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THERMAL ELECTROCYCLIC RING-OPENING OF CYCLOBUTENES: STEREOSELECTIVE ROUTES TO FUNCTIONALISED CONJUGATED (*Z,E*)- AND (*E,E*)-2,4-DIENALS

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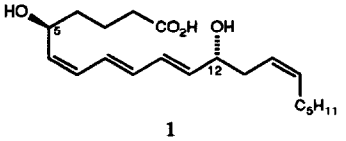
Abstract: The cyclobutenecarbaldehyde **12** undergoes thermal electrocyclic ring-opening at low temperature, producing the (2*Z*,4*E*)-hexadienal **13** exclusively. By contrast, unsymmetrical derivatives of *cis*-3-cyclobutene-1,2-dicarboxylic acid undergo ring-opening at 80–110 °C with low levels of stereoselectivity, which vary according to the balance of the electronic and, to a lesser extent, the steric nature of the substituents located on the rehybridising carbon atoms.

Much effort has been expended recently on the synthesis of conjugated dienes, which are structural components of a range of biologically active molecules, including various lipoxygenase-derived arachidonic acid metabolites (*e.g.* leukotriene B_4 **1**),[2] insect pheromones,[3] trichothecenes,[4] and fatty acids.[5] Procedures which lead to (*Z,E*)-dienes are especially useful, and certain eliminations,[3,6] couplings,[7] and fragmentations[8] can be used for their preparation. In other methods the stereocontrol is based on a pericyclic process, *e.g.* the cheletropic extrusion of SO_2 from 3-sulpholenes,[9] and the electrocyclic ring-opening of 2-oxabicyclo[3.1.0]hex-3-enes[10] and 2*H*-pyrans.[11] The thermal electrocyclic ring-opening of cyclobutenes has also been used as a source of conjugated dienes,[12,13] but its value as a route to single (*Z,E*)-isomers is undermined by the ambiguity of the symmetry-based selection rule, which defines two allowed modes of conrotatory ring-opening.[14] Thus heating an unsymmetrical *cis*-disubstituted cyclobutene can in principle produce either of two isomeric (*Z,E*)-dienes.



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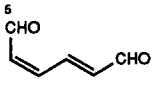

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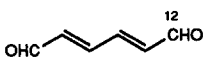

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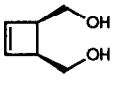
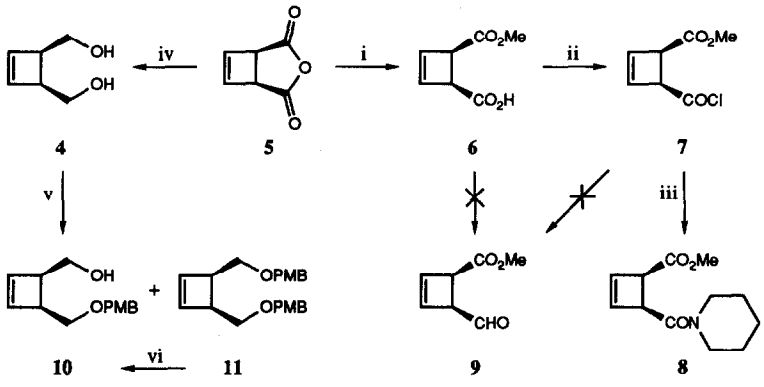


4

We were interested in identifying the factors which determine the conrotatory preferences of unsymmetrical cyclobutenes, which in other respects seemed ideal for use as diene precursors, and undertook a study with this objective. Specific targets included synthetic equivalents of the dialdehydes **2** and **3**, suitable for elaboration to analogues of leukotriene B_4 **1** *via* olefination and nucleophilic additions. Our observations, herein described in detail,[15] indicate that the conrotation process is more sensitive to the electronic, as opposed to steric, nature of the substituents, and that the diol **4** is a particularly useful source of functional, isomerically pure diene units.

Approaches to 2-Cyclobutene-1-carboxaldehydes and Related Compounds

The anhydride **5** is a convenient starting point for the preparation of *cis*-1,2-disubstituted-3-cyclobutenes. It is a distillable crystalline solid which can be prepared in good yield *via* the [2 + 2] photoaddition of acetylene to maleic anhydride.[16] Methanolysis of **5** gave the unsymmetrical ester–acid **6**, and the latter was transformed into the acid chloride **7**, which was characterised as the amide **8** (Scheme 1). Since our targets were aldehydes, various attempts were made to reduce **6** to the aldehyde–ester **9** using the mixed anhydride method,[17] but gave mainly the diol **4**, which was obtained more directly by treating the anhydride **5** with $LiAlH_4$ in tetrahydrofuran (THF).[18] Reductions of **7** with lithium tri-*t*-butoxyaluminium hydride[19] or bis(triphenylphosphine)copper(I) borohydride[20] were also ineffective, each giving a complex mixture rather than the desired aldehyde–ester **9**.



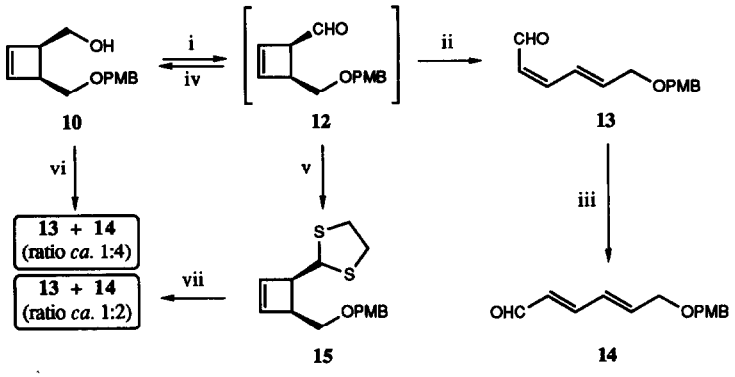
SCHEME 1 (PMB = 4-methoxybenzyl) *Reagents:* i, MeOH, reflux, 0.5 h (99%); ii, oxalyl chloride, $CHCl_3$, 0 °C, 6 h (97%); iii, piperidine, CH_2Cl_2, 20 °C, 1 h (91%); iv, $LiAlH_4$, THF, 0 °C, 0.5 h, then reflux, 72 h (96%); v, NaH, DMF, PMB–Br, 0 °C, 2 h, then 20 °C, 14 h (83%); vi, DDQ, CH_2Cl_2–H_2O, 20 °C, 16 h (75%).

To initiate the alternative, oxidative, approach to aldehydes of the desired type, the diol **4** was protected as the monoether **10** by treatment with NaH and 4-methoxybenzyl bromide in *N*,*N*-dimethylformamide (DMF), which also gave a small amount of the diether **11**. The 4-methoxybenzyl protecting group was chosen on the basis of the mild oxidative conditions required to cleave it [2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), CH_2Cl_2, H_2O],[21] which appeared to be compatible with the presence of a strained double bond within the substrate. This was confirmed in model experiments, including the conversion of the diether **11**, an unwanted by-product in the etherification reaction, into the more useful monoether **10**. An additional advantage of using the 4-methoxybenzyl protecting group in this series became apparent later.

Oxidation of the alcohol **10** under Swern conditions[22,23] at –78 °C generated the aldehyde **12**, which underwent electrocyclic ring-opening prior to reaching to room temperature. The high field ^1H n.m.r. spectrum of the product indicated that it was almost exclusively the (2*Z*,4*E*)-hexadienal **13** [$J_{2,3}$ 11 Hz; $J_{4,5}$ 15 Hz; δ 10.15 (d, *J* 8 Hz, >95% of CHO region)].[24] Evidence for the formation of **12** *en route* to **13** was obtained in two experiments. Firstly, the alcohol **10** was regenerated from the cold oxidation product by treating it with sodium borohydride. Secondly, reaction of the cold oxidation mixture with 1,2-ethanedithiol and titanium(IV) chloride[25] gave the dithiolane **15**.

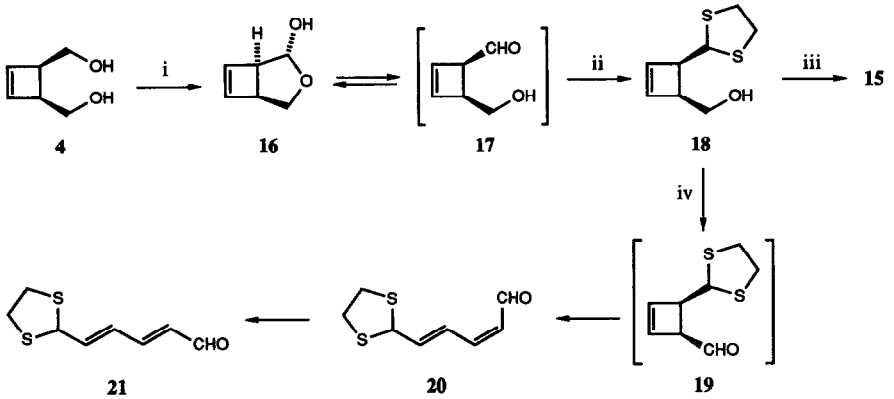
On standing in solution in deuteriochloroform, the dienal **13** was transformed into the thermodynamically more stable (2*E*,4*E*)-isomer **14** (semicarbazone, m.p. 197 °C), the process being much slower at –10 °C, but markedly accelerated by the addition of acid. The isomerisation of **13** to **14** was also extensive when the

alcohol **10** was oxidised with pyridinium chlorochromate (PCC),[26] and when the dithiolane **15** was hydrolysed by treatment with methyl iodide in aqueous base. The conditions under which the dienal **13** can be manipulated without isomerisation are thus expected to be limited.



SCHEME 2 *Reagents:* i, oxalyl chloride, Me_2SO, CH_2Cl_2 or THF, –78 °C, 1 h, then Et_3N, –78 °C, 10 min; ii, warm to 20 °C (86% over two steps); iii, *p*-TsOH–$CHCl_3$ or HCl–H_2O (100%); iv, $NaBH_4$, EtOH-MeOH, –78 to +20 °C, 3 h; v, ethanedithiol, $TiCl_4$, –78 °C, 0.5 h (45%); vi, PCC, Celite, CH_2Cl_2, 20 °C, 2 h (86%); vii, Na_2CO_3, MeI, H_2O, Me_2CO, 20 °C, 3 d (62%).

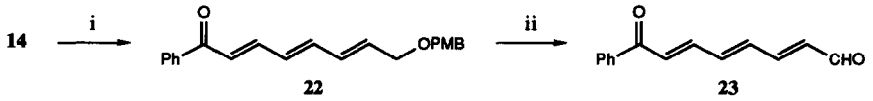
Another protected form of the (*E*,*E*)-dialdehyde **3** was prepared from the lactol **16**, which can be obtained from the diol **4** by oxidation with pyridinium dichromate (PDC).[27] The lactol exists in equilibrium with the thermally labile hydroxyaldehyde **17**, which was trapped as the dithiolane **18** (3,5-dinitrobenzoate, m.p. 116 °C) using ethanedithiol–$TiCl_4$.[25] Methoxybenzylation of **18** provided an authentic sample of the dithiolane **15**. Oxidation of **18** with PCC gave the (2*E*,4*E*)-hexadienal **21**, which is presumably generated from the aldehyde **19** *via* thermal electrocyclic ring-opening to the (2*Z*,4*E*)-dienal **20**, followed by isomerisation under the conditions of the oxidation (Scheme 3).



SCHEME 3 *Reagents:* i, PDC, oxalic acid, CH_2Cl_2, 20 °C, 4 h (75%); ii, ethanedithiol, $TiCl_4$, –78 to +20 °C, 1 h (83%); iii, KH, 18-crown-6, PMB–Br, THF (50%); iv, PCC, Celite, CH_2Cl_2, 20 °C, 14 h (40%).

A second advantage of using the PMB protecting group for the monoether **10** was revealed in the course of a model olefination sequence. The standard deprotection of the trienone **22**, obtained *via* treatment of the

(*E*,*E*)-dienal **14** with a phenacyl Wittig reagent, gave the trienal **23** directly (Scheme 4), the latent aldehyde group at the other terminus of the polyene chain being conveniently unmasked in a single oxidation step.



SCHEME 4 i, $PhCOCH{=}PPh_3$, THF, reflux (45%); ii, DDQ, CH_2Cl_2–H_2O, 20 °C, 20 h (77%).

Electrocyclic Ring-opening of Derivatives of *cis*-3-Cyclobutene-1,2-dicarboxylic Acid

The anhydride **5** was readily transformed into unsymmetrical derivatives of *cis*-3-cyclobutene-1,2-dicarboxylic acid, and these provided an opportunity to compare the effects of various carbonyl substituents on the thermal electrocyclic ring-opening reaction (Table 1). The ester–acid **6** proved quite stable in chloroform at 62 °C, but isomerised rapidly at 110 °C to give a 2:1 mixture of the two allowed conrotation products **24** and **25**. Trost and McDougal observed a similar degree of stereoselection (3:1) with the corresponding *n*-butyl ester–acid, and were able to assign the stereochemistry of the products by ^1H n.m.r. spectroscopy.[13] The products shown in Table 1 also exhibited diagnostic ^1H n.m.r. signals, and chemical correlations were used to confirm the assignments. For example, the ester–acid chloride **7** gave a 4:1 mixture of **26** and **27**, treatment of which with water, followed by crystallisation, provided a pure sample of **24**. In contrast, fractional crystallisation of the 2:1 mixture of **24** and **25** obtained from the ester–acid **6** invariably returned mixtures. The 2:1 mixture of **24** and **25** was also transformed into a 2:1 mixture of **26** and **27** *via* treatment with oxalyl chloride.

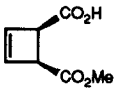
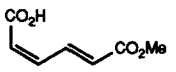
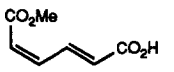
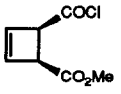
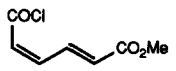
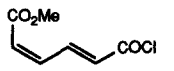
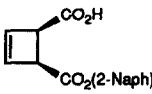
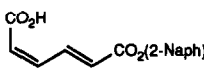
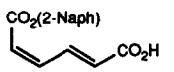
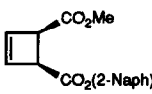
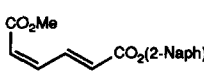
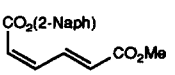
STARTING MATERIAL	REACTION CONDITIONS	PRODUCTS	RATIO
 **6**	toluene 110 °C 1 h	 **24**  **25**	2:1
 **7**	toluene 110 °C 1 h	 **26**  **27**	4:1
 **28**	$ClCH_2CH_2Cl$ 83 °C 10 h	 **29**  **30**	1:1
 **31**	toluene 110 °C 2 h	 **32**  **33**	1:1.4

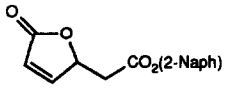
TABLE 1 Thermal electrocyclic ring-opening of derivatives of *cis*-3-cyclobutene-1,2-dicarboxylic acid

Ring-opening of the ester–acid **28** gave essentially equal amounts of the dienes **29** and **30**, whose structures could not be unequivocally assigned from the respective ^1H n.m.r. spectra. However, they were distinguished

via the facile base-catalysed cyclisation of the (*E*,*Z*)-isomer **29** to the lactone **34**.[13,28] Although it is tempting to conclude that the difference in stereoselectivity observed with the ester–acids **6** and **28** reflects the differing conrotatory preferences of the naphthyl and methyl ester groups, hydrogen bonding effects operating through the free carboxyl group could be contributing to the observed results.[13] However, with the mixed diester **31** the effects of the two ester functions can be directly compared, and the ring-opening reaction gave a slight excess of the (2*Z*,4*E*)-product **33**. It can thus be concluded that the methoxycarbonyl group tends to undergo 'outward' conrotation (*i.e.* adopt the *E*-configuration) more readily than the 2-naphthoxycarbonyl group.

Mechanistic Considerations

On the basis of steric effects alone it might be predicted that the thermal electrocyclic ring-opening of a cyclobutene **35**, in which the substituent Y (or Z) is larger than the group X, would lead mainly to a diene **36**, with the bulky group being inclined to move outward during the conrotation process so as to minimise steric interactions within the transition state and product. However, over the years this argument has repeatedly been shown to be inadequate, failing to account for the unusually high or 'contrasteric' selectivity implicit in examples such as (in order of outward conrotatory preference) Cl > CO_2H,[29] Me > Et,[30] and F > CF_3.[31] Rondan and Houk recently studied this reaction computationally,[32] and reached the conclusion that orbital interactions within the transition state give rise to a tendency for π-donor substituents to undergo outward conrotation, while inward conrotation is favoured by π-acceptor groups. The results in Table 1 are consistent with this, and indicate that the disposition of the various acyl groups towards inward conrotation follows the order COCl > CO_2H ≈ CO_2(2-Naph) > CO_2Me. The preferential formation of **33** from **31**, another contrasteric result, presumably reflects the greater π-donor capacity of OMe compared to OAr, which in turn makes the aryl ester function slightly more powerful as a π-acceptor.



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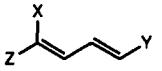
35



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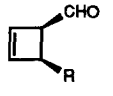
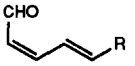


37 R = H
39 R = Alkyl



38 R = H
40 R = Alkyl

The behaviour of the aldehyde **12** is consistent with the strong preference of a formyl group for inward conrotation, an electronic effect whose existence was recently confirmed with the parent system **37**, which undergoes thermal ring-opening to give the (*Z*)-dienal **38** exclusively.[33,34] The presence of the alkoxyalkyl substituent at C-4 of the aldehyde **12** serves to reinforce the inward conrotatory preference of the formyl group, since its own preference is for the outward conrotation required of it. Because of this complementarity, the ring-opening of **12** occurs rapidly and at sub-ambient temperature, whereas the parent system **37** has a half-life of *ca.* 50 h at 25 °C.[33] This effect appears to be general, with other substrates of the form **39** also undergoing ring-opening at low temperature, and producing (2*Z*,4*E*)-dienals **40** exclusively.[35]

In summary, it seems that high and predictable stereoselectivity in the thermal electrocyclic ring-opening of cyclobutenes of the form **35** can be ensured by arranging that the substituents X and Y (or X and Z) possess complementary conrotatory preferences, and that this complementarity is more reliably based on differences in the electronic, rather than the steric, nature of the substituents. The aldehyde group is likely to be particularly useful in this context, since it is possesses a dominating (*Z*)-selective conrotatory preference, and is also versatile synthetically. Applications of these principles are currently under investigation.

EXPERIMENTAL

All compounds are racemic. Melting points were determined using an Electrothermal apparatus and are uncorrected. Unless otherwise stated, i.r. spectra were of liquid paraffin ('Nujol') mulls on sodium chloride plates, recorded on Pye-Unicam SP3-100, Perkin-Elmer 297, or Perkin-Elmer 1710FT spectrometers. N.m.r. spectra were measured for solutions in deuteriochloroform unless otherwise indicated, with tetramethylsilane as the internal standard, on Varian EM 360 (60 MHz), Varian CFT-20 (80 MHz), Perkin-Elmer R32 (90 MHz), or Bruker (200, 300, and 400 MHz) instruments. U.v. spectra were recorded for ethanolic solutions using a Pye-Unicam SP800 spectrometer. Mass spectra were measured on Kratos MS30 (70 eV EI), Finnegan 4500 (low resolution ammonia CI), or Kratos Concept S1 (high resolution ammonia CI) instruments.

Starting materials and solvents were routinely purified by conventional techniques.[36] Organic solutions were dried using anhydrous magnesium sulphate and concentrated by rotary evaporation. Analytical thin layer chromatography (t.l.c.) was carried out on Camlab Polygram SIL G/UV_{254} plates. Preparative (column) chromatography was carried out using 60H silica gel (Merck 7736 and hand-bellows pressure, or Merck 9385 and the flash technique[37]). Compositions of solvent mixtures are quoted as ratios of volume. 'Petroleum' refers to a light petroleum fraction, b.p. 40–60 °C, unless otherwise stated. 'Ether' refers to diethyl ether.

cis-*3-cyclobutene-1,2-dicarboxylic anhydride* **5**. – Modified versions of the apparatus[16b] and procedure[16a] described by Bloomfield and Owsley were used. The reaction vessel was a Pyrex glass cylinder (Jencons H18/19/0108), cut to a length of 35 cm and calibrated at 2.4 litres with the lamp housing in place. The use of a thermocouple-controlled cooling coil device was unnecessary. The light source was the element from a Thorn MBF/U 1000 W Kolorlux Hg lamp. The triple-walled Dewar lamp housing had an outside diameter of 90 mm and measured 320 mm from the bottom tip to the ring seal.

CAUTION - ACETYLENE IS HAZARDOUS AND SUBJECT TO STRICT SAFETY REGULATIONS.[38]

In a typical run, maleic anhydride (39.3 g, 0.40 mol), acetophenone (10.0 ml, 10.3 g, 0.09 mol), and ethyl acetate (1600 ml) were placed in a 2.6 litre Pyrex vessel with a polypropylene lid, through which were fitted a triple-walled immersion-well lamp housing, a fritted gas bubbler, a low-temperature thermometer, and a gas outlet tube. With the supply of cooling water to the lamp flowing and a continuous stream of nitrogen passing through the solution, the whole reactor was cooled to –65 to –70 °C in a bucket of solid carbon dioxide and acetone. Acetylene gas was then passed into the mixture at a high flow rate until the volume of the solution had risen to the 2.4 litre mark. The acetylene supply was stopped, and irradiation commenced. More acetylene was added periodically so as to maintain the solution within 5 mm of the 2.4 litre mark. *Exhaust gases (acetylene and nitrogen) were carefully ducted into a powerful extraction system.* The reaction was monitored by evaporating 1 ml portions for examination by ^{1}H n.m.r. spectroscopy. At the end of the reaction (12 h), the solution was allowed to reach room temperature overnight with the nitrogen bubbling, thus purging the excess of acetylene. Evaporation to dryness under reduced pressure gave a yellow solid, which was triturated with hexane - ether (1:1; 100 ml). The solid was collected, washed with hexane, and distilled to obtain the pure anhydride **5** (37.5 g, 75%), b.p. 120–125 °C (6 mmHg), m.p. 89.5–90 °C (ether) (lit.[39] 89 °C); ν_{max} 1860, 1840, and 1780 cm^{-1}; δ (300 MHz) 4.02 (2 H, s, 1-H, 2-H) and 6.46 (2 H, s, 3-H, 4-H).

cis-*3-Cyclobutene-1,2-dimethanol* **4**. – The anhydride **5** (6.20 g, 50 mmol) was added portionwise to a stirred suspension of lithium aluminium hydride (7.60 g, 0.2 mol) in THF (350 ml) under nitrogen at 0 °C. When the

initial reaction had subsided (*ca.* 0.5 h), the mixture was heated under reflux for 72 h. The mixture was then cooled to 0 °C, and the excess of reagent then destroyed by the slow addition of 2 M KOH (50 ml). The suspension was stirred for 15 min and ether (150 ml) then added. The resulting precipitate was filtered off and washed with several portions of ether. The filtrate was evaporated, the residue dissolved in dichloromethane, and the solution dried and evaporated. Distillation of the residue under reduced pressure afforded the pure diol **4** (5.47 g, 96%), b.p. 95–100 °C (4 mmHg) (lit.[18] 'a clear oil'); ν_{max} (neat) 3300br, 1600, 1140, and 1020 cm^{-1}; δ (300 MHz) 3.07 (2 H, br s, OH), 3.20 (2 H, dt, *J* 6, 14 Hz, 1'-H, 2'-H), 3.68 (2 H, dd, *J* 14, 16 Hz, 1-H, 1"-H), 3.81 (2 H, dd, *J* 6, 16 Hz, 1-H, 1"-H), and 6.00 (2 H, s, 3',4'-H_2). The diol can also be isolated by flash chromatography, eluting with dichloromethane - ethyl acetate 3:1).

cis-*3-Cyclobutene-1,2-dicarboxylic acid monomethyl ester* **6**. – The anhydride **5** (1.0 g) in methanol (20 ml) was heated under reflux for 0.5 h. Evaporation of the excess of methanol gave the *title compound* **6** (1.25 g, 99%), which formed colourless needles, m.p. 57 °C (petroleum) (Found: C, 54.0; H, 5.5. $C_7H_8O_4$ requires C, 53.85; H, 5.2%); ν_{max} (FT) 3072br, 1738, 1438, 1341, 1281, 1207, 1112, 1034, and 778 cm^{-1}; δ (300 MHz) 3.67 (3 H, s, OMe), 3.94 (2 H, s, 1'-H and 2'-H), 6.24 (1 H, d, *J* 3 Hz, 3'-H or 4'-H), 6.26 (1 H, d, *J* 3 Hz, 4'-H or 3'-H), and 10.5 (1 H, br s, OH); m/z (CI, peaks > 1%) 174 ($M + NH_4^+$, 100%), 157 (M + 1, 12), 156 (8), 111 (1), and 110 (1).

Methyl cis-*4-(chlorocarbonyl)-2-cyclobutene-1-carboxylate* **7**. – To a stirred solution of **6** (78 mg, 0.5 mmol) in chloroform (3 ml) at 0 °C under N_2 was added oxalyl chloride (0.22 ml, 320 mg, 2.5 mmol), and the mixture was stirred at 0 °C for 6 h. The excess of oxalyl chloride was removed by evaporation under reduced pressure. The ^1H n.m.r. spectrum (90 MHz) of the crude product indicated that the starting material had been consumed. The *title compound* **7** (85 mg, 97%) was obtained as an unstable colourless oil; ν_{max} (FT, neat) 2955, 1795, 1740, 1437, 1341, 1300, 1277, 1258, 1203, 1175, 1135, 1115, 1036, 900, 841, 796, 743, and 633 cm^{-1}; δ (300 MHz) 3.70 (3 H, s, OMe), 4.04 (1 H, d, *J* 5 Hz, 1'-H), 4.23 (1 H, d, *J* 5 Hz, 4'-H), and 6.30 (2 H, br s, 2'-H and 3'-H).

cis-*Methyl 4-(*N*-piperidinocarbonyl)-2-cyclobutene-1-carboxylate* **8**. – To a stirred solution of **6** (78 mg, 0.5 mmol) in chloroform (3 ml) at 0 °C under N_2 was added oxalyl chloride (0.22 ml, 0.32 g, 2.5 mmol), and the mixture was kept at 0 °C for 3 h. The excess of oxalyl chloride was removed by evaporation *in vacuo*. The crude acid chloride was dissolved in dichloromethane (5 ml) under N_2 and treated dropwise with a solution of piperidine (47 mg, 0.55 mmol) in dichloromethane (2 ml). After stirring for 1 h at room temperature, the mixture was washed with M hydrochloric acid (10 ml) and saturated aqueous sodium hydrogen carbonate. The organic phase was dried and evaporated to dryness, and the oily residue (107 mg) purified by flash chromatography, eluting with dichloromethane - ethyl acetate (3:2), which gave the *title compound* **8** (102 mg, 91%) as a colourless oil ($M + H^+$, 224.1282. $C_{12}H_{18}NO_3$ requires 224.1287); ν_{max} (FT, neat) 2938, 2855, 1733, 1641, 1439, 1252, 1223, 1197, 1140, 1028, and 778 cm^{-1}; δ (300 MHz) 1.4–1.4 (6 H, m, 3"-H_2, 4"-H_2, and 5"-H_2), 3.2–3.4 (4 H, m, 2"-H_2 and 6"-H_2), 3.66 (3 H, s, OMe), 3.87 (1 H, d, *J* 5 Hz, 4'-H), 4.10 (1 H, d, *J* 5 Hz, 1'-H), 6.19 (1 H, d, *J* 3 Hz, 3'-H), and 6.29 (1 H, d, *J* 3 Hz, 2'-H); m/z (CI, peaks > 2%) 241 ($M + NH_4^+$, 26%), 224 (M + 1, 100), 201 (14), 197 (4), 188 (2), 184 (22), 180 (13), 134 (2), 131 (7), 114 (2), and 91 (2).

cis-4-[[(4-Methoxyphenyl)methoxy]methyl]-2-cyclobutene-1-methanol **10**. – Method A: A stirred suspension of sodium hydride (60% oil dispersion; 480 mg, 12 mmol; washed with two portions of petroleum) in DMF (15 ml) under nitrogen at 0 °C was treated dropwise over 15 min with a solution of the diol **4** (680 mg, 6 mmol) in DMF (10 ml). After 0.5 h a solution of freshly distilled 4-methoxybenzyl bromide[40] (1.2 g, 6 mmol) in DMF (10 ml) was added dropwise over 0.5 h. After a further 2 h the reaction mixture was allowed to warm up to room temperature and stirred for 14 h. Ice-water (15 g) was then added, and the mixture was extracted with ether (3 x 30 ml). The organic extract was washed with water (4 x 15 ml) and brine (25 ml), dried, and evaporated, and the residue purified by flash chromatography (elution with ethyl acetate - petroleum 1:3). Early fractions of the eluate contained *cis-1,2-bis[(4-methoxyphenyl)methoxy]methyl-3-cyclobutene* **11** (212 mg, 10%) (*M* + H^+, 355.1914; $C_{22}H_{27}O_4$ requires 355.1909); ν_{max} (FT, neat) 2908, 2854, 1612, 1586, 1513, 1464, 1361, 1302, 1248, 1173, 1088, 1036, 819, 759, and 737 cm^{-1}; δ (300 MHz) 3.21 (2 H, ddd, *J* <1, 6, 6 Hz, 1'-H and 4'-H), 3.45–3.65 (4 H, m, 1-H_2 and 1"-H_2), 3.78 (6 H, s, 2 x OMe), 4.39 (4 H, s, 2 x OCH_2Ar), 6.16 (2 H, s, 2'-H and 3'-H), 6.85 (4 H, d, *J* 8.5 Hz, 3,5-ArH), and 7.21 (4 H, d, *J* 8.5 Hz, 2,6-ArH); m/z (CI; peaks >2%) 372 (M + NH_4^+, 9.5%), 256 (2), 255 (6), 252 (43), 235 (10), 174 (13), 156 (3), 155 (46), 139 (5), 138 (76), 122 (6), 121 (100), and 94 (2); R_f values (acetone - petroleum 3:7) 0.53; (ethyl acetate - petroleum 2:3) 0.65. Later fractions of the eluate gave the *title compound* **10** (1.16 g, 83%) as a colourless oil (*M* + NH_4^+, 252.1593; $C_{14}H_{22}NO_3$ requires 252.1600); ν_{max} (FT, neat) 3450br, 3043, 2909, 1612, 1514, 1464, 1303, 1249, 1175, 1074, 1035, 818, and 722 cm^{-1}; λ_{max} 226, 266, 273, and 279sh nm; δ (300 MHz) 3.15–3.30 (2 H, m, 1'-H, 4'-H), 3.45–3.65 (5 H, m, 1-H_2, 1"-H_2, and OH), 3.77 (3 H, s, OMe), 4.46 (2 H, s, OCH_2Ar), 5.96, 5.99 (each 1 H, dd, *J* <1, 3 Hz, 2'-H and 3'-H), 6.85 (2 H, d, *J* 8.5 Hz, 3,5-ArH), and 7.23 (2 H, d, *J* 8.5 Hz, 2,6-ArH); m/z (CI; peaks >2%) 252 (M + NH_4^+, 35%), 235 (M + 1, 10), 174 (2), 156 (2), 155 (35), 139 (4), 138 (72), 122 (7), 121 (100), and 94 (2). R_f values (acetone - petroleum 3:7) 0.40; (ethyl acetate - petroleum 2:3) 0.38.

Method B: To a stirred solution of **11** (1.42 g, 4.0 mmol) in dichloromethane - water (50:1; 35 ml) was added dropwise a solution of DDQ (0.91 g, 4.0 mmol) in dichloromethane over a period of 0.5 h. The reaction mixture was stirred at room temperature for 16 h and then dried over $MgSO_4$. The solids were filtered off and washed with several aliquots of dichloromethane. The filtrate was evaporated and the residue chromatographed over silica gel using petroleum - ethyl acetate (3:1) as eluant, giving the starting material **11** (135 mg, 9.5%), 4-methoxybenzaldehyde (550 mg), and the desired product **10** (704 mg, 75%).

6-[(4-Methoxyphenyl)methoxy]-(2Z,4E)-hexadienal **13**. – To a stirred solution of oxalyl chloride (0.25 ml, 364 mg, 2.87 mmol) in dichloromethane (8 ml) at –78 °C under N_2 was added dropwise a solution of dimethylsulphoxide (0.5 ml, 550 mg, 7 mmol) in dichloromethane (2 ml). After 15 min, a solution of **10** (468 mg, 2.0 mmol) in dichloromethane (4 ml) was added dropwise over a period of 10 min. The reaction mixture was stirred at –78 °C for 1 h and then quenched at –78 °C with triethylamine (1.25 ml, 0.91 g, 9 mmol). The mixture was maintained at –78 °C for a further 10 min. and then allowed to warm up to room temperature over *ca.* 0.5 h. Water (5 ml) was added, and the mixture was extracted with dichloromethane (3 x 15 ml). The extract was washed with brine, dried, and evaporated. Flash chromatography of the residue, eluting with ether - hexane (3:7), afforded the *title compound* **13** (397 mg, 86%; purity >95% by 400 MHz ^1H n.m.r.) as an oil (*M* + NH_4^+, 250.1436. $C_{14}H_{20}NO_3$ requires 250.1443); ν_{max} (FT, neat) 2854, 1671, 1640, 1613, 1586, 1514, 1465, 1359, 1303, 1249, 1174, 1112, 1035, 955, and 820 cm^{-1}; λ_{max} 226 and 270 nm; δ (400 MHz)

3.79 (3 H, s, OMe), 4.15 (2 H, dd, *J* 2, 5 Hz, 6-H_2), 4.48 (2 H, s, OCH_2Ar), 5.85 (1 H, dd, *J* 8, 11 Hz, 2-H), 6.19 (1 H, ddd, *J* 5, 5, 15 Hz, 5-H), 6.89 (2 H, d, *J* 9 Hz, 3,5-ArH), 6.94 (1 H, dd, *J* 11, 11 Hz, 3-H), 7.24 (1 H, ddt, *J* 2, 11, 15 Hz, 4-H), 7.26 (2 H, d, *J* 9 Hz, 2,6-ArH), and 10.15 (1 H, d, *J* 8 Hz, 1-H); m/z (CI, peaks > 2%) 250 (M + NH_4^+, 12%), 233 (M + 1, 2), 163 (5), 148 (4), 146 (14), 138 (16), 137 (5), 122 (6), 121 (100), and 81 (2); R_f (hexane - ethyl acetate 3:2) 0.50.

6-[(4-Methoxyphenyl)methoxy]-(2E,4E)-hexadienal **14**. – A sample of **10** (468 mg, 2.0 mmol) was oxidised using the Swern procedure described above, and then quenched at –78 °C with triethylamine (1.25 ml, 0.91 g, 9 mmol). The mixture was maintained at –78 °C for a further 10 min. and then allowed to warm up to room temperature over *ca.* 0.5 h. 2 M Hydrochloric acid (5 ml) was added, the mixture was stirred for a further 1 h, and then extracted with dichloromethane (3 x 15 ml). The combined extract was washed with saturated aqueous sodium hydrogen carbonate (10 ml) and brine, dried, and evaporated. Flash chromatography of the residue, eluting with hexane - ethyl acetate (7:3), gave the *title compound* **14** (404 mg, 87%) as a pale yellow oil (*M* + NH_4^+, 250.1435. $C_{14}H_{20}NO_3$ requires 250.1443); ν_{max} (FT, neat) 2928, 1683, 1645, 1612, 1514, 1464, 1361, 1303, 1249, 1163, 1102, 1034, 989, and 820 cm^{-1}; λ_{max} 226 and 269 nm; δ (300 MHz) 3.76 (3 H, s, OMe), 4.10 (2 H, dd, *J* 1.5, 5 Hz, 6-H_2), 4.45 (2 H, s, OCH_2Ar), 6.10 (1 H, dd, *J* 8, 15 Hz, 2-H), 6.27 (1 H, dt, $J_{5,6}$ 5, $J_{4,5}$ 15 Hz, 5-H), 6.52 (1 H, ddd, *J* 1.5, 11, 15 Hz, 4-H), 6.86 (2 H, d, *J* 8.5 Hz, 3,5-ArH), 7.07 (1 H, dd, *J* 11, 15 Hz, 3-H), 7.24 (2 H, d, *J* 8.5 Hz, 2,6-ArH), and 9.51 (1 H, d, *J* 8 Hz, 1-H); m/z (CI, peaks > 3%), 250 (M + NH_4^+, 37%), 233 (M + 1, 1), 232 (M^+, 1), 214 (3), 198 (5), 192 (15), 155 (31), 154 (15), 139 (4), 138 (73), 137 (5), 122 (7), 121 (100), 105 (4), 104 (3), and 88 (39); R_f (hexane - ethyl acetate 3:2) 0.47.

The semicarbazone, prepared in the usual manner from the aldehyde **14** and purified by flash chromatography (elution with acetone - petroleum 9:1), had m.p. 197 °C (acetone) (Found: C, 62.3; H, 6.7; N, 14.4. $C_{15}H_{19}N_3O_3$ requires C, 62.3; H, 6.6; N, 14.5%); δ (200 MHz, $CDCl_3$ + d_6-DMSO) 3.73 (3 H, s, OMe), 4.0 (2 H, d, *J* 5.5 Hz, 6-H_2), 4.37 (2 H, s, OCH_2Ar), 5.6 (1 H, br s, NH), 5.83 (1 H, dt, *J* 5.5, 14 Hz, 5-H), 6.15 (1 H, dd, *J* 9, 15 Hz, 2-H), 6.15–6.45 (2 H, m, 3-H and 4-H), 6.80 (2 H, d, *J* 8.5 Hz, 3,5-ArH), 7.18 (2 H, d, *J* 8.5 Hz, 2,6-ArH), 7.45 (1 H, d, *J* 9 Hz, 1-H), 7.5 (1 H, s, NH), and 9.7 (1 H, br s, NH); m/z (EI) no molecular ion. R_f (acetone - petroleum 9:1) 0.32.

Oxidation of the diol monoether **10** *with PCC*. – A solution of **10** (126 mg, 0.54 mmol) in dichloromethane (10 ml) was stirred with pyridinium chlorochromate (250 mg, 1.2 mmol) and Celite 521 (0.3 g) for 2 h. Ether (25 ml) was then added, the solution was filtered through a short column of silica gel eluting with ether, and the eluate was evaporated. Flash chromatography of the residue (elution with dichloromethane) gave a mixture of the (*Z*,*E*)- and (*E*,*E*)-hexadienals **13** and **14** (ratio 1:4 by ^1H n.m.r. spectroscopy; total 108 mg, 86%).

Isomerisation of **13** *to the* (E,E)*-hexadienal* **14**. – A deuteriochloroform solution of **13** was divided between three n.m.r. tubes. The first was stored at room temperature in daylight, the second was stored at room temperature in the dark, and the third was stored at –10 °C in the dark. The ^1H n.m.r. spectra of the solutions were recorded periodically, monotoring the doublets at δ 10.15 (due to **13**) and 9.55 (due to **14**). After 4 days there was complete conversion of **13** into **14** in both of the samples stored at room temperature, while the sample stored at –10 °C was essentially unchanged **13**. Addition of a crystal of *p*-toluenesulphonic acid to the latter and storage for a further 24 h at –10 °C effected complete isomerisation into **14**.

Confirmation of the formation of **12** *by* in situ *reduction.* – The Swern oxidation of **10** was carried out as above. After the addition of the triethylamine the mixture was stirred at –78 °C for 0.5 h. An aliquot (1 ml) was removed and worked up as before. Analysis of the crude product by ^{1}H n.m.r. spectroscopy indicated the exclusive presence of the (*Z,E*)-dienal **13**. An aliquot (1 ml) was stirred for 1.5 h at –78 °C with a solution of sodium borohydride (120 mg, 3 mmol) in ethanol (9 ml). The mixture was then allowed to warm to room temperature and treated with 4 M hydrochloric acid (5 ml). The volume was reduced *in vacuo* and the product extracted into dichloromethane (3 x 10 ml). The extract was dried, evaporated, and analysed by ^{1}H n.m.r. spectroscopy and t.l.c., both of which indicated the exclusive presence of the diol monoether **10**.

Confirmation of the formation of **12** *by reaction with 1,2-ethanedithiol and titanium(IV) chloride.* – Dry dimethylsulphoxide (0.60 ml, 660 mg, 8.46 mmol) was added to a solution of oxalyl chloride (0.24 ml, 350 mg, 2.75 mmol) in dichloromethane (8 ml) at –78 °C. The alcohol **10** (717 mg, 3.06 mmol) in dichloromethane (2 ml) was added over 5 min, and the reaction mixture was then stirred for 0.5 h at –78 °C before being quenched by the addition of triethylamine (1.25 ml, 910 mg, 9.0 mmol). After a further 0.5 h at –78 °C, a portion (1 ml; about one-eleventh) of the reaction mixture was transferred under nitrogen to another flask at –78 °C which contained 1,2-ethanedithiol (35 µl, 39 mg, 0.41 mmol). The mixture was stirred for 1 min and then treated with titanium(IV) chloride (dropwise until an orange-red colour persisted). After 0.5 h at –78 °C, the mixture was treated with water (2 ml), allowed to reach room temperature, and extracted with dichloromethane (5 x 10 ml). The extract was washed with brine and dried. T.l.c. showed one major product [R_f (ethyl acetate - petroleum 1:9) 0.25], and flash chromatography gave **15** (36 mg, about 45% based on oxalyl chloride) which was identical (t.l.c., ^{1}H n.m.r.) to an authentic sample prepared by alkylation of the dithiolane **18** (*vide infra*).

Dethioacetalisation of **15**. – A mixture of the dithiolane **15** (31 mg, 0.1 mmol), sodium carbonate (0.5 g), iodomethane (1 ml), acetone (4.7 ml), and water (0.3 ml) was stirred at room temperature for 60 h. The mixture was then filtered and the filtrate dried and evaporated. Analysis of the residual oil by ^{1}H n.m.r. spectroscopy indicated that the product was a mixture of the (*Z,E*)- and (*E,E*)-hexadienals **13** and **14** (ratio *ca.* 1:2; total 15 mg, 62%).

(1α,2α,5α)-3-Oxabicyclo[3.2.0]hept-6-en-2-ol **16**. – A mixture of the diol **4** (560 mg, 4.9 mmol), pyridinium dichromate[27] (7.5 g, 20 mmol), and oxalic acid (50 mg) in dichloromethane (35 ml) was stirred at room temperature for 4 h. Ether (25 ml) and Celite 521 (7.5 g) were then added, and the mixture was filtered through a pad of Celite 521. The residue was washed with ether, and the filtrate carefully evaporated. Rapid flash chromatography, eluting with dichloromethane - ethyl acetate (9:1), gave a fraction containing the volatile *title compound* **16** (415 mg, 75%), contaminated with less than 5% of the ring-opened 6-hydroxy-2,4-hexadienals [by ^{1}H n.m.r. spectroscopy]. The lactol **16** was observed to sublime when kept at –10 °C overnight, and a sample purified by sublimation on to a cold trap (–40 °C) *in vacuo* had m.p. 46–48 °C; δ (200 MHz) 2.7 (1 H, br s, OH), 3.34 (1 H, d, *J* 4 Hz, 1-H), 3.49 (1 H, t, *J* 4 Hz, 5-H), 3.7–3.9 (2 H, m, 4-H_2), 5.33 (1 H, s, 2-H), and 6.08 (2 H, 2 x s, 6-H and 7-H). In a concentration-dependent phenomenon, coupling between H-2 and the hydroxyl proton of **16** was sometimes evident, and gave rise to the following spectrum; δ (80 MHz) 2.35 (1 H, d, *J* 2.5 Hz, OH), 5.33 (1 H, d, *J* 2.5 Hz, 2-H), *etc.*

cis-*4-(1,3-Dithiolan-2-yl)-2-cyclobutene-1-methanol* **18**. – A solution of the lactol **16** (100 mg, 0.89 mmol) in dichloromethane (5 ml) under argon was cooled to –78 °C and treated with 1,2-ethanedithiol (0.09 ml, 101 mg, 1.08 mmol) and titanium(IV) chloride (0.05 ml, 87 mg, 0.46 mmol).[25] The mixture was allowed to warm up to room temperature and stirred for 1 h. Water (4 ml) was then added and the mixture was extracted with dichloromethane (2 x 10 ml). The extract was washed with brine (5 ml), dried, and evaporated. Flash chromatography of the residue, eluting with dichloromethane - ethyl acetate (9:1), gave the *title compound* **18** (140 mg, 83%), m.p. 71 °C (petroleum - dichloromethane - methanol 9:1:1); ν_{max} (FT) 3391, 3325, 1056, 1019, 770, and 705 cm^{-1}; δ (300 MHz) 3.1–3.3 (7 H, m, 1'-H, 4'-H, 4"-H_2, 5"-H_2, and OH), 3.74 (1 H, dd, *J* 5 and 11 Hz, 1-H), 3.87 (1 H, dd, *J* 7 and 11 Hz, 1-H), 4.61 (1 H, d, *J* 11 Hz, 2"-H), 6.15–6.20 (1 H, narrow m, 2'-H and 3'-H); m/z (EI; peaks >10%) 188 (M^+, 2%), 105 (100), 97 (22), and 61 (14).

The 3,5-dinitrobenzoate was prepared by treating the dithiolane **18** (115 mg, 0.61 mmol) in dichloromethane (20 ml) and pyridine (0.5 ml, 0.49 g, 6.2 mmol) with 3,5-dinitrobenzoyl chloride (200 mg, 0.87 mmol), and stirring the mixture at room temperature overnight. Saturated aqueous sodium hydrogen carbonate (5 ml) was then added, and the mixture extracted with dichloromethane (3 x 10 ml). The organic extract was washed with water (2 x 10 ml), dried, and evaporated. Flash chromatography, eluting with acetone - petroleum (1:4), gave cis-*4-(1,3-dithiolan-2-yl)-2-cyclobutene-1-methanol 3,5-dinitrobenzoate* (105 mg, 45%), m.p. 116 °C [chloroform - petroleum (b.p. 60–80 °C), 1:2] (Found: C, 47.0; H, 3.6; N, 7.5, S, 16.9. $C_{15}H_{14}N_2O_6S_2$ requires C, 47.1; H, 3.7; N, 7.3; S, 16.8%); ν_{max} 3080, 1725, 1540, 1340, 1275, and 715 cm^{-1}; δ (60 MHz) 3.2–3.8 (2 H, m, 1'-H, 4'-H), 3.35 (4 H, s, 4"-H_2, 5"-H_2), 4.5–4.9 (3 H, m, 1-H_2 and 2"-H), 6.35 (2 H, s, 2'-H and 3'-H), and 9.4 (3 H, s, ArH).

cis-*2-[4-[[(4-Methoxyphenyl)methoxy]methyl]-2-cyclobuten-1-yl]-1,3-dithiolane* **15** – A solution of **18** (124 mg, 0.66 mmol) in THF (3.5 ml) under argon at room temperature was stirred with potassium hydride (35 wt. % dispersion; 83 mg, 0.73 mmol) until the evolution of hydrogen ceased (about 15 min). A solution of 4-methoxybenzyl bromide[40] (132 mg, 0.66 mmol) in THF (1 ml) was then added, followed by 18-crown-6 (18 mg, 0.07 mmol). After stirring for 16 h at room temperature, the mixture was treated with water (1 ml) and extracted with dichloromethane (2 x 20 ml). The extract was dried and evaporated, and the residual yellow oil purified by flash chromatography, eluting with ethyl acetate - petroleum (3:17), which afforded the *title compound* **15** (102 mg, 50%) as an oil (*M* + H^+, 309.0976. $C_{16}H_{21}O_2S_2$ requires 309.0983); ν_{max} (FT, neat) 2922, 2853, 1612, 1586, 1513, 1464, 1361, 1302, 1277, 1248, 1173, 1087, 1035, 820, 774, and 708 cm^{-1}; δ (300 MHz) 3.10–3.25 (6 H, m, 1'-H, 4'-H, 4-H_2, and 5-H_2), 3.55 (1 H, dd, *J* 6.2, 9.6 Hz, 1"-H), 3.66 (1 H, dd, *J* 6.1, 9.6 Hz, 1"-H), 3.78 (3 H, s, OMe), 4.45 (2 H, narrow ABq, *J* 11.5 Hz, OCH_2Ar), 4.60 (1 H, d, *J* 10.5 Hz, 2-H), 6.11 (1 H, d, *J* 2.9 Hz, 2'-H or 3'-H), 6.21 (1 H, d, *J* 2.9 Hz, 3'-H or 2'-H), 6.86 (2 H, d, *J* 8.5 Hz, 3,5-ArH), and 7.26 (2 H, d, *J* 8.5 Hz, 2,6-ArH); m/z (CI, peaks > 15%), 326 (M + NH_4^+, 15%), 309 (M + 1, 100), 187 (60), and 121 (66); R_f (ethyl acetate - petroleum 1:9) 0.25.

5-(1,3-Dithiolan-2-yl)-(E,E)*-2,4-pentadienal* **21**. – A mixture of **18** (30 mg, 0.16 mmol), PDC (100 mg, 0.5 mmol), and Celite 521 (0.1 g) in dichloromethane (10 ml) was stirred at 20 °C for 14 h. The product was filtered through a short column of silica gel, eluting with ether, and the filtrate was evaporated. Flash chromatography of the residue, eluting with acetone - petroleum (1:4), gave the *title compound* **21** (12 mg, 40%) as an oil (*M* + H^+, 187.0256. $C_8H_{11}OS_2$ requires 187.0251); δ (300 MHz) 3.2–3.4 (4 H, m, 4'-H_2

and 5'-H_2), 5.07 (1 H, d, *J* 9 Hz, 2'-H), 6.12 (1 H, dd, *J* 8, 15 Hz, 2-H), 6.17 (1 H, dd, *J* 9, 15 Hz, 5-H), 6.35 (1 H, dd, *J* 10.5, 15 Hz, 4-H), 7.05 (1 H, dd, *J* 10.5, 15 Hz, 3-H), and 9.53 (1 H, d, *J* 8 Hz, 1-H).

8-Oxo-8-phenylocta-2E,4E,6E-trienal **23**. – A stirred solution of phenacyltriphenylphosphonium bromide (1.85 g, 4.0 mmol) in THF (10 ml) at 0 °C under argon was treated dropwise with a solution of *n*-butyllithium in hexane (1.6 M; 2.5 ml, 4.0 mmol). After 20 min a solution of the aldehyde **14** (460 mg, 2.0 mmol) in THF (2 ml) was added. The reaction mixture was stirred at 20 °C for 14 h and then under reflux for 28 h. The mixture was treated with hydrochloric acid (1 M; 3 ml), extracted with chloroform (3 x 25 ml), and the extract dried, filtered through a small pad of silica gel, and evaporated. Flash chromatography of the residue, eluting with ether - hexane (1:3), gave 1-phenyl-8-[(4-methoxyphenyl)methoxy]-octa-2*E*,4*E*,6*E*-trien-1-one **22** (302 mg, 45%); λ_{max} 226 and 331 nm; δ (90 MHz) 3.85 (3 H, s, OMe), 4.1 (2 H, d, *J* 5 Hz, 8-H_2), 4.5 (2 H, s, OCH_2Ar), 6.0 (1 H, dt, *J* 5, 15 Hz, 7-H), 6.3–7.1 (4 H, m, 2,4,5,6-H), 6.9 (2 H, d, *J* 8.5 Hz, 3,5-ArH), 7.3 (2 H, d, *J* 8.5 Hz, 2,6-ArH), 7.2–7.6 (4 H, m, 3,4,5-H of PhCO group and 3-H), and 7.95 (2 H, dd, *J* 2, 8 Hz, 2,6-H of PhCO group). A solution of the trienone **22** (167 mg, 0.5 mmol) in dichloromethane (20 ml) containing water (0.5 ml) was stirred with DDQ (180 mg, 0.8 mmol) for 20 h. The mixture was then filtered and the residue washed with more dichloromethane. The combined filtrate and washings were dried and evaporated, and the residue purified by flash chromatography (elution with dichloromethane - ethyl acetate 19:1), which gave the *title compound* **23** (82 mg, 77%), m.p. 114 °C (ether - petroleum) (Found: C, 79.1; H, 5.9. $C_{14}H_{12}O_2$ requires C, 79.2; H, 5.7%); ν_{max} 1680, 1645, 1610, 1600, 1265, 1105, 1020, 700, and 675 cm^{-1}; δ (90 MHz) 6.3 (1 H, dd, *J* 8, 15 Hz, 2-H), 6.8–7.6 (8 H, m, 3,4,5-H of PhCO group and 3,4,5,6,7-H), 7.95 (2 H, dd, *J* 2, 8 Hz, 2,6-ArH), and 9.65 (1 H, d, *J* 8 Hz, 1-H); m/z (EI; peaks >20%) 212 (M^+, 42%), 183 (29), 144 (43), 107 (26), 105 (92), 78 (19), and 77 (100).

Ring-opening of cis-*3-cyclobutene-1,2-dicarboxylic acid monomethyl ester* **6**. – Method A: A stirred solution of **6** (56 mg, 0.36 mmol) in chloroform (3 ml) was heated under reflux for 2 h. T.l.c. of the cooled solution showed that the starting material remained unchanged. Method B: A stirred solution of **6** (56 mg, 0.36 mmol) in toluene (3 ml) was heated under reflux for 1 h. Removal of the solvent *in vacuo* left a white solid (57 mg, 100%) whose ^1H n.m.r. spectrum (300 MHz) indicated that it was a 2:1 mixture of the ester–acids **24** and **25**. An attempt to recrystallise the crude product from ether gave a mixture of **24** and **25** in the same ratio as colourless needles, m.p. 84–85 °C; [**24**] δ (300 MHz) 3.78 (3 H, s, OMe), 5.98 (1 H, d, *J* 11 Hz, 5-H), 6.14 (1 H, d, *J* 15 Hz, 2-H), 6.73 (1 H, dd, *J* 11, 11 Hz, 4-H), and 8.35 (1 H, dd, *J* 11, 15 Hz, 3-H); [**25**] δ (300 MHz) 3.77 (3 H, s, OMe), 6.02 (1 H, d, *J* 11 Hz, 2-H), 6.10 (1 H, d, *J* 15 Hz, 5-H), 6.66 (1 H, dd, *J* 11, 11 Hz, 3-H), and 8.48 (1 H, dd, *J* 11, 15 Hz, 4-H). A pure sample of **24** was prepared by hydrolysis of the acid chloride **26** (*vide infra*).

Ring-opening of methyl cis-*4-(chlorocarbonyl)-2-cyclobutene-1-carboxylate* **7**. – A solution of **7** (44 mg, 0.25 mmol) in toluene (3 ml) was heated under reflux for 1 h, and the solution then allowed to cool to room temperature. The solvent was removed by evaporation *in vacuo*. The ^1H n.m.r. spectrum (90 MHz) of the solid residue (42 mg) indicated that the conversion of **7** into methyl 6-chloro-6-oxo-(2*E*,4*Z*)-hexadienoate **26** and methyl 6-chloro-6-oxo-(2*Z*,4*E*)-hexadienoate **27** was quantitative and that the ratio **26**:**27** was 4:1; δ (300 MHz) [**26**] 3.77 (3 H, s, OMe), 6.23 (1 H, d, *J* 11 Hz, 5-H), 6.24 (1 H, d, *J* 15 Hz, 2-H), 6.65 (1 H, dd, *J* 11, 11 Hz, 4-H), and 8.03 (1 H, dd, *J* 11, 15 Hz, 3-H); [**27**] 3.77 (3 H, s, OMe), 6.20–6.25 (obscured, 2-

H), 6.27 (1 H, d, *J* 15 Hz, 5-H), 6.82 (1 H, dd, *J* 11, 11 Hz, 3-H), and 8.61 (1 H, dd, *J* 11, 15 Hz, 4-H). The mixture of **26** and **27** (ratio 4:1) was treated with water and the solid product isolated. Recrystallisation from carbon tetrachloride - petroleum (b.p. 60–80 °C) gave pure *2E,4Z-hexadienedioic acid 1-methyl ester* **24** as colourless needles (15 mg), m.p. 95–96 °C (*M* + NH_4^+, 174.0759. $C_7H_{12}NO_4$ requires 174.0766); ν_{max} (FT) 1723, 1683, 1634, 1598, 1314, 1266, 1244, 1192, and 1172 cm^{-1}; δ (300 MHz) as above; m/z (CI) 174 (M + NH_4^+, 100%). When the ester–acid chloride **7** (44 mg, 0.25 mmol) was heated under reflux in chloroform (3 ml) for 2 h, no ring-opening was detected (by 90 MHz ^1H n.m.r. spectroscopy).

Preparation of the ester–acid chlorides **26** *and* **27** *from the ester–acids* **24** *and* **25**. – To a stirred solution of **24** and **25** (ratio 2:1; total 39 mg, 0.25 mmol) in chloroform (2 ml) at 0 °C under N_2 was added oxalyl chloride (90 μl, 130 mg, 1.0 mmol), and the mixture maintained at 0 °C for 6 h. The excess of oxalyl chloride was removed by evaporation *in vacuo*. The ^1H n.m.r. spectrum (300 MHz) of the residue indicated that there had been *ca.* 70% conversion of the acids into the corresponding mixture of **26** and **27** (2:1).

cis-*3-Cyclobutene-1,2-dicarboxylic acid mono(2-naphthyl) ester* **28**. – A magnetically stirred solution of the anhydride **5** (100 mg, 0.8 mmol), 2-naphthol (116 mg, 0.8 mmol), and 4-dimethylaminopyridine (DMAP) (25 mg, 0.2 mmol) in dichloromethane (4 ml) was heated under reflux for 24 h. The cooled reaction mixture was then washed with 2M hydrochloric acid (10 ml) and water (10 ml), dried, and evaporated. The residual oil was purified by flash chromatography, eluting with dichloromethane to remove the unreacted 2-naphthol, and then with ethyl acetate - dichloromethane (1:1), gave the *title compound* **28** (170 mg, 79%) as a pale yellow solid, m.p. 110–111 °C (toluene) (Found: C, 71.3; H, 4.8. $C_{16}H_{12}O_4$ requires C, 71.6; H, 4.5%); ν_{max} (FT) 1749, 1700, 1330, 1266, 1257, 1226, 1209, 1156, 1135, 1119, 976, and 799 cm^{-1}; δ (300 MHz) 4.08 (1 H, d, *J* 5 Hz, 2'-H), 4.19 (1 H, d, *J* 5 Hz, 1'-H), 6.29 (1 H, d, *J* 3 Hz, 3'-H or 4'-H), 6.41 (1 H, d, *J* 3 Hz, 4'-H or 3'-H), 7.18 (1 H, dd, *J* 2.3, 8.9 Hz, 3-ArH), 7.35–7.45 (2 H, m, ArH), 7.50 (1 H, d, *J* 2.3 Hz, 1-ArH), and 7.70–7.75 (3 H, m, ArH); m/z (CI) 286 (M + NH_4^+, 100%).

Ring-opening of cis-*3-cyclobutene-1,2-dicarboxylic acid mono(2-naphthyl) ester* **28**. – A stirred solution of **28** (25 mg, 0.093 mmol) in 1,2-dichloroethane (4 ml) was heated under reflux (83 °C). Samples were periodically removed and analysed by 300 MHz ^1H n.m.r. spectroscopy, revealing the simultaneous formation of the ester–acids **29** and **30** in essentially equal quantities. The ratio **28**:[**29** + **30**] was 1:1 after 2 h, and 4:1 after 5 h; none of the lactone **34** was evident. After 23 h the mixture was found to contain only **29**, **30**, and the lactone **34** (ratio approximately 1:2:1); [**29**] δ (300 MHz) 6.05 (1 H, d, *J* 11.5 Hz, 5-H), 6.36 (1 H, d, *J* 15.5 Hz, 2-H), 6.81 (1 H, t, *J* 11.5 Hz, 4-H), 7.0–7.9 (7 H, m, ArH), and 8.58 (1 H, dd, *J* 11.5, 15.5 Hz, 3-H); [**30**] δ (300 MHz) see below.

cis-*3-Cyclobutene-1,2-dicarboxylic acid 1-(2-naphthyl) 2-methyl ester* **31**. – A magnetically stirred solution of the acid **28** (0.30 g, 1.12 mmol) in ether (15 ml) at 0 °C was treated dropwise with ethereal diazomethane until nitrogen evolution was no longer evident and the solution acquired a permanent yellow colour. The mixture was allowed to stir for a further 2 minutes, and the solvent then removed, giving the *title compound* **31** (0.30 g, 95%) as a colourless solid, m.p. 65–66 °C (MeOH) (*M* + NH_4^+, 300.1241. $C_{17}H_{18}NO_4$ requires 300.1236); ν_{max} (FT) 1745, 1735, 1327, 1254, 1240, 1198, and 802 cm^{-1}; δ (300 MHz) 3.71 (3 H, s, OMe),

4.10 (1 H, d, *J* 4.9 Hz, 2'-H), 4.19 (1 H, d, *J* 4.9 Hz, 1'-H), 6.34 (1 H, d, *J* 2.8 Hz, 3'-H or 4'-H), 6.41 (1 H, d, *J* 2.8 Hz, 4'-H or 3'-H), 7.26 (1 H, dd, *J* 2.2, 8.9 Hz, 3-ArH), 7.40–7.50 (2 H, m, ArH), 7.56 (1 H, d, *J* 2.2 Hz, 1-ArH), and 7.75–7.85 (3 H, m, ArH); m/z (CI) 300 ($M + NH_4^+$, 100%).

Ring-opening of the diester **31**. – A stirred solution of **31** (50 mg, 0.18 mmol) in toluene (10 ml) was heated under reflux for 1 h. Removal of the solvent *in vacuo* left an oil whose ^1H n.m.r. spectrum (300 MHz) indicated that it contained the diesters **32** and **33** in a ratio of 1:1.4. The spectrum of the major product **33** was identical to that of the product obtained by methylation of a sample of **30** (*vide infra*); [**32**] δ (300 MHz) 3.78 (3 H, s, OMe), 6.04 (1 H, d, *J* 11.5 Hz, 5-H), 6.33 (1 H, d, *J* 15.5 Hz, 2-H), 6.73 (1 H, t, *J* 11.5 Hz, 4-H), 7.1–7.9 (7 H, m, ArH), and 8.62 (1 H, dd, *J* 11.5, 15.5 Hz, 3-H); [**33**] δ (300 MHz) as below.

2Z,4E-Hexadienedioic acid 1-(2-naphthyl) 6-methyl ester **33**. – A magnetically stirred solution of the acid **30** (75 mg, 0.28 mmol) in methanol (3 ml) at 0 °C was treated dropwise with ethereal diazomethane until nitrogen evolution was no longer evident and a pale yellow colour persisted. The mixture was allowed to stir for a further 2 minutes, and the solvent then removed, giving the *title compound* **33** (74 mg, 94%) as an off-white solid, m.p. 106–108 °C (MeOH) (*M* + NH_4^+, 300.1238. $C_{17}H_{18}NO_4$ requires 300.1236); ν_{max} (FT) 1733, 1715, 1596, 1316, 1268, 1218, 1181, 1153, and 1148 cm^{-1}; δ (300 MHz) 3.75 (3 H, s, OMe), 6.17 (1 H, d, *J* 15.5 Hz, 5-H), 6.23 (1 H, d, *J* 11.5 Hz, 2-H), 6.82 (1 H, t, *J* 11.5 Hz, 3-H), 7.1–7.9 (7 H, m, ArH), and 8.47 (1 H, dd, *J* 11.5, 15.5 Hz, 4-H); m/z (CI, peaks > 10%) 302 (19%) and 300 ($M + NH_4^+$, 100).

2,5-Dihydro-5-oxo-2-furanacetic acid 2-naphthyl ester **34**. – A stirred solution of **28** (500 mg, 1.87 mmol) in toluene (5 ml) was heated under reflux for 3 h. A crystal of DMAP was then added and the heating continued for a further 1 h. The cooled solution was washed successively with 2 M hydrochloric acid (5 ml) and 2 M sodium carbonate (5 ml), and dried. Evaporation gave *2,5-dihydro-5-oxo-2-furanacetic acid 2-naphthyl ester* **34** (200 mg, 40%), m.p. 103–104 °C (MeOH) (Found: C, 71.3; H, 4.4. $C_{16}H_{12}O_4$ requires C, 71.6; H, 4.5%); ν_{max} (FT) 1785, 1754, 1599, 1341, 1244, 1214, 1159, 1120, 1038, 926, 866, 823, and 763 cm^{-1}; δ (300 MHz) 2.97 (1 H, dd, *J* 7.1, 16.6 Hz, 2-H), 3.12 (1 H, dd, *J* 7.0, 16.6 Hz, 2-H), 5.50–5.56 (1 H, m, 2'-H), 6.23 (1 H, dd, *J* 2.0, 5.7 Hz, 4'-H), 7.22 (1 H, dd, *J* 2.3, 8.8 Hz, 3-ArH), 7.44–7.53 (2 H, m, ArH), 7.56 (1 H, d, *J* 2.3 Hz, 1-ArH), 7.66 (1 H, dd, *J* 1.5, 5.7 Hz, 3'-H), and 7.7–7.9 (3 H, m, ArH); m/z (CI) 286 ($M + NH_4^+$, 100%). The carbonate extract from above was acidified with 2 M hydrochloric acid and extracted with dichloromethane (3 x 15 ml). The extract was dried and evaporated to obtain *2Z,4E-hexadienedioic acid 1-(2-naphthyl) ester* **30** (120 mg, 24%), m.p. 166–168 °C (toluene) (Found: C, 71.8; H, 4.5. $C_{16}H_{12}O_4$ requires C, 71.6; H, 4.5%); ν_{max} (FT) 1729, 1710, 1627, 1598, 1283, 1212, and 1172 cm^{-1}; δ (300 MHz) 6.17 (1 H, d, *J* 15.5 Hz, 5-H), 6.27 (1 H, d, *J* 11.5 Hz, 2-H), 6.84 (1 H, t, *J* 11.5 Hz, 3-H), 7.26 (1 H, dd, *J* 2.2, 8.9 Hz, 3-ArH), 7.4–7.5 (2 H, m, ArH), 7.62 (1 H, d, *J* 2.2 Hz, 1-ArH), 7.75–7.90 (3 H, m, ArH), and 8.55 (1 H, dd, *J* 11.5, 15.5 Hz, 4-H); m/z (CI) 286 ($M + NH_4^+$, 100%).

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