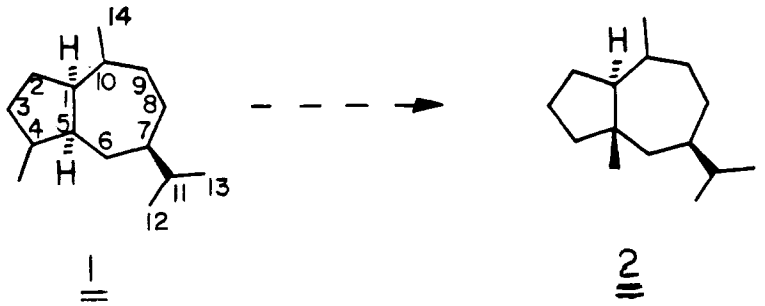
MOLECULAR STRUCTURE OF A *CIS*-DECALIN-TYPE EUDESMANOLIDE AND ITS FORMATION FROM A GUAIANOLIDE-1(10)-EPOXIDE

NIKOLAUS H. FISCHER, YUNG-FUNG WU-SHIH, GIACOMO CHIARI, FRANK R. FRONCZEK and STEVEN F. WATKINS

Department of Chemistry, Louisiana State University, Baton Rouge, Louisiana 70803

ABSTRACT.—Treatment of a guaianolide-1(10)-epoxide with BF_3-etherate provided a *cis*-decalin-type eudesmanolide and a 1α-fluoro-10β-hydroxyguaianolide as the major products. The formation of the eudesmanolide involves migration of C-5 from C-1 to C-10, and the fluoroguaianolide must be formed by BF_3 and/or HF-catalyzed opening of the 1(10)-epoxide group. The structures of the two new compounds were inferred from nmr and mass spectral data. The molecular structure of the new eudesmanolide was determined by single crystal x-ray diffraction analysis.

A number of pathways for the biogenesis of pseudoguaianolides via the germacranolide-guaianolide route have been suggested (1–3). However, no biogenetic type *in vitro* conversion of a guaianolide (**1**) to a pseudoguaianolide skeleton (**2**), a



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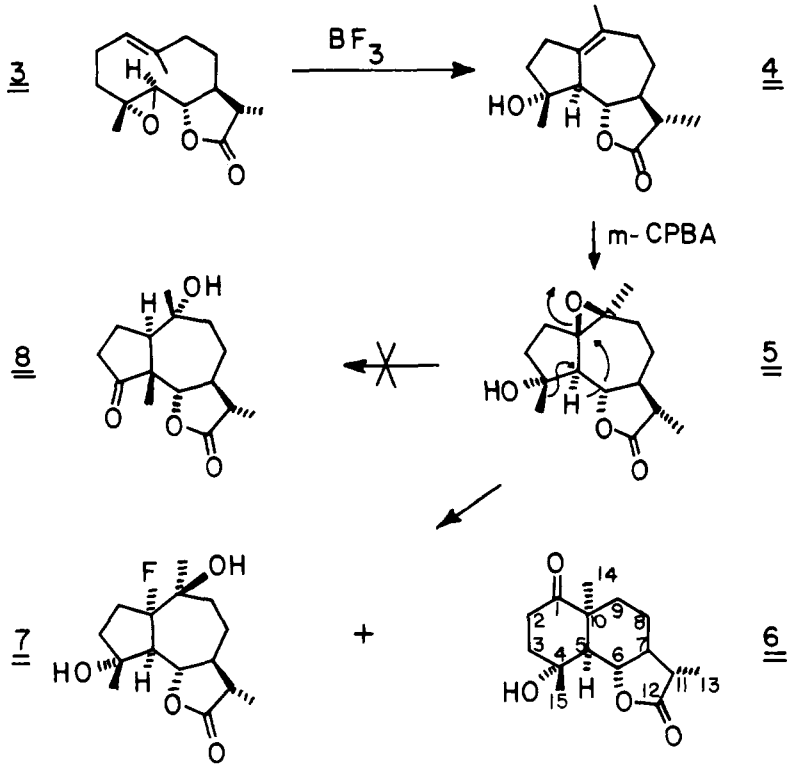
process which must involve a C–4 to C–5 methyl shift, has yet been reported. It has been demonstrated in laboratory conversions that germacra-1 (10)-4,5-dienes, as well as their 1 (10)-epoxide derivatives, can be transformed to the *trans*-decalin type eudesmanolides and that guaianolides result from Lewis acid-catalyzed cyclizations of germacrolide-4,5-epoxides (4). For instance, treatment of dihydroparthenolide (**3**) with BF_3-etherate provided the guaianolide (**4**) with high regio- and stereospecificity (5). Due to the availability of large amounts of dihydroparthenolide (**3**) from the local ragweed *Ambrosia artemisiifolia* L., experiments were designed to use this compound as starting material for a possible biogenetic type transformation of a germacrolide to a pseudoguaianolide. We present here the results of our attempts to convert a guaianolide-1 (10)-epoxide to the pseudoguaianolide skeleton.

RESULTS AND DISCUSSION

Detailed analysis of the BF_3-mediated cyclization products of dihydroparthenolide (**3**) gave no indication of the formation of the desired pseudoguaianolide skeleton (6). The *in vivo* conversion of a guaianolide to a pseudoguaianolide could possibly involve a guaianolide 1 (10)-epoxide precursor following a reaction path indicated by the flow of arrows in formula (**5**) to give (**8**) (1).

The conversion of the guaianolide (**4**) to the respective epoxide (**5**) with *m*-chloroperbenzoic acid in chloroform at room temperature proceeded smoothly.



SCHEME 1. Chemical transformations of dihydroparthenolide (**3**).

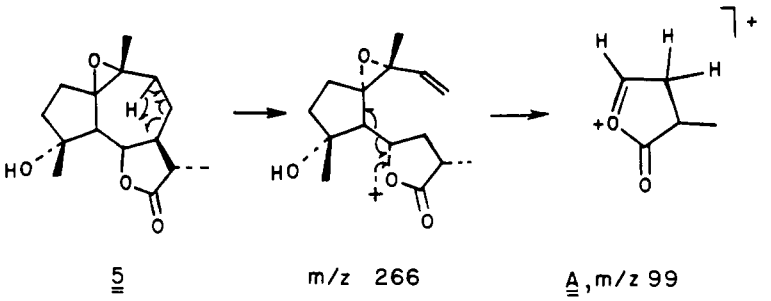
The crystalline epoxide (**5**), $C_{15}H_{22}O_4$, mp 111–113°, showed ir absorptions typical for a hydroxyl group (3450 cm^{-1}), γ-lactone (1785 cm^{-1}) and an epoxide ring (1245 cm^{-1}, 870 cm^{-1}). The structure of (**5**) without the configuration at C-1 and C-10 was inferred from the correlation of its ^{1}H-nmr spectral parameters with those of its precursor (**4**). The doublet due to the vinyl methyl at 1.70 ppm in (**4**) had disappeared; instead, a sharp three-proton singlet at 1.46 ppm was found in (**5**) (table 1). The mass spectrum of epoxide (**5**) gave a parent peak at *m/z* 266, a base peak at *m/z* 99, and other intense peaks at *m/z* 208, 190, 150,

TABLE 1. ^{1}H nmr parameters[a] of 1(10)-epoxyguaianolide (**5**) and its derivatives.

	5	6	7
H-5	2.70 br	2.05 d (9.0)	2.70 d (11.0)
H-6	4.07 dd (10.0)	3.48 dd (11.0)	4.62 dd (10.0)
C-4Me	1.29 s	1.54 s	1.32 s
C-10Me	1.46 s	1.51 s	1.27 d (1.0)
C-11Me	1.19 d (7.0)	1.18 d (7.0)	1.21 d (7.0)

[a]Spectra were obtained in $CDCl_3$ at 100 MHz; Chemical shifts are presented in parts per million (δ-scale) relative to TMSi as an internal standard; s = singlet; d = doublet; m = multiplet; br = broad; Line separations or coupling constants in Hertz (Hz) are given in parentheses.

97. The base peak at m/z 99 could be due to ion **A** formed as outlined in scheme 2. The peaks at m/z 208 and 190 might have been caused by the loss of C_3H_6O (58 m.u.) and the additional loss of H_2O from the fragment m/z 208, respectively.



SCHEME 2. Mass spectral fragmentation of guaianolide epoxide (**5**).

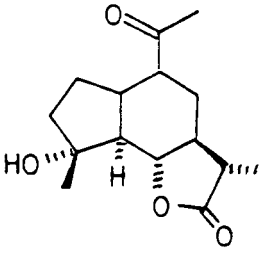
Two possible epoxides, 1 (10)-α and/or 1 (10)-β, could be expected from guaianolide (**4**), but inspection of stereomodels gave no clue as to the face of preferential attack of the peracid. BF_3-Catalyzed rearrangement of the β-epoxide (**5**) would, for stereoelectronic reasons, be more likely to form the pseudoguaianolide (**8**) since generation of a cationic center at C–1 might follow a C–5 to C–1 hydride shift and C–4 to C–5 methyl shift with antiperiplanar arrangement of the migrating units thus allowing a concerted rearrangement.

Treatment of epoxide (**5**) with boron trifluoride in ether resulted in a number of products, as shown by tlc analysis. The reaction mixture, when chromatographed on silica gel, afforded two major compounds as well as very small amounts of minor products which were not further investigated.

One of the major products of the BF_3-catalyzed rearrangement reaction was obtained as a crystalline material, $C_{15}H_{23}O_4F$, mp 177–179°. Single crystal x-ray diffraction studies (7) of the fluorine-containing compound showed that it represented the 1α-fluoro-10β-hydroxyguaianolide (**7**). Fluorination of the 1 (10)-epoxide (**5**) at C–1 by a nucleophilic attack of fluoride is uncommon. Although the details of the formation of (**7**) from (**5**) are not known, it is most likely that the non-distilled, commercial BF_3-etherate used in this reaction contained HF, which must have attacked the epoxide ring by simple acid-catalyzed opening. This unusual reaction of the epoxide was fortuitous in that it allowed assignment of the epoxide stereochemistry in the parent compound (**5**). Since the hydroxyl group at C–10 in (**7**) is β-oriented, the epoxide group in the precursor must have also had a β-configuration, as shown in (**5**).

The less polar of the two major constituents represented a crystalline substance, $C_{15}H_{22}O_4$, mp 170–172°, which in the ir spectrum showed absorptions for hydroxyl(s) at 3525 cm^{-1}, a lactonic function at 1760 cm^{-1} and carbonyl at 1700 cm^{-1}. The 100 MHz ^{1}H-nmr spectrum (table 1) exhibited a pair of doublets at 3.48 ppm and a doublet at 2.05 ppm, which were assigned to H–6 and H–5, respectively. An upfield shift of the H–5 and H–6 signals combined with a downfield shift of the signals due to the C–4 methyl group at 1.43 ppm, and C–10-methyl absorption at 1.51 ppm indicated that a skeletal rearrangement of the guaianolide skeleton had taken place.

The ir absorption at 1700 cm^{-1} suggested the presence of a ketone group since no aldehyde signal was observed in the ^1H-nmr spectrum. Several ketones had to be considered as possible rearrangement products. Structures (**9**) and (**10**) were excluded on the basis that treatment of an nmr sample of the new compound with $D_2O/NaOD$ gave no H/D-exchange which should have caused disappearance of the methyl signals in (**9**) and the H-5 doublet at 2.05 ppm in (**10**).



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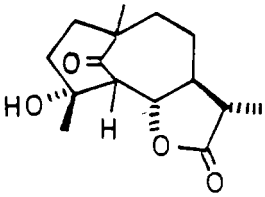

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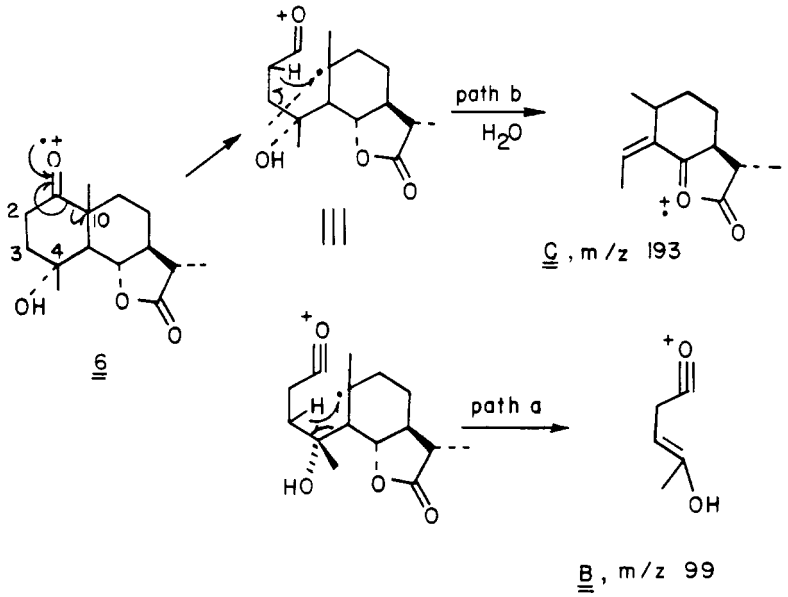
Other possible structures were excluded mainly on the basis of mass spectral assignments. The presence of intense peaks at *m/z* 193 was interpreted as being due to a fragmentation between C-1/C-10 and C-3/C-4 to give ion **C**, *m/z* 193 by a process shown in scheme 3. The base peak at *m/z* 99 could have resulted from hydrogen rearrangement followed by formation of ion **B**, or it could be due to ion **A** derived from the lactone moiety.

Definitive structural data of the eudesmanolide (**6**) were obtained by single crystal X-ray diffraction. This established that lactone **6** represented a *cis*-



SCHEME 3. Mass spectral fragmentation of the *cis*-decalin eudesmanolide (**6**).

decalin skeleton (figure 1). The conversion of the guaianolide 1 (10)-epoxide (**5**) to the eudesmanolide **6**, which must involve a shift of C–5 from C–1 to C–10, requires comment. Formation of the fluoroguaianolide (**7**) indicated a β-configuration of the epoxide oxygen in **5**. For a concerted BF_3-initiated rearrangement of **5** with a β-epoxide function, formation of a *trans*-decalin skeleton would have been predicted on grounds of anitperiplanar arrangements of the migrating groups. Formation of the *cis*-decalin skeleton **6** either indicates a non-stereospecific rearrangement or the starting material used for the rearrangement could have represented a mixture of α- and β-1 (10)-epoxides. Careful inspection of a 100 MHz ^1H nmr spectrum of **5** did not, however, indicate a mixture of isomers.

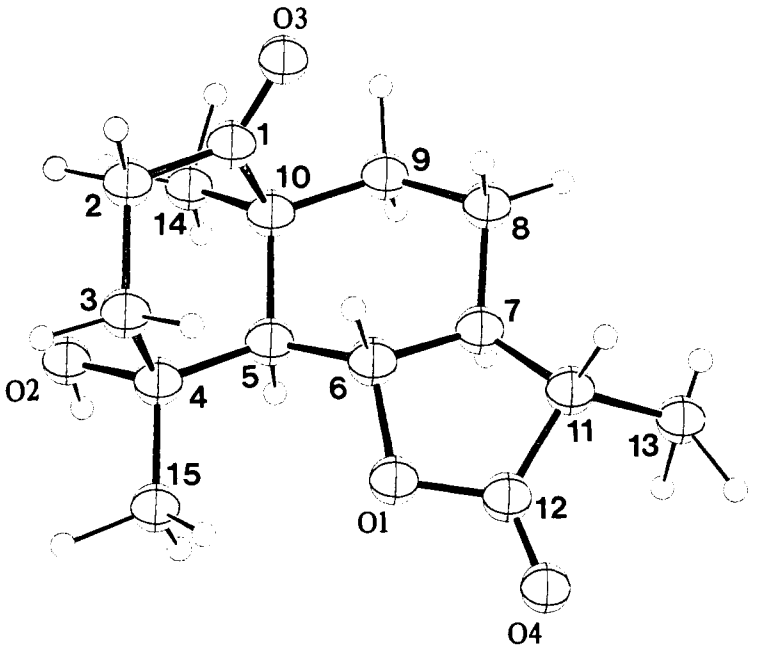


FIG. 1. Molecular structure of the eudesmanolide **6**.

EXPERIMENTAL[1]

PLANT MATERIAL.—A bulk collection of *Ambrosia artemisiifolia* L. was made in the East Baton Rouge Parish on December 12, 1974, (Fischer-Ohmstede No. 27, voucher deposited at the Louisiana State University Herbarium at Baton Rouge). The plant extraction and isolation of dihydroparthenolide (**3**) were carried out as previously described (9). About 1.5 g of crude (**3**) per 1 kg of plant material was obtained from the crude terpenoid extract after several days of standing at room temperature. Recrystallization from isopropyl alcohol provided colorless crystals, mp 137.5° (Lit (5) 137°).

BF_3-CATALYZED CYCLIZATION OF DIHYDROPARTHENOLIDE (**3**).—A solution of dihydroparthenolide (500 mg) in 50 ml of dry ether was treated with 4 ml BF_3-etherate and left at room temperature for 1.5 hrs and worked up as described in the literature (5). The crude crystalline

[1]Melting points were determined in capillaries on a Thomas-Hoover apparatus and are uncorrected. Infra-red spectra were taken on a Perkin-Elmer model 621 Spectrophotometer. Ultraviolet spectra were recorded on a Cary 14 Spectrometer. Low resolution mass spectra were obtained at 70eV on a Hitachi Perkin-Elmer model RMS-4 and on a LKB–9000 mass spectrometer. ^1H nmr spectra were recorded on a Varian HA 100 instrument. Elemental analyses were performed by Mr. Ralph Seab, Department of Chemistry, Louisiana State University, Baton Rouge.

material (390 mg) was dissolved in chloroform and chromatographed over silica gel with isopropyl alcohol-benzene (8:92 by volume) as the elutant; 285 mg of pure crystalline (**4**), mp 124–126° (Lit: 127°) (5), was obtained.

GUAIANOLIDE 1(10)-EPOXIDE (**5**).—A solution of 200 mg of (**4**) and 200 mg *m*-chloroperbenzoic acid in 8 ml of chloroform was left at room temperature for 2 days. The chloroform solution was washed with 5% aq. $NaHCO_3$ then with water, dried over Na_2SO_4, and filtered. Removal of the solvent *in vacuo* gave a syrup which was chromatographed over silica gel. Elution of the column with amyl acetate provided 90 mg of pure crystalline epoxide (**5**), mp 111–113°; ir (KBr) 3575, 3450, 1785, 1405, 1380, 1320, 1245, 1190, 1162, 1142, 1110, 1035, 1012, 995, 988 and 870 cm^{-1}; uv end absorption; ms, *m/z* M^+: 266 (13.5%), M–CH_3: 251 (35), M–H_2O: 248 (43), M–CH_3–H_2O: 233 (14), M–C_2H_3O: 223 (22), M–58: 208 (53), M–58–18): 190 (93), M–116: 150 (63), **A**: 99 (100), M–C_6H_9O: 97 (96), $C_2H_3O^+$: 43 (18).

Anal. calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.43; H, 8.25%.

TABLE 2. Coordinates (x10^4) for *cis*-decaline type eudesmanolide (**6**).

Atom	X/A	Y/B	Z/C
C1	5076(13)	4560(20)	3291(13)
C2	4482(12)	3486(21)	1922(13)
C3	5431(13)	1996(21)	1960(11)
C4	7013(11)	2541(18)	2409(11)
C5	7633(10)	3545(18)	3909(9)
C6	7702(10)	2478(16)	5227(10)
C7	8402(10)	3418(17)	6712(10)
C8	7389(12)	4745(20)	6755(11)
C9	7169(13)	5910(21)	5426(12)
C10	6673(11)	5102(16)	3877(12)
C11	8805(10)	2000(16)	7842(9)
C12	9181(10)	682(17)	6997(11)
C13	10092(15)	2389(22)	9385(11)
C14	6713(14)	6486(18)	2773(14)
C15	7949(13)	1039(20)	2432(12)
01	8627(7)	1015*	5529(7)
02	6944(7)	3590(16)	1180(7)
03	4326(8)	4945(15)	3936(10)
04	9893(9)	−543(14)	7478(8)

*This value was assigned to fix the origin in the polar space group, and was not refined.

BF_3-CATALYZED REARRANGEMENT OF (**5**).—A solution of the epoxide (**5**) (300 mg) in 30 ml of dry ether was treated with 3 ml of BF_3 etherate and left at room temperature for 4 hrs. Quenching with 60 ml of water and evaporation of the organic phase *in vacuo* left a purple residue which was taken up in 50 ml of chloroform. The solution was washed 3 times with aq. 5% $NaHCO_3$, water and then dried over Na_2SO_4. Filtration and evaporation left a purple-brown residue which was chromatographed over silica gel; 3 ml fractions were collected. The column was eluted first with 300 ml of isopropyl alcohol-benzene (4:96 by volume) and then with 300 ml of isopropyl alcohol-benzene (15:85 by volume). Fractions 77–88 contained 70 mg of crude **6** which, after recrystallization from ethyl acetate-diethyl ether, gave colorless platelets (**6**), mp 170–172°; ir (film): 3525, 1760, 1700, 1460, 1455, 1380, 1330, 1275, 1235, 1190, 1170, 1135, 1115, 1050, 1018 and 984 cm^{-1}; uv, λmax (MeOH) 208 nm (ε, 2.43 x 10^4); ms, *m/z* M^+: 266 (11.4), M–H_2O: 248 (26), M–H_2O–CO: 220 (46), M–CH_3–H_2O–CO: 205 (31), M(73: **C**, 193 (73), M–91: 175 (34), M–101; 165 (55), M–116: 150 (83), **A** and/or **B**: 99 (100), 93 (31), 71 (16), 43 (16).

Anal. calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.46; H, 8.13%.

Treatment of (**6**) with $NaOD/D_2O$ did not result in a loss of a methyl signal or the H–5 signal in the ^{1}Hnmr spectrum.

Fractions 120–123 provided 30 mg of (**7**). Recrystallization from ethyl acetate-diethyl ether gave colorless needles, mp 177–179°; ir (film): 3450, 1760, 1450, 1380, 1345, 1320, 1195, 1150, 1100, 1070, 1050, 1020, 985 and 930 cm^{-1}; uv, λ max (MeOH) 208 nm (ε, 2.61 x 10^4); ms, *m/z* M^+: 286 (2%), M–OH: 269 (70), M–HF: 266 (18), M–CH_3–H_2O: 253 (46), M–HF–OH: 249 (75), M–HF–H_2O: 248 (99.8), M–HF–H_2O–CH_3: 233 (52), M–HF–2H_2O: 230 (48), M–81: 205 (67), M–93: 193 (59), M–95: 191 (95), M–96: 190 (99.5), **A**: 99 (75), C_4H_7O: 71 (40), C_3H_7O: 58 (10), C_2H_3O: 43 (100).

Anal. calcd. for $C_{15}H_{23}O_4F$: C, 63.35; H, 8.45. Found: C, 62.79; H, 8.24%.

SINGLE CRYSTAL X-RAY DIFFRACTION DATA OF COMPOUND **6**.—Crystals of **6** were obtained as large, colorless plates from ethyl acetate-ethyl ether solution. They were somewhat poorly formed, and diffraction quality material could only be obtained by cutting small, well-formed regions from the large crystals. A fragment approximately 0.20 x 0.12 x 0.05 mm was glued to the tip of a glass fiber and mounted in random orientation on an Enraf-Nonius CAD4 automated diffractometer. Graphite-monochromatized MoKα radiation was used to make all measurements.

CRYSTAL DATA.—$C_{15}H_{22}O_4$, MW=266.3, monoclinic space group $P2_1$, a=10.087(8), b=8.082(6), c=9.792(10) Å, β=114.45(3)°, Z=2, d_c=1.22 g cm^{-3}, MoKα radiation, λ=0.71069 Å μ(MoKα)=0.81 cm^{-1}.

Intensity data were collected by ω–2θ scans of variable speed designed to yield approximately equal intensities of 1000 net counts for all reflections of significant intensity. Background measurements were made at the beginning and end of each scan, and the intensities were corrected for background. Periodic remeasurement of standard reflections during the course of the data collection indicated no appreciable decay in the X-ray beam. All data within one quadrant having $6° \leq 2\theta \leq 46°$ were measured as described above. Lorentz and polarization corrections were applied to the data. Of the 1165 data measured, 853 had observable intensities and were used in further calculations.

The structure was solved by routine application of the direct methods program MULTAN78 and refined by weighted least squares methods based upon F to R=0.101 and Rw=0.078. The weighting scheme employed was $w = 0.063/(\sigma^2(f) + .0055\ F^2)$. Hydrogen atoms were easily discernible from difference maps but were placed in calculated positions for refinement purposes. Coordinates for nonhydrogen atoms are given in table 2, and observed and calculated structure factors are listed in the supplementary material. Standard deviations for bond distances are estimated to be 0.01–0.02 Å.

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