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ORIGINAL PAPER

X-ray Crystal Structures of Intermediates of the Stereoselective (±)-Grandisol Synthesis Based on the Remote Alkylation Protocol

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Abstract Starting from easily prepared (cyclobutylsulfonyl)benzene (**1**), a stereoselective synthesis of (±)-grandisol, accomplished in nine steps, with an overall yield of ca. 18 %, has been presented by Monteiro and Stefani (Eur J Org Chem 14:2659–2663, 2001). Most of the synthetic intermediates were secured in good to excellent yields as crystalline compounds requiring no or minimal purification, should being amenable to scale up. The structures and absolute stereochemistry of (**2**), (**3**), (**4a**), (**5**), (**8**) and (**9**) were established by IR and NMR (^{1}H, ^{13}C) spectroscopies and confirmed by X-ray diffraction analysis. Compound (**2**) crystallizes in orthorhombic *Pbca*, $a = 16.0565(5)$, $b = 9.5144(6)$, $c = 23.9728(7)$ Å, the (**3**) crystallizes in monoclinic $P2_1/c$, $a = 5.6390(5)$, $b = 17.8630(16)$, $c = 12.8678(12)$ Å and $\beta = 111.928(7)°$, the (**4a**) crystallizes in monoclinic $P2_1/c$, $a = 5.7002(9)$ Å, $b = 17.2752(14)$ Å, $c = 14.9168(9)$ Å and $\beta = 109.464(8)°$. The other three cyclobutylsulfonyl derivatives crystallize in the same monoclinic space group $P2_1/c$ with cell parameters (**5**) $a = 8.072(4)$, $b = 11.486(9)$, $c = 14.565(8)$ Å and $\beta = 101.373(4)°$, (**8**) $a = 11.3448(2)$, $b = 7.9377(1)$, $c = 18.5329(4)$ Å and $\beta = 94.147(1)°$ and (**9**) $a = 37.7571(9)$, $b = 11.4434(3)$, $c = 8.1824(2)$ Å and $\beta = 90.748(1)°$.

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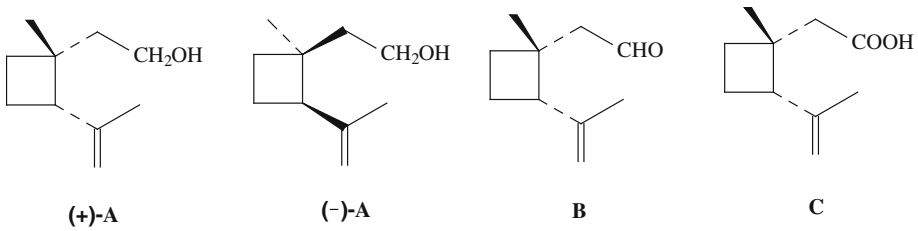
Keywords Grandisol · Stereoselective synthesis · Alkylation · Crystal structure

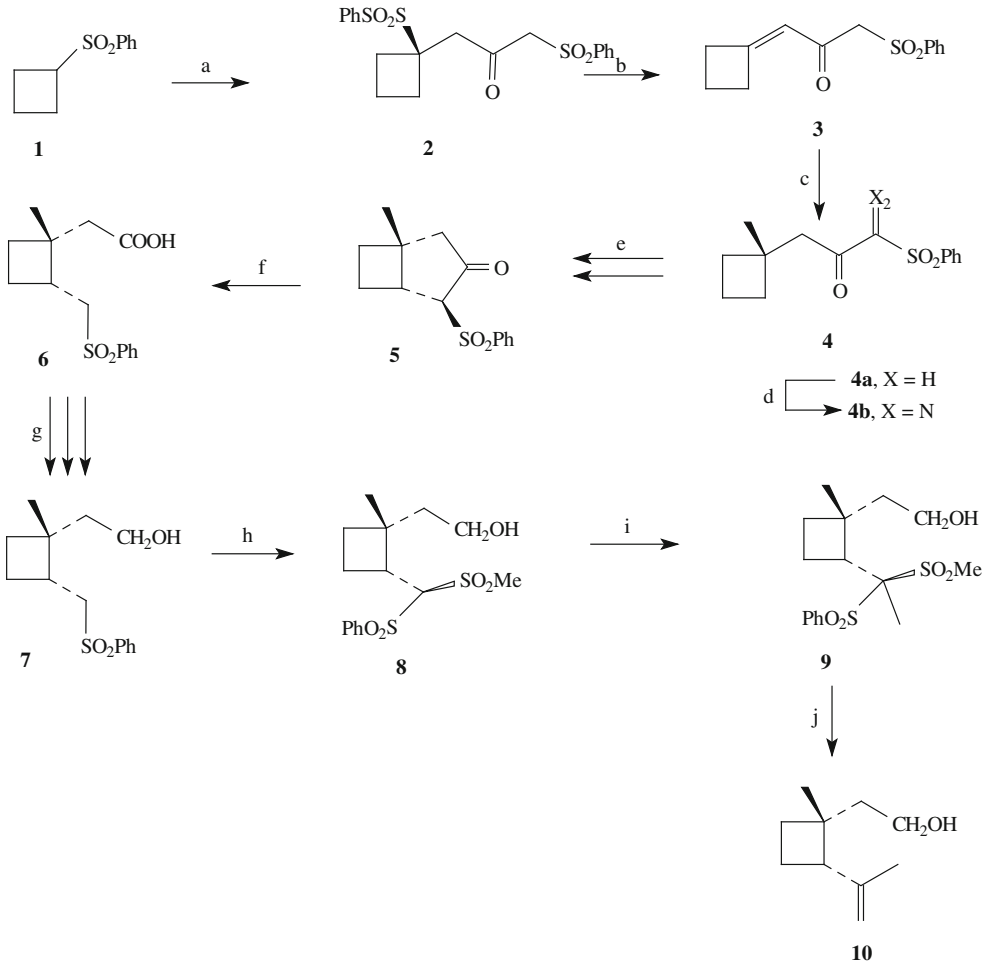
Introduction

(±)-Grandisol (**A**), *cis*-2-(2-isopropenyl-1-methylcyclobutyl)ethanol, is one of the components of the male-produced pheromone of the cotton boll weevil *Anthonomus grandis* Boheman, which is a very important pest in the cotton fields in USA, Central America, Brazil and conifer infestation in North America and Central Europe [1–3]. This monoterpenoide pheromone can be isolated in two enantiomeric forms, (+)-**A** and (−)-**A**, both chemical structures show comparable biological activity [3]. Two other well-known components of pheromone are grandisal (**B**) and grandisoic acid (**C**), being the first component was found in pheromone of weevils of the genus *Pissodes* and the second one in plum curculio *Conotrachelus nenuphar* Herbts [3] (Scheme 1).

Due to its high commercial value and an alternative to classical pesticides, these cyclobutane derivatives have been attracted the attention of many organic chemists and a large number of syntheses of *racemic* and optically active grandisol have already been published [4]. Since the cotton boll weevil *A. grandis* can only recognize the natural pheromone enantiomer (+)-grandisol [5], the synthesis of this *racemic*-terpene become economically very attractive if the product is to be used in traps for control infestation [2]. We report the X-ray crystal structures of the intermediates (**2**), (**3**), (**4a**), (**5**), (**8**) and (**9**) (Scheme 2) obtained from the reported [2] stereoselective and short synthesis exploiting the versatile chemistry of the benzenesulfonyl ($-SO_2Ph$) moiety, avoiding labile intermediates and the use of expensive reagents, which are found in many of the reported grandisol syntheses.

Scheme 1 Grandisol enantiomers and their oxidized derivatives





Scheme 2 The remote alkylation strategy in the synthesis of grandisol (**10**). *a* i. MeLi, THF, −15 °C; ii. 2-(phenylsulfanylmethyl)oxirane; iii, H_2O_2, HOAc; iv, Jones reagent, room temp.: *b* NaOH, MeOH, room temp.: *c* $AlMe_3$, CuBr, THF, 0 °C: *d* 2-Chloro-1-ethylpyridinium tetrafluoroborate, NaN_3, NaOAc, MeOH, 0 °C, *e* $Rh_2(OAc)_4$, CH_2Cl_2, reflux: *f* i. NaOH, MeOH, reflux; ii. H^+: *g* $Me_2S{\cdot}BH_3$: *h* i. MeLi, THF, −15 °C; ii. Me_2S_2; iii. H_2O_2, HOAc: *i* i. *t*-$BuMe_2SiCl$, Et_3N, DMAP, CH_2Cl_2, room temp.: ii. NaOH, MeI, BTEAC, C_6H_6–H_2O: iii. Dowesx 50 × 8, MeOH, room temp.: *j* MeLi, THF, −15 °C

Experimental

Synthesis, IR, NMR and CHN Analyses

The synthesis and above physical methods have already been described [2]. However, new NMR experiments (COSY, HMQC and HMBC) were recorded again on a VARIAN MERCURY PLUS spectrometer, with the aim of locating safely all atoms of hydrogen and carbon.

*1-Phenyl-ulfonyl-3-(1-phenylsulfonylcyclobutyl)acetone (**2**)*

(15.5 g, 96.6 %), mp 130–132 °C. IR: ν = 1,711, 1,320, 1,290, 1,142, 1,072, 728 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.90–2.12 (m. 2H), 2.27–2.37 (m, 2H), 2.71–2.81 (m, 2H), 3.16 (s, 2H), 4.28 (s, 2H), 7.55–7.62 (m, 4H), 7.67–7.76 (m, 2H), 7.86–7.90 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 14.9, 27.3, 46.7, 64.5, 67.4, 128.0, 129.1, 129.3, 129.7, 129.9,

134.17, 134.3, 134.8, 138.4, 194.4. Anal.: calc. for $C_{19}H_{20}O_5S_2$: C, 58.14; H, 5.14. Found: C, 57.96; H, 5.27.

*1-Cyclobutylidene-3-(phenylsulfonyl)acetone (**3**)*

(4.85 g, 97.1 %), mp 71–72 °C. IR: v = 1,690, 1,628, 1,354, 1,309, 1,276, 1,173, 1,060, 895, 758 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.13 (quint. J = 7.8 Hz, 2H), 2.86–2.93 (m, 2H), 3.08–3.16 (m, 2H), 4.15 (s, 2H), 6.23 (quint. J = 2.4 Hz, 1H), 7.54–7.60 (m, 2H), 7.65–7.70 (m, 1H), 7.88–7.91 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 17.8, 33.0, 34.8, 67.0, 119.7, 128.0, 129.0, 129.4, 129.9, 133.9, 138.7, 172.6, 185.7. Anal.: calc. for $C_{13}H_{14}O_3S$: C, 63.38; H, 5.64. Found: C, 61.97; H, 5.39.

*1-(1-Methylcyclobutyl)-3-(phenylsulfonyl)acetone (**4a**)*

(3.4 g, 79.9 %), mp 82–83 °C. IR: v = 1,715, 1,315, 1,241, 1,144, 745 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.15 (s, 3H), 1.72–1.99 (m, 6H), 2.84 (s, 2H), 4.10 (s, 2H), 7.55–7.61 (m, 2H), 7.66–7.72 (m, 1H), 7.87–7.91 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 15.4, 25.5, 33.3, 36.4, 55.3, 67.9, 127.9, 129.0, 133.9, 138.4, 197.0. Anal.: calc. for $C_{14}H_{18}O_3S$: C, 63.13; H, 6.81. Found: C, 62.89; H, 6.79.

(1R, 4R*, 8S*)-1-Methyl-4-(phenylsulfonyl)bicycle[3.3.0]heptan-3-one (**5**)*

(10.8 g, 78.8 %), mp 105–106 °C. IR: 1,745, 1,305, 1,144, 1,080, 753, 730 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.43 (s, $^5CH_3$), 1.52–1.64/2.40–2.54 (m, $^2CH_2$), 1.82–1.91/1.97–2.08 (m, $^3CH_2$), 2.41/2.62 (d, J = 18 Hz, $^6CH_2$), 3.24 (d, J = 5,7 Hz, ^1CH), 3.66 (s, ^8CH), 7.45–7.61 (m, $^{11,13}CH$), 7.66–7.73 (m, ^{12}CH), 7.81–7.85 (m, $^{10,14}CH$). ^{13}C NMR ($CDCl_3$): δ 21.2 (^2C), 26.3 (^5C), 31.8 (^3C), 40.4 (^4C), 41.0 (^1C), 52.1 (^6C), 78.5 (^8C), 128.6 ($^{10,14}C$), 129.0 ($^{11,13}C$), 134.0 (^{12}C), 137.3 (^9C), 208.0 (^7C). Anal.: calc. for $C_{14}H_{16}O_3S$ (264.3 g/mol): C, 63.61; H, 6.10. Found: C, 63.17; H, 5.83.

(1R, 4R*, 8R*)-2-{1-Methyl-2-[(methylsulfonyl)(phenylsulfonyl)methyl]-cyclobutyl}ethanol (**8**)*

(5.20 g, 87.9 %), mp 160–162 °C. IR: 3,549 (br), 1,315, 1,150, 1,125, 1,081, 755 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.34 (s, $^7CH_3$), 1.74–1.82 (m, $^3CH_2$), 1.86–2.82 (m, $^2CH_2$), 2.04–2.14/2.48–2.62 ($^5CH_2$), 2.62–2.89 (m, ^1CH), 3.08 (s, $^9CH_3$), 3.71–3.89 (m, $^6CH_2$), 4.63 (d, J = 9 Hz, ^8CH), 7.40–7.60 (m, $^{12,14}CH$), 7.65–7.71 (m, ^{13}CH), 7.91–7.95 (m, $^{11,15}CH$). ^{13}C NMR ($CDCl_3$): δ 22.6 (^5C), 28.0 (^7C), 30.2 (^3C), 36.6 (^2C), 39.7 (^9C), 41.0 (^1C), 43.1 (^4C), 59.3 (^6C), 82.3 (^8C), 128.8 ($^{12,14}C$), 129.2 ($^{11,15}C$), 134.3 (^{13}C), 139.9 (^{10}C). Anal.: calc. for $C_{15}H_{22}O_5S_2$ (346.5): C, 52.00; H, 6.40. Found: C, 51.76; H, 6.38.

(1R, 4R*, 8R*)-2-{1-Methyl-2-[1-(methylsulfonyl)-1-(phenylsulfonyl)-ethyl]-cyclobutyl}ethanol (**9**)*

(2.65 g, 96 %), mp 161–172 °C. IR: 3,422 (br), 1,318, 1,302, 1,148, 1,072, 955 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.38 (s, $^7CH_3$), 1.68–1.79/1.91–2.01 (m, $^3CH_2$), 1.82 (s, $^{16}CH_3$), 2.02–2.14 ($^5CH_2$), 2.23–2.43 (m, $^2CH_2$), 3.08 (s, $^9CH_3$), 3.16 (dd, ^1CH), 3.71–3.89 (m, $^6CH_2$), 7.40–7.60 (m, $^{11,15}CH$), 7.65–7.71 (m, ^{13}CH), 7.91–7.95 (m, $^{12,14}CH$). ^{13}C NMR ($CDCl_3$): δ 11.4 (^{16}C), 22.2 (^5C), 28.5 (^7C), 30.8 (^3C), 37.2 (^2C), 38.2 (^9C), 45.0 (^1C), 46.7 (^4C), 59.3 (^6C), 88.9 (^8C), 128.8 ($^{11,15}C$), 129.2 ($^{12,14}C$), 134.3 (^{13}C), 139.9 (^{10}C). Anal.: calc. for $C_{16}H_{24}O_5S_2$ (360.5): C, 53.31; H, 6.71. Found: C, 53.07; H, 6.53.

Crystal Structure

The compounds (**2**), (**3**), (**4a**), (**5**), (**8**) and (**9**) were obtained as a white product and single crystals were obtained from MeOH by slow evaporation at room temperature. The X-ray measurements were carried out in a Enraf–Nonius Kappa-CCD diffractometer for (**2**), (**3**), (**4a**), (**5**), (**8**) and on Bruker Smart Apex II-CCD instrument for (**9**) with graphite monochromated Mo-$K\alpha$ radiation (λ = 0.71073 Å) at room temperature. Data of (**9**) have been corrected by absorption using the multiscan method. Structure solutions were accomplished with Direct Methods and the refinements were performed using full matrix least-squares on F^2. Hydrogen atoms were placed in idealized positions and refined isotropic with riding constraints. The compounds Ortep representations are shown in Figs. 1, 2, 3, 4, 5 and 6 with their labeling scheme. Crystal and refinement details are given in Tables 1 and 2 and selected bond lengths and angles with their estimated standard deviations are compiled in Tables 3 and 4. Software used: data collection: *Collect* [6]; data reduction: *DENZO-SCALEPACK* [7]; multiscan absorption correction [8]; structure solution: *SHELXS97* [9]; structure refinement: *SHELXL97* [9], molecular graphics: *ORTEP3 for Windows* [10]; preparation of material for publication: *WingX* [11].

Results and Discussion

Crystal Structure of Compound (**2**)

Wilson has been reported [12] that the ideal bond distances for cyclobutane is 1.54 Å. The range of observed values in (**2**) was 1.529(3)–1.559(3) Å, so there is no correlation of

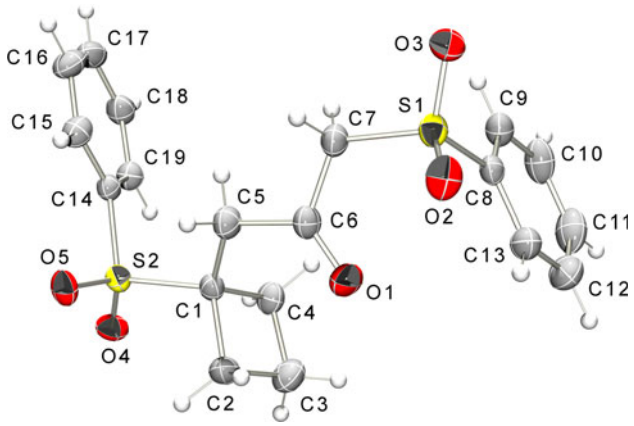


Fig. 1 ORTEP of compound (**2**), with 30 % probability displacement ellipsoids

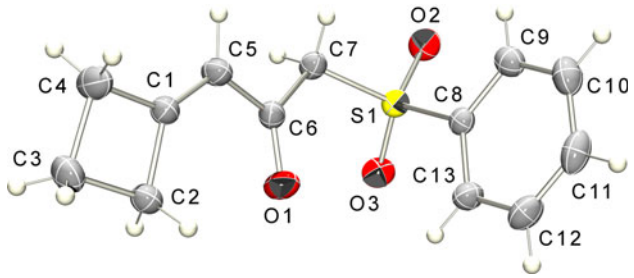


Fig. 2 ORTEP of compound (**3**), with 30 % probability displacement ellipsoids

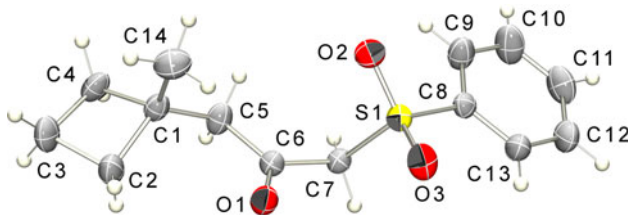


Fig. 3 ORTEP of compound (**4a**), with 30 % probability displacement ellipsoids

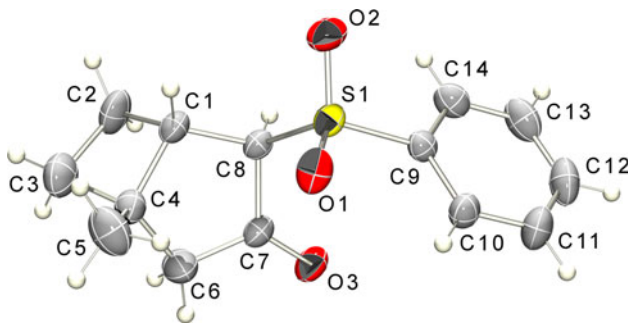


Fig. 4 ORTEP of compound (**5**), with 30 % probability displacement ellipsoids

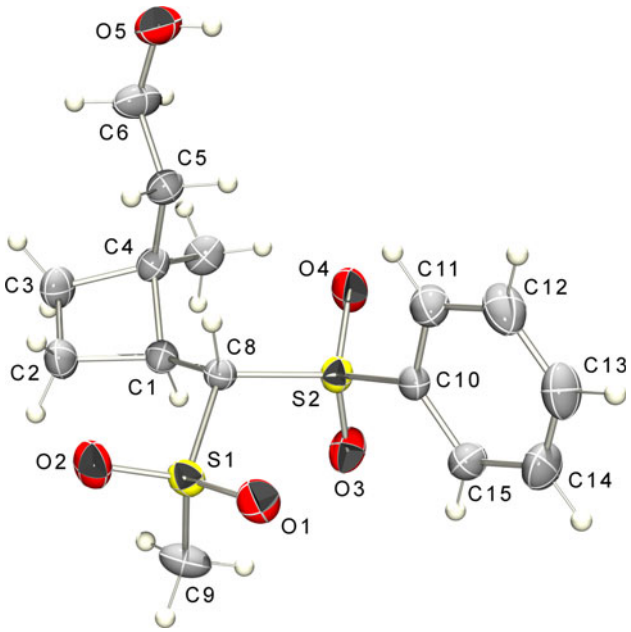


Fig. 5 ORTEP of compound (**8**), with 30 % probability displacement ellipsoids

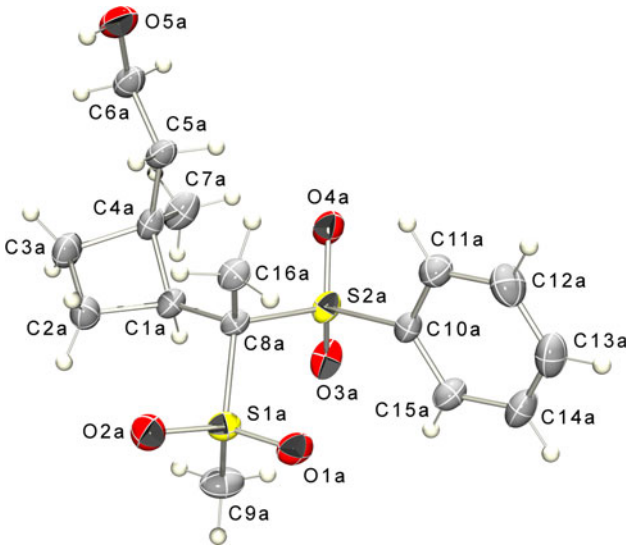


Fig. 6 ORTEP of compound (**9**), with 30 % probability displacement ellipsoids

this bond length with the nature of the phenylsulfonyl group bonded to the C(1) quaternary atom. The two S(1)–$C(8)_{aryl}$ = 1.757(2) and S(2)–$C(14)_{aryl}$ = 1.766(2) Å bond lengths of each of the two phenylsulfonyl moieties have some double bond character since they are lightly shorter than the single S(1)–C(7) = 1.774(2) and S(2)–C(1) = 1.779(2) Å bond distances. The bond length C(6)–O(1) = 1.190(3) Å show the typical double-bond character and suggest that C(6) is sp^2 hybridized while the bond angle C(5)–C(6)–C(7) = 112.73(18)° corroborate to that,

as expected. The four bonds S(1)–O(2) = 1.4272(18), S(1)–O(3) = 1.4338(18), S(2)–O(4) = 1.4421(16) and S(2)–O(5) = 1.4414(16) Å observed for (**2**) are comparable in length to those found in others phenylsulfonyl derivatives [13, 14]. The two phenyl rings make a dihedral angle of 15.85(0.14)° with respect to each other and the cyclobutyl ring make dihedral angles of 26.83(0.15)° and 12.41(0.17)° with the phenyl rings of the C(4)-phenylsulfonyl and C(7)-phenylsulfonyl moieties, respectively. The torsion angle defined by C(6)–C(7)–S(1)–C(8) = 58.41(19)° is higher than the torsion angle defined by C(6)–C(5)–C(1)–C(4) = −52.8(3)° to minimize the possible intramolecular interactions. The Cremer and Pople [15] puckering parameter (q_2 = −0.0982(3) Å shows that the cycle-butyl ring is puckered, with a dihedral angle among C(4), C(1), C(2) and C(2), C(3), C(4) of 10.2(2)°.

Crystal Structure of Compound (**3**)

The C(1)–C(5) = 1.330(2), C(5)–C(6) = 1.460(2) and C(6)–O(1) = 1.213(2) Å bond distances values reflect the electron delocalization in the C(4)–C(5)–C(6)–O(1) chain, indicating ethene formation at C(1)–C(5) bond due phenylsulfonyl ($PhSO_2$–) elimination from acetone (**2**). As consequence of this elimination with formation of sp^2-C(1) atom, the range of 1.498(2)–1.534(3) Å for bond distances values observed in cyclobutylidene ring of (**3**) shows that these bond distances are shorter than that related ones found in (**2**), as expected (see Table 2). The C(6)–O(1) = 1.213(2) Å bond distance is about 0.023 Å longer than the related bond found in (**2**), these observations confirm the above-mentioned electron delocalization. The S=O, S–C_{aryl} and S–C_{alkyl} distances are in good agreement with equivalent bond distances observed in (**2**) (Table 1) and in other related compounds [13, 14].

The torsion angle defined by C(6)–C(7)–S(1)–C(8) = 58.65(16)° and the torsion angle defined by C(6)–C(5)–C(1)–C(4) = −176.2(2)° is a consequence of C(1)–C(5) double bond formation. The cyclobutyl ring make dihedral angle of 85.82(13)° with phenyl ring while the equivalent dihedral angle found in (**2**) was of 12.87(17)°. The Cremer and Pople [15] puckering parameter (q_2 = 0.078(8) Å shows that the four-membered ring is twisted, with a dihedral angle among C(4), C(1), C(2) and C(2), C(3), C(4) of 8.4(3)°.

Crystal Structure of Compound (**4a**)

The C(1)–C(2) = 1.544(3), C(1)–C(4) = 1.550(3), C(1)–C(5) = 1.512(2) and C(5)–C(6) = 1.498(2) Å bond distances are significant higher than the equivalent C(1)–C(2) = 1.498(2), C(1)–C(4) = 1.508(3), C(1)–C(5) = 1.330(2) and C(5)–C(6) = 1.460(2) Å found in (**3**) due to the rehybridization of C(4) atom from sp^2 to sp^3 during construction of the quaternary centre, C(4), by a 1-4-addition of a methyl group to acetone (**3**). So, the C(6)–O(1) = 1.213(2) Å bond distance is shorter than the equivalent bond found in (**3**), as expected. The cyclobutyl ring make dihedral angle of 32.06(18)° with phenyl ring while the equivalent dihedral angle found in (**3**) was of 85.78(8)°. The torsion angles defined by C(6)–C(7)–S(1)–C(8) = −168.56(12)° and by C(6)–C(5)–C(1)–C(4) = −163.54(18)° indicate that C(8) and C(4) atoms point roughly in opposite directions. The Cremer and Pople [15] puckering parameter (q_2 = −0.230(3) Å shows that the four-membered ring is twisted, with a dihedral angle among C(4), C(1), C(2) and C(2), C(3), C(4) of 24.0(3)°.

Crystal Structure of Compound (**5**)

In compound (**5**) the rings are *cis*-fused and the Cremer and Pople [15] puckering parameters show that the four-membered ring is puckered [Q_2 = −0.222(3) Å] and the five-membered ring is in an envelope conformation [Q_2 = 0.192(2) Å and φ_2 = 28.3(7)°]. The seven-membered ring is too puckered [Q = 1.052(3), φ_2 = 226.07(14) and φ_3 = 147.3(5)°].

The geometry around the S(1) atom is described as distorted tetrahedral in which the C8–S1–C9 and O1–S1–O2 bond angles values are 106.20(8) and 118.50(10)°, respectively. The quaternary carbon C4 is too tetrahedrally bonded with their angles ranging from 88.55(18) to 118.04(19)°. Two torsion angles as a result of rotation across C8–S1bond are C1–C8–S1–O1 = 62.37(15) and C1–C8–S1–O2 = −66.13(16)°, indicating that the molecule adopts a alternate *gauche* conformation when viewed along the C8–S1. The four- and five-membered rings make a dihedral angles of 23.5(2)° with respect to each other and the phenyl ring makes dihedral angles of 50.71(14) and 49.1(2)° with the four- and five-membered rings, respectively.

The S1–O1 = 1.4316(16), S1–O2 = 1.4343(16), C8–S1 = 1.7953(18) and C9–S1 = 1.765(2) Å bond distances are in good agreement with other related bonds previously reported [13, 14]. The phenylsulfonyl and junction methyl groups are in *cis*-positions with respect to each other. The C1–C4 = 1.566(3) and C7–O3 = 1.195(2) Å bond distance are consistent with the expected values [14].

Crystal Structures of Compounds (**8**) and (**9**)

The substitution of the H atom in (**8**) by the more bulky methyl group in (**9**) does not favor the modification in the crystal packing of the molecules in each case (Figs. 5 and 6) and only the monoclinic ($P2_1/c$) crystal system was observed. There are two crystallographically independent molecules (denoted by *a* and *b*) for compound (**9**), thus there are not significant differences in angles and distances

Table 1 Crystallographic data for the compounds (**2**), (**3**) and (**4a**)

	(**2**)	(**3**)	(**4a**)
Crystal data			
Chemical formula	$C_{19}H_{20}O_5S_2$	$C_{13}H_{14}O_3S$	$C_{14}H_{18}O_3S$
Chemical formula weight	392.49	250.31	266.35
Cell setting	Orthorhombic	Monoclinic	Monoclinic
Space group	*Pbca*	$P2_1/c$	$P2_1/c$
a (Å)	16.0565(5)	5.6390(5)	5.7002(9)
b (Å)	9.5144(6)	17.8630(16)	17.2752(14)
c (Å)	23.9728(7)	12.8678(12)	14.9168(9)
α (°)	90	90	90
β (°)	90	111.928(7)	109.464(8)
γ (°)	90	90	90
V (Å^3)	3,662.3(3)	1,202.4(2)	1,384.9(3)
Z	8	4	4
D_x (Mg cm^{-3})	1.424	1.383	1.278
Radiation type	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$
Wavelength (Å)	0.71073	0.71073	0.71073
No. Of reflections for cell parameters	7,853	4,847	5,261
θ range (°)	2.9–27.5	2.9–27.5	2.9–27.5
μ (mm^{-1})	0.32	0.26	0.23
Temperature (K)	298(2)	298(2)	298(2)
Crystal form	Prism	Needle	Prism
Crystal size (mm)	0.24 × 0.18 × 0.15	0.43 × 0.1 × 0.1	0.11 × 0.13 × 0.17
Crystal colour	Colourless	Colourless	Colourless
Data collection			
Diffractometer	Enraf–Nonius KappaCCD	Enraf–Nonius KappaCCD	Enraf–Nonius KappaCCD
Data collection method	ω scan	ω scan	ω scan
Absorption correction	Multi-scan	Multi-scan	Multi-scan
No. of measured reflections	7,821	5,298	5,772
No. of independent reflections	4,176	2,744	3,067
No. of observed reflections	3,047	2,013	2,258
Criterion for observed reflections	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$
R_{int}	0.029	0.055	0.033
θ_{max} (°)	27.5	27.6	27.5
Range of h, k, l	$-20 \le h \le 20$	$-7 \le h \le 7$	$-7 \le h \le 7$
	$-12 \le k \le 12$	$-22 \le k \le 22$	$-22 \le k \le 21$
	$-30 \le l \le 31$	$-16 \le l \le 16$	$-19 \le l \le 19$
Refinement			
Refinement on	F^2	F^2	F^2
$R[F^2 > 2\sigma(F^2)]$	0.049	0.046	0.047
$wR(F^2)$	0.148	0.131	0.154
S	1.05	1.08	1.08
Number of reflections used in refinement	4,176	2,744	3,067
No. of parameters used	235	154	164
H-atom treatment	Constrained	Constrained	Constrained
$(\Delta/\sigma)_{\text{max}}$	<0.001	0.001	0.001
$\Delta\rho_{\text{max}}$ (e Å^{-3})	0.48	0.21	0.21
$\Delta\rho_{\text{min}}$ (e Å^{-3})	−0.43	−0.33	−0.28
Extinction method	None	None	None

Table 2 Crystallographic data for compounds (**5**), (**8**) and (**9**)

	(**5**)	(**8**)	(**9**)
Crystal data			
Chemical formula	$C_{14}H_{16}O_3S$	$C_{15}H_{22}O_5S_2$	$C_{16}H_{24}O_5S_2$
Chemical formula weight	264.33	346.45	360.47
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$	$P2_1/c$
a (Å)	8.0720(4)	18.5329(4)	37.7935(12)
b (Å)	11.4860(9)	7.9377(1)	11.4478(3)
c (Å)	14.5650(8)	11.3448(2)	8.1883(3)
α (°)	90	90	90
β (°)	101.373(4)	94.147(1)	90.763(1)
γ (°)	90	90	90
V (Å^3)	1,314.79(1)	1,664.55(5)	3,542.4(2)
Z	4	4	8
$F(000)$	560	736	1,536
D_x (Mg cm^{-3})	1.335	1.382	1.352
Radiation type	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$
Wavelength (Å)	0.71073	0.71073	0.71073
θ range (°)	3.13–27.52	3.60–27.48	3.06–25.35
μ (mm^{-1})	0.244	0.339	0.322
Temperature (K)	298(2)	298(2)	298(2)
Crystal form	Irregular	Irregular	Irregular
Crystal size (mm)	0.44 × 0.11 × 0.05	0.20 × 0.18 × 0.07	0.05 × 0.26 × 0.37
Crystal colour	Colourless	Colourless	Colourless
Data collection			
Diffractometer	Enraf–Nonius Kappa-CCD	Enraf–Nonius Kappa-CCD	Smart APEX II-CCD
Data collection method	ω scan	ω scan	ω/φ scan
Absorption correction	None	None	Multi-scan
No. of measured reflections	5,719	30,235	23,541
No. of independent reflections	3,002	3,781	6,439
No. of observed reflections	2,432	2,353	4,457
Criterion for observed reflections			
R_{int}	0.0319	0.078	0.0705
θ_{max} (°)	27.52	27.48	25.35
Range of h, k, l	$-10 \le h \le 10$	$-23 \le h \le 24$	$-45 \le h \le 45$
	$-14 \le k \le 14$	$-9 \le k \le 10$	$-11 \le k \le 13$
	$-18 \le l \le 18$	$-14 \le l \le 11$	$-9 \le l \le 9$
Refinement			
Refinement on	F^2	F^2	F^2
$R[F^2 > 2\sigma(F^2)]$	0.0507	0.0502	0.0478
$wR(F^2)$	0.1463	0.1204	0.1194
S	1.047	1.041	1.062
Number of reflections used in refinement	3,002	3,781	6,439
No. of parameters used	164	201	421
H-atom treatment	H-atom parameters constrained	H-atom parameters constrained	H-atom parameters constrained
Weighting scheme			
$(\Delta/\sigma)_{max}$			0.001
$\Delta\rho_{max}$ (e Å^{-3})	0.40	0.23	0.42
$\Delta\rho_{min}$ (e Å^{-3})	−0.31	−0.39	−0.53
Extinction coefficient	0.082(11)	*None*	None

Table 3 Selected bond lengths (Å) and angles (°) for the compounds (**2**), (**3**) and (**4a**)

	(**2**)	(**3**)	(**4a**)
C(1)–C(2)	1.559(3)	1.498(2)	1.544(3)
C(2)–C(3)	1.532(3)	1.534(3)	1.531(3)
C(3)–C(4)	1.529(3)	1.518(3)	1.539(3)
C(1)–C(4)	1.556(3)	1.508(3)	1.550(3)
C(1)–C(5)	1.518(3)	1.330(2)	1.512(2)
C(5)–C(6)	1.522(3)	1.460(2)	1.498(2)
C(6)–C(7)	1.506(3)	1.525(2)	1.525(2)
O(1)–C(6)	1.190(3)	1.213(2)	1.215(2)
S(1)–C(7)	1.774(2)	1.7732(19)	1.7801(18)
S(1)–C(8)	1.757(2)	1.7628(19)	1.7551(18)
S(1)–O(2)	1.4338(18)	1.4391(13)	1.4311(14)
S(1)–O(3)	1.4272(18)	1.4359(13)	1.4300(15)
C(2)–C(1)–C(4)	89.09(16)	91.63(14)	89.58(16)
C(1)–C(2)–C(3)	89.34(17)	88.84(14)	87.69(16)
C(2)–C(3)–C(4)	91.10(17)	89.84(14)	88.53(16)
C(1)–C(4)–C(3)	89.56(17)	89.09(15)	89.09(15)
C(2)–C(1)–C(5)	118.70(18)	134.06(17)	118.09(18)
C(1)–C(5)–C(6)	116.52(18)	121.66(16)	116.42(16)
C(5)–C(6)–C(7)	112.73(18)	114.82(15)	116.29(15)
O(2)–S(1)–O(3)	118.12(11)	118.19(8)	118.59(10)

Table 4 Selected bond lengths (Å) and angles (°) for compounds (**5**), (**8**) and (**9**)

	(**5**)	(**8**)	(**9**)
C(1)–C(2)	1.542(3)	1.545(3)	1.550(4)
C(2)–C(3)	1.535(4)	1.530(3)	1.524(4)
C(3)–C(4)	1.546(3)	1.547(3)	1.552(4)
C(1)–C(4)	1.566(3)	1.585(3)	1.590(3)
C(4)–C(5)	1.512(3)	1.523(3)	1.531(4)
C(4)–C(6)	1.513(3)	1.525(3)	1.516(4)
S(1)–C(8)	1.795(2)	1.812(2)	1.849(2)
S(1)–O(1)	1.4316(15)	1.4293(18)	1.431(2)
S(1)–O(2)	1.4343(16)	1.4334(18)	1.4404(19)
S(1)–C(9)	1.765(2)	1.744(3)	1.752(3)
C(6)–C(7)	1.505(3)		
O(3)–C(7)	1.195(2)		
C(2)–C(1)–C(4)	87.97(2)	88.23(17)	87.9(2)
C(2)–C(3)–C(4)	88.96(18)	90.15(18)	90.2(2)
C(1)–C(4)–C(5)	118.04(2)	113.13(18)	115.9(2)
C(8)–S(1)–C(9)	106.20(8)	106.19(12)	109.49(12)
O(2)–S(1)–C(8)	106.80(9)	107.69(10)	105.92(12)
O(1)–S(1)–O(2)	118.5(1)	117.47(11)	117.86 (12)
O(3)–S(2)–O(4)		118.41(13)	119.04(12)
C(8)–S(2)–C(10)		110.48(10)	111.93(12)
S(2)–C(8)–S(1)		112.88(11)	111.42(13)
C(1)–C(8)–S(2)		109.30(15)	106.84(17)
S(1)–C(8)–C(1)	110.57(12)	112.34(15)	107.99(16)
C(1)–C(8)–C(7)	105.13(15)		
C(1)–C(4)–C(6)	104.31(17)		
C(2)–C(1)–C(8)	117.56(17)		
O(1)–S(1)–C(8)	108.03(10)		
S(1)–C(8)–C(7)	111.29(12)		

for both structures. Both compounds exhibit intermolecular hydrogen bonds, which helps in stabilizing the crystal structure. In (**8**) two intramolecular hydrogen bonds can be observed O5(*a*)–H5(*a*)···O5(*b*) = 1.88; O5(*b*)–H5(*b*)···O5(*a*) = 1.91 Å and in (**9**) only one O5–H5···O2 = 2.27 Å.

The C8–S1 = 1.812(2) and C8–S2 = 1.820(2) Å bond distances, observed for compounds (**8**) and C8*a*–S1*a* = 1.849(2) and C8*a*–S2*a* = 1.840(2) Å observed for (**9**), are almost equal in length to that of C_{alkyl}–S = 1.82 Å, which is the sum of the covalent radii [16] for S and C atoms. However, an increased interaction of the S2 atom with the π-system of the phenyl ring is indicated by the $C10_{aryl}$–S2 distances of 1.757(2) in (**8**) and of 1.766(3) Å in (**9**), which are shorter than the average C_{alkyl}–S distance (1.82 Å). In compound (**8**), the four almost identical S=O bond distances [1.4291(18), 1.4303(18), 1.4311(18) and 1.4328(18) Å] and O=S=O angles [117.48(11) and 118.42(13)°] compare quite favorably with the distances [1.431(2), 1.4409(19), 1.4323(18) and 1.4386(18) Å] and angles [117.86(12) and 119.04(11)°] observed for compound (**9**). The major palpable difference between the compounds (**8**) and (**9**) is present in the C4 quaternary carbon atom. Methylation of this center resulted in reducing of the angles C1–C8–S1, C1–C8–S2 and S1–C8–S2 of respectively, 4.53; 1.50 and 2.62°.

The most significant difference in the bond angles of the compound (**8**) when compared to its methylated compound (**9**) is localized over the C8. In (**8**), this carbon atom possesses three tetrahedral angles ranging from 109.56(14) to 112.87(11)°, while in (**9**) range from 106.8(2) to 111.48(18)° (see Table 2), as expected. The C8–S1 bond distances of 1.820(2) and 1.849(2) Å observed for compounds (**8**) and (**9**), respectively, are the most discrepant values observed among them.

Infrared Spectroscopy

The IR spectrum of compound (**1**) showed characteristic strong bands for $\nu(CH_2)$, $\delta(CH_2)$, δ_{as}(O=S=O) and δ_{sy}(O=S=O) vibrations observed at 2,950, 1,446, 1,306 and 1,087 cm^{-1}, respectively. The bands at 763 and 690 cm^{-1} were assigned to out of plane ring bending, δ_{ar}(C–H), related to monosubstituted aromatic ring. In compound (**2**) the ν(C=O) and δ_{ar}(C–H) were observed at 1,711 and 728 cm^{-1}, while δ_{as}(O=S=O) and δ_{sy}(O=S=O) were exhibited at 1,320, 1,290 and 1,142, 1,072 cm^{-1}. By

elimination reaction, appearing the ν(C=C) band at 1,628 cm^{-1} that displaced the ν(C=O) of carbonyl band to lower frequency at 1,690 cm^{-1}. By construction of the C(4) quaternary centre by 1,4-addition of a methyl group to ketone (**3**), the IR spectrum of (**4a**) showed ν(C=O) typical band at 1,715 cm^{-1}, as expected. The δ_{as}(O=S=O) and δ_{sy}(O=S=O) vibrations were observed at 1,315 and 1,144 cm^{-1}, respectively, while the δ_{ar}(C–H) bands are observed at 895, 752 cm^{-1} for sulfonyl unsaturated ketone (**3**) and at 745 cm^{-1} for sulfonyl saturated ketone (**4a**).

The IR spectrum for the sulfone (**5**) shows the presence of strong intensity band centered at 1,745 cm^{-1} which can be assigned with confidence to stretching vibration of the carbonyl, ν(C=O), group. It is interesting to note that this ν(C=O) mode appear at higher frequencies than the corresponding mode observed at 1,715 cm^{-1} for acyclic β-ketosulfone (**4a**). Usually, cyclopentanones absorbs at 1,745 cm^{-1} due to angular torsion promoted by five-membered ring. Other fundamental characteristics for sulfones are ν_{as}(O=S=O) and ν_{sy}(O=S=O) vibrations modes, observed in the 1,350–1,300 and 1,160–1,120 cm^{-1} regions [17], respectively. Thus, two strong absorptions centered at 1,305 and 1,144 cm^{-1} can be assigned with security to the ν_{as}(O=S=O) and ν_{sy}(O=S=O) vibrations. These stretching vibrations are located at 1,315, 1,150 cm^{-1} for disulfone (**8**) and at 1,318, 1,148 cm^{-1} for disulfone (**9**).

The most significant difference in the IR spectrum of the sulfone (**5**) when compared to the vibrational spectra of the disulfones (**8**) and (**9**) is the disappearance of the ν(C=O) stretching vibration in (**5**) and appearance of strong absorption centered at 3,549(sh) in (**8**) and at 3,422(sh) cm^{-1} in (**9**), which are assigned to ν(O–H) stretching. The relatively strong bands centered at 1,081 in (**8**) and at 1,072 cm^{-1} in (**9**) can be assigned to ν(C–O) stretching vibrations.

(^{1}H, ^{13}C) NMR Spectroscopy

NMR spectra were recorded on a VARIAN MERCURY PLUS spectrometer (7.05 T) operating at 300 MHz for ^{1}H and at 75.46 MHz for ^{13}C. The compounds (**2**), (**3**), (**4a**), (**5**), (**8**) and (**9**) were dissolved in $CDCl_3$ having TMS (Me_4Si) as internal reference; the chemical shifts were expressed in δ (ppm) and coupling constants as *J* (Hz). All hydrogens/carbons were matched to the numbers registered by X-ray technique to characterize the compounds. The methyl group of 1-methylcyclobutyl of compound (**4a**) represented the shieldest hydrogens at δ 1.15 (δ_C 25.5). The homoallylic hydrogens of cyclobutyl ring, related to (**3**), appeared as quintet at δ 2.13 (δ_C 17.8) with $J = 7.8$ Hz), when the hydrogens at same positions for (**2**) and (**4a**), showed as multiplet between δ 1.72 and 2.12 (δ_C 19.4 and 15.3). The cyclobutyl hydrogens in the allylic position for (**3**) were displaced to higher shifts, δ 3.08–3.16 (δ_C 33.0 and 34.8), than the observed multiplets for cyclobutyl hydrogens of(**2**) and (**4a**), at δ 1.99–2.81(δ_C 27.3 and 33.3). For all three compounds (**2**), (**3**) and (**4a**), the singlet αCH_2 to sulfonylketones were exhibited between δ 4.10 and 4.28 (δ_C 66.9, 67.0, 64.4), being much more deshielded than the singlet αCH_2, close to cyclobutyl ring of the compound (**2**) and (**4a**), assigned at 3.16 (δ_C 46.7) and δ 2.84 (δ_C 55.3) and, respectively. The olefinic hydrogen of (**3**), coupled to allylic of cyclobutyl ring showed as quintet at δ 6.20 (δ_C 119.7) ($J = 2.4$ Hz). There was no displacement shift for the aromatic hydrogens of those compounds (**2**), **3**) and (**4a**), as registered between δ 6.60 and 7.90 (δ_C 127.9 and 138.7).

In the structure (**5**), the methyl group (C5) showed as singlet at δ 1.43 (δ_C 26.3). The four and five-membered rings, respectively, exhibited the shifted displacements between δ 1.52 adn 3.66 for hydrogens and δ 21.2–88.9 for methylene (CH_2) carbons. Despite of diasterotopic hydrogens at C6 (δ 52.1) were showed at 2.41 and 2.62 ($J = 18$ Hz), the other ones such as C2–H and C3–H were observed as multiplet and not doublet duplet. The chemical shifts for the aromatic hydrogens were identified in following sequence for the C10 and C14 (δ_H 7.81–7.85; δ_C 128.6), for the C11 and C13 (δ_H 7.45–7.61; δ_C 129.0) and for the C12 (δ_H 7.25–7.66; δ_C 134.0). The aromatic quaternary carbon (C9) at δ 137.3 and the carbonyl group (C2) at δ 208.0 were marked by HMQC technique. Both compounds (**8**) and (**9**), the chemical shifts for their hydrogens and carbons are very closed, except to the additional methyl group (C16, δ 1.82) displaced in the structure of (**9**) and their respective quaternary carbons at C8 absorbing at δ 8.23 and 88.9. The resonance hydrogen signals from δ 1.34 to δ 3.89 (aliphatic hydrogens) and δ 7.40 to δ 7.95 (aromatic hydrogens) were assigned by the homonuclear (COSY). All carbons were matched to respective hydrogen by the homonuclear and heteronuclear two-dimensional experiments (COSY, HMQC and HMBC) done using the field gradient mode.

Supporting Information Available

Crystallographic data for the structural analysis of the compounds have been deposited at the Cambridge Crystallographic Data Center (CCDC). The CCDC numbers are 847420 (**2**), 847421 (**3**) 847422 (**4a**), 847984 (**5**), 847986 (**8**) and 847985 (**9**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, United Kingdom; Fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.

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