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Alkaloids from *Narcissus bujei* (Amaryllidaceae)☆

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Abstract

Eleven alkaloids have been isolated from whole plants of *Narcissus bujei* (Amaryllidaceae). The alkaloids 11-*O*-acetylhaemanthamine and bujeine are reported for the first time. The structure and stereochemistry of these new alkaloids have been determined by physical and spectroscopic methods. The X-ray diffraction analysis of *O*-methyllycorenine hydrochloride has been performed.

Keywords: Narcissus bujei; Amaryllidaceae; Alkaloids; Homolycorine; 8-*O*-demethylhomolycorine; Masonine; Lycorenine; *O*-methyllycorenine; *O*-methyloduline; Crinamine; Haemanthamine; 11-*O*-acetylhaemanthamine; Tazettine; Bujeine

1. Introduction

Narcissus bujei, belonging to the *Pseudonarcissi* DC. section (Fernández-Casas, 1984) is an Amaryllidaceae species endemic to the southern region of the Iberian Peninsula. Recently, its histological and anatomical features have been studied (Dorda & Fernández-Casas, 1994). The present investigation deals with the isolation and characterization of eleven alkaloids from whole plants of this hitherto unstudied species. Homolycorine, an alkaloid widely distributed in the genus *Narcissus* (Bastida, Viladomat, & Codina, 1998), *O*-methyllycorenine, previously reported from both *N. muñozii-garmendiae* (Codina et al., 1993) and *N. pseudonarcissus* cv. Carlton (Kreh & Matusch, 1995; Kreh, Matusch, & Witte, 1995) and the new alkaloid 11-*O*-acetylhaemanthamine (**1**) were found to be the principal constituents. According to the literature, homolycorine and *O*-methyllycorenine are cytotoxic agents against fibroblastic LMTK cells (Weniger et al., 1995). In addition, homolycorine is also known to induce delayed hypersensitivity in animals (Gude, Hausen, Heitsch, & König, 1988). Bujeine (**2**), is the first crinane-type alkaloid with a three-membered α-5,10b-bridge. Following the characteristic pattern observed in *Narcissus* species, all the 5,10b-ethanophenanthridine alkaloids reported here belong to the α-series (Bastida et al., 1998).

2. Results and discussion

Compound **1**, $C_{19}H_{21}NO_5$, isolated as an amorphous solid, was identified as 11-*O*-acetylhaemanthamine. The IR spectrum displayed an intense absorption band at 1737 cm^{-1} characteristic of an ester carbonyl group as well as a band at 932 cm^{-1} for the methylenedioxy group. Its MS showed the parent base peak at *m*/*z* 343 $[M]^+$ and characteristic fragments at *m*/*z* 283, 268, 252, 224 and 181, following the fragmentation pattern of the 5,10b-ethanophenanthridine compounds with a bridge substituent and an unsaturated C-ring (Longevialle, Fales, Highet, & Burlingame, 1973). The absolute configuration of the alkaloid was determined from the CD spectrum, which was qualitatively similar to that of the known (+)-haemanthamine (with an α-ethano bridge), with a minimum at 249 nm (Ali, Ramadan, & Frahm, 1984; Wagner, Pham, & Döpke,

☆ Part 25 in the series "*Narcissus* alkaloids". For part 24 see Viladomat et al., 1997 [Viladomat, F., Sellés, M., Codina, C. and Bastida, J., *Planta Medica*, 1997, 63, 583.].

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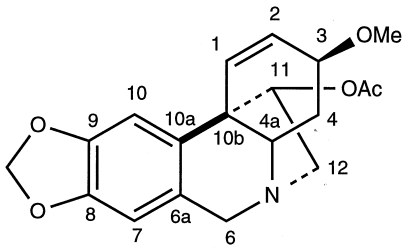

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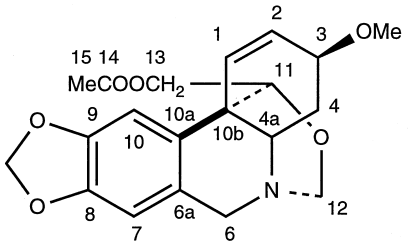

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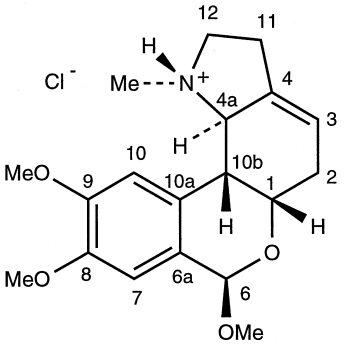

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1996). The ^{1}H NMR spectrum (500 MHz, $CDCl_3$) (Table 1), exhibited: (i) five singlets at δ 6.90, 6.46, 5.89, 3.36 and 1.97 for the two aromatic protons, the methylenedioxy, the methoxyl and the acetoxy groups, respectively. The aromatic proton singlet at δ 6.90 was assigned to H-10 because of spatial proximity with H-1 (ROESY experiment (Bax & Davis, 1985)) (Table 2). The acetoxy group (δ 1.97) was assigned to the 11 position because of a pronounced deshielding effect on H-11 (δ 4.96) in relation with haemanthamine ($\Delta\delta \sim 1$ ppm) (Pabuççuoglu et al., 1989) and also by the long range W coupling between H-4a and H-11*endo*, giving support to the 11*exo* assignment of the acetoxy group; (ii) two olefinic protons at δ 6.35 d and 6.16 ddd, the multiplicities of which were in agreement with the *trans* relationship between the C-3 substituent and the 5,10b-ethano bridge; the magnitude of the coupling constants amongst H-3 (δ 3.85) and H-2, H-4α and H-4β, led us to assign the *pseudoequatorial* disposition for H-3; (iii) the large coupling ($J = 13.5$ Hz), which is due to their *trans*-diaxial relationship, allowed the ddd at δ 3.35 and the ddd at δ 1.93 to be assigned to H-4a and H-4α, respectively; (iv) the assignment of the C-6 and C-12 protons was supported by the NOE effect observed between H-12*endo* (δ 3.40) and H-6α (δ 3.71), as well as between H-6β (δ 4.34) and H-4a. In addition, both H-6β and H-12*endo* protons were assigned to lower fields due to their *syn*-relation with the nitrogen lone pair.

The ^{13}C NMR spectrum of **1** (Table 1) was consistent with a crinane-type skeleton which contains 19 carbon atoms, ten of which displayed resonances in the shift range $\delta > 90$ ppm. The lowfield signals were five singlets for the acetoxy carbonyl group and the quaternary carbons of ring A, two doublets for the non-quaternary aromatic carbons (C-7 and C-10), two doublets for the olefinic carbons and one triplet for the methylenedioxy group. The aliphatic shift range is characterized by one singlet (C-10b), three methine carbons (C-3, C-4a, and C-11), three triplets (C-4, C-6 and C-12) and two quartets for the methoxyl and acetoxy methyl carbons. The C-11 chemical shift (δ 80.2, d), was consistent with the presence of the acetoxy substituent in that position. The assignment of the carbon signals was confirmed taking into account the HMQC (Bax & Subramanian, 1986) and HMBC (Bax & Summers, 1986) connectivities (Table 1).

Compound **2**, $C_{20}H_{23}NO_6$, was isolated from fraction V and the name bujeine is proposed for this alkaloid. Its IR spectrum showed an intense absorption at 1737 cm^{-1} characteristic of an ester carbonyl band, as well as a band at 934 for the methylenedioxy group. The MS showed the molecular ion peak at m/z 373, the base peak at m/z 271, and important fragments at m/z 343, 329, 301, 285, 153 and 69. Its molecular ellipticity showed a standard CD-curve qualitatively similar to those of some other related (+)-crinane alkaloids (Ali et al., 1984), with a minimum at 252 nm. The ^{1}H and ^{13}C NMR spectra ($CDCl_3$) (Table 3) were similar to those of compound **1**, but several important differences were observed: (i) an AB system at δ 4.82 and 4.51 assigned to the C-12 protons, the lowfield shifts and multiplicities of which were significantly different from the usual crinane-type alkaloids. This would only be the case if there were an heteroatom between C-11 and C-12. In addition, the C-12 carbon resonance (δ 81.0) was sufficiently deshielded to support this assumption; (ii) the presence of the acetoxymethyl group at position 11 was indicated by the COSY correlation (Table 4) between H-11 and the two C-13 protons, as well as the usual proton and carbon resonances attributable to the

Table 1. ^{1}H NMR, HMQC and HMBC data for compound **1**[a]

H	δ	Correlated C-atom	
		HMQC	HMBC
1	6.35 d (10.0)	127.5 d	C-3, C-4a, C-10a, C-10b
2	6.16 ddd (10.0, 5.0, 1.0)	129.5 d	C-3, C-4, C-10b
3	3.85 ddd (5.0, 4.5, 1.5)	72.4 d	C-1, C-2, C-4a, 3-OMe
4α	1.93 ddd (13.5, 13.5, 4.5)	28.2 t	C-3, C-4a, C-10b
4β	2.01 dddd (13.5, 5.0, 1.5, 1.0)	28.2 t	C-2, C-3, C-4a, C-10b
4a	3.35 dd (13.5, 5.0)	62.8 d	C-4, C-6, C-10a, C-11, C-12
6α	3.71 d (17.0)	61.0 t	C-4a, C-6a, C-7, C-8, C-10a, C-12
6β	4.34 d (17.0)	61.0 t 126.2 s (C-6a)	C-6a, C-7, C-8, C-10a, C-12
7	6.46 s	106.6 d 146.5 s (C-8) 146.5 s (C-9)	C-6, C-8, C-9, C-10a, C-10b
10	6.90 s	103.9 d 134.2 s (C-10a) 49.2 s (C-10b)	C-6, C-6a, C-8, C-9, C-10a, C-10b
11	4.96 ddd (7.0, 3.5, 1.0)	80.2 d	C-4a, C-10a, CO
12*endo*	3.40 dd (14.0, 7.0)	60.4 t	C-4a, C-6, C-10b
12*exo*	3.31 dd (14.0, 3.5)	60.4 t	C-4a, C-6, C-10b
OCH_2O	5.89 s	100.9 t	C-8, C-9
3-OMe	3.36 s	56.5 q	C-3
11-OAc	1.97 s	21.2 q 170.0 s (*CO*Me)	CO

[a]Chemical shifts in ppm rel. to TMS. Coupling constants (*J*) in Hz. C-multiplicities were determined by DEPT data.

acetate group. The *endo* disposition for the C-11 substituent was indicated by the NOESY contour correlations (Table 4) between H-11*exo* and H-4α, as well as between 2H-13 and H-10.

The chirality of the alkaloids of the homolycorine/lycorenine-type cannot be determined from physical and spectrometric techniques. In addition, little is reported on the crystallographic data of these compounds (Clardy, Chan, & Wildman, 1972; Gopalakrishna, Watson, Silva, & Pacheco, 1978; Latvala et al., 1995a); thus the absolute configurations have been reported with reservation. In the former analyses, the enantiomer used in the refinement is based on the β-orientation of the C-4a proton, the reason for which other homolycorine/lycorenine alkaloids were previously considered to be R-configured at this centre (Latvala et al., 1995a). In order to determine if this was the case, the HCl salt of *O*-methyllycorenine was prepared and the molecular structure of recrystallized *O*-methyllycorenine hydrochloride (**3**), illustrated in Fig. 1, was determined by simple crystal X-ray analysis. The presence of the chlorine atom allowed us to determine the chirality of this structure using the Flack coefficient (Flack, 1983). The coefficient obtained [–0.01(8)] for the given coordinates (see Section 3), indicated that **3** possesses inverse chirality to that which has been previously proposed (Codina et al., 1993; Kreh & Matusch, 1995; Kreh et al., 1995).

Table 2. Scalar and spatial correlation of the protons of compound **1**

H	COSY	NOESY
1	H-2	H-2, H-10
2	H-1, H-3	H-1, H-3
3	H-2, H-4α, H-4β	H-2, H-4α, H-4β, 3-OMe
4α	H-3, H-4β, H-4a	H-3, H-4β, H-4a, H-12*exo*
4β	H-3, H-4α, H-4a	H-3, H-4α, H-4a
4a	H-4α, H-4β	H-4α, H-4β, H-6β
6α	H-6β	H-6β, H-7, H-12*endo*
6β	H-6α	H-4a, H-6α, H-7
7		H-6α, H-6β
10		H-1
11	H-12*endo*, H-12 *exo*	H-12*endo*, H-12*exo*
12*endo*	H-11, H-12*exo*	H-6α, H-11, H-12*exo*
12*exo*	H-11, H-12*endo*	H-4α, H-11, H-12*endo*
OCH_2O		
3-OMe		H-3
11-OAc		

3. Experimental

3.1. General

M.p.'s were uncorr. IR spectra were measured in dry film. EIMS at 70 eV. ^{1}H, ^{13}C NMR, DEPT, ^{1}H COSY, HMQC, HMBC and ROESY spectra were

Table 3. ^{1}H NMR, HMQC and HMBC data for compound **2**[a]

H	δ	Correlated C-atom	
		HMQC	HMBC
1	6.38 d (10.0)	131.4 d	C-2, C-3, C-4a, C-10a, C-10b
2	6.08 dd (10.0, 4.8)	129.1 d	C-3, C-4, C-10b
3	3.89 ddd (4.8, 4.6, 1.5)	72.5 d	C-1, C-2, C-4a, 3-OMe
4α	2.43 ddd (13.5, 13.5, 4.6)	26.7 t	C-4a, C-10b
4β	2.06 ddd (13.5, 4.0, 1.5)	26.7 t	C-2, C-3, C-10b
4a	3.29 dd (13.5, 4.0)	53.4 d	C-4, C-12
6α	4.04 d (17.0)	57.6 t	C-4a, C-6a, C-7, C-10a, C-12
6β	4.45 d (17.0)	57.6 t	C-6a, C-7, C-8, C-10a, C-12
		131.8 s (C-6a)	
7	6.57 s	105.7 d	C-6, C-8, C-9, C-10a
		146.2 s (C-8)	
		145.5 s (C-9)	
10	6.81 s	105.4 d	C-6a, C-8, C-9, C-10b
		129.1 s (C-10a)	
		36.9 s (C-10b)	
11	3.93 dd (8.3, 3.0)	75.3 d	C-10a, C-13
12*endo*	4.51 d (11.0)	81.0 t	C-4a, C-6, C-11
12*exo*	4.82 d (11.0)	81.0 t	C-4a, C-6, C-11
13a	4.27 dd (11.6, 3.0)	64.6 t	C-14
13b	3.58 dd (11.6, 8.3)	64.6 t	C-11, C-14
		170.8 s (C-14)	
15	2.00 s	20.9 q	C-14
OCH_2O	5.91 s	100.8 t	C-8, C-9
3-OMe	3.36 s	56.5 q	C-3

[a]Chemical shifts in ppm rel. to TMS. Coupling constants (J) in Hz. C-multiplicities were determined by DEPT data.

recorded in a Varian VXR 500, using the solvent specified and TMS as internal standard. Chemical shifts were reported in δ units (ppm) and coupling constants (J) in Hz. Silica gel Merck (70–230 mesh) and silica gel SDS chromagel 60 A CC (230–400 mesh) were used for CC and flash CC, respectively. Sephadex LH-20 Pharmacia was used for gel filtration and silica gel 60 F_{254} (Merck) for analyt. (0.25 mm) and prep. (1 mm) TLC. Spots on chromatograms were detected under UV light (254 nm) and by Dragendorff's reagent.

Table 4. Scalar and spatial correlation of the protons of compound **2**

H	COSY	NOESY
1	H-2	H-2, H-10, H-13a
2	H-1, H-3	H-1, H-3
3	H-2, H-4α, H-4β	H-2, H-4α, H-4β, 3-OMe
4α	H-3, H-4β, H-4a	H-3, H-4β, H-4a, H-11, H-12*exo*
4β	H-3, H-4α, H-4a	H-3, H-4α, H-4a
4a	H-4α, H-4β	H-4α, H-4β, H-6β
6α	H-6β	H-6β, H-7, H-12*endo*
6β	H-6α	H-4a, H-6α, H-7
7		H-6α, H-6β
10		H-1, H-13a, H-13b
11	H-13a, H-13b	H-4α, H-12*exo*, H-13a
12*endo*	H-12*exo*	H-6α, H-12*exo*
12*exo*	H-12*endo*	H-4α, H-11, H-12*endo*
13a	H-11, H-13b	H-1, H-10, H-11, H-13b
13b	H-11, H-13a	H-10, H-11, H-13a
15		
OCH_2O		
3-OMe		H-3

3.2. Plant material

Whole plants of *Narcissus bujei* (Fdez. Casas) Fdez. Casas were collected in April 1994, during the flowering period, in the Sierra de Cabra, Córdoba (Spain). Samples were authenticated by Dr Alfonso Susanna and a voucher specimen (No. 900191) has been deposited in the Herbarium of the Institut Botànic, Barcelona.

3.3. Extraction and isolation of alkaloids

Fresh whole plants (aerial parts and bulbs) of *N. bujei* (8.2 kg) were crushed and macerated with EtOH for 48 h. The extract was evapd under red. pres., the residue dissolved in H_2O and acidified with 5% H_2SO_4 to pH 4. After removing neutral material with Et_2O, the acidic soln was extracted with CH_2Cl_2 to provide extract A. Basifying the aq. soln up to pH 8–9 with

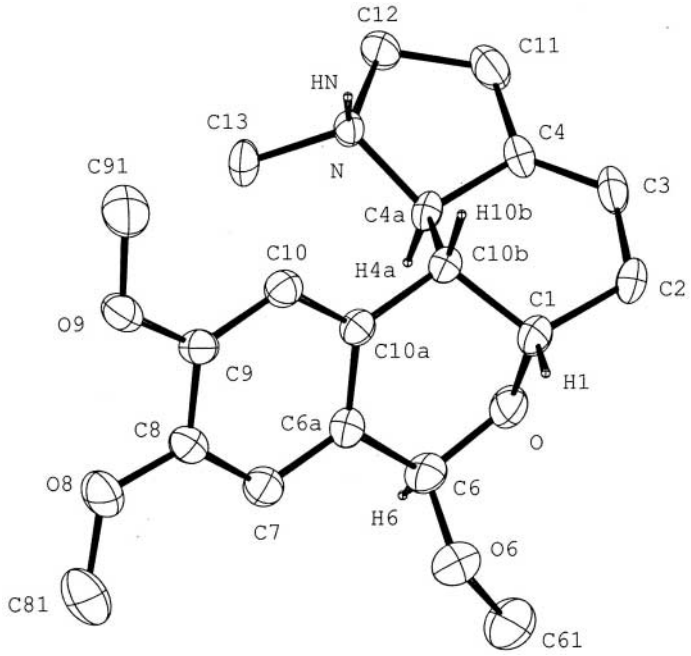

Fig. 1.

10% NH_3 and extracting it with CH_2Cl_2 gave extract C. Finally, the CH_2Cl_2–MeOH (3:2) extraction of the basic soln gave extract D. Extract A (4.1 g) was chromatographed by CC on silica gel eluting with CH_2Cl_2–MeOH (19:1), increasing the gradient for the last steps until (4:1). Two frs were obtained: fr. I was purified by Sephadex LH-20 and compound **1** (225 mg) was isolated. Homolycorine crystallized directly from fr. II; recrystallization with MeOH afforded 1.57 g. The rest of fr. II was chromatographed by flash CC using a Me_2CO–MeOH step gradient as solvent. After final purification on Sephadex LH-20, lycorenine (30 mg) and more homolycorine (440 mg) were isolated. Extracts C (6.5 g) and D (2.5 g) were first chromatographed in the same way as extract A. Two frs were obtained from extract C (III and IV) and three from extract D (V, VI and VII). Fr. III was purified by prep. TLC using EtOAc–MeOH (9:1) as solvent affording haemanthamine (32 mg) and 8-*O*-demethylhomolycorine (24 mg). Fr. IV was chromatographed by flash CC using a EtOAc–Me_2CO step gradient up to pure Me_2CO; after combination of similar frs, followed by further prep. TLC, eluting twice with MeOH and Me_2CO as solvents, *O*-methyllycorenine (120 mg) haemanthamine (45 mg) and crinamine (17 mg) were isolated. Fr. V was chromatographed by flash CC using a Me_2CO–MeOH step gradient as solvent, followed by further prep. TLC eluting twice with Me_2CO as solvent, giving haemanthamine (18 mg), homolycorine (39 mg), **2** (24 mg) and masonine (33 mg). Finally, after purification by similar processing to that for fr. V, fr. VI afforded *O*-methyllycorenine (42 mg) and tazettine (8 mg) and fr. VII, *O*-methyloduline (10 mg), lycorenine (15 mg), *O*-methyllycorenine (88 mg) and crinamine (12 mg).

3.4. 11-O-Acetylhaemanthamine (**1**)

Found: C, 65.32; H, 6.19; N, 4.01. $C_{19}H_{21}NO_5$ requires: C, 66.46; H, 6.16; N, 4.08%. M.p. 92–96°C. $[\alpha]_D^{22}$ −9.1° (MeOH; *c* 0.55); CD $[\Theta]_{249}$ −4607, $[\Theta]_{277}$ +4297. IR υ_{max} cm^{-1}: 2933, 2898, 1737 (>C=O), 1504, 1482, 1373, 1321, 1241, 1087, 1036, 932 (OCH_2O), 846, 732. EIMS 70 eV, *m/z* (rel. int.): 343 $[M]^+$ (100), 284 (26), 283 (27), 282 (10), 268 (20), 252 (26), 240 (20), 238 (11), 228 (13), 227 (10), 226 (12), 225 (33), 224 (52), 223 (19), 213 (15), 212 (16), 211 (30), 210 (30), 209 (19), 188 (20), 183 (13), 181 (35), 153 (18), 152 (16), 115 (19), 87 (12). ^1H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$), see Table 1.

3.5. Bujeine (**2**)

HRMS *m/z* 373.1532 (calcd 373.1525 for $C_{20}H_{23}NO_6$). M.p. 140–142°C. $[\alpha]_D^{20}$ +129.4° (MeOH; *c* 0.11); CD $[\Theta]_{252}$ −2815, $[\Theta]_{278}$ +2264. IR υ_{max} cm^{-1}: 2872, 2361, 1737 (>C=O), 1504, 1486, 1369, 1241, 1091, 1039, 973, 934 (OCH_2O), 856, 734. EIMS 70 eV, *m/z* (rel. int.): 373 $[M]^+$ (34), 372 (48), 344 (23), 343 (93), 329 (44), 301 (84), 287 (27), 286 (22), 285 (79), 272 (32), 271 (100), 211 (22), 181 (25), 153 (40), 135 (22), 84 (22), 71 (30), 69 (77). ^1H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (50 MHz, $CDCl_3$), see Table 3.

Homolycorine (Bastida et al., 1987), 8-*O*-demethylhomolycorine (Latvala et al., 1995b), masonine (Kreh & Matusch, 1995), lycorenine (Codina, Viladomat, Bastida, Rubiralta, & Quirion, 1992), *O*-methyllycorenine (Codina et al., 1993), 6-*O*-methyloduline (Kreh & Matusch, 1995), crinamine (Likhitwitayawuid et al., 1993), haemanthamine (Pabuçç?uoglu et al., 1989) and tazettine (Ghosal, Kumar, & Singh, 1984) were identified by a comparison of their chromatographic and spectroscopic properties ($[\alpha]_D$, CD, IR, MS, ^1H and ^{13}C NMR) with those of authentic samples obtained from other plant sources.

3.6. X-ray crystal structure analyses

A prismatic colourless crystal (0.1 × 0.1 × 0.2 mm) of **3** ($C_{19}H_{24}ClNO_4$), recrystallized from MeOH, was selected and mounted on an Enraf-Nonius CAD4 four-circle diffractometer. Unit-cell parameters were determined from automatic centering of 25 reflections ($12 < \theta < 21°$) and refined by the least-squares method. Crystal data: monoclinic, $P2_1$, $a = 8.4698(8)$, $b = 6.917(5)$, $c = 16.600(6)$ Å, $\beta = 96.257(2)°$, $Z = 2$. Intensities were collected with graphite monochroma-

tized MoKα radiation, using $\omega/2\theta$ scan-technique. 3027 reflections were measured in the range $2.42 \leq \theta \leq 29.97$. 1917 reflections were assumed as observed applying the condition $I > 2\sigma(I)$. Three reflections were measured every 2 h as orientation and intensity control, significant intensity decay was observed (8.3%). Lorentz-polarization intensity decay was applied but no absorption corrections were made. The structure was resolved by direct methods, using SHELXS computer program (Sheldrick, 1990) and refined by full-matrix least-squares method on F^2 with SHELX93 computer program (Sheldrick, 1994), using 2977 reflections, very negative intensities were not assumed. The function minimized was $\Sigma w||F_o|^2 - |F_c|^2|^2$, where $w = [\sigma^2(I) + (0.0660P)^2]^{-1}$ and $P = (|F_o|^2 + 2|F_c|^2)/3$, f, f' and f'' were taken from the International Tables of X-ray Crystallography (Cromer & Ibers, 1974). The chirality was defined from the Flack coefficient [–0.01(8)] (Flack, 1983). Four H atoms were located from a difference synthesis and refined with an overall isotropic temperature factor using a riding model, and 22 H-atoms were computed and refined with an overall isotropic temperature factor using a riding model. The final R (on F) factor was 0.040, wR (on $|F|^2$) = 0.098 and the goodness of fit = 1.045 for all observed reflections. The number of refined parameters was 245. Max. shift/esd = 3.8, mean shift/esd = 0.02. Maximum and minimum peaks in the final difference synthesis were 0.474 and –0.349 eÅ^{-3}, respectively. The crystallographic data has been deposited at the Cambridge Crystallographic Data Center, UK (No. 101164).

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