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The Preparation and Electrocyclic Ring-opening of Cyclobutenes: Stereocontrolled Approaches to Substituted Conjugated Dienes and Trienes

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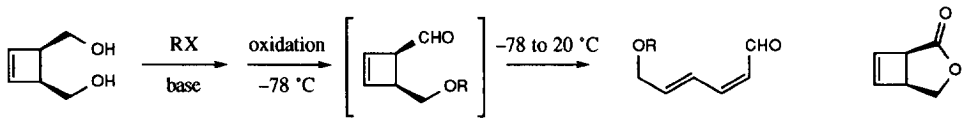
Abstract: Thermal electrocyclic ring-opening of 4-alkyl-2-cyclobutene-1-carbaldehydes occurs at low temperature to give (2*Z*,4*E*)-alkadienals exclusively, and the process is exploited in transforming *cis*-3-cyclobutene-1,2-dimethanol **1** into a variety of naturally occurring 1,3,5-alkatrienes and 2,4-decadienoates. Desymmetrisation of **1** with *Pseudomonas fluorescens* lipase gives access to both enantiomers of 3-oxabicyclo[3.2.0]hept-6-en-2-one **4**, for use in stereocontrolled routes to 6-oxygenated (2*Z*,4*E*)-alkadienals.

On the basis of orbital symmetry considerations, it is predicted that the thermal electrocyclic ring-opening of an unsymmetrical *cis*-1,4-disubstituted 2-cyclobutene might produce two isomeric (*Z*,*E*)-dienes.[2] However, recent studies have demonstrated that the stereochemical outcome of the process is strongly influenced by the electronic effects of the allylic substituents, with π-donors preferring 'outward' conrotation and π-acceptors more readily undergoing the alternative 'inward' motion.[3-5] In this context we showed that monoprotection and Swern oxidation of *cis*-2-cyclobutene-1,4-dimethanol **1** leads to a cyclobutene **2** whose allylic substituents (formyl, alkoxyalkyl) have complementary conrotation preferences, and which as a consequence undergoes thermal electrocyclic ring-opening at low temperature to give the (*Z*,*E*)-dienal **3** exclusively (Scheme 1).[3,6] We considered that the above principle might be usefully exploited in approaches to naturally occurring conjugated polyenes, including some of the many biologically-active systems which bear oxygen substituents in allylic positions, and we herein describe in detail[7] the results of our efforts directed toward this objective, which reveal the diol **1** and the derived lactones (+)-**4** and (–)-**4** to be potentially versatile diene precursors.

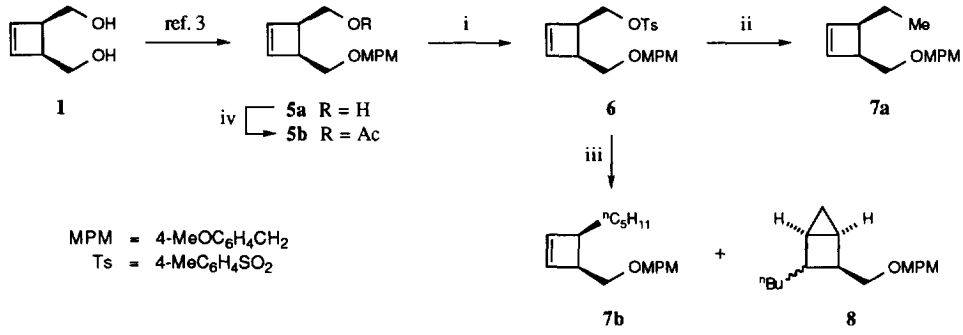


1 **2** **3** (2*Z*,4*E*) isomeric purity >97% **4**

SCHEME 1 (R = 4-MeOC$_6$H$_4$CH$_2$)

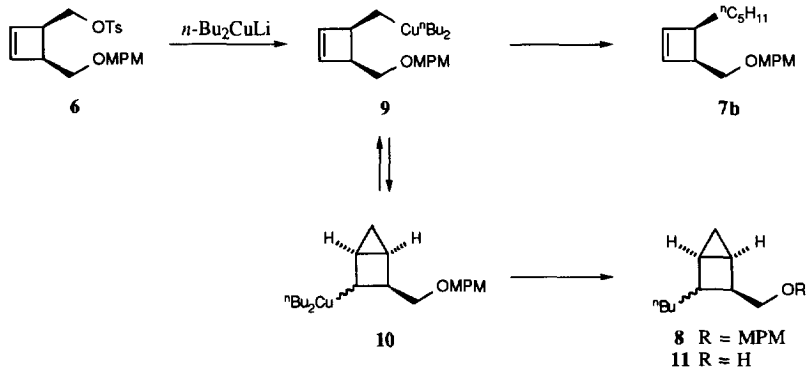
For applications in polyene synthesis it was necessary to develop general methods by which substituents could be included at the termini of a (*Z*,*E*)-diene fragment such as **3**. We surmised that it would be most convenient to introduce the (*E*)-terminal group at the cyclobutene stage, prior to the electrocyclic ring-opening

reaction, and to achieve this the monoether **5a**, available from the diol **1** as described,[3] was first converted into the tosylate **6** and then treated with the appropriate cuprate reagent (Scheme 2). Using lithium dimethylcuprate provided the ethyl-substituted cyclobutene **7a**, whereas the *n*-butyl reagent afforded **7b**, together with varying amounts of a by-product which was tentatively identified as the 2,3-disubstituted bicyclo[2.1.0]pentane **8**.



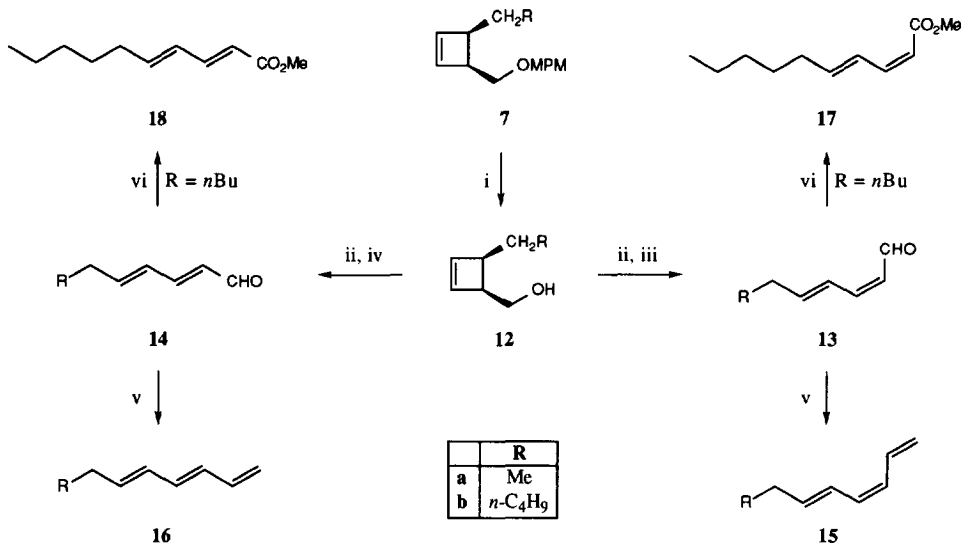
SCHEME 2 *Reagents:* i, *n*-BuLi, THF-hexane, *p*-$MeC_6H_4SO_2Cl$, −78 to 20 °C (83%); ii, Me_2CuLi, Et_2O, −10 to 0 °C (78%); iii, *n*-Bu_2CuLi, Et_2O-hexane, −10 to 0 °C (75% of **7b**; ≤15% of **8**); iv, Ac_2O, pyridine, DMAP, CH_2Cl_2, 20 °C, 2 h (92%).

The skeletal rearrangement leading to the bicyclo[2.1.0]pentane **8** is similar to those described by Posner and coworkers,[8] who studied the reactions of homoallylic tosylates and halides with organocopper reagents. Various mechanisms have been postulated for organocopper addition reactions, most involving the formation of transient copper(III) species which subsequently undergo reductive elimination of the coupled product. The putative intermediates **9** and **10** leading to the observed products are shown in Scheme 3. Deprotection of the ether **8** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[9] gave the alcohol **11** in 86% yield.



SCHEME 3 (MPM = 4-$MeOC_6H_4CH_2$)

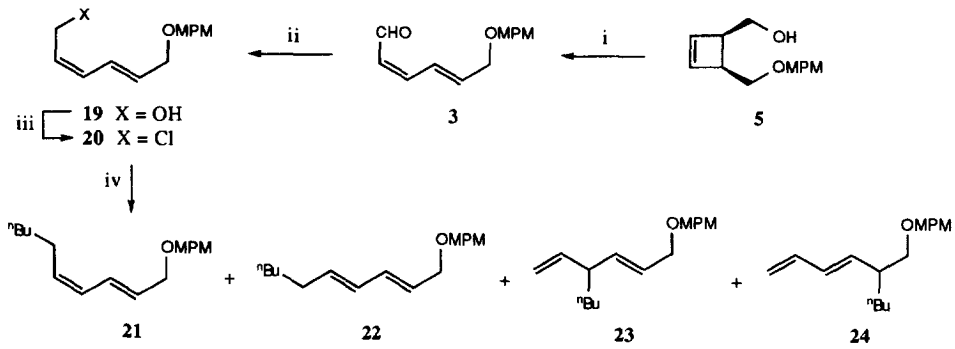
Deprotection of the ether **7a** using DDQ gave the alcohol **12a**, which was transformed into the (*Z*,*E*)-dienal **13a** *via* Swern oxidation at −78 °C (Scheme 4). Florisil chromatography was used to isolate **13a** with high (>97%)[10] isomeric purity, otherwise the product was accompanied by trace amounts of the more stable (*E*,*E*)-isomer **14a**, which could be obtained pure by quenching the oxidation at 20 °C and isolating the product by silica gel chromatography. Wittig methylenation was used to convert the dienals **13a** and **14a** into the respective (3*Z*,5*E*)- and (3*E*,5*E*)-1,3,5-octatrienes **15a** and **16a**, which are components of the female sex attractant of the brown seaweed *Fucus serratus*.[11,12]



SCHEME 4 (MPM = 4-$MeOC_6H_4CH_2$) *Reagents:* i, DDQ, CH_2Cl_2-H_2O, 20 °C, 2 h; ii, oxalyl chloride, Me_2SO, CH_2Cl_2, –78 °C, 1 h; iii, Et_3N, –78 to 20 °C, Florisil column; iv, –78 to 20 °C, then Et_3N, silica gel column; v, $Ph_3P{=}CH_2$, THF, 0 to 20 °C; vi, MnO_2, NaCN, MeOH.

Repeating the sequence described above, the pentylcyclobutene **7b** was transformed into the alcohol **12b**, and hence the isomeric dienals **13b** and **14b**. Wittig methylenation of these aldehydes gave the respective 1,3,5-undecatrienes **15b** and **16b**, which occur naturally in the essential oil of galbanum (*Ferula galbaniflua*)[13] and the Hawaiian seaweed *Dictyopteris plagiogramma*;[14] the (3*E*,5*Z*)-triene **15b** is also valued as a fragrance in the perfume industry.[15] Oxidation of the dienals **13b** and **14b** with manganese(IV) oxide and sodium cyanide in methanol[16] gave the respective methyl esters **17** and **18**. The (2*Z*,4*E*)-isomer **17**[17] is a pheromone component of the forest pest *Pityogenes chalcographus*,[17a] and a component of stillingia oil, which is obtained from the seeds of *Sapium sebiferum*, the Chinese tallow tree.[18] The (*E*,*E*)-decadienoate **18** is a component of the flavour principles of the Bartlett pear.[19]

A substituent to be located at the eventual (*Z*)-terminus of a (*Z*,*E*)-diene fragment prepared in the above manner must be introduced after the electrocyclic ring-opening, since the formyl group is required as the (*Z*)-selective control element during the conrotation process. In an initial attempt to determine whether side-chains could be coupled *via* nucleophilic displacement reactions (as proved effective with the tosylate **6**), the (2*Z*,4*E*)-dienol **19**, prepared by reduction of the aldehyde **3**,[3] was converted into the chloride **20** and treated with lithium dibutylcuprate at –78 °C in THF (Scheme 5). The reaction gave four products, as judged by 300 MHz ^1H n.m.r. spectroscopy and t.l.c. on silica gel impregnated with silver nitrate, and preparative chromatography of the mixture over this medium gave clean samples of the α-alkylated product **21**, the γ-alkylated product **23**, the ε-alkylated product **24**, and a mixed fraction containing the two α-alkylated products **21** and **22**. The clean S_N2 displacement of the chloride **20** was thus potentially troublesome, and its reactions with a range of butylcopper and Grignard reagents were investigated in an attempt to optimise the formation of the desired product **21** (Table 1). Analysis of the crude reaction mixtures by 300 MHz ^1H-n.m.r. spectroscopy was facilitated by the readily distinguishable benzylic signals of each product. The copper mediated reactions are clearly of little synthetic value, although the variation in product distribution is of mechanistic interest.[20]

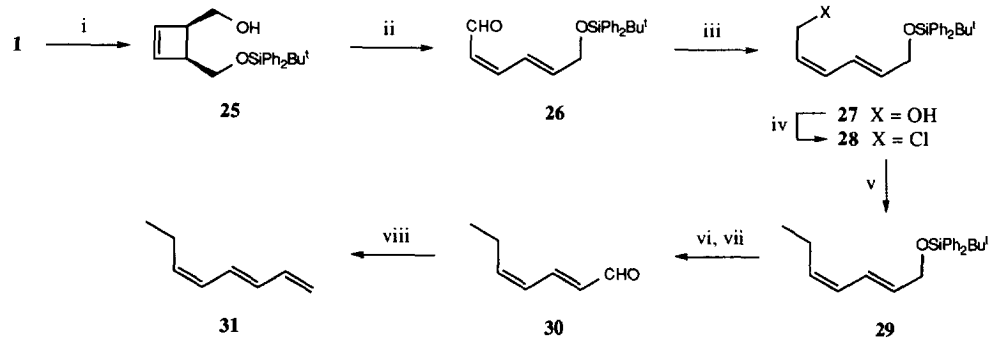


SCHEME 5 (MPM = 4-$MeOC_6H_4CH_2$) *Reagents:* i, see ref. 3; ii, $LiBH_4$, THF, 0 to 20 °C (83%); iii, $MeSO_2Cl$, LiCl, collidine, DMF, 0 to 20 °C (71%); iv, see Table 1.

ENTRY	ORGANOMETALLIC REAGENT	SOLVENT	PRODUCT DISTRIBUTION (%) 21	22	23	24
1	*n*-Bu_2CuLi	THF	14	7	29	50
2	*n*-Bu_2CuLi–Me_2S	THF–HMPA	36	18	36	10
3	*n*-BuMgCl, CuCl	THF	50	25	25	0
4	*n*-BuMeCuMgBr	THF	0	16	84	0
5	*n*-BuMgCl	THF	73	9	18	0
6	*n*-BuMgCl	Et_2O	45	19	36	0
7	*n*-BuMgCl	THF–DMPU	26	4	70	0

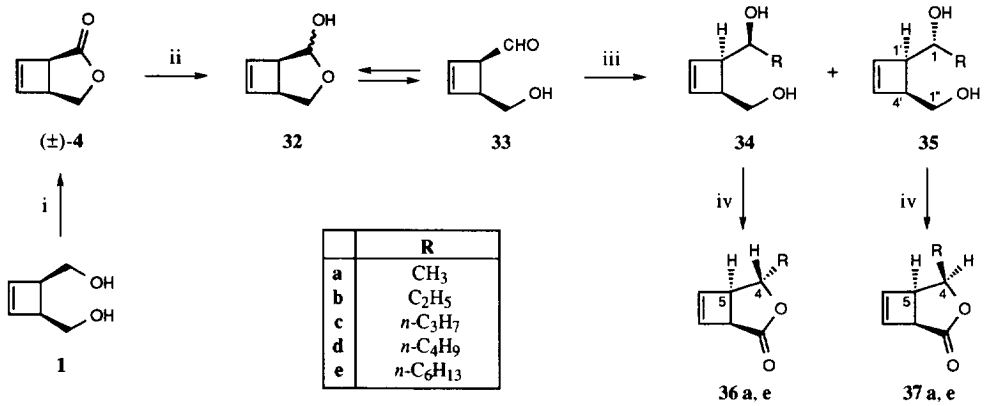
TABLE 1 REACTIONS OF ORGANOMETALLIC REAGENTS WITH THE CHLORODIENE **20**

To facilitate later deprotection the diol **1** was monosilylated[21] to obtain the cyclobutenemethanol **25**, and the latter proved to be a suitable starting point for (2*E*,4*Z*)-dienal preparation as illustrated in Scheme 6. Swern oxidation of **25** gave the (2*Z*,4*E*)-dienal **26**, which was immediately transformed into the alcohol **27** and hence the chloride **28**.[22] Treating the chloride **28** with methylmagnesium bromide gave the direct (S_N2) displacement product **29** (79% yield), and sequential desilylation and oxidation using tetra-*n*-propylammonium perruthenate (TPAP)/*N*-methylmorpholine *N*-oxide (NMO)[23] gave the (2*E*,4*Z*)-dienal **30**. Methylenation of the dienal **30** afforded (3*E*,5*Z*)-octatriene **31**, the remaining isomer of the mixture found in *Fucus serratus*.[11]



SCHEME 6 *Reagents:* i, NaH, THF, *t*-$BuPh_2SiCl$, (93%); ii, oxalyl chloride, Me_2SO, CH_2Cl_2, –78 °C, 2 h, Et_3N, –78 to 20 °C, Florisil column (83%); iii, $LiBH_4$, THF (78%); iv, $MeSO_2Cl$, LiCl, collidine, DMF, 0 to 20 °C (86%); v, MeMgBr, toluene-THF (79%); vi, nBu_4NF, THF (91%); vii, TPAP, NMO, 4Å sieves, CH_2Cl_2, 20 °C (73%); viii, $Ph_3P{=}CH_2$, THF, 0 to 20 °C (>85%).

Considering the various means by which a cyclobutene might be transformed into a polyene with oxygen substituents in the allylic positions, there are clear advantages in establishing the desired functionality and configuration within the cyclobutene prior to ring-opening. Such a strategy allows the exploitation of both the stability and the exaggerated topology of the cyclobutene relative to those of the (*Z*,*E*)-diene target. With this in mind we carried out a series of additions of organometallic reagents to the known lactol **32**,[3] which exists in equilibrium with the aldehyde **33**, in which the pendant hydroxymethyl group is well positioned to mediate *via* coordination effects the stereocontrolled addition of nucleophiles to the formyl group (Scheme 7).



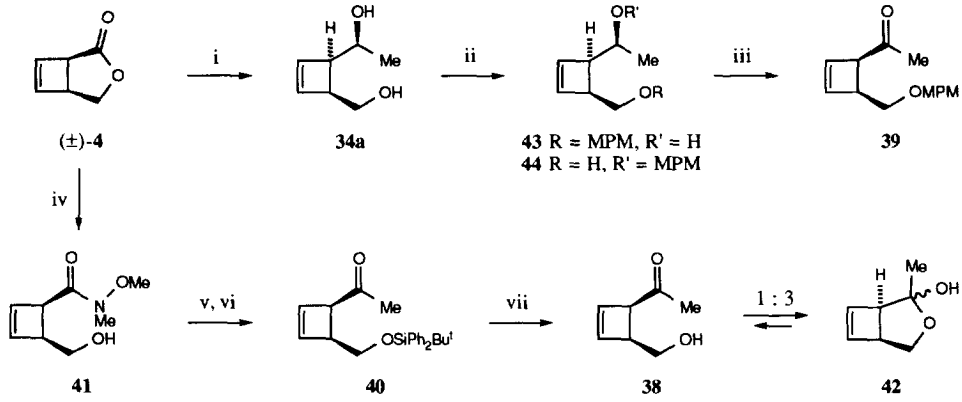
SCHEME 7 *Reagents:* i, PCC, Celite® 521, CH_2Cl_2, 20 °C (67%); ii, DIBAH, THF-hexanes, –78 °C, 1 h; iii, RM, –78 °C, 1 h, then +20 °C, 1 h; iv, TPAP, NMO, 4Å sieves, CH_2Cl_2, 25 °C.

Treatment of the lactol **32**, generated *in situ* from the lactone (±)-**4**, with various organometallic reagents gave good yields of the mixed diols **34** and **35**, with the former predominant (Table 2). In the methyl series the diastereoselectivity of the addition process was improved on changing from the lithium to the Grignard reagent, and was essentially complete using a methyltitanium reagent[25] (entry 4). While it was possible to distinguish and assay the diols **34** and **35** *via* 300 MHz ^{1}H-n.m.r. spectroscopy, the relative stereochemistry of the diols in two series (**a** and **e**) was established by oxidation of the isolated diols **34** and **35** to the respective lactones **36** and **37** with TPAP/NMO.[26] The value of the vicinal coupling constant $J_{4,5}$ in these rigid bicyclic structures is consistent with the *exo* and *endo* orientations of the R-substituents, as depicted for **36** and **37** respectively. The structures of the diols of series **b**–**d** were assigned by analogy (and characteristic ^{1}H-n.m.r. signals).

ENTRY	R	M	ADDITIVE	MAJOR PRODUCT	ISOLATED YIELD (%)	RATIO 34 : 35
1	CH_3	Li	–	**34a**	65	4 : 1
2	CH_3	MgBr	–	**34a**	74	14 : 1
3	CH_3	MgBr	$ZnBr_2$	**34a**	72	16 : 1
4	CH_3	$Ti(O^iPr)_3$	–	**34a**	86	> 99 : 1
5	C_2H_5	MgBr	–	**34b**	70	9 : 1
6	n-C_3H_7	MgCl	–	**34c**	69	6 : 1
7	n-C_4H_9	MgCl	–	**34d**	69	7 : 1
8	n-C_6H_{13}	MgBr	–	**34e**	66	6 : 1

TABLE 2[24] REACTIONS OF ORGANOMETALLIC REAGENTS WITH THE LACTOL **32**

We also studied the addition of hydride reagents to the series of ketones **38–40**, there being the possibility that reversing the sequence of nucleophilic additions to the lactone **4** (shown in Scheme 7) would result in the diol **35** becoming the major product. Unlike the corresponding aldehydes, each of the ketones was stable at room temperature, although the 300 MHz ^{1}H n.m.r. spectrum of the parent system indicated that it existed in solution as a mixture of the ketone form **38** and two lactols **42**, with the latter predominating (Scheme 8).

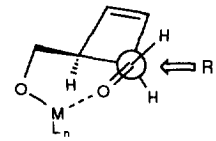


(±)-4 **34a** 43 R = MPM, R' = H; 44 R = H, R' = MPM **39** **41** **40** **38** **42**

SCHEME 8 (MPM = 4-MeOC$_6$H$_4$CH$_2$) *Reagents:* i, see Table 2 (entry 4); ii, NaH, MPMBr, THF (66%, plus 15% of **44**); iii, TPAP, NMO, 4Å sieves, CH_2Cl_2, 25 °C (71%); iv, MeONHMe.HCl, Me_3Al (84%); v, *t*$BuPh_2SiCl$, imidazole, DMF-THF; vi, MeMgBr, THF, 0 °C (68% over two steps); vii, HF, MeCN-H_2O, 20 °C (63%).

Treating the ketone/lactol mixture (**38** + **42**) with hydride reagents gave good yields of the expected diols with diastereoselectivity up to 9:1, but **34a** was again the major product (Table 3). In fact it was the non-selective reducing agents which afforded the highest nett yields of the minor product **35a** (entries 2 and 3). Moderate levels of stereoselectivity were generally observed on reduction of the protected ketones **39** and **40**, but the major product was invariably that derived from **34a**.

From a mechanistic viewpoint, the formation of a diol **34** *via* the addition of an organometallic reagent to the lactol **33** (Scheme 7) is consistent with the approach of the nucleophile to the less hindered face of a chelated arrangement such as **48**. The proximity of the carbonyl and hydroxymethyl groups, inevitable by virtue of their *cis* disposition and the rigidity of the cyclobutene ring, engenders the coordination. The variation in selectivity on changing the metal from Li to Ti or adding a Lewis acid ($ZnBr_2$) are in accord with such a model.[27]



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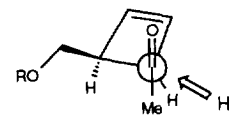

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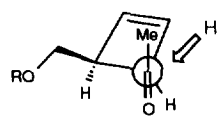

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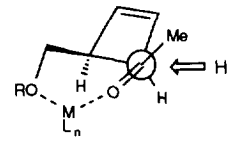

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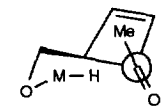

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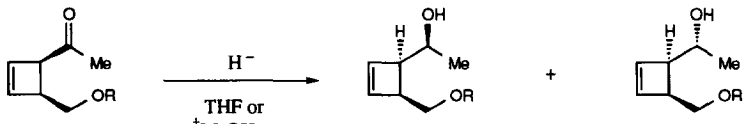


(±)-38–40 **34a** R = H **35a**
43 R = MPM **45**
46 R = $SiPh_2Bu^t$ **47**

ENTRY	KETONE	REAGENT	INITIAL T(°C)	PRODUCTS Major	PRODUCTS Minor	TOTAL YIELD (%)	DIOL RATIO
1	**38**	$LiBH_4$–Et_3B	–78	**34a**	**35a**	83	2 : 1
2	**38**	$LiBH_4$–$ZnBr_2$	–78	**34a**	**35a**	73	1 : 1
3 †	**38**	$NaBH_4$	+20	**34a**	**35a**	86	1 : 1
4	**38**	DIBAH	–78	**34a**	**35a**	91	2 : 1
5 ‡	**38**	$Zn(BH_4)_2$	–78	**34a**	**35a**	63	5 : 1
6	**38**	$NaBH(OAc)_3$	+20	**34a**	**35a**	76	9 : 1
7	**39**	DIBAH	–78	**43**	**45**	86	5 : 1
8	**39**	$LiBHEt_3$	–78	**43**	**45**	73	3 : 1
9	**39**	$LiBH_4$	–78	**43**	**45**	77	3 : 1
10	**39**	$LiAlH_4$	–78	**43**	**45**	72	3 : 1
11	**39**	$KBH(Bu^s)_3$	–78	**43**	**45**	–¶	2 : 1
12 ‡	**39**	$Zn(BH_4)_2$	0	**43**	**45**	–¶	4 : 1
13	**40**	DIBAH	–78	**46**	**47**	73	7 : 1
14	**40**	DIBAH–$ZnBr_2$	–78	**46**	**47**	60	4 : 1
15	**40**	$LiBH_4$	–78	**46**	**47**	57	2 : 1
16	**40**	$LiAlH_4$	–78	**46**	**47**	59	3 : 1
17	**40**	$Zn(BH_4)_2$	–78	**46**	**47**	53	2 : 1
18	**40**	$NaBH(Bu^s)_3$	–78	**46**	**47**	64	3 : 1
19	**40**	$LiAlH(OBu^t)_3$	–78	**46**	**47**	81	10 : 1

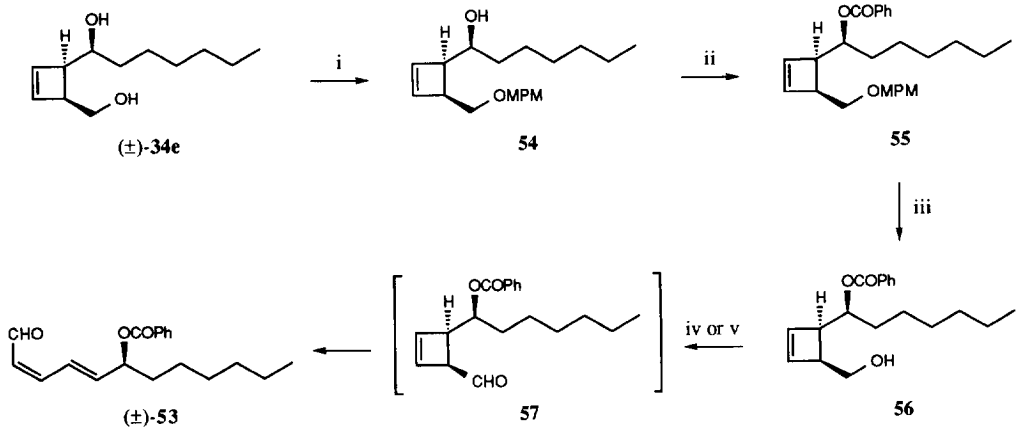
¶ Yield not determined

TABLE 3[24] REACTIONS OF HYDRIDE REAGENTS WITH THE KETONES **38–40**

In the hydride additions (Table 3), the formation of **43** and **46** from the respective ketones **39** and **40** is consistent with the approach of the hydride reagent to the less hindered face of a conformation such as **49**, which corresponds to a Felkin-Anh open chain model,[28] although the above results (and molecular models[29]) suggest that an alternative conformation such as **50** is also readily accessible. As might be anticipated, the selectivity is optimal when a sterically encumbered hydride reagent is used in conjunction with a substrate bearing a bulky, poorly coordinating 4'-substituent (Table 3, entry 19). Moreover the proportion of diol **47** obtained on reducing **40** with diisobutylaluminium hydride (DIBAH) is enhanced in the presence of $ZnBr_2$ (entries 13 and 14), implying that a chelated arrangement **51** (*cf.* **48**) is also possible but not predominant, while the selectivity obtained using sodium triacetoxyborohydride (Table 3, entry 6), whose reducing ability is potentiated by coordination to an hydroxyl group,[30] is consistent with the internal delivery of hydride *via* a conformation such as **52**. In summary, the results of the hydride addition reactions seem to indicate a finely balanced distribution of substrate conformations and, as a consequence, competing mechanistic pathways.

The potential of the above chemistry as a source of oxygenated (*Z*,*E*)-dienals is illustrated in Scheme 9, which shows how the diol (±)-**34e** was transformed into the 6-substituted (2*Z*,4*E*)-dodecadienal (±)-**53**.[31] The diol was monoprotected as the methoxybenzyl ether **54**, which was benzoylated under standard conditions to obtain the ester **55**. Treatment of the ester **55** with DDQ gave the alcohol **56**, which was oxidised to obtain the (*Z*,*E*)-dienal **53** in good yield (>97% isomeric purity by ^{1}H n.m.r.). The dienal (*R*)-**53** has been prepared as a mixture of isomers using Wittig olefination reactions (13 steps from L-arabinose, <2% yield).[31]

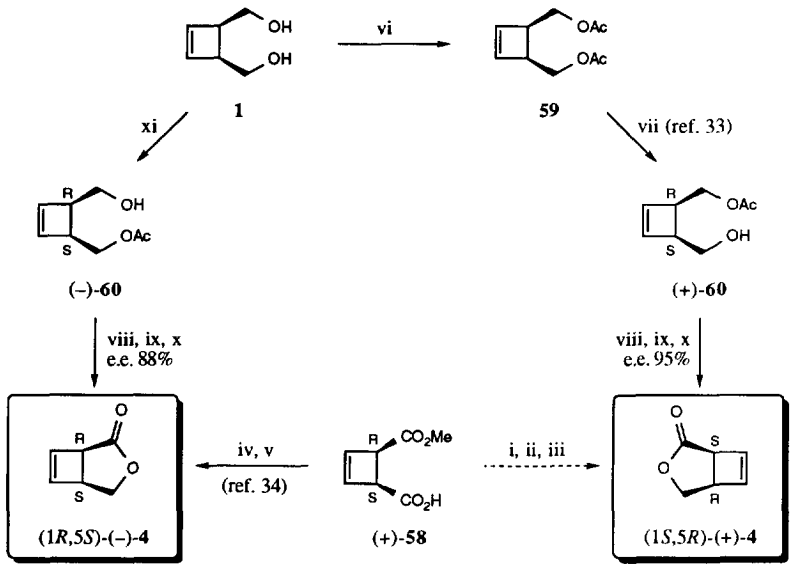
The intermediate aldehyde **57** was significantly more stable than the analogue **2** and the precursors of **13**, being directly observable among the products (by ^{1}H n.m.r. spectroscopy) when the alcohol **56** was oxidised with TPAP/NMO. Its persistence compared to **2** can be attributed, at least in part, to the diminished electron donor capability of the acyloxy (relative to the alkoxy) group, which will reduce the preference of the (oxy)alkyl substituent for 'outward' conrotation.[3–5] Thus the activation barrier to electrocyclic ring-opening, which includes significant contributions from each of the conrotating (allylic) substituents according to its electronic properties, might be manipulated through judicious but essentially minor structural modifications.



SCHEME 9 (MPM = 4-MeOC$_6$H$_4$CH$_2$) *Reagents:* i, NaH, THF, MPM–Br (86%); ii, PhCOCl, pyridine (82%); iii, DDQ, CH_2Cl_2–H_2O, 20 °C (89%); iv, oxalyl chloride, Me_2SO, CH_2Cl_2, –78 °C, 1 h, then Et_3N, –78 to 20 °C, (72%); v, TPAP, NMO, 4Å sieves, CH_2Cl_2, 0 °C (75%).

In order to develop this methodology so that it could be used to prepare dienals such as **53** with absolute stereocontrol, we required access to both enantiomers of the lactone **4**. Its racemic form was first obtained *via* a photochemical [2 + 2] cycloaddition,[32] but is more conveniently obtained from the diol **1** (Scheme 7) or by reduction of the acid-ester (±)-**58**[3] with calcium borohydride. Applying this sequence (Scheme 10, steps i–iii) to (+)-**58**, which is available (86% e.e.) from the corresponding diester using pig liver esterase,[33–35] offers one route to the lactone (+)-**4**. The preparation of (–)-**4** from the acid-ester (+)-**58** (Scheme 10) is described in a patent,[34] but the lactone (–)-**4** reported in this work appears to have been wrongly assigned as (1*S*,5*R*).[33]

It has also been established that the *meso*-diacetate **59** can be desymmetrised by partial hydrolysis with *Pseudomonas fluorescens* lipase (PFL), generating the monoacetate (+)-**60** (75% yield, >97% e.e.).[33] For the purpose of comparison a sample of (±)-**60** was prepared by debenzylation of the MPM derivative (±)-**5b** (*cf.* Scheme 2). The monoacetate (+)-**60** was transformed into the (1*S*,5*R*)-lactone (+)-**4** as shown in Scheme 10. Although our current procedure for oxidising **60** is not particularly efficient, the product (+)-**4** is of high optical purity (e.e. 95% by g.l.c.). Moreover, we found that by using PFL in the transacetylation mode[36] the diol **1** could be transformed directly into the monoacetate (–)-**60**, and hence the enantiomeric lactone (–)-**4** (e.e. 88%).



SCHEME 10 *Reagents:* i, KOH, H_2O; ii, $CaBH_4$; iii, HCl–H_2O (70% over 3 steps); iv, $(COCl)_2$; v, $NaBH_4$ (65% over 2 steps); vi, Ac_2O, pyridine (96%); vii, PFL, pH 7, 32 °C (75%); viii, Jones' reagent; ix, MeOH, MeONa; x, HCl–H_2O (41–47% over 3 steps); xi, PFL, vinyl acetate, 25 °C, 2 h (96%).

The availability of both enantiomers of the lactone **4** from the diol **1** renders accessible both enantiomeric series of (*Z,E*)-dienals such as **53** (Scheme 9) *via* a convenient and stereoselective reaction sequence, from the same achiral starting material and using the same enzyme. Further development and applications of this chemistry in the synthesis of biologically active polyenes are in progress and will be described in due course.

EXPERIMENTAL

All compounds are racemic unless their names are preceded by appropriate stereochemical descriptors. Melting points were determined using an Electrothermal apparatus and are uncorrected. Unless otherwise stated, i.r. spectra were of thin films on sodium chloride plates, recorded on a Perkin-Elmer 1710FT spectrometer. N.m.r. spectra were measured on a Bruker AC300 instrument at 300 MHz (^1H) and 75.47 MHz (^{13}C) for solutions in deuteriochloroform with tetramethylsilane as the internal standard, unless otherwise indicated. Mass spectra were measured on a Finnegan 4500 (low resolution) or Kratos Concept S1 (high resolution) instruments using the ammonia CI method unless stated. Data for most of the peaks of intensity <20% of that of the base peak are omitted. U.v. spectra were recorded on a Pye-Unicam SP8 spectrophotometer. Optical rotations were measured at 589 nm using an AA-10 polarimeter (Optical Activity Ltd.).

Starting materials and solvents were routinely purified by conventional techniques.[37] 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. The chromatograms were visualized by the use of u.v. light or the following developing agents; methanolic phosphomolybdic acid (PMA), ethanolic vanillin or potassium permanganate. Unless otherwise indicated, preparative (column) chromatography was carried out on 60H silica gel (Merck 9385) or Florisil (60–100 mesh) using the flash technique.[38] 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.

*3-Oxabicyclo[3.2.0]hept-6-en-2-one (±)-***4**

Method A: To a stirred solution of the diol **1**[3] (4.0 g, 35 mmol) and Celite® 521 (20 g) in dichloromethane (150 ml) was added pyridinium chlorochromate (PCC; 22.6 g, 105 mmol), and the resulting brown mixture stirred at room temperature for 14 h. The mixture was then filtered, the solids washed with ether, and the combined organics evaporated. The brown residue was purified by flash chromatography (elution with dichloromethane - hexane 2:1) to give the *title compound* (±)-**4** (2.56 g, 67%) as a colourless oil, b.p. 60 °C (0.6 mmHg) (Found: C, 65.4; H, 5.5. $C_6H_6O_2$ requires C, 65.45; H, 5.5%) (M + H^+, 111.0440; $C_6H_7O_2$ requires 111.0446); ν_{max} 2973, 2908, 1759, 1373, 1245, 1169, 1086, 1052, 983, 913, 867, 823, 774 and 706 cm^{-1}; δ (300 MHz) 3.52–3.57 (2 H, m, 1-H and 5-H), 4.16–4.25 (2 H, m, 4-H_2), 6.23 and 6.29 (each 1 H, d, *J* 3 Hz, 6-H and 7-H); m/z 128 (M + NH_4, 100%), 65 (15); R_f (dichloromethane - ethyl acetate 4:1) 0.65, $KMnO_4$ stain.

Method B: To a stirred solution of the half-ester (±)-**58**[3] (2.5 g, 16 mmol) in ethanol (75 ml) at room temperature was added potassium hydroxide (0.9 g, 16 mmol). After 0.5 h powdered calcium chloride (4.56 g, 40 mmol) was added followed, dropwise, by a solution of sodium borohydride (1.55 g, 40 mmol) in 1 M KOH (19 ml). After 6 h the solution was acidified with 2 M hydrochloric acid (30 ml) and stirred for a further 12 h. The ethanol was evaporated, the residual solution was extracted with dichloromethane (5 x 25 ml), and the combined organics were washed with brine (2 x 50 ml), dried and evaporated. Purification as for method A gave the lactone (±)-**4** (1.23 g, 70%).

Method C: *cis*-3-Cyclobutene-1,2-dicarboxylic anhydride[3] (2.0 g, 16 mmol) was added portionwise to a stirred suspension of lithium aluminium hydride (1.0 g, 26 mmol) in THF (25 ml) under N_2 at 0 °C. The mixture was heated under reflux for 48 h, cooled to 0 °C, and the excess of reagent destroyed by the slow addition of 2 M aqueous potassium hydroxide (5 ml). The suspension was stirred for 15 min and ether (50 ml) then added. The resulting precipitate was filtered off and washed with several portions of ether, the filtrate was evaporated and the residue dissolved in dichloromethane (25 ml), dried and evaporated. Purification as for method A gave the lactone (±)-**4** (1.15 g, 65%). Later fractions contained the diol **1** (0.27 g, 15%).

Method D: To a stirred solution of methyl *cis*-4-(chlorocarbonyl)-2-cyclobutene-1-carboxylate[3] (175 mg, 1.0 mmol) in THF (5 ml) at 0 °C under N_2 was added sodium borohydride (116 mg, 3.0 mmol). After stirring at room temperature for 3 h the solution was acidified with 2 M hydrochloric acid and stirred for a further 2 h. The mixture was extracted with dichloromethane (3 x 10 ml) and the combined organics washed with brine (10 ml), dried and evaporated. Purification as for method A gave the lactone (±)-**4** (53 mg, 49%).

Method E: To a stirred solution of the monoacetate (±)-**60** (156 mg, 1.0 mmol) in acetone (2 ml) at 0 °C was added dropwise Jones' reagent [prepared by adding chromium(VI) oxide (27 g) to a solution of concentrated H_2SO_4 (23 ml) in water (77 ml)] until a dark orange colour persisted (*ca.* 1 ml). After stirring at room temperature for 3 h ethyl acetate (10 ml) and brine (10 ml) were added. The organic layer was separated and the aqueous layer further extracted with ethyl acetate (5 x 10 ml). The combined organics were dried and evaporated to a brown residue which was dissolved in methanol (5 ml). Sodium methoxide (168 mg, 3.0 mmol) was added and the solution was stirred at room temperature for 3 h. The methanol was reduced in volume by evaporation and 2 M hydrochloric acid (10 ml) was added. After stirring at room temperature for 12 h the solution was extracted with dichloromethane (5 x 10 ml) and the combined organics washed with brine (10 ml), dried and evaporated. Purification as for method A gave the lactone (±)-**4** (47 mg, 43%).

cis-*[4-[[(4-Methoxyphenyl)methoxy]methyl]-2-cyclobuten-1-yl]methyl acetate* **5b**

To a stirred solution of **5a**[3] (234 mg, 1.0 mmol) and 4-dimethylaminopyridine (DMAP) (6.1 mg, 0.05 mmol) in dichloromethane (5 ml) and pyridine (0.1 ml, 98 mg, 1.2 mmol) under N_2 was added acetic anhydride (0.25 ml, 0.27 g, 2.65 mmol), and the reaction mixture was stirred at room temperature for 2 h. T.l.c. (ethyl acetate - hexane 3:7) indicated that the starting material had been consumed. The solution was washed successively with water (2 x 20 ml), M HCl (10 ml), and saturated aqueous sodium hydrogen carbonate (10 ml), dried, and evaporated. Flash chromatography of the residue eluting with dichloromethane gave the *title compound* **5b** (255 mg, 92%) as a colourless oil (*M* + NH_4^+, 294.1706. $C_{16}H_{24}NO_4$ requires 294.1705); ν_{max} 2912,

2855, 1738, 1613, 1515, 1465, 1384, 1302, 1246, 1174, 1089, 1035, 820 and 739 cm^{-1}; δ (300 MHz) 1.98 (3 H, s, MeCO), 3.15–3.25 (2 H, m, 1'-H and 4'-H), 3.51 (2 H, d, *J* 7 Hz, 1"-H_2), 3.77 (3 H, s, OMe), 4.11 (1 H, dd, *J* 7, 11 Hz, 1-H), 4.26 (1 H, dd, *J* 7, 11 Hz, 1'-H), 4.40 (2 H, s, OCH_2Ar), 6.08 (2 H, d, *J* 3 Hz, 2'-H or 3'-H), 6.11 (2 H, d, *J* 3 Hz, 3'-H or 2'-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 294 (M + NH_4^+, 100%), 155 (38), 138 (38) and 121 (29); R_f (ethyl acetate - hexane 3:7) 0.40; (dichloromethane) 0.44.

cis-*[4-[[(4-Methoxyphenyl)methoxy]methyl]-2-cyclobuten-1-yl]methyl 4-methylphenylsulphonate* **6**

To a stirred solution of **5a**[3] (2.5 g, 10 mmol) in THF (50 ml) at –20 °C was added dropwise *n*-butyllithium in hexane (1.3 M; 8.2 ml, 10 mmol). After 1 h the solution was cooled to –78 °C and a solution of *p*-toluenesulphonyl chloride (2.08 g, 11 mmol) in THF (40 ml) was added dropwise. After 3 h at –78 °C the reaction mixture was allowed to return to room temperature over 1 h and water (50 ml) then added. The mixture was extracted with ether (3 x 50 ml) and the combined organic extracts washed with water (2 x 50 ml), brine (50 ml), dried and evaporated. Flash chromatography of the yellow residue (elution with petroleum - ethyl acetate 4:1) gave the *title compound* **6** (3.22 g, 83%) as a colourless oil which, on cooling, gave a white solid, m.p. 32–34 °C (*M* + NH_4^+, 406.1678. $C_{21}H_{28}NO_5S$ requires 406.1688); ν_{max} 2914, 2856, 1612, 1514, 1465, 1361, 1303, 1248, 1189, 1177, 1097, 1035, 951, 817, 781 and 665 cm^{-1}; δ (300 MHz) 2.42 (3 H, s, ArMe), 3.15–3.25 (2 H, m, 1'-H and 4'-H), 3.40–3.50 (2 H, m, 1"-H_2), 3.79 (3 H, s, OMe), 4.09 (1 H, dd, *J* 8 and 10 Hz, 1-H), 4.25 (1 H, dd, *J* 7 and 10 Hz, 1-H), 4.33 (2 H, s, OCH_2Ar), 6.02 (1 H, d, *J* 3 Hz, 2'-H or 3'-H), 6.08 (1 H, d, *J* 3 Hz, 3'-H or 2'-H), 6.85 (2 H, d, *J* 8.5 Hz, 3,5-H_2 of $ArCH_2$), 7.17 (2 H, d, *J* 8.5 Hz, 2,6-H_2 of $ArCH_2$), 7.30 (2 H, d, *J* 8 Hz, 3,5-H_2 of $ArSO_3$) and 7.75 (2 H, d, *J* 8 Hz, 2,6-H_2 of $ArSO_3$); m/z 406 (M + NH_4^+, 16%), 310 (13), 286 (92), 155 (75), 138 (21), 131 (46), 114 (54), 94 (18) and 69 (100); R_f (petroleum - ethyl acetate 4:1) 0.30, PMA stain and u.v. active.

cis-*3-Ethyl-4-[[(4-methoxyphenyl)methoxy]methyl]-1-cyclobutene* **7a**

To a stirred solution of lithium dimethylcuprate (11.6 mmol) under nitrogen at –10 °C [prepared by treatment of copper(I) iodide (2.2 g, 11.6 mmol) in ether (110 ml) with methyllithium in ether (1.5 M, 15.5 ml, 23.2 mmol)] was added a solution of the tosylate **6** (3.0 g, 7.7 mmol) in ether (70 ml) over 20 min. The reaction mixture was stirred at 0 °C for 2 h and at room temperature for 12 h, and then quenched with saturated aqueous ammonium chloride (75 ml). The precipitate was filtered and washed with ether. The layers were separated, and the aqueous layer further extracted with ether (3 x 50 ml) the combined organic extracts were washed with brine (50 ml), dried and evaporated. Flash chromatography of the residue (elution with petroleum - ether 9:1) gave the *title compound* **7a** (1.39 g, 78%) as a volatile colourless oil (*M* + NH_4^+, 250.1809. $C_{16}H_{24}NO_2$ requires 250.1807); ν_{max} 3036, 2999, 2957, 2930, 2872, 1613, 1513, 1463, 1442, 1361, 1302, 1248, 1173, 1094, 1038, 820 and 727 cm^{-1}; δ (300 MHz) 0.91 (3 H, t, *J* 7 Hz, 2"-H_3), 1.25–1.4 (1 H, m, 1"-H), 1.5–1.65 (1 H, m, 1"-H), 2.81 (1 H, ddd, $J_{1',4'}$ 5, $J_{1",4'}$ 5, $J_{1",4'}$ 10 Hz, 4'-H), 3.1–3.2 (1 H, m, 1'-H), 3.45–3.55 (2 H, m, 1-H_2), 3.79 (3 H, s, OMe), 4.43 (2 H, s, OCH_2Ar), 6.08 (1 H, d, *J* 3 Hz, 2'-H or 3'-H), 6.23 (1 H, d, *J* 3 Hz, 3'-H or 2'-H), 6.86 (2 H, d, *J* 8.5 Hz, 3,5-ArH), and 7.25 (2 H, d, *J* 8.5 Hz, 2,6-ArH); m/z (CI, peaks > 2%) 250 (M + NH_4^+, 100%), 232 (M^+, 1), 155 (95), 138 (58) and 121 (31); R_f (petroleum - ether 4:1) 0.50, PMA stain and u.v. active.

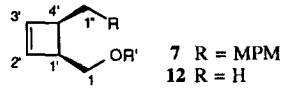
cis-*3-[[(4-Methoxyphenyl)methoxy]methyl]-4-pentyl-1-cyclobutene* **7b**

To a stirred solution of lithium di-*n*-butylcuprate (2 mmol) under N_2 at –20 °C [prepared by treatment of copper(I) iodide (380 mg, 2 mmol) in ether (20 ml) with *n*-butyllithium in hexane (1.25 M, 3.2 ml, 4 mmol)] was added a solution of **6** (517 mg, 1.33 mmol) in ether (15 ml) over 10 min. The mixture was stirred for a further 3 h at –20 °C and quenched with saturated aqueous ammonium chloride (20 ml). The precipitate was filtered, washed with ether (30 ml) and the resultant organic layer separated, and the aqueous layer further extracted with ether (3 x 20 ml). The combined organics were washed with water (3 x 30 ml), brine (30 ml), dried and evaporated, giving a yellow residue which was chromatographed (elution with pentane - toluene 3:2) to obtain first the *title compound* **7b** (274 mg, 75%) as a pale yellow oil (M + NH_4^+, 292.2270; $C_{18}H_{30}NO_2$

requires 292.2276); ν_{max} 2954, 2926, 2854, 1613, 1586, 1513, 1465, 1442, 1360, 1302, 1248, 1173, 1093, 1038, 821 and 732 cm^{-1}; δ (300 MHz) 0.87 (3 H, t, *J* 7 Hz, 5"-H_3), 1.17–1.41 (7 H, m, 1"-H, 2"-H_2, 3"-H_2 and 4"-H_2), 1.52–1.56 (1 H, m, 1"-H), 2.85–2.90 (1 H, m, 4'-H), 3.11–3.17 (1 H, m, 1'-H), 3.45–3.55 (2 H, m, 1-H_2), 3.79 (3 H, s, OMe), 4.42 (2 H, s, OCH_2Ar), 6.05 and 6.19 (each 1 H, d, *J* 3 Hz, 2'-H and 3'-H), 6.86 (2 H, d, *J* 8.5 Hz, 3,5-ArH), 7.24 (2 H, d, *J* 8.5 Hz, 2,6-ArH); m/z (CI; peaks > 10%) 292 (M + NH_4, 95%), 155 (50), 138 (95), 121 (100); R_f (pentane - toluene 1:1) 0.3, PMA stain.

Later fractions contained *3-*n*-butyl-2-[[(4-methoxyphenyl)methoxy]methyl]bicyclo[2.1.0]pentane* **8** (55 mg, 15%), a pale yellow oil (M + NH_4^+, 292.2274; $C_{18}H_{30}NO_2$ requires 292.2276); ν_{max} 2955, 2930, 2856, 1613, 1514, 1465, 1363, 1302, 1248, 1173, 1088, 910, 820 and 733 cm^{-1}; δ_H (300 MHz) 0.35 (1 H, ddd, $J_{2',3'}$ 5, $J_{3',4'}$ 5, J_{gem} 5 Hz, 3'-H_a), 0.67 (1 H, d, J_{gem} 5 Hz, 3'-H_b), 0.85 (3 H, t, *J* 7 Hz, 4"-H_3), 1.00–1.29 (6 H, m, 1"-H_2, 2"-H_2 and 3"-H_2), 1.54–1.59 (2 H, m, 2',4'-H), 2.44–2.51 (1 H, m, 5'-H), 2.64–2.72 (1 H, m, 1'-H), 3.17 and 3.26 (each 1 H, dd, $J_{1,1'}$ 7.5, J_{gem} 9.5 Hz, 1-H_2), 3.78 (3 H, s, OMe), 4.35 and 4.40 (each 1 H, d, J_{gem} 11.7 Hz, OCH_2Ar), 6.85 (2 H, d, *J* 8.5 Hz, 3,5-ArH), 7.23 (2 H, d, *J* 8.5 Hz, 2,6-ArH); δ_C 6.20, 12.29, 13.91, 14.19, 15.69, 22.78, 25.99, 22.92, 35.35, 35.47, 55.27, 68.38, 70.41, 72.74, 113.70, 129.29, 130.75 and 159.07; m/z (CI; peaks > 10%) 292 (M + NH_4, 95%), 236 (18), 172 (12), 155 (75), 138 (100), 121 (70); R_f (pentane - toluene 1:1) 0.28, PMA stain.

Numbering systems used (for consistency)



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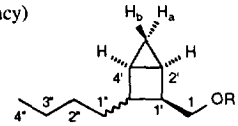
12 R = H



8 R = MPM
11 R = H

*3-*n*-butylbicyclo[2.1.0]pentane-2-methanol* **11**

To a stirred solution of **8** (50 mg, 0.18 mmol) in dichloromethane - water (50:1, 5 ml) was added dropwise a solution of DDQ (54 mg, 0.24 mmol) in dichloromethane (3 ml). After 3 h at room temperature magnesium sulphate was added to remove any water. The solids were filtered and washed with dichloromethane (10 ml). The filtrate was evaporated to a residue which was purified by flash chromatography (elution with toluene - pentane 5:1) and gave first *p*-methoxybenzaldehyde and then the *title compound* **11** (24 mg, 86%) as a colourless oil (M + NH_4^+, 172.1707; $C_{10}H_{22}NO$ requires 172.1701); ν_{max} 3337, 3058, 2928, 2857, 1467, 1378, 1122, 1026, 969 and 777 cm^{-1}; δ_H (300 MHz) 0.35 (1 H, ddd, $J_{2',3'}$ 5, $J_{3',4'}$ 5, J_{gem} 5 Hz, 3'-H_a), 0.68 (1 H, d, J_{gem} 5 Hz, 3'-H_b), 0.82 (3 H, t, *J* 7 Hz, 4"-H_3), 0.98–1.26 (6 H, m, 1"-H_2, 2"-H_2 and 3"-H_2), 1.49–1.59 (2 H, m, 2'-H and 4'-H), 1.73 (1 H, s, OH), 2.39–2.49 (1 H, m, 5'-H), 2.52–2.62 (1 H, m, 1'-H), 3.33 (1 H, dd, $J_{1,1'}$ 7, J_{gem} 11 Hz, 1-H), 3.40 (1 H, dd, $J_{1,1'}$ 8, J_{gem} 11 Hz, 1-H); δ_C 5.84, 11.43, 13.75, 14.03, 22.62, 25.90, 29.21, 35.19, 37.35, 60.60; m/z (CI; peaks > 10%) 172 (M + NH_4, 50%), 154 (M^+, 38), 137 (100), 123 (10), 95 (14), 81 (12).

cis-*4-Ethyl-2-cyclobutene-1-methanol* **12a**

To a stirred solution of **7a** (232 mg, 1.0 mmol) in dichloromethane - water (50:1; 15 ml) was added dropwise a solution of DDQ (272 mg, 1.2 mmol) in dichloromethane (10 ml) over a period of 0.5 h. The reaction mixture was stirred at room temperature for 2 h and then dried over $MgSO_4$. The solids were filtered off and washed with dichloromethane (10 ml). The filtrate was evaporated to dryness and the residue washed through a short column of Florisil (3 g) with ether (50 ml). The eluate was evaporated and the yellow residue purified by flash chromatography (elution with petroleum - ether 4:1), which gave 4-methoxybenzaldehyde (128 mg, 94%) and the *title compound* **12a** (102 mg, 91%), a volatile pale yellow liquid (*M* + NH_4^+, 130.1231. $C_7H_{16}NO$ requires 130.1232); ν_{max} 3343br, 3125, 3040, 2958, 2930, 2874, 1462, 1377, 1086, 1043, 1015, 733 and 722 cm^{-1}; δ (300 MHz) 0.90 (3 H, t, *J* 7 Hz, 2"-H_3), 1.30–1.45 (2 H, m, 1"-H and OH), 1.50–1.65 (1 H, m, 1"-H), 2.79 (1 H, ddd, $J_{1',4'}$ 5, $J_{1",4'}$ 5, $J_{1",4'}$ 10 Hz, 4'-H), 3.04 (1 H, ddd, *J* 5, 6.5, and 7.5 Hz, 1'-H), 3.67 (1 H, dd, *J* 6.5 and 11 Hz, 1-H), 3.74 (1 H, dd, *J* 7.5 and 11 Hz, 1-H), 6.08 (1 H, d, *J* 3 Hz, 2'-H or 3'-H) and 6.25 (1 H, d, *J* 3 Hz, 3'-H or 2'-H); m/e (CI), 130 (M + NH_4^+, 64%) and 95 (100); R_f (dichloromethane - ether 1:1) 0.7, PMA stain.

Hepta-(2Z,4E)-dienal **13a**

To a stirred solution of oxalyl chloride (0.12 ml, 175 mg, 1.37 mmol) in dichloromethane (5 ml) at –78 °C under N_2 was added a solution of dimethylsulphoxide (DMSO; 0.2 ml, 220 mg, 2.8 mmol) in dichloromethane (2 ml). After 15 min a solution of **12a** (112 mg, 1.0 mmol) in dichloromethane (5 ml) was added dropwise over a period of 10 min. The reaction mixture was maintained at –78 °C for 1 h and then treated with triethylamine (0.7 ml, 505 mg, 5 mmol). After a further 10 min at –78 °C the mixture was allowed to warm up to room temperature over *ca.* 0.5 h. The solution was washed with water (2 x 25 ml) and brine, dried, and evaporated. Chromatography of the residue over Florisil, eluting with pentane - ether (3:1), yielded the *title compound* **13a** (100 mg, 92%; >97% isomeric purity by n.m.r.) as a yellow liquid (M + NH_4^+, 128.1083. $C_7H_{14}NO$ requires 128.1075); ν_{max} 2968, 2934, 2875, 1676, 1639, 1574, 1225, 1163, 1111, 1012, 989, and 954 cm^{-1}; δ_H (300 MHz) 1.06 (3 H, t, J 7 Hz, 7-H_3), 2.24 (2 H, dq, $J_{5,6}$ 6, $J_{6,7}$ 7 Hz, 6-H_2), 5.76 (1 H, dd, J 8 and 10.5 Hz, 2-H), 6.19 (1 H, dt, $J_{5,6}$ 6, $J_{4,5}$ 14 Hz, 5-H), 6.90 (1 H, dd, J 10.5 and 11.5 Hz, 3-H), 6.96 (1 H, dd, J 11.5 and 14 Hz, 4-H) and 10.15 (1 H, d, J 8 Hz, 1-H); δ_C 12.75, 26.10, 123.24, 125.73, 148.06, 148.41, 190.38; m/z 128 (M + NH_4^+, 100%), 111 (58), 81 (20); R_f (ether -petroleum 1:2) 0.5, PMA stain and u.v. active.

Hepta-(2E,4E)-dienal **14a**

To a stirred solution of oxalyl chloride (0.12 ml, 175 mg, 1.37 mmol) in dichloromethane (5 ml) at –78 °C under N_2 was added a solution of DMSO (0.2 ml, 220 mg, 2.8 mmol) in dichloromethane (2 ml). After 15 min a solution of **12a** (112 mg, 1.0 mmol) in dichloromethane (5 ml) was added dropwise over a period of 10 min. The reaction mixture was maintained at –78 °C for 1 h and then allowed to reach room temperature over 1 h. Triethylamine (0.7 ml, 505 mg, 5 mmol) was then added, followed by water (10 ml). The organic layer was separated and the aqueous layer extracted with dichloromethane (3 x 20 ml). The combined organic extracts were washed with water (3 x 30 ml) and brine (30 ml), dried, and evaporated. Flash chromatography of the residue , eluting with ether - petroleum (1:4), afforded the *title compound* **14a** (96 mg, 87%; >97% isomeric purity by n.m.r.) as a volatile colourless liquid (M + NH_4^+, 128.1073. $C_7H_{14}NO$ requires 128.1075); ν_{max} 2968, 2935, 2876, 1685, 1642, 1600, 1167, 1122, 1107, 1013, 988 and 606 cm^{-1}; δ (300 MHz) 1.05 (3 H, t, J 7 Hz, 7-H_3), 2.10–2.30 (2 H, m, 6-H_2), 6.06 (1 H, dd, J 8 and 15 Hz, 2-H), 6.25–6.35 (2 H, m, 4-H and 5-H), 7.07 (1 H, dd with fine splitting, J 10 and 15 Hz, 3-H) and 9.51 (1 H, d, J 8 Hz, CHO); m/z (CI, peaks > 5%) 128 (M + NH_4^+, 100%), 111 (M + H, 12), and 81 (7); R_f (petroleum - ether 2:1) 0.5, PMA stain and u.v active.

(1,3Z,5E)-Octatriene **15a**[11]

To a stirred solution of methylene triphenylphosphorane [prepared from methyltriphenylphosphonium bromide (357 mg, 1.0 mmol) and *n*-butyllithium (2.5 M in hexane, 0.4 ml, 1.0 mmol) in THF (3 ml) at 0 °C] under N_2 was added the aldehyde **13a** (55 mg, 0.5 mmol) in THF (1 ml). After 1 h the solution was allowed to warm to room temperature and after a further 1 h water (5 ml) was added and the mixture extracted with pentane (3 x 5 ml). The combined organic solution was washed with water (3 x 5 ml), brine (10 ml), dried and the solvent removed at atmospheric pressure. The residue was applied to a plug of silica, eluted with pentane, and the eluate carefully distilled off at atmospheric pressure to obtain the *title compound* **15a** (47 mg, 86%) as a volatile colourless liquid; ν_{max} 2965–2874, 1640, 1619, 1462, 1439, 1322, 1217, 974, 943 and 903 cm^{-1}; δ_H (300 MHz) 1.01 (3 H, t, J 7.5 Hz, 8-H_3), 2.14 (2 H, ddq, $J_{5,7}$ 1.5, $J_{6,7}$ 6.5, $J_{7,8}$ 7.5 Hz, 7-H_2), 5.09 (1 H, br d, J 10.5 Hz, 1'-H), 5.18 (1 H, dd, $J_{1,1'}$ 1.9, $J_{1,2}$ 16.7 Hz, 1-H), 5.77 (1 H, dt, $J_{6,7}$ 6.5, $J_{5,6}$ 15 Hz, 6-H), 5.87 and 5.96 (each 1 H, dd, J 10.5 and 10.5 Hz, 3-H and 4-H), 6.48 (1 H, ddt, $J_{5,7}$ 1.5, $J_{4,5}$ 10.5, $J_{5,6}$ 15 Hz, 5-H), 6.79 (1 H, overlapping ddd, $J_{1',2}$ 10.5, $J_{2,3}$ 10.5, $J_{1,2}$ 16.7 Hz, 2-H); δ_C 13.40, 25.89, 117.06, 124.53, 127.75, 130.24, 132.18, 138.11; λ_{max} (hexane) 252, 262, 272 nm.

(1,3E,5E)-Octatriene **16a**[11]

The procedure described above for the preparation of **15a** was repeated with the aldehyde **14a** (55 mg, 0.5 mmol) in THF (1 ml). Removal of the pentane by careful distillation at atmospheric pressure gave the *title*

compound **16a** (48 mg, 88%); ν_{max} 2963–2850, 1687, 1660, 1643, 1626, 1585, 1462, 1416, 1366, 1261, 1095, 1006, 973 and 801 cm^{-1}; δ (300 MHz) 0.99 (3 H, t, *J* 7.5 Hz, 8-H_3), 2.11 (2 H, dq, $J_{6,7}$ 7.5, $J_{7,8}$ 7.5 Hz, 7-H_2), 5.02 (1 H, dd, $J_{1,1'}$ 1.4, $J_{1',2}$ 10 Hz, 1'-H), 5.15 (1 H, dd, $J_{1,1'}$ 1.4, $J_{1,2}$ 16.5 Hz, 1-H), 5.75 (1 H, dt, $J_{6,7}$ 7.5, $J_{5,6}$ 15 Hz, 6-H), 6.0–6.2 (3 H, m, 3-H, 4-H and 5-H), 6.33 (1 H, ddd, $J_{1',2}$ 10, $J_{2,3}$ 10, $J_{1,2}$ 16.5 Hz, 2-H); λ_{max} (hexane) 252, 262, 272 nm.

cis-*4-Pentyl-2-cyclobutene-1-methanol* **12b**

To a stirred solution of **7b** (274 mg, 1.0 mmol) in dichloromethane - water (50:1; 15 ml) was added dropwise a solution of DDQ (272 mg, 1.2 mmol) in dichloromethane (15 ml). The reaction mixture was stirred at room temperature for 3 h and then dried over $MgSO_4$. The solids were filtered off and washed with dichloromethane (20 ml). The filtrate was evaporated to dryness and the residue residue purified by flash chromatography (elution with toluene - pentane 5:1), which gave 4-methoxybenzaldehyde followed by the *title compound* **12b** (122 mg, 79%) a pale yellow oil (M + NH_4^+, 172.1697; $C_{10}H_{22}NO$ requires 172.1701); ν_{max} 3351, 3041, 2956, 2926, 2872, 2856, 1644, 1467, 1378, 1026 and 729 cm^{-1}; δ_H (300 MHz) 0.86 (3 H, t, *J* 6.5 Hz, 5"-H_3), 1.23–1.49 (7 H, m, 1"-H, 2"-H_2, 3"-H_2 and 4"-H_2), 1.51–1.56 (1 H, m, 1"-H), 2.88 (1 H, ddd, $J_{1',4'}$ 5, $J_{1",4'}$ 5 and 10 Hz, 4'-H), 3.02–3.08 (1 H, m, 1'-H), 3.68 (1 H, dd, $J_{1,1'}$ 6.5, J_{gem} 10.5 Hz, 1-H), 3.76 (1 H, dd, $J_{1,1'}$ 7.5, J_{gem} 10.5 Hz, 1-H), 6.07 and 6.24 (both 1 H, d, *J* 3 Hz, 2'-H and 3'-H); δ_C 14.07, 22.65, 27.95, 29.50, 32.03, 46.24, 48.51, 63.18, 136.17, 142.14; m/z 172 (M + NH_4, 100%); R_f (pentane - ethyl acetate 1:1) 0.5, PMA stain.

Deca-(2Z,4E)-dienal **13b**

To a stirred solution of oxalyl chloride (0.12 ml, 175 mg, 1.37 mmol) in dichloromethane (5 ml) at –78 °C under N_2 was added a solution of DMSO (0.2 ml, 220 mg, 2.8 mmol) in dichloromethane (2 ml). After 15 min a solution of **12b** (154 mg, 1.0 mmol) in dichloromethane (5 ml) was added dropwise over a period of 10 min. The reaction mixture was maintained at –78 °C for 2 h and then treated with triethylamine (0.7 ml, 505 mg, 5 mmol). After a further 15 min at –78 °C the mixture was allowed to warm up to room temperature over 0.75 h. The solution was washed with water (3 x 25 ml) and brine (25 ml), dried, and evaporated to obtain the *title compound* **13b** (126 mg, 83%) as a yellow liquid which needed no further purification and was used immediately; (M + NH_4^+, 170.1542; $C_{10}H_{20}NO$ requires 170.1545); ν_{max} 2958, 2929, 2858, 1671, 1637, 1574, 1466, 1379, 1230, 1159, 1114, 1012 and 953 cm^{-1}; δ_H (300 MHz) 0.86 (3 H, t, *J* 7 Hz, 10-H_3), 1.21–1.45 (6 H, m, 7-H_2, 8-H_2 and 9-H_2), 2.19 (2 H, dt, $J_{5,6}$ 7, $J_{6,7}$ 7 Hz, 6-H_2), 5.74 (1 H, dd, $J_{1,2}$ 8, $J_{2,3}$ 10.5 Hz, 2-H), 6.15 (1 H, dt, $J_{5,6}$ 7, $J_{4,5}$ 14 Hz, 5-H), 6.89 (1 H, dd, $J_{2,3}$ 10.5, $J_{3,4}$ 11.5 Hz, 3-H), 6.95 (1 H, dd, $J_{3,4}$ 11.5, $J_{4,5}$ 14 Hz, 4-H), 10.13 (1 H, d, $J_{1,2}$ 8 Hz, 1-H); δ_C 13.92, 22.38, 28.23, 31.32, 33.01, 124.11, 125.64, 147.27, 148.11, 190.41; m/z 170 (M + NH_4, 15%), 102 (100), 74 (28); R_f (pentane - dichloromethane 1:1) 0.5, u.v. active.

Deca-(2E,4E)-dienal **14b**

The procedure described above for the preparation of **14a** was repeated with the alcohol **12b** (154 mg, 1.0 mmol), keeping the solution at –78 °C for 2 h and then allowing it to reach room temperature over 1 h before adding the triethylamine. Chromatography (elution with petroleum - dichloromethane 1:1) gave the *title compound* **14b** (137 mg, 90%) as a yellow liquid (M + NH_4^+, 170.1547; $C_{10}H_{20}NO$ requires 170.1545); ν_{max} 2958, 2929, 2857, 1683, 1640, 1613, 1514, 1467, 1454, 1163, 1112, 1013 and 988 cm^{-1}; δ (300 MHz) 0.87 (3 H, t, *J* 7 Hz, 10-H_3), 1.16–1.59 (6 H, m, 7-H_2, 8-H_2 and 9-H_2), 2.19 (2 H, dt, $J_{5,6}$ 7, $J_{6,7}$ 7 Hz, 6-H_2), 6.05 (1 H, $J_{1,2}$ 8, $J_{2,3}$ 15 Hz, 2-H), 6.25–6.30 (2 H, m, 4-H and 5-H), 7.06 (1 H, dd, $J_{3,4}$ 10, $J_{2,3}$ 15 Hz, 3-H), 9.51 (1 H, d, *J* 8 Hz, 1-H); m/z 170 (M + NH_4, 100%), 153 (M + H, 12); R_f (pentane - dichloromethane 1:1) 0.48, u.v. active.

Undeca-(1,3Z,5E)-triene **15b**[13,14]

To a stirred solution of methylene triphenylphosphorane [prepared from methyltriphenylphosphonium bromide

(227 mg, 0.64 mmol) and *n*-butyllithium (2.5 M in hexane, 0.23 ml, 0.57 mmol) in THF (3 ml) at 0 °C] under N_2 was added a solution of the aldehyde **13b** (76 mg, 0.5 mmol) in THF (2 ml). After 1 h the solution was allowed to return to room temperature and after a further 1 h water (5 ml) was added and the mixture extracted with pentane (3 x 10 ml). The combined organic extracts were washed with water (3 x 10 ml), brine (10 ml), dried and evaporated to a yellow residue which was washed through a plug of silica (eluting with pentane) to give the *title compound* **15b** (72 mg, 96%) as a pale yellow oil; ν_{max} 2957, 2928, 2859, 1687, 1467, 1379, 988 and 975 cm^{-1}; δ (300 MHz) 0.87 (3 H, t, *J* 7 Hz, 11-H_3), 1.08–1.44 (6 H, m, 8-H_2, 9-H_2 and 10-H_2), 2.12 (2 H, m, 7-H_2), 5.09 (1 H, d, $J_{1,2}$ 10 Hz, 1-H), 5.19 (1 H, dd, $J_{1,1'}$ 1.5, $J_{1',2}$ 16.8 Hz, 1'-H), 5.73 (1 H, dt, $J_{6,7}$ 7, $J_{5,6}$ 15 Hz, 6-H), 5.88–6.00 (2 H, m, 3-H and 4-H), 6.47 (1 H, $J_{4,5}$ 7, $J_{5,6}$ 15 Hz, 5-H), 6.79 (1 H, ddd, $J_{1,2}$ 10, $J_{2,3}$ 10, $J_{1',2}$ 16.8 Hz, 2-H); λ_{max} (hexane) 254, 264, 273 nm.

Undeca-(1,3E,5E)-triene **16b**[13,14]

The procedure described above for the preparation of **15b** was repeated with the aldehyde **14b** (76 mg, 0.5 mmol) in THF (2 ml). Removal of the pentane at atmospheric pressure gave the *title compound* **16b** (68 mg, 90%) as a pale yellow oil; ν_{max} 3021, 2958, 2927, 2857, 1642, 1627, 1585, 1467, 1005, 909 and 735 cm^{-1}; δ (300 MHz) 0.87 (3 H, t, *J* 7 Hz, 11-H_3), 1.19–1.42 (6 H, m, 8-H_2, 9-H_2, 10-H_2), 2.07 (2 H, dt, $J_{6,7}$ 7, $J_{7,8}$ 7 Hz, 7-H_2), 5.02 (1 H, dd, $J_{1,1'}$ 1.4, $J_{1',2}$ 10 Hz, 1'-H), 5.15 (1 H, dd, $J_{1,1'}$ 1.4, $J_{1,2}$ 16.7 Hz, 1-H), 5.71 (1 H, dt, $J_{6,7}$ 7, $J_{5,6}$ 14.5 Hz, 6-H), 6.00–6.24 (3 H, m, 3-H, 4-H and 5-H), 6.34 (1 H, ddd, $J_{1',2}$ 10, $J_{2,3}$ 10, $J_{1,2}$ 16.7 Hz, 2-H).

Methyl (2Z,4E)-decadienoate **17**[17,18]

To a stirred solution of the aldehyde **13b** (76 mg, 0.5 mmol) in methanol (10 ml) was added manganese dioxide (795 mg, 10 mmol) and sodium cyanide (100 mg, 2 mmol) followed by glacial acetic acid (0.03 ml). The resulting suspension was stirred at room temperature for 3 h, filtered and the filtrate evaporated. The residue was redissolved in water (10 ml) and extracted with ether (3 x 10 ml), the combined organic extracts were washed with water (2 x 10 ml), brine (10 ml), dried and evaporated. Flash chromatography of the residue (elution with petroleum - dichloromethane 3:1) gave the *title compound* **17** (80 mg, 88%) as a pale yellow oil (M + NH_4^+, 200.1650; $C_{11}H_{22}NO_2$ requires 200.1650); ν_{max} 2955, 2929, 2858, 1719, 1640, 1602, 1460, 1438, 1413, 1379, 1278, 1198, 1174, 1140, 1074, 1001, 963, 895, 826 and 740 cm^{-1}; δ (300 MHz) 0.86 (3 H, t, *J* 7 Hz, 10-H_3), 1.20–1.46 (6 H, m, 7-H_2, 8-H_2 and 9-H_2), 2.17 (2 H, dt, $J_{5,6}$ 7, $J_{6,7}$ 7 Hz, 6-H_2), 3.69 (3 H, s, CO_2Me), 5.53 (1 H, d, *J* 11.3 Hz, 2-H), 6.05 (1 H, dt, $J_{5,6}$ 7, $J_{4,5}$ 15 Hz, 5-H), 6.53 (1 H, dd, $J_{2,3}$ 11.3, $J_{3,4}$ 11.3 Hz, 3-H), 7.32 (1 H, dd with fine splitting, $J_{3,4}$ 11.3 Hz, $J_{4,5}$ 15 Hz, 4-H); δ_C 14.03, 22.51, 28.48, 31.47, 33.01, 51.07, 114.95, 126.85, 145.70, 146.11, 167.03; m/z 200 (M + NH_4, 100%), 183 (M + H, 20).

Methyl (2E,4E)-decadienoate **18**[19]

The above procedure leading to **17** was repeated using the aldehyde **14b**. Flash chromatography, eluting with petroleum - dichloromethane (3:1), gave the *title compound* **18** (78 mg, 86%) as a pale yellow oil (M + NH_4^+, 200.1655; $C_{11}H_{22}NO_2$ requires 200.1650); ν_{max} 2955, 2929, 2858, 1721, 1645, 1617, 1435, 1312, 1265, 1246, 1202, 1175, 1142, 1000, 914 and 876 cm^{-1}; δ (300 MHz) 0.87 (3 H, t, *J* 7 Hz, 10-H_3), 1.21–1.45 (6 H, m, 7-H_2, 8-H_2 and 9-H_2), 2.13 (2 H, dt, $J_{5,6}$ 7, $J_{6,7}$ 7 Hz, 6-H_2), 3.72 (3 H, s, CO_2Me), 5.76 (1 H, d, *J* 15.5 Hz, 2-H), 6.10–6.15 (2 H, m, 4-H and 5-H), 7.24 (1 H, dd, $J_{3,4}$ 10, $J_{2,3}$ 15.5 Hz, 3-H); δ_C 13.97, 22.44, 28.33, 31.34, 32.93, 51.42, 118.59, 128.24, 145.03, 145.41, 167.76, 188.56; m/z 200 (M + NH_4, 100%), 183 (M + H, 25).

6-[(4-Methoxyphenyl)methoxy]-(2Z,4E)-hexadienol **19**

To a stirred solution of the (2Z,4*E*)-hexadienal **3** (250 mg, 1.1 mmol) in THF (10 ml) at 0 °C under N_2 was added lithium borohydride (35 mg, 1.6 mmol). After 2 h at 0 °C the reaction mixture was allowed to reach room temperature and stirred for a further 1 h. The excess reagent was destroyed by the addition of saturated aqueous ammonium chloride (20 ml). The mixture was extracted with ether (3 x 20 ml), the combined extracts

washed with water (3 x 20 ml), brine (20 ml) dried and evaporated. The pale yellow residue was purified by flash chromatography (elution with hexane - ethyl acetate 3:2) to obtain the *title compound* **19** (207 mg, 83%) as a clear oil (M + NH_4^+, 252.1603; $C_{14}H_{22}NO_3$ requires 252.1600); ν_{max} 3400br, 2838, 1612, 1586, 1514, 1464, 1359, 1303, 1249, 1147, 1101,1034 and 958 cm^{-1}; δ (300 MHz) 2.23 (1 H, br s, OH), 3.77 (3 H, s, OMe), 4.02 (2 H, d, $J_{5,6}$ 6 Hz, 6-H_2), 4.25 (2 H, d, *J* 7 Hz, 1-H_2), 4.42 (2 H, s, OCH_2Ar), 5.57 (1 H, dt, $J_{1,2}$ 7, $J_{2,3}$ 11 Hz, 2-H), 5.79 (1 H, dt, $J_{5,6}$ 6, $J_{4,5}$ 15 Hz, 5-H), 6.05 (1 H, dd, $J_{2,3}$ 11, $J_{3,4}$ 11 Hz, 3-H), 6.51 (1 H, dd, $J_{3,4}$ 11, $J_{4,5}$ 15 Hz, 4-H), 6.86 (2 H, d, *J* 8.5 Hz, 3,5-ArH), 7.24 (2 H, d, *J* 8.5 Hz, 2,6-ArH); m/z 252 (M + NH_4, 15%), 234 (M^+, 2), 138 (38), 121 (100); R_f (hexane - ethyl acetate 3:2) 0.25, PMA stain and u.v. active.

1-Chloro-6-[(4-methoxyphenyl)methoxy]hexa-(2Z,4E)-diene **20**

To a stirred solution of the (2Z,4*E*)-hexadienol **19** (105 mg, 0.45 mmol), lithium chloride (76 mg, 1.8 mmol) and *s*-collidine (110 mg, 0.9 mmol) in DMF (3 ml) at 0 °C under N_2 was added dropwise methanesulphonyl chloride (103 mg, 0.9 mmol). The mixture was stirred at 0 °C for 2 h and at room temperature for a further 2 h. Water (10 ml) was added and the mixture extracted with ether (3 x 15 ml). The combined organic extracts were washed with water (3 x 15 ml), brine (15 ml), dried and evaporated. The residue was purified by flash chromatography (elution with hexane - dichloromethane 1:1) to obtain the *title compound* **20** (85 mg, 71%) as a colourless oil (M + NH_4^+, 270.1257. $C_{14}H_{21}{}^{35}ClNO_2$ requires 270.1261); ν_{max} 3003, 1612, 1586, 1513, 1464, 1302, 1248, 1173, 1103, 1066, 1035, 988 and 951 cm^{-1}; δ (300 MHz) 3.79 (3 H, s, OMe), 4.06 (2 H, d, *J* 6 Hz, 6-H_2), 4.19 (2 H, d, *J* 8 Hz, 1-H_2), 4.45 (2 H, s, OCH_2Ar), 5.60 (1 H, dt, $J_{1,2}$ 8, $J_{2,3}$ 11 Hz, 2-H), 5.90 (1 H, dt, $J_{5,6}$ 6, $J_{4,5}$ 15 Hz, 5-H), 6.15 (1 H, dd, $J_{2,3}$ 11, $J_{3,4}$ 11 Hz, 3-H), 6.54 (1 H, dd, $J_{3,4}$ 11, $J_{4,5}$ 15 Hz, 4-H), 6.87 (2 H, d, *J* 8.5 Hz, 3,5-ArH), 7.26 (2 H, d, *J* 8.5 Hz, 2,6-ArH); m/z 270 (M + NH_4, 3%), 138 (60), 121 (100); R_f (hexane - dichloromethane 1:1) 0.33, PMA stain and u.v. active.

Reaction of **20** *with Butylcopper Reagents (Table 1)*

The chlorodiene **20** was treated with various butylcopper reagents as described below, with identical work-up procedures (as for entry 1). The ratio of dienes obtained in each reaction (Table 1) was estimated from the 300 MHz ^1H n.m.r. spectrum of the crude product, integrating over the range δ 3.1–4.2 ppm. The signals due to the benzylic CH_2 of each of the compounds **21**–**24** were clearly resolved within this region.

Entry 1: To a stirred solution of the cuprate (0.8 mmol) at –78 °C under N_2 [prepared by treatment of copper(I) iodide (152 mg, 0.8 mmol) in THF (10 ml) with *n*-butyllithium in hexane (1.3 M, 1.31 ml, 1.6 mmol) with stirring at –10 °C for 0.5 h] was added a solution of **20** (100 mg, 0.4 mmol) in THF (5 ml). After 1 h at –78 °C the solution was allowed to return to –10 °C and stirred for 2 h. Saturated ammonium chloride (10 ml) was added, the mixture was extracted with ether (3 x 15 ml), and the combined extracts washed with water (3 x 15 ml), brine (20 ml), dried and evaporated.

Entry 2: To a stirred solution of the cuprate (0.8 mmol) at –78 °C under N_2 [prepared by treatment of CuBr - Me_2S (165 mg, 0.8 mmol) in THF (5 ml) and HMPA (5 ml) with *n*-butyllithium in hexane (1.3 M, 1.31 ml, 1.6 mmol) with stirring at –10 °C for 0.5 h] was added a solution of **20** (100 mg, 0.4 mmol) in THF (5 ml). After 1 h at –78 °C the solution was allowed to return to –10 °C, stirred for 2 h, and worked up as for entry 1.

Entry 3: To copper(I) chloride (3 mg, 0.03 mmol) in THF (2 ml) at –20 °C under N_2 was added *n*-butylmagnesium chloride in THF (2.0 M, 0.3 ml, 0.6 mmol) with stirring for 10 min. The temperature was lowered to –78 °C and **20** (75 mg, 0.3 mmol) in THF (2 ml) was added dropwise. After 2 h at –78 °C the solution was allowed to reach 0 °C, stirred for 2 h, and worked up as for entry 1.

Entry 4: To a stirred suspension of copper(I) iodide (114 mg, 0.6 mmol) in THF (3 ml) at –78 °C under N_2 was added MeLi in ether (1.5 M, 0.4 ml, 0.6 mmol). To the yellow precipitate was added *n*-butylmagnesium chloride in THF (2.0 M, 0.3 ml, 0.6 mmol). After 15 min the chloride **20** (50 mg, 0.2 mmol) in THF (1 ml) was added. The solution was kept at –78 °C for 1 h, allowed to reach 0–10 °C and worked up as for entry 1.

Entries 5, 6 and 7: To a stirred solution of **20** (75 mg, 0.3 mmol) in ether, THF or THF - DMPU (1:1) (3 ml) at –78 °C under N_2 was added *n*-butylmagnesium chloride in ether (2.0 M, 0.3 ml, 0.6 mmol). After 2 h at

–78 °C the mixture was allowed to warm to 20 °C, stirred until complete, and worked up as for entry 1.
The following compounds were obtained by chromatography of the above products over silver nitrate on silica gel +200 mesh (Aldrich 24,876-2), eluting with hexane - ether (12:1):
1-[(4-Methoxyphenyl)methoxy]deca-(2E,4Z)-diene **21** (M + NH_4^+, 292.2278; $C_{18}H_{30}NO_2$ requires 292.2276); ν_{max} 2956, 2928, 2855, 1613, 1586, 1514, 1465, 1358, 1302, 1248, 1173, 1108,1085, 1038, 986 and 820 cm^{-1}; δ (300 MHz) 0.87 (3 H, t, *J* 7 Hz, 10-H_3), 1.23–1.38 (6 H, m, 7-H_2, 8-H_2 and 9-H_2), 2.13 (2 H, dt, $J_{5,6}$ 7.5, $J_{6,7}$ 7.5 Hz, 6-H_2), 3.78 (3 H, s, OMe), 4.03 (2 H, d, $J_{1,2}$ 6 Hz, 1-H_2), 4.43 (2 H, s, OCH_2Ar), 5.43 (1 H, dt, $J_{5,6}$ 7.5, $J_{4,5}$ 11 Hz, 5-H), 5.73 (1 H, dt, $J_{1,2}$ 6, $J_{2,3}$ 15 Hz, 2-H), 5.98 (1 H, dd, $J_{3,4}$ 11, $J_{4,5}$ 11 Hz, 4-H), 6.51 (1 H, dd, $J_{3,4}$ 11, $J_{2,3}$ 15 Hz, 3-H), 6.85 (2 H, d, *J* 8.5 Hz, 3,5-ArH), 7.25 (2 H, d, *J* 8.5 Hz, 2,6-ArH); m/z 292 (M + NH_4, 46%), 155 (30), 138 (100), 121 (80).
3-Butyl-6-[(4-methoxyphenyl)methoxy]hexa-(1,4E)-diene **23** (M + NH_4^+, 292.2297; $C_{18}H_{30}NO_2$ requires 292.2276); ν_{max} 2999, 2956, 2929, 2857, 1636, 1613, 1514, 1466, 1361, 1302, 1276, 1249, 1173, 1096, 1037, 974 and 821 cm^{-1}; δ (300 MHz) 0.86 (3 H, t, *J* 7 Hz, 4'-H_3), 1.19–1.42 (6 H, m, 1'-H_2, 2'-H_2 and 3'-H_2), 2.66–2.71 (1 H, m, 3-H), 3.78 (3 H, s, OMe), 3.94 (2 H, d, $J_{5,6}$ 5 Hz, 6-H_2), 4.41 (2 H, s, OCH_2Ar), 4.94–5.00 (2 H, m, 1-H_2), 5.54–5.58 (2 H, m, 4-H and 5-H), 5.62–5.74 (1 H, m, 2-H), 6.86 (2 H, d, *J* 8.5 Hz, 3,5-ArH), 7.24 (2 H, d, *J* 8.5 Hz, 2,6-ArH); m/z 292 (M + NH_4, 80%), 274 (M + H, 10), 170 (10), 155 (60), 142 (15), 138 (100), 121 (90), 69 (20).
5-[[(4-Methoxyphenyl)methoxy]methyl]nona-(1,3E)-diene **24** (M + NH_4^+, 292.2273; $C_{18}H_{30}NO_2$ requires 292.2276); ν_{max} 2956, 2930, 2858, 1613, 1514, 1248, 1092, 1038 and 1004 cm^{-1}; δ (300 MHz) 0.85 (3 H, t, *J* 7 Hz, 9-H_3), 1.15–1.30 (5 H, m, 6-H, 7-H_2 and 8-H_2), 1.5–1.55 (1 H, m, 6-H), 2.3–2.4 (1 H, m, 5-H), 3.33 (2 H, d, *J* 6.5 Hz, 1'-H_2), 3.78 (3 H, s, OMe), 4.41 (2 H, s, OCH_2Ar), 4.97 (1 H, dd, $J_{1a,1b}$ 1, $J_{1a,2}$ 10 Hz, 1-H_a), 5.09 (1 H, dd, $J_{1a,1b}$ 1, $J_{1b,2}$ 17 Hz, 1-H_b), 5.52 (1 H, dd, $J_{4,5}$ 8.5, $J_{3,4}$ 15 Hz, 4-H), 6.06 (1 H, dd, $J_{2,3}$ 10, $J_{3,4}$ 15 Hz, 3-H), 6.30 (1 H, ddd, $J_{1a,2}$ 10, $J_{2,3}$ 10, $J_{1b,2}$ 17 Hz, 2-H), 6.85 (2 H, d, *J* 8.5 Hz, 3,5-ArH), 7.22 (2 H, d, *J* 8.5 Hz, 2,6-ArH); m/z 292 (M + NH_4, 45%), 275 (M + H, 4), 177 (20), 160 (100), 155 (22), 138 (35), 121 (32).
1-[(4-Methoxyphenyl)methoxy]deca-(2*E*,4*E*)-diene **22** was not isolated pure by chromatography, the relevant fractions invariably being contaminated with **21**. However, the following n.m.r. signals were assigned to **22**: δ (300 MHz) 0.87 (3 H, t, *J* 7 Hz, 10-H_3), 1.23–1.38 (6 H, m, 7-H_2, 8-H_2 and 9-H_2), 2.04 (2 H, dt, $J_{5,6}$ 7.0, $J_{6,7}$ 7.0 Hz, 6-H_2), 3.78 (3 H, s, OMe), 3.99 (2 H, d, $J_{1,2}$ 6.3 Hz, 1-H_2), 4.42 (2 H, s, OCH_2Ar), [the peaks corresponding to 5-H, 2-H and 4-H were obscured), 6.20 (1 H, dd, $J_{3,4}$ 10.5, $J_{2,3}$ 15 Hz, 3-H), 6.85 (2 H, d, *J* 8.5 Hz, 3,5-ArH), 7.25 (2 H, d, *J* 8.5 Hz, 2,6-ArH).

cis-*4-(*t*-Butyldiphenylsilyloxymethyl)-2-cyclobutene-1-methanol* **25**
To a stirred solution of sodium hydride (60% oil dispersion, 395 mg, 10 mmol) in THF (25 ml) at room temperature under N_2 was added the diol (±)-**1** (1.14 g, 10 mmol) in THF (5 ml). After 30 min *t*-butylchlorodiphenylsilane (2.75 g, 10 mmol) was added to the solution. After 2 h the solution was poured on to ether (100 ml), washed with 10% aq. K_2CO_3 (30 ml), water (30 ml), brine (30 ml), dried and evaporated, giving a pale yellow residue. Flash chromatography (elution with hexane - ether 5:1) gave the *title compound* **25** (3.27 g, 93%) as a colourless oil, which on storage in a freezer gave a white solid (M + H, 353.1940; $C_{22}H_{29}O_2Si$ requires 353.1937); ν_{max} 3469, 3048, 2930, 2858, 1589, 1472, 1428, 1392, 1362, 1113, 1070, 1036, 823 and 781 cm^{-1}; δ (300 MHz) 1.04 (9 H, s, CMe_3), 3.16–3.23 (1 H, m, 1'-H or 4'-H), 3.28–3.34 (1 H, m, 1'-H or 4'-H), 3.78–3.85 (5 H, m, 1-H_2, 1"-H_2 and OH), 5.83 and 6.02 (each 1 H, d, *J* 3 Hz, 2'-H and 3'-H), 7.42 and 7.67 (10 H, 2 x m, 2 x C_6H_5); m/z 353 (M + H, 100%), 274 (25), 196 (15), 94 (18), 58 (22); R_f (hexane - ether 5:1) 0.4, PMA stain and u.v. active.

*6-(*t*-Butyldiphenylsilyloxy)-(2Z,4E)-hexadienal* **26**
To a stirred solution of oxalyl chloride (0.88 ml, 10 mmol) in dichloromethane (25 ml) at –78 °C under N_2 was added dropwise a solution of DMSO (1.43 ml, 20 mmol) in dichloromethane (5 ml). After 25 min a solution of the monoether **25** (1.76 g, 5.0 mmol) in dichloromethane (15 ml) was added dropwise over 10 min. After 2 h at –78 °C the reaction was quenched with triethylamine (5.6 ml, 40 mmol) and after 15 min the reaction was

allowed to warm up to room temperature over 1 h. Water (30 ml) was added, and the aqueous layer further extracted with dichloromethane (25 ml). The combined organics were washed with water (3 x 30 ml), brine (30 ml), dried, evaporated and the residue purified by chromatography over Florisil, eluting with pentane - ether (9:1), to obtain the *title compound* **26** (1.4 g, 83%) as a colourless oil (M + H, 351.1778; $C_{22}H_{27}O_2Si$ requires 351.1780); ν_{max} 3446, 3071, 2931, 2857, 1673, 1642, 1589, 1472, 1428, 1391, 1362, 1260, 1221, 1113, 1011, 964, 823 and 740 cm^{-1}; δ (300 MHz) 1.07 (9 H, s, CMe_3), 4.35 (2 H, br d, 6-H_2), 5.83 (1 H, dd, $J_{1,2}$ 8, $J_{2,3}$ 11 Hz, 2-H), 6.17 (1 H, dt, $J_{5,6}$ 4, $J_{4,5}$ 15 Hz, 5-H), 6.97 (1 H, dd, $J_{2,3}$ 11, $J_{3,4}$ 11 Hz, 3-H), 7.38 and 7.65 (11 H, 2 x m, 4-H and 2 x C_6H_5), 10.18 (1 H, d, *J* 8 Hz, 1-H); m/z 368 (M + NH_4, 60%), 351 (M + H, 35), 274 (100), 258 (30), 216 (38), 196 (50); R_f (pentane - ether 5:1) 0.6, PMA stain and u.v. active.

6-(t-Butyldiphenylsilyloxy)-(2Z,4E)-hexadienol **27**[22]

To a stirred solution of **26** (700 mg, 2 mmol) in THF (25 ml) at 0 °C under N_2 was added lithium borohydride (88 mg, 4 mmol). The solution was allowed to warm up to room temperature and after 30 min the excess reagent was destroyed by the addition of saturated aq. ammonium chloride (30 ml). The mixture was extracted with ether (3 x 30 ml), the combined extracts washed with water (3 x 30 ml), brine (30 ml), dried and evaporated. The pale yellow residue was purified by flash chromatography (elution with pentane - ether 4:1) to obtain the *title compound* **27** (549 mg, 78%) as a colourless oil (M + H, 353.1939; $C_{22}H_{29}O_2Si$ requires 353.1937); ν_{max} (nujol) 3342, 3071, 3015, 2931, 2857, 1656, 1589, 1472, 1428, 1371, 1302, 1260, 1188, 1113, 1049, 957, 823 and 395 cm^{-1}; δ (300 MHz) 1.05 (9 H, s, CMe_3), 1.48 (1 H, s, OH), 4.25 (2 H, d, *J* 5 Hz, 6-Hz), 4.29 (2 H, d, *J* 7 Hz, 1-H_2), 5.57 (1 H, dt, $J_{1,2}$ 7, $J_{2,3}$ 11 Hz, 2-H), 5.80 (1 H, dt, $J_{5,6}$ 5, $J_{4,5}$ 15 Hz, 5-H), 6.09 (1 H, dd, $J_{2,3}$ 11, $J_{3,4}$ 11 Hz, 3-H), 6.56 (1 H, dd, $J_{3,4}$ 11, $J_{4,5}$ 15 Hz, 4-H), 7.38 and 7.65 (10 H, 2 x m, 2 x C_6H_5); m/z 370 (M + NH_4, 60%), 274 (100), 216 (30), 196 (55), 114 (22); R_f (pentane - ether 3:1) 0.4, PMA stain and u.v. active.

1-Chloro-6-(t-butyldiphenylsilyloxy)hexa-2Z,4E-diene **28**[22]

To a solution containing the alcohol **27** (352 mg, 1 mmol), lithium chloride (84 mg, 2 mmol) and *s*-collidine (144 mg, 1.2 mmol) in dry DMF (10 ml) at 0 °C was added methanesulphonyl chloride (126 mg, 1.1 mmol). The resulting mixture was stirred at 0 °C for 1 h and then at room temperature for 1 h. The reaction mixture was poured onto water (40 ml) and extracted with ether - hexane (2:1) (3 x 30 ml). The organic layers were washed with water (3 x 30 ml) saturated copper nitrate solution (30 ml), brine (30 ml), dried and evaporated. The residue was purified by flash chromatography (elution with pentane - ether 20:1) to obtain the *title compound* **28** (320 mg, 86%) as a colourless oil (M + NH_4^+, 388.1877; $C_{22}H_{31}ClNOSi$ requires 388.1863); ν_{max} 3071, 2959, 2931, 2892, 2857, 1428, 1113, 1056, 985, 949, 823, 740 and 702 cm^{-1}; δ (300 MHz) 1.07 (9 H, s, CMe_3), 4.18 (2 H, d, *J* 8 Hz, 1-H_2), 4.28 (2 H, d, *J* 5 Hz, 6-H_2), 5.57 (1 H, dt, $J_{1,2}$ 8, $J_{2,3}$ 11 Hz, 2-H), 5.88 (1 H, dt, $J_{5,6}$ 5, $J_{4,5}$ 15 Hz, 5-H), 6.16 (1 H, dd, $J_{2,3}$ 11, $J_{3,4}$ 11 Hz, 3-H), 6.60 (1 H, dd, $J_{3,4}$ 11, $J_{4,5}$ 15 Hz, 4-H), 7.37 and 7.67 (10 H, 2 x m, 2 x C_6H_5); m/z (CI; peaks > 50%) 388 (M + NH_4, 100%), 157 (50); R_f (pentane - ethyl acetate 20:1) 0.5, PMA stain and u.v. active.

1-(t-Butyldiphenylsilyloxy)hepta-(2E,4Z)-diene **29**

To a stirred solution of the chloride **28** (185 mg, 0.5 mmol) in THF (10 ml) at –78 °C under N_2 was added dropwise methylmagnesium bromide (1.5 M, 0.66 ml, 1.0 mmol). The solution was allowed to return to room temperature and stirred for 12 h. Saturated aq. ammonium chloride (20 ml) was added and the mixture was extracted with ether - pentane (2:1, 3 x 25 ml). The combined organic phase was washed with water (3 x 25 ml), brine, dried and evaporated. Chromatography of the residue (elution with pentane) gave the *title compound* **29** (138 mg, 79%) as a colourless oil (M + NH_4^+, 368.2396; $C_{23}H_{34}NOSi$ requires 368.2410); ν_{max} 3071, 3050, 3013, 2961, 2931, 2893, 2857, 1590, 1487, 1472, 1463, 1428, 1390, 1370, 1362, 1148, 1113, 1066, 1043, 1030, 1008, 998, 965, 949 and 871 cm^{-1}; δ (300 MHz) 1.01 (3 H, t, *J* 7.5 Hz, 7-H_3), 1.09 (9 H, s, CMe_3), 2.19 (2 H, dq, $J_{6,7}$ 7.5, $J_{5,6}$ 7.5 Hz, 6-H_2), 4.28 (2 H, d, *J* 5 Hz, 1-H_2), 5.45 (1 H, dt, $J_{5,6}$ 7.5, $J_{4,5}$ 11 Hz, 5-H), 5.75 (1 H, dt, $J_{1,2}$ 5, $J_{2,3}$ 15 Hz, 2-H), 5.98 (1 H, dd, $J_{4,5}$ 11, $J_{3,4}$ 11

Hz, 4-H), 6.60 (1 H, dd, $J_{3,4}$ 11, $J_{2,3}$ 15 Hz, 3-H), 7.42 and 7.69 (10 H, 2 x m, 2 x C_6H_5); m/z 368 ($M + NH_4^+$, 100%), 274 (30), 196 (25), 129 (75), 112 (90), 95 (80); R_f (pentane) 0.25, PMA stain and u.v. active.

Hepta-(2E,4Z)-dienal **30**

To a stirred solution of the silane **29** (100 mg, 0.28 mmol) in THF (5 ml) at 20 °C under N_2 was added tetra-*n*-butylammonium fluoride (TBAF) in THF (1 M, 0.5 ml, 0.5 mmol). After 3 h the solvent was evaporated and the residue purified by chromatography (elution with pentane - ether 4:1) to obtain *hepta-(2E,4Z)-dienol* (28 mg, 91%) as a colourless oil (M^+, 112.0887; $C_7H_{12}O$ requires 112.0883); δ_H (300 MHz) 0.96 (3 H, t, *J* 7.5 Hz, 7-H_3), 1.92 (1 H, s, OH), 2.17 (2 H, dq, $J_{5,6}$ 7.5, $J_{6,7}$ 7.5 Hz, 6-H_2), 4.15 (2 H, d, *J* 6 Hz, 1-H_2), 5.41 (1 H, dt, $J_{5,6}$ 7.5, $J_{4,5}$ 11 Hz, 5-H), 5.77 (1 H, dt, $J_{1,2}$ 6, $J_{2,3}$ 15 Hz, 2-H), 5.93 (1 H, dd, $J_{3,4}$ 11, $J_{4,5}$ 11 Hz, 4-H), 6.51 (1 H, dd, $J_{3,4}$ 11, $J_{2,3}$ 15 Hz, 3-H); δ_C 14.13, 21.00, 63.38, 126.64, 126.95, 131.52, 134.59; m/z (EI) 112 (M^+, 16%), 95 (100), 83 (62), 67 (15); R_f (pentane - ether 4:1) 0.3, PMA stain and u.v. active. To a stirred solution of NMO (33 mg, 0.33 mmol) and 4Å sieves (10 mg) in dichloromethane (1 ml) at room temperature under N_2 was added hepta-(2*E*,4*Z*)-dienol (25 mg, 0.22 mmol) in dichloromethane (1 ml). TPAP (5 mol %) was then added and the solution stirred for 3 h. The mixture was filtered through a short plug of silica gel (elution with pentane - ether 8:1). Concentration of the eluate at 1 atm. gave the *title compound* **30** (18 mg, 73%) as a pale yellow liquid ($M + NH_4^+$, 128.1078; $C_7H_{14}NO$ requires 128.1075); ν_{max} 3436, 2104, 1672, 1631, 1461, 1156 and 1115 cm^{-1}; δ_H (300 MHz) 1.06 (3 H, t, *J* 7.5 Hz, 7-H_3), 2.34 (2 H, dq, $J_{5,6}$ 7.5, $J_{6,7}$ 7.5 Hz, 6-H_2), 5.97 (1 H, dt, $J_{5,6}$ 7.5, $J_{4,5}$ 11 Hz, 5-H), 6.11 (1 H, dd, $J_{1,2}$ 8, $J_{2,3}$ 15 Hz, 2-H), 6.21 (1 H, dd, $J_{3,4}$ 11, $J_{4,5}$ 11 Hz, 4-H), 7.43 (1 H, dd, $J_{3,4}$ 11, $J_{2,3}$ 15 Hz, 3-H), 9.58 (1 H, d, *J* 8 Hz, 1-H); δ_C 13.73, 21.67, 125.99, 131.63, 145.25, 146.65, 193.89; m/z 128 ($M + NH_4$, 100%), 111 ($M + H$, 55), 88 (25); R_f (pentane - ether 3:1) 0.6, PMA stain and u.v. active.

(1,3E,5Z) Octatriene **31**[11]

To a stirred solution of methylene triphenylphosphorane [prepared from methyltriphenylphosphonium bromide (97 mg, 0.27 mmol) and *n*-butyllithium (2.5 M in hexane, 0.11 ml, 0.27 mmol) in THF (1 ml) at 0 °C] under N_2 was added the aldehyde **30** (15 mg, 0.14 mmol) in THF (0.5 ml). After 1 h the solution was allowed to warm to room temperature and after a further 1 h water (5 ml) was added and the mixture extracted with pentane (3 x 5 ml). The combined organics washed with water (3 x 5 ml), brine (10 ml), dried and the solvent removed at atmospheric pressure. The residue was applied to a plug of silica, eluted with pentane, and the eluate carefully distilled off at atmospheric pressure to obtain the *title compound* **31** (13 mg, 85%); ν_{max} 2967, 1933, 2874, 2856, 2253, 1640, 1625, 1463, 1096, 1067, 1007 and 907 cm^{-1}; δ (300 MHz) 0.95 (3 H, t, *J* 7.5 Hz, 8-H_3), 2.16 (2 H, dq, $J_{6,7}$ 7.5, $J_{7,8}$ 7.5 Hz, 7-H_2), 5.02 (1 H, d, $J_{1',2}$ 10.5 Hz, 1'-H), 5.15 (1 H, d, $J_{1,2}$ 16.5 Hz, 1-H), 5.42 (1 H, dt, $J_{6,7}$ 7.5, $J_{5,6}$ 11 Hz, 6-H), 5.93 (1 H, t, $J_{5,6}$ 11, $J_{4,5}$ 11 Hz, 5-H), 6.15 (1 H, dd, $J_{2,3}$ 10.5, $J_{3,4}$ 14.5 Hz, 3-H), 6.35 (1 H, ddd, $J_{1',2}$ 10.5, $J_{2,3}$ 10.5, $J_{1,2}$ 16.5 Hz, 2-H) and 6.45 (1 H, dd, $J_{4,5}$ 11, $J_{3,4}$ 14.5 Hz, 4-H) (the assignments for 3-H and 4-H are tentative and may be reversed); λ_{max} (hexane) 253, 263, 273 nm.

General procedure for the in situ *reaction of the lactol* **32** *with organometallic reagents (Table 2)*

A stirred solution of the lactone (±)-**4** (110 mg, 1.0 mmol) in THF (5 ml) at –78 °C under N_2 was treated with a solution of DIBAH in hexane (1.0 M, 1.0 ml, 1.0 mmol). The reaction mixture was stirred at –78 °C for 1 h and then treated with the additive (if any), and then the organometallic reagent (3 mol equiv.). After a further 1 h at –78 °C the mixture was allowed to warm to room temperature over 1 h and stirred at room temperature to ensure completion (typically 1 h). The reaction mixture was cooled to 0 °C, quenched with 1 M hydrochloric acid (20 ml), saturated with NaCl and extracted with ether (3 x 20 ml). The combined extract was washed with brine (20 ml), dried and evaporated. The residue was analysed by 300 MHz ^1H n.m.r. spectroscopy to determine the composition of the reaction mixture and the products then isolated by flash chromatography (elution with ethyl acetate - dichloromethane mixtures as required). See Table 2 for product ratios and yields. The minor products **35b** and **35c** were evident in n.m.r. spectra but were not fully characterised.

1S*,1'R*,4'S**-4-Hydroxymethyl-2-cyclobutene-1-ethanol* **34a**
A colourless oil (M + NH_4^+, 146.1180; $C_7H_{16}NO_2$ requires 146.1181); ν_{max} 3304br, 3045, 2969, 1490, 1373, 1314, 1290, 1170, 1093, 1076, 1053, 1021, 971, 882 and 719 cm^{-1}; δ (300 MHz) 1.21 (3 H, d, *J* 6 Hz, 2-H_3), 2.86 (1 H, dd, $J_{1',4'}$ 4, $J_{1,1'}$ 10 Hz, 1'-H), 3.17 (1 H, ddd, $J_{1',4'}$ 4,$J_{1'',4'}$ 4 and 11.5 Hz, 4'-H), 3.66 (1 H, dd, $J_{1'',4'}$ 11.5, J_{gem} 11.5 Hz, 1''-H), 3.78–3.93 (4 H, m, 1-H, 1''-H and 2 OH), 5.99 (2 H, s, 2'-H and 3'-H); m/z 146 (M + NH_4, 100%), 129 (M + H, 45), 128 (43), 93 (20); R_f (dichloromethane - ethyl acetate 1:1) 0.32, vanillin and $KMnO_4$ stain.

1S*,1'R*,4'S**-4-Hydroxymethyl-2-cyclobutene-1-propanol* **34b**
A colourless oil (M + NH_4^+, 160.1331; $C_8H_{18}NO_2$ requires 160.1337); ν_{max} 3308br, 3045, 2963, 2923, 1463, 1379, 1343, 1290, 1191, 1161, 1104, 1086, 1056, 1020, 967, 771 and 724 cm^{-1}; δ (300 MHz) 0.98 (3 H, t, *J* 7.5, 3-H_3), 1.35–1.45 (1 H, m, 7 lines, 2-H), 1.59–1.68 (1 H, m, 12 lines, 2-H), 2.92 (1 H, dd, $J_{1',4'}$ 4, $J_{1,1'}$ 10.5 Hz, 1'-H), 3.18 (1 H, ddd, $J_{1',4'}$ 4, $J_{1'',4'}$ 4 and 11.5 Hz, 4'-H), 3.57–3.83 (5 H, m, 1-H, 1''-H_2 and 2 OH), 6.00 (2 H, s, 2'-H and 3'-H); m/z 160 (M + NH_4, 100%), 143 (M + H, 100), 142 (62), 125 (85), 107 (82); R_f (dichloromethane - ethyl acetate 3:2) 0.45, vanillin and $KMnO_4$ stain.

1S*,1'R*,4'S**-4-Hydroxymethyl-2-cyclobutene-1-butanol* **34c**
A colourless oil (M + NH_4^+, 174.1497; $C_9H_{20}NO_2$ requires 174.1494); ν_{max} 3308br, 3046, 2959, 1643, 1466, 1379, 1323, 1290, 1214, 1191, 1159, 1114, 1084, 1056, 1030, 988, 943 and 725 cm^{-1}; δ (300 MHz) 0.91 (3 H, t, *J* 6.5, 4-H_3), 1.31–1.58 (4 H, m, 2-H_2 and 3-H_2), 2.89 (1 H, dd, $J_{1',4'}$ 4, $J_{1,1'}$ 10 Hz, 1'-H), 3.17 (1 H, ddd, $J_{1',4'}$ 4, $J_{1'',4'}$ 4 and 11 Hz, 4'-H), 3.62–3.81 (3 H, m, 1-H and 1'-H_2), 3.90 (2 H, br s, 2 x OH), 5.99 (2 H, s, 2'-H and 3'-H); m/z 174 (M + NH_4, 100%), 157 (M + H, 100), 139 (62), 121 (60); R_f (ethyl acetate - dichloromethane 1:1) 0.3, vanillin and $KMnO_4$ stain.

1S*,1'R*,4'S**-4-Hydroxymethyl-2-cyclobutene-1-pentanol* **34d**
A colourless oil (M + NH_4^+, 188.1656; $C_{10}H_{22}NO_2$ requires 188.1650); ν_{max} 3326br, 3045, 2956, 2930, 2872, 1658, 1640, 1467, 1379, 1320, 1290, 1263, 1190, 1157, 1115, 1076, 1052, 1021, 991 and 886 cm^{-1}; δ (300 MHz) 0.88 (3 H, t, J 7 Hz, 5-H_3), 1.21–1.59 (6 H, m, 2-H_2 , 3-H_2 and 4-H_2), 2.90 (1 H, dd, $J_{1',4'}$ 4, $J_{1,1'}$ 10.5 Hz, 1'-H), 3.17 (1 H, ddd, $J_{1',4'}$ 4, $J_{1'',4'}$ 4 and 11.5 Hz, 4'-H), 3.62–3.93 (3 H, m, 1-H and 1''-H_2), 4.04 (2 H, br s, 2 x OH), 5.99 (2 H, s, 2'-H and 3'-H); m/z 188 (M + NH_4, 100%), 171 (M + H, 50), 153 (75), 135 (80); R_f (dichloromethane - ethyl acetate 3:1) 0.5, vanillin and $KMnO_4$ stain.

1S*,1'R*,4'S**-4-Hydroxymethyl-2-cyclobutene-1-heptanol* **34e**
A colourless oil (M + H^+, 199.1700; $C_{12}H_{23}O_2$ requires 199.1698); ν_{max} 3305br, 3045, 2928, 2858, 1467, 1290, 1154, 1081, 1053, 1022, 939 and 726 cm^{-1}; δ (300 MHz) 0.86 (3 H, t, *J* 6.5 Hz, 7-H_3), 1.26–1.56 (10 H, m, 2-H_2 , 3-H_2, 4-H_2, 5-H_2 and 6-H_2), 2.91 (1 H, dd, $J_{1',4'}$ 4, $J_{1,1'}$ 10.5 Hz, 1'-H), 3.18 (1 H, ddd, $J_{1',4'}$ 4, $J_{1'',4'}$ 4 and 11.5 Hz, 4'-H), 3.64–3.83 (5 H, m, 1-H, 1''-H_2 and 2 x OH), 6.00 (2 H, s, 2'-H and 3'-H); m/z 216 (M + NH_4, 100%), 199 (M + H, 28), 181 (42), 163 (42); R_f (dichloromethane - ether 4:1) 0.4, vanillin and $KMnO_4$ stain.

1R*,1'R*,4'S**-4-Hydroxymethyl-2-cyclobutene-1-ethanol* **35a**
A colourless oil (M + NH_4^+, 146.1178; $C_7H_{16}NO_2$ requires 146.1181); ν_{max} 3318br, 3050, 2966, 2926, 1456, 1373, 1287, 1125, 1049, 770 and 733 cm^{-1}; δ (300 MHz) 1.26 (3 H, d, *J* 6.5 Hz, 2-H_3), 1.87 (2 H, br s, 2 x OH), 3.01 (1 H, dd, $J_{1,1'}$ 3, $J_{1',4'}$ 4 Hz, 1'-H), 3.13 (1 H, ddd, $J_{1',4'}$ 4, $J_{1'',4'}$ 4 and 4 Hz, 4'-H), 3.87 (2 H, d, *J* 4 Hz, 1''-H_2), 4.07 (1 H, dq, $J_{1,1'}$ 3, $J_{1,2}$ 6.5 Hz 1-H), 6.19 (2 H, s, 2'-H and 3'-H); m/z 146 (M + NH_4, 100%), 129 (M + H, 95), 111 (25), 93 (20); R_f (dichloromethane - ethyl acetate 1:1) 0.2, vanillin and $KMnO_4$ stain.

1R*,1'R*,4'S**-4-Hydroxymethyl-2-cyclobutene-1-pentanol* **35d**
A colourless oil (M + NH_4^+, 188.1657; $C_{10}H_{22}NO_2$ requires 188.1650); ν_{max} 3309, 3047, 2956, 2930,

2872, 1467, 1378, 1125, 1051, 1019, 768 and 741 cm^{-1}; δ (300 MHz) 0.89 (3 H, t, *J* 7 Hz, 5-H_3), 1.18–1.54 (6 H, m, 2-H_2 , 3-H_2 and 4-H_2), 3.05–3.07 (1 H, m, 1'-H), 3.11–3.15 (1 H, m, 4'-H), 3.81–3.86 (5 H, m, 1-H, 1"-H_2 and 2 x OH), 6.13 and 6.17 (each 1 H, d, *J* 3 Hz, 2'-H and 3'-H); m/z 188 (M + NH_4, 100%), 171 (M + H, 98), 153 (30), 135 (40); R_f (dichloromethane - ethyl acetate 3:1) 0.45, vanillin and $KMnO_4$ stain.

1R*,1'R*,4'S*-*4-Hydroxymethyl-2-cyclobutene-1-heptanol* **35e**
A colourless oil (M + H^+, 199.1693; $C_{12}H_{23}O_2$ requires 199.1698); ν_{max} 3305br, 3049, 2929, 2858, 1467, 1059, 1021, 989, 909, 770 and 734 cm^{-1}; δ (300 MHz) 0.86 (3 H, t, *J* 7 Hz, 7-H_3), 1.27–1.58 (10 H, m, 2-H_2, 3-H_2, 4-H_2, 5-H_2 and 6-H_2), 3.04–3.06 (1 H, m, 1'-H), 3.10–3.17 (1 H, m, 4'-H), 3.39 (2 H, br s, 2 x OH), 3.76–3.96 (3 H, m, 1-H and 1"-H_2), 6.11 and 6.16 (each 1 H, d, *J* 3 Hz, 2'-H and 3'-H); m/z 216 (M + NH_4, 80%), 199 (M + H, 100), 181 (22), 163 (38); R_f (dichloromethane - ether 4:1) 0.35, vanillin and $KMnO_4$ stain.

exo-*4-Methyl-3-oxabicyclo[3.2.0]hept-6-en-2-one* **36a**
To a stirred solution of **34a** (128 mg, 1.0 mmol) in dichloromethane (10 ml) at room temperature under N_2 was added NMO (351 mg, 3.0 mmol), powdered 4Å sieves (500 mg) and TPAP (35 mg, 0.1 mmol).[26] After stirring for 24 h the mixture was filtered through a short column of silica (elution with dichloromethane - hexane 5:1), which gave the *title compound* **36a** (88 mg, 71%) as a colourless oil (M + H^+, 125.0608; $C_7H_9O_2$ requires 125.0602); ν_{max} 1756 cm^{-1}; δ (300 MHz) 1.28 (3 H, d, *J* 6.5 Hz, Me), 3.15 (1 H, dd, $J_{4,5}$ *ca.* 1, $J_{1,5}$ 3.4 Hz, 5-H), 3.65 (1 H, d, $J_{1,5}$ 3.4 Hz, 1-H), 4.51 (1 H, br q, *J ca.* 1, 6.5 Hz, 4-H), 6.27 (1 H, d, *J* 2.8 Hz, 6-H), and 6.31 (1 H, d, *J* 2.8 Hz, 7-H); m/z (CI; peaks > 2%) 142 (M + NH_4, 100%), 125 (M + H, 5); R_f (dichloromethane - hexane 4:1) 0.3, $KMnO_4$ stain.

exo-*4-Hexyl-3-oxabicyclo[3.2.0]hept-6-en-2-one* **36e**
The procedure used for the lactone **36a** was repeated with the diol **34e** (0.5 mmol scale). Elution with dichloromethane gave the *title compound* **36e** (59 mg, 61%) as an oil (M + H^+, 195.1385; $C_{12}H_{19}O_2$ requires 195.1385); ν_{max} 1756 cm^{-1}; δ (300 MHz) 0.84 (3 H, br t, *J* 7.1 Hz, 6'-H_3), 1.2–1.4 (8 H, m, 2',3',4',5'-H_8), 1.45–1.6 (2 H, m, 1'-H_2), 3.21 (1 H, dd, $J_{4,5}$ *ca.* 1, $J_{1,5}$ 3.3 Hz, 5-H), 3.62 (1 H, d, $J_{1,5}$ 3.3 Hz, 1-H), 4.36 (1 H, br t, *J ca.* 1, 6.4 Hz, 4-H), 6.27 (1 H, d, *J* 2.7 Hz, 6-H), and 6.31 (1 H, d, *J* 2.7 Hz, 7-H); m/z 212 (M + NH_4, 100%), 195 (M + H, 10); R_f (dichloromethane - hexane 4:1) 0.3, $KMnO_4$ stain.

endo-*4-Methyl-3-oxabicyclo[3.2.0]hept-6-en-2-one* **37a**
The procedure used for the lactone **36a** was repeated with the diol **35a** (0.5 mmol scale). The *title compound* **37a** (42 mg, 68%) was isolated as a pale yellow oil (M + H^+, 142.0876; $C_7H_{12}NO_2$ requires 142.0868); ν_{max} 1757 cm^{-1}; δ (300 MHz) 1.37 (3 H, d, *J* 6.4 Hz, Me), 3.56 (1 H, dd, $J_{4,5}$ 6.8, $J_{1,5}$ 3.5 Hz, 5-H), 3.64 (1 H, d, $J_{1,5}$ 3.5 Hz, 1-H), 4.57 (1 H, dq, *J* 6.4, 6.8 Hz, 4-H), 6.28 (1 H, d, *J* 2.6 Hz, 6-H), and 6.32 (1 H, d, *J* 2.6 Hz, 7-H); m/z 142 (M + NH_4, 100%); R_f (dichloromethane - hexane 4:1) 0.3, $KMnO_4$ stain.

endo-*4-Hexyl-3-oxabicyclo[3.2.0]hept-6-en-2-one* **37e**
The procedure used for the lactone **36a** was repeated with the diol **35e** (0.2 mmol scale). Elution of the column with dichloromethane gave the *title compound* **37e** (14 mg, 57%) as a colourless oil (M + H^+, 195.1389; $C_{12}H_{19}O_2$ requires 195.1385); ν_{max} 1759 cm^{-1}; δ (300 MHz) 0.87 (3 H, br t, *J* 7.0 Hz, 6'-H_3), 1.2–1.4 (8 H, m, 2',3',4',5'-H_8), 1.55–1.65 (1 H, m, 1'-H), 1.75–1.85 (1 H, m, 1'-H), 3.57 (1 H, dd, $J_{4,5}$ 6.7, $J_{1,5}$ 3.5 Hz, 5-H), 3.65 (1 H, d, $J_{1,5}$ 3.5 Hz, 1-H), 4.38 (1 H, dt, *J* 6.7, 6.4 Hz, 4-H), 6.28 (1 H, d, *J* 2.7 Hz, 6-H) and 6.32 (1 H, d, *J* 2.7 Hz, 7-H); m/z (CI; peaks > 5%) 212 (M + NH_4, 100%), 195 (M + H, 8); R_f (dichloromethane - hexane 4:1) 0.3, $KMnO_4$ stain.

1S*,1'R*,4'S**-4-[[(4-Methoxyphenyl)methoxy]methyl]-2-cyclobutene-1-ethanol* **43**
To a stirred suspension of sodium hydride (60% oil dispersion, 40 mg, 1.0 mmol) in THF (5 ml) at room temperature under N_2 was added the diol **34a** (128 mg, 1.0 mmol) in THF (1 ml), and the mixture stirred for 0.5 h. 4-Methoxybenzyl bromide (200 mg, 1.0 mmol) was then added, and the stirring continued for 3 h. The reaction mixture was then poured onto ether (20 ml), washed with 10% aq. K_2CO_3 (10 ml), brine (10 ml), dried and evaporated. ^{1}H N.m.r. analysis of the yellow residue indicated a 4:1 mixture of the compounds **43** and **44** which were resolved by flash chromatography (elution with petroleum - ethyl acetate 5:1). Early fractions contained the *title compound* **43** (164 mg, 66%), a pale yellow oil (M + H$^+$, 249.1497; $C_{15}H_{21}O_3$ requires 249.1490); ν_{max} 3457br, 2967, 2906, 1613, 1514, 1369, 1303, 1250, 1175, 1097, 1071, 1036, 822 and 725 cm^{-1}; δ (300 MHz) 1.16 (3 H, d, *J* 6 Hz, 2-H$_3$), 2.84 (1 H, dd, $J_{1',4'}$ 4, $J_{1,1'}$ 10 Hz, 1'-H), 3.26 (1 H, ddd, $J_{1',4'}$ 4, $J_{1'',4'}$ 4 and 12 Hz, 4'-H), 3.56 (1 H, dd, J_{gem} 10, $J_{1'',4'}$ 12 Hz, 1''-H), 3.65 (1 H, dd, $J_{1'',4'}$, J_{gem} 10 Hz, 1''-H), 3.76–3.81 (4 H, m, OMe and 1-H), 4.24 (1 H, s, OH), 4.44 and 4.48 (each 1 H, d, J_{gem} 13 Hz, OCH$_2$Ar), 5.96 and 6.00 (each 1 H, d, *J* 3 Hz, 2'-H and 3'-H), 6.85 (2 H, d, *J* 8.5 Hz, 3,5-ArH), 7.24 (2 H, *J* 8.5 Hz, 2,6-ArH); m/z 249 (M + H, 15%), 121 (100); R$_f$ (petroleum - ethyl acetate 3:1) 0.5, PMA stain.
Later fractions of the eluate afforded 1'S*,4'R*,1''S**-4-[1-[(4-methoxyphenyl)methoxy]ethyl]-2-cyclobutene-1-methanol* **44** (37 mg, 15%) as a pale yellow oil (M + H$^+$, 249.1491; $C_{15}H_{21}O_3$ requires 249.1490); ν_{max} 3458br, 2968, 2897, 2837, 1612, 1514, 1465, 1442, 1422, 1373, 1303, 1251, 1174, 1101, 1078, 1034, 822 and 722 cm^{-1}; δ (300 MHz) 1.28 (3 H, d, *J* 6 Hz, 2''-H$_3$), 2.98 (1 H, dd, $J_{1',4'}$ 4, $J_{4',1''}$ 10 Hz, 4'-H), 3.14–3.19 (1 H, m, 1'-H), 3.57–3.76 (4 H, m, 1-H$_2$, 1''-H and OH), 3.77 (3 H, s, OMe), 4.28 and 4.59 (each 1 H, d, J_{gem} 10.5 Hz, OCH$_2$Ar), 6.00 and 6.03 (each 1 H, d, *J* 3 Hz, 2'-H and 3'-H), 6.85 (2 H, d, *J* 8.5 Hz, 3,5-ArH), 7.26 (2 H, *J* 8.5 Hz, 2,6-ArH); m/z 266 (M + NH$_4$, 6%), 249 (M + H, 15), 138 (25), 121 (100); R$_f$ (ethyl acetate - petroleum 1:3) 0.4, PMA stain.

cis-*1-[4-[[(4-Methoxyphenyl)methoxy]methyl]-2-cyclobuten-1-yl]ethanone* **39**
To a stirred solution of the monoether **43** (248 mg, 1.0 mmol) in dichloromethane (10 ml) at room temperature under N_2 was added NMO (351 mg, 3.0 mmol), powdered 4Å sieves (500 mg) and TPAP (35 mg, 0.1 mmol). After stirring for 4 h the mixture was filtered through a short column of silica (elution with petroleum - ether 3:1), and the eluate evaporated to obtain the *title compound* **39** (175 mg, 71%) as a colourless oil (M + H$^+$, 247.1336; $C_{15}H_{19}O_3$ requires 247.1334); ν_{max} 2913, 2857, 2838, 1704, 1613, 1586, 1514, 1465, 1358, 1303, 1249, 1174, 1095, 1076, 1035, 821 and 731 cm^{-1}; δ (300 MHz) 2.15 (3 H, s, 2-H$_3$), 3.35–3.55 (3 H, m, 1''-H$_2$ and 4'-H), 3.77 (3 H, s, OMe), 3.82 (1 H, d, $J_{1',4'}$ 4 Hz, 1'-H), 4.28 and 4.32 (each 1 H, d, J_{gem} 11.5 Hz, OCH$_2$Ar), 6.14–6.17 (2 H, m, 2'-H and 3'-H), 6.83 (2 H, d, *J* 8.5 Hz, 3,5-ArH), 7.18 (2 H, *J* 8.5 Hz, 2,6-ArH); m/z 264 (M + NH$_4$, 18%), 247 (M + H, 2), 154 (52), 137 (45), 121 (100), 109 (32); R$_f$ (petroleum - ethyl acetate 3:1) 0.45, vanillin stain.

N-*Methoxy*-N-*methyl* cis-*4-(hydroxymethyl)-2-cyclobutene-1-carboxamide* **41**
To a stirred suspension of *N,O*-dimethylhydroxylamine hydrochloride (1.17 g, 12 mmol) in dichloromethane (30 ml) at 0 °C under N_2 was added dropwise trimethylaluminium in hexanes (2.0 M, 6.0 ml, 12 mmol). The mixture was stirred at 0 °C for 20 min and treated dropwise with a solution of the lactone (±)-**4** (660 mg, 6 mmol) in dichloromethane (10 ml). After 1 h the reaction was quenched with 2 M hydrochloric acid (25 ml), saturated with NaCl and extracted with dichloromethane (3 x 25 ml). The combined extract was washed with water (25 ml), brine (25 ml), dried and evaporated to give the *title compound* **41** (855 mg, 84%) as a pale yellow oil (M + H$^+$, 172.0972; $C_8H_{14}NO_3$ requires 172.0973); ν_{max} 3428br, 2937, 1762, 1640, 1425, 1385, 1295, 1174, 1105, 1068, 1013, 984 and 726 cm^{-1}; δ (300 MHz) 3.17 (3 H, s, NMe), 3.32–3.38 (1 H, m, 4-H), 3.60–3.75 (3 H, m, 1'-H$_2$ and OH), 3.69 (3 H, s, OMe), 4.04 (1 H, br s, 1-H), 6.13 (2 H, br s, 2-H and 3-H); m/z 189 (M + NH$_4$, 5%), 171 (M + H, 100), 154 (10), 128 (15).

cis-1-[4-(t-Butyldiphenylsilyloxymethyl)-2-cyclobuten-1-yl]ethanone **40**

To a stirred solution of the amide **41** (513 mg, 3.0 mmol) in DMF - THF (1:1, 10 ml) at room temperature under N_2 was added imidazole (224 mg, 3.3 mmol) followed by *t*-butyldiphenylsilyl chloride (906 mg, 3.3 mmol). After 3 h water (15 ml) was added, and the mixture extracted with ether (3 x 25 ml). The combined extract was washed with water (25 ml), brine (25 ml), dried and evaporated to give N-*methoxy*-N-*methyl* *cis-4-(t-butyldiphenylsilyloxymethyl)-2-cyclobutene-1-carboxamide* (970 mg, 79%) as a pale yellow oil (M + H^+, 410.2129; $C_{24}H_{32}NO_3Si$ requires 410.2151); ν_{max} 1653 cm^{-1}; δ (300 MHz) 1.02 (9 H, s, CMe_3), 3.07 (3 H, s, NMe), 3.32–3.38 (1 H, m, 4-H), 3.58 (3 H, s, NOMe), 3.67 (1 H, dd, $J_{1',4}$ 7.5, J_{gem} 10 Hz, 1'-H), 3.87 (1 H, dd, $J_{1',4}$ 7, J_{gem} 10 Hz, 1'-H), 4.09 (1 H, br s, 1-H), 6.13 (1 H, br s, 3-H), 6.23 (1 H, br s, 2-H), 7.31–7.42 and 7.62–7.65 (10 H, 2 x m, 2 x C_6H_5); m/z 410 (M + H, 50), 207 (18), 154 (20), 145 (55), 128 (100); R_f (dichloromethane - ethyl acetate 4:1) 0.65, $KMnO_4$ stain. To a stirred solution of the above amide (409 mg, 1.0 mmol) in THF (5 ml) at 0 °C under N_2 was added methylmagnesium bromide (1.5 M in toluene - THF 3:1, 1.3 ml, 2.0 mmol). The reaction was allowed to warm to room temperature and after 3 h recooled to 0 °C and 2 M hydrochloric acid (10 ml) was added dropwise. The mixture was extracted with ether (3 x 15 ml) and the combined extract washed with water (25 ml), brine (25 ml) dried and evaporated. The residue was chromatographed (elution with petroleum - ether 15:1) to obtain the *title compound* **40** (313 mg, 86%) as a colourless oil (M + H^+, 365.1938; $C_{23}H_{29}O_2Si$ requires 365.1937); ν_{max} 3071, 3051, 2959, 2931, 2894, 2858, 1705, 1472, 1463, 1428, 1357, 1172, 1141, 1113, 1091, 1065, 1007, 999, 910, 824, 737 and 702 cm^{-1}; δ (300 MHz) 1.01 (9 H, s, CMe_3), 2.25 (3 H, s, MeCO), 3.40–3.42 (1 H, m, 4'-H), 3.68–3.71 (2 H, m, 1"-H), 3.86 (1 H, d, $J_{1',4'}$ 4.5 Hz, 1'-H), 6.09 (1 H, br s, 3'-H), 6.17 (1 H, br s, 2'-H), 7.33–7.41 and 7.60–7.67 (10 H, 2 x m, 2 x C_6H_5); m/z 382 (M + NH_4, 15%), 365 (M + H, 80), 274 (100), 149 (30), 133 (70), 116 (45); R_f (petroleum - ether 8:1) 0.5, $KMnO_4$ stain.

cis-4-(1-Oxoethyl)-2-cyclobutene-1-methanol **38**

To a stirred solution of the ketone **40** (364 mg, 1.0 mmol) in acetonitrile (3 ml) at room temperature was added a solution of aqueous hydrofluoric acid (40% HF; 0.1 ml) in acetonitrile (5 ml). After 1 h the mixture was concentrated *in vacuo* and purified by chromatography (elution with dichloromethane - ether 2:1), which gave the *title compound* **38** as a 1:3 mixture with the *2-methyl-3-oxabicyclo[3.2.0]hept-6-en-2-ols* **42** (total 79 mg, 63%). A colourless oil (M + H^+, 127.0758; $C_7H_{11}O_2$ requires 127.0759); ν_{max} 3042, 2965, 2959, 2942, 2879, 1694, 1384, 1351, 1255, 1114, 1077, 1030, 979, 938, 929, 817 and 754 cm^{-1}; δ (300 MHz) [**38**] 2.24 (3 H, s, MeCO), 6.15 and 6.24 (each 1 H, d, *J* 3 Hz, 2'-H and 3'-H) (the peaks corresponding to 1'-H, 4'-H and 1-H_2 were obscured); [**42**] 1.49 (3 H, s, 2-Me), 3.24 (1 H, d, $J_{1,5}$ 3.4 Hz), 3.43 (1 H, dd, $J_{1,5}$ 3.4, $J_{4,5}$ 5.3 Hz, 5-H), 3.69 (1 H, d, J_{gem} 9.2 Hz, 4-H), 3.77 (1 H, dd, $J_{4,5}$ 5.3, J_{gem} 9.2 Hz, 4-H), 6.05 and 6.11 (each 1 H, d, *J* 3 Hz, 6-H and 7-H); m/z 144 (M + NH_4, 62%), 127 (M + H, 46), 109 (100); R_f (dichloromethane - ether 1:1) 0.4, vanillin stain.

General procedure for reductions of the ketones **38–40** *(Table 3)*

Method A (entries 1–6): A stirred solution of the ketone **38** (25 mg, 0.2 mmol) in THF or ether (2 ml) at –78 °C under N_2 was treated with the additive (0.2 mmol) (if any) followed, after 2 h, with the reducing agent (3 mol equiv.). After a further 4 h at –78 °C the mixture was allowed to warm up to room temperature and stirred until the reaction was complete (typically overnight). The reaction mixture was cooled to 0 °C and treated with 2 M hydrochloric acid (3 ml), saturated with NaCl and extracted with ether (3 x 5 ml). The combined extract was washed with brine (5 ml), dried and evaporated. The residue was analyzed by 300 MHz ^1H n.m.r. spectroscopy to determine the composition of the reaction mixture (see Table 3 for product ratios and yields). The products were resolved by chromatography (elution with dichloromethane - ethyl acetate 10:1). The data for **34a** and **35a** are given above. The procedure for run 3 was as above but the solvent was methanol and the reaction was carried out at room temperature. The procedure for run 6 was as follows: To a stirred solution of the ketone **38** (25 mg, 0.2 mmol) in THF (2 ml) at room temperature was added sodium triacetoxyborohydride (212 mg, 1.0 mmol). After stirring for 4 d the solvent was removed by evaporation, brine (5 ml) was added

and the mixture extracted with dichloromethane (5 x 5 ml). The combined extract was dried, evaporated and analysed as above.

Method B (entries 7–10): A stirred solution of ketone **39** (25 mg, 0.1 mmol) in THF (1 ml) at –78 °C under N_2 was treated with the reducing agent (3 equiv.). After 2 h at –78 °C the mixture was allowed to warm to 0 °C over a further 2 h, quenched with 2 M hydrochloric acid (3 ml), saturated with NaCl and extracted with ether (3 x 5 ml). The combined extract was washed with brine (5 ml), dried and evaporated. The residue was analysed and resolved as for method A.

Method C (entry 11): To a stirred solution of **39** (12 mg, 0.05 mmol) in THF (1 ml) at –78 °C under Ar was added a solution of potassium tris(*sec*-butyl)borohydride (K-selectride) in THF (1.0 M; 0.1 ml, 0.1 mmol). The reaction mixture was maintained at –78 °C for 2 h and then allowed to stir at room temperature for 0.5 h. Aqueous sodium hydroxide (10%; 2 ml) was added and the mixture was extracted with ether (3 x 10 ml). The combined extracts were washed with brine, dried, and evaporated. The residue was analysed as for method A.

Method D (entry 12): To prepare 0.1 M $Zn(BH_4)_2$ in ether,[39] a stirred suspension of sodium borohydride (37.8 mg, 1.0 mole) in ether (4.5 ml) under Ar was treated with a solution of zinc chloride in ether (1.0 M, 0.5 ml, 0.5 mmol). The mixture was stirred at room temperature for 3 h and left standing until the precipitation of white solid had ceased. The supernatant was used for the following reduction step. To a stirred solution of **39** (12 mg, 0.05 mmol) in ether (1 ml) at 0 °C under Ar was added the solution of zinc borohydride in ether (0.1 M, 1.0 ml, 0.1 mmol). The reaction mixture was maintained at 0 °C for 1.5 h and then quenched with saturated aqueous ammonium chloride (2 ml). After stirring at 0 °C for 10 min, the mixture was extracted with ether (3 x 10 ml) and the combined extracts washed with brine, dried, and evaporated. The residue was analysed as for method A.

Method E (entries 13–19): A stirred solution of ketone **40** (36 mg, 0.2 mmol) in THF (3 ml) at –78 °C under N_2 was treated with the additive (0.2 mmol) (if any), and after 1 h the reducing agent (3 mol equiv.). After a further 2 h at –78 °C the mixture was allowed to warm to 0 °C, quenched with 2 M hydrochloric acid (5 ml), saturated with NaCl and extracted with ether (3 x 5 ml). The combined extract was washed with brine (5 ml), dried and evaporated. The products were isolated by chromatography (elution with petroleum - ether 10:1), which gave 1S*,1'R*,4'S*-*4-(t-butyldiphenylsilyloxy)methyl-2-cyclobutene-1-ethanol* **46** as a colourless oil (M + H^+, 367.2085; $C_{23}H_{31}O_2Si$ requires 367.2093); ν_{max} ($CDCl_3$) 3478, 3071, 3048, 2963, 2931, 2893, 2859, 1740, 1590, 1472, 1446, 1428, 1392, 1369, 1299, 1113, 1064, 1035, 1007, 999, 823, 807, 740 and 720 cm^{-1}; δ (300 MHz) 1.04 (9 H, s, CMe_3), 1.25 (3 H, d, *J* 6 Hz, 2-H_3), 2.97 (1 H, dd, $J_{1',4'}$ 3.5, $J_{1,1'}$ 10 Hz, 1'-H), 3.16–3.22 (1 H, m, 4'-H), 3.77–3.86 (2 H, m, 1"-H_2), 3.93–4.02 (1 H, m, 1-H), 4.56 (1 H, s, OH), 5.83 and 6.00 (each 1 H, d, *J* 3 Hz, 2'-H and 3'-H), 7.35–7.46 and 7.67–7.70 (10 H, 2 x m, 2 x C_6H_5); m/z 384 (M + NH_4, 48%), 367 (M + H, 100), 274 (15); R_f (petroleum - ether 8:1) 0.45, $KMnO_4$ stain.

Later fractions of the eluate gave 1R*,1'R*,4'S*-*4-(t-butyldiphenylsilyloxy)methyl-2-cyclobutene-1-ethanol* **47** as a colourless oil (M + H^+, 367.2121; $C_{23}H_{31}O_2Si$ requires 367.2093); ν_{max} 3402, 2962, 2931, 2893, 2859, 1473, 1428, 1113, 1074, 1008, 999, 909, 824, 734 and 702 cm^{-1}; δ (300 MHz) 1.03 (9 H, s, CMe_3), 1.25 (3 H, d, *J* 6 Hz, 2-H_3), 2.98 (1 H, dd, $J_{1',4'}$ 4, $J_{1,1'}$ 4 Hz, 1'-H), 3.05 (1 H, ddd, $J_{1',4'}$ 4, $J_{1'',4'}$ 4 and 4 Hz, 4'-H), 3.40 (1 H, s, OH), 3.80–3.91 (2 H, m, 1"-H_2), 4.05–4.13 (1 H, m, 1-H), 6.04 and 6.21 (each 1 H, d, *J* 3 Hz, 2'-H and 3'-H), 7.35–7.46 and 7.65–7.69 (10 H, 2 x m, 2 x C_6H_5); m/z 384 (M + NH_4, 18%), 367 (M + H, 100); R_f (petroleum - ether 8:1) 0.2, $KMnO_4$ stain.

1S*,1'R*,4'S*-*4-[[(4-Methoxyphenyl)methoxy]methyl]-2-cyclobutene-1-heptanol* **54**

A stirred suspension of sodium hydride (60% oil dispersion, 220 mg, 5.5 mmol) in THF (15 ml) at room temperature under N_2 was added the diol (±)-**34e** (1.1 g, 5.5 mmol) in THF (10 ml). After stirring for 0.5 h 4-methoxybenzyl bromide (1.1 g, 5.5 mmol) in THF (10 ml) was added. After 12 h the mixture was diluted with ether (75 ml), washed with 10% aq. K_2CO_3 (25 ml) and brine (25 ml), dried and evaporated. The yellow residue was chromatographed (elution with dichloromethane - hexane 2:1) to obtain the *title compound* **54** (1.5 g, 86%) as a pale yellow oil (M + H^+, 319.2262; $C_{20}H_{31}O_3$ requires 319.2273); ν_{max} 3466, 3040, 2954, 2929, 2857, 1613, 1586, 1514, 1465, 1442, 1360, 1303, 1250, 1175, 1074, 1037, 822 and 729 cm^{-1}; δ (300 MHz) 0.87 (3 H, t, *J* 7 Hz, 7-H_3), 1.19–1.64 (10 H, m, 2-H_2, 3-H_2, 4-H_2, 5-H_2 and 6-H_2), 2.90 (1 H, dd,

$J_{1',4'}$ 4, $J_{1,1'}$ 10.5 Hz, 1'-H), 3.26 (1 H, ddd, $J_{1',4'}$ 4, $J_{1'',4'}$ 4 and 11.5 Hz, 4'-H), 3.52–3.67 (3 H, m, 1-H and 1"-H_2), 3.78 (3 H, s, OMe), 4.15 (1 H, s, OH), 4.47 (2 H, s, OCH_2Ar), 5.95 and 6.01 (each 1 H, d, *J* 3 Hz, 2'-H and 3'-H), 6.85 (2 H, d, *J* 8.5 Hz, 3,5-ArH), 7.24 (2 H, d, *J* 8.5 Hz, 2,6-ArH); m/z 319 (M + H, 20%), 154 (18), 137 (22), 121 (100); R_f (petroleum - ether 2:1) 0.6, $KMnO_4$ stain.

1S*,1'R*,4'S*-*1[4-[[(4-Methoxyphenyl)methoxy]methyl]-2-cyclobuten-1-yl]heptyl benzoate* **55**

A solution of **54** (954 mg, 3.0 mmol), benzoyl chloride (560 mg, 4.0 mmol) and 4-pyrrolidinopyridine (10 mg) in pyridine (5 ml) was stirred at room temperature for 6 h. The solution was reduced in volume by evaporation and ether (20 ml) was added. The mixture washed with 1 M hydrochloric acid (2 x 10 ml), water (3 x 10 ml), and brine (10 ml), dried and evaporated. The yellow residue was chromatographed (elution with dichloromethane - hexane 2:1) to obtain the *title compound* **55** (1.04 g, 82%) as a pale yellow oil (M + NH_4^+, 423.2539; $C_{27}H_{38}O_4$ requires 423.2535); ν_{max} 2955, 2930, 1714, 1451, 1315, 1274, 1113, 1070, 1026, 734 and 711 cm^{-1}; δ (300 MHz) 0.85 (3 H, t, *J* 7 Hz, 7-H_3), 1.16–1.50 (8 H, m, 3-H_2, 4-H_2, 5-H_2 and 6-H_2), 1.62–1.80 (2 H, m, 2-H_2), 3.20–3.22 (1 H, m, 4'-H), 3.26 (1 H, dd, $J_{1',4'}$ 4, $J_{1,1'}$ 10 Hz, 1'-H), 3.48 and 3.57 (each 1 H, dd, $J_{1'',4'}$ 7, J_{gem} 9.5 Hz, 1"-H_2), 3.74 (3 H, s, OMe), 4.22 and 4.28 (each 1 H, d, J_{gem} 11.5 Hz, OCH_2Ar), 5.26–5.33 (1 H, m, 1-H), 6.05 and 6.20 (each 1 H, d, *J* 3 Hz, 2'-H and 3'-H), 6.72 (2 H, d, *J* 8.5 Hz, 3,5-ArH), 7.07 (2 H, d, *J* 8.5 Hz, 2,6-ArH), 7.38–7.56 (3 H, m, 3,4,5-COArH), 8.01 (2 H, d, *J* 8 Hz, 2,6-COArH); m/z 440 (M + NH_4, 30%), 423 (M + H, 65%), 300 (20), 241 (28), 121 (100); R_f (dichloromethane - petroleum 2:1) 0.5, $KMnO_4$ stain and u.v. active.

1'S*,1"S*,4'R*-*4-[1-Benzoyloxyheptyl]-2-cyclobutene-1-methanol* **56**

To a stirred solution of **55** (844 mg, 2.0 mol) in dichloromethane-water (50:1, 30 ml) was added DDQ (681 mg, 3.0 mmol) in dichloromethane (10 ml) over 10 min. The reaction mixture was stirred at room temperature for 6 h and then dried over $MgSO_4$. The solids were filtered off and washed with dichloromethane, the filtrate was evaporated, and the brown residue purified by chromatography (elution with hexane - dichloromethane 3:1), giving first 4-methoxybenzaldehyde followed by the *title compound* **56** (450 mg, 89%), a pale yellow oil (M + H^+, 303.1960; $C_{19}H_{27}O_3$ requires 303.1960); ν_{max} 3416br, 2930, 2858, 1718, 1602, 1467, 1451, 1357, 1314, 1275, 1177, 1112, 1070, 1026, 736 and 711 cm^{-1}; δ (300 MHz) 0.83 (3 H, t, *J* 7 Hz, 7-H_3), 1.23–1.34 (8 H, m, 3-H_2, 4-H_2, 5-H_2, 6-H_2), 1.60–1.81 (2 H, m, 2-H_2), 1.96 (1 H, s, OH), 3.13 (1 H, m, 4'-H), 3.28 (1 H, dd, $J_{1',4'}$ 4, $J_{1,1'}$ 11.5 Hz, 1'-H), 3.65–3.78 (2 H, m, 1"-H_2), 5.28–5.35 (1 H, m, 1-H), 6.08 and 6.19 (each 1 H, d, *J* 3 Hz, 2'-H and 3'-H), 7.39–7.56 (3 H, m, 3,4,5-ArH), 8.02 (2 H, d, *J* 8 Hz, 2,6-ArH); m/z 320 (M + NH_4, 35%), 303 (M + H, 20), 181 (28), 163 (20), 138 (20), 121 (100); R_f (petroleum - ether 1:1) 0.4, $KMnO_4$ stain and u.v. active.

*6-Benzoyloxy-(2Z,4E)-dodecadienal (±)-***53**

Method A: To a stirred solution of oxalyl chloride (92 mg, 0.75 mmol) in dichloromethane (3.0 ml) at –78 °C under N_2 was added a solution of DMSO (147 mg, 1.9 mmol) in dichloromethane (2 ml). After 15 min a solution of the alcohol **56** (151 mg, 0.5 mmol) in dichloromethane (2 ml) was added dropwise over 10 min. The reaction mixture was maintained at –78 °C for a further 2 h and then treated with triethylamine (243 mg, 2.4 mmol). After a further 15 min at –78 °C the mixture was allowed to warm up to room temperature over 45 min. The solution was washed with water (10 ml), brine (10 ml), dried, evaporated and the residue washed through a short column of Florisil (elution with dichloromethane) to obtain the *title compound* (±)-**53** (108 mg, 72%) as a pale yellow oil (M + NH_4^+, 318.2059; $C_{19}H_{28}NO_3$ requires 318.2069); ν_{max} 2930, 2858, 1718, 1674, 1644, 1452, 1315, 1271, 1111, 912, 734 and 713 cm^{-1}; δ (300 MHz) 0.83 (3 H, t, *J* 7 Hz, 12-H_3), 1.15–1.53 (8 H, m, 8-H_2, 9-H_2, 10-H_2, 11-H_2), 1.70–1.86 (2 H, m, 7-H_2), 5.62 (1 H, dt, $J_{5,6}$ 6, $J_{6,7}$ 6 Hz, 6-H), 5.86 (1 H, dd, $J_{1,2}$ 8, $J_{2,3}$ 11 Hz, 2-H), 6.14 (1 H, dd, $J_{5,6}$ 6, $J_{4,5}$ 15 Hz, 5-H), 6.91 (1 H, dd, $J_{2,3}$ 11, $J_{3,4}$ 11 Hz, 3-H), 7.23 (1 H, dd, $J_{3,4}$ 11, $J_{4,5}$ 15 Hz, 4-H), 7.38–7.60 (3 H, m, 3,4,5-ArH), 7.95–8.06 (2 H, m, 2,6-ArH), 10.14 (1 H, d, $J_{1,2}$ 8 Hz, 1-H); m/z 318 (M + NH_4, 100%), 301 (M + H, 12), 198 (72), 179 (90), 105 (56).

Method B: To a stirred of the alcohol **56** (151 mg, 0.5 mmol) in dichloromethane (5 ml) at 0 °C under N_2 was added NMO (175 mg, 1.5 mmol), powdered 4Å sieves (200 mg) and TPAP (35 mg, 0.1 mmol). After stirring for 0.5 h the mixture was washed through a short column of Florisil (elution with dichloromethane), giving a pale yellow oil (112 mg, 75%) whose 300 MHz ^{1}H n.m.r. spectrum indicated that it was a 1:1 mixture of the dienal **53** and the cyclobutenealdehyde **57**. After 1 h a new 300 MHz ^{1}H n.m.r. spectrum of the product indicated that the conversion of **57** into **53** was complete.

cis-*3-Cyclobutene-1,2-dimethanol diacetate* **59**

A mixture of the diol **1** (684 mg, 6.0 mmol), acetic anhydride (1.32 g, 13 mmol) and pyridine (1.5 ml) was stirred at room temperature for 6 h. Saturated aqueous sodium hydrogen carbonate (25 ml) was added and the mixture extracted with dichloromethane (3 x 25 ml). The combined organic solution was washed with 1 M hydrochloric acid (2 x 25 ml), water (25 ml), brine (25 ml), dried and evaporated. Chromatography of the residue (elution with dichloromethane - ethyl acetate 4:1) gave the *title compound* **59** (1.08 g, 91%) as a colourless oil (M + NH_4^+, 216.1231; $C_{10}H_{18}NO_4$ requires 216.1236); ν_{max} 3300, 3050, 2956, 2909, 1827, 1735, 1451, 1386, 1366, 1236, 1124, 1035, 975 and 741 cm^{-1}; δ (300 MHz) 1.95 (6 H, s, 2 x COMe), 3.12–3.18 (2 H, m, 1'-H and 4'-H), 4.10–4.12 (4 H, m, 1-H_2 and 1"-H_2), 6.02 (2 H, s, 2'-H and 3'-H); m/z 216 (M + NH_4, 100%); R_f (dichloromethane - ethyl acetate 2:1) 0.8, $KMnO_4$ stain.

cis-*3-Cyclobutene-1,2-dimethanol monoacetate (±)*-**60**

Method A: A mixture of the diol **1** (450 mg, 3.95 mmol), acetic anhydride (405 mg, 3.95 mmol) and pyridine (315 mg, 3.95 mmol) was stirred at room temperature for 3 h. Saturated aqueous sodium hydrogen carbonate (10 ml) was added and the mixture extracted with dichloromethane (3 x 10 ml). The combined organic solution was washed with 1 M hydrochloric acid (2 x 15 ml), water (15 ml), brine (15 ml), dried and evaporated. Chromatography of the residue (elution with dichloromethane - ethyl acetate 4:1) gave first the diacetate **59** (186 mg, 24%), followed by the *title compound* (±)-**60** (298 mg, 44%) as a colourless oil (M + H^+, 157.0870; $C_8H_{13}O_3$ requires 157.0865); ν_{max} 3450br, 2955, 1733, 1438, 1280, 1112, 1033 and 740 cm^{-1}; δ (300 MHz) 2.00 (3 H, s, MeCO), 2.68 (1 H, br s, OH), 3.09–3.20 (2 H, m, 1'-H and 4'-H), 3.68 (2 H, d, *J* 7 Hz, 1-H_2), 4.10 (1 H, dd, $J_{1",4'}$ 8.5, J_{gem} 11.5 Hz, 1"-H), 4.27 (1 H, dd, $J_{1",4'}$ 6, J_{gem} 11.5 Hz, 1"-H), 6.04 and 6.07 (each 1 H, d, *J* 2.5 Hz, 2'-H and 3'-H); m/z 174 (M + NH_4, 100%), 157 (M + H, 12%); R_f (dichloromethane - ethyl acetate 2:1) 0.4, $KMnO_4$ stain.

Method B: To a stirred solution of the ester-ether (±)-**5b** (138 mg, 0.5 mmol) in a mixture of dichloromethane (5 ml) and water (0.1 ml) was added a solution of DDQ (136 mg, 0.6 mmol) in dichloromethane (5 ml). After stirring at room temperature for 3 h, t.l.c. indicated that the starting material had been consumed. The mixture was dried with magnesium sulphate, filtered, and the residue washed with dichloromethane. The filtrate was evaporated to dryness, and the residue passed through a short plug of Florisil, eluting with ether (50 ml). Evaporation of the ether and chromatography of the residue, eluting with ethyl acetate - dichloromethane (1:9), gave 4-methoxybenzaldehyde (66 mg), followed by the *title compound* (±)-**60** (71 mg, 91%), which was identical to the material prepared by method A.

(+)-cis-*3-Cyclobutene-1,2-dimethanol monoacetate (+)*-**60**[33]

To a stirred solution of the diacetate **59** (980 mg, 5.0 mmol) in phosphate buffer (pH 7.0, 20 ml) at room temperature was added *Pseudomonas fluorescens* lipase (20 mg). The pH was maintained by addition of 0.5 M sodium hydroxide and after the addition of 0.8 mol equivalents of alkali (18.5 h), the mixture was extracted with dichloromethane (3 x 50 ml). The aqueous layer was saturated with sodium chloride and extracted with more dichloromethane (2 x 20 ml). The combined extracts were dried and evaporated, and the residue was chromatographed to obtain the *title compound* (+)-**60** (476 mg, 61%) as a colourless oil, with spectroscopic data as for the racemic compound (±)-**60**; $[\alpha]_D^{20}$ +8.5° (*c* 2.0, chloroform).

(–)-cis-*3-Cyclobutene-1,2-dimethanol monoacetate (–)*-**60**

To a stirred solution of *Pseudomonas fluorescens* lipase (100 mg) and vinyl acetate (10 ml) at room

temperature under N_2 was added the diol **1** (560 mg, 5.0 mmol). After 2 h the enzyme was removed by filtration and washed with vinyl acetate (10 ml). The filtrate was evaporated and the residue chromatographed (elution with dichloromethane - ethyl acetate 4:1) to obtain the *title compound* (–)-**60** (750 mg, 96%) as a colourless oil, with spectroscopic data as for the racemic compound (±)-**60**; $[\alpha]_D^{20}$ –7.5° (*c* 2.0, chloroform).

*(1S,5R)-3-Oxabicyclo[3.2.0]hept-6-en-2-one (+)-**4***

The monoacetate (+)-**60** (156 mg, 1.0 mmol) was converted into the lactone **4** as described above for the preparation of (±)-**4** (method E). Flash chromatography (elution with dichloromethane - hexane 2:1) gave the *title compound* (+)-**4** (52 mg, 47%) as a colourless oil, spectroscopically identical to the racemate (±)-**4**. Analysis by g.l.c. indicated that the enantiomer ratio (–):(+) was 2.48:97.52 (95% e.e.). G.l.c. conditions: Chiraldex B-TA column, 50m x 0.25mm, 130 °C isothermal, FID temperature 300 °C, injector temperature 200 °C, H_2 carrier gas, 20 psi. Retention times: (–)-**4**, 9.4 min; (+)-**4**, 12.1 min.

*(1R,5S)-3-Oxabicyclo[3.2.0]hept-6-en-2-one (–)-**4***

The procedure described above for the preparation of (+)-**4** was repeated using the monoacetate (–)-**60** (156 mg, 1.0 mmol), and gave the *title compound* (–)-**4** (45 mg, 41%) as a colourless oil. Analysis by g.l.c. as described for (+)-**4** indicated that the enantiomer ratio (–):(+) was 94.2:5.8 (88.4% e.e.).

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