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Total synthesis of acetylenic carotenoids

1. Synthesis of optically active 2-*E*-((4*R*)-4-hydroxy-2,6,6-trimethylcyclohex-1-enyl)-3-methyl-2-penten-4-yn-1-al, a C_{15}-synthon

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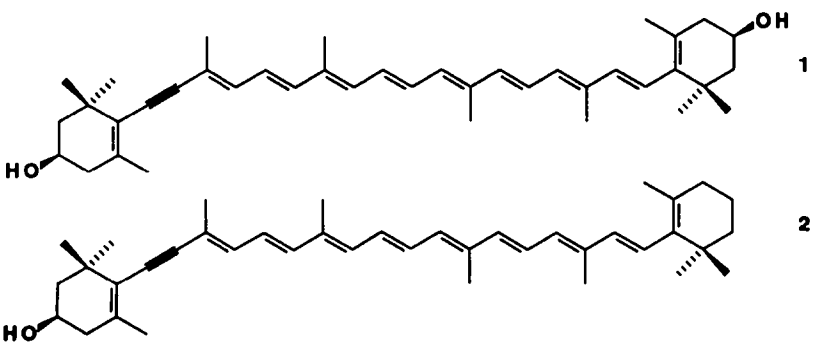
Abstract: The title compound was synthesised in the optically active form in seven steps from (4*R*,6*R*)-actinol in 34% overall yield. The relative configuration within the C_{15}-key intermediate acet-ylenic triol, 2-*E*-5-((1*S*,4*R*,6*R*)-1,4-dihydroxy-2,2,6-trimethylcyclohexyl)-3-methyl-2-penten-4-yn-1-ol, was determined by X-ray crystallographic analysis.

Introduction

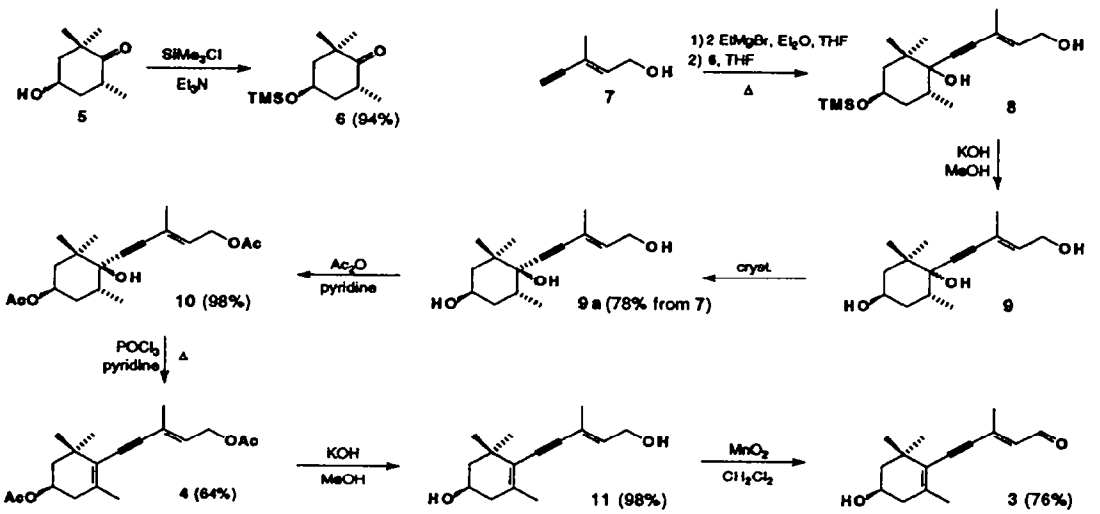
The total synthesis of optically active all-*E*-(3*R*,3'*R*)-diatoxanthin (**1**, Scheme 1) has been accomplished by a C_{15}+C_{10}+C_{15} approach with 22% overall yield in thirteen steps and in 6% overall yield in a fourteen step route.[1] Also, all-*E*-(3*R*)-7,8-didehydrocryptoxanthin (**2**) was synthesised with 23% overall yield by a similar approach. For these syntheses, the optically active C_{15}-acetylenic hydroxy aldehyde **3**, Scheme 2, was required. The synthesis of **3** is reported here.



Scheme 1.

Results and discussion

A key intermediate in the synthesis of the target compound **3**, presented in Scheme 2, was the acetylenic diacetate **4**. This diacetate was first synthesised in the racemic form by Weedon and co-workers[2] from 4,4-ethylenedioxo-2,2,6-trimethylcyclohexanone, and was later also used by Ito's group as starting material in the total synthesis of the norcarotenoids pyrrhoxanthin and peridinin in the racemic form.[3,4]



Scheme 2.

The optically active C_9-ketone actinol (**5**) is a widely used synthon in carotenoid synthesis,[5] also employed by Yamano and Ito[4] for the synthesis of optically active peridinin.[4] They obtained the C_{15}-acetylenic diacetate **4** in 55% yield from the protected actinol **6** and the protected (as TMS ether) acetylenic alcohol **7** by treatment with butyl lithium in dry diethyl ether, followed by separation of the epimeric products as diacetates.

In our modified route the diastereomeric triols **9** were obtained from the TMS ether **6**. Generation of ethylmagnesium bromide from magnesium and ethyl bromide, followed by reaction with the unprotected acetylenic alcohol **7** to generate the proper Grignard reagent and reaction with the protected ketone **6** afforded the diol **8** in a stereoselective reaction. Alkaline hydrolysis gave the triols **9**, and fractional crystallisation from diethyl ether provided the pure triol **9a**.

The configuration of the actylenic triol **9a** was here confirmed by X-ray crystallographic analysis, see Fig. 1. Only the relative configuration was established by the X-ray experiment, and the enantiomer shown in Fig.1 was drawn to conform to the absolute configuration of the starting material **5**.

The *prim.* and *sec.* hydroxy groups in **9a** were protected as acetates (**10**), and the subsequent elimination reaction of **10** effected with phosphorus oxychloride in pyridine. The acetylenic diol **9a** and the corresponding diacetate **10** have the *tert.* hydroxy group in equatorial and the neighbouring proton in axial position as proved by the X-ray analysis. Recent ^{1}H NMR arguments by Yamano and Ito[4] for the diacetate **10** favour the same relative configuration and conformation. Hence the elimination is an axial-equatorial syn elimination, disfavoured in an E2 reaction. Weedon and co-workers[2] reported 33% yield for this elimination

reaction with phosphorus oxychloride in pyridine at room temperature, whereas elimination at El conditions in hot acetic acid - acetic anhydride gave the 2-*Z* isomer in 60% yield. Yamano and Ito[4] reported 67% yield for the elimination with phosphorus oxychloride in hot pyridine. In this work yields of 11-24% of the 2-*E* diacetate **4** were obtained with phosphorus oxychloride at room temperature and 64% yield in hot pyridine. The overall yield of **4** was 50% based on the protected hydroxy cyclohexanone **6**, in line with previous yields.[4]

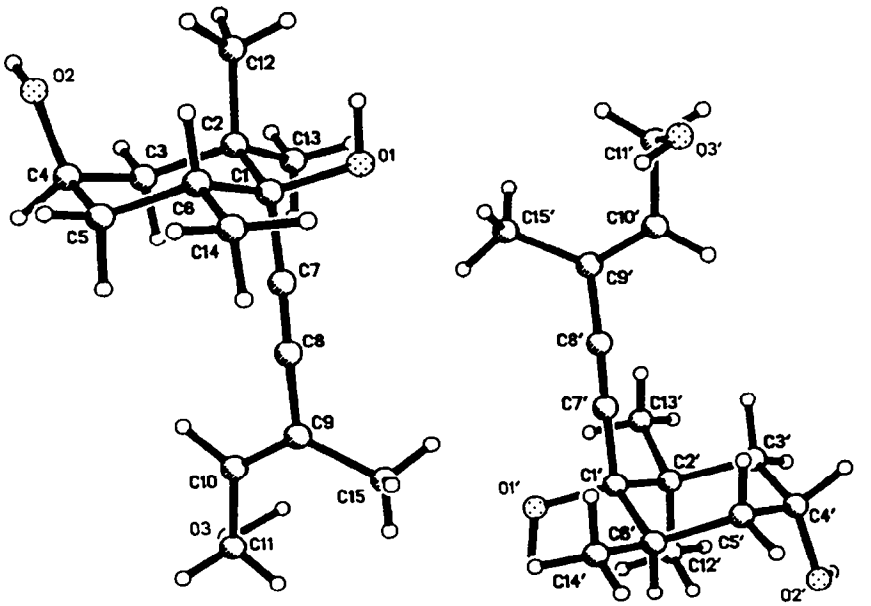


Fig.1. A computer generated perspective drawing of the acetylenic triol **9a**. Both molecules in the asymmetric unit are shown, and they are related by a pseudo-inversion center in the middle of the picture.

Alkaline hydrolysis of the acetylenic diacetate **4** afforded the diol **11**, and allylic oxidation of **11** with manganese dioxide furnished the C_{15}-acetylenic aldehyde **3** in an overall yield of 34% from (4*R*,6*R*)-actinol (**5**).

Experimental

General methods. These were as recently given in detail.[6] Pyridine was distilled over solid potassium hydroxide. Assignments of NMR signals are for each compound based on ^{1}H-^{1}H COSY data, and on reported chemical shifts for protons and carbon atoms in carotenoids.[7] Carbon atoms and protons in side chains are given primed numbers.

(4 R,*6* R*)-2,2,6-trimethyl-4-trimethylsiloxycyclohexan-1-one (6).* To (4*R*,6*R*)-4-hydroxy-2,2,6-trimethylcyclohexan-1-one (actinol, **5**, $[\alpha]^{20}_D$=-113.7 , c=0.0214 (MeOH) consistent with reported data,[8] 30.0 g, 0.19 mol) in dry diethyl ether (190 ml) was added triethylamine (26 g) and the mixture cooled to 0 °C. During 2h, trimethylsilyl chloride (25 ml, 0.20 mol) was added. The reaction mixture was kept at 0 °C - 20 °C for 15 h, ice-water added and the product extracted with diethyl ether. The organic phase was washed with brine and water and dried over anhydrous sodium sulphate, solvents were evaporated and the residue distilled. The product (b.p. 105-107 °C, *ca.* 20 mmHg) was obtained as a colourless oil in 94% yield (41.0 g, 0.18 mol), 99%

pure as indicated by GC (BP-1 capillary column, temperature program 40 °C 4 min: 10 °C min^{-1} to 280 °C; 10 min).

MS [IP 70 eV, 150 °C *m/z* (% rel.int.)]: 228 (44, [M]), 170 (29, [M-58]), 146 (63, [M-82]), 130 (25, [M-98]), 82 (17), 75 (64), 73 (100); ^{1}H NMR ($CDCl_3$) δ 0.137 [*s*, 9 H, Me in TMSO-], 1.005 [d, 3 H, *J* 6.4 Hz, Me-6], 1.009 [*s*, 3 H, Me-2], 1,321 [s, 3 H, Me-2], 1,60 [*td*, 1 H, *J* 2.9 Hz, *J* 13.2 Hz, H-5ax], 1.67 [*dd*, 1H, *J* 3.9 Hz, *J* 14.7 Hz, H-3ax], 1.89 [*dt*, 1 H, *J* 2.9 Hz, *J* 14.7 Hz, H-3eq], 2.01 [*m*, 1 H, H-5eq], 3.17 [*m*, 1H, H-6], 4.10 [*m*, 1 H, H-4].

2-E-5-((1'S,4'R,6'R)-1',4'-Dihydroxy-2',2',6'-trimethylcyclohexyl)-3-methyl-2-penten-4-yn-1-ol (9a). Ethyl bromide (11.1 g, 7.7 ml, 0.10 mol) was added dropwise to magnesium (2.6 g, 0.11 mol) in dry diethyl ether (600 ml) to maintain a gentle reflux. The mixture was refluxed for another 30 min and cooled to 20 °C. Then **7** (4.9 g, 51.0 mmol) in dry THF (30 ml) was added dropwise to maintain a gentle reflux. The reaction mixture was refluxed for another 30 min and cooled to 20 °C. The protected actinol (**6**, 7.8 g, 34.0 mmol) in dry THF (30 ml) was added during 10 min. The resulting reaction mixture was refluxed for 20 h, and cooled to 0°C. Cold saturated aqueous ammonium chloride (ca. 300 ml) was added and the mixture was stirred at 0 °C for 1 h. The product was extracted with diethyl ether, the organic phase washed several times with brine followed by water and the solvents were evaporated. TLC (System 2) of the oily residue indicated the presence of excess **7** and the main product **8**. The protected triol **8** was dissolved in 5% potassium hydroxide in methanol (150 ml) and the mixture stirred at 20 °C for 2 h and concentrated to *ca.* 30 ml. Water was added and the product extracted with diethyl ether. The organic phase was washed with brine and water, and dried over anhydrous sodium sulphate. Solvents were evaporated to give a light yellow oily residue (10.3 g). The produet was isolated by crystallisation from diethyl ether, as a colourless solid in 78% yield (6.67 g, 26.5 mmol). ^{1}H NMR indicated the presence of only one of the two possible diastereomers. Repeated crystallisation from acetone - hexane afforded **9a** as long (> 5 mm), colourless needles. The product was assigned the (1'*S*,4'*R*,6'*R*) configuration by X-ray crystallographic analysis, see below.

M.p. 132 °C; UV λmax (dichloromethane) 230 nm , λmax (ethanol) 228 nm; IR (KBr) cm^{-1} 3374-3284 s (OH), 3000-2884 (CH), 2170 w (C≡C), 1426 m, 1254 m, 1066 m, 1038 m, 1008 m; MS [IP 30 eV, 160 °C *m/z* (% rel.Int.)]: 252 (41, [M]), 234 (5, [M-18]), 203 (3), 178 (6), 156 (4), 148 (11), 107 (11), 101 (22), 75 (18), 59 (51), 43 (100); ^{1}H NMR ($CDCl_3$) δ 1.070 [*d*, 3 H, *J* 6.2 Hz, Me-6'], 1.097 [*s*, 3 H, Me-2'], 1.236 [*s*, 3 H, Me-2'], 1.55-1.75 [*m*, 4 H, ring methylene protons], 1.840 [*d*, 3 H, *J* 1.5 Hz, Me-3], 2.34 [*m*, 1 H, H-6'], 4.04 [*m*, 1 H, H-4'], 4.23 [*d*, 2 H, *J* 6.8 Hz, H-1], 5.95 [*tq*, 1 H, *J* 1.5 Hz, *J* 6.8 Hz, H-2] $[\alpha]^{20}_D$=-22.4 (c=0.006, MeOH).

2-E-5-((1'S,4'R,6'R)-4'-Acetoxy-1'-hydroxy-2',2',6'-trimethylcyclohexyl)-3-methyl-2-penten-4-yn-1-ol 1-acetate (10). Acetic anhydride (21.8 ml, 0.24 mmol) was added dropwise to a solution of **9a** (4.15 g, 16.5 mmol) in dry pyridine (70 ml). The reaction mixture was stirred at 20 °C for 24 h and poured into water. The product was extracted with dichloromethane. The organic phase was washed with water and dried over anhydrous sodium sulphate. TLC (System 1) indicated only one product, less polar than **9a**. Solvents were evaporated to yield **10** as a colourless oil in 98% yield (5.47 g, 16.2 mmol) > 95% pure, as indicated by ^{1}H NMR, TLC and HPLC (System 4).

UV λmax (ethanol) 228 nm; MS [IP 50 eV, 170 °C *m/z* (% rel.int.)] 336 (0.2, [M]), 276 (76, [M-60]), 258 (1, [M-18-60]), 234 (6, [M-42-60]), 216 (31, [M-60-60]), 203 (21), 194 (17), 178 (19), 160 (95), 147

(24), 145 (36), 134 (36), 106 (73), 43 (100); ^{1}H NMR ($CDCl_3$) δ 1.065 [*d*, 3 H, *J* 6.4 Hz, Me-6'], 1.095 [*s*, 6H, Me-2'], 1.60-1.70 [*m*, 4 H, ring methylene protons], 1.874 [s, 3 H, Me-3], 2.037 [*s*, 3 H, Me in AcO], 2.072 [*s*, 3 H, Me in AcO], 2.24 [*m*, 1 H, H-6'], 4.64 [*d*, 2 H, *J* 6.5 Hz, H-1], 4.95 [*m*, 1 H, H-4'], 5.90 [*tq*, 1H, *J* 1.5 Hz, *J* 7.3 Hz, H-2], $[\alpha]^{29}_D$=-23.6 (c=0.086, MeOH), *cf.* reported -24.1.[4]

2-E-5-((4'R)-4'-Acetoxy-2',6',6'-trimethylcyclohex-1'-enyl)-3-methyl-2-penten-4-yn-1-ol 1-acetate (4). i) To the preceding diacetate **10** (0.37 g, 1.1 mmol) in dry pyridine (8 ml) was added freshly distilled phosphorus oxychloride (1 ml) during 2 min. The reaction mixture was stirred at 20 °C for 5 days, and cooled to 0°C. Ice was added followed by water and the product was extracted with diethyl ether. The organic phase was washed with brine and water, and dried over anhydrous sodium sulphate. The solvents were evaporated and the residue was submitted to CC, to give **4** as a colourless oil in 24% yield (0.083 g, 0.26 mmol) and recovered starting material (45%, 0.17 g, 0.50 mmol).

ii) **10** (1.34 g, 4.0 mmol) in dry pyridine (25 ml) was added freshly distilled phosphorus oxychloride (2.5 ml) during 2 min. The mixture was stirred at 75-80 °C for 20 h and then cooled to 0 °C. Workup as described above and CC afforded **4** as a colourless oil in 64% yield (0.814 g, 2.56 mmol) > 99% pure, as indicated by ^{1}H NMR, TLC and HPLC (System 4).

UV λmax (ethanol) 266 nm; IR (liq.) cm^{-1} 2963-2868 s (CH), 2188 m (C≡C), 1740 s (acetate), 1363 m, 1233 s (acetate), 1027 s, 969 m; MS [IP 40 eV, 170 °C *m/z* (% rel.int)]: 276 (11, [M-42]), 258 (100, [M-60]), 216 (11, [M-42-60]), 198 (21, [M-60-60]), 188 (33), 183 (36), 173 (35), 43 (32); ^{1}H NMR ($CDCl_3$) δ 1.151 [*s*, 3 H, Me-6'], 1.173 [*s*, 3 H, Me-6'], 1.54 [*m*, 1 H, H-5'ax], 1.82 [m, 1 H, H-5'eq], 1.882 [*s*, 3 H, Me-2'], 1.917 [s, 3 H, Me-3], 2.037 [*s*, 3 H, Me in AcO], 2.066 [*s*, 3 H, Me in AcO], 2.12 [*dd*, 1 H, *J* 4,4 Hz, *J* 17.7 Hz, H-3'ax], 2.48 [*dd*, 1 H, *J* 5.4 Hz, *J* 17.6 Hz, H-3'eq], 4.66 [*d*, 2 H, *J* 7.3 Hz, H-1], 5.03 [*m*, 1 H, H-4'], 5.89 [*tq*, 1 H, *J* 1.5 Hz, *J* 7.3 Hz, H-2], $[\alpha]^{28}_D$=-48.5 (c=0.082, MeOH), *cf.* reported -48.5.[4]

2-E-5-((4'R)-4'-Hydroxy-2',6',6'-trimethylcyclohex-1'-enyl)-3-methyl-2-penten-4-yn-1-ol (11). Compound **4** (0.40 g, 1.26 mmol) was treated with 5% potassium hydroxide (30 ml) at 20 °C for 2 h. The solution was concentrated to *ca.* 5 ml and water added. The product was extracted with diethyl ether. The organic phase was washed with brine and water and dried over anhydrous sodium sulphate. TLC (System 2) indicated one product only, more polar than the starting material **4**. Solvents were evaporated to give **11** as a colourless oil in 98% yield (0.29 g, 1.24 mmol) > 98% pure, as indicated by ^{1}H NMR, TLC and HPLC (System 4).

UV λmax (ethanol) 265 nm; MS [IP 70 eV, 170 °C *m/z* (% rel.int.)]: 234 (100, [M]), 216 (18, [M-18]), 206 (10, [M-25]), 201 (32), 198 (4, [M-18-18]), 173 (27), 166 (15), 152 (34), 147 (23), 135 (21), 119 (27), 105 (26), 82 (28), 43 (46): ^{1}H NMR ($CDCl_3$) δ 1.124 [*s*, 3 H, Me-6'], 1.175 [*s*, 3 H, Me-6'], 1.44 [*m*, 1 H, H-5'ax], 1.83 [*m*, 1 H, H-5'eq], 1.886 [*s*, 3 H, Me-2'], 1.897 [*s*, 3 H, Me-3], 2.09 [*m*, 1 H, H-3'ax], 2.42 [*m*, 1 H, H-3'eq], 3.96 [*m*, 1 H, H-4'], 4.25 [*d*, 2 H, *J* 6.8 Hz, H-1], 5.97 [*tq*, 1 H, *J* 1.5 Hz, *J* 6.8 Hz, H-2]; $[\alpha]^{27}_D$=-78.2 (c=0.064, MeOH).

2-E-5-((4'R)-4'-hydroxy-2',6',6'-trimethylcyclohex-1'-enyl)-3-methyl-2-penten-4-yn-1-al (3). Compound **11** (0.53 g, 2.26 mmol) was dissolved in dichloromethane (60 ml). Manganous dioxide (6.4 g) was added and the reaction mixture kept at 20 °C under vigorous stirring. The reaction was monitored by TLC (System 1). After 20 h, the reaction mixture was filtered, the solvent was evaporated, the residue dissolved in a minimal

volume of benzene and submitted to CC. The product **3** was isolated as a light yellow oil in 76% yield (0.40 mg, 1.72 mmol) >95% pure, as indicated by ^{1}H NMR, TLC and HPLC (System 1).

UV λmax 336 nm; IR (Nujol mull) cm^{-1} 3400 m (OH), 3000-2800 s (CH), 2190 m (C≡H), 1675 s (conj. CH=O), 1590 s; MS [IP 70 eV, 170 °C *m/z* (% rel.int.)] 232 (96, [M]), 214 (27, [M-18]), 206 (18, [M-26]), 199 (100), 173 (55), 147 (52), 133 (39), 105 (32), 95 (31), 82 (54), 69 (72), 43 (45); ^{1}H NMR ($CDCl_3$) δ 1.130 [*s*,3 H, M-6'], 1.184 [*s*, 3 H, Me-6'], 1.45 [*m*, 1 H, H-5'ax], 1.83 [*m*, 1 H, H-5'eq], 1.935 [*s*, 3 H, Me-2'], 2.09 [*m*, 1 H, H-3'ax], 2.34 [*d*, 3 H, *J* 1.5 Hz, Me-3], 2.47 [*m*, 1 H, H-3'eq], 4.00 [*m*, 1 H, H-4'], 6.20 [*dd*, 1 H, *J* 1.5 Hz, *J* 8.3 Hz, H-2], 10.03 [*d*, 1 H, *J* 8.3 Hz, H-1]; ^{13}C NMR ($CDCl_3$) δ 22.6 [Me at C-2'], 25.2 [Me at C-3(?)], 29.7 [Me at C-6'], 30.3 [Me at C-6'], 36.5 [C-6'], 41.6 [C-3'], 46.2 [C-5'], 64.6 [C-4'], 95.8 and 98.3 [C-4 and C-5], 123.6 [C-1'], 132.4 [C-2], 141.4 and 142.2 [C-3 and C-2'], 190.2 [C-1]; $[\alpha]^{29}_D$=-61.5 (c=0.004, MeOH); CD nm (Δε) EPA (diethyl ether - isopentane - ethanol 5 : 5 : 2): 205 (-0.6), 212 (-1.6), 220 (-0.8), 226 (-0.7).

Single crystal X-ray diffraction analysis of acetylenic triol ***9a***. A crystal of dimensions 0.2 x 0.4 x 0.6 mm^3 was used to collect all X-ray data. Experiments were done at room temperature (25 °C) using a Siemens R3M diffractometer and Cu Kα radiation (1.5418 Å). Preliminary diffraction photographs showed monoclinic symmetry, and cell parameters of a=10.547(2), b=10.671(2), c=13.593(3) Å, and β=97.18(2)° were obtained from a least-squares fit of diffractometer measured 2θ-values. A total of 2345 reflections were measured using variable speed 2θ-scans, and 2204 reflections were symmetry unique. After correction for Lorentz, polarization and background effects, 2053 (95%) were judged observed ($|F| \geq 4.0\ \sigma(F)$). The structure was solved by direct methods using the SHELXTL Plus program and refined using SHELX-93. Fullmatrix least-squares refinements on F^2 gave a final discrepancy index of 5.38%. There was a surprising amount of difficulty in refining the structure. While the real space group is $P2_1$, most of the atoms are related to a symmetry mate by an inversion center at 0.0, 0.0 0.5 (Figure 1). In the early stages of refinement, it was essential to require equivalent bonds in the two independent molecules to have identical bond lengths.

Acknowledqements

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