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ABIETANE AND ICETEXANE DITERPENOIDS FROM THE ROOTS OF *SALVIA ASPERA*

BALDOMERO ESQUIVEL,* MARGARITA FLORES, SIMÓN HERNÁNDEZ-ORTEGA, R. A. TOSCANO and T. P. RAMAMOORTHY

Instituto de Química de la Universidad Nacional Autónoma de México. Circuito Exterior, Cd. Universitaria, Coyoacán 04510, México, D.F.

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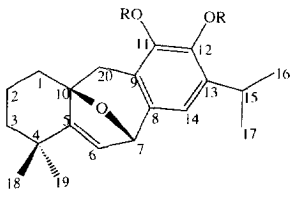
Key Word Index—*Salvia aspera*; Labiatae; roots; icetexane and abietane diterpenoids; salviasperanol; 5,6-dihydro-6α-hydroxysalviasperanol; 6-epi-demethylesquirolin D.

Abstract—From the roots of *Salvia aspera*, two new icetexane diterpenoids (salviasperanol and 5,6-dihidro-6α-hydroxysalviasperanol) and one new abietane derivative (6-epi-demethylesquirolin D) were isolated in addition to the previously known diterpenoids sugiol, taxodione and demethylsalvicanol. The structures of the new compounds were established by spectroscopic means. An X-ray analysis was performed on salviasperanol.

INTRODUCTION

The phytochemical study of the aerial parts of several species of *Salvia*, subgenus Calosphace, led to the isolation of a number of diterpenes mainly of the neoclerodane type in more than the 80% of the species studied [1]. Some abietane and icetexane type diterpenoids have been isolated from spp. belonging to Section Erythrostachys and Tomentellae [2, 3]. On the other hand, phytochemical studies of the aerial parts and roots of European and Asiatic *Salvia* spp. led to the isolation of a number of diterpenoids with an abietane skeleton in almost 100% of the species studied. While the chemical composition of the roots of several European and Asiatic salvias is known and the presence of abietane quinones in the roots of these plants has been postulated as a chemotaxonomic character of the genus [4], the content of the roots of American salvias is poorly documented. As a part of our continuing systematic study of the genus, we have undertaken the analysis of the roots of Mexican *Salvia* spp.. In this paper we report on the diterpenoid content of the roots of *Salvia aspera* M. *et* G., a shrub placed in the section Conzattiana of the subgenus Calosphace [5].



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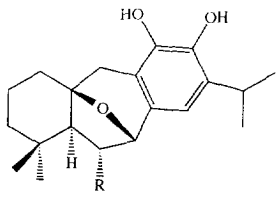
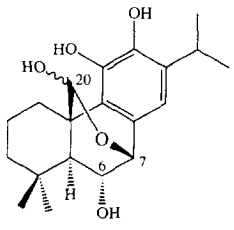
6 R = Ac

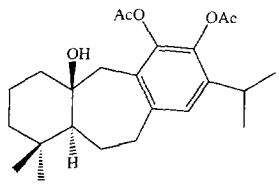


2 R = OH

5 R = H



3 (20*R*)



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RESULTS AND DISCUSSION

Extraction of the roots of *S. aspera* afforded, after extensive chromatographic purification, the previously known abietane-type diterpenoids sugiol [6] and taxodione [7]. The icetexane diterpenoid demethylsalvicanol [8] was isolated as its diacetyl derivative **4**. In addition, we isolated two new icetexane and one new abietane diterpenoids to which we assigned the structures **1**–**3** on the basis of the following considerations.

Compound **1** ($C_{20}H_{26}O_3$, MS), named salviasperanol, showed IR bands for phenolic groups (3500, 3420 cm^{-1}) and aromatic double bonds (1620 cm^{-1}). The ^1H NMR spectrum (Table 1) showed signals for two secondary

*Author to whom correspondence should be addressed.

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Table 1. ^{1}H NMR spectral data for compounds **1**–**3** and **5**, **6** ($CDCl_3$, 200 MHz)

H	1*	2	3†	5	6‡
6	6.04 *dd*	4.30 *t*	4.03 *t*	2.33 *ddd*	6.02 *d*
	(2.1, 0.8)	(6.2)	(4.4)	(11.4, 9.7, 7.7)	(2)
6α	—	—	—	1.44 *dt*	—
				(11.4, 2.5)	
7	5.07 *d*	4.72 *d*	4.63 *d*	4.92 *dd*	5.15 *d*
	(2.1)	(6.2)	(4.4)	(7.7, 2.5)	(2)
14	6.43 *s*	6.54 *s*	6.73 *s*	6.41 *s*	6.8 *s*
15	3.08 *hept*	3.12 *hept*	3.27 *quint*	3.08 *quint*	2.95 *quint*
	(6.8)	(6.8)	(6.8)	(7)	(6)
3H-16	1.24 *d*	1.24 *d*	1.21 *d*	1.23 *d*	1.2 *d*
	(6.8)	(6.8)	(6.8)	(7)	(6)
3H-17	1.30 *d*	1.23 *d*	1.20 *d*	1.22 *d*	1.15 *d*
	(6.8)	(6.8)	(6.8)	(7)	(6)
3H-18	1.02 *s*	1.03 *s*	1.06 *s*	0.93 *s*	1.15 *s*
3H-19	1.12 *s*	1.01 *s*	1.04 *s*	0.91 *s*	1.0 *s*
20A	2.88 *d*	2.76 *d*	5.36 *s*	3.16 *d*	2.75 *d*
	(16.5)	(16)		(17.6)	(16)
20B	2.65 *d*	2.43 *d*		2.69 *d*	2.5 *d*
	(16.5)	(16)		(17.6)	(16)
OAc					2.30 *s*§
R-OH	5.12 *br s*	5.2 *br s*	6.75 *br s*	5.0 *br s*	—
	5.35 *br s*	5.25 *br s*	7.45 *br s*	5.2 *br s*	

*Assignments confirmed by ^{1}H–^{1}H 2D COSY spectra.
†Run in $CDCl_3$–DMSO-d_6 (4:1) solution.
‡Run at 80 MHz.
§Six protons intensity.

methyl groups at δ1.24 (*d*, J = 6.8 Hz) and δ1.30 (*d*), coupled with a proton responsible of an heptuplet at δ3.08 (J = 6.8 Hz). These signals indicated the presence of an aromatic isopropyl group. A singlet at δ6.43 was ascribed to one aromatic proton and two broad singlets, exchangeable with D_2O, at δ5.12 and δ5.35, were assigned to two hydroxy phenol groups. These data indicated the presence of a pentasubstituted aromatic ring in **1**, similar to that present in demethylsalvicanol [8]. The ^{13}C NMR spectrum (Table 2) was in agreement with this conclusion and also showed signals for four methylene groups at δ38.6 (C-1), 19.0 (C-2), 40.0 (C-3), 30.2 (C-20) and only two additional methyl groups at δ29.9 (C-18) and 27.7 (C-19) indicating an icetexane type skeleton for salviasperanol (**1**) [3, 9]. That **1** possesses a trisubstituted double bond was deduced from the presence of two additional sp^2 carbon atoms in the ^{13}C NMR spectrum; a singlet (δ149.5) and a doublet (δ128.3), ascribed to C-5 and C-6, respectively. A double doublet, observed in the ^{1}H NMR spectrum of **1** (Table 1), at δ6.04 was assigned to the olefinic proton H-6. Homonuclear 2D COSY experiments indicated that H-6 is longe-range coupled (J = 0.8 Hz) with a complex signal at δ2.1 ascribed to H-1β by HETCOR experiments and with a doublet at δ5.07 (J = 2.1 Hz) which was ascribed to the geminal proton of an ethereal function. The chemical shift of this signal indicated a benzylic and allylic nature for this proton and was assigned to H-7. The ethereal function present in **1** must be cyclic, as indicated by its molecular formula. In the ^{13}C NMR spectrum of **1** (Table 2) two signals due to oxygenated sp^3 carbon atoms were observed, a doublet at δ79.9 ascribed to C-7 and a singlet at δ83.75, assigned to C-10.

The structure proposed for **1** was confirmed by X-ray diffraction analysis. The computer generated perspective drawing of salviasperanol is shown in Fig. 1. The A ring in the structure of **1**, adopts a distorted chair conformation, flattened at C-5, the five- and six-membered heterocyclic ring exhibit envelope and sofa conformations respectively, having the oxygen atom O-1 as a common flap. The essentially planar aromatic ring is almost coplanar to the mean plane formed by the C-7, C-8, C-9, C-20 and C-10 atoms of the pirane moiety (angle between planes 3.5°). The isopropyl group is tilted, so that one of the methyl groups, C-16, lies nearly perpendicular (torsion angle C-14, C-13, C-15, C-16 = 99.4°) to the aromatic ring. Phenolic H-atoms are involved in the formation of intramolecular (O-3–H-3 → O-2: 2.15 Å) and intermolecular (O-2–H-2 → O-1: 1.97 Å) hydrogen bonds; the latter giving arise to formation of endless chains parallel to the (100) direction, responsible for the crystal packing. Figure 1 shows only the relative stereochemistry of salviasperanol, since attempts to obtain a suitable derivative for absolute stereochemistry determination were unsuccessful.

Catalytic hydrogenation of **1** was possible only when PtO_2 was used as catalyst. The ^{1}H NMR spectrum of the dihydro derivative **5** (Table 1) was in agreement with the

Table 2. ^{13}C NMR data for compounds **1**–**3** ($CDCl_3$, 50 MHz)*

C	1	2	3
1	38.6 *t*	29.6 *t*	29.3 *t*
2	19.0 *t*	15.2 *t*	18.2 *t*
3	40.0 *t*	39.0 *t*	40.9 *t*
4	33.6 *s*	31.3 *s*	33.5 *s*
5	149.5 *s*	58.1 *d*	56.3 *s*
6	128.3 *d*	77.9 *d*	68.9 *d*
7	79.9 *d*	78.4 *d*	73.7 *d*
8	131.4 *s*	126.6 *s*	128.7 *s*
9	117.0 *s*	117.3 *s*	122.1 *s*
10	83.8 *s*	80.5 *s*	46.8 *s*
11	142.6 *s*	142.3 *s*	143.2 *s*
12	139.9 *s*	140.6 *s*	142.9 *s*
13	131.0 *s*	132.3 *s*	133.9 *s*
14	112.1 *d*	115.7 *d*	115.7 *d*
15	27.0 *d*	27.2 *d*	26.7 *d*
16	22.4 *q*	22.6 *q*	22.5 *q*
17	22.8 *q*	22.6 *q*	22.4 *q*
18	29.9 *q*	30.1 *q*	33.2 *q*
19	27.7 *q*	27.8 *q*	22.9 *q*
20	30.2 *t*	30.4 *t*	91.0 *d*

*Multiplicities were determined by the DEPT pulse sequence.

Assignments were confirmed by the ^{1}H–^{13}C HETCOR spectra.

structure proposed for it. Acetylation of **1** yielded the oily derivative **6**. The IR spectrum of **6** showed the absence of hydroxyl absorptions and a band at 1770 cm^{-1} due to the aromatic acetate groups.

The mass spectrum of the second icetexane-type diterpenoid isolated from the roots of *S. aspera* was consistent with the molecular formula $C_{20}H_{28}O_4$. Structure **2** was proposed for it, based on spectroscopic data. Its IR spectrum showed bands for hydroxy phenolic groups (3693, 3604, 3551 cm^{-1}) and aromatic double bonds (1601, 1539 cm^{-1}). The ^{1}H and ^{13}C NMR spectra of **2** were similar to those of **1**, however, they revealed that it was devoid of the 5,6 double bond (Tables 1 and 2). A triplet observed at δ4.30 (J = 6.2 Hz) in the ^{1}H NMR spectrum of **2** was assigned to the geminal proton of an hydroxyl group. The coupling constant of this signal indicated an α orientation for this hydroxyl group, which was located at the C-6 position. This proton was coupled with H-7, the geminal proton of the ethereal ring, which was responsible for a doublet at δ4.72. The *trans* fusion depicted in **2** was established with the aid of the coupling constant (J = 6.2 Hz) found for H-6, and by comparison with related bicyclic systems [10]. On the basis of the above findings, **2** is 5,6-dihydro-6α-hydroxysalviasperanol.

The mass spectrum of **3** showed the molecular ion at m/z 348, consistent with a molecular formula $C_{20}H_{28}O_5$ and seven unsaturation units. The spectral data found for **3** indicated that this compound possessed an abietane-type skeleton. The ^{13}C NMR spectrum of **3** (Table 2) showed five singlets between δ122 and 143, and one doublet at δ115.7, indicating that four of these unsaturations corresponded to a pentasubstituted aromatic ring [8]. A singlet at δ6.73 in the ^{1}H NMR spectrum of **3** was ascribed to the aromatic H-14. The characteristic signals of an isopropyl group bound to an aromatic ring, as well as two broad singlets, exchangeable with D_2O, corresponding to the hydroxy phenolic groups at the C-11 and C-12 positions, were also observed in the ^{1}H NMR spectrum of **3** (Table 1). Two singlets at δ1.04 (3H) and 1.04 (3H) were ascribed to the C-18 and C-19 methyl groups. The angular methyl group (C-20), frequently found in abietane-type diterpenes, was not observed. A singlet at δ5.36 indicated that C-20 was part of a cyclic hemiketalic group closed to C-7. Therefore, a doublet at δ4.63 (J = 4.4 Hz) was ascribed to the geminal proton of

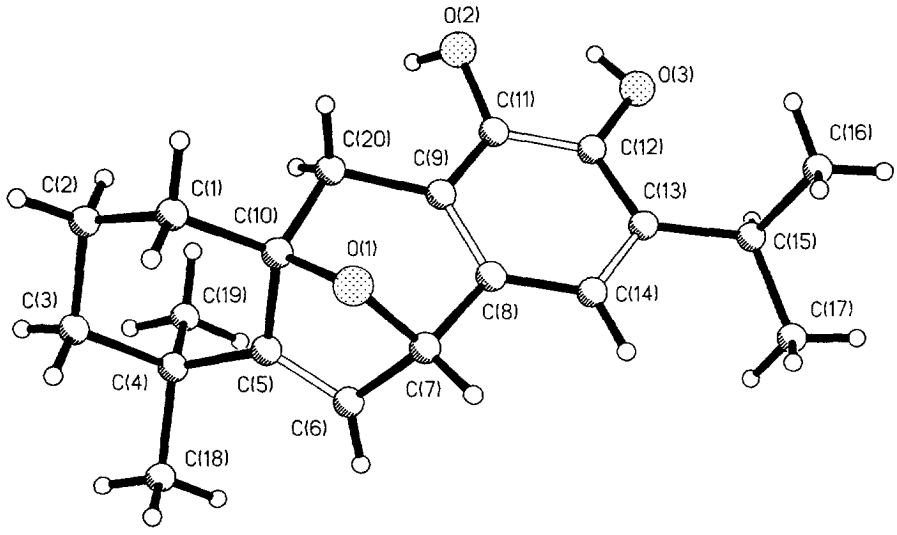

Fig. 1. Computer generated perspective drawing of salviasperanol (**1**), showing atom numbering.

the hemiketalic ring closure, i.e. H-7. It was coupled with a proton responsible of a triplet at δ4.03 (J = 4.4 Hz), ascribed to H-6, which must be bound to a carbon atom bearing an additional hydroxy group. The coupling constants of H-6 suggested an α-equatorial orientation for this hydroxy group and an α-axial orientation for H-5, as compared with the related compound 16-hydroxyisorosmanol [11]. The presence of three doublets at δ91.0 (C-20), 73.7 (C-7) and 68.9 (C-6) in the ^{13}C NMR spectrum of **3** was in agreement with the previous discussion (Table 2). The chemical shift of the C-19 methyl group (δ1.04) suggested a 20*R* configuration, i.e. the hydroxy group of the hemiketalic moiety points toward the C ring of **3**, otherwise an strong deshielding must be expected for this methyl group. A careful inspection of a Dreiding model of **3** supports this conclusion.

The structure of **3** is close to that proposed for esquirolin D, an abietane-type diterpenoid isolated from *Coleus eskirolii* [12]. However, in esquirolin D, a β orientation for the C-6 hydroxy group was proposed. The presence of an additional methyl group in the ketalic moiety of esquirolin D was not found in **3**. On the basis of the above findings **3** must be 6-epi-demethylesquirolin D.

Compounds **1**, **5** and **3** showed no lethal effects in the brine shrimp (*Artemia salina*). On the other hand **4** was active at 55 ppm.

It is of interest to note that from the aerial parts of *S. aspera* only tri-nor-dammarane triterpenoids and neoclerodane diterpenoids were isolated [13]. The presence of abietane and icetexane diterpenoids in the roots of *S. aspera* (subgenus Calosphace) could be of phytogeographical importance, since the same chemical profile have been found in the roots of *S. coulterii* [14], placed in the same subgenus, and from the roots of *S. apiana* [15], an American species belonging to the subgenus Audibertia and also from the roots of the European *S. canariensis* [16], placed in the subgenus *Salvia*. Abietane-derived diterpenoids have been also isolated from the roots of *S. lavanduloides* (personal communication from Dr Emma Maldonado, Instituto de Química UNAM), *S. fruticulosa* [17] and *S. melissodora* (Esquivel *et al.*, unpublished results), species also belonging to subgenus Calosphace [5].

EXPERIMENTAL

Mps: Uncorr.; EI-MS: 70 eV, direct inlet; UV, MeOH; ^{1}H NMR: 200 MHz, $CDCl_3$, unless noted otherwise; ^{13}C NMR: 50 MHz, $CDCl_3$, TMS as int. standard. Plant material was collected in the state of Puebla (México) and a voucher specimen (MEXU544950) is deposited in the herbarium of the Instituto de Biología de la UNAM.

Extraction, fractionation and isolation of the diterpenoids from the roots of Salvia aspera. Dried and powdered roots of *S. aspera* (1.506 kg) were extracted with Me_2CO for 4 days at room temp. The solvent was removed *in vacuo* to yield 62.7 g of a gummy residue which was partitioned between MeOH–H_2O (4:1) and C_6H_6–petrol (1:1). The aq. methanolic fraction was concd *in vacuo*, H_2O was added and the mixture was extracted with EtOAc. The organic phase was dried with Na_2SO_4 and the solvent removed to yield 25.9 g of a gum, which was subjected to vacuum chromatography over silica gel. Mixtures of petrol–EtOAc and EtOAc–MeOH of increasing polarity were used as eluents. From the fractions eluted with petrol–EtOAc (9:1) salviasperanol (**1**) (260 mg) was isolated. Some fractions eluted with petrol–EtOAc (9:1) were combined and purified by flash chromatography (CH_2Cl_2–Me_2CO, 24:1) to yield **2** (12 mg) as an amorphous powder. Some fractions eluted with petrol–EtOAc (6:4) were rechromatographed over silica gel, using mixtures of CH_2Cl_2 of increasing polarity as eluents, to yield 13 mg of clovandiol and 24 mg of **3** as a crystalline solid. From the fractions eluted with petrol–EtOAc (17:3) of the original column, 6 mg of taxodione, 2 mg of sugiol and 13 mg of clovandiol were isolated after extensive chromatorgaphic purifications.

The C_6H_6–petrol phase (25.9 g) of the original partition was subjected to vacuum chromatography in a similar manner as the polar phase, to yield an additional crop of taxodione (56 mg) and β-sitosterol (13 mg). Some fractions eluted with petrol–EtOAc (9:1) (494 mg) wee combined and treated with Ac_2O–pyridine in the usual manner to yield 613 mg of a crude mixture which was subjected to flash chromatography using petrol–Me_2CO (17:3), after crystallization from petrol–EtOAc, **4** (20 mg) was isolated.

Salviasperanol (**1**). Amorphous solid, mp 203–205°; $[\alpha]_D$ − 31.5 ($CHCl_3$; *c* 0.2); UV λ_{max} nm (log ε): 205 (3.13), 275 (4.5), 280 (4.6); IR ν_{max}^{nujol} cm^{-1}: 3500, 3420, 3230, 1620, 1260, 1160, 855; ^{1}H NMR: Table 1; ^{13}C NMR: Table 2; MS *m/z* (rel. int.): 314 (16.9), 301 (1.2), 299 (30), 285 (100), 267 (30), 257 (40), 243 (17), 215 (97.9), 173 (45), 115 (30), 91 (30), 83 (30), 55 (50), 43 (50), 41 (99). $C_{20}H_{26}O_2$ requires $[M]^+$ at *m/z* 314.

5,6-Dihydro-6α-hydroxysalviasperanol (**2**). Amorphous solid, mp 184–190°; $[\alpha]_D$ − 20 ($CHCl_3$; *c* 0.1); UV λ_{max} nm (log ε): 205 (4.5), 270 (3.8); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3693, 3604, 3551, 1601, 1539, 1451, 1259, 1006, 929; ^{1}H NMR: Table 1; ^{13}C NMR: Table 2; MS *m/z* (rel. int.): 332 (13.7), 314 (5.9), 301 (2.9), 285 (3), 206 (20), 194 (20), 179 (50), 91 (50). 69 (50), 57 (30), 55 (30), 43 (82), 41 (100). $C_{20}H_{28}O_4$ requires $[M]^+$ at *m/z* 332.

6-epi-Demethylesquirolin D (**3**). Mp 203–205°; $[\alpha]_D$ − 56 ($CHCl_3$; *c* 0.2); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3616, 3534, 1451, 1392, 1033, 1011; ^{1}H NMR: Table 1; ^{13}C NMR: Table 2; MS *m/z* (rel. int.): 348 (5.5), 331 (12.5), 330 (55), 303 (20), 302 (60), 301 (40), 273 (50), 232 (30), 231 (100), 115 (3)), 91 (20), 69 (30), 55 (30), 43 (50), 41 (50). $C_{20}H_{28}O_5$ requires $[M]^+$ at *m/z* 348.

Acetylation of salviasperanol (**1**). Compound **1** (60 mg) in pyridine (0.5 ml) was treated with Ac_2O (0.5 ml) for 10 hr at room temp. After usual work-up and flash chromatography purification, 40 mg of **6** was obtained as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770, 1630, 1170, 1050, 1090, 880.; ^{1}H NMR: Table 1; MS *m/z* (rel. int.): 398 (3), 383 (4), 370 (5), 369 (10), 356 (10), 341 (30), 327 (20), 309 (20), 299 (10), 268 (20), 267 (100). $C_{24}H_{30}O_5$ required $[M]^+$ at *m/z* 398.

Catalytic hydrogenation of salviasperanol (**1**). Compound **1** (30 mg) in EtOAc (5 ml) was treated with H_2 in

the presence of PtO_2 (12 mg) as catalyst at room temp. for 6 days. After usual work-up and flash chromatography purification, **5** was isolated as a crystalline solid, mp 196° dec; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3604, 3543, 1633, 1596, 1500, 1268, 1253; ^1H NMR: Table 1; MS *m/z* (rel. int.): 318 (2), 317 (20), 316 (100), 301 (20), 298 (20), 283 (15), 273 (10), 255 (30), 245 (20), 233 (15), 231 (20), 229 (20), 219 (20), 205 (20), 179 (20), 175 (20), 128 (30), 115 (30), 91 (30), 55 (40), 43 (50), 41 (70). $C_{20}H_{28}O_3$ requires $[M]^+$ at *m/z* 316.

X-Ray structure determination of salviasperanol (**1**). A single crystal of dimension of $0.40 \times 0.17 \times 0.14$ mm, was obtained from slow evaporation of petrol–EtOAc and mounted on a Nicolet P3/F diffractometer with Ni-filtered Cu-K_α radiation ($\lambda = 1.54178$ Å). Orthorhombic system, space group $P2_12_12_1$, with dimensions cell $a = 5.777$ (1) Å, $b = 11.841$ (2) Å, $c = 24.868$ (5) Å, $Z = 4$, $D_X = 1.228$ g cm^{-3}, $m = 0.64$ mm^{-1}, $F(000) = 680$, $M_r = 314.4$. Refined unit-cell parameters were determined by least-squares treatment of the diffractometer setting angles of 25 reflections ($8.27 < 2\theta < 22.31°$), range of $0 < h < 6$, $0 < k < 12$, $0 < l < 25$, with variable scan speed (min 4; max 29.9° min^{-1}). From a total of 1056 independent measurements, those 1005 reflections with $[F > 3.0\sigma(F_0)]$ were retained for the structure analysis and the usual Lorentz and polarization corrections were applied.

The structure was solved by direct methods [18, 19]. 214 parameters were refined by full-matrix least-squares with positional and anisotropic thermal parameters for non-H atoms. Hydrogen atoms were placed in calculated positions. Hydrogens on O-11 and O-12 were located in a difference Fourier map and then refined. All hydrogens with isotropic thermal factor $U = 0.06$ A. Final $R = 7.25$ ($R_W = 7.69$).

Non-hydrogen atom positional parameters, bonds lengths and angles, anisotropic thermal parameters, hydrogen atom parameters and a list of observed and calculated structure amplitudes have been deposited with the Cambridge Crystallographic Data Centre. Neutral atom scattering factors used in the structure–factor calculations were taken from ref. [20].

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