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CAROTANE SESQUITERPENES FROM *FERULA LINKII*

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Key Word Index—*Ferula linkii*; Umbelliferae; sesquiterpenes; carotane; felikiol; webiol; ferutriol; lancerotol.

Abstract—Five new carotane sesquiterpenes have been isolated from *Ferula linkii*. These were the 3-angelate of felikiol, angelate- and epoxyangelate of webiol, 5-isovalerate of ferutriol and veratrate of lancerotol, and the already known *p*-hydroxybenzoate- and *p*-methoxybenzoate of lancerotol. The structures of the 3-angelate of felikiol and epoxyangelate of webiol were determined by X-ray analysis.

INTRODUCTION

The genus *Ferula* is chemically characterized by its content in coumarins and sesquiterpenes [1]. From *Ferula linkii* Webb, a species endemic to the Canary Islands, we isolated two dienic triterpenes of the oleanane type [2] and several carotane sesquiterpenes [3, 4]. In this paper we now describe the isolation and structural determination of further new carotane sesquiterpenes obtained from this plant.

RESULTS AND DISCUSSION

The least polar new compound isolated was the 3-angelate of felikiol to which the structure **1** was assigned on the basis of the following considerations. High resolution mass spectrometry of compound **1** was in accordance with the formula $C_{20}H_{30}O_4$. Its IR spectrum showed bands of hydroxyl, carbonyl and ester groups. In the ^{1}H NMR spectrum could be observed the signals of an angelate, an isopropyl group, an angular methyl and a methyl group attached to a carbon with an oxygen function. The molecular ion at *m/z* 386 and fragments formed by losses of water and angelic acid were present in its mass spectrum.

Hydrolysis of **1** gave the alcohol **2**, $C_{15}H_{26}O_3$. Of the three oxygens of this molecule, one must be a carbonyl group (1700 cm^{-1}) and the others must form part of two tertiary hydroxyl groups (3590 cm^{-1}), because no geminal protons to an oxygen function are observed in its ^{1}H NMR spectrum. The methyl group at C-3 must be geminal to the ester group in **1**, because with respect to **2** a difference in the chemical shift of this methyl can be observed (δ 1.25 and 1.55 for **1** and **2** respectively). The position of the other hydroxyl group at C-6, and not at C-10, was deduced from the ^{13}C NMR spectrum of **1** (Table 1).

Reduction of compound **2** with sodium borohydride afforded the two epimeric alcohols **3** and **4**. One of these (**4**) formed an acetonide **5**, but the other (**3**) did not. The formation of this acetonide **5** indicated that the new alcohol, formed by reduction of the ketone, was at C-2, C-4 or C-5. As this compound **1** must be biogenetically derived from carotol (**6**) [5, 6], we think that the carbonyl group was at C-2. The two triols formed in the reduction of **2** are different from linkitriol (**7**) [3] and **8**; the latter was obtained by permanganate oxidation of carotol (**6**) [6]. The structures of the two triols were given as **3** and **4**. Of these two compounds the β-configuration at the hydroxyl group at C-2 was assigned to **4**, which forms the acetonide **5**, because in this case the two hydroxyl groups at C-2 and C-3 are on the same face of the molecule.

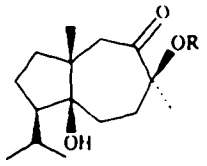
To confirm the structure of the 3-angelate of felikiol we submitted a crystal to an X-ray analysis. In this way the structure **1** (Fig. 1) was obtained.

We also isolated two new compounds (**9** and **10**) with the same skeleton, the only difference between them being in the nature of the acid that was esterified to a tertiary hydroxyl group present in the molecule. These acids were identified by their ^{1}H NMR spectra as angelic and expoxyangelic acids. Hydrolysis of the two esters of **9** and **10** gave the same alcohol **11**, with a molecular formula of $C_{15}H_{22}O_3$ and to which we have named webiol. Its IR spectrum showed absorptions of hydroxyl and carbonyl groups and its UV spectrum showed a band of an α,β-unsaturated ketone (239 nm). The ^{1}H NMR spectrum showed signals of four methyls and two methylene groups, the latter allylic to two different carbonyl groups. These two methylene groups are also allylic to tetrasubstituted carbons and their resonances are two pairs of doublets, the first centred at δ 2.53 and 2.83 and the second at 2.21 and 2.34. No vinylic protons are observed in this spectrum, therefore the double bond of the α,β-unsaturated ketone must be tetrasubstituted. In a carotane skeleton the only possible place for this double bond must be between C-6 and C-10. The carbonyl group must be at C-9 and not at C-5, because its IR absorption at 1690 cm^{-1} is too high for a conjugated ketone in a seven membered ring. We located the second carbonyl group at C-2 on the basis of biogenetic considerations. The tertiary alcohol group was assigned at C-3, but its stereochemistry was undetermined. In order to know this stereochemistry and to confirm the C-2 carbonyl group position the epoxiangelate of webiol was submitted to an X-ray analysis. In this way the structure **10** (Fig. 2) was determined for this product. Thus the new compounds isolated from the plant were the angelate of webiol (**9**) and the epoxiangelate of webiol (**10**).

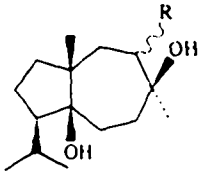
Table 1. ^{13}C NMR data (50.32 MHz)

C	1	3	4	7	8	10	11	13	14
1	47.9	39.5*	42.2*	38.3	43.0*	43.5	51.2*	134.2	41.1*
2	205.8	76.2	74.3	75.1	73.2	207.0	212.9	140.9	61.3
3	85.1	74.6	76.1	75.3	72.9	87.4	79.0	71.3	56.8
4	37.4	40.4*	44.8*	41.3	45.9*	40.3	37.5	50.8	47.3
5	32.8*	37.0	35.6*	35.3	32.7†	21.3	22.3	67.6	67.4
6	83.5	82.6	82.6	83.4	83.4	174.0	176.0	55.8	63.4
7	47.2	47.8	46.6	47.3	46.5	41.4	42.3	44.7	43.4
8	32.4	33.0	34.4	33.9	33.3†	49.1	48.7*	32.0	32.2
9	25.2	26.7	25.8	26.3	25.6	204.5	206.3	41.4	41.3*
10	53.8	57.8	58.9	56.3	58.2	174.0	176.6	86.3	86.5
11	27.4	29.4	28.2	28.6	27.6	25.5	24.9	38.0	37.9
12	21.4†	21.6†	21.6†	21.5*	21.6‡	20.3*	20.6†	17.3*	17.1†
13	22.9†	23.4†	23.1†	23.3*	23.5‡	20.7*	20.7†	18.5*	18.3†
14	23.4‡	25.7‡	23.9‡	23.9	24.2	21.6	25.9‡	21.8	19.2
15	24.3‡	26.2‡	19.4‡	25.9	29.1	30.1	27.6‡	32.0	24.5

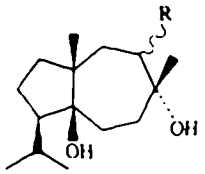
*†‡The assignments for these signals may be reversed.



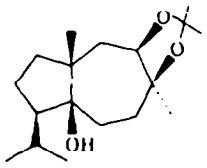
1 R = Ang
2 R = H



3 R = α-OH
4 R = β-OH



7 R = β-OH
8 R = α-OH



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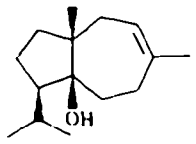

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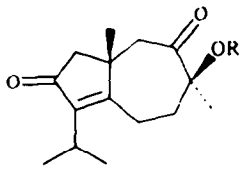
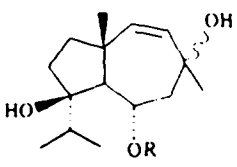
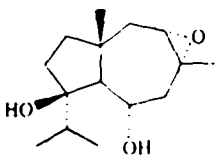


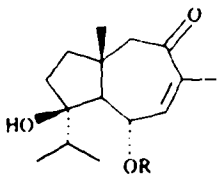
9 R = Ang
10 R = Epox-Ang
11 R = H



12 R = Val
13 R = H



14



15 R = H
16 R = —CO—C_6H_4OH
17 R = —CO—C_6H_4OMe
18 R = —CO—$C_6H_3(OMe)_2$

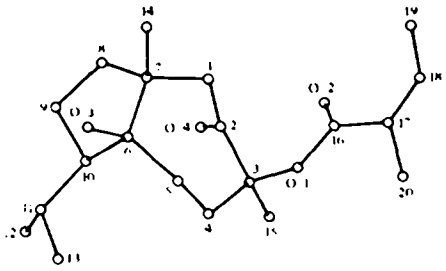


Fig. 1. X-ray molecular model of the 3-angelate of felikiol (**1**).

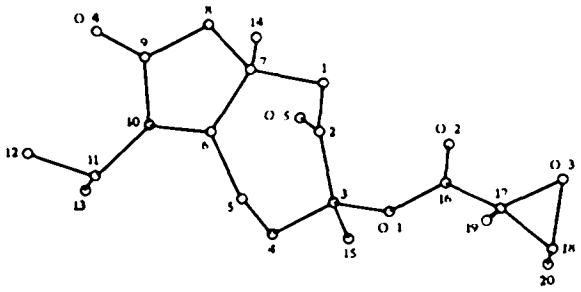


Fig. 2. X-ray molecular model of the epoxyangelate of webiol (**10**).

Another new compound isolated from this species was the 5-isovalerate of ferutriol (**12**). Its IR spectrum contained absorptions of hydroxyl and ester groups. The ^{1}H NMR spectrum showed a complex signal of three hydrogens between δ 5.60 and 5.80, but in deuterobenzene two types of signals could be observed. These were a double doublet typical of the proton geminal to the ester at C-5 and a broad singlet at 5.55 assignable to the two hydrogens of a double bond situated between totally substituted carbons. Also in this spectrum two methyl and two isopropyl groups were detected. The mass spectrum of **12** showed a fragment at *m/z* 295 $[M-C_3H_7]^+$. This loss of an isopropyl group is typical of a carotane sesquiterpene with a hydroxylic function at C-10 [7].

Hydrolysis of **12** gave the triol **13**. Its ^{1}H NMR spectrum showed the signals of an isopropyl group, two methyls, the geminal proton to the secondary alcohol and two vinylic hydrogens. These are not equivalent as in the case of the ester **12**, resonating now as to doublets centred at δ 5.41 and 5.72. The ^{13}C NMR of **13** (Table 1) confirmed its structure, especially the C-1, C-2 position for the double bond and not the alternative C-7, C-8 location. In Table 1 the carbon resonances of **14** are also included for comparison with **13**. The stereochemistry of the tertiary alcohol at C-3 in this new product, the isovalerate of ferutriol (**12**), remained undetermined.

Other compounds isolated from this plant were three different esters of the same alcohol **15**, which were identified as the *p*-hydroxybenzoate-, *p*-methoxybenzoate- and veratrate of lancerotol (**16**, **17** and **18**, respectively). The substances **16** and **17** were isolated previously from *Ferula lancerottensis* [8], and **18** was a new natural compound. Hydrolysis of **18** gave **15**, identical with a authentic sample of lancerotol [8].

Finally we describe here some of the characteristics of the molecular structures of **1** and **10**. Figures 1 and 2 show a perspective view of these molecules. Both compounds present similar conformation for the rings system, the seven membered rings have a twist-chair conformation and the five membered ring has an envelope conformation. The substituent at C-3 (O-1) has a β-configuration in both compounds. The packing of the molecules are due to hydrogen bonds between O-3 and O-4 (O-3 . . . O-4 = 2.898 A, O-4 . . . H-O-3 = 2.02 A) in compound **10**. There are not contacts closer than the sum of the apropriate van der Waals radii for compound **1**.

EXPERIMENTAL

Mps: uncorr.; IR: $CHCl_3$; NMR: $CDCl_3$; MS: 70 eV (probe). Column chromatography was performed on silica gel 0.063-0.2 mm. The substances were crystallized from petrol-EtOAc except where otherwise indicated.

Isolation of the sesquiterpenes. The compounds were obtained in accordance with the experimental data reported in ref. [2] and by several dry CC runs of a complex mixture of sesquiterpenes. The substances isolated were: **1** (300 mg), **16** (100 mg), **9** (90 mg), **10** (80 mg), **12** (80 mg), **18** (60 mg) and **17** (2 g).

3-Angelate of felikiol (**1**). Mp 106-108°; $[M]^+$ at *m/z* 336.2296. $C_{20}H_{32}O_4$ requires 336.2300; IR ν_{max} cm^{-1}: 3590, 3000, 2940, 2860, 1700, 1450, 1360, 1140, 1040, 850. ^{1}H NMR (90 MHz): δ 0.95 and 1.02 (each 3H, *d*, *J* = 5 Hz, H-12 and H-13), 1.05 and 1.55 (each 3H, *s*, H-14 and H-15), 2.30 and 2.56 (each 1H, *d*, *J* = 12 Hz, H-1), 6.15 (1H, *c*, Ang). EIMS *m/z* (rel. int.): 366 $[M]^+$ (1), 277 (1), 253 (4), 236 (10), 218 (6), 193 (36), 175 (33).

3-Angelate of webiol (**9**). Obtained as a gum, $[M]^+$ at *m/z* 332.1976. $C_{20}H_{28}O_4$ requires 332.1987; IR ν_{max} cm^{-1}: 3020, 3000, 2940, 2860, 1715, 1450, 1360, 1140, 1090, 990, 970. ^{1}H NMR (90 MHz): δ 1.11 and 1.19 (each 3H, *d*, *J* = 2 Hz, H-12 and H-13), 1.21 and 1.52 (each 3H, *s*, H-14 and H-15), 6.23 (1H, *c*, Ang); EIMS *m/z* (rel. int.): 332 $[M]^+$, 290, 249, 232, 208.

3-Epoxyangelate of webiol (**10**). Mp 82-84°; $[M-C_5H_8O_3]^+$ at *m/z* 232.1442. $C_{15}H_{20}O_2$ requires 232.1464; IR ν_{max} cm^{-1}: 3075, 3000, 2950, 2920, 2860, 1740, 1715, 1690, 1625, 1600, 1455, 1410, 1370, 1320, 1270, 1150, 1100, 995, 855; UV λ_{max} nm: 242; ^{1}H NMR (200 MHz): δ 1.08 and 1.12 (each 3H, *d*, *J* = 5 Hz, H-12 and H-13), 1.17 (3H, *s*, H-14), 1.36 (3H, *d*, *J* = 5 Hz, H-5"), 1.44 (3H, *s*, H-3"), 1.64 (3H, *s*, H-15), 3.09 (1H, *c*, *J* = 5 Hz, H-4"); EIMS *m/z*: 348 $[M]^+$, 333, 320, 232, 207, 189, 149, 121.

5-Isovalerate of ferutriol (**12**). Mp 54-56° (petrol); $[M-C_3H_7]^+$ at *m/z* 295.1835. $C_{17}H_{27}O_4$ requires 295.1909; IR ν_{max} cm^{-1}: 3580, 3440, 3000, 2950, 2920, 2860, 1705, 1460, 1450, 1380, 1365, 1290, 1230, 1160, 1090, 1075, 1035, 1025, 900; ^{1}H NMR (90 MHz): δ 0.80-1.09 (12H, complex signal), 1.23 and 1.49 (each 3H, *s*, H-14 and H-15), 5.50 (2H, *d*, *J* = 2 Hz, H-1 and H-2), 5.59 (1H, *br d*, H-5), ^{1}H NMR (90 MHz, C_6D_6): δ 0.78-1.06 (12H, complex signal), 1.29 and 1.57 (each 3H, *s*), 5.55 (2H, *br s*, H-1 and H-2), 5.75 (1H, *br d*, H-5); EIMS *m/z* (rel. int.): 295 $[M-C_3H_7]^+$ (1), 277 (1), 236 (3), 221 (2), 218 (3), 193 (15), 175 (100).

Veratrate of lancerotol (**18**) $[M]^+$ at *m/z* 416.2233. $C_{24}H_{32}O_6$ 416.2199; ^{1}H NMR (60 MHz): δ 0.90 (6H, *t*, H-12 and H-13), 1.24 (3H, *s*, H-14), 1.88 (3H, *br s*, H-15), 2.68 (2H, *s*, H-1), 3.92 and 3.94 (3H, *s*), 6.22 (2H, *br d*, H-4 and H-5), 6.88 (1H, *d*, *J* = 8 Hz), 7.55 (1H, *d*, *J* = 2 Hz), 7.75 (1H, *c*, *J* = 8 and 2 Hz). EIMS *m/z* (rel. int.): 416 $[M]^+$ (5), 234 (10), 216 (2), 191 (71), 182 (100), 165 (100).

Hydrolysis of compound **1**. The 3-angelate of felikiol (**1**) (170 mg) in MeOH (1 ml) was treated with methanolic KOH (3%) (10 ml) at room temp. for 48 hr. Extraction in the usual way afforded **2** $[M]^+$ at *m/z* 254.1877. $C_{15}H_{26}O_3$ requires 254.1881; ^{1}H NMR (90 MHz): δ 0.95 (3H, *s*, H-14), 0.93 and 1.03 (each 3H, *d*, *J* = 6 Hz, H-12 and H-13), 1.25 (3H, *s*, H-15), 2.03 and 2.89

(each 1H, *d*, *J* = 12 Hz, H-1); EIMS *m/z* (rel. int.): 254 $[M]^+$ (8), 236 (1), 226 (3), 211 (7), 193 (41), 183 (15), 175 (12).

Reduction of compound **2**. Compound **2** (74 mg) in MeOH (5 ml) was treated with sodium borohydride (15 mg) at 0° for 4 hr. Usual work up afforded a mixture of two products, which were separated by chromatography. Elution with petrol–EtOAc (80%) gave **3** (30 mg), $[M]^+$ at *m/z* 256.2061. $C_{15}H_{28}O_3$ requires 256.2039. ^{1}H NMR (90 MHz): δ0.88 and 0.98 (each 3H, *d*, *J* = 6 Hz, H-12 and H-13), 1.05 and 1.22 (each 3H, *s*, H-14 and H-15), 3.62 (1H, *d*, *J* = 9 Hz); EIMS *m/z* (rel. int): 256 $[M]^+$ (2), 238 (4), 223 (3), 209 (4), 205 (2), 195 (10), 185 (10), 167 (11). Further elution afforded **4** (40 mg), mp 32–34°, $[M]^+$ at *m/z* 256.2061. $C_{15}H_{28}O_3$ requires 256.2039. ^{1}H NMR (90 MHz): 0.96 (6H, *t*, *J* = 6 Hz, H-12 and H-13), 1.10 and 1.22 (each 3H, *s*, H-14 and H-15), 3.72 (1H, *dd*, *J* = 9 and 4 Hz); EIMS *m/z* (rel. int.): 256 $[M]^+$ (2), 238 (3), 223 (7), 213 (2), 209 (1), 205 (3), 194 (15), 185 (35), 172 (57), 167 (26), 159 (2).

Acetonide of compound **4**. Compound **4** (40 mg), dry Me_2CO (3 ml) and $CuSO_4$ (150 mg) were stirred at room temp. for 24 hr. The mixture was chromatographed, eluting with petrol–EtOAc (10%) to afford the acetonide **5** (30 mg), mp 92–94° (petrol–$CHCl_3$); ^{1}H NMR (60 MHz): δ0.96 (6H, *t*, *J* = 6 Hz, H-12 and H-13), 1.03, 1.18, 1.37 and 1.43 (each 3H, *s*), 3.96 (1H, *dd*, *J* = 10 and 4 Hz, H-2); EIMS *m/z* (rel. int.): 296 $[M]^+$ (4), 281 (8), 263 (3), 238 (4), 221 (30), 203 (21), 195 (8).

Hydrolysis of compounds **9** *and* **10**. Compound **9** (90 mg) in C_6H_6 (0.5 ml) saponified as above for **1**. The reaction time in this case was 1 hr. Usual work up gave **11** (70 mg), mp 64–66° (from petrol Me_2CO), $[M]^+$ at *m/z* 250.1562. $C_{15}H_{22}O_3$ requires 250.1568; IR ν_{max} cm^{-1}: 3480, 3000, 2950, 2920, 2860, 1695, 1690, 1620, 1450, 990; UV λ_{max} nm: 239. ^{1}H NMR (200 MHz): δ1.10, 1.13, 1.16 and 1.26 (each 3H, *s*), 2.21 and 2.34 (each 1H, *d*, *J* = 11 Hz, H-9), 2.56 and 2.83 (each 1H, *d*, *J* = 11 Hz, H-1); EIMS *m/z* (rel. int): 250 $[M]^+$ (21), 232 (8), 206 (100), 193 (11), 189 (14). When **10** was treated in the same way as **9**, the same alcohol **11** was obtained.

Hydrolysis of compound **12**. Compound **12** (40 mg) in C_6H_6 (0.15 ml) was saponified as above for **1**. The reaction time in this case was 3 days. Usual work up afforded **13** (30 mg) as a gum, $[M-C_3H_7]^+$ at *m/z* 211.1323. $C_{12}H_{19}O_3$ requires 211.1334; IR ν_{max} cm^{-1}: 3590, 3430, 3000, 2960, 2920, 2850, 1460, 1370, 1300, 1160, 1030, 970, 920, 870; ^{1}H NMR (60 MHz): 0.85 and 0.95 (each 3H, *d*, *J* = 4 Hz, H-12 and H-13), 1.24 and 1.45 (each 3H, *s*, H-14 and H-15), 5.41 and 5.72 (each 1H, *d*, *J* = 12 Hz, H-1 and H-2); EIMS *m/z* (rel. int.): 236 $[M-H_2O]^+$ (2), 211 (46), 193 (55), 175 (66).

X-Ray data for compounds **1** *and* **10**. Table 2 gives the crystal data for both compounds. The data were measured on a four-circle diffractometer with monochromated CuKα radiation (λ = 1.5418 Å), the $\omega/2\theta$ scan technique and a speed of 1/min were used. No crystal decomposition was observed during the data collection processes. No absorption corrections were applied. Scattering factors for neutral atoms and anomalous dispersion corrections for oxygen and carbon atoms were taken from the literature [9].

The two crystal structures were solved using the program MULTAN [10]. Most of the remaining calculations were performed with the X-Ray 70 System [11]. The structures were first refined anisotropically with units weights. Not all the H-atoms were located at difference maps, some of them, the methyl groups C-12 and C-13 in both compounds, were fixed at idealized positions (C–H = 1.00 Å, H–C–H = 104°) and were included in the refinement as fixed isotropic contributors. Both compounds present large temp. factors for the carbon atoms C-12 and C-13, and these are specially large for compound **10**. During the last cycles of refinement the positional and thermal factors for C-11, C-12 and C-13 of compound **10** were kept fixed. A convenient weighting scheme was chosen to obtain flat dependence of $\langle w\Delta^2F \rangle$ vs $\langle Fo \rangle$ and vs $\langle \sin\theta/\lambda \rangle$ [12]. Several cycles of weighted anisotropic refinement gave the following weighted and unweighted discrepancy indices: R = 0.05 and R_w = 0.046 for compound **1**, and R = 0.061 and R_w = 0.076 for compound **10**. The absolute configuration [13] of both compounds was determined by comparing the 73 (ΔFc 0.06 for compound **1**) and 60 (ΔFe 0.07 for compound **10**) more relevant Bijvoet pairs giving the following average Bijvoet differences: 0.223 for the right enantiomer vs 0.268 for the wrong one for compound **1**; 0.569 for the right enantiomer vs 0.593 for the wrong one for compound **10**.

The Cremer's parameters [14] for the five membered ring are: Q = 0.17 Å and ϕ = −22° for compound **1**, and Q = 0.42 Å and ϕ = −98° for compound **10**. The dominant symmetry of the rings system [15] is a mirror symmetry.

Final atom coordinates, list of temperature factors, hydrogen atom positions, and final structure factors have been deposited at the Cambridge Crystallographic Data Centre.

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Table 2. Crystal data for compounds **1** and **10**

	Compound **1**	Compound **10**
Chemical formula	$C_{20}H_{28}O_5$	$C_{20}H_{32}O_4$
Lattice type	Orthorhombic P212121	Orthorhombic P212121
a = (Å)	13.9312 (3)	14.8409 (6)
b =	12.2460 (5)	12.3538 (10)
c =	11.8997 (4)	10.6438 (3)
Z	4	4
M_r (g·mol^{-1})	348.438	336.469
Dc (g·cm^{-3})	1.1400	1.1452
M(CuKα) cm^{-1}	6.239	5.895
Crystal size	0.2 × 0.2 × 0.3 mm	0.3 × 0.25 × 0.15 mm
Number of observed reflexions $I > 2\sigma(I)$	2772	1080

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