# CRYSTAL STRUCTURE OF THE NATIVE SESQUITERPENE LACTONE ARCTOLIDE*

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X-Ray structure analysis of the native sesquiterpenic lactone arctolide (*I*) was performed. The results gave evidence that the relative configuration of the hydroxy group at C(3) in the initially suggested arctolide formula (*II*) has to be corrected to β. Related to this modification, formulas of some other native lactones and derivatives which had been correlated with arctolide before were also corrected.

In our previous paper dealing with arctolide (*I*) we suggested its structure – including its absolute configuration – as expressed by formula *II* (ref.[1]). The relative configurations of substituents at C(1), C(5), C(7) and C(8) were determined based on $^1$H NMR spectra whereas those of the oxygen functions at C(3) and C(10) were derived particularly based on the intramolecular hydrogen bonds observed in the IR spectra of arctolide and some of its structure analogues[1]. Since the initially proposed arctolide structure (*II*) with the α-configuration of the hydroxy group at C(3) was later subject to criticism[2], we decided to verify the arctolide structure by X-ray diffraction analysis.

Figure 1 shows a perspective view of the arctolide molecule (*I*). The coordinates of the non-hydrogen atoms, bond lengths, bond angles and endocyclic torsion angles are given in Tables I – IV, respectively. Figure 1 and Table IV indicate that the ring junctions in this tricyclic molecule are cis at C(1)–C(5) and trans at C(7)–C(8). The acetoxy group at C(3) is β-oriented while the oxirane ring at C(10) is α. The cycloheptane ring is a twist-chair whose approximate twofold axis of symmetry passes through C(5) and the midpoint of the C(8)–C(9) bond ($TC_5$ form). This configuration is quite different from that adopted by the trans-fused guaian-8,12-olides, mikanokryptin[3],

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xerantholide[4] and its iodo derivative[5], which in the solid state approximate the $C_9$ chair, but is similar to that found in otoimbricatin A (ref.[6]), although its seven-membered ring is appreciably distorted towards the $C_8$ chair form. The $TC_5$ conformation observed in arctolide is much more common for exomethylenecycloheptane in C(6)-trans-lactonised guaianolides where it has been found in solstitialin[7], 3-oxograndolide[8], salograviolide A (ref.[9]), grossheimin[10] and, in a somewhat distorted form, in 8-epiisolippidiol[11].

Both the cyclopentane and γ-lactone rings are puckered to an appreciable extent; the average values of the five endocyclic torsion angles are 22.0(12.2)° and 24.1(11.1)°, respectively. The two rings adopt the α-envelope conformation with the flap at C(5) and C(7), respectively. The C=O and ethylene groups of the γ-lactone deviate significantly from coplanarity, the C(13)–C(11)–C(12)–O(12) torsion angle being 22.6(9)°. The signs of the C=C–C=O and C(11)–C(7)–C(8)–O(8) torsion angles are paired as in the majority of sesquiterpene lactones. The bond lengths and bond angles are mostly within the normal ranges. The $C(sp^3)$–$C(sp^2)$ distances vary from 1.507(5) to 1.561(6) Å, the longest being at the C(1)–C(5) carbocyclic ring junction. The C(5)–O(5) distance of 1.453(8) Å is longer than expected for the $C(sp^3)$–OH bond which, for example, in some of the above guaianolides ranges from 1.408(4) to 1.431(3) Å (refs[3,6–11]) with an average of 1.421(8) Å. The C(5)–OH distances in C(5) oxygenated guaianolides whose structure has been determined[12–14] with a relatively high precision are within the range of 1.411(7) to 1.439(6) Å, with an average of 1.423(10) Å. Thus, the bond in question is, within 3σ, at the upper limit of $C(sp^3)$–hydroxy bond lengths.

The hydroxy group at C(5) acts as a donor in a weak hydrogen bond with the screw axis related lactone carbonyl oxygen. The O(5)–HO(5), O(5)...O(12$^i$) and

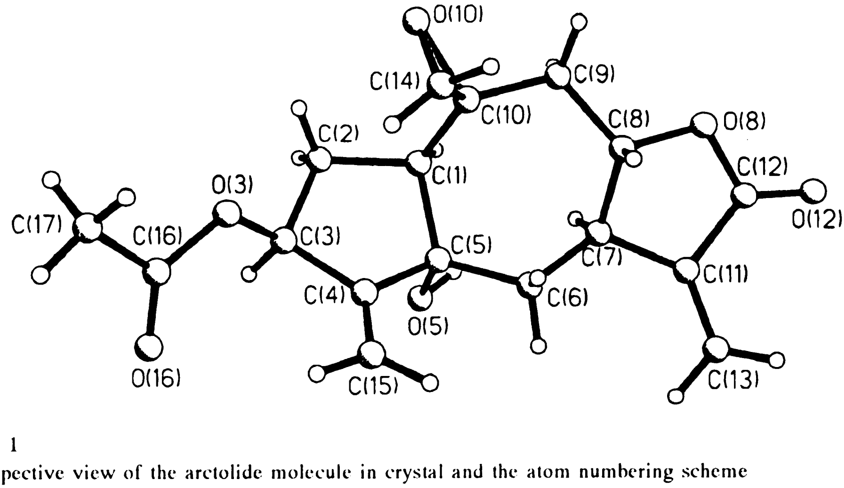


FIG. 1

A perspective view of the arctolide molecule in crystal and the atom numbering scheme

HO(5)...O(12$^i$) distances are 0.89(4). 3.009(4) and 2.14(4) Å while the O(5)–HO(5)...O(12$^i$) angle is 165(3)° (symmetry code: (i) $-x - 2$, $-1/2 + y$, $-z - 1$). As shown in Fig. 2, the molecules connected by intermolecular hydrogen bonds form chains parallel to the *y* direction.

It follows from the above facts that the true relative configuration of arctolide is represented by formula *I*, which differs from the initially proposed formula[1] in the β-orientation of the acetoxy group at C(3). This formula also involves the absolute configuration as has been derived previously[1].

In relation to the revision of the arctolide structure *I*, the configuration at C(3) must also be corrected for some structure analogues and derivatives which have been correlated with arctolide particularly by means of their $^1$H NMR spectra[1,15,16]. In our previous paper on arctolide[1] we mentioned two hydrogenation products of this native

TABLE I
Atomic coordinates (. $10^4$) and equivalent isotopic displacement coefficients (Å$^2$ . $10^3$)

| Atom | *x* | *y* | *z* | $U_{eq}$$^a$ |
|---|---|---|---|---|
| C(1) | -6672(4) | -3633(8) | -2184(3) | 37(1) |
| C(2) | -5622(4) | -4130(9) | -1104(4) | 47(2) |
| C(3) | -4078(4) | -4222(8) | -1617(4) | 43(1) |
| C(4) | -4231(4) | -3794(8) | -2981(4) | 41(1) |
| C(5) | -5807(4) | -4127(8) | -3367(4) | 39(1) |
| C(6) | -6248(4) | -3281(8) | -4587(4) | 42(1) |
| C(7) | -7884(4) | -3146(8) | -4796(3) | 37(1) |
| C(8) | -8497(4) | -1520(8) | -4232(3) | 41(1) |
| C(9) | -8659(5) | -1504(8) | -2839(4) | 48(2) |
| C(10) | -7228(4) | -1810(8) | -2154(3) | 43(1) |
| C(11) | -8484(4) | -2991(8) | -6092(4) | 40(1) |
| C(12) | -9910(5) | -2134(8) | -5955(4) | 44(2) |
| C(13) | -7949(5) | -3379(10) | -7177(4) | 65(2) |
| C(14) | -6240(6) | -375(9) | -1917(5) | 60(2) |
| C(15) | -3230(5) | -3143(10) | -3686(4) | 58(2) |
| C(16) | -1737(5) | -3324(9) | -865(4) | 52(2) |
| C(17) | -992(5) | -2095(11) | -15(5) | 75(2) |
| O(3) | -3181(3) | -3008(7) | -945(3) | 49(1) |
| O(5) | -5925(4) | -5969(6) | -3489(3) | 49(1) |
| O(8) | -9927(4) | -1357 | -4832(3) | 54(1) |
| O(10) | -7179(4) | -996(7) | -956(3) | 65(1) |
| O(12) | -10951(3) | -2070(7) | -6659(3) | 56(1) |
| O(16) | -1157(3) | -4445(8) | -1423(3) | 66(1) |

$^a$ Equivalent isotropic $U$ defined as one-third of the trace of the orthogonalized $U_{ij}$ tensor.

lactone and their trichloroacetylcarbamates. Their formulas must be corrected to *IIIa*, *IVa*, and *IIIb*, *IVb*. Rather recently we described the isolation of four – among others – sesquiterpenic lactones from the species *Arctotis grandis* THUNB. which, according to their $^1$H NMR spectra, are analogous to arctolide[15]. Now we correct the structure of

TABLE II
Bond lengths (Å) in arctolide molecule

| Atoms | Bond length | Atoms | Bond length |
|---|---|---|---|
| C(1)-C(2) | 1.547(6) | C(1)-C(5) | 1.561(6) |
| C(1)-C(10) | 1.518(8) | C(2)-C(3) | 1.535(6) |
| C(3)-C(4) | 1.508(6) | C(3)-O(3) | 1.445(7) |
| C(4)-C(5) | 1.525(6) | C(4)-C(15) | 1.307(7) |
| C(5)-C(6) | 1.518(6) | C(5)-O(5) | 1.453(8) |
| C(6)-C(7) | 1.523(5) | C(7)-C(8) | 1.523(8) |
| C(7)-C(11) | 1.495(5) | C(8)-C(9) | 1.507(5) |
| C(8)-O(8) | 1.461(5) | C(9)-C(10) | 1.517(6) |
| C(10)-C(14) | 1.465(8) | C(10)-O(10) | 1.437(6) |
| C(11)-C(12) | 1.484(7) | C(11)-C(13) | 1.310(6) |
| C(12)-O(8) | 1.353(6) | C(12)-O(12) | 1.212(5) |
| C(14)-O(10) | 1.443(7) | C(16)-C(17) | 1.487(9) |
| C(16)-O(3) | 1.354(5) | C(16)-O(16) | 1.194(8) |

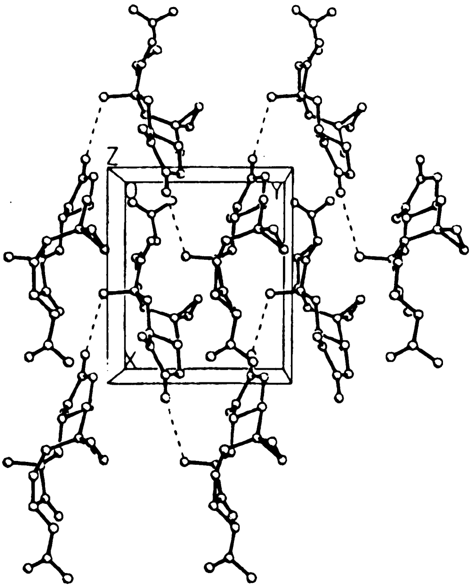
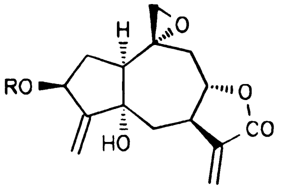
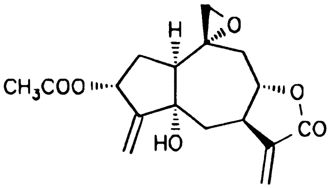


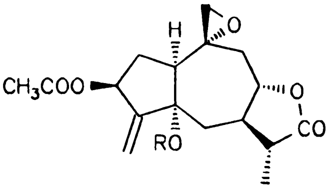
FIG. 2
View of the packing arrangement of the arctolide molecules. Broken lines indicate intermolecular hydrogen bonds



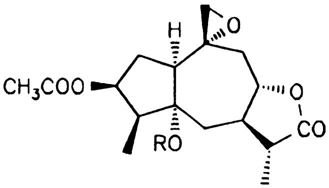
*I*, R = $COCH_3$
*VI*, R = $COCH(CH_3)CH_2CH_3$
*VII*, R = $COCH_2CH_3$
*VIII*, R = H
*XII*, R = $COCH(CH_3)_2$



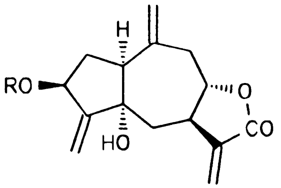
*II*



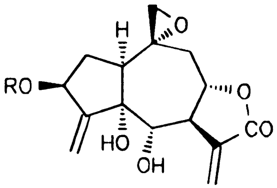
*IIIa*, R = H
*IIIb*, R = $CONHCOCCl_3$



*IVa*, R = H
*IVb*, R = $CONHCOCCl_3$



*V*, R = $COCH_3$
*XI*, R = $COCH_2CH_3$



*IX*, R = $COCH_2CH(CH_3)_2$
*X*, R = $COCH(CH_3)CH_2CH_3$

TABLE III
Bond angles (°) in arctolide molecule

| Atoms | Angle | Atoms | Angle |
|---|---|---|---|
| C(2)-C(1)-C(5) | 103.2(3) | C(2)-C(1)-C(10) | 115.3(4) |
| C(5)-C(1)-C(10) | 115.3(4) | C(1)-C(2)-C(3) | 108.2(3) |
| C(2)-C(3)-C(4) | 105.5(3) | C(2)-C(3)-O(3) | 108.3(4) |
| C(4)-C(3)-O(3) | 112.5(4) | C(3)-C(4)-C(5) | 107.5(3) |
| C(3)-C(4)-C(15) | 126.5(4) | C(5)-C(4)-C(15) | 125.8(4) |
| C(1)-C(5)-C(4) | 103.4(3) | C(1)-C(5)-C(6) | 117.6(4) |
| C(4)-C(5)-C(6) | 113.6(4) | C(1)-C(5)-O(5) | 106.3(4) |
| C(4)-C(5)-O(5) | 105.3(4) | C(6)-C(5)-O(5) | 109.7(4) |
| C(5)-C(6)-C(7) | 114.0(3) | C(6)-C(7)-C(8) | 111.8(4) |
| C(6)-C(7)-C(11) | 119.5(3) | C(8)-C(7)-C(11) | 99.8(4) |
| C(7)-C(8)-C(9) | 116.5(4) | C(7)-C(8)-O(8) | 103.5(3) |
| C(9)-C(8)-O(8) | 109.5(3) | C(8)-C(9)-C(10) | 112.4(3) |
| C(1)-C(10)-C(9) | 115.4(4) | C(1)-C(10)-C(14) | 121.1(4) |
| C(9)-C(10)-C(14) | 119.7(5) | C(1)-C(10)-O(10) | 115.5(4) |
| C(9)-C(10)-O(10) | 112.3(4) | C(14)-C(10)-O(10) | 59.6(3) |
| C(7)-C(11)-C(12) | 104.9(3) | C(7)-C(11)-C(13) | 132.3(4) |
| C(12-C(11)-C(13) | 122.7(4) | C(11)-C(12)-O(8) | 108.4(3) |
| C(11)-C(12)-O(12) | 130.4(5) | O(8)-C(12)-O(12) | 121.2(4) |
| C(10)-C(14)-O(10) | 59.2(3) | C(17)-C(16)-O(3) | 111.3(5) |
| C(17)-C(16)-O(16) | 125.4(5) | O(3)-C(16)-O(16) | 123.3(5) |
| C(3)-O(3)-C(16) | 117.6(5) | C(8)-O(8)-C(12) | 109.3(3) |
| C(10)-O(10)-C(14) | 61.2(3) | | |

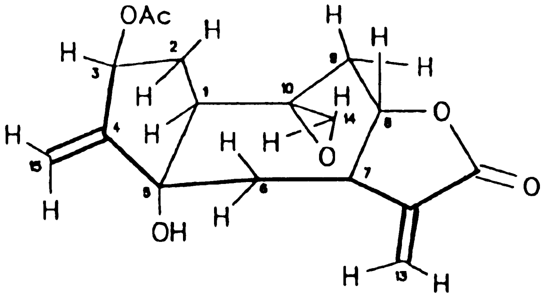


FIG. 3
Schematic view on the conformation of the arctolide molecule in solution

10,14-deoxyarctolide, 3-deacetyl-3-(2′-methyl)butyrylarctolide and deacetylarctolide in the sense of formulas *V* – *VIII*. Somewhat more recently we described nine sesquiterpenic lactones as the components of the species *Venidium hirsutum* BEROL., out of which eight are structure analogues of arctolide, as indicated by their $^1$H NMR spectra[16]. Therefore we propose for venidiolide A, venidiolide B, 3-deacetyl-3-propionyl-10,14-deoxoarctolide and 3-deacetyl-3-isobutyrylarctolide the corrected formulas *IX* – *XII*. The four remaining lactones from *V. hirsutum*[16] which are analogous to arctolide are identical with those obtained from *Arctotis grandis*[15], whose revised formulas *V* – *VIII* have been mentioned.

Analysis of the intramolecular hydrogen bonds based on the corrected arctolide structure (*I*) leads to some interesting conclusions concerning its conformation. As mentioned above, a single intermolecular hydrogen bond was found in the arctolide crystal, viz. between C(5)OH and C=O of the lactone ring. Investigation of intramolecular hydrogen bonds by IR spectroscopy in conjunction with the splitting

TABLE IV
Endocyclic torsion angles (°) in arctolide molecule

| Atoms | Angle |
|---|---|
| Five-membered ring | |
| C(5)-C(1)-C(2)-C(3) | 20.9(5) |
| C(2)-C(1)-C(5)-C(4) | -33.1(5) |
| C(1)-C(2)-C(3)-C(4) | -0.4(5) |
| C(2)-C(3)-C(4)-C(5) | -21.3(5) |
| C(3)-C(4)-C(5)-C(1) | 34.4(5) |
| Seven-membered ring | |
| C(10)-C(1)-C(5)-C(6) | -32.5(6) |
| C(5)-C(1)-C(10)-C(9) | 83.7(5) |
| C(1)-C(5)-C(6)-C(7) | -41.9(6) |
| C(5)-C(6)-C(7)-C(8) | 87.6(5) |
| C(6)-C(7)-C(8)-C(9) | -76.3(5) |
| C(7)-C(8)-C(9)-C(10) | 58.4(6) |
| C(8)-C(9)-C(10)-C(1) | -73.9(5) |
| γ-Lactone ring | |
| O(8)-C(8)-C(7)-C(11) | 36.1(4) |
| C(7)-C(8)-O(8)-C(12) | -26.8(5) |
| C(8)-C(7)-C(11)-C(12) | -33.3(5) |
| C(7)-C(11)-C(12)-O(8) | 19.0(5) |
| C(11)-C(12)-O(8)-C(8) | 5.2(5) |

constants in the $^1$H NMR spectra[1] suggested that the conformation of arctolide in solution will be different from that in the crystal. The hydrogen bond between C(5)O–H and the C(10), C(14)-epoxy oxygen (3 551 cm$^{-1}$) can establish readily if the seven-membered ring adopts the conformation shown in Fig. 3 (analogous to conformation *A* which has been suggested by us previously[1] based on $^1$H NMR data), where the above epoxy ring is sufficiently close to the hydrogen atom of the C(5)OH group. The intramolecular hydrogen bond between C(5)O–H and C(3)OCOCH$_3$, on the other hand, appears to be much more difficult to form, and its establishment was interpreted in our previous paper[1] as an argument against the transoid orientation of the two groups. A new detailed conformation analysis of arctolide by means of Dreiding models revealed that under the condition of the "optimum" rotamer the distance between the hydrogen atom of the C(5)OH group and the carbonyl oxygen atom of the C(3)OCOCH$_3$ group can attain values about 3.5 Å, which still makes possible formation of the intramolecular hydrogen bond which has been identified based on the IR spectra (3 588 cm$^{-1}$).

## EXPERIMENTAL

### X-Ray Structural Analysis of Arctolide

*Crystal data.* $C_{17}H_{20}O_6$, m.p. 142 – 144 °C, monoclinic, space group $P2_1$, $a = 9.205(2)$, $b = 7.831(2)$, $c = 10.752(2)$ Å, $\beta = 90.97(3)°$, $V = 774.9(3)$ Å$^3$, $D_x = 1.373$ g cm$^{-3}$, $Z = 2$, $\lambda(MoK_\alpha) = 0.71069$ Å, $\mu = 0.10$ mm$^{-1}$.

*Crystallographic measurements.* A crystal approximately 0.55 × 0.5 × 0.2 mm in size, grown from a methanol–ethyl ether mixture, was used for obtaining crystallographic data on a Syntex $P2_1$ diffractometer using graphite monochromatized $MoK_\alpha$ radiation. The lattice constants and orientation matrix were derived from a least squares fit of 15 centered reflections. Intensities were measured using the $\theta - 2\theta$ scan technique with the scan rate directly dependent on the net count obtained on rapid pre-scans for each reflection. Two standard reflections were measured after collecting every 100 reflections, and their intensity variation did not exceed 3.3%. One-fourth of the reciprocal sphere was collected such that $h$ and $k$ were non-negative. 1 620 unique reflections were measured; out of them 1 144 were considered observed ($F > 4\sigma(F)$). The background and integrated intensity for each reflection were evaluated by a profile analysis according to Lehmann and Larsen[17] using the PRADIR program[18]. The Lorentz and polarization factors were applied in converting the intensities to structure factor amplitudes but no absorption correction was deemed necessary ($\mu(MoK_\alpha) = 0.10$ mm$^{-1}$).

*Structure analysis.* The structure was elucidated by direct methods using the SHELXS86 program[19] and refined using $F$ magnitudes by full-matrix least squares of SHELX76 (ref.[20]). The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed at calculated positions and subjected to constrained refinement with a common isotropic displacement parameter $U = 0.06$ Å$^2$, except for the hydrogen atom of the hydroxy group which was located from a difference Fourier map and its positional and isotropic displacement parameters were allowed to vary. The absolute configuration could not be determined by the anomalous dispersion method. The function minimized was $\sum(|F_o|) - |F_c|)^2$ with $w = 1/[\sigma^2(F_o) + 0.0003F_o^2]$, where $\sigma(F_o)$ is the standard deviation of the observed amplitudes, based on counting statistics. Convergence was attained at $R = 0.045$ ($wR = 0.050$) for the 1 144 observed reflections and 212 refined parameters. The final difference map showed minima and maxima ranging from −0.19 to 0.16 e Å$^{-3}$. The PLUTO program[21] was used for drawing and the PARST program[22] for geometry calculations, as implemented in the CRYSRULER package[23].

## REFERENCES

1. Buděšínský M., Šaman D., Pelnař J., Vašíčková S., Drożdż B., Grabarczyk H., Le Viêt Ngoc Phuong, Holub M.: Collect. Czech. Chem. Commun. *54*, 166 (1989).
2. Tsichritzis F., Jakupovic J., Bohlmann F.: Phytochemistry *29*, 195 (1990).
3. Bovill M. J., Guy M. H. P., Sim G. A., White D. N. J., Herz W.: J. Chem. Soc., Perkin Trans. 2 *1979*, 53.
4. Rychlewska U.: Pol. J. Chem. *55*, 1895 (1981).
5. Watson W. H., Miski M., Mabry T. J.: Acta Crystallogr., C *43*, 2180 (1987).
6. Soriano-Garcia M., Toscano R. A., Guerrero C.: Acta Crystallogr., C *41*, 538 (1985).
7. Thiessen W. E., Hope H.: Acta Crystallogr., B *26*, 554 (1970).
8. Rychlewska U.: Acta Crystallogr., C *41*, 540 (1985).
9. Rychlewska U., Szczepanska B., Daniewski W. M., Nowak G.: J. Crystallogr. Spectrosc. Res., in press.
10. Rychlewska U.: Unpublished results.
11. Rychlewska U., Kisiel W.: Acta Crystallogr., C *47*, 129 (1991).
12. Itô T., Shimizu T., Fujimoto Y., Tatsuno T.: Acta Crystallogr., B *34*, 1009 (1978).
13. Seaman F. C., Malcolm A. J., Fronczek F. R., Lee I.-Y., Fischer N. H.: Phytochemistry *23*, 817 (1984).
14. Korp J. D., Bernal I., Fischer N. H., Leonard C., Lee I.-Y., Le Van N.: J. Heterocycl. Chem. *19*, 181 (1982).
15. Buděšínský M., Le Viêt Ngoc Phuong, Perez N., Daniewski W. M., Wawrzun A., Gumulka M., Vašíčková S., Šaman D., Drożdż B., Grabarczyk H., Rychlewska U., Holub M.: Collect. Czech. Chem. Commun. *54*, 473 (1989).
16. Buděšínský M., Grabarczyk H., Daniewski W. M., Wawrzun A., Gumulka M., Šaman D., Drożdż B., Holub M.: Collect. Czech. Chem. Commun. *54*, 1919 (1989).
17. Lehman M. S., Larsen F. K.: Acta Crystallogr., A *30*, 580 (1974).
18. Jaskólski M.: *PRADIR Program Upgrading Syntex P2₁ Software to Include On-Line Profile Analysis and Floppy-Discs Output.* University of Poznan, Poznan 1990.
19. Sheldrick G. M.: *SHELX86. Program for Crystal Structure Solution.* University of Göttingen, Göttingen 1986.
20. Sheldrick G. M.: *SHELX76. Program for Crystal Structure Determination.* University of Cambridge, Cambridge 1976.
21. Motherwell W. D. S., Clegg W.: *PLUTO78. Program for Plotting Molecular and Crystal Structures.* University of Cambridge, Cambridge 1978.
22. Nardelli M.: Comput. Chem. *7*, 95 (1983).
23. Rizzoli C., Sangermano V., Calestani G., Andretti G. D.: *CRYSRULER Package Ver. 1.0.* University of Parma, Parma 1986.

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