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Synthesis of Some Substituted Oxaspiro[4,5]decanenones by Way of Intermolecular Diels-Alder Reaction of Alkylidene 2,3-Dimethoxybutenolides Obtained From L-Ascorbic Acid

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Abstract

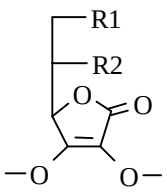
L-Ascorbic acid **1** has been transformed into the (*Z*)-butenolide aldehyde **8** which reacted in Wittig reactions to give mainly the (*Z*),(*E*)-dienobutenolides **9a-e** in good yields. A Diels-Alder reaction of the (*Z*)-dienobutenolide **9a** with diethyl maleate **10** under pressure at 140°C produced only a diastereomeric mixture of the substituted oxaspiro[4,5]decanenones [(±)-**12** and (±)-**13**] by way of intermolecular cycloaddition of two molecules of **9a**. The structure of the pure diastereomer **12a** of the main product (±)-**12** was established by single-crystal X-ray crystallography.

Keywords: L-Ascorbic acid, (Z)-butenolides, Diels-Alder reaction, Wittig reaction,oxaspiro[4,5]decanones

Introduction

The spirolactone skeleton is incorporated in several natural products and in some synthetic flavouring agents and perfumes [1-4].

In our previous work [5] we discovered a simple and efficient stereoselective synthesis of (*Z*)- and (*E*)-alkylidene 2,3-dimethoxybutenolides from readily available and inexpensive carbohydrate L-ascorbic acid **1**. Several derivatives of **1**, such as **5a** and **6a** (Scheme 1), **5b** (R^1=OTs, R^2=OH), **5c** (R^1=R^2=OSO_2Me), **5d** (R^1=Br, R^2=OAc) and **6b** [R=$CH(CO_2Et)SO_2Ph$] were synthesized [5]. Since elimination of water from **5** to **6** proceeds exclusively in a *trans* manner, the dienes **6** have a (Z) configuration at the exocyclic double bond. This structure has been further proven by X-ray analysis of the corresponding 6-azido derivative **6c** ($R=N_3$) [5]. Careful acidic hydrolysis of the corresponding bromoacetate **5d** [5] produced 6-bromo-6-deoxy-2,3-di-*O*-methyl-L-ascorbic acid **5e** (R^1=Br, R^2=OH).



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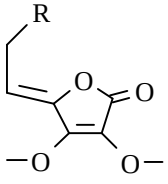

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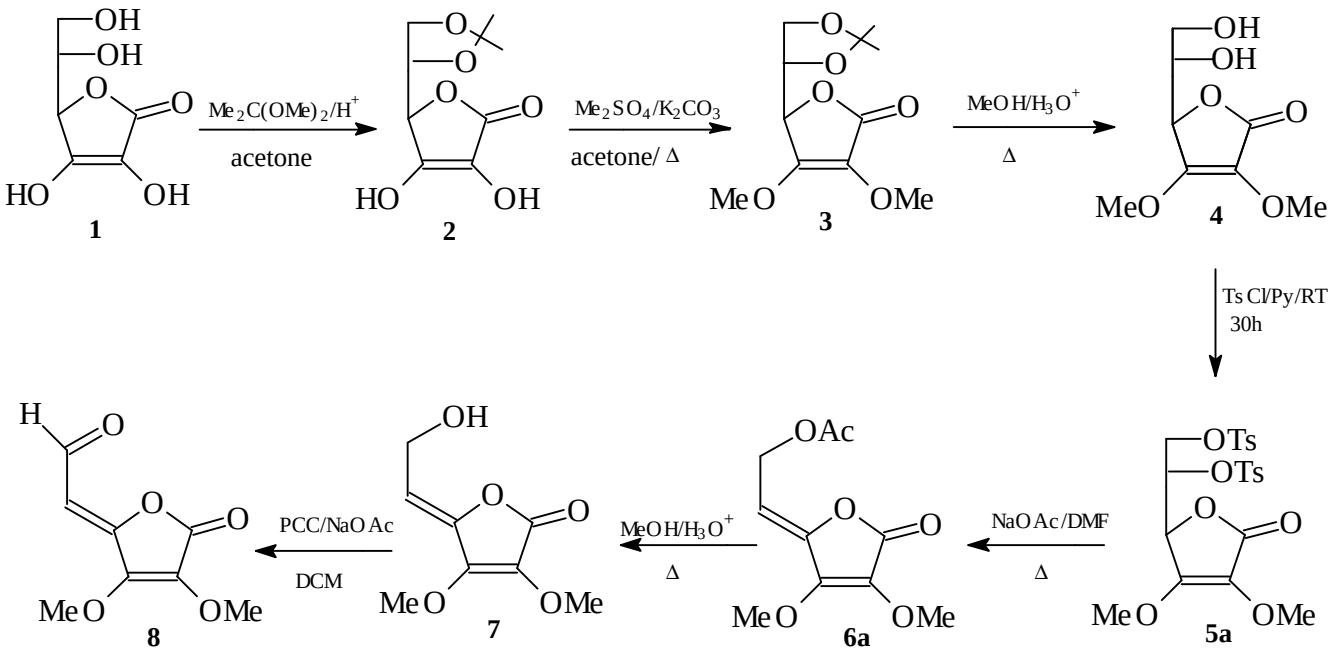


Scheme 1.

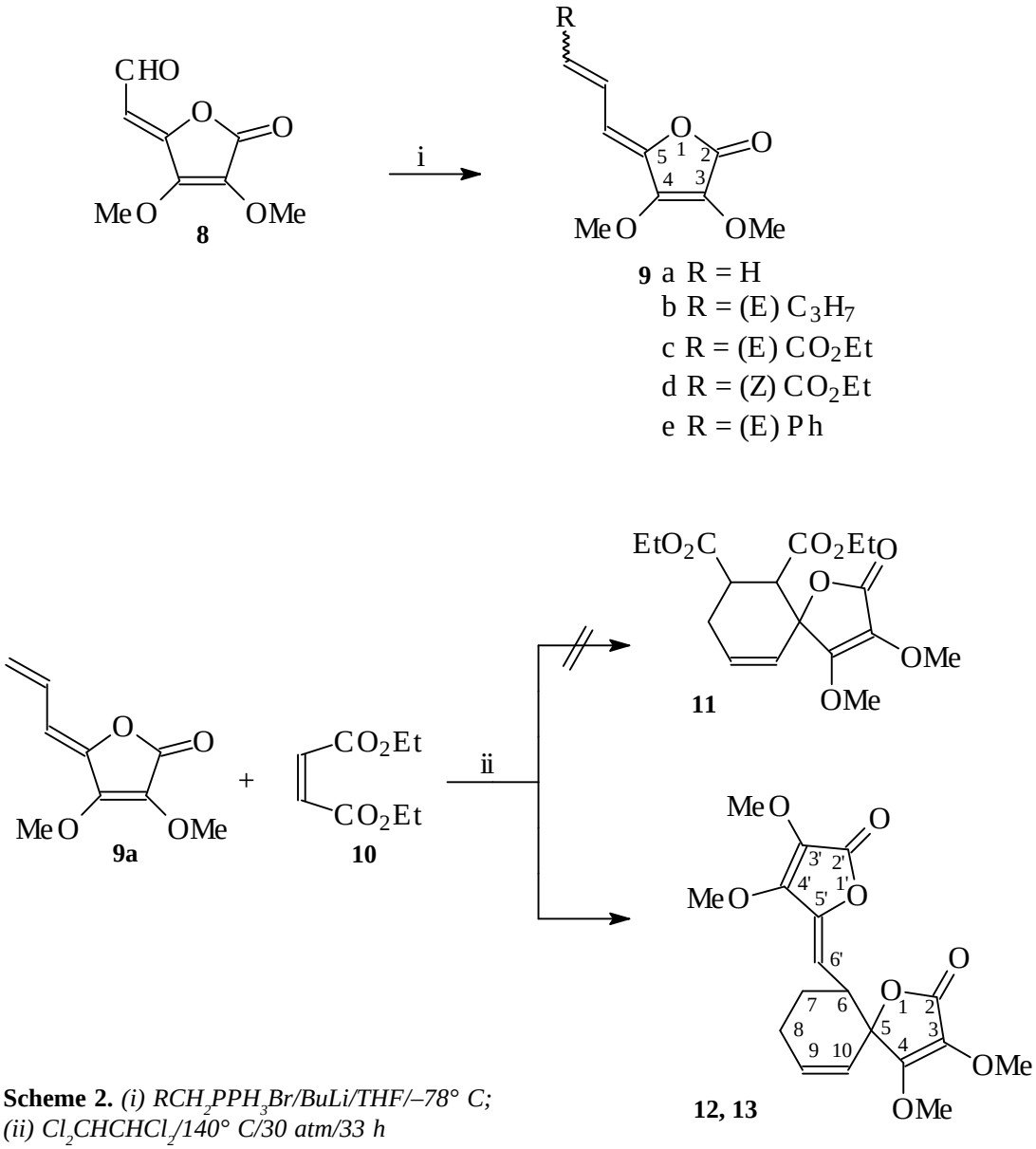
We were interested in the possibility of synthesizing polyfunctional oxaspiro[4,5]decanenones similar to **11** from **1** using the chemistry indicated in Schemes 1and 2. Surprisingly, none of the anticipated diethyl maleate-dienobutenolide-derived cycloaddition products **11** were found to be generated. Instead, the substituted oxaspiro[4,5]decanenones (±)-**12** and presumably (±)-**13** were formed instead, with (±)-**12** as the main product.

Results and Discussion.

The (*Z*)-butenolide aldehyde **8** could be easily obtained by the oxidation of the corresponding allylic alcohol **7** that was accessible from the reported (*Z*)-acetate **6a** [5] by acid hydrolysis. Oxidation of the allylic alcohol **7** was attempted using several oxidising agents [6], e.g. Jones reagent, pyridinium chlorochromate (PCC), MnO_2/Charcoal, Ag_2O/Celite, of which only PCC and MnO_2/Charcoal proved suitable.

However, for convenience and because of shorter reaction times the PCC reagent was used, although MnO_2/Charcoal was superior with higher yields, but required about 36h for complete conversion of starting material to product. The (Z)-butenolide aldehyde **8** reacted smoothly with a variety of Ylids in THF at -78°C in the Wittig reaction to produce the triene systems **9a-e** shown in scheme 2. In all the cases either the (*E*)-isomer was produced exclusively (e.g. **9b** and **9e**), or it was produced as the major product, as in the case with **9c**.

It was evident from the ^{1}H-NMR characteristics of the olefinic protons that the (*E*)-geometric isomers existed in the locked-hydrogen bonded six-membered ring conformation (I, Fig.1), rather than in a type II conformation (Fig.1). This follows from the observation that in all the (*Z*,*E*)-isomers **9a-c** and **9e**, the proton H_c located at C-6 resonated at about 6 ppm. In the case of the (*Z*,*Z*)-isomer **9d**, the chemical shifts of the protons H_a and H_c were very similar (δ~6 ppm), despite the geminal co-existence of the -CO_2Et group which in theory should effect the chemical shift of the proton H_a. However, the relatively low chemical shift (δ 7.27 ppm, theoretically calculated to be δ ~7 ppm from standard NMR correlation tables) of the proton H_b in **9d** suggests its existence in conformation IV, in which it is possible for it to experience some long-range interaction with the lactone oxygen, rather than in conformation III in which it is remote from the lactone oxygen. On the other hand, however, the proton H_a in the triene **9c** resonated at δ 7.27 ppm, being remarkably deshielded. This deshielding was presumably a result of **9c** adopting conformation I in which the proton H_a is hydrogen bonded to the lactone oxygen in addition to the deshielding arising from the carbonyl of the ester group. In the case of **9b**, the deshielding effect of the hydrogen bonding and the shielding effect of the alkyl group are presumably very similar because there is not an appreciable change in the chemical shift of the proton H_a. Similarly in **9e**, the deshielding



Scheme 2. *(i) RCH_2PPH_3Br/BuLi/THF/–78° C; (ii) $Cl_2CHCHCl_2$/140° C/30 atm/33 h*

effect of the proton H_a prevails with a partial contribution to the effect from the aromatic ring.

Our next objective was to examine the behaviour of the dienes **9** towards dienophiles. We chose **9a** for this work because the corresponding cyclo-adducts contain one fewer asymmetric centre and the regiochemistry of the reaction was thought to be less demanding. The diene **9a** failed to produce any cycloaddition products with a variety of dienophiles at atmospheric pressure and at various elevated temperatures in a variety of solvents.

We then subjected **9a** to a Diels-Alder cycloaddition reaction with an equivalent amount of diethyl maleate in 1,1,2,2-tetrachloroethane in an autoclave at 140°C and 30 atm pressure for 33 h. The reaction produced two products with very similar R_f (~0.4) values according to TLC (light petroleum:ethyl acetate, 4:1). Flash chromatography enabled these products to be separated into three fractions. The first fraction was identified as pure oxaspiro[4,5]decanenone (±)-**12.** The second fraction was as a mixture of two racemic products [(±)-**12** / (±)-**13**, 80:20] according to ^{1}H-NMR, as was third fraction, which contained slightly more oxaspiro[4,5]decanenone (±)-**13** (35%) than the second fraction. The main product was the *endo* product (±)-**12**, obtained as single crystals by recrystallisation (CH_2Cl_2/light petroleum). It was analysed by X-ray crystallography and shown to have the structure given in Figures 3-5 and Tables 1-3.

Predictably the major product of the cycloaddition reaction, (±)-**12**, has the favourable so-called *ortho* regiochemistry as well as *endo* stereoselectivity in accordance with the rules for Diels-Alder reactions based on molecular orbital theory [7]. The *endo/exo* transition states for the formation of (±)-**12** and (±)-**13** are shown in Figure 2. Surprisingly, none of the

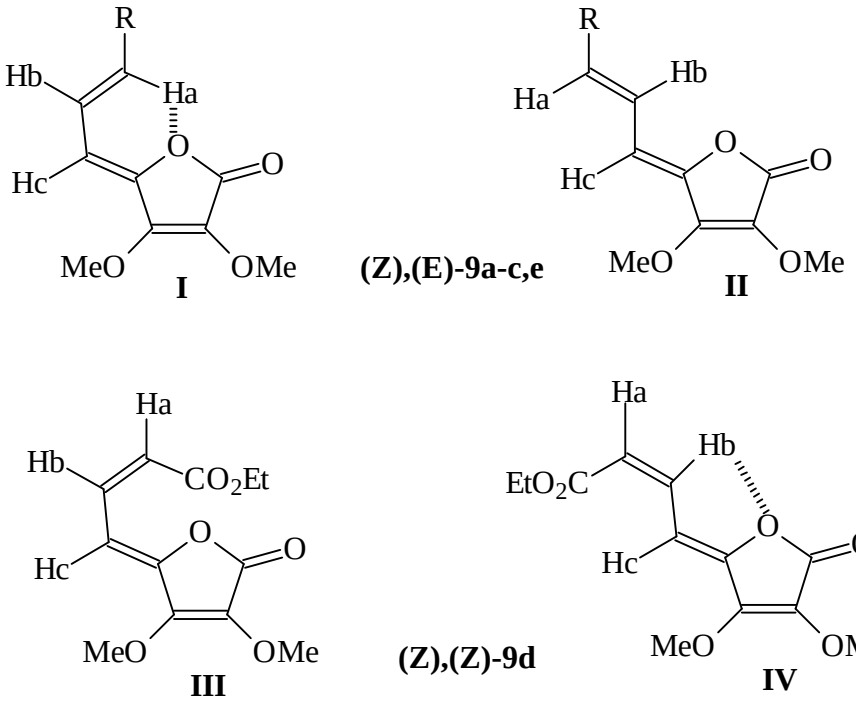


Figure 1.

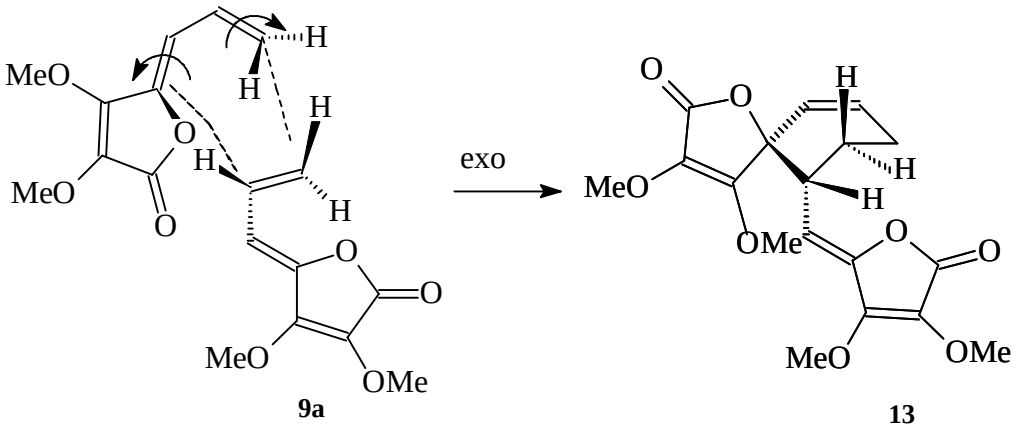


Figure 2.

Table 1. *Atomic coordinates (× 10⁴) and equivalent isotropic displacements (Å × 10³) for* **12a**. *U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.*

	x	y	z	U(eq)
O(1)	593(2)	8002(2)	7612(2)	52(1)
O(2)	-414(3)	7450(2)	5846(2)	74(1)
O(3)	3178(3)	7200(2)	5569(2)	61(1)
O(4)	5091(3)	7925(2)	7952(2)	62(1)
O(5)	3974(3)	4735(2)	8195(2)	70(1)
O(6)	5913(4)	3401(3)	7601(2)	103(1)
O(7)	2923(3)	1196(2)	6676(2)	77(1)
O(8)	-120(3)	2757(2)	7343(2)	75(1)
C(1)	784(4)	7615(3)	6568(3)	51(1)
C(2)	2585(4)	7482(3)	6531(2)	48(1)
C(3)	3445(4)	7805(3)	7527(2)	45(1)
C(4)	2255(3)	8139(3)	8314(2)	45(1)
C(5)	2656(4)	9643(3)	8889(2)	55(1)
C(6)	2587(4)	9996(3)	9914(3)	62(1)
C(7)	2073(5)	8969(4)	10636(3)	75(1)
C(8)	1189(4)	7535(3)	1006(2)	68(1)
C(9)	2158(4)	7019(3)	9107(2)	51(1)
C(10)	1367(4)	5567(3)	8527(2)	56(1)
C(11)	2195(4)	4554(3)	8114(2)	57(1)
C(12)	4435(6)	3514(4)	7648(3)	72(1)
C(13)	2887(5)	2533(3)	7202(2)	60(1)
C(14)	1563(5)	3156(3)	7500(2)	58(1)
C(15)	-805(5)	1450(4)	6645(3)	79(1)
C(16)	3600(5)	1153(4)	5695(3)	83(1)
C(17)	6296(4)	7515(4)	7266(3)	86(1)
C(18)	2608(5)	5786(4)	5011(3)	83(1)

anticipated diethyl maleate-dienobutenolide-derived cycloaddition products **11** was formed. It is known that in compounds containing exocyclic double bonds, such as, for example, protoanemonin [1], the exocyclic double bond acts exclusively as the dienophile, reacting with dienes to furnish spiro adducts in good yields. In our case the exocyclic double bond was uniquely used as part of the diene system rather than as the dienophile entity.

Table 2a. *Bond lengths (Å) of* **12a**.

O(1)-C(1)	1.364(3)	O(1)-C(4)	1.469(3)
O(2)-C(1)	1.207(3)	O(3)-C(2)	1.377(3)
O(3)-C(18)	1.427(4)	O(4)-C(3)	1.332(3)
O(4)-C(17)	1.438(3)	O(5)-C(12)	1.384(4)
O(5)-C(11)	1.396(4)	O(6)-C(12)	1.203(4)
O(7)-C(13)	1.359(4)	O(7)-C(16)	1.423(4)
O(8)-C(14)	1.332(4)	O(8)-C(15)	1.434(4)
C(1)-C(2)	1.461(4)	C(2)-C(3)	1.331(4)
C(3)-C(4)	1.502(4)	C(4)-C(5)	1.494(4)
C(4)-C(9)	1.548(4)	C(5)-C(6)	1.313(4)
C(6)-C(7)	1.478(4)	C(7)-C(8)	1.529(4)
C(8)-C(9)	1.527(4)	C(9)-C(10)	1.500(4)
C(10)-C(11)	1.319(4)	C(11)-C(14)	1.447(4)
C(12)-C(13)	1.458(5)	C(13)-C(14)	1.340(4)

Conclusions.

In conclusion this work has demonstrated a route for the formation of the interesting molecules (±)-**12** and (±)-**13** through several easy and high-yielding steps from L-ascorbic acid **1** as an inexpensive starting material. (±)-**12** and (±)-**13** are interesting because their deprotection should yield products that contain the ene-diol functionality. The latter is usually responsible for the anti-oxidant properties of **1,** but is more lipophilic.

Experimental.

Melting points are uncorrected and were determined on a Gallencamp Electrothermal apparatus. Infrared spectra were recorded with a Perkin-Elmer 783 spectrophotometer with a data station. ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ using a Bruker AC 250 spectrometer operating at 250 and 62.9 MHz, respectively. Chemical shifts (δ) are in ppm downfield from tetramethylsilane as internal standard, *J* values are given in Hz. Mass spectra were recorded with either a VG 7070 or a VG Trio-1 quadrupole mass spectrometer fitted with a Hewlett-Packard 5890 GC. Microanalyses were performed by the University of Sheffield microanalytical laboratory. TLC analyses were done using Merck Silica Gel 60

Table 2b. *Bond angles in degrees for* **12a**.

C(1)-O(1)-C(4)	109.8(2)	C(2)-O(3)-C(18)	114.2(2)	C(3)-O(4)-C(17)	118.6(2)
C(12)-O(5)-C(11)	107.7(3)	C(13)-O(7)-C(16)	115.5(2)	C(14)-O(8)-C(15)	118.7(3)
O(2)-C(1)-O(1)	121.6(3)	O(2)-C(1)-C(2)	129.7(3)	O(1)-C(1)-C(2)	108.7(3)
C(3)-C(2)-O(3)	129.9(3)	C(3)-C(2)-C(1)	108.3(3)	O(3)-C(2)-C(1)	121.6(3)
C(2)-C(3)-O(4)	134.1(3)	C(2)-C(3)-C(4)	110.6(3)	O(4)-C(3)-C(4)	115.2(2)
O(1)-C(4)-C(5)	108.7(2)	O(1)-C(4)-C(3)	102.5(2)	C(5)-C(4)-C(3)	112.5(2)
O(1)-C(4)-C(9)	108.5(2)	C(5)-C(4)-C(9)	111.9(2)	C(3)-C(4)-C(9)	112.1(2)
C(6)-C(5)-C(4)	123.9(3)	C(5)-C(6)-C(7)	124.5(3)	C(6)-C(7)-C(8)	111.7(3)
C(9)-C(8)-C(7)	111.1(3)	C(10)-C(9)-C(8)	111.7(2)	C(10)-C(9)-C(4)	110.9(2)
C(8)-C(9)-C(4)	110.2(2)	C(11)-C(10)-C(9)	126.0(3)	C(10)-C(11)-C(5)	121.9(3)
C(10)-C(11)-C(14)	130.5(3)	O(5)-C(11)-C(14)	107.6(3)	O(6)-C(12)-O(5)	120.7(4)
O(6)-C(12)-C(13)	130.8(3)	O(5)-C(12)-C(13)	108.5(3)	C(14)-C(13)-O(7)	129.9(3)
C(14)-C(13)-C(12)	107.3(3)	O(7)-C(13)-C(12)	122.6(3)	O(8)-C(14)-C(13)	133.7(3)
O(8)-C(14)-C(11)	117.3(3)	C(13)-C(14)-C(11)	109.0(3)		

F_{254} TLC aluminium sheets. All solvents were dried and distilled using standard techniques. All organic solutions were dried over anhydrous $MgSO_4$. THF was distilled under nitrogen from potassium benzophenone ketyl before use. Light petroleum refers to the fraction boiling in the range 40-60°C.

(Z)-3,4-Dimethoxy-5-(2-hydroxyethylidene)butenolide (**7**)

A mixture of the crude acetate **6** [5] (10.5 g, 46 mmol), methanol (50 mL) and 2M HCl acid (15 mL) was refluxed until TLC (ethyl acetate:light petroleum, 1:1) showed the absence of the starting material **6**. The crude product was extracted with ethyl acetate (100 mL).After drying the organic layer was evaporated to yield a residue which was then purified by flash chromatography (ethyl acetate:light petroleum, 1:1). This gave the alcohol **7** (6.16 g, 72%) as an oil which solidified as needles. Mp and spectroscopic properties were similar to those described in the literature [5].

(Z)-3,4-Dimethoxy-5-(formylmethylidene)butenolide (**8**)

To a magnetically stirred mixture of **7** (9.00 g, 48.3 mmol) containing powdered anhydrous sodium acetate (1.00 g, 12.2 mmol) and powdered dried molecular sieves (11.3 g) in dry CH_2Cl_2 (150 mL), pyridinium chlorochromate (PCC) (15.8 g, 72.5 mmol) was added slowly in three portions. After 20 min. TLC analysis of the reaction mixture indicated the absence of starting material and the mixture was filtered through a sintered glass funnel containing silica gel as filtering aid. The organic solution after drying was evaporated to yield a residue which was purified by flash chromatography (ethyl acetate: light petroleum, 2:3) to give the aldehyde **8** (4.90 g, 55%) as a light yellow solid, mp 60-62°C.
IR (KBr): ν = 1765 (CO), 1660 (C=CO), 1640 cm^{-1}(CHO).
^{1}H-NMR: δ = 4.06 (3H, s, OMe), 4.16 (3H, s , OMe), 5.70 (1H, d , *J*=7.5, C=CH), 10.10 (1H, d , J=7.5, CHO).
MS: m/z =184 (M^+, 100%); HRMS: m/z = 184.0368 (M^+) $C_8H_8O_5$ requires 184.0372 (M^+). Found: C 52.13, H 4.32; $C_8H_8O_5$ requires C 52.17, H 4.35.

(Z)-3,4-Dimethoxy-5-(propenylidene)butenolide (**9a**)

The typical procedure for the reaction of aldehyde 8 with the Ylids in the Wittig reaction is demonstrated by the synthesis of **9a**: to a dry (oven-baked or flame-dried) 250 mL 3-necked flask under nitrogen containing the phosphonium salt (5.42 mmol) in dry THF (50 mL), a solution of butyl lithium (1.60 M, 6mmol) was added under stirring at -78°C. The reaction mixture was stirred at -78°C until it had acquired a golden-yellow colour indicating Ylid formation (usually about 20 min). The aldehyde **8** (5.42 mmol) in dry THF (10 mL) was introduced using a syringe and the reaction mixture stirred at -78°C for a further 20 min and then overnight at RT. After filtration through a sintered funnel containing silica gel as filtering aid and washing with ethyl acetate (50 mL), the organic solution was evaporated to yield an oily residue which was flash chromatographed (ethyl acetate:petrol, 1:3) to give the pure diene product **9a** (70%), oil.
^{1}H-NMR: δ = 4.09 (3H, s, OMe), 4.33 (3H, s, OMe), 5.33-6.50 (3H, m, 6-H,8-2H), 6.62-7.48 (1H, td , *J*=2 and 11.5,

Table 3. *Hydrogen coordinates (× 10⁴) and isotropic displacement parameters (Å² × 10³) for* **12a**.

	x	y	z	U(eq)
H(5A)	2963(4)	10396(3)	8480(2)	80
H(6A)	2911(4)	10986(3)	10219(3)	80
H(7A)	1326(5)	9392(4)	11078(3)	80
H(7B)	3065(5)	8786(4)	11102(3)	80
H(8A)	53(4)	7662(3)	9693(2)	80
H(8B)	1103(4)	6823(3)	10482(2)	80
H(9A)	3296(4)	6916(3)	9431(2)	80
H(10A)	146(4)	5356(3)	8442(2)	80
H(15A)	-2023(5)	1304(4)	6615(3)	80
H(15B)	-543(5)	1521(4)	5936(3)	80
H(15C)	-316(5)	653(4)	6915(3)	80
H(16A)	3566(5)	170(4)	5382(3)	80
H(16B)	2932(5)	1653(4)	5204(3)	80
H(16C)	4762(5)	1608(4)	5838(3)	80
H(17A)	7422(4)	766(4)	7681(3)	80
H(17B)	6008(4)	6515(4)	6977(3)	80
H(17C)	6267(4)	8084(4)	6686(3)	80
H(18A)	3053(5)	5668(4)	4346(3)	80
H(18B)	3014(5)	5634(4)	4865(3)	80
H(18C)	1381(5)	5634(4)	4865(3)	80

7-H). HRMS: m/z =182.0579 (M^+). $C_9H_{10}O_4$ requires 182.0576 (M^+).

(Z),(E)-3,4-Dimethoxy-5-(hex-2-enylidene)butenolide (**9b**)

A similar reaction from **8** gave **9b** (61%), oil. ^{1}H-NMR: δ = 0.94 (3H, t , *J*=7.5, Me), 1.46 (2H, sextet, *J*=7.5, CH_2), 2.23 (2H, q , *J*=7.5, =C-CH_2), 3.92 (3H, s , OMe), 4.16 (3H, s , OMe), 5.78 (1H, td, *J*=2 and 11.5, 8-H), 6.14 (1H, d , *J*=11.5, 6-H), 6.42 (1H, t , *J*=11.5, 7-H). MS: m/z = 224 (M^+, 100%). HRMS: m/z = 224.1040 (M^+). $C_{12}H_{16}O_4$ requires 224.1044 (M^+).

The reaction of the Ylid of ethoxycarbonyl methyltriphenylphosphine with the aldehyde **8** produced two products which were separated by flash chromatography to give first (*Z*),(*E*)-3,4-*O*-dimethyl-5-(3-ethoxycarbonylpropenylidene)butenolide **9c** (34.8%) as an oil, and second (*Z*),(*Z*)-3,4-*O*-dimethyl-5-(3-ethoxycarbonylpropenylidene)-butenolide **9d** (29.7%).

(Z),(E)-3,4-Dimethoxy-5-(3-ethoxycarbonylpropenylidene)-butenolide (**9c**)

^{1}H-NMR: δ = 1.30 (3H, t , *J*=7.5, Me), 3.96 (3H, s , OMe), 4.15 (3H, s , OMe), 4.22 (2H, q , *J*=7.5, OCH_2), 5.84 (1H, d , *J*=11.5, 6-H), 7.02 (1H, t, *J*=11.5, 7-H), 7.30 (1H, *J*= 11.5, 8-H). MS: m/z = 254 (M^+, 15%), 209 (M-CO_2Et, 16%), 208 (48%). HRMS: m/z = 254.0780 (M^+), $C_{12}H_{14}O_6$ requires 254.0786 (M^+).

(Z),(Z)-3,4-Dimethoxy-5-(3-ethoxycarbonylpropenylidene)-butenolide (**9d**)

^{1}H-NMR: δ = 1.30 (3H, t , *J*= 7.5, Me), 3.96 (3H, s, OMe), 4.18 (3H, s, OMe), 4.23 (2H, q, *J*= 7.5, OCH_2), 5.90 (1H, d , *J*= 11.5, 6-H), 5.96 (1H, d , *J*= 11.5, 8-H), 7.63 (1H, dd, *J*= 2 and 11.5, 7-H). HRMS: m/z = 254.0788 (M^+), $C_{12}H_{14}O_6$ requires 254.0786 (M^+).

(Z),(E)-3,4-Dimethoxy-5-(3-phenylprop-2-enylidene)-butenolide (**9e**)

A similar reaction from **8** gave (*Z*),(E)-3,4-O-Dimethyl-5-(3-phenylprop-2-enylidene)butenolide **9e** (57%) as oily solid. ^{1}H-NMR: δ = 3.95 (3H, s, OMe), 4.15 (3H, s, OMe), 6.05 (1H, d, *J*= 11.5, 6-H), 6.72 (2H, d, *J*= 15.5, 7-H and 8-H), 7.15-7.50 (5H, m, Ar). HRMS: m/z = 258.0883 (M^+), $C_{15}H_{14}O_4$ requires 258.0888 (M^+).

Diels-Alder cycloaddition reaction of **9a** *with diethyl maleate* **10**

A solution of the diene **9a** (1.120 g, 6.15 mmol) and **10** (1.101 g, 6.40 mmol) in 1,1,2,2-tetrachloroethane (1 mL) in a 25 mL flask was stirred and heated under nitrogen in an autoclave at 140°C and 30 atm. pressure for 33 h. Examination of the reaction mixture by TLC (ethyl acetate:light petroleum, 1:4) showed the presence of **10**, the starting diene **9a** and two other products at lower R_f values. Flash chromatographed (ethyl acetate:light petroleum, 1:4) of the raw material gave an inseparable mixture of **9a**, **10** and the solvent 1,1,2,2-tetrachloroethane followed by 3 fractions. The first fraction yieded the racemic *endo* oxaspiro[4,5]decanenone (±)-**12** (135 mg) as an oil which solidified. The second gave an *endo/exo* mixture of oxaspiro[4,5]decanenones (33 mg) in the form of oil which also solidified. The last fraction contained slightly more racemic *exo* oxaspiro[4,5]decanenones (87 mg) as an oil which also solidified.

The first fraction (±)-**12**

Recrystallised from a mixture of CH_2Cl_2 and light petroleum; colourless plates; mp 118-120°C.

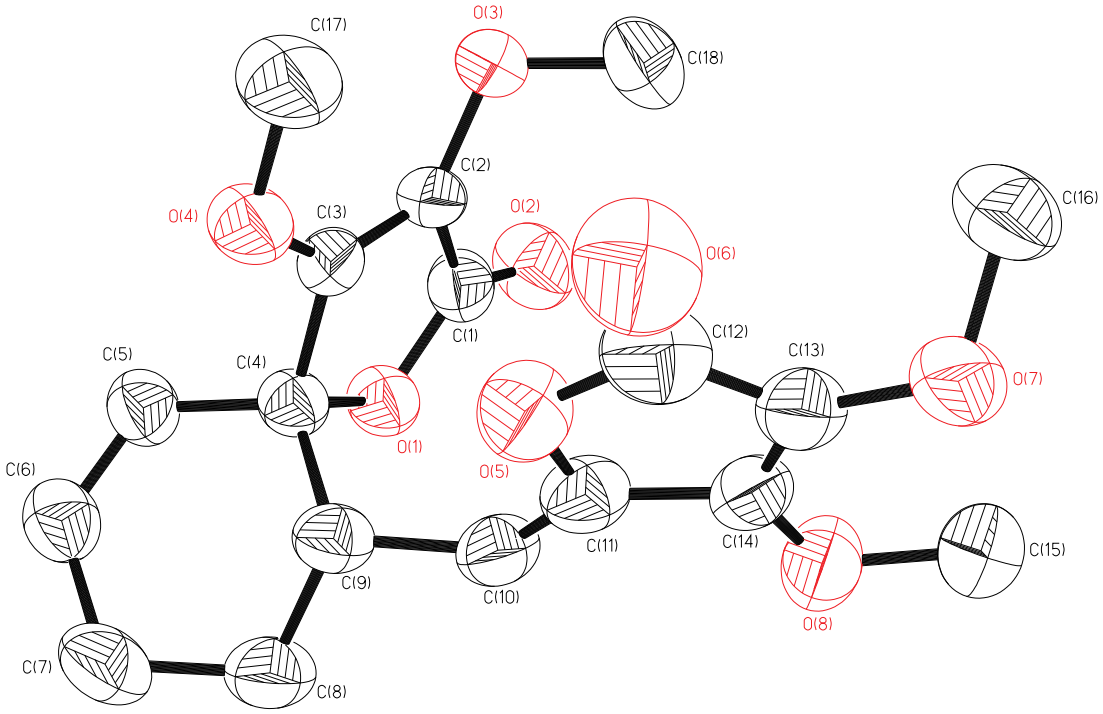


Figure 3. *ORTEP diagram and the atomic numbering of* **12a**.

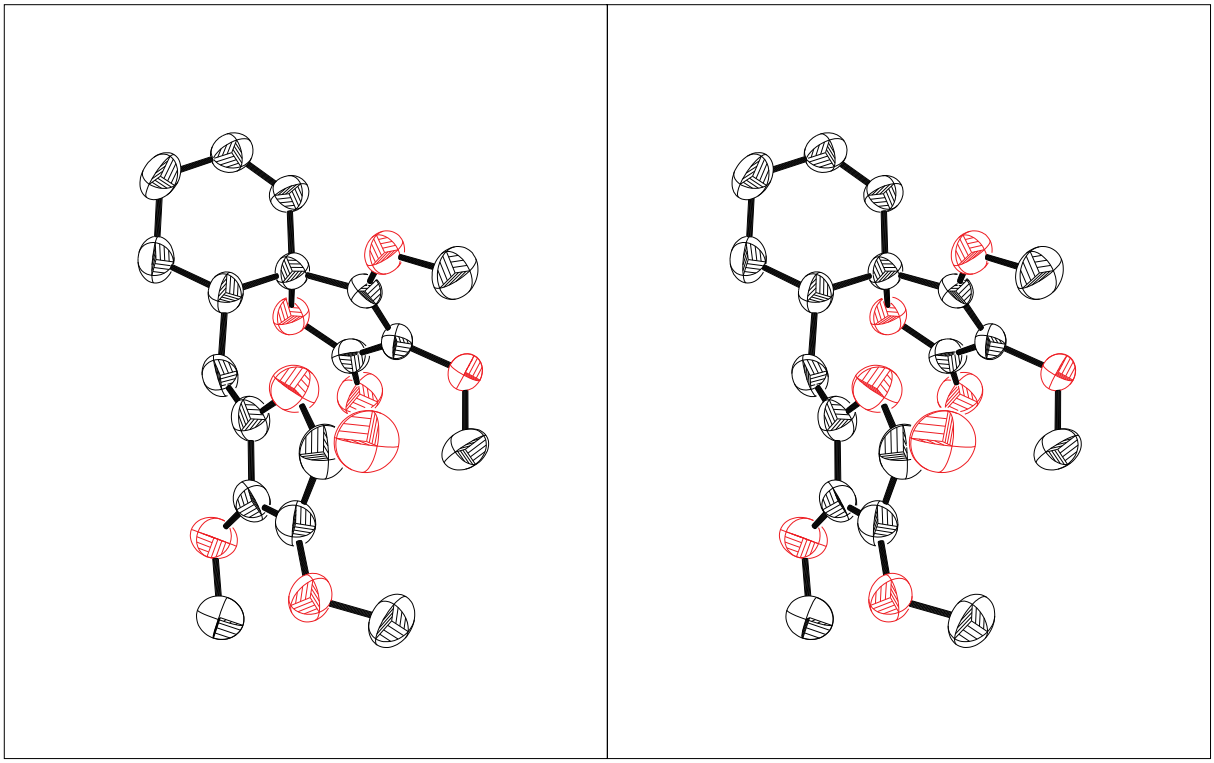


Figure 4. *Stereo view of* **12a**.

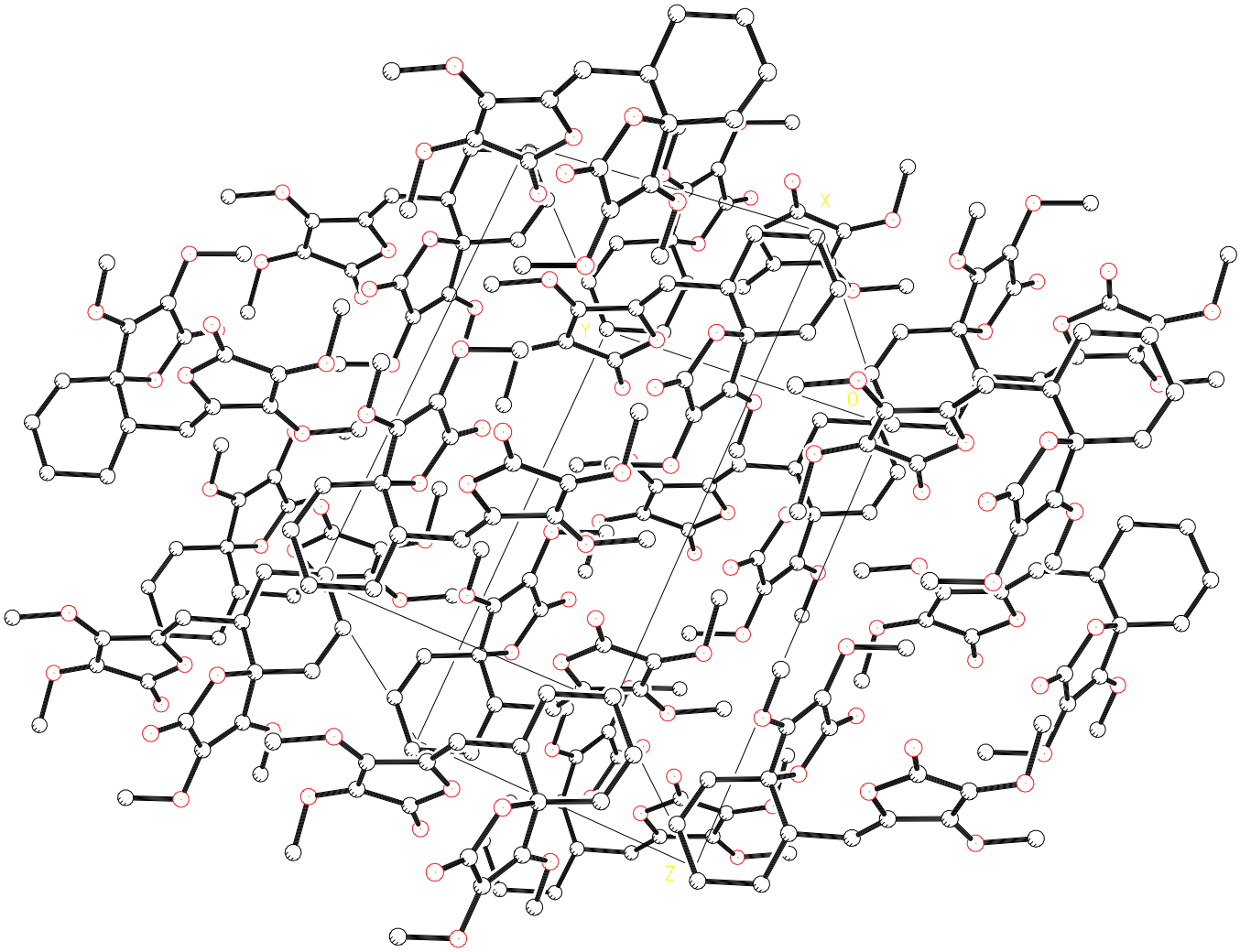


Figure 5. *Molecular packing of* **12a**.

^{1}H-NMR: δ = 1.78 (2H, m, 7-H), 2.20 (2H, m, 8-H), 3.23 (1H, qd, *J* = 4 and 9.8, 6-H), 3.75 (3H, s, OMe), 3.91 (3H, s, OMe), 4.12 (6H,s, OMe), 5.15 (1H, d, *J* = 9.8, 6'-H), 5.46 (1H, dt, *J* = 9.8 and 1.8, 10-H), 6.25 (1H, tt, J = 9.8 and 2.5, 9-H). ^{13}C-NMR: d = 24.51(2C), 36.72, 59.27, 59.42, 60.37, 60.61, 78.29, 106.36, 122.53, 123.57, 124.36, 136.21, 142.73, 148.62, 161.70, 164.53, 168.71. MS: m/z = 364 (M^+,5%), 182 (100%). HRMS: m/z = 364.1108 (M^+), $C_{18}H_{20}O_8$ requires 364.1158 (M^+).

The second fraction [(±)-**12**/(±)-**13** *80:20]*

Recrystallised from a mixture of CH_2Cl_2 and light petroleum as a colourless powder; mp 113-115°C.
^{1}H-NMR: δ = 1.73-1.88 (1.3H, m, 7-H), 1.93-2.15 (0.8H, m, 7-H), 2.20 (2.4H, m, 8-H), 3.33 (0.9H, td, *J* = 4 and 9.8, 6-H), 3.48 (0.2H, td, *J* = 4 and 9.8, 6-H), 3.82 (3H, m, OMe), 3.91 (3H, m, OMe), 4.13 (3H, m, OMe), 4.17 (3H, m, OMe), 5.04 (0.7H, d, *J* = 11.5, 6'-H), 5.16 (0.2H, d, *J* = 11.5, 6'-H), 5.36 (0.8H, dt, *J* = 9.8 and 1.8, 10-H), 5.46 (0.3H, dt, *J* = 9.8 and 1.8, 10-H), 6.13 (0.7H, tt, *J* = 9.8 and 2.5,9-H), 6.24 (0.3H, tt, *J* = 9.8 and 2.5, 9-H). HRMS: m/z = 364.1108 (M^+), $C_{18}H_{20}O_8$ requires 364.1158 (M^+).

The third fraction [(±)-**12**/(±)-**13** *65:35]*

Recrystallised from CH_2Cl_2/light petroleum as a colourless powder; mp 101-103°C.
^{1}H-NMR: δ = 1.72-1.90 (1.15H, m, 7-H), 1.92-2.15 (0.85H, m, 7-H), 2.15-2.30 (2H, m, 8-H), 3.33 (0.85H, td, *J* = 9.8 and 4,6-H), 3.48 (0.25H, td, *J* = 9.8 and 4, 6-H), 3.82 (3H, s, OMe), 3.90 (3H, s, OMe), 4.10 (3H, s, OMe), 4.15 (3H, s, OMe), 5.03 (0.70H, d, *J* = 11.5, 6'-H), 5.14 (0.08H, d, *J* = 11.5, 6'-H), 5.35 (0.65H, dt, *J* = 11.5 and 1.8,10-H), 5.47 (0.38H, dt, *J* = 9.8 and 2.5, 10-H), 6.12 (0.70H, m, 9-H), 6.22 (0.23H, m, 9-H). HRMS: m/z = 364.1106 (M^+), $C_{18}H_{20}O_8$ requires 364.1158 (M^+). Found: C 59.34, H 5.44; $C_{18}H_{20}O_8$ requires C 59.34, H 5.49.

6-Bromo-6-deoxy-2,3-di-O-*methyl-L-ascorbic acid* (**5e**)

Careful acidic hydrolysis of the corresponding bromoacetate **5d** [5] produced **5e** as a whitish solid. This was then purified by flash chromatography (ethyl acetate:light petroleum, 1:1), mp = 95-97°C.
^{1}H-NMR: δ = 3.08 (1H, bs, OH), 3.57 (2H, d, J = 7.8, 6-H), 3.83 (3H, s, OMe), 4.08 (1H, td, J = 7.8 and < 2, 5-H), 4.18 (3H, s, OMe), 4.95 (1H, fine d, J < 2, 4-H). MS: m/z = 266/268 (M^+, 5%), 144 (100%). Found: C 35.88, H 4.07, Br 29.85, $C_8H_{11}O_5Br$ requires C 35.95, H 4.12, Br 29.96.

Crystal and X-ray data of **12a**

$C_{18}H_{20}O_8$ M=364.36, recrystallized from ether as colourless blocks; crystal dimensions 0.55 x 0.30 x 0.25 mm. Triclinic, a=7.986(2), b=9.436(3), c=12.680(3) Å, a=96.94(2)°, b=98.29(2)°, g=96.16(2)°, volume 928.9(4) Å^3, Z=2, density (calculated) 1.303 g/cm^3. Space group $P\bar{1}$ (C_i^1, No.2), Mo-Kα radiation (l=0.71073Å), absorbtion coefficient μ(Mo-Kα)=0.103 mm^{-1}, F(000)=384. Three dimensional X-ray data were collected at a temperature of 293(2) K in the 2θ range 3.50 to 40.00° on a Siemens P4 diffractometer by the omega scan method. Of the 2298 reflections measured, all of which were corrected for Lorentz and polarization effects, but not for absorption, 1728 independent reflections exceeded the significance level $|F| / \sigma(|F|) > 4.0$. The structure was solved by direct methods and refined by the full matrix least squares method. Refinement converged at a final R-value of 0.0381 (wR_2=0.1050 for all 1728 unique data, 235 parameters, mean and maximum δ/σ 0.000, 0.000), with allowance for the thermal anisotropy of all non-hydrogen atoms. Minimum and maximum final electron density -0.140 and 0.131 e·Å^{-3}. A weighting scheme $w=1/[\sigma^2(Fo^2)+0.0655*P)^2+0.00*P]$ where $P=(Fo^2+2*Fc^2)/3$ was used in the latter stages of refinement. Complex scattering factors were taken from the program package SHELXL93 as implemented on the Viglen 486dx computer [8].

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