposure. This inhibition was total at 12 h with compounds **(1)**, **(2)**, **(4)**, **(5)** and **(8)**. On the other hand, in phosphate buffer solution (PBS), 75% of adult worms were still mobile after 18 h (Table 5). Statistical analysis showed that the compounds inhibited the larval migration and motility of *H. contortus*

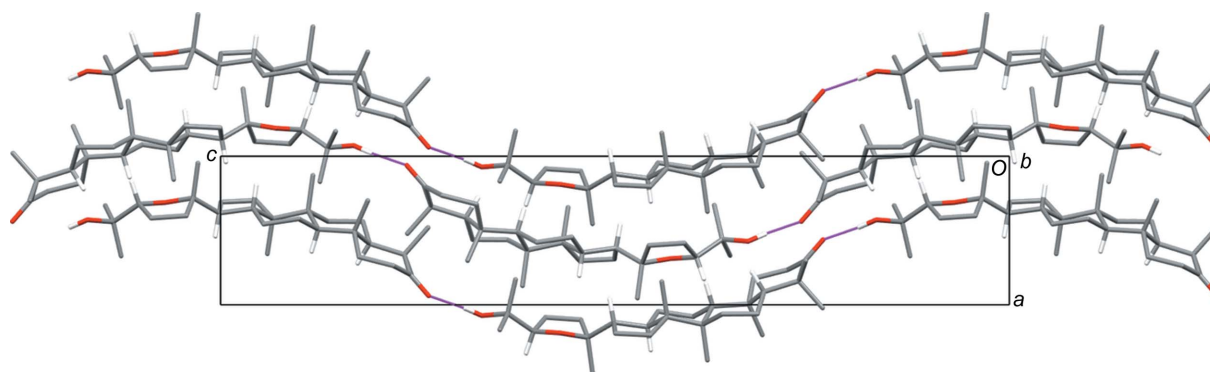


Figure 4

The crystal packing of **(3)**, viewed down the *b* axis, showing the O–H...O hydrogen bonds (magenta dashed lines) linking the molecules into wave-like chains. Most H atoms have been omitted for clarity.

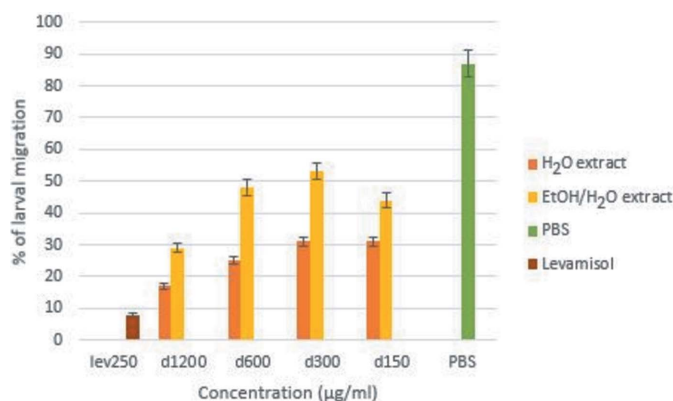


Figure 5
The effect on *H. contortus* larval migration caused by *C. glutinosum* extracts.

adult worms within the same time as levamisole, compared with the negative control ($p < 0.001$). On adult worms, the inhibitory effect varied with time ($p < 0.001$) and flavonoids; in particular, 5-demethylsinensetin, (**1**), would be responsible for the known anthelmintic activity of the plant.

Indeed, the class of polyphenols is strongly suspected as being the active agent in the anthelmintic effect of plants (Ayers *et al.*, 2008). Condensed tannins are frequently reported as being responsible for such effects, for example, in the report by Hoste *et al.* (2018). Nonetheless, other reports do link anthelmintic properties to flavonoids (Paolini *et al.*, 2003; Barrau *et al.*, 2005). Given the results of the *in vivo* tests, the known anthelmintic activity of *C. glutinosum* appears to be related to the presence of the flavonoids isolated from this plant. Thus, following the report that *C. glutinosum* is an anthelmintic plant (Alowanou *et al.*, 2019), the present study has allowed the anthelmintic capacity of the different compounds isolated from this plant to be ranked and highlighted. It appears that these compounds, although less active than the positive reference control, have a larvicidal and vermifugal effect on *H. contortus*, with 5-demethylsinensetin, (**1**), being the most active. The decrease in the migration of infesting larvae and the reduction of the motility of adult worms could disrupt their settlement in the mucosal wall of the digestive tract and thus ensure their progressive elimination from the

Table 5
The motility (%) of adult *H. contortus* worms in the presence of the isolated compounds ($150 \mu\text{g ml}^{-1}$), as determined by an adult worm motility inhibition assay (AMIA).

Compound	Time					
	3 h	6 h	9 h	12 h	15 h	18 h
5-Demethylsinensetin, (1)	100	50	0	0	0	0
Umuhengerin, (2)	100	75	0	0	0	0
Ocotillone, (3)	100	100	25	25	0	0
Lupeol, (4)	100	100	0	0	0	0
β -Sitosterol, (5)	100	100	0	0	0	0
Oleanolic acid, (6)	100	100	25	0	0	0
Betulonic acid, (7)	100	100	25	25	0	0
Corymbosin, (8)	100	100	0	0	0	0
β -Sitosterol glucoside, (9)	100	50	25	25	0	0
Levamisol	25	0	0	0	0	0
PBS	100	100	100	100	100	75

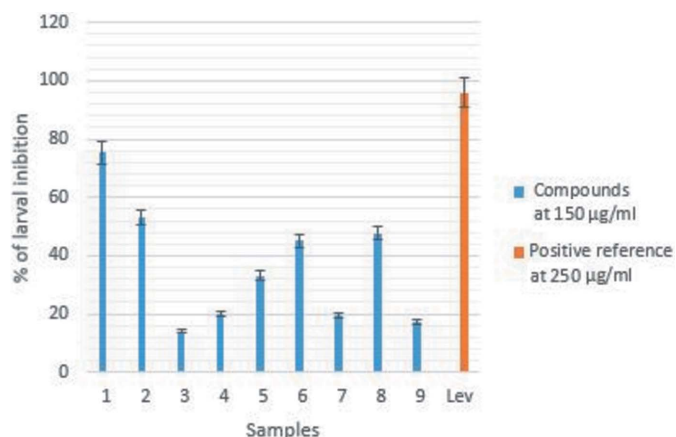


Figure 6
Inhibition of *H. contortus* larval migration by the compounds isolated from *C. glutinosum*.

infested animal (Dedehou *et al.*, 2014). These results could serve as a basis for a conformational analysis leading to the proposal of a new compound with a broader spectrum of activity than current commercially available anthelmintics.

4. Conclusion

The phytochemical investigation of the leaves of *C. glutinosum* led to the isolation of nine known compounds, which were characterized using spectroscopic analyses and by comparison with literature data. The crystal structures of two compounds were described for the first time in the present work and four compounds have been isolated for the first time from the genus *Combretum*. The flavonoids isolated from the plant presented the best *in vitro* activity on *H. contortus*. The results of this study could be verified *in vivo* on sheep in order to gain further insight into and enhance the status of this plant.

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Anthelmintic flavonoids and other compounds from *Combretum glutinosum* Perr. ex DC (Combretaceae) leaves

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Computing details

For both structures, data collection: *CrysAlis PRO* (Rigaku Oxford Diffraction, 2021); cell refinement: *CrysAlis PRO* (Rigaku Oxford Diffraction, 2021); data reduction: *CrysAlis PRO* (Rigaku Oxford Diffraction, 2021); program(s) used to solve structure: SHELXT2018 (Sheldrick, 2015a); program(s) used to refine structure: *SHELXL2018* (Sheldrick, 2015b); molecular graphics: OLEX2 (Dolomanov *et al.*, 2009) and *Mercury* (Macrae *et al.*, 2020); software used to prepare material for publication: *SHELXL2018* (Sheldrick, 2015b) and *PLATON* (Spek, 2020).

5-Hydroxy-6,7-dimethoxy-2-(3,4,5-trimethoxyphenyl)chromen-4-one (2)

Crystal data

$C_{20}H_{20}O_8$

$M_r = 388.36$

Triclinic, $P\bar{1}$

$a = 4.97902$ (15) Å

$b = 18.5654$ (5) Å

$c = 19.1368$ (3) Å

$\alpha = 89.5065$ (18)°

$\beta = 84.322$ (2)°

$\gamma = 89.375$ (2)°

$V = 1760.12$ (8) Å³

$Z = 4$

$F(000) = 816$

$D_x = 1.466$ Mg m⁻³

Melting point: 466 K

Cu $K\alpha$ radiation, $\lambda = 1.54184$ Å

Cell parameters from 10239 reflections

$\theta = 3.3\text{--}78.2^\circ$

$\mu = 0.96$ mm⁻¹

$T = 160$ K

Needle, pale yellow

$0.17 \times 0.03 \times 0.01$ mm

Data collection

Rigaku Oxford Diffraction XtaLAB Synergy
dual radiation
diffractometer

Radiation source: micro-focus sealed X-ray
tube, PhotonJet (Cu) X-ray source

Mirror monochromator

Detector resolution: 5.81 pixels mm⁻¹

ω scans

Absorption correction: gaussian

Numerical absorption correction based on
Gaussian integration over a multifaceted crystal
model (Coppens *et al.*, 1965) plus an empirical
(using intensity measurements) absorption
correction using spherical harmonics (*CrysAlis
PRO*; Rigaku Oxford Diffraction, 2021)

$T_{\min} = 0.694$, $T_{\max} = 1.000$

34916 measured reflections

6662 independent reflections

5215 reflections with $I > 2\sigma(I)$

$R_{\text{int}} = 0.060$

$\theta_{\max} = 70.1^\circ$, $\theta_{\min} = 3.3^\circ$

$h = -6 \rightarrow 6$

$k = -22 \rightarrow 22$

$l = -23 \rightarrow 22$

Refinement

Refinement on F^2

Least-squares matrix: full

$R[F^2 > 2\sigma(F^2)] = 0.047$

$wR(F^2) = 0.113$

$S = 1.05$

6661 reflections

524 parameters

0 restraints

Primary atom site location: dual

Secondary atom site location: difference Fourier map

Hydrogen site location: inferred from neighbouring sites

H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0439P)^2 + 0.954P]$

where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{\max} = 0.001$

$\Delta\rho_{\max} = 0.44 \text{ e } \text{\AA}^{-3}$

$\Delta\rho_{\min} = -0.23 \text{ e } \text{\AA}^{-3}$

Extinction correction: SHELXL2018

(Sheldrick, 2015b),

$F_c^* = kF_c[1 + 0.001x F_c^2 \lambda^3 / \sin(2\theta)]^{-1/4}$

Extinction coefficient: 0.00064 (15)

Special details

Experimental. Data collection and full structure determination done by Prof. Anthony Linden:

anthony.linden@chem.uzh.ch

The financial support from the Swiss National Science Foundation (R'Equip grant no. 206021_164018) and the University of Zurich for the purchase of the X-ray diffractometer used in this work is gratefully acknowledged.

Solvent used: dichloromethane / MeOH Cooling Device: Oxford Cryosystems Cryostream 800 Crystal mount: on a cryo-loop Frames collected: 5692 Seconds exposure per frame: 3.5-14.0 Degrees rotation per frame: 0.5 Crystal-detector distance (mm): 32.0 Client: Placide Toklo Sample code: G10 (L2102)

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Refinement. There are two symmetry-independent molecules in the asymmetric unit. Their conformations differ mainly in the orientations of the C6/C26 and C14/C34 methoxy groups.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (\AA^2)

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{iso}}^*/U_{\text{eq}}$
O1	0.8422 (3)	0.85801 (7)	0.42135 (7)	0.0221 (3)
O4	1.3522 (3)	1.02957 (7)	0.40490 (7)	0.0257 (3)
O5	1.1747 (3)	1.06246 (8)	0.28553 (8)	0.0273 (3)
H5	1.259 (6)	1.0611 (16)	0.3243 (16)	0.052 (9)*
O6	0.8350 (3)	1.03119 (7)	0.18570 (7)	0.0259 (3)
O7	0.5323 (3)	0.91317 (8)	0.19914 (7)	0.0278 (3)
O13	0.6742 (3)	0.63636 (8)	0.56501 (8)	0.0324 (4)
O14	0.9692 (3)	0.64850 (8)	0.67492 (7)	0.0280 (3)
O15	1.2499 (3)	0.76492 (8)	0.69432 (7)	0.0264 (3)
C2	1.0127 (4)	0.87011 (10)	0.47147 (9)	0.0197 (4)
C3	1.1858 (4)	0.92593 (11)	0.46730 (10)	0.0222 (4)
H3	1.302837	0.931941	0.503074	0.027*
C4	1.1959 (4)	0.97653 (10)	0.40948 (10)	0.0205 (4)
C4A	1.0182 (4)	0.96151 (10)	0.35638 (10)	0.0199 (4)
C5	1.0124 (4)	1.00467 (10)	0.29491 (10)	0.0216 (4)
C6	0.8454 (4)	0.98775 (10)	0.24420 (10)	0.0219 (4)
C7	0.6810 (4)	0.92629 (11)	0.25317 (10)	0.0227 (4)
C8	0.6811 (4)	0.88307 (11)	0.31284 (10)	0.0220 (4)

H8	0.569965	0.841766	0.318877	0.026*
C8A	0.8482 (4)	0.90209 (10)	0.36319 (10)	0.0202 (4)
C9	1.0055 (5)	1.00522 (12)	0.12617 (11)	0.0323 (5)
H91	0.992408	1.037996	0.086210	0.048*
H92	0.947640	0.957036	0.113962	0.048*
H93	1.192845	1.002897	0.137705	0.048*
C10	0.3684 (4)	0.84999 (11)	0.20370 (11)	0.0280 (5)
H101	0.283392	0.844604	0.160018	0.042*
H102	0.228375	0.854585	0.243201	0.042*
H103	0.481453	0.807570	0.210999	0.042*
C11	0.9878 (4)	0.81357 (10)	0.52674 (10)	0.0205 (4)
C12	0.8257 (4)	0.75395 (11)	0.51883 (10)	0.0229 (4)
H12	0.722807	0.751012	0.479732	0.028*
C13	0.8161 (4)	0.69871 (11)	0.56883 (10)	0.0246 (4)
C14	0.9623 (4)	0.70409 (10)	0.62693 (10)	0.0218 (4)
C15	1.1193 (4)	0.76461 (11)	0.63504 (10)	0.0211 (4)
C16	1.1352 (4)	0.81938 (11)	0.58467 (10)	0.0216 (4)
H16	1.244991	0.860170	0.589721	0.026*
C17	0.5090 (5)	0.63036 (13)	0.50876 (12)	0.0356 (5)
H171	0.622361	0.632223	0.463913	0.053*
H172	0.377958	0.670236	0.510834	0.053*
H173	0.413018	0.584477	0.512823	0.053*
C18	0.7326 (5)	0.64279 (12)	0.72304 (11)	0.0326 (5)
H181	0.577442	0.632168	0.697239	0.049*
H182	0.700503	0.688358	0.748115	0.049*
H183	0.757423	0.603916	0.756847	0.049*
C19	1.4212 (4)	0.82473 (11)	0.70315 (11)	0.0269 (4)
H191	1.563147	0.826701	0.663895	0.040*
H192	1.503526	0.819113	0.747337	0.040*
H193	1.314256	0.869417	0.704262	0.040*
O21	0.6336 (3)	0.41743 (7)	0.14003 (7)	0.0228 (3)
O24	0.1754 (3)	0.40137 (8)	-0.02513 (7)	0.0293 (3)
O25	0.3923 (3)	0.27616 (8)	-0.05320 (7)	0.0304 (3)
H25	0.277 (7)	0.3183 (18)	-0.0513 (16)	0.060 (9)*
O26	0.7475 (3)	0.16941 (8)	-0.01936 (7)	0.0274 (3)
O27	1.0071 (3)	0.18272 (7)	0.09442 (7)	0.0255 (3)
O33	0.7591 (3)	0.57926 (8)	0.33934 (7)	0.0285 (3)
O34	0.4623 (3)	0.69559 (8)	0.32162 (7)	0.0277 (3)
O35	0.1347 (3)	0.70599 (8)	0.21774 (7)	0.0291 (3)
C22	0.4571 (4)	0.47098 (10)	0.12585 (10)	0.0222 (4)
C23	0.3019 (4)	0.46705 (10)	0.07207 (10)	0.0227 (4)
H23	0.180196	0.505462	0.064500	0.027*
C24	0.3164 (4)	0.40596 (11)	0.02590 (10)	0.0237 (4)
C24A	0.5018 (4)	0.34887 (11)	0.04278 (10)	0.0227 (4)
C25	0.5328 (4)	0.28491 (11)	0.00271 (10)	0.0235 (4)
C26	0.7070 (4)	0.23045 (11)	0.02062 (10)	0.0234 (4)
C27	0.8500 (4)	0.23940 (11)	0.07986 (10)	0.0226 (4)
C28	0.8242 (4)	0.30238 (11)	0.11937 (10)	0.0235 (4)

H28	0.922459	0.308319	0.158985	0.028*
C28A	0.6515 (4)	0.35595 (10)	0.09928 (10)	0.0223 (4)
C29	0.5399 (5)	0.11670 (13)	-0.00512 (14)	0.0411 (6)
H291	0.574139	0.076188	-0.037390	0.062*
H292	0.364031	0.138599	-0.011647	0.062*
H293	0.539726	0.099334	0.043389	0.062*
C30	1.1603 (4)	0.18836 (12)	0.15355 (10)	0.0264 (4)
H301	1.286255	0.228525	0.146054	0.040*
H302	1.261785	0.143480	0.159052	0.040*
H303	1.037808	0.196933	0.196033	0.040*
C31	0.4562 (4)	0.53040 (11)	0.17705 (10)	0.0221 (4)
C32	0.6212 (4)	0.52478 (11)	0.23269 (10)	0.0246 (4)
H32	0.736495	0.484111	0.236443	0.030*
C33	0.6130 (4)	0.57957 (11)	0.28203 (10)	0.0232 (4)
C34	0.4487 (4)	0.64015 (11)	0.27564 (10)	0.0238 (4)
C35	0.2863 (4)	0.64500 (11)	0.21945 (10)	0.0243 (4)
C36	0.2899 (4)	0.58987 (11)	0.17089 (10)	0.0246 (4)
H36	0.178331	0.592921	0.133453	0.030*
C37	0.9133 (5)	0.51605 (12)	0.35099 (12)	0.0344 (5)
H371	1.055913	0.510170	0.312294	0.052*
H372	0.795294	0.474012	0.353395	0.052*
H373	0.994727	0.520461	0.395305	0.052*
C38	0.2177 (5)	0.71117 (14)	0.36545 (12)	0.0370 (5)
H381	0.080883	0.729958	0.336433	0.056*
H382	0.253563	0.747195	0.400399	0.056*
H383	0.151818	0.666988	0.389418	0.056*
C39	-0.0272 (5)	0.71420 (12)	0.16030 (11)	0.0283 (5)
H391	0.089433	0.713598	0.115945	0.042*
H392	-0.126193	0.760117	0.164593	0.042*
H393	-0.155624	0.674506	0.161066	0.042*

Atomic displacement parameters (\AA^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0252 (7)	0.0241 (7)	0.0172 (6)	-0.0027 (6)	-0.0031 (5)	0.0053 (5)
O4	0.0301 (8)	0.0240 (7)	0.0230 (7)	-0.0068 (6)	-0.0027 (6)	0.0032 (6)
O5	0.0336 (8)	0.0245 (7)	0.0242 (7)	-0.0066 (6)	-0.0048 (6)	0.0068 (6)
O6	0.0328 (8)	0.0246 (7)	0.0200 (7)	0.0032 (6)	-0.0023 (6)	0.0068 (6)
O7	0.0326 (8)	0.0292 (8)	0.0228 (7)	-0.0061 (6)	-0.0088 (6)	0.0040 (6)
O13	0.0427 (9)	0.0273 (8)	0.0282 (8)	-0.0129 (7)	-0.0071 (7)	0.0029 (6)
O14	0.0317 (8)	0.0240 (7)	0.0269 (7)	0.0011 (6)	0.0020 (6)	0.0105 (6)
O15	0.0323 (8)	0.0267 (7)	0.0209 (7)	-0.0050 (6)	-0.0066 (6)	0.0072 (6)
C2	0.0208 (10)	0.0233 (10)	0.0145 (9)	0.0033 (8)	0.0000 (7)	0.0009 (7)
C3	0.0250 (10)	0.0241 (10)	0.0172 (9)	0.0000 (8)	-0.0009 (8)	0.0015 (8)
C4	0.0210 (10)	0.0209 (10)	0.0189 (9)	0.0014 (8)	0.0017 (8)	-0.0010 (7)
C4A	0.0206 (10)	0.0207 (9)	0.0177 (9)	0.0021 (7)	0.0002 (7)	0.0010 (7)
C5	0.0253 (10)	0.0172 (9)	0.0216 (9)	0.0007 (8)	0.0018 (8)	0.0014 (7)
C6	0.0254 (10)	0.0221 (10)	0.0178 (9)	0.0032 (8)	-0.0005 (8)	0.0032 (7)

C7	0.0229 (10)	0.0249 (10)	0.0201 (9)	0.0019 (8)	-0.0021 (8)	-0.0010 (8)
C8	0.0207 (10)	0.0227 (10)	0.0223 (10)	-0.0034 (8)	0.0000 (8)	0.0008 (8)
C8A	0.0235 (10)	0.0212 (9)	0.0153 (9)	0.0016 (8)	0.0017 (7)	0.0026 (7)
C9	0.0442 (14)	0.0327 (12)	0.0188 (10)	0.0012 (10)	0.0021 (9)	0.0041 (8)
C10	0.0302 (11)	0.0270 (11)	0.0276 (11)	-0.0033 (9)	-0.0073 (9)	-0.0007 (8)
C11	0.0224 (10)	0.0205 (9)	0.0174 (9)	0.0036 (8)	0.0025 (7)	0.0025 (7)
C12	0.0248 (10)	0.0259 (10)	0.0177 (9)	-0.0009 (8)	-0.0006 (8)	0.0018 (8)
C13	0.0260 (11)	0.0230 (10)	0.0240 (10)	-0.0038 (8)	0.0015 (8)	0.0007 (8)
C14	0.0240 (10)	0.0214 (10)	0.0189 (9)	0.0021 (8)	0.0021 (8)	0.0059 (7)
C15	0.0223 (10)	0.0234 (10)	0.0171 (9)	0.0027 (8)	0.0007 (7)	0.0024 (7)
C16	0.0245 (10)	0.0222 (10)	0.0173 (9)	0.0005 (8)	0.0015 (8)	0.0015 (7)
C17	0.0410 (14)	0.0377 (13)	0.0283 (11)	-0.0137 (10)	-0.0029 (10)	-0.0006 (10)
C18	0.0373 (13)	0.0335 (12)	0.0251 (11)	-0.0027 (10)	0.0062 (9)	0.0093 (9)
C19	0.0287 (11)	0.0270 (11)	0.0261 (10)	-0.0027 (9)	-0.0085 (9)	0.0030 (8)
O21	0.0258 (7)	0.0213 (7)	0.0215 (7)	0.0012 (6)	-0.0028 (6)	-0.0014 (5)
O24	0.0345 (9)	0.0306 (8)	0.0240 (7)	0.0027 (6)	-0.0100 (6)	-0.0028 (6)
O25	0.0376 (9)	0.0312 (8)	0.0237 (7)	0.0050 (7)	-0.0103 (6)	-0.0059 (6)
O26	0.0307 (8)	0.0291 (8)	0.0220 (7)	0.0015 (6)	-0.0008 (6)	-0.0060 (6)
O27	0.0324 (8)	0.0233 (7)	0.0218 (7)	0.0071 (6)	-0.0078 (6)	-0.0015 (6)
O33	0.0359 (9)	0.0262 (7)	0.0246 (7)	0.0039 (6)	-0.0094 (6)	-0.0047 (6)
O34	0.0301 (8)	0.0262 (7)	0.0270 (7)	-0.0012 (6)	-0.0034 (6)	-0.0066 (6)
O35	0.0354 (9)	0.0265 (8)	0.0268 (7)	0.0062 (6)	-0.0100 (6)	-0.0043 (6)
C22	0.0239 (10)	0.0212 (10)	0.0207 (9)	-0.0026 (8)	0.0016 (8)	0.0023 (8)
C23	0.0253 (10)	0.0199 (9)	0.0226 (10)	0.0002 (8)	-0.0009 (8)	0.0004 (8)
C24	0.0251 (10)	0.0272 (10)	0.0183 (9)	-0.0034 (8)	-0.0001 (8)	0.0017 (8)
C24A	0.0234 (10)	0.0227 (10)	0.0210 (9)	-0.0017 (8)	0.0024 (8)	0.0007 (8)
C25	0.0244 (10)	0.0309 (11)	0.0153 (9)	-0.0040 (8)	-0.0017 (8)	0.0009 (8)
C26	0.0263 (11)	0.0263 (10)	0.0169 (9)	0.0017 (8)	0.0019 (8)	-0.0018 (8)
C27	0.0226 (10)	0.0246 (10)	0.0196 (9)	0.0010 (8)	0.0021 (8)	0.0025 (8)
C28	0.0246 (10)	0.0269 (10)	0.0189 (9)	-0.0001 (8)	-0.0012 (8)	-0.0015 (8)
C28A	0.0252 (10)	0.0224 (10)	0.0187 (9)	-0.0024 (8)	0.0022 (8)	-0.0019 (8)
C29	0.0437 (14)	0.0321 (12)	0.0456 (14)	-0.0049 (11)	0.0065 (11)	-0.0107 (11)
C30	0.0290 (11)	0.0305 (11)	0.0201 (10)	0.0005 (9)	-0.0050 (8)	0.0006 (8)
C31	0.0239 (10)	0.0246 (10)	0.0169 (9)	-0.0070 (8)	0.0034 (8)	-0.0007 (8)
C32	0.0270 (11)	0.0236 (10)	0.0227 (10)	-0.0034 (8)	0.0013 (8)	-0.0004 (8)
C33	0.0262 (11)	0.0269 (10)	0.0162 (9)	-0.0054 (8)	-0.0002 (8)	-0.0004 (8)
C34	0.0270 (11)	0.0252 (10)	0.0190 (9)	-0.0062 (8)	0.0002 (8)	-0.0013 (8)
C35	0.0272 (11)	0.0220 (10)	0.0230 (10)	-0.0028 (8)	0.0022 (8)	-0.0016 (8)
C36	0.0277 (11)	0.0244 (10)	0.0215 (10)	-0.0029 (8)	-0.0002 (8)	0.0007 (8)
C37	0.0409 (13)	0.0297 (11)	0.0337 (12)	0.0084 (10)	-0.0100 (10)	-0.0014 (9)
C38	0.0369 (13)	0.0446 (14)	0.0288 (12)	0.0055 (11)	0.0007 (10)	-0.0104 (10)
C39	0.0299 (11)	0.0298 (11)	0.0258 (10)	0.0010 (9)	-0.0054 (9)	-0.0018 (9)

Geometric parameters (Å, °)

O1—C2	1.364 (2)	O21—C22	1.363 (2)
O1—C8A	1.374 (2)	O21—C28A	1.385 (2)
O4—C4	1.259 (2)	O24—C24	1.262 (2)

O5—C5	1.350 (2)	O25—C25	1.347 (2)
O5—H5	0.89 (3)	O25—H25	0.96 (3)
O6—C6	1.379 (2)	O26—C26	1.375 (2)
O6—C9	1.435 (3)	O26—C29	1.436 (3)
O7—C7	1.355 (2)	O27—C27	1.348 (2)
O7—C10	1.433 (3)	O27—C30	1.431 (2)
O13—C13	1.369 (2)	O33—C33	1.375 (2)
O13—C17	1.424 (3)	O33—C37	1.423 (3)
O14—C14	1.378 (2)	O34—C34	1.366 (2)
O14—C18	1.426 (3)	O34—C38	1.437 (3)
O15—C15	1.363 (2)	O35—C35	1.356 (2)
O15—C19	1.428 (3)	O35—C39	1.432 (3)
C2—C3	1.352 (3)	C22—C23	1.350 (3)
C2—C11	1.481 (3)	C22—C31	1.481 (3)
C3—C4	1.443 (3)	C23—C24	1.441 (3)
C3—H3	0.9500	C23—H23	0.9500
C4—C4A	1.443 (3)	C24—C24A	1.453 (3)
C4A—C8A	1.395 (3)	C24A—C28A	1.381 (3)
C4A—C5	1.420 (3)	C24A—C25	1.418 (3)
C5—C6	1.379 (3)	C25—C26	1.388 (3)
C6—C7	1.411 (3)	C26—C27	1.409 (3)
C7—C8	1.390 (3)	C27—C28	1.396 (3)
C8—C8A	1.384 (3)	C28—C28A	1.384 (3)
C8—H8	0.9500	C28—H28	0.9500
C9—H91	0.9800	C29—H291	0.9800
C9—H92	0.9800	C29—H292	0.9800
C9—H93	0.9800	C29—H293	0.9800
C10—H101	0.9800	C30—H301	0.9800
C10—H102	0.9800	C30—H302	0.9800
C10—H103	0.9800	C30—H303	0.9800
C11—C16	1.394 (3)	C31—C36	1.384 (3)
C11—C12	1.395 (3)	C31—C32	1.410 (3)
C12—C13	1.395 (3)	C32—C33	1.391 (3)
C12—H12	0.9500	C32—H32	0.9500
C13—C14	1.392 (3)	C33—C34	1.395 (3)
C14—C15	1.394 (3)	C34—C35	1.410 (3)
C15—C16	1.393 (3)	C35—C36	1.387 (3)
C16—H16	0.9500	C36—H36	0.9500
C17—H171	0.9800	C37—H371	0.9800
C17—H172	0.9800	C37—H372	0.9800
C17—H173	0.9800	C37—H373	0.9800
C18—H181	0.9800	C38—H381	0.9800
C18—H182	0.9800	C38—H382	0.9800
C18—H183	0.9800	C38—H383	0.9800
C19—H191	0.9800	C39—H391	0.9800
C19—H192	0.9800	C39—H392	0.9800
C19—H193	0.9800	C39—H393	0.9800

C2—O1—C8A	119.99 (15)	C22—O21—C28A	119.46 (15)
C5—O5—H5	102 (2)	C25—O25—H25	102.5 (19)
C6—O6—C9	112.55 (15)	C26—O26—C29	113.59 (16)
C7—O7—C10	117.56 (15)	C27—O27—C30	117.56 (15)
C13—O13—C17	117.24 (16)	C33—O33—C37	117.01 (16)
C14—O14—C18	114.50 (16)	C34—O34—C38	115.63 (17)
C15—O15—C19	116.81 (15)	C35—O35—C39	116.94 (16)
C3—C2—O1	122.21 (17)	C23—C22—O21	122.18 (17)
C3—C2—C11	126.43 (18)	C23—C22—C31	126.15 (18)
O1—C2—C11	111.31 (17)	O21—C22—C31	111.65 (17)
C2—C3—C4	121.18 (18)	C22—C23—C24	121.52 (19)
C2—C3—H3	119.4	C22—C23—H23	119.2
C4—C3—H3	119.4	C24—C23—H23	119.2
O4—C4—C3	122.45 (18)	O24—C24—C23	122.70 (19)
O4—C4—C4A	122.08 (17)	O24—C24—C24A	121.89 (18)
C3—C4—C4A	115.46 (17)	C23—C24—C24A	115.40 (17)
C8A—C4A—C5	117.33 (18)	C28A—C24A—C25	118.42 (18)
C8A—C4A—C4	120.46 (17)	C28A—C24A—C24	120.02 (18)
C5—C4A—C4	122.19 (18)	C25—C24A—C24	121.56 (18)
O5—C5—C6	119.56 (17)	O25—C25—C26	119.12 (18)
O5—C5—C4A	119.64 (18)	O25—C25—C24A	120.29 (19)
C6—C5—C4A	120.80 (18)	C26—C25—C24A	120.59 (18)
O6—C6—C5	120.40 (18)	O26—C26—C25	121.26 (18)
O6—C6—C7	120.07 (18)	O26—C26—C27	119.84 (18)
C5—C6—C7	119.53 (17)	C25—C26—C27	118.87 (18)
O7—C7—C8	124.16 (18)	O27—C27—C28	124.22 (18)
O7—C7—C6	114.70 (17)	O27—C27—C26	114.54 (17)
C8—C7—C6	121.12 (18)	C28—C27—C26	121.24 (18)
C8A—C8—C7	117.91 (18)	C28A—C28—C27	118.23 (18)
C8A—C8—H8	121.0	C28A—C28—H28	120.9
C7—C8—H8	121.0	C27—C28—H28	120.9
O1—C8A—C8	116.08 (17)	C24A—C28A—C28	122.62 (18)
O1—C8A—C4A	120.61 (17)	C24A—C28A—O21	121.36 (18)
C8—C8A—C4A	123.30 (17)	C28—C28A—O21	116.01 (17)
O6—C9—H91	109.5	O26—C29—H291	109.5
O6—C9—H92	109.5	O26—C29—H292	109.5
H91—C9—H92	109.5	H291—C29—H292	109.5
O6—C9—H93	109.5	O26—C29—H293	109.5
H91—C9—H93	109.5	H291—C29—H293	109.5
H92—C9—H93	109.5	H292—C29—H293	109.5
O7—C10—H101	109.5	O27—C30—H301	109.5
O7—C10—H102	109.5	O27—C30—H302	109.5
H101—C10—H102	109.5	H301—C30—H302	109.5
O7—C10—H103	109.5	O27—C30—H303	109.5
H101—C10—H103	109.5	H301—C30—H303	109.5
H102—C10—H103	109.5	H302—C30—H303	109.5
C16—C11—C12	120.92 (18)	C36—C31—C32	120.70 (18)
C16—C11—C2	119.42 (18)	C36—C31—C22	119.96 (18)

C12—C11—C2	119.61 (17)	C32—C31—C22	119.32 (18)
C13—C12—C11	119.40 (19)	C33—C32—C31	119.15 (19)
C13—C12—H12	120.3	C33—C32—H32	120.4
C11—C12—H12	120.3	C31—C32—H32	120.4
O13—C13—C14	115.32 (17)	O33—C33—C32	124.41 (19)
O13—C13—C12	124.60 (19)	O33—C33—C34	115.10 (17)
C14—C13—C12	120.07 (19)	C32—C33—C34	120.49 (19)
O14—C14—C13	121.26 (18)	O34—C34—C33	118.92 (18)
O14—C14—C15	118.58 (18)	O34—C34—C35	121.41 (18)
C13—C14—C15	120.03 (17)	C33—C34—C35	119.54 (18)
O15—C15—C16	124.40 (18)	O35—C35—C36	124.79 (19)
O15—C15—C14	115.18 (17)	O35—C35—C34	115.04 (17)
C16—C15—C14	120.42 (18)	C36—C35—C34	120.17 (19)
C15—C16—C11	119.13 (19)	C31—C36—C35	119.93 (19)
C15—C16—H16	120.4	C31—C36—H36	120.0
C11—C16—H16	120.4	C35—C36—H36	120.0
O13—C17—H171	109.5	O33—C37—H371	109.5
O13—C17—H172	109.5	O33—C37—H372	109.5
H171—C17—H172	109.5	H371—C37—H372	109.5
O13—C17—H173	109.5	O33—C37—H373	109.5
H171—C17—H173	109.5	H371—C37—H373	109.5
H172—C17—H173	109.5	H372—C37—H373	109.5
O14—C18—H181	109.5	O34—C38—H381	109.5
O14—C18—H182	109.5	O34—C38—H382	109.5
H181—C18—H182	109.5	H381—C38—H382	109.5
O14—C18—H183	109.5	O34—C38—H383	109.5
H181—C18—H183	109.5	H381—C38—H383	109.5
H182—C18—H183	109.5	H382—C38—H383	109.5
O15—C19—H191	109.5	O35—C39—H391	109.5
O15—C19—H192	109.5	O35—C39—H392	109.5
H191—C19—H192	109.5	H391—C39—H392	109.5
O15—C19—H193	109.5	O35—C39—H393	109.5
H191—C19—H193	109.5	H391—C39—H393	109.5
H192—C19—H193	109.5	H392—C39—H393	109.5
C8A—O1—C2—C3	1.9 (3)	C28A—O21—C22—C23	-1.5 (3)
C8A—O1—C2—C11	-175.76 (16)	C28A—O21—C22—C31	177.03 (16)
O1—C2—C3—C4	0.9 (3)	O21—C22—C23—C24	-0.7 (3)
C11—C2—C3—C4	178.19 (18)	C31—C22—C23—C24	-179.03 (18)
C2—C3—C4—O4	178.87 (18)	C22—C23—C24—O24	-179.26 (19)
C2—C3—C4—C4A	-2.3 (3)	C22—C23—C24—C24A	1.8 (3)
O4—C4—C4A—C8A	179.86 (18)	O24—C24—C24A—C28A	-179.74 (19)
C3—C4—C4A—C8A	1.0 (3)	C23—C24—C24A—C28A	-0.8 (3)
O4—C4—C4A—C5	1.4 (3)	O24—C24—C24A—C25	-0.2 (3)
C3—C4—C4A—C5	-177.49 (18)	C23—C24—C24A—C25	178.72 (18)
C8A—C4A—C5—O5	-179.46 (17)	C28A—C24A—C25—O25	-179.38 (18)
C4—C4A—C5—O5	-1.0 (3)	C24—C24A—C25—O25	1.1 (3)
C8A—C4A—C5—C6	-0.3 (3)	C28A—C24A—C25—C26	0.9 (3)

C4—C4A—C5—C6	178.22 (18)	C24—C24A—C25—C26	-178.69 (19)
C9—O6—C6—C5	96.8 (2)	C29—O26—C26—C25	-81.1 (2)
C9—O6—C6—C7	-84.3 (2)	C29—O26—C26—C27	100.8 (2)
O5—C5—C6—O6	-2.8 (3)	O25—C25—C26—O26	2.9 (3)
C4A—C5—C6—O6	178.01 (17)	C24A—C25—C26—O26	-177.32 (18)
O5—C5—C6—C7	178.36 (17)	O25—C25—C26—C27	-178.96 (18)
C4A—C5—C6—C7	-0.8 (3)	C24A—C25—C26—C27	0.8 (3)
C10—O7—C7—C8	-1.0 (3)	C30—O27—C27—C28	-1.1 (3)
C10—O7—C7—C6	177.71 (17)	C30—O27—C27—C26	179.43 (17)
O6—C6—C7—O7	3.4 (3)	O26—C26—C27—O27	-4.0 (3)
C5—C6—C7—O7	-177.72 (17)	C25—C26—C27—O27	177.90 (18)
O6—C6—C7—C8	-177.77 (17)	O26—C26—C27—C28	176.58 (18)
C5—C6—C7—C8	1.1 (3)	C25—C26—C27—C28	-1.6 (3)
O7—C7—C8—C8A	178.50 (18)	O27—C27—C28—C28A	-178.78 (18)
C6—C7—C8—C8A	-0.2 (3)	C26—C27—C28—C28A	0.6 (3)
C2—O1—C8A—C8	175.87 (17)	C25—C24A—C28A—C28	-1.9 (3)
C2—O1—C8A—C4A	-3.2 (3)	C24—C24A—C28A—C28	177.69 (19)
C7—C8—C8A—O1	179.96 (17)	C25—C24A—C28A—O21	179.13 (17)
C7—C8—C8A—C4A	-1.0 (3)	C24—C24A—C28A—O21	-1.3 (3)
C5—C4A—C8A—O1	-179.78 (16)	C27—C28—C28A—C24A	1.1 (3)
C4—C4A—C8A—O1	1.7 (3)	C27—C28—C28A—O21	-179.81 (17)
C5—C4A—C8A—C8	1.2 (3)	C22—O21—C28A—C24A	2.5 (3)
C4—C4A—C8A—C8	-177.30 (18)	C22—O21—C28A—C28	-176.54 (17)
C3—C2—C11—C16	6.3 (3)	C23—C22—C31—C36	-1.8 (3)
O1—C2—C11—C16	-176.16 (16)	O21—C22—C31—C36	179.73 (17)
C3—C2—C11—C12	-171.25 (19)	C23—C22—C31—C32	176.7 (2)
O1—C2—C11—C12	6.3 (2)	O21—C22—C31—C32	-1.8 (2)
C16—C11—C12—C13	-1.5 (3)	C36—C31—C32—C33	0.7 (3)
C2—C11—C12—C13	176.03 (18)	C22—C31—C32—C33	-177.84 (18)
C17—O13—C13—C14	176.33 (19)	C37—O33—C33—C32	-4.7 (3)
C17—O13—C13—C12	-5.1 (3)	C37—O33—C33—C34	175.24 (18)
C11—C12—C13—O13	-176.99 (19)	C31—C32—C33—O33	178.34 (18)
C11—C12—C13—C14	1.6 (3)	C31—C32—C33—C34	-1.6 (3)
C18—O14—C14—C13	-77.4 (2)	C38—O34—C34—C33	-117.8 (2)
C18—O14—C14—C15	106.7 (2)	C38—O34—C34—C35	66.5 (2)
O13—C13—C14—O14	2.6 (3)	O33—C33—C34—O34	5.5 (3)
C12—C13—C14—O14	-176.11 (18)	C32—C33—C34—O34	-174.62 (18)
O13—C13—C14—C15	178.42 (18)	O33—C33—C34—C35	-178.68 (17)
C12—C13—C14—C15	-0.3 (3)	C32—C33—C34—C35	1.2 (3)
C19—O15—C15—C16	-2.3 (3)	C39—O35—C35—C36	-1.7 (3)
C19—O15—C15—C14	177.64 (17)	C39—O35—C35—C34	178.13 (18)
O14—C14—C15—O15	-5.2 (3)	O34—C34—C35—O35	-4.1 (3)
C13—C14—C15—O15	178.89 (17)	C33—C34—C35—O35	-179.81 (18)
O14—C14—C15—C16	174.79 (17)	O34—C34—C35—C36	175.76 (18)
C13—C14—C15—C16	-1.2 (3)	C33—C34—C35—C36	0.0 (3)
O15—C15—C16—C11	-178.80 (18)	C32—C31—C36—C35	0.6 (3)
C14—C15—C16—C11	1.3 (3)	C22—C31—C36—C35	179.06 (18)
C12—C11—C16—C15	0.1 (3)	O35—C35—C36—C31	178.90 (19)

C2—C11—C16—C15 -177.44 (17) C34—C35—C36—C31 -0.9 (3)

Hydrogen-bond geometry (Å, °)

<i>D</i> —H··· <i>A</i>	<i>D</i> —H	H··· <i>A</i>	<i>D</i> ··· <i>A</i>	<i>D</i> —H··· <i>A</i>
O5—H5···O4	0.89 (3)	1.75 (3)	2.595 (2)	159 (3)
O25—H25···O24	0.96 (3)	1.68 (3)	2.591 (2)	155 (3)

(5*R*,8*R*,9*R*,10*R*,13*R*,14*R*,17*S*)-17-[(2*S*,5*R*)-5-(2-Hydroxypropan-2-yl)-2-methyloxolan-2-yl]-4,4,8,10,14-pentamethyl-1,2,5,6,7,9,11,12,13,15,16,17-dodecahydrocyclopenta[*a*]phenanthren-3-one (3)

Crystal data

C₃₀H₅₀O₃

M_r = 458.70

Orthorhombic, *P*2₁2₁2₁

a = 6.37386 (6) Å

b = 12.10746 (11) Å

c = 33.8928 (3) Å

V = 2615.55 (4) Å³

Z = 4

F(000) = 1016

D_x = 1.165 Mg m⁻³

Cu *Kα* radiation, λ = 1.54184 Å

Cell parameters from 21446 reflections

θ = 2.6–76.2°

μ = 0.56 mm⁻¹

T = 160 K

Plate, colourless

0.24 × 0.19 × 0.05 mm

Data collection

Oxford Diffraction SuperNova dual radiation diffractometer

Radiation source: micro-focus sealed X-ray tube, SuperNova (Cu) X-ray source

Mirror monochromator

Detector resolution: 10.3801 pixels mm⁻¹

ω scans

Absorption correction: gaussian

Numerical absorption correction based on gaussian integration over a multifaceted crystal model (Coppens *et al.*, 1965) plus an empirical (using intensity measurements) absorption correction using spherical harmonics (CrysAlis PRO; Rigaku Oxford Diffraction, 2021)

T_{min} = 0.614, *T_{max}* = 1.000

26797 measured reflections

5424 independent reflections

5324 reflections with *I* > 2σ(*I*)

R_{int} = 0.018

θ_{max} = 76.3°, θ_{min} = 2.6°

h = -7→7

k = -12→15

l = -42→39

Refinement

Refinement on *F*²

Least-squares matrix: full

R[*F*² > 2σ(*F*²)] = 0.032

wR(*F*²) = 0.089

S = 1.03

5424 reflections

310 parameters

0 restraints

Primary atom site location: dual

Secondary atom site location: difference Fourier map

Hydrogen site location: inferred from neighbouring sites

H atoms treated by a mixture of independent and constrained refinement

w = 1/[σ²(*F_o*²) + (0.0576*P*)² + 0.4171*P*]

where *P* = (*F_o*² + 2*F_c*²)/3

(Δ/σ)_{max} = 0.001

Δρ_{max} = 0.23 e Å⁻³

Δρ_{min} = -0.14 e Å⁻³

Absolute structure: Flack *x* determined using 2226 quotients [(*I*⁺)-(*I*⁻)]/[(*I*⁺)+(*I*⁻)] (Parsons *et al.*, 2013)

Absolute structure parameter: -0.07 (4)

Special details

Experimental. Data collection and full structure determination done by Prof. Anthony Linden:

anthony.linden@chem.uzh.ch

Solvent used: dichloromethane / MeOH Cooling Device: Oxford Instruments Cryojet XL Crystal mount: on a cryo-loop

Frames collected: 2026 Seconds exposure per frame: 3.5-14.0 Degrees rotation per frame: 0.8 Crystal-detector distance (mm): 52.0 Client: Placide Toklo Sample code: CCG3 (L2101)

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (\AA^2)

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{iso}}^*/U_{\text{eq}}$
O3	0.0614 (2)	0.56528 (11)	0.76377 (4)	0.0366 (3)
O20	0.68894 (19)	0.47972 (9)	0.43024 (3)	0.0267 (2)
O25	0.5723 (2)	0.56885 (11)	0.33129 (4)	0.0383 (3)
H25	0.523 (5)	0.533 (2)	0.3098 (9)	0.064 (8)*
C1	0.3227 (3)	0.65364 (12)	0.67560 (4)	0.0237 (3)
H11	0.372968	0.724695	0.664664	0.028*
H12	0.195700	0.631884	0.660685	0.028*
C2	0.2636 (3)	0.67035 (13)	0.71904 (5)	0.0272 (3)
H21	0.383434	0.705011	0.732882	0.033*
H22	0.143704	0.722196	0.720494	0.033*
C3	0.2054 (2)	0.56533 (13)	0.74025 (4)	0.0236 (3)
C4	0.3385 (2)	0.46238 (13)	0.73290 (4)	0.0226 (3)
C5	0.4116 (2)	0.45682 (12)	0.68894 (4)	0.0188 (3)
H5	0.281213	0.438591	0.673871	0.023*
C6	0.5604 (3)	0.35971 (13)	0.68050 (4)	0.0260 (3)
H61	0.703880	0.378314	0.689480	0.031*
H62	0.512931	0.293418	0.695096	0.031*
C7	0.5619 (3)	0.33575 (12)	0.63620 (4)	0.0252 (3)
H71	0.419165	0.313371	0.627931	0.030*
H72	0.657416	0.272910	0.631022	0.030*
C8	0.6320 (2)	0.43510 (12)	0.61106 (4)	0.0185 (3)
C9	0.5085 (2)	0.54127 (12)	0.62390 (4)	0.0185 (3)
H9	0.360501	0.527212	0.615499	0.022*
C10	0.4939 (2)	0.56510 (12)	0.66945 (4)	0.0195 (3)
C11	0.5794 (3)	0.64105 (12)	0.59911 (5)	0.0294 (4)
H111	0.500748	0.707373	0.607671	0.035*
H112	0.730310	0.654847	0.603899	0.035*
C12	0.5438 (3)	0.62294 (13)	0.55480 (5)	0.0301 (4)
H121	0.391393	0.619297	0.549339	0.036*
H122	0.602645	0.686024	0.539868	0.036*
C13	0.6481 (2)	0.51636 (12)	0.54125 (4)	0.0200 (3)
H13	0.802446	0.525914	0.545313	0.024*
C14	0.5806 (2)	0.41520 (11)	0.56615 (4)	0.0180 (3)
C15	0.7030 (3)	0.32294 (13)	0.54484 (4)	0.0260 (3)

H151	0.637064	0.250069	0.549519	0.031*
H152	0.850337	0.320332	0.554027	0.031*
C16	0.6918 (3)	0.35461 (12)	0.50053 (5)	0.0259 (3)
H161	0.591387	0.306133	0.486510	0.031*
H162	0.831463	0.346643	0.488066	0.031*
C17	0.6177 (2)	0.47688 (12)	0.49860 (4)	0.0210 (3)
H17	0.463304	0.475829	0.493403	0.025*
C18	0.8707 (2)	0.44709 (17)	0.61720 (5)	0.0308 (4)
H181	0.942299	0.382284	0.606306	0.046*
H182	0.901022	0.452861	0.645468	0.046*
H183	0.920345	0.513756	0.603717	0.046*
C19	0.7012 (3)	0.60844 (15)	0.68675 (5)	0.0301 (4)
H191	0.674285	0.643034	0.712398	0.045*
H192	0.762195	0.663044	0.668751	0.045*
H193	0.799351	0.546840	0.690139	0.045*
C20	0.7195 (3)	0.54464 (13)	0.46553 (4)	0.0235 (3)
C21	0.9537 (3)	0.56494 (16)	0.47150 (5)	0.0335 (4)
H211	1.025188	0.494256	0.475736	0.050*
H212	0.974672	0.612534	0.494551	0.050*
H213	1.011747	0.601056	0.448031	0.050*
C22	0.6000 (3)	0.65290 (14)	0.45674 (5)	0.0332 (4)
H221	0.458482	0.651127	0.468784	0.040*
H222	0.677386	0.717209	0.467389	0.040*
C23	0.5841 (5)	0.66006 (16)	0.41220 (6)	0.0493 (6)
H231	0.663996	0.724317	0.402167	0.059*
H232	0.435919	0.667410	0.403866	0.059*
C24	0.6782 (3)	0.55194 (14)	0.39679 (5)	0.0290 (3)
H241	0.824204	0.566913	0.387394	0.035*
C25	0.5587 (3)	0.49359 (14)	0.36403 (5)	0.0287 (3)
C26	0.6673 (5)	0.38558 (18)	0.35407 (6)	0.0534 (6)
H261	0.599919	0.352188	0.330977	0.080*
H262	0.656627	0.335036	0.376565	0.080*
H263	0.815451	0.399764	0.348232	0.080*
C27	0.3300 (4)	0.4732 (2)	0.37400 (8)	0.0544 (6)
H271	0.258291	0.544080	0.377597	0.082*
H272	0.320624	0.430056	0.398405	0.082*
H273	0.263273	0.432252	0.352442	0.082*
C28	0.5200 (3)	0.46709 (16)	0.76308 (5)	0.0309 (4)
H281	0.593564	0.537809	0.760579	0.046*
H282	0.618130	0.406468	0.757973	0.046*
H283	0.463258	0.459995	0.789841	0.046*
C29	0.2025 (3)	0.36060 (14)	0.74188 (5)	0.0319 (4)
H291	0.158615	0.362360	0.769587	0.048*
H292	0.284021	0.293369	0.736939	0.048*
H293	0.078292	0.361165	0.724853	0.048*
C30	0.3448 (3)	0.39001 (14)	0.55941 (5)	0.0263 (3)
H301	0.261228	0.455077	0.566392	0.039*
H302	0.302654	0.327509	0.575989	0.039*

H303 0.321528 0.371522 0.531607 0.039*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O3	0.0359 (7)	0.0451 (7)	0.0287 (6)	0.0077 (6)	0.0136 (5)	0.0054 (5)
O20	0.0382 (6)	0.0251 (5)	0.0169 (5)	0.0019 (5)	0.0004 (4)	-0.0011 (4)
O25	0.0547 (8)	0.0376 (7)	0.0226 (6)	0.0011 (6)	-0.0077 (6)	0.0024 (5)
C1	0.0317 (8)	0.0195 (6)	0.0199 (7)	0.0031 (6)	0.0060 (6)	-0.0006 (5)
C2	0.0343 (8)	0.0239 (7)	0.0234 (7)	0.0028 (6)	0.0078 (6)	-0.0038 (6)
C3	0.0241 (7)	0.0305 (8)	0.0163 (6)	0.0013 (6)	-0.0005 (5)	-0.0011 (6)
C4	0.0245 (7)	0.0264 (7)	0.0168 (6)	0.0006 (6)	0.0012 (5)	0.0014 (5)
C5	0.0186 (6)	0.0201 (6)	0.0178 (6)	0.0000 (6)	-0.0001 (5)	-0.0002 (5)
C6	0.0311 (8)	0.0257 (7)	0.0211 (7)	0.0097 (7)	0.0024 (6)	0.0030 (6)
C7	0.0347 (8)	0.0185 (6)	0.0225 (7)	0.0059 (6)	0.0046 (6)	0.0011 (5)
C8	0.0170 (6)	0.0196 (6)	0.0189 (6)	0.0017 (5)	0.0028 (5)	-0.0014 (5)
C9	0.0203 (6)	0.0175 (6)	0.0176 (6)	-0.0008 (5)	0.0027 (5)	-0.0021 (5)
C10	0.0196 (7)	0.0209 (7)	0.0181 (6)	-0.0015 (5)	0.0020 (5)	-0.0027 (5)
C11	0.0472 (10)	0.0175 (7)	0.0235 (7)	-0.0024 (7)	0.0129 (7)	-0.0023 (5)
C12	0.0482 (10)	0.0186 (7)	0.0234 (7)	0.0055 (7)	0.0114 (7)	0.0017 (6)
C13	0.0224 (7)	0.0182 (6)	0.0194 (6)	-0.0010 (5)	0.0046 (5)	-0.0018 (5)
C14	0.0179 (6)	0.0157 (6)	0.0204 (7)	0.0003 (5)	0.0031 (5)	-0.0018 (5)
C15	0.0341 (9)	0.0201 (7)	0.0237 (7)	0.0054 (6)	0.0046 (6)	-0.0030 (5)
C16	0.0328 (8)	0.0215 (7)	0.0234 (7)	0.0005 (6)	0.0055 (6)	-0.0044 (6)
C17	0.0219 (7)	0.0219 (7)	0.0193 (6)	-0.0005 (5)	0.0030 (6)	-0.0022 (5)
C18	0.0179 (7)	0.0494 (10)	0.0250 (7)	0.0034 (7)	0.0004 (6)	-0.0054 (7)
C19	0.0262 (8)	0.0373 (8)	0.0269 (8)	-0.0104 (7)	0.0022 (6)	-0.0084 (7)
C20	0.0279 (8)	0.0245 (7)	0.0180 (7)	-0.0018 (6)	0.0032 (6)	-0.0026 (6)
C21	0.0301 (8)	0.0444 (10)	0.0260 (8)	-0.0102 (8)	0.0050 (7)	0.0010 (7)
C22	0.0457 (10)	0.0271 (8)	0.0267 (8)	0.0041 (7)	0.0080 (7)	0.0026 (6)
C23	0.0884 (17)	0.0286 (9)	0.0307 (9)	0.0071 (10)	-0.0128 (11)	-0.0005 (7)
C24	0.0321 (8)	0.0325 (8)	0.0222 (7)	-0.0033 (7)	0.0006 (6)	0.0030 (6)
C25	0.0342 (9)	0.0297 (8)	0.0222 (7)	0.0034 (7)	-0.0024 (6)	0.0005 (6)
C26	0.0894 (18)	0.0405 (10)	0.0302 (9)	0.0235 (12)	-0.0139 (11)	-0.0088 (8)
C27	0.0383 (11)	0.0647 (14)	0.0602 (13)	-0.0147 (11)	-0.0085 (10)	0.0096 (11)
C28	0.0330 (8)	0.0396 (9)	0.0200 (7)	0.0043 (7)	-0.0051 (6)	0.0002 (6)
C29	0.0398 (9)	0.0293 (8)	0.0266 (8)	-0.0041 (7)	0.0085 (7)	0.0037 (6)
C30	0.0215 (7)	0.0348 (8)	0.0226 (7)	-0.0082 (6)	0.0015 (6)	-0.0029 (6)

Geometric parameters (Å, °)

O3—C3	1.216 (2)	C15—H151	0.9900
O20—C24	1.4334 (19)	C15—H152	0.9900
O20—C20	1.4446 (17)	C16—C17	1.555 (2)
O25—C25	1.439 (2)	C16—H161	0.9900
O25—H25	0.90 (3)	C16—H162	0.9900
C1—C2	1.533 (2)	C17—C20	1.533 (2)
C1—C10	1.544 (2)	C17—H17	1.0000

C1—H11	0.9900	C18—H181	0.9800
C1—H12	0.9900	C18—H182	0.9800
C2—C3	1.507 (2)	C18—H183	0.9800
C2—H21	0.9900	C19—H191	0.9800
C2—H22	0.9900	C19—H192	0.9800
C3—C4	1.528 (2)	C19—H193	0.9800
C4—C29	1.537 (2)	C20—C21	1.527 (2)
C4—C28	1.545 (2)	C20—C22	1.545 (2)
C4—C5	1.5627 (19)	C21—H211	0.9800
C5—C6	1.537 (2)	C21—H212	0.9800
C5—C10	1.5589 (19)	C21—H213	0.9800
C5—H5	1.0000	C22—C23	1.515 (2)
C6—C7	1.529 (2)	C22—H221	0.9900
C6—H61	0.9900	C22—H222	0.9900
C6—H62	0.9900	C23—C24	1.532 (3)
C7—C8	1.540 (2)	C23—H231	0.9900
C7—H71	0.9900	C23—H232	0.9900
C7—H72	0.9900	C24—C25	1.520 (2)
C8—C18	1.542 (2)	C24—H241	1.0000
C8—C9	1.5691 (19)	C25—C27	1.517 (3)
C8—C14	1.5756 (19)	C25—C26	1.518 (3)
C9—C11	1.539 (2)	C26—H261	0.9800
C9—C10	1.5731 (18)	C26—H262	0.9800
C9—H9	1.0000	C26—H263	0.9800
C10—C19	1.538 (2)	C27—H271	0.9800
C11—C12	1.534 (2)	C27—H272	0.9800
C11—H111	0.9900	C27—H273	0.9800
C11—H112	0.9900	C28—H281	0.9800
C12—C13	1.523 (2)	C28—H282	0.9800
C12—H121	0.9900	C28—H283	0.9800
C12—H122	0.9900	C29—H291	0.9800
C13—C17	1.5346 (19)	C29—H292	0.9800
C13—C14	1.5484 (19)	C29—H293	0.9800
C13—H13	1.0000	C30—H301	0.9800
C14—C15	1.5421 (19)	C30—H302	0.9800
C14—C30	1.550 (2)	C30—H303	0.9800
C15—C16	1.551 (2)		
C24—O20—C20	109.23 (12)	C15—C16—H161	110.4
C25—O25—H25	107.1 (19)	C17—C16—H161	110.4
C2—C1—C10	113.27 (13)	C15—C16—H162	110.4
C2—C1—H11	108.9	C17—C16—H162	110.4
C10—C1—H11	108.9	H161—C16—H162	108.6
C2—C1—H12	108.9	C20—C17—C13	117.94 (12)
C10—C1—H12	108.9	C20—C17—C16	114.31 (12)
H11—C1—H12	107.7	C13—C17—C16	102.63 (12)
C3—C2—C1	114.03 (13)	C20—C17—H17	107.1
C3—C2—H21	108.7	C13—C17—H17	107.1

C1—C2—H21	108.7	C16—C17—H17	107.1
C3—C2—H22	108.7	C8—C18—H181	109.5
C1—C2—H22	108.7	C8—C18—H182	109.5
H21—C2—H22	107.6	H181—C18—H182	109.5
O3—C3—C2	119.93 (15)	C8—C18—H183	109.5
O3—C3—C4	121.69 (15)	H181—C18—H183	109.5
C2—C3—C4	118.30 (13)	H182—C18—H183	109.5
C3—C4—C29	107.99 (13)	C10—C19—H191	109.5
C3—C4—C28	106.12 (13)	C10—C19—H192	109.5
C29—C4—C28	108.70 (13)	H191—C19—H192	109.5
C3—C4—C5	110.85 (12)	C10—C19—H193	109.5
C29—C4—C5	108.81 (12)	H191—C19—H193	109.5
C28—C4—C5	114.18 (13)	H192—C19—H193	109.5
C6—C5—C10	110.90 (12)	O20—C20—C21	109.20 (13)
C6—C5—C4	113.21 (12)	O20—C20—C17	104.91 (12)
C10—C5—C4	117.92 (12)	C21—C20—C17	113.77 (13)
C6—C5—H5	104.4	O20—C20—C22	103.63 (12)
C10—C5—H5	104.4	C21—C20—C22	111.79 (15)
C4—C5—H5	104.4	C17—C20—C22	112.74 (13)
C7—C6—C5	109.37 (12)	C20—C21—H211	109.5
C7—C6—H61	109.8	C20—C21—H212	109.5
C5—C6—H61	109.8	H211—C21—H212	109.5
C7—C6—H62	109.8	C20—C21—H213	109.5
C5—C6—H62	109.8	H211—C21—H213	109.5
H61—C6—H62	108.2	H212—C21—H213	109.5
C6—C7—C8	113.39 (13)	C23—C22—C20	105.87 (14)
C6—C7—H71	108.9	C23—C22—H221	110.6
C8—C7—H71	108.9	C20—C22—H221	110.6
C6—C7—H72	108.9	C23—C22—H222	110.6
C8—C7—H72	108.9	C20—C22—H222	110.6
H71—C7—H72	107.7	H221—C22—H222	108.7
C7—C8—C18	106.56 (13)	C22—C23—C24	105.36 (15)
C7—C8—C9	109.92 (11)	C22—C23—H231	110.7
C18—C8—C9	112.36 (12)	C24—C23—H231	110.7
C7—C8—C14	110.77 (12)	C22—C23—H232	110.7
C18—C8—C14	110.49 (12)	C24—C23—H232	110.7
C9—C8—C14	106.79 (11)	H231—C23—H232	108.8
C11—C9—C8	110.13 (11)	O20—C24—C25	108.54 (13)
C11—C9—C10	114.16 (12)	O20—C24—C23	105.68 (13)
C8—C9—C10	116.89 (11)	C25—C24—C23	116.75 (16)
C11—C9—H9	104.8	O20—C24—H241	108.5
C8—C9—H9	104.8	C25—C24—H241	108.5
C10—C9—H9	104.8	C23—C24—H241	108.5
C19—C10—C1	108.60 (13)	O25—C25—C27	109.45 (16)
C19—C10—C5	114.48 (13)	O25—C25—C26	110.28 (15)
C1—C10—C5	106.80 (12)	C27—C25—C26	110.3 (2)
C19—C10—C9	112.69 (12)	O25—C25—C24	103.81 (14)
C1—C10—C9	107.56 (11)	C27—C25—C24	113.24 (16)

C5—C10—C9	106.35 (11)	C26—C25—C24	109.54 (15)
C12—C11—C9	112.27 (13)	C25—C26—H261	109.5
C12—C11—H111	109.2	C25—C26—H262	109.5
C9—C11—H111	109.2	H261—C26—H262	109.5
C12—C11—H112	109.2	C25—C26—H263	109.5
C9—C11—H112	109.2	H261—C26—H263	109.5
H111—C11—H112	107.9	H262—C26—H263	109.5
C13—C12—C11	110.60 (14)	C25—C27—H271	109.5
C13—C12—H121	109.5	C25—C27—H272	109.5
C11—C12—H121	109.5	H271—C27—H272	109.5
C13—C12—H122	109.5	C25—C27—H273	109.5
C11—C12—H122	109.5	H271—C27—H273	109.5
H121—C12—H122	108.1	H272—C27—H273	109.5
C12—C13—C17	119.54 (13)	C4—C28—H281	109.5
C12—C13—C14	112.62 (12)	C4—C28—H282	109.5
C17—C13—C14	103.40 (11)	H281—C28—H282	109.5
C12—C13—H13	106.9	C4—C28—H283	109.5
C17—C13—H13	106.9	H281—C28—H283	109.5
C14—C13—H13	106.9	H282—C28—H283	109.5
C15—C14—C13	100.20 (11)	C4—C29—H291	109.5
C15—C14—C30	106.20 (12)	C4—C29—H292	109.5
C13—C14—C30	110.17 (12)	H291—C29—H292	109.5
C15—C14—C8	117.25 (12)	C4—C29—H293	109.5
C13—C14—C8	110.34 (11)	H291—C29—H293	109.5
C30—C14—C8	111.97 (12)	H292—C29—H293	109.5
C14—C15—C16	104.54 (12)	C14—C30—H301	109.5
C14—C15—H151	110.8	C14—C30—H302	109.5
C16—C15—H151	110.8	H301—C30—H302	109.5
C14—C15—H152	110.8	C14—C30—H303	109.5
C16—C15—H152	110.8	H301—C30—H303	109.5
H151—C15—H152	108.9	H302—C30—H303	109.5
C15—C16—C17	106.85 (12)		
C10—C1—C2—C3	-52.7 (2)	C17—C13—C14—C15	47.73 (14)
C1—C2—C3—O3	-140.65 (16)	C12—C13—C14—C30	66.56 (17)
C1—C2—C3—C4	42.4 (2)	C17—C13—C14—C30	-63.86 (14)
O3—C3—C4—C29	27.4 (2)	C12—C13—C14—C8	-57.59 (17)
C2—C3—C4—C29	-155.70 (14)	C17—C13—C14—C8	171.99 (11)
O3—C3—C4—C28	-88.97 (19)	C7—C8—C14—C15	-67.19 (16)
C2—C3—C4—C28	87.89 (17)	C18—C8—C14—C15	50.65 (18)
O3—C3—C4—C5	146.54 (15)	C9—C8—C14—C15	173.13 (12)
C2—C3—C4—C5	-36.60 (19)	C7—C8—C14—C13	179.01 (12)
C3—C4—C5—C6	175.52 (13)	C18—C8—C14—C13	-63.14 (16)
C29—C4—C5—C6	-65.86 (16)	C9—C8—C14—C13	59.34 (14)
C28—C4—C5—C6	55.75 (18)	C7—C8—C14—C30	55.91 (16)
C3—C4—C5—C10	43.72 (17)	C18—C8—C14—C30	173.76 (13)
C29—C4—C5—C10	162.33 (13)	C9—C8—C14—C30	-63.76 (15)
C28—C4—C5—C10	-76.06 (17)	C13—C14—C15—C16	-37.61 (15)

C10—C5—C6—C7	-64.66 (17)	C30—C14—C15—C16	77.04 (15)
C4—C5—C6—C7	160.17 (13)	C8—C14—C15—C16	-156.95 (13)
C5—C6—C7—C8	58.91 (18)	C14—C15—C16—C17	14.67 (16)
C6—C7—C8—C18	73.02 (16)	C12—C13—C17—C20	68.69 (18)
C6—C7—C8—C9	-48.98 (17)	C14—C13—C17—C20	-165.19 (12)
C6—C7—C8—C14	-166.76 (13)	C12—C13—C17—C16	-164.70 (13)
C7—C8—C9—C11	179.51 (13)	C14—C13—C17—C16	-38.58 (14)
C18—C8—C9—C11	61.03 (17)	C15—C16—C17—C20	143.52 (13)
C14—C8—C9—C11	-60.27 (15)	C15—C16—C17—C13	14.60 (16)
C7—C8—C9—C10	47.09 (16)	C24—O20—C20—C21	-86.45 (16)
C18—C8—C9—C10	-71.39 (16)	C24—O20—C20—C17	151.25 (13)
C14—C8—C9—C10	167.31 (12)	C24—O20—C20—C22	32.81 (16)
C2—C1—C10—C19	-68.02 (17)	C13—C17—C20—O20	172.24 (12)
C2—C1—C10—C5	55.92 (17)	C16—C17—C20—O20	51.50 (16)
C2—C1—C10—C9	169.75 (12)	C13—C17—C20—C21	52.95 (18)
C6—C5—C10—C19	-65.98 (16)	C16—C17—C20—C21	-67.79 (17)
C4—C5—C10—C19	66.85 (17)	C13—C17—C20—C22	-75.68 (17)
C6—C5—C10—C1	173.79 (12)	C16—C17—C20—C22	163.58 (13)
C4—C5—C10—C1	-53.38 (16)	O20—C20—C22—C23	-21.93 (19)
C6—C5—C10—C9	59.14 (15)	C21—C20—C22—C23	95.54 (19)
C4—C5—C10—C9	-168.02 (12)	C17—C20—C22—C23	-134.80 (17)
C11—C9—C10—C19	-56.11 (18)	C20—C22—C23—C24	4.5 (2)
C8—C9—C10—C19	74.46 (16)	C20—O20—C24—C25	-156.38 (13)
C11—C9—C10—C1	63.56 (16)	C20—O20—C24—C23	-30.43 (19)
C8—C9—C10—C1	-165.87 (12)	C22—C23—C24—O20	14.8 (2)
C11—C9—C10—C5	177.68 (13)	C22—C23—C24—C25	135.56 (18)
C8—C9—C10—C5	-51.75 (15)	O20—C24—C25—O25	-175.45 (13)
C8—C9—C11—C12	59.20 (18)	C23—C24—C25—O25	65.33 (19)
C10—C9—C11—C12	-166.99 (14)	O20—C24—C25—C27	65.9 (2)
C9—C11—C12—C13	-54.3 (2)	C23—C24—C25—C27	-53.3 (2)
C11—C12—C13—C17	175.09 (14)	O20—C24—C25—C26	-57.7 (2)
C11—C12—C13—C14	53.44 (19)	C23—C24—C25—C26	-176.89 (18)
C12—C13—C14—C15	178.15 (14)		

Hydrogen-bond geometry (Å, °)

<i>D</i> —H... <i>A</i>	<i>D</i> —H	H... <i>A</i>	<i>D</i> ... <i>A</i>	<i>D</i> —H... <i>A</i>
O25—H25...O3 ⁱ	0.90 (3)	2.03 (3)	2.9325 (18)	172 (3)

Symmetry code: (i) $-x+1/2, -y+1, z-1/2$.