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Stereo- and Enantioselective Routes to Functionalised Cyclohexenes *via* Heterodiene Cycloadditions of 6-Oxocyclohexene-1-carbaldehydes with Ketene Acetals

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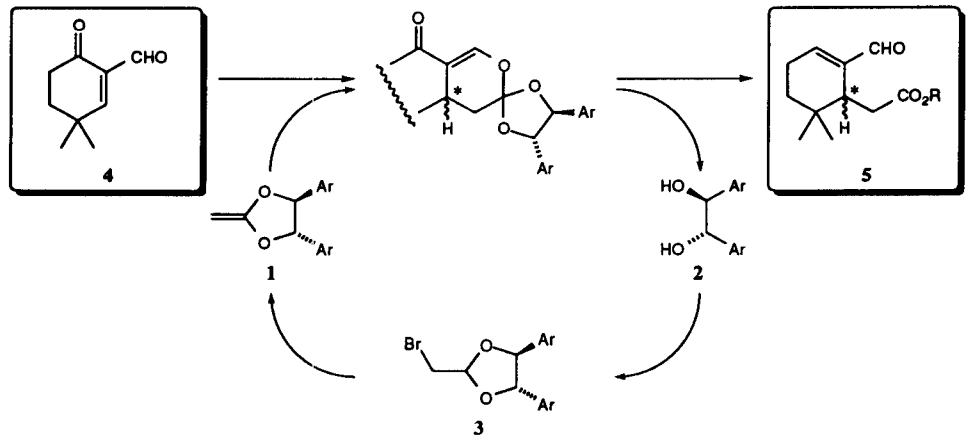
Abstract: Various substituted cyclohexenes related to α-cyclocitral have been prepared using the heterodiene cycloadditions of 2-formyl-4,4-dimethyl-2-cyclohexen-1-one **4** with ketene acetals as the pivotal step. The key intermediates are accessible in homochiral form *via* an auxiliary-based sequence in which a C_2-symmetric ketene acetal derived from 1,2-*bis*(2-methylphenyl)ethane-1,2-diol **2a** serves as the 2π component. The diol **2a** can be recovered in optically pure form.

The [4π + 2π] cycloaddition of α,β-unsaturated carbonyl compounds (1-oxabutadienes) to alkenes can be an efficient route to dihydropyrans.[1] Since the dominant orbital interaction in such a reaction is that between the LUMO of the 4π component and the HOMO of the dienophile, pairings in which the heterodiene and alkene bear electron-acceptor and electron-donor groups respectively can be particularly effective. This principle is well recognised and has been exploited in synthesis.[2]

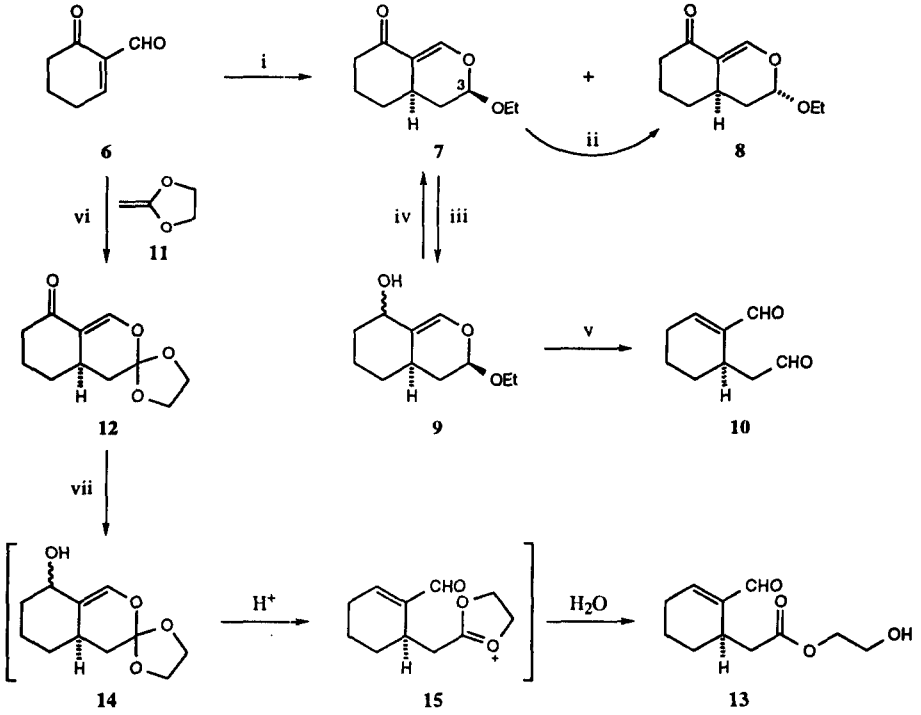
Our interest in cycloadditions of this type[3,4] prompted us to prepare a series of C_2-symmetric ketene acetals **1**, starting with the corresponding diols **2** and proceeding *via* the derived bromoacetals **3**, for use as electron-rich dienophiles.[5] In seeking to exploit these in synthesis we envisaged that their reaction with 2-formyl-4,4-dimethyl-2-cyclohexen-1-one **4** could provide access to various terpenoids, many of which are of biological, pharmacological and commercial interest[6] and which continue to provide a focus for synthetic effort.[7] The details of the resulting study, which ultimately provided routes to functionalised homochiral α-cyclohomogeranyl systems such as ester-aldehydes **5** (Scheme 1), are herein described.[8]



SCHEME 1

PII: S0040-4020(99)00764-4

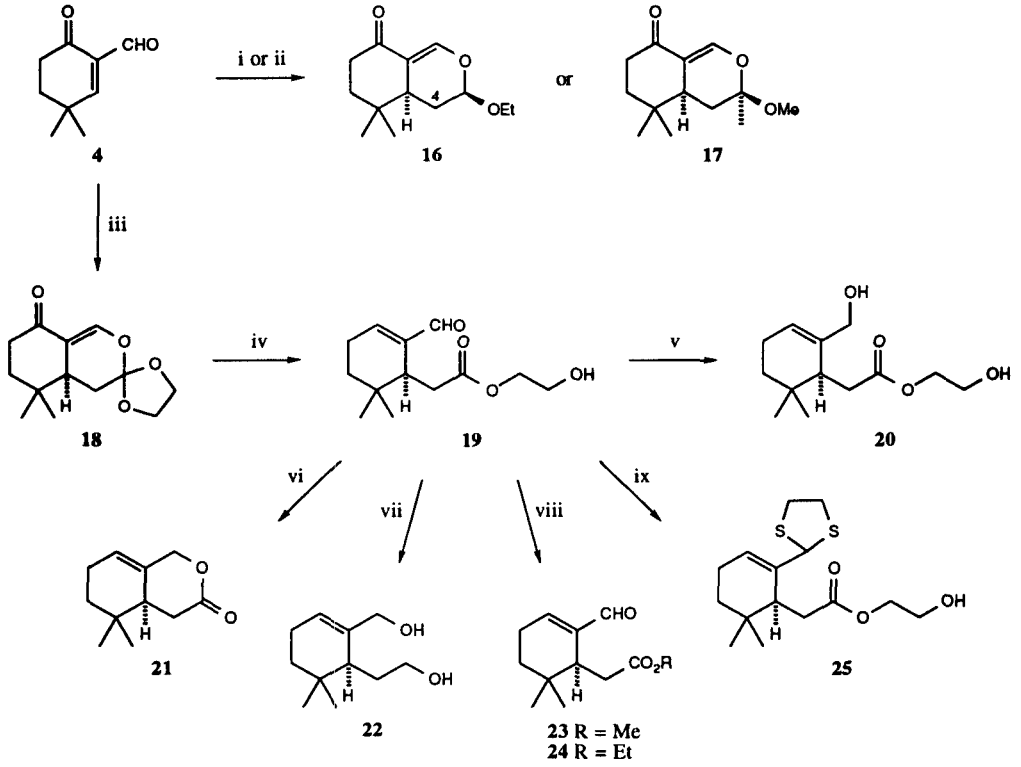
In initial experiments we explored the potential of the aldehyde **6** as a heterodiene. Although readily accessible,[9,10] this aldehyde is quite labile and was generally used without storage. Freshly prepared **6** reacted with ethoxyethene rapidly at room temperature to give a good yield of the *endo* (*cis*)- and *exo* (*trans*)-cycloadducts **7** and **8** (ratio 6:1). The major product **7** was identified *via* its ^{1}H NMR spectrum, which confirmed that 3-H was axial ($J_{3,4\beta}$ 10 Hz). The conversion of **7** into **8** (which is more stable due to the anomeric effect) was conveniently brought about using trifluoroacetic acid in dichloromethane (Scheme 2).[11,12] Similar behaviour of related systems has been described.[4,13]



SCHEME 2 *Reagents:* i, Ethoxyethene, 20 °C, 3 h (91%); ii, CF_3CO_2H, CH_2Cl_2, 5–10 °C, 72 h (75%); iii, L-Selectride®, THF, –78 °C, 3 h, then –5 °C, aq. NaOH, aq. H_2O_2 (87%); iv, MnO_2, CH_2Cl_2; v, PTSA, CH_2Cl_2, 10 min (95%); vi, **11**, CH_2Cl_2, 0 °C, 24 h (77%); vii, as iii, then v (79% over two steps).

Reacting the cycloadduct **7** with L-selectride®[14] in tetrahydrofuran (THF) gave a product from which **7** could be regenerated by treatment with active manganese(IV) oxide, and which was presumed to contain one or both of the epimeric alcohols **9**. Predictably, this product was labile and yielded no isolable products when attempts were made to functionalise it using hexachloroacetone/triphenylphosphine,[15] tetrachloromethane and triphenylphosphine,[16] *t*-butyldimethylsilyl chloride/imidazole/DMF, or acetic anhydride/pyridine. The product **9** was especially sensitive to traces of acid, and its decomposition over one hour in $CDCl_3$ was conveniently followed by ^{1}H NMR spectroscopy. The decomposition product was identified as the dialdehyde **10**, and the sequence which generated this from **7** was to prove useful in other contexts. For example, when **6** was allowed to react with the ketene acetal **11**,[17] the derived cycloadduct **12** could be transformed into the ester-aldehyde **13** by reduction followed by treatment with *p*-toluenesulfonic acid (PTSA). It is assumed that the formation of **13** proceeds *via* the acid-catalysed elimination of water from the alcohol(s) **14** followed by hydrolysis of the resulting oxonium species **15**.

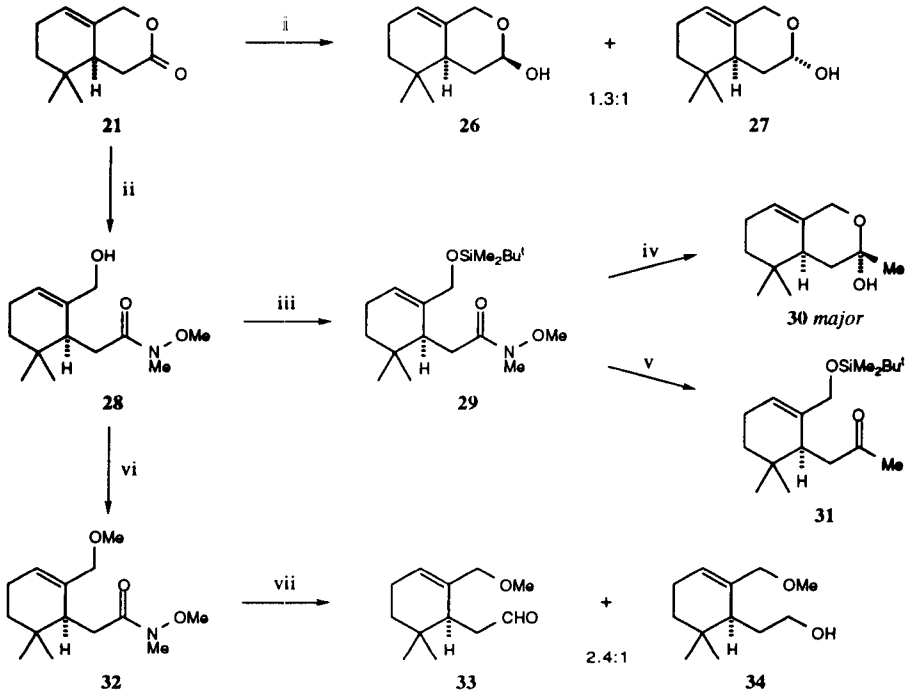
Cycloadditions of the methyl-substituted aldehyde **4** were predictably slower than those of **6**. The reaction with ethoxyethene,[18] complete after three days at 20 °C, gave the *endo*-cycloaddition product **16** in high yield, whereas treating **4** with 2-methoxypropene provided the cycloadduct **17** in poor yield only after several weeks[19] (Scheme 3). Similarly the reaction of **4** with the ketene acetal **11** proceeded at room temperature, producing the spirocyclic adduct **18** in 63% yield.



SCHEME 3 *Reagents:* i, Ethoxyethene, CH_2Cl_2, 20 °C, 3 d (87%); ii, 2-methoxypropene, CH_2Cl_2, 20 °C, 28 d (29%); iii, **11**, CH_2Cl_2, 20 °C, >3 d (63%); iv, L-Selectride®, THF, 20 °C, 0.5 h, then silica gel (64%); v, $NaBH(OAc)_3$, THF, 20 °C, 12 h (89%); vi, $NaBH(OAc)_3$, AcOH, 20 °C, 12 h (86%); vii, $NaBH_4$, EtOH, 0 °C (43%); viii, RONa/ROH, 20 °C, 0.5–4 h (**23**, 75%; **24**, 62%); ix, ethanedithiol, $TiCl_4$, CH_2Cl_2, –78 °C (79%).

Upon subjecting the adduct **18** to a sequence similar to that used to prepare **13**, it was transformed into the ester-aldehyde **19**, which proved to be a versatile precursor of functionalised α-cyclohomogeranyl systems. For example, reducing **19** with sodium triacetoxyborohydride in THF gave mainly the ester-alcohol **20**, together with the corresponding lactone **21**. Using the same reducing agent but with acetic acid as the solvent provided the lactone **21** exclusively. Contrastingly, the treatment of **19** with sodium borohydride in ethanol gave the diol **22** in modest yield. It is presumed that in the latter process the reduction of the ester group is assisted by coordination of the reagent to the nearby hydroxyl group(s). Similar neighbouring group participation can be invoked in the transesterification reactions of **19** under basic conditions, which deliver the ester-aldehydes **23** and **24** in fair yields.[20] Finally it was found that the aldehyde group of **19** could be selectively protected as a dithiolane by employing the mild conditions described by Bulman-Page *et al.*,[21] which afforded **25** in good yield.

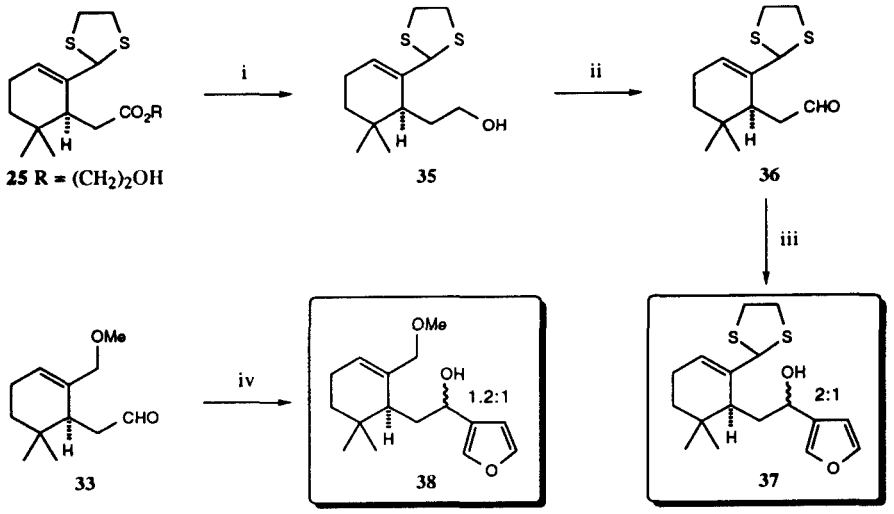
The potential of the lactone **21** and ester **25** as terpene fragments prompted further investigation of their properties. Reduction of **21** with diisobutylaluminium hydride (DIBAH) generated the lactols **26** and **27** as a mixture in which the former predominated (Scheme 4). More significantly, Weinreb's amidation method[22] was effective in transforming the lactone **21** into the amide **28** which, after hydroxyl protection (required to curb relactonisation), possessed some of the expected versatility[23] as an acylating agent. For example, reacting the derived silyl ether **29** with methyllithium, followed by acid work-up, gave mainly the lactol **30** whose structure was deduced by comparing its ^{1}H n.m.r. spectrum with those of **27** and **28**. The observed preference (>9:1) for axial hydroxyl and equatorial methyl groups in **30** is consistent with the anticipated electronic (anomeric) and steric effects. When the reaction of **29** with methyllithium was quenched under milder conditions, the silyl group was retained and the methyl ketone **31** was isolated.



SCHEME 4 *Reagents:* i, DIBAH, THF, –78 °C, 0.5 h (89%); ii, MeONHMe.HCl, Me_3Al, CH_2Cl_2, 0 °C, 0.5 h (96%); iii, t-$BuMe_2SiCl$, imidazole, THF, 20 °C, 14 h (87%); iv, MeLi, Et_2O, THF, –78 °C, 0.5 h, then 1M HCl, 20 °C (60%); v, MeLi, Et_2O, THF, –78 °C, 0.5 h, then 0.1M HCl, 0 °C (61%); vi, MeI, Ag_2O, 20 °C, 24 h (98%); vii, $LiAlH_4$, THF, –78 °C, 2 d (61%).

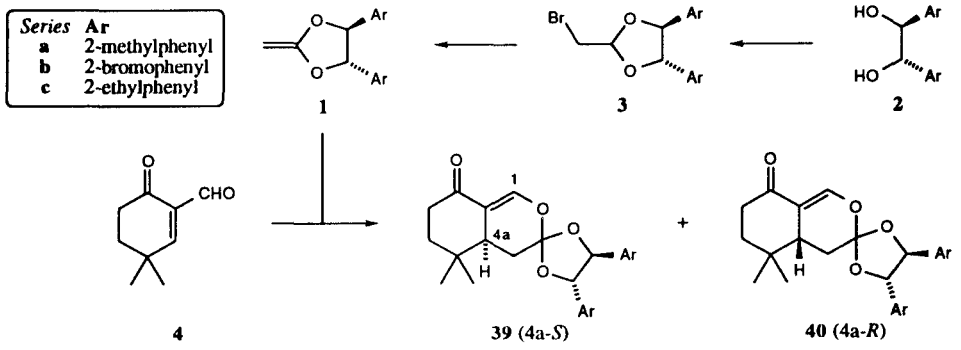
Protection of the allylic hydroxyl group of **28** by methylation gave the ether-amide **32** (98%), whose reactions with hydride reagents offered a route to the potentially useful aldehyde **33**. Treatment of **32** with DIBAH gave **33** in only 21% yield, while lithium aluminium hydride (LAH) in THF at –78 °C converted **32** into a mixture of the aldehyde **33** (43%) and the corresponding alcohol **34** (18%). Attempts to prepare an aldehyde from the silyl-protected amide **29** using DIBAH at –78 °C or LAH at 20 °C met with no success, presumably because of adverse steric effects. However, a second aldehyde of this type proved accessible from the dithiolane-ester **25** by LAH reduction to the alcohol **35** followed by oxidation with pyridine-sulfur trioxide complex,[24] which afforded **36** in modest yield (Scheme 5).

Since furan and butenolide moities are incorporated within various sesquiterpene structures,[25] the reactions of the aldehydes **33** and **36** with 3-lithiofuran were briefly studied. The dithiolane-aldehyde **36** proved the more promising in this context, furnishing the diastereoisomers **37** in 41% yield (ratio 2:1 by ^{1}H NMR spectroscopy) (Scheme 5). In comparison the ether-aldehyde **33** gave a mixture of isomers **38** (36%), the ratio this time being close to 1:1. The relative stereochemistry of the major carbinol **37** remains to be elucidated. It should be mentioned that the reaction of 3-lithiofuran with the Weinreb amide **29** was fruitless, presumably reflecting once again the hindered nature of the carbonyl group.



SCHEME 5 *Reagents:* i, $LiAlH_4$, THF, 0 °C, 15 min (97%); ii, Et_3N, CH_2Cl_2, SO_3-py, DMSO, 20 °C, 16 h (38%); iii, 3-lithiofuran, THF, −78 °C, 15 min (36%); iv, 3-lithiofuran, THF, −78 °C, 40 min (41%).

In principle the absolute stereochemistry of the above intermediates can be controlled *via* the use of a homochiral 2π component in the initial cycloaddition step. When the ketene acetals **1a–c** were used for this purpose, the *bis*(*o*-tolyl) system **1a**[5] turned out to be the most effective. The diol **2a** is available in both enantiomeric forms[5] and provided crystalline intermediates throughout the sequence (Scheme 6). Thus, stirring a THF solution of **1a** and an equivalent of the aldehyde **4** for 3–4 days at room temperature on various scales consistently provided good yields of the mixed cycloadducts **39a** and **40a**.



SCHEME 6

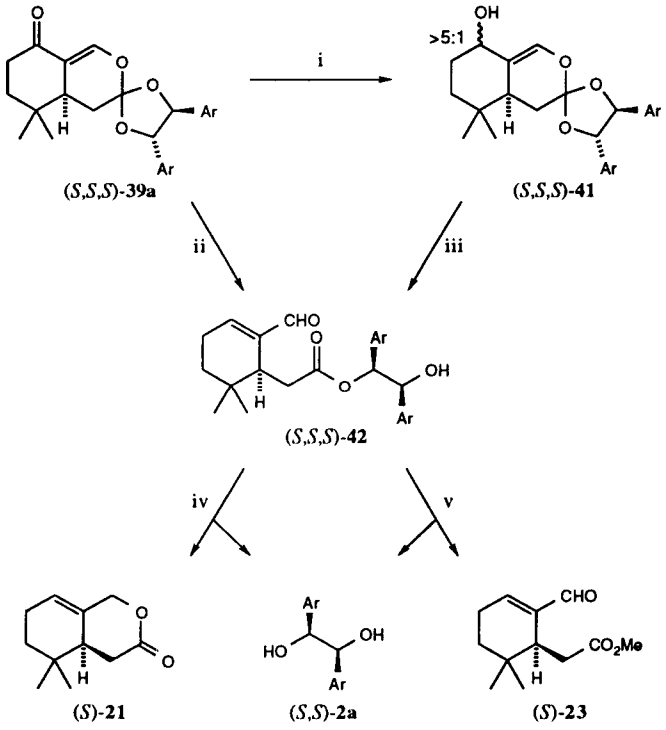
Crystallisation from ether gave **39a** as a single diastereoisomer. The ketene acetals **1b** and **1c** were slightly more selective than **1a** (Table 1), but they were not so easy to prepare and the adducts not so crystalline.

Entry	Ketene acetal	Scale mmol	Reaction Temp. °C	Reaction Time h	Total yield 39 + 40 (%)	Major product	Ratio 39 : 40	Isolated yield of 39 (%)
1	**1a**	7	20	96	86	**39a**	3.3 : 1	55
2	**1a**	27	20	65	89	**39a**	3.4 : 1	57
3	**1a**	7	−28	96	44	**39a**	4.5 : 1	24
4	**1b**	0.4	20	96	70	**39b**	4.6 : 1	9
5	*ent*-**1c**	0.03	0	72	42	*ent*-**39c**	5.5 : 1 †	–

† Ratio refers to *ent*-**39c** : *ent*-**40c**; the major product was not isolated in this case.

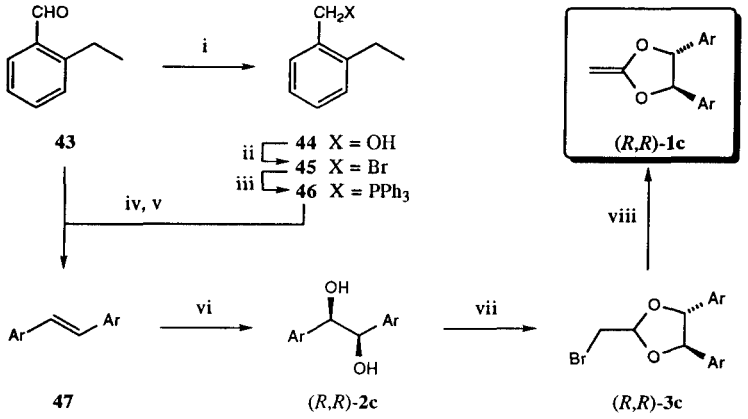
TABLE 1. Cycloadditions of Ketene Acetals **1** to the Aldehyde **4**.

Reduction of the cycloadduct **39a** with L-selectride® as before gave an epimeric mixture of alcohols **41**, which readily rearranged to the ester **42** (Scheme 7). The latter was transformed into the lactone (*S*)-**21** or the ester-aldehyde (*S*)-**23** using methods similar to those described in Scheme 3, with concomitant release of the (recyclable) auxiliary diol (*S,S*)-**2a** in good yield and high optical purity (≥98%).



SCHEME 7 (Ar = 2-methylphenyl) *Reagents:* i, L-Selectride®, THF, 20 °C, 2.5 h, then ice, rapid isolation (70%); ii, L-Selectride®, THF, 20 °C, 2.5 h, then H_2O (77%); iii, *p*-TsOH, CH_2Cl_2, 20 °C, 1 h (75%); iv, $NaBH(OAc)_3$, toluene, 80 °C, 40 min, then aq. HCl, 48 h (**21**, 60%; **2a**, 68%); v, MeOH, cat. MeONa, 20 °C, 20 h (**23**, 68%; **2a**, 94%).

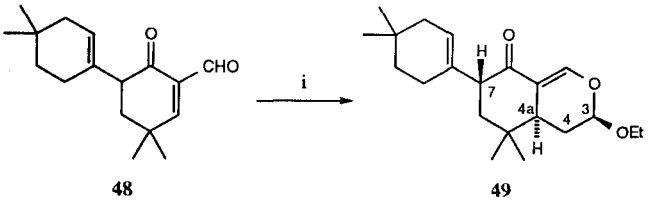
The structures of the major cycloadducts **39** (Scheme 6) are assigned on the basis of the previously discussed transition state model (see Figure 1).[5] The increased diastereoselection with **1c** (prepared as shown in Scheme 8) compared to **1a** is intriguing, since the extra methyl groups in this system are assumed to be located in positions which are relatively remote from the cycloaddition termini.

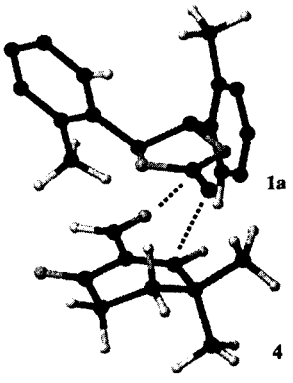


SCHEME 8 (Ar = 2-ethylphenyl) *Reagents:* i, $NaBH_4$, EtOH (99%); ii, PPh_3-Br_2, CH_2Cl_2 (80%); iii, PPh_3, toluene, reflux, 16 h (66%); iv, n-BuLi, THF, −78 to −10°C, then **43**, 20 °C, 4 h; v, $TeCl_4$, $CHCl_3$, reflux, 16 h (52% over two steps); vi, $K_3Fe(CN)_6$, K_2CO_3, $(DHQD)_2PHAL$, OsO_4, t-BuOH, H_2O, $MeSO_2NH_2$, 20 °C, 4 d (91%); vii, $BrCH_2CH(OEt)_2$, PTSA, 120 °C, 2 h (46%); viii, t-BuOK, Aliquat 336®, THF, 0 °C, 2 h (90%).

Further insight into the effect of substituents on these cycloadditions was provided by the aldehyde **48**. This was obtained as a by-product during the preparation of the aldehyde **4**, *via* a sequence initiated by the base-induced coupling of 4,4-dimethylcyclohexanone, followed by dehydration, formylation and selenium-mediated dehydrogenation. Reacting **48** with ethoxyethene yielded the cycloadduct **49** as a single diastereoisomer in 96% yield (Scheme 9). The stereochemistry of **49** was assigned on the basis of its ^1H NMR spectrum, which was consistent with the axial disposition of 4a-H and 7-H. It thus appears that a significant degree of facial selectivity is induced in the heterodiene π-system of **48** by the preference of the remote substituent for an equatorial orientation.[26] Whether this can be exploited as a stereocontrol element in this type of cycloaddition remains to be determined. Further studies involving this and related issues are in progress and will be described in due course.

FIGURE 1. Proposed Arrangement for the Addition of **1a** to **4**. Some of the hydrogen atoms have been omitted for clarity.





SCHEME 9 *Reagents:* i, ethoxyethene, CH_2Cl_2, 20 °C, 3 d (96%).

EXPERIMENTAL

All compounds are racemic unless their names are preceded by stereochemical descriptors. Melting points were determined using an Electrothermal apparatus and are uncorrected. Unless otherwise stated, i.r. spectra were of thin films on NaCl plates, recorded on a Perkin-Elmer 1710FT spectrometer. N.m.r. spectra were measured on a Bruker AC300 instrument at 300 MHz (^{1}H) 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. 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[27] and most reactions were carried out under nitrogen or argon. Organic solutions were dried using anhydrous magnesium sulfate 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 visualised 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.[28] 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. The aldehydes **4** and **6** were prepared using the method described by Liotta *et al.*[9] (see also the details of the preparation of the aldehyde **48**, below).

cis- and trans-3-Ethoxy-3,4,4a,5,6,7-hexahydro-8H-2-benzopyran-8-one **7** *and* **8**

2-Formylcyclohex-2-en-1-one **6** (0.60 g, 4.84 mmol) was stirred with ethoxyethene (6 ml, 4.52 g, 63 mmol) at room temperature for 3 h and the mixture then concentrated under reduced pressure. The residue was purified by flash chromatography (elution with ethyl acetate - petroleum 2:3), which afforded the *trans*-isomer **8** (0.126 g, 0.64 mmol, 13%) and then the *cis*-isomer **7** (0.740 g, 3.78 mmol, 78%) (total 91%). The *cis*-isomer **7** was an oil (*M* + H$^+$, 197.1169. $C_{11}H_{17}O_3$ requires 197.1178); ν_{max} (FT, neat) 1674, 1588, 1220, 1150, 1076, 1024, 999 and 847 cm^{-1}; δ_H 1.22 (3 H, t, *J* 7 Hz, Me), 1.50 (1 H, ddd, *J* 10, 12.5, 12.5 Hz, 4β-H_{ax}), 1.6–1.75 (2 H, m, 6-H_2), 1.9–2.0 (2 H, m, 5-H_2), 2.09 (1 H, ddd, *J* 2, 5, 12.5 Hz, 4α-H_{eq}), 2.21 (1 H, ddd, *J* 6.5, 13, 18 Hz, 7-H_{ax}), 2.4–2.5 (1 H, m, 7-H_{eq}), 2.5–2.6 (1 H, m, 4a-H), 3.58 and 3.95 (both 1 H, dq, *J* 7, 9.5 Hz, OCH_2), 5.00 (1 H, dd, *J* 2, 10 Hz, 3-H), 7.36 (1 H, d, *J* 2 Hz, 1-H); m/z (peaks > 10%), 214 (M + NH_4^+, 21%), 197 (M + H$^+$, 100). The *trans*-isomer **8** was an oil (*M* + H$^+$, 197.1176. $C_{11}H_{17}O_3$ requires 197.1178); ν_{max} (FT, neat) 2930, 2869, 1677, 1591, 1273, 1215, 1175, 1149, 1120, 1080, 1068, 1018, 979, 902, 841 and 823 cm^{-1}; δ_H 1.17 (3 H, t, *J* 7 Hz, Me), 1.41 (1 H, ddd, *J* 2, 12.5, 12.5 Hz, 4β-H_{ax}), 1.65–1.85 (2 H, m, 6-H_2), 1.85–2.05 (3 H, m, 4α-H_{eq}, 5-H_2), 2.25 (1 H, ddd, *J* 6.5, 13, 18 Hz, 7-H_{ax}), 2.4–2.55 (1 H, m, 7-H_{eq}), 2.55–2.7 (1 H, m, 4a-H), 3.57 and 3.82 (both 1 H, dq, *J* 7, 9.5 Hz, OCH_2), 5.16 (1 H, t, *J* 2 Hz, 3-H), 7.34 (1 H, d, *J* 2 Hz, 1-H); m/z (peaks > 10%), 214 (M + NH_4^+, 30%), 198 (13), 197 (M + H$^+$, 100)); R_f values (ethyl acetate - petroleum 2:3) **7**, 0.36; **8**, 0.45.

Acid-catalysed equilibration of **7** *and* **8**

A solution of **7** (1.1. g, 5.61 mmol) in dichloromethane (130 ml) was stirred with trifluoroacetic acid (0.78 ml, 1.15 g, 10.1 mmol) at 5–10 °C for 3 days. The solution was then washed with saturated aq. sodium hydrogen carbonate (3 x 60 ml) and brine (60 ml), dried and concentrated. The residue was purified by chromatography (elution with ethyl acetate - petroleum 2:3) to obtain the *trans*-isomer **8** (0.667 g, 61%) and the *cis*-isomer **7** (0.209 g, 19%) (the conversion yield of **8** was thus 75%).

3-Ethoxy-3,4,4a,5,6,7-hexahydro-8H-2-benzopyran-8-ols **9**

To a stirred solution of L-selectride® in THF (1.0 M; 5.1 ml, 5.1 mmol) at –78 °C under argon was added dropwise a solution of the ketone **7** (1.0 g, 5.1 mmol) in anhydrous THF (3 ml) over a period of 10 min. The solution was stirred at –78 °C for 3 h and then allowed to warm to –5 °C. Aq. sodium hydroxide (3 M; 4.3 ml,

12.9 mmol) was added dropwise over 20 min, stirring and maintaining the mixture at –5 to 0 °C. Aq. hydrogen peroxide (30%; 2.85 ml, 31 mmol) was then added dropwise over 30 min, maintaining the mixture at 0 °C and then allowed to stir at room temperature for 0.5 h to ensure complete oxidation. After dilution with water (20 ml) and saturating with sodium chloride, the mixture was extracted with ether (5 x 100 ml). The combined extracts were washed with brine, dried and concentrated. The crude product was purified by flash chromatography (elution with ethyl acetate), to obtain the alcohol **9** as an acid-sensitive colourless solid (732 mg, 72%), δ_H (60 MHz, d_6-acetone) 0.9–2.4 (10 H, m, 4-H_2, 4a-H, 5-H_2, 6-H_2, 7-H_2, OH), 1.3 (3 H, t, Me), 3.4–4.6 (3 H, m, OCH_2 and 8-H), 4.9 (1 H, dd, *J* 2, 8 Hz, 3-H) and 6.5 (1 H, br s, 1-H). As a dilute solution in deuteriochloroform, the alcohol **9** decomposed in *ca.* 0.5 h. The n.m.r. spectrum of the solution showed low field signals indicating the presence of the dialdehyde **10** [δ_H (60 MHz) 6.9 (1 H, t, *J* 4 Hz, C*H*=CCHO), 9.4 (1 H, s, CH=CC*H*O) and 9.8 (1 H, narrow m, CH_2CHO)]. The alcohol **9** was cleanly converted back into the bicycle **7** by stirring with active manganese dioxide in dichloromethane.

2-Formyl-2-cyclohexene-1-acetaldehyde **10**

To a stirred solution of L-selectride® in THF (1.0 M; 1.28 ml, 1.28 mmol) at –78 °C under argon was added dropwise a solution of the cycloadduct **7** (0.25 g, 1.28 mmol) in THF (3 ml) over a period of 10 min. The solution was stirred at –78 °C for 3 h and then allowed to warm to –5 °C. Aq. sodium hydroxide (3 M; 1.075 ml, 3.23 mmol) was added dropwise over 20 min, stirring and maintaining the mixture at –5 to 0 °C. Aq. hydrogen peroxide (30%; 0.71 ml, 7.72 mmol) was then added dropwise over 30 min while maintaining the mixture at 0 °C. After stirring at room temperature for 0.5 h to ensure complete oxidation, the mixture was diluted with water (10 ml), saturated with sodium chloride and extracted with ether (5 x 20 ml). The combined extracts were washed with brine, dried and concentrated to obtain the crude alcohol **2** as a colourless oil (220 mg, 87%). This was dissolved in dichloromethane (20 ml) and stirred with *p*-toluenesulfonic acid (50 mg) for 10 min. The solution was then washed with aq. sodium hydrogen carbonate, dried and evaporated to give the crude product **10** (160 mg, 83%). Flash chromatography (elution with CH_2Cl_2) gave the *title compound* **10** (59 mg, 30%) as a colourless oil (*M* + NH_4^+, 170.1183. $C_9H_{16}NO_2$ requires 170.1181); ν_{max} (FT, neat) 2935, 2867, 2822, 2724, 1723, 1683, 1637, 1451, 1420, 1170 and 691 cm^{-1}; δ_H 1.5–1.7 (4 H, m, 5'-H_2, 6'-H_2), 2.3 (1 H, m, 4'-H), 2.33 (1 H, ddd, *J* 3, 9.5, 16.5 Hz, 2-H), 2.67 (1 H, ddd, *J* 1.5, 3.5, 16.5 Hz, 2-H), 3.1 (1 H, m, 1'-H), 6.85 (1 H, t, *J* 3.5 Hz, 3'-H), 9.32 (1 H, s, C=C–CHO), 9.70 (1 H, dd, *J* 1.5, 3 Hz, CH_2CHO); m/z 170 (M + NH_4^+, 100%), 153 (M + H^+, 28).

4,4a,6,7-Tetrahydrospiro[3H-2-benzopyran-3,2'-[1,3]dioxolan]-8(5H)-one **12**

A stirred solution of **6** (1.60 g, 12.9 mmol) in dichloromethane (15 ml) at 0 °C under argon was treated portionwise with 2-methylene-1,3-dioxolane **11**[17] (5.0 g, 58 mmol). After 24 h the solvent was evaporated off and the residual oil chromatographed over basic alumina, eluting with dichloromethane - petroleum (3:1), to obtain the crude product (2.1 g, 77%). Crystallisation from ethanol gave the pure *title compound* **12** (1.031 g, 38%, 2 crops) as colourless crystals, m.p. 79–80 °C (ethanol) (*M* + H^+, 211.0971. $C_{11}H_{15}O_4$ requires 211.0970); ν_{max} (FT, neat) 2925, 2855, 1671, 1594, 1462, 1377, 1217, 1204, 1184, 1052, 1022, 1009, 992, 959, 947, 854, 607 and 589 cm^{-1}; δ_H 1.28 (1 H, m, 5-H_{ax}), 1.6–2.6 (total 5 H, m, 5-H_{eq}, 6-H_2, 7-H_2), 1.76 (1 H, t, *J* 13 Hz, 4-H_{ax}), 2.03 (1 H, dd, *J* 5, 13 Hz, 4-H_{eq}), 2.7–2.8 (1 H, m, 4a-H), 4.0–4.4 (4 H, m, 4'-H_2, 5'-H_2), 7.28 (1 H, d, *J* 2.5 Hz, 1-H); m/z (peaks >10%) 228 (M + NH_4^+, 10%), 212 (18), 211 (100).

2-Hydroxyethyl 2-formyl-2-cyclohexene-1-acetate **13**

To a stirred solution of L-selectride® in THF (1.0 M; 0.48 ml, 0.48 mmol) at –78 °C under argon was added dropwise a solution of the ketone **12** (100 mg, 0.476 mmol) in THF (2 ml) over a period of 10 min. The solution was stirred at –78 °C for 3 h and then allowed to warm to –5 °C. Aq. sodium hydroxide (3 M; 1.075 ml, 3.23 mmol) was added dropwise over 20 min, stirring and maintaining the mixture at –5 to 0 °C. Aq. hydrogen peroxide (30%; 0.71 ml, 7.72 mmol) was then added dropwise over 30 min while maintaining the mixture at 0 °C. After stirring at room temperature for 0.5 h to ensure complete oxidation, the mixture was diluted with water (10 ml), saturated with sodium chloride and extracted with ether (5 x 20 ml). The combined

extracts were washed with brine, dried and concentrated to obtain the intermediate alcohol **14** as a colourless oil (110 mg). This was dissolved in dichloromethane (20 ml) and stirred with *p*-toluenesulfonic acid (10 mg) for 10 min. The solution was then washed with aq. sodium hydrogen carbonate, dried, evaporated and the residue chromatographed, eluting with ethyl acetate - dichloromethane (1:1), to obtain the *title compound* **13** (80 mg, 79%) as a colourless oil ($M + H^+$, 213.1125. $C_{11}H_{17}O_4$ requires 213.1127); ν_{max} (FT, neat) 3448 (br.), 2940, 2869, 1732, 1683, 1637, 1454, 1419, 1381, 1307, 1285, 1259, 1170, 1082, 1029 and 691 cm^{-1}; δ_H 1.6–1.7 (4 H, m, 5'-H_2, 6'-H_2), 2.2–2.4 (2 H, m, 4'-H_2), 2.25 (1 H, dd, *J* 9.5, 15.5 Hz, 2-H), 2.5–2.7 (1 H, br s, OH), 2.62 (1 H, dd, *J* 4.5, 15.5 Hz, 2-H), 2.95–3.05 (1 H, m, 1'-H), 3.75–3.80 (2 H, m, 2"-H_2), 4.15–4.20 (2 H, m, 1"-H_2), 6.83–6.86 (1 H, m, 3'-H), 9.31 (1 H, s, CHO); m/z 230 ($M + NH_4^+$, 100%), 213 ($M + H^+$, 25), 195 (23).

*cis-3-Ethoxy-3,4,4a,5,6,7-hexahydro-5,5-dimethyl-8*H*-2-benzopyran-8-one* **16**

To the aldehyde **4** (113 mg, 0.74 mmol) in dichloromethane (15 ml) was added ethoxyethene (2 ml) and the solution was stirred at room temperature for 3 days. T.l.c. indicated that the reaction was complete and the solution was evaporated, giving the *title compound* **16** (145 mg, 87%) as a pale yellow oil ($M + H^+$, 225.1476. $C_{13}H_{21}O_3$ requires 225.1491); δ_H 0.84 (3 H, s, 5-CH_3), 1.01 (3 H, s, 5-CH_3), 1.24 (3 H, t, *J* 7 Hz, OCH_2CH_3), 1.53 (1 H, ddd, *J* 10, 12.5, 12.5 Hz, 4β-H_{ax}), 1.60–1.66 (2 H, m, 6-H_2), 2.02 (1 H, ddd, *J* 2, 5, 12.5 Hz, 4α-H_{eq}), 2.3–2.4 (1 H, m, 7-H_2), 2.42 (1 H, ddd, *J* 2, 5, 12.5 Hz, 4a-H), 3.59 and 3.98 (both 1 H, dq, *J* 7, 9.5 Hz, OCH_2), 5.00 (1 H, dd, *J* 2, 9.5 Hz, 3-H), 7.46 (1 H, d, *J* 2 Hz, 1-H); m/z 225 ($M + H^+$, 100%).

*rel(3R,4aS)-3,4,4a,5,6,7-Hexahydro-3-methoxy-3,5,5-trimethyl-8*H*-2-benzopyran-8-one* **17**

To the aldehyde **4** (100 mg, 0.66 mmol) in dichloromethane (15 ml) was added 2-methoxypropene (0.95 g, 13 mmol, 20 equiv.) and the solution was stirred at room temperature. T.l.c. indicated that the reaction was proceeding slowly and more 2-methoxypropene was added occasionally. After 4 weeks the mixture was evaporated to dryness to give an orange oil (293 mg) which was chromatographed on silica (30 g), eluting with petroleum - ethyl acetate (6:1), which gave the *title compound* **17** (43 mg, 29%) as a yellow oil. The ^1H n.m.r. spectrum of this material was poorly resolved and the compound was re-chromatographed to give **17** (18 mg, 12%) as a pale yellow oil ($M + H^+$, 225.1488. $C_{13}H_{21}O_3$ requires 225.1491); ν_{max} 1713 cm^{-1}; δ_H 0.85 (3 H, s, 5-CH_3), 1.01 (3 H, s, 5-CH_3), 1.36 (3 H, s, 3-CH_3), 1.55–1.75 (4 H, m, 4-H_2, 6-H_2), 2.25–2.35 (3 H, m, 4a-H, 7-H_2), 3.37 (3 H, s, OCH_3), 7.46 (1 H, d, *J* 2 Hz, 1-H); m/z 225 ($M + H^+$, 100%).

*4,4a,6,7-Tetrahydro-5,5-dimethylspiro[3*H*-2-benzopyran-3,2'-[1,3]dioxolan]-8(5*H*)-one* **18**

A stirred solution of the aldehyde **4** (5.01 g, 33 mmol) in dry dichloromethane (75 ml) at 0 °C under Ar was treated portionwise with 2-methylene-1,3-dioxolane **11**[17] (4.0 g, 46.5 mmol). The reaction was monitored by t.l.c. and after 3 days was still incomplete, so a further portion of 2-methylene-1,3-dioxolane **11** (1.7 g, 20 mmol) was added. The mixture was stirred at room temperature for a further 7 days and then evaporated to an orange oil which was chromatographed over silica gel (400 g), eluting with petroleum - ethyl acetate (5:1), to obtain the *title compound* **18** (4.92 g, 63%) as a colourless solid ($M + H^+$, 239.1283. $C_{13}H_{19}O_4$ requires 239.1283); ν_{max} 1682 cm^{-1}; δ_H 0.78 (3 H, s, 5-CH_3), 0.96 (3 H, s, 5-CH_3), 1.5–1.75 (3 H, m, 4β-H_{ax}, 6-H_2), 1.86 (1 H, dd, *J* 5, 12.5 Hz, 4α-H_{eq}), 2.25–2.32 (2 H, m, 7-H_2), 2.53 (1 H , ddd, *J* 2, 5, 13 Hz, 4a-H), 3.98–4.12 (3 H, m, 4'-H, 5'-H_2), 4.18–4.28 (1 H, m, 4'-H), 7.29 (1 H, d, *J* 2 Hz, 1-H); δ_C 198.1 (C-8), 152.2 (C-1), 120.6 (C-3 or C-8a), 113.8 (C-8a or C-3), 65.8 (C-4'), 64.1 (C-5'), 40.6, 37.0, 35.2, 31.2 (C-5), 28.8 and 28.2 (5-Me_2), 19.0 (C-6); m/z 256 ($M + NH_4^+$, 16%), 239 ($M + H^+$, 100), 186 (11).

2-Hydroxyethyl 2-formyl-6,6-dimethyl-2-cyclohexene-1-acetate **19**

A stirred solution of the cycloadduct **18** (4.92 g, 21 mmol) in THF (50 ml) at room temperature was treated with L-selectride® in THF (1.0 M, 21 ml, 21 mmol). The mixture turned red and was shown by t.l.c. to have gone to completion almost immediately. The solution was evaporated and re-dissolved in ether (80 ml). The

ethereal solution was washed well with water, dried over anhydrous sodium sulfate, filtered and evaporated to dryness to give a yellow oil (6.57 g). Chromatography over silica gel (300 g), eluting with ethyl acetate - petroleum (1:1) gave the *title compound* **19** (3.189 g, 64%) as a pale yellow oil which solidified upon cooling in an ice-bath ($M + NH_4^+$, 258.1713. $C_{13}H_{24}NO_4$ requires 258.1705); ν_{max} 3445 (br.), 1733 (br.) cm^{-1}; δ_H 0.83 (3 H, s, 6'-CH_3), 0.91 (3 H, s, 6'-CH_3), 1.29 (1 H, ddd, *J* 3, 6, 14 Hz, 5'-H_{eq}), 1.50 (1 H, ddd, *J* 7, 9.5, 14 Hz, 5'-H_{ax}), 2.10 (1 H, dd, *J* 6.5, 14.5 Hz, 2-H), 2.25–2.4 (2 H, m, 4'-H_2), 2.43 (1 H, dd, *J* 6.5, 14.5 Hz, 2-H), 2.77 (1 H, t, *J* 6.5 Hz, 1'-H), 3.79 (2 H, apparent t, *J* 4.5 Hz, 2"-H_2), 4.05–4.23 (2 H, m, 1"-H_2), 6.80 (1 H, t, *J* 3.5 Hz, 3'-H), 9.34 (1 H, s, CHO); m/z 258 ($M + NH_4^+$, 100%), 241 ($M + H^+$, 78), 223 (34), 196 (20).

2-Hydroxyethyl 2-hydroxymethyl-6,6-dimethyl-2-cyclohexene-1-acetate **20** and *1,4,4a,5,6,7-Hexahydro-5,5-dimethyl-3*H*-2-benzopyran-3-one* **21**

Method 1: A stirred solution of the ester-aldehyde **19** (50 mg, 0.21 mmol) in THF (5 ml) under Ar at room temperature was treated with sodium triacetoxyborohydride (49 mg, 0.23 mmol). T.l.c. after 14 h indicated that the reaction was incomplete, so a second portion of sodium triacetoxyborohydride (49 mg, 0.23 mmol) was added and the stirring continued for a further 4 h, after which the reaction had gone to completion. The mixture was diluted with ether (25 ml) and washed successively with water and saturated sodium hydrogen carbonate solution. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to dryness to give the crude ester **20** (45 mg, 89%) as a pale yellow oil. Analysis by ^1H n.m.r. spectroscopy after standing in based-washed deuteriochloroform for *ca.* 1 h indicated the presence of the lactone **21** (**20:21** ratio *ca.* 7:3) and a pure sample of **20** could not be isolated. The following signals could be attributed to **20**; δ_H 0.87 (3 H, s, 6'-CH_3), 0.93 (3 H, s, 6'-CH_3), 2.27 (1 H, dd, *J* 6.5, 15 Hz, 2-H), 2.52 (1 H, dd, *J* 5, 15 Hz, 2-H), 3.75–3.85 (2 H, m, 2"-H_2), 3.93 (1 H, d, *J* 12.5 Hz, C*H*OH), 4.06 (1 H, d, *J* 13.5 Hz, C*H*OH), 4.15–4.30 (2 H, m, 1"-H_2), 5.64 (1 H, t, *J* 3.5 Hz, 3'-H).

Method 2: A solution of the ester-aldehyde **19** (101 mg, 0.42 mmol) in glacial acetic acid (3 ml) was stirred with sodium triacetoxyborohydride (221 mg, 1.04 mmol) at 20–25 °C overnight. The mixture was diluted with dichloromethane (20 ml) and the organic phase washed successively with water (10 ml) and saturated aq. sodium hydrogen carbonate (2 x 10 ml). Drying and evaporation left a pale yellow oil (89 mg), which was chromatographed over silica gel (elution with dichloromethane) to obtain the *title compound* (±)-**21** (65 mg, 86%) as a colourless oil ($M + NH_4^+$, 198.1486. $C_{11}H_{20}NO_2$ requires 198.1494); ν_{max} 1746 cm^{-1}; δ_H 0.75 (3 H, s, 5-CH_3), 0.95 (3 H, s, 5-CH_3), 1.41 (2 H, t, *J* 7 Hz, 6-H_2), 2.05–2.10 (2 H, m, 7-H_2), 2.26–2.36 (2 H, m, 4-H, 4a-H), 2.61–2.71 (1 H, m, 4-H), 4.57 (1 H, d, *J* 13 Hz, 1-H), 4.69 (1 H, d, *J* 13 Hz, 1-H), 5.67 (1 H, br. s, 8-H); δ_C 173.4 (C-3), 130.2 (C-8a), 123.4 (C-8), 71.3 (C-1), 41.6, 35.5, 31.4, 28.2, 22.6, 19.6 (C-4, C-4a, C-5, C-6, C-7, 2 x CH_3); m/z 198 ($M + NH_4^+$, 100%), 181 ($M + H^+$, 92), 80 (21).

2-Hydroxymethyl-6,6-dimethyl-2-cyclohexene-1-ethanol **22**

A solution of the ester-aldehyde **19** (30 mg, 0.125 mmol) in ethanol (5 ml) at –8 °C was treated with sodium borohydride (5 mg, 0.14 mmol) and the reaction monitored by t.l.c. The reduction appeared to be proceeding slowly and it was therefore allowed to warm slightly to 0 °C. T.l.c. after 90 min. suggested that the reaction had stopped, so a second portion of sodium borohydride (5 mg, 0.14 mmol) was added. After 3 h the reaction was quenched with 0.1 M hydrochloric acid (10 ml) and diluted with ether (20 ml). The organic phase was washed well with water (2 x 8 ml) and saturated aq. sodium hydrogen carbonate (2 x 8 ml), dried and evaporated. The residual colourless oil (23 mg) was chromatographed, eluting with ethyl acetate - petroleum (1:1), which gave the *title compound* **22** (10 mg, 43%) as a colourless oil ($M + NH_4^+$, 202.1805. $C_{11}H_{24}NO_2$ requires 202.1807); δ_H 0.87 (3 H, s, 6'-CH_3), 0.90 (3 H, s, 6'-CH_3), 1.16 (1 H, dt, *J* 5, 13 Hz, 5'-H), 1.40 (1 H, dt, *J* 8, 13 Hz, 5'-H), 1.49–1.61 (1 H, m, 2-H), 1.69–1.79 (1 H, m, 2-H), 1.85–1.90 (1 H, br s, 1'-H), 1.95–2.05 (2 H, m, 4'-H_2), 2.69 (2 H, br. s, 2 x OH), 3.55–3.65 (1 H, m, 1-H), 3.70–3.78 (1 H, m, 1-H), 4.00 (1 H, d, *J* 12.5 Hz, C*H*OH), 4.16 (1 H, d, *J* 12.5 Hz, C*H*OH), 5.53 (1 H, t, *J* 3.5 Hz, 3'-H); m/z 202 ($M + NH_4^+$, 29%), 93 (22), 76 (100).

Methyl 2-formyl-6,6-dimethyl-2-cyclohexene-1-acetate **23**

To the ester-aldehyde **19** (50 mg, 0.21 mmol) in methanol (10 ml) was added a portion (1 ml, 0.21 mmol) of a solution of sodium (48 mg) in methanol (10 ml), and the mixture was stirred at room temperature under Ar until the reaction appeared to be complete by t.l.c. (4 h). The product was filtered through a small plug of silica gel and the filtrate evaporated. The resulting orange oil (70 mg) was chromatographed, eluting with dichloromethane, to give the *title compound* (±)-**23** (33 mg, 75%) as a colourless oil (*M* + H^+, 211.1322. $C_{12}H_{19}O_3$ requires 211.1334); ν_{max} (neat) 1735, 1685 cm^{-1}; δ_H 0.82 (3 H, s, 6'-CH_3), 0.90 (3 H, s, 6'-CH_3), 1.2–1.3 (1 H, m, 5'-H_{eq}), 1.49 (1 H, ddd, *J* 7, 10, 14 Hz, 5'-H_{ax}), 2.15 (1 H, dd, *J* 5, 15 Hz, 2-H), 2.25–2.4 (3 H, m, 2-H, 4'-H_2), 2.80 (1 H, br. t, *J* 6.5 Hz, 1'-H), 3.62 (3 H, s, OCH_3), 6.77 (1 H, t, *J* 3.5 Hz, 3'-H), 9.37 (1 H, s, CHO); m/z 228 (M + NH_4^+, 100%), 211 (M + H^+, 50).

Ethyl 2-formyl-6,6-dimethyl-2-cyclohexene-1-acetate **24**

To the ester-aldehyde **19** (50 mg, 0.21 mmol) in ethanol (10 ml) was added a portion (1 ml, 0.21 mmol) of a solution of sodium (48 mg) in methanol (10 ml), and the mixture was stirred at room temperature under Ar for 20 min. The product was filtered through a small plug of silica gel and the filtrate evaporated. The resulting oil was chromatographed, eluting with dichloromethane, to obtain the *title compound* (±)-**24** (29 mg, 62%) as a very pale yellow oil (*M* + NH_4^+, 242.1734. $C_{13}H_{24}NO_3$ requires 242.1756); ν_{max} 1733, 1683 cm^{-1}; δ_H 0.84 (3 H, s, 6'-CH_3), 0.93 (3 H, s, 6'-CH_3), 1.24 (3 H, t, *J* 7 Hz, OCH_2CH_3), 1.20–1.35 (1 H, m, 5'-H), 1.45–1.55 (1 H, m, 5'-H), 2.17 (1 H, dd, *J* 5, 15 Hz, 2-H), 2.22–2.45 (3 H, m, 2-H, 4'-H_2), 2.83 (1 H, br. t, *J ca.* 6 Hz, 1'-H), 4.10 (2 H, q, *J* 7 Hz, OCH_2), 6.78 (1 H, t, *J* 3.5 Hz, 3'-H), 9.40 (1 H, s, CHO); m/z 242 (M + NH_4^+, 100%), 225 (27).

2-Hydroxyethyl 2-(1,3-dithiolan-2-yl)-6,6-dimethyl-2-cyclohexene-1-acetate **25**

A solution of the ester-aldehyde **19** (50 mg, 0.21 mmol) in dichloromethane (1.5 ml) at –78 °C was treated with 1,2-ethanedithiol (0.03 ml, 0.36 mmol, 1.7 equiv.) and titanium tetrachloride in dichloromethane (1.0 M, 0.11 ml, 0.11 mmol, 0.5 equiv.), and then allowed to warm up to room temperature. After 2.5 h the mixture was quenched with water and the organic layer was washed with aq. potassium hydroxide (20%; 1 ml), dried and evaporated. The residual pale yellow oil (67 mg) was chromatographed, eluting firstly with dichloromethane and then dichloromethane - ether (10:1), which gave the *title compound* **25** (52 mg, 79%) as a colourless oil (*M* + H^+, 317.1246. $C_{15}H_{25}O_3S_2$ requires 317.1245); ν_{max} 3448 (br.), 1735 cm^{-1}; δ_H 0.85 (6 H, s, 6'-Me_2), 1.12 (1 H, br. dd, *J* 6, 14 Hz, 5'-H_{eq}), 1.35–1.45 (1 H, m, 5'-H_{ax}), 1.95–2.05 (2 H, m, 4'-H_2), 2.25 (1 H, br. s, OH), 2.42 (1 H, dd, *J* 8, 17 Hz, 2-H), 2.5–2.6 (2 H, m, 1'-H, 2-H), 3.10–3.20 (3 H, m, 4"-H, 5"-H_2), 3.25–3.4 (1 H, m, 4"-H), 3.78 (2 H, br. s, 2"'-H_2), 4.18 (2 H, t, *J* 4.5 Hz, 1"'-H_2), 5.10 (1 H, s, 2"-H), 5.87 (1 H, br. t, *J* 3.5 Hz, 3'-H); δ_C 174.0 (CO), 137.7 (C-2'), 124.9 (C-3'), 66.1, 61.1, 57.7 (C-2", C-1"', C-2"'), 42.0, 39.4, 38.4, 37.6, 32.5 (C-6'), 29.7, 27.2, 25.8, 22.9; m/z 317 (M + H^+, 30%), 316 (39), 255 (19), 247 (32), 212 (100), 105 (41).

1,4,4a,5,6,7-Hexahydro-5,5-dimethyl-3H-2-benzopyran-3-ols **26** *and* **27**

A solution of the lactone (±)-**21** (21 mg, 0.12 mmol) in THF (3 ml) at –78 °C was treated with DIBAH in THF (1.0 M, 0.12 ml, 0.12 mmol). T.l.c. showed an immediate reaction. The mixture was quenched with hydrochloric acid (1.0 M, 1 ml), allowed to warm to room temperature and diluted with ether (20 ml). The mixture was washed with water and saturated aq. sodium hydrogen carbonate, and the organic phase dried and evaporated. The residual yellow oil (22 mg) was chromatographed, eluting with dichloromethane, to obtain the mixed *title compounds* **26** and **27** (19 mg, 89%; ratio 1.3:1 by ^1H n.m.r. spectroscopy) as a colourless oil (*M* + NH_4^+, 200.1658. $C_{11}H_{22}NO_2$ requires 200.1651); ν_{max} 3391 cm^{-1}; δ_H 0.77 (3 H, s, 5-CH_3), 0.78 (3 H, s, 5-CH_3*), 0.91 (3 H, s, 5-CH_3), 0.92 (3 H, s, 5-CH_3*), 1.20 (1 H, ddd, *J* 9, 13.5, 13.5 Hz, 4β-H_{ax}*), 1.2–1.4 (m, 6-H_2*, 6-H_2), 1.46 (1 H, ddd, *J* 3.5, 13, 13 Hz, 4β-H_{ax}), 1.85 (1 H, dd, *J* 4, 13 Hz, 4α-H_{eq}), 1.85–2.10 (m, 4α-H_{eq}*, 4a-H*, 7-H_2*, 7-H_2), 2.33 (1 H, apparent br. d, *J* 13 Hz, 4a-H), 3.02 (1 H, br. s, exchanges with D_2O, OH), 3.49 (1 H, d, *J* 4.5 Hz, exchanges with D_2O, OH*), 3.79 (1 H, d, *J* 12.5 Hz, 1-

H), 3.99 (1 H, d, *J* 13 Hz, 1-H*), 4.18 (1 H, d, *J* 13 Hz, 1-H*), 4.48 (1 H, d, *J* 12.5 Hz, 1-H), 4.82 (1 H, br. d, *J* 9 Hz, 3-H_{ax}*), 5.39 (1 H, br. s, 3-H_{eq}), 5.51 (2 H, br. s, 8-H, 8-H*) [peaks (*) due to the major isomer **26** were assigned using a 2-D (COSY) spectrum]; m/z 200 ($M + NH_4^+$, 25%) 182 (100), 165 (33).

2-Hydroxymethyl-N-*methoxy*-N-*methyl-6,6-dimethyl-2-cyclohexene-1-acetamide* **28**

A stirred solution of *N,O*-dimethylhydroxylamine hydrochloride (105 mg, 1.1 mmol) in dichloromethane (4 ml) under Ar at 0 °C was treated with trimethylaluminium in hexanes (2.0 M; 0.55 ml, 1.1 mmol). The mixture was stirred for 10 min and then added to a solution of the lactone **21** (65 mg, 0.36 mmol) in dichloromethane (4 ml). T.l.c. showed that there had been an immediate reaction, so the mixture was quenched at 0 °C with hydrochloric acid (2 M, 2 ml). The organic layer was separated and washed with water (3 x 5 ml) and saturated aq. sodium hydrogen carbonate (2 x 5 ml), dried and evaporated to obtain the *title compound* **28** (84 mg, 96%) as a pale yellow oil which was used without further purification ($M + H^+$, 242.1762. $C_{13}H_{24}NO_3$ requires 242.1756); ν_{max} 3428 (br.), 1652 cm^{-1}; δ_H 0.84 (3 H, s, 6'-CH_3), 0.91 (3 H, s, 6'-CH_3), 1.26 (1 H, ddd, *J* 6, 6, 13.5 Hz, 5'-H), 1.38 (1 H, ddd, *J* 7.5, 7.5, 13.5 Hz, 5'-H), 1.95–2.05 (2 H, br. s, 4'-H_2), 2.28 (1 H, dd, *J* 7, 16.5 Hz, 2-H), 2.5–2.7 (2 H, m, 2-H, 1'-H), 3.17 (3 H, s, NCH_3), 3.66 (3 H, s, OCH_3), 3.82 (1 H, d, *J* 13 Hz, C*H*OH), 3.94 (1 H, d, *J* 13 Hz, C*H*OH), 5.59 (1 H, br. s, 3'-H); m/z 242 ($M + H^+$, 100%), 224 (25), 198 (20).

2-(t-Butyldimethylsilyloxymethyl)-N-*methoxy*-N-*methyl-6,6-dimethyl-2-cyclohexene-1-acetamide* **29**

To a stirred solution of the amide **28** (78 mg, 0.32 mmol) in THF (2 ml) under Ar was added *t*-butyldimethylsilyl chloride (59 mg, 0.39 mmol) followed by imidazole (33 mg, 0.48 mmol), whereupon a white precipitate was formed. The mixture was stirred overnight and then diluted with ether (25 ml) and washed with water (3 x 10 ml). The organic phase was dried and evaporated, giving a pale yellow oil (114 mg) which was chromatographed (elution with petroleum - ethyl acetate 10:1) to obtain the *title compound* **29** (100 mg, 87%) as a colourless oil ($M + H^+$, 356.2633. $C_{19}H_{38}O_3NSi$ requires 356.2621); δ_H 0.02 (3 H, s, $SiCH_3$), 0.03 (3 H, s, $SiCH_3$), 0.80 (3 H, s, 6'-CH_3), 0.87 (12 H, br. s, 6'-CH_3 and *t*-Bu), 1.17 (1 H, ddd, *J* 4.5, 4.5, 13.5 Hz, 5'-H), 1.45 (1 H, ddd, *J* 8.5, 8.5, 13.5 Hz, 5'-H), 1.95–2.05 (2 H, br. s, 4'-H_2), 2.23 (1 H, dd, *J* 3.5, 16.5 Hz, 2-H), 2.35–2.40 (1 H, m, 1'-H), 2.61 (1 H, br. dd, *J* 7, 16.5 Hz, 2-H), 3.15 (3 H, s, NCH_3), 3.65 (3 H, s, OCH_3), 4.00 (2 H, br. s, CH_2OSi), 5.63 (1 H, br. s, 3'-H); m/z 356 ($M + H^+$, 7%), 93 (24), 76 (100).

*1,4,4aα,5,6,7-Hexahydro-3β,5,5-trimethyl-3*H*-2-benzopyran-3α-ol* **30**

To a stirred solution of the amide **29** (21 mg, 0.059 mmol) in THF (2 ml) at –78 °C under Ar was added methyllithium in ether (1.4 M, 0.215 ml, 0.30 mmol). T.l.c. indicated an immediate reaction, so the mixture was quenched with hydrochloric acid (2 M, 1 ml) and allowed to warm to room temperature. The organic layer was diluted with ether (15 ml), separated, washed with water (3 x 5 ml) and saturated aq. sodium hydrogen carbonate (2 x 5 ml), dried and evaporated. The resulting pale yellow oil (17 mg) was chromatographed, eluting with dichloromethane, affording the *title compound* **30** (7 mg, 60%) as a white solid ($M + NH_4^+$, 214.1810. $C_{12}H_{24}O_2N$ requires 214.1807); δ_H 0.77 (3 H, s, 5-CH_3), 0.92 (3 H, s, 5-CH_3), 1.2–1.5 (3 H, m, 4β-H_{ax}, 6-H_2), 1.42 (3 H, s, 3-CH_3), 1.87 (1 H, dd, *J* 5, 13 Hz, 4α-H_{eq}), 1.9–2.1 (3 H, m, 7-H_2, OH), 2.28 (1 H, br. d, *J* 13 Hz, 4a-H), 3.83 (1 H, d, *J* 12.5 Hz, 1-H), 4.42 (1 H, br. d, *J* 12.5 Hz, 1-H), 5.51 (1 H, br. s, 8-H); m/z 179 [$(M - H_2O + H)^+$, 100%]. The axial 3α-OH arrangement in **30** was assigned after comparison of its ^1H n.m.r. signals with those of the lactols **26** and **27**. A small amount (<10%) of the 3β-OH epimer was also evident in the spectrum of **30** obtained as above.

2-(t-Butyldimethylsilyloxymethyl)-6,6-dimethyl-2-cyclohexene-1-propan-2-one **31**

To a stirred solution of the amide **29** (15 mg, 0.042 mmol) in THF (2 ml) at –78 °C under Ar was added methyllithium in ether (1.4 M, 0.10 ml, 0.14 mmol). T.l.c. indicated an immediate reaction and, keeping the mixture at 0 °C, it was quenched with hydrochloric acid (0.1 M, 2 ml) and diluted with ether (15 ml). The

organic phase was separated, washed with water (3 x 5 ml) and saturated aq. sodium hydrogen carbonate (2 x 5 ml), dried and evaporated. The resulting orange oil (11 mg) was chromatographed, eluting with dichloromethane, affording the *title compound* **31** (8 mg, 61%) as a colourless oil (*M* + H^+, 311.2404. $C_{18}H_{35}O_2Si$ requires 311.2406); ν_{max} 1719 cm^{-1}; δ_H 0.01 (3 H, s, $SiCH_3$), 0.02 (3 H, s, $SiCH_3$), 0.74 (3 H, s, 6'-CH_3), 0.87 (12 H, s, ^tBu and 6'-CH_3), 1.16 (1 H, ddd, *J* 5, 5, 13.5 Hz, 5'-H), 1.38 (1 H, ddd, *J* 8.5, 8.5, 13.5 Hz, 5'-H), 1.95–2.05 (2 H, br. s, 4'-H_2), 2.13 (3 H, s, $COCH_3$), 2.3–2.6 (3 H, m, 1-H_2, 1'-H), 3.92 (1 H, dd, *J* 1.5, 13 Hz, CHOSi), 3.97 (1 H, dd, *J* 1.5, 13 Hz, CHOSi), 5.59 (1 H, br. s, 3'-H); m/z 311 (M + H^+, 37%), 179 (100).

2-Methoxymethyl-N-*methoxy*-N-*methyl-6,6-dimethyl-2-cyclohexene-1-acetamide* **32**

A solution of the amide **28** (84 mg, 0.35 mmol) in iodomethane (2 ml) under Ar was treated with silver(I) oxide (0.87 g, 7 mmol). After stirring for 14 h, t.l.c. (elution with ethyl acetate - petroleum 1:1) indicated that some of the amide **32** remained, so further portions of iodomethane (2 ml) and silver (I) oxide (0.44 g, 3.5 mmol) were added. After a total of 24 h the mixture was filtered through Celite® and the residue washed with ether. The combined filtrate was evaporated, giving the *title compound* **32** (87 mg, 98%) as a pale yellow oil (*M* + H^+, 256.1910. $C_{14}H_{26}O_3N$ requires 256.1912); δ_H 0.81 (3 H, s, 6'-CH_3), 0.89 (3 H, s, 6'-CH_3), 1.19 (1 H, ddd, *J* 5, 5, 13.5 Hz, 5'-H), 1.42 (1 H, ddd, *J* 8, 8, 13.5 Hz, 5'-H), 1.95–2.05 (2 H, br. s, 4'-H_2), 2.29 (1 H, dd, *J* 3.5, 16.5 Hz, 2-H), 2.35–2.65 (2 H, m, 2-H, 1'-H), 3.15 (3 H, s, NCH_3), 3.24 (3 H, s, CH_2OCH_3), 3.65 (3 H, s, $NOCH_3$), 3.68 (1 H, d, *J* 12 Hz, $CHOCH_3$), 3.83 (1 H, d, *J* 12 Hz, $CHOCH_3$), 5.64 (1 H, t, *J ca.* 1 Hz, 3'-H); m/z 256 (M + H^+, 100%).

2-Methoxymethyl-6,6-dimethyl-2-cyclohexene-1-acetaldehyde **33** and *2-methoxymethyl-6,6-dimethyl-2-cyclohexene-1-ethanol* **34**

A solution of the amide **32** (85 mg, 0.33 mmol) in THF (3 ml) under Ar was stirred in a cryobath at –78 °C for 0.5 h and then treated with an excess of lithium aluminium hydride (*ca.* 40 mg, 1 mmol). The mixture was stirred at –78 °C for 48 h, carefully quenched with hydrochloric acid (1 M, 2 ml) and allowed to warm to room temperature. The mixture was then diluted with ether (30 ml), washed with water (3 x 10 ml) and saturated aq. sodium hydrogen carbonate (2 x 10 ml), dried and evaporated to give a colourless oil. Chromatography, eluting with ethyl acetate - petroleum (1:4), gave the aldehyde **33** (28 mg, 43%) and the alcohol **34** (12 mg, 18%) as colourless oils. The aldehyde **33** (*M* + NH_4^+, 214.1808. $C_{12}H_{24}O_2N$ requires 214.1808) had δ_H 0.79 (3 H, s, 6'-CH_3), 0.92 (3 H, s, 6'-CH_3), 1.15–1.40 (2 H, m, 5'-H_2), 1.95–2.05 (2 H, m, 4'-H_2), 2.35 (1 H, ddd, *J* 2.5, 7, 18 Hz, 2-H), 2.40–2.50 (3 H, m, 1'-H, 2-H), 3.19 (3 H, s, OCH_3), 3.62 (1 H, d, *J* 11.5 Hz, $CHOCH_3$), 3.84 (1 H, dd, *J* 1, 11.5 Hz, $CHOCH_3$), 5.66 (1 H, br. t, *J* 3.5 Hz, 3'-H), 9.70 (1 H, t, *J* 2.5 Hz, CHO); m/z 214 (M + NH_4^+, 100%). The alcohol **34** (*M* + NH_4^+, 216.1962. $C_{12}H_{26}O_2N$ requires 216.1963) had ν_{max} 3419 (br.) cm^{-1}; δ_H 0.88 (3 H, s, 6'-CH_3), 0.90 (3 H, s, 6'-CH_3), 1.16 (1 H, dt, *J* 4.5, 13 Hz, 5'-H), 1.35–1.60 (2-H, m, 2-H, 5'-H), 1.70–1.80 (2 H, m, 2-H, 1'-H), 1.95–2.05 (2 H, m, 4'-H_2), 2.36 (1 H, br. s, OH), 3.26 (3 H, s, OCH_3), 3.55–3.7 (2 H, m, 1-H_2), 3.71 (1 H, d, *J* 12 Hz, $CHOCH_3$), 4.06 (1 H, dd, *J* 1.5, 12 Hz, $CHOCH_3$), 5.56 (1 H, br. t, *J* 3.5 Hz, 3'-H); m/z 216 (M + NH_4^+, 100%), 199 (38).

2-(1,3-Dithiolan-2-yl)-6,6-dimethyl-2-cyclohexene-1-ethanol **35**

A solution of the ester **25** (295 mg, 0.93 mmol) in THF (10 ml) at 0 °C was treated with an excess of lithium aluminium hydride (110 mg, 2.9 mmol). The mixture was stirred at 0 °C for 15 min and carefully quenched by the dropwise addition of aq. potassium hydroxide (2 M, 6 ml). The mixture was then diluted with ether (40 ml), washed with water (4 x 15 ml), dried and evaporated to give the *title compound* **35** (223 mg, 97%) as a pale yellow oil which solidified on freezing and was suitable for use without further purification (*M* + H^+, 259.1187. $C_{13}H_{23}OS_2$ requires 259.1190); ν_{max} 3386 (br.) cm^{-1}; δ_H 0.84 (3 H, s, 6'-CH_3), 0.92 (3 H, s, 6'-CH_3), 1.05–1.25 (1 H, m, 5'-H), 1.40–1.65 (2 H, m, 2-H, 5'-H), 1.70–1.90 (2 H, m, 2-H, 1'-H), 1.95–2.05 (2 H, m, 4'-H_2), 3.10–3.25 (3 H, m, 4"-H, 5"-H_2), 3.30–3.40 (1 H, m, 4"-H), 3.60–3.75 (2 H,

m, 1-H_2), 5.15 (1 H, s, 2"-H), 5.90 (1 H, t, *J* 3.5 Hz, 3'-H); δ_C 138.5 (C-2'), 123.6 (C-3'), 63.2 (C-1), 58.2 (C-2"), 43.0, 39.1, 37.9, 35.9, 32.6 (C-6'), 30.0, 28.0, 26.4, 23.0; m/z 259 (M + H^+, 11%), 165 (100).

2-(1,3-Dithiolan-2-yl)-6,6-dimethyl-2-cyclohexene-1-acetaldehyde **36**

To a solution of the alcohol **35** (22 mg, 0.085 mmol) in dichloromethane (0.5 ml) at room temperature under Ar was added triethylamine (26 mg, 0.26 mmol), followed by a solution of sulfur trioxide pyridine complex (41 mg, 0.26 mmol) in dry dimethylsulfoxide (0.5 ml). The mixture was stirred for 16 h, but t.l.c. showed that the reaction was incomplete and more sulfur trioxide pyridine complex (41 mg, 0.26 mmol) and triethylamine (26 mg, 0.26 mmol) were added. T.l.c. after a further 1.5 h showed that the reaction had gone to completion. The mixture was treated with hydrochloric acid (0.1 M, 5 ml) and extracted with ether (3 x 5 ml). The extract was washed with saturated aq. sodium hydrogen carbonate (3 x 5 ml), dried and evaporated to give a brown oil (25 mg), which was chromatographed (elution with ethyl acetate - petroleum 20:1) to obtain the *title compound* **36** (8 mg, 38%) as a colourless oil (*M* + H^+, 257.1034. $C_{13}H_{21}OS_2$ requires 257.1034); δ_H 0.80 (3 H, s, 6'-CH_3), 0.88 (3 H, s, 6'-CH_3), 1.10–1.20 (1 H, m, 5'-H), 1.39 (1 H, ddd, *J* 9, 9, 13.5 Hz, 5'-H), 1.95–2.15 (2 H, m, 4'-H_2), 2.58 (1 H, ddd, *J* 2, 7.5, 18 Hz, 2-H), 2.60–2.70 (2 H, m, 2-H, 1'-H), 3.10–3.25 (3 H, m, 4"-H, 5"-H_2), 3.30–3.40 (1 H, m, 4"-H), 5.13 (1 H, s, 2"-H), 5.87 (1 H, t, *J* 3.5 Hz, 3'-H), 9.78 (1 H, br. s, CHO); δ_C 202.3 (CHO), 137.2 (C-2'), 125.5 (C-3'), 58.3 (C-2"), 47.7, 39.4, 39.0, 38.9, 32.4 (C-6'), 30.0, 28.1, 25.8, 23.0; m/z 257 (M + H^+, 58%), 198 (100), 181 (31).

α-(3-Furyl)-2-(1,3-dithiolan-2-yl)-6,6-dimethyl-2-cyclohexene-1-ethanol **37**

A solution of freshly prepared 3-bromofuran[29] (75 mg, 0.5 mmol) in THF (2 ml) at –78 °C was treated with *n*-butyllithium in hexane (1.35 M, 0.22 ml, 0.3 mmol) and stirred for 70 min. A solution of the aldehyde **36** (13 mg, 0.051 mmol) in THF (0.5 ml) at –78 °C was then added and the mixture was stirred for 15 min, whereupon t.l.c. showed the reaction to be complete. The reaction was quenched with saturated aq. ammonium chloride (3 ml), allowed to warm to room temperature and diluted with ether (15 ml). The organic phase was washed with water (3 x 5 ml), dried and evaporated. The residual brown oil (17 mg) was chromatographed, eluting with dichloromethane, to give the *title compounds* **37**. The *major diastereoisomer* (4 mg, 24%) eluted first, and was a pale yellow oil (*M* – H_2O + H^+, 307.1162. $C_{17}H_{23}OS_2$ requires 307.1190); δ_H 0.88 (3 H, s, 6'-CH_3), 0.97 (3 H, s, 6'-CH_3), 1.1–1.4 (2 H, m, 5'-H_2), 1.69 (1 H, ddd, *J* 2, 10.5, 15.5 Hz, 2-H), 1.85 (1 H, ddd, *J* 3, 7, 15.5 Hz, 2-H), 2.0–2.1 (2 H, m, 4'-H_2), 2.23 (1 H, br. d, *J* 7 Hz, 1'-H), 2.44 (1 H, d, *J* 5.5 Hz, OH), 3.1–3.3 (3 H, m, 4"-H, 5"-H_2), 3.3–3.4 (1 H, m, 4"-H), 4.6–4.7 (1 H, m, 1-H), 5.30 (1 H, s, 2"-H), 5.89 (1 H, t, *J* 3.5 Hz, 3'-H), 6.39 (1 H, s, 4"'-H), 7.37 (2 H, br. s, 2"'-H and 5"'-H); m/z 307 [(M – H_2O + 1)$^+$, 5%], 290 (49), 273 (36), 264 (33), 231 (99), 229 (32), 200 (29), 198 (100), 186 (31), 184 (20), 128 (78). The *minor diastereoisomer* (2 mg, 12%) was a colourless oil (*M* – H_2O + H^+, 307.1171. $C_{17}H_{23}OS_2$ requires 307.1190); δ_H 0.85 (3 H, s, 6'-CH_3), 0.98 (3 H, s, 6'-CH_3), 1.1–1.2 (1 H, m, 5'-H), 1.4–1.6 (2 H, m, 2-H, 5'-H), 1.73 (1 H, d, *J* 3.5 Hz, OH), 1.85 (1 H, t, *J* 5.5 Hz, 1'-H), 1.95–2.10 (3 H, m, 2-H, 4'-H_2), 2.93–3.02 (1 H, m, 4"-H), 3.08–3.19 (2 H, m, 4"-H, 5"-H), 3.3–3.4 (1 H, m, 5"-H), 4.75 (1 H, dt, *J* 3.5, 7 Hz, 1-H), 4.91 (1 H, br. s, 2"-H), 5.99 (1 H, t, *J* 3.5 Hz, 3'-H), 6.45 (1 H, d, *J* 1 Hz, 4"'-H), 7.36–7.46 (2 H, m, 2"'-H, 5"'-H); m/z 307 [(M – H_2O + H)$^+$, 26%], 251 (25), 198 (44), 186 (100), 147 (22).

α-(3-Furyl)-2-methoxymethyl-6,6-dimethyl-2-cyclohexene-1-ethanol **38**

A solution of freshly prepared 3-bromofuran[29] (122 mg, 0.83 mmol) in THF (2 ml) at –78 °C was treated with *n*-butyllithium in hexane (1.35 M, 0.52 ml, 0.7 mmol) and stirred for 30 min. A solution of the aldehyde **33** (27 mg, 0.14 mmol) in THF (1 ml) at –78 °C was then added and the mixture stirred for 40 min, whereupon t.l.c. showed the reaction to be complete. The reaction was quenched with hydrochloric acid (1 M, 2 ml), allowed to warm to room temperature and diluted with ether (20 ml). The organic phase was washed with water (3 x 5 ml) and saturated aq. sodium hydrogen carbonate (2 x 5 ml), dried and evaporated. The residual

orange oil (48 mg) was chromatographed, eluting with dichloromethane, to give the *title compound* **38** (mixed diastereoisomers, 15 mg, 41%) as a pale yellow oil ($M + NH_4^+$, 282.2069. $C_{16}H_{28}NO_3$ requires 282.2069). The diastereoisomer ratio *ca.* 1.2:1 by ^1H n.m.r. spectroscopy. The assignments are tentative and the signals attributed to the major diastereoisomer are indicated thus (*); δ_H 0.89 (3 H, s, CH_3), 0.90 (3 H, s, CH_3*), 0.92 (3 H, s, CH_3), 0.93 (3 H, s, CH_3*), 1.15–1.3 (1 H, m, 5'-H), 1.35–1.7 (2 H, m, 2-H, 5'-H), 1.8–2.1 (4 H, m, 2-H, 1'-H, 4'-H_2), 2.78 (1 H, br. s, OH), 3.25 (3 H, s, OMe), 3.30 (3 H, s, OMe*), 3.58 (1 H, br. s, OH*), 3.69 (1 H, d, *J* 12 Hz, C*H*OMe), 3.83 (1 H, d, *J* 12 Hz, C*H*OMe*), 3.96 (1 H, d, *J* 12 Hz, C*H*OMe), 4.12 (1 H, d, *J* 12 Hz, C*H*OMe*), 4.60 (1 H, br. d, *J* 9.5 Hz, 1-H*), 4.76 (1 H, dd, *J* 4.5, 8.5 Hz, 1-H), 5.54 (1 H, br. s, 3'-H*), 5.61 (1 H, br. s, 3'-H), 6.36 (1 H, d, *J* 1 Hz, 4"-H*), 6.40 (1 H, d, *J* 1 Hz, 4"-H), 7.35–7.4 (4 H, m, 2"-H, 5"-H); m/z 282 ($M + NH_4^+$, 21%) 247 (100), 215 (37).

*3,4,4a**S**,5,6,7-Hexahydro-5,5-dimethyl-4'**S**,5'**S**-bis(2-methylphenyl)spiro[8H-2-benzopyran-3,2'-[1,3]dioxolan]-8-one* **39a** *and (4a**R**,4'**S**,5'**S**)-isomer* **40a**

Table 1, entry 1: To a solution of (*S*,*S*)-**1a**[5,30] (1.86 g, 7.0 mmol) in THF (50 ml) at room temperature was added a solution of the aldehyde **4** (1.06 g, 7.0 mmol) in THF (10 ml) and the mixture was stirred for 4 d, after which time the aldehyde **4** was no longer detectable by t.l.c. The solvent was evaporated and the residue chromatographed, eluting with dichloromethane - ethyl acetate (10:1), to obtain the mixed cycloadducts **39a** and **40a** (total 2.51 g, 86%, ratio *ca.* 3.3:1). Crystallisation from ether at –30 °C gave the *title compound* **39a** (1.62 g, 55%, d.e. >98%), m.p. 167–169 °C (Found: C, 77.28; H, 7.28. $C_{27}H_{30}O_4$ requires C, 77.48; H, 7.22%) (*M* + H^+, 419.2228. $C_{27}H_{31}O_4$ requires 419.2222); $[\alpha]_D^{20}$ +132 ±3 (*c* 1.0, acetone); ν_{max} (Nujol) 1675, 1590, 1200, 990, 880, 765 cm^{-1}; δ_H 0.93 (3 H, s, 5-Me), 1.11 (3 H, s, 5-Me), 1.65 (3 H, s, ArMe), 1.76 (3 H, s, ArMe), 1.65–1.80 (2 H, m, 6-H_2), 1.97 (1 H, apparent t, *J ca.* 13 Hz, 4-H_{ax}), 2.25 (1 H, dd, *J* 5, 12.5 Hz, 4-H_{eq}), 2.39–2.44 (2 H, m, 7-H_2), 2.76 (1 H, ddd, *J* 2.5, 5, 13 Hz, 4a-H), 5.26 (1 H, d, *J* 9 Hz, 5'-H or 4'-H), 5.57 (1 H, d, *J* 9 Hz, 4'-H or 5'-H), 6.97 and 7.04 (each 1 H, d, *J* 7.5 Hz, 3"-H and 3"'-H), 7.13–7.29 (4 H, m, 4"-H, 5"-H, 4"'-H, 5"'-H), 7.58 (2 H, apparent t, *J ca.* 7 Hz, 6"-H and 6"'-H), 7.66 (1 H, d, *J* 2 Hz, 1-H); m/z 419 (M + H^+, 100%), 230 (11). The minor (*R*,*S*,*S*)-isomer **40a** had δ_H 5.39 (1 H, d, *J* 9 Hz, 4'-H or 5'-H).

Table 1, entry 2: To a solution of the bromoacetal (*S*,*S*)-**3a**[5] (10.29 g, 29.63 mmol) in THF (150 ml) at 0 °C was slowly added potassium *t*-butoxide (10.0 g, 89 mmol). The suspension became faintly yellow. A solution of Aliquat® 336[30] (3.01 g, 7.45 mmol) in THF (20 ml) was then slowly added and the reaction mixture was stirred at 0 °C until the bromoacetal **3a** was no longer detectable by ^1H n.m.r. spectroscopy (*ca.* 40 min). To analyse the reaction, a 0.5 ml sample of the mixture was filtered through a small glass column containing 0.5 g of basic alumina which had been previously washed with dry ether (1 ml); the column was rinsed with more ether (1 ml) and the combined ethereal solution was concentrated and analysed by ^1H n.m.r. spectroscopy (the analysis was completed in *ca.* 10 min). The dioxolane **1a** has characteristic signals at δ_H 1.82 (6 H, s, 2 x ArMe), 3.44 (2 H, s, C=CH_2) and 5.35 (2 H, s, 4-H and 5-H). After removal of the THF by rotary evaporation (t ≤ 0.5 h, 0 °C), the residue was shaken with ether (100 ml) and the resulting suspension filtered under Ar through a 5 cm diameter glass column containing basic alumina (100 g) which had been previously washed with THF (100 ml) and ether (50 ml) to remove any absorbed water. The column was washed with a further portion of ether (100 ml). This filtration procedure required about 7 min. The combined ethereal solution was concentrated by rotary evaporation (20 min, room temperature) to obtain (*S*,*S*)-**1a** (≥7.1 g, 26.7 mmol, 90%) as a colourless oil which was used directly for the next step.

To the solution of the dioxolane (*S*,*S*)-**1a** (*ca.* 27 mmol), prepared as described above, in THF (100 ml) at room temperature was added a solution of the aldehyde **4** (4.10 g, 26.94 mmol) in THF (20 ml) and the mixture was stirred at room temperature for 65 h. Evaporation of the solvent afforded the mixed cycloadducts **39a** and **40a** (10.0 g, 89%, ratio *ca.* 3.4:1), which was dissolved in ether and cooled to –35 °C to obtain the cycloadduct (*S*,*S*,*S*)-**39a** (4.25 g, 38%, d.e. >98%). Concentrating the mother liquor and chromatography of the residue, eluting with dichloromethane - ethyl acetate (10:1) gave some unreacted aldehyde **4** (0.66 g, 16%) and a further portion mixed cycloadducts **39a** and **40a** (4.00 g) which upon crystallisation from ether at –35 °C yielded more (*S*,*S*,*S*)-**39a** (two crops, 2.18 g, 19%, d.e. >98%). The total yield of (*S*,*S*,*S*)-**39a**

was thus 6.43 g (57%).

Table 1, entry 3: To a solution of (*S*,*S*)-**1a**[5,30] (1.86 g, 7.02 mmol) in THF (50 ml) at –28 °C was added a solution of the aldehyde **4** (801 mg, 5.26 mmol) in THF (7 ml) and the mixture was stirred for 4 d, after which time the aldehyde **4** was no longer detectable by t.l.c. The solvent was evaporated and the residue chromatographed, eluting with dichloromethane - ethyl acetate (10:1), to obtain the mixed cycloadducts **39a** and **40a** (972 mg, 44%, ratio *ca.* 4.5:1). Crystallisation from ether at –30 °C gave the cycloadduct (*S*,*S*,*S*)-**39a** (537 mg, 24%; d.e. >98%).

4'S,5'S-bis*(2-Bromophenyl)-3,4,4aS,5,6,7-hexahydro-5,5-dimethylspiro[8H-2-benzopyran-3,2'-[1,3]dioxolan]-8-one* **39b** *and (4'S,5'S,4 a R)-isomer* **40b**

Table 1, entry 4: To a solution of (*S*,*S*)-**1b** [prepared from the bromoacetal (*S*,*S*)-**3b** (195 mg, 0.41 mmol) as described above][5] in THF (3 ml) at room temperature was added the aldehyde **4** (57.3 mg, 0.37 mmol) in THF (1 ml) and the mixture was stirred for 4 d, after which time t.l.c. indicated that the aldehyde **4** had been consumed. Evaporation of the solvent and chromatography of the residue, eluting with dichloromethane - ethyl acetate (10:1), gave the mixed cycloadducts **39b** and **40b** (145 mg, 70%, ratio *ca.* 4.5:1). Crystallisation from chloroform - petroleum (b.p. 60–80 °C) gave the *title compound* **39b** (18.2 mg, 9%, d.e. >98%), m.p. 209–210 °C (*M* + H$^+$, 547.0152. $C_{25}H_{25}O_4Br_2$ requires 547.0121); $[\alpha]_D^{20}$ –9 ±3 (*c* 0.34, acetone); ν_{max} (Nujol) 1675 cm^{-1}; δ_H 0.93 (3 H, s, 5-Me), 1.11 (3 H, s, 5-Me), 1.64–1.80 (2 H, m, 6-H$_2$), 1.97 (1 H, apparent t, *J ca.* 13 Hz, 4-H$_{ax}$), 2.26 (1 H, dd, *J* 5, 12.5 Hz, 4-H$_{eq}$), 2.42 (2 H, dd, *J* 5, 9 Hz, 7-H$_2$), 2.75 (1 H, ddd, *J* 2.5, 5, 13 Hz, 4a-H), 5.52 (1 H, d, *J* 9 Hz, 5'-H or 4'-H), 5.76 (1 H, d, *J* 9 Hz, 4'-H or 5'-H), 7.10–7.22 (2 H, m, 4"-H, 4"'-H), 7.35–7.40 (3 H, m, 5"-H, 5"'-H, 3"'-H or 3"-H), 7.45 (1 H, d, *J ca.* 7 Hz, 3"-H or 3"'-H), 7.63 (1 H, d, *J* 2.5 Hz, 1-H), 7.62–7.66 (2 H, m, 6"-H, 6"'-H); m/z 552 (42%), 551 (M + H$^+$, $^{81}Br_2$, 63), 550 (85), 549 (M + H$^+$, ^{81}Br + ^{79}Br, 100), 548 (43), 547 (M + H$^+$, ^{79}Br + ^{79}Br, 43), 230 (72), 228 (21), 214 (34), 213 (45), 212 (45), 195 (22), 184 (73), 178 (35), 170 (36), 167 (44). The minor product **40b** had characteristic n.m.r. signals at δ_H 5.5–5.6 (2 H, ABq, 4'-H, 5'-H) and 7.54 (1 H, d, *J* 2.5 Hz, 1-H).

4'R,5'R-bis*(2-Ethylphenyl)-3,4,4aR,5,6,7-hexahydro-5,5-dimethylspiro[8H-2-benzopyran-3,2'-[1,3]dioxolan]-8-one* **39c** *and (4'R,5'R,4 a S)-isomer* **40c**

Table 1, entry 5: A 5 ml round-bottomed flask, equipped with magnetic follower and containing (*R*,*R*)-**3c** (11.5 mg, 0.030 mmol) in THF (0.5 ml) under Ar, was cooled to 0 °C and treated with potassium *t*-butoxide (10.3 mg, 0.092 mmol) followed by a solution of Aliquat® 336[30] (25 mg, 0.06 mmol) in THF (0.5 ml) the mixture was stirred at 0 °C for 2 h. After evaporation of the solvent the residue was suspended in ether and filtered through a column containing basic alumina to remove excess starting materials and potassium bromide, eluting with a further small portion of ether. The filtrate was evaporated to give the crude dioxolane (*R*,*R*)-**1c**, which was dissolved in THF (1 ml), cooled to 0 °C treated with the aldehyde **4** (4.6 mg, 0.030 mmol) in THF (0.5 ml). The mixture was stirred at 0 °C for 3 d, monitoring the reaction by t.l.c. [dichloromethane - petroleum (b.p. 60–80 °C) - ethyl acetate 10:1:1]. Evaporation of the solvent gave the crude cycloadducts **39c** and **40c** as a mixture which was purified by chromatography, eluting with dichloromethane - petroleum (b.p. 60–80 °C) - ethyl acetate (10:1:1), followed by toluene - ethyl acetate (5:2), which gave the mixed *title compounds* **39c** and **40c** (5.6 mg, 42%, ratio *ca.* 5.5:1) (*M* + H$^+$, 447.2535. $C_{29}H_{35}O_4$ requires 447.2535); δ_H (signals due to both diastereoisomers unless indicated) 0.69 (3 H, t, *J* 7.5 Hz, ArCH$_2$C*H*$_3$), 0.76 (3 H, t, *J* 7.5 Hz, ArCH$_2$C*H*$_3$), 0.92 (3 H, s, 5-Me), 1.11 (3 H, s, 5-Me), 1.65–1.80 (2 H, m, 6-H$_2$), 1.9–2.3 (6 H, m, 4-H$_2$ and 2 x ArCH$_2$), 2.37–2.43 (2 H, m, 7-H$_2$), 2.76 (1 H, ddd, *J* 2.5, 5, 13 Hz, 4a-H), 5.33 (0.83 H, d, *J* 9 Hz, 5'-H or 4'-H of major), 5.35 (0.17 H, d, *J* 9 Hz, 5'-H or 4'-H of minor), 5.46 (0.17 H, d, *J* 9 Hz, 4'-H or 5'-H of minor), 5.65 (0.83 H, d, *J* 9 Hz, 4'-H or 5'-H of major), 6.97–7.10 (2 H, m, 3"-H and 3"'-H), 7.15–7.35 (4 H, m, 4"-H, 5"-H, 4"'-H, 5"'-H), 7.57 (0.17 H, d, *J* 2.5 Hz, 1-H of minor), 7.60–7.64 (2 H, m, 6"-H and 6"'-H), 7.66 (0.83 H, d, *J* 2.5 Hz, 1-H of major) ; m/z 447 (M + H$^+$, 100%).

3,4,4aS,5,6,7-Hexahydro-5,5-dimethyl-4'S,5'S-bis(2-methylphenyl)spiro[8H-2-benzopyran-3,2'-[1,3]dioxolan]-8-ols **41**

(S,S,S)-1,2-bis(2-Methylphenyl)-2-hydroxyethyl (2-formyl-6,6-dimethyl-2-cyclohexen-1-yl)acetate **42**

Method 1: To a vigorously stirred solution of the ortholactone (*S,S,S*)-**39a** (234 mg 0.56 mmol) in THF (10 ml) at room temperature was added dropwise a solution of L-selectride® in THF (1.0 M; 0.68 ml, 0.68 mmol). The stirring was maintained for 2.5 h, monitoring by t.l.c. (eluting with dichloromethane - ether 10:1, visualising with vanillin). After adding ice (*ca.* 0.5 g) the stirring was continued for 0.5 h to hydrate the intermediate lithium salt. After removal of solvents *in vacuo*, the products were partitioned between ether and water, and the combined ether phases dried and evaporated. Chromatography of the residue, eluting with dichloromethane - ether (10:1), gave the *title compound* (*S,S,S*)-**42** (182 mg, 77%) and recovered ortholactone **39a** (14.5 mg, 6.2%). The product (*S,S,S*)-**42** thus obtained was an amorphous solid, m.p. 74–77 °C (*M* + H^+, 421.2383. $C_{27}H_{33}O_4$ requires 421.2379); $[\alpha]_D^{20}$ +76 ±5 (*c* 0.48, acetone); ν_{max} (Nujol) 3400 (br.), 1735, 1680, 1581 cm^{-1}; δ_H 0.87 (3 H, s, 6-Me), 0.90 (3 H, s, 6'-Me), 1.25–1.35 (1 H, m, 5'-H), 1.4–1.6 (1 H, m, 5'-H), 1.73 (3 H, s, ArMe), 1.78 (3 H, s, ArMe), 2.12 (1 H, dd, *J* 6.5, 14.5 Hz, 2-H), 2.25–2.4 (2 H, m, 4'-H_2), 2.51 (1 H, dd, *J* 6.5, 14.5 Hz, 2-H), 2.94 (1 H, t, *J* 6.5 Hz, 1'-H), 5.27 (1 H, d, *J* 9 Hz, 2"-H), 5.95 (1 H, d, *J* 9 Hz, 1"-H), 6.8–6.9 (3 H, m, 3'-H, 3-H_{Ar} and 3-$H_{Ar'}$), 7.04–7.20 (5 H, m, 4,5-H_{Ar}, 4,5-$H_{Ar'}$ and OH), 7.44 (1 H, dd, *J ca.* 1.5, 7.5 Hz, 6-$H_{Ar'}$), 7.68 (1 H, br d, *J ca.* 7.5 Hz, 6-H_{Ar}), 9.40 (1 H, s, CHO); m/z 422 (13%), 421 (M + H^+, 100), 419 (10), 214 (14).

Method 2: A stirred solution of the ortholactone **39a** (0.936 g, 2.24 mmol) in THF (40 ml) at 20 °C under Ar was treated dropwise with L-selectride® in THF (1.0 M; 2.72 ml, 2.72 mmol). After 2.5 h the reaction was quenched with ice, stirred for a further 0.5 h and then extracted with ether (3 x 30 ml). Drying and evaporation gave an oil (0.9 g) which was chromatographed, eluting with dichloromethane - ether (10:1), to obtain the mixed carbinols **41** as a colourless oil (0.662 g, 1.57 mmol, 70%). The estimated C-8 epimer ratio was ≥ 5:1 (from ^1H n.m.r. signals due to H-1); δ_H 0.88 (3 H, s, 5-Me), 1.00 (3 H, s, 5-Me), 1.3–1.55 (3 H, m, 6-H_2 and 7-H), 1.64 (3 H, s, ArMe), 1.74 (3 H, s, ArMe), 1.85–1.95 (1 H, m, 7-H), 2.11 (1 H, apparent t, *J ca.* 12 Hz, 4-H_{ax}), 2.2–2.4 (1 H, m, 4-H_{eq} and 4a-H), 4.1–4.2 (1 H, m, 8-H), 5.22 (1 H, d, *J* 9 Hz, 5'-H or 4'-H), 5.50 (1 H, d, *J* 9 Hz, 4'-H or 5'-H), 6.65 (1 H, t, *J* 2 Hz, 1-H), 6.95 and 7.02 (each 1 H, d, *J* 7 Hz, 3-H_{Ar} and 3-$H_{Ar'}$), 7.1–7.3 (4 H, m, 4,5-H_{Ar}, 4,5-$H_{Ar'}$), 7.60 (1 H, dd *J ca.* 1, 8 Hz, 6-$H_{Ar'}$), 7.64 (1 H, dd *J ca.* 1, 8 Hz, 6-H_{Ar}); the minor epimer showed a characteristic signal at δ_H 6.54 (1 H, t, *J* 2 Hz, 1-H).

To a stirred solution of the mixed carbinols **41** (0.430 g 1.022 mmol) in dichloromethane (10 ml) at room temperature was added *p*-toluenesulfonic acid (50 mg, 0.29 mmol). After 1 h the organic phase was washed with 1 M potassium carbonate (2 x 10 ml), dried and evaporated. Chromatography of the residual greenish oil (0.401 g) over silica gel (14 g), eluting with dichloromethane - ether (10:1), gave the *title compound* (*S,S,S*)-**42** (0.324 g, 75%), with spectroscopic properties identical to the material obtained previously.

*(S)-(2-Hydroxymethyl-6,6-dimethyl-2-cyclohexen-1-yl)acetic acid lactone (–)-***21**

To a stirred solution of sodium triacetoxyborohydride (2.4 g, 11.32 mmol) in toluene (87 ml) at 82 °C (bath temperature) was added dropwise a solution of the ester-aldehyde (*S,S,S*)-**42** (295 mg, 0.70 mmol) in toluene (10 ml). After 40 min the mixture was cooled to room temperature, treated with 0.5 M hydrochloric acid (15 ml) stirred at room temperature for 2 d. Concentration *in vacuo* gave a colourless oil (258 mg) which was chromatographed, eluting with dichloromethane - ethyl acetate (9:1), to obtain the *title compound* (*S*)-**21** (76 mg, 0.42 mmol, 60%), $[\alpha]_D^{20}$ –46 ±5 (*c* 0.48, acetone). Other data were identical to those obtained from (±)-**21** obtained previously. Later fractions of eluate gave the (*S,S*)-diol **2a** (115 mg, 0.475 mmol, 68%) as a colourless crystalline solid whose analysis by ^1H n.m.r. as described[5] indicated an e.e. >98%.

*(S)-Methyl (2-formyl-6,6-dimethyl-2-cyclohexen-1-yl)acetate (–)-***23**

A solution of the ester-aldehyde (*S,S,S*)-**42** (236 mg, 0.56 mmol) in methanol (10 ml) under Ar was treated with sodium methoxide (6 mg, 0.11 mmol) and stirred at room temperature for 20 h. The solvent was evaporated and the residue partitioned between ether (50 ml) and water (10 ml). The organic phase was dried,

evaporated and the residual pale yellow oil chromatographed, eluting with dichloromethane - ether (9:1). The initial fractions gave the *title compound* **23** (80 mg, 0.38 mmol, 68%) as a yellowish oil, $[\alpha]_D^{20}$ –69 ±5 (*c* 0.61, acetone). Other data were identical to those obtained from (±)-**23** obtained previously. Later fractions of eluate gave the (*S,S*)-diol **2a** (128 mg, 0.53 mmol, 94%) as a colourless crystalline solid whose analysis by ^{1}H n.m.r. as described[5] [2 mg of recovered diol, 12 mg Pr(hfc)$_3$] indicated an e.e. >98%.

(2-Ethylphenyl)methanol **44**

A mixture of sodium borohydride (90 mg, 2.38 mmol) and ethanol (2 ml) was stirred under reflux, treated dropwise with a solution of 2-ethylbenzaldehyde **43**[31] (90 mg, 0.67 mmol) in ethanol (0.5 ml), and the reflux maintained until gas evolution stopped (*ca.* 4 h). After cooling and evaporation of the ethanol the residue was partitioned between water (0.5 ml) and ethyl acetate (1.5 ml) with vigorous stirring for 1 h. The aqueous phase was separated and extracted with more ethyl acetate (3 x 1.5 ml) the combined organic phases were dried and evaporated, giving the alcohol **44** (90 mg, 99%) which was employed in the next step without further purification (lit.[32] colourless oil, b.p. 229 °C); δ_H 1.22 (3 H, t, *J* 7.5 Hz, CH_2CH_3), 2.70 (2 H, q, *J* 7.5 Hz, CH_2CH_3), 4.71 (2 H, s, CH_2O), 7.16–7.36 (4 H, m, ArH).

Bromo(2-ethylphenyl)methane **45**

To a suspension prepared from triphenylphosphine (210 mg, 0.80 mmol) and bromine (128 mg, 0.80 mmol) in dichloromethane (5 ml) at 0 °C was added a solution of the alcohol **44** (91 mg, 0.67 mmol) in dichloromethane (0.5 ml). The mixture was stirred at room temperature for 4 h and then under reflux overnight. After cooling and evaporation, the residue was extracted with ether (2 x 1.5 ml) and the combined extracts were filtered through a short silica column. Evaporation of the filtrate gave the title compound **45** (106 mg, 80%), which was employed in the next step without further purification (lit.[32] m.p. 34 °C); δ_H 1.27 (3 H, t, *J* 7.5 Hz, CH_2CH_3), 2.76 (2 H, q, *J* 7.5 Hz, CH_2CH_3), 4.53 (2 H, s, CH_2Br), 7.13–7.31 (4 H, m, ArH).

(2-Ethylphenyl)methyltriphenylphosphonium bromide **46**

A mixture of the bromide **45** (101.4 mg, 0.51 mmol) and triphenylphosphine (144 mg, 0.55 mmol) in toluene (5 ml) was stirred under reflux for 16 h, cooled to room temperature and filtered. Drying the solid *in vacuo* gave the phosphonium salt **46** (155 mg, 66%), which was used in the next step without further purification.

(E)-1,2- bis*(2-Ethylphenyl)ethene* **47**

A 25ml round-bottomed flask equipped with magnetic follower and containing the phosphonium salt **46** (155 mg, 0.336 mmol) and THF (10 ml) under Ar was cooled to –78 °C and treated dropwise with *n*-BuLi in hexane (1.35 M; 0.25 ml, 0.337 mmol). The mixture was kept at –78 °C for 1 h and then at –10 °C for 20 min to produce the ylid, which was then treated with 2-ethylbenzaldehyde **43**[31] (43.5 mg, 0.324 mmol) in THF (0.5 ml). The mixture was then stirred at room temperature for 4 h, evaporated and the residue extracted with ether (2 x 1.5 ml). The combined ethereal extract was filtered through a silica column and evaporated to obtain the alkene **47** and the corresponding *Z*-isomer (52.4 mg, 68%, *E/Z* ratio 2:1). The mixture was heated under reflux in chloroform (2 ml) with tellurium(IV) chloride[33] (2 mg, 0.007 mmol) for 16 h, after which time the isomerisation was complete (t.l.c. analysis). After evaporation of the chloroform the residue was distilled (Kugelrohr, 150–200 °C, 0.01 mmHg) and then chromatographed, eluting with petroleum, which gave the *title compound* **47** (39.7 mg, 52%) as a solid, m.p. 138–139 °C (chloroform - petroleum) (*M* + NH_4^+, 254.1908. $C_{18}H_{24}N$ requires 254.1909); δ_H 1.23 (6 H, t, *J* 7.5 Hz, CH_2CH_3), 2.67 (4 H, q, *J* 7.5 Hz, CH_2CH_3), 6.76 (2 H, s, 1-H, 2-H), 6.86–6.92 (4 H, m, ArH), 7.05–7.2 (4 H, m, ArH); m/z 254 (M + NH_4^+, 100%), 236 (24).

*(R,R)-1,2-*bis*(2-Ethylphenyl)-1,2-ethanediol (+)-***2c**

A 10 ml round-bottomed flask equipped with a magnetic follower was charged with *t*-butanol (2 ml), water (2 ml), a finely ground mixture of potassium ferricyanide (104 mg, 0.316 mmol), potassium carbonate (42 mg,

0.304 mmol) and hydroquinidine 1,4-phthalazinediyl diether [$(DHQD)_2PHAL$][34] (1.0 mg, 0.0013 mmol), followed by OsO_4 (2.5% w/w in *t*-butanol, 2.0 mg, 0.0002 mmol). After stirring for a few minutes at room temperature, powdered methanesulfonamide (24 mg, 0.25 mmol) was added, followed by the powdered stilbene **47** (25 mg, 0.106 mmol). The slurry was stirred vigorously at room temperature the progress of the reaction monitored by t.l.c., eluting with petroleum (b.p. 60–80 °C) - ethyl acetate (2:1). After 4 days the reaction had finished the mixture was treated with powdered $Na_2S_2O_3$ (1.2 g, 7.6 mmol) and stirred for a further 1 h. The solvents were then removed *in vacuo* the residue was treated with water and extracted with ethyl acetate (3 x 2 ml). The extract was dried and evaporated, and the residue purified by chromatography, eluting with petroleum (b.p. 60–80 °C) - ethyl acetate (2:1) to obtain the *title compound* (*R,R*)-**2c** (26 mg, 91%), m.p. 108–110 °C (*M* + NH_4^+, 288.1969. $C_{18}H_{26}NO_2$ requires 288.1963); $[\alpha]_D^{20}$ +22 ±5 (*c* 0.91, acetone); δ_H 0.88 (6 H, t, *J* 7.5 Hz, 2 x CH_2Me), 1.98 (2 H, dq, *J* 7.5, 15 Hz, 2 x *CH*Me), 2.23 (2 H, dq, *J* 7.5, 15 Hz, 2 x *CH*Me), 2.85 (2 H, s, 2 x OH), 5.06 (2 H, s, 2 x *CH*OH), 6.98 (2 H, dd, *J* 1.5, 7.5 Hz, 3-H, 3'-H), 7.12–7.23 (4 H, m, 4-H, 5-H, 4'-H, 5'-H), 7.61 (2 H, dd, *J* 1.5, 7.5 Hz, 6-H, 6'-H); m/z 288 (M + NH_4^+, 99%), 271 (M + H^+, 100).

(R,R)-4,5-bis(2-Ethylphenyl)-2-bromomethyl-1,3-dioxolane **3c**

Using a procedure similar to that described previously,[5] the diol (+)-**2c** (18.1 mg, 0.067 mmol), bromoacetaldehyde diethylacetal (1 ml) and *p*-toluenesulfonic acid hydrate (30 mg, 0.16 mmol) were heated at 100–120 °C (bath temperature) for 2 h. After neutralisation, extraction and evaporation as described, the excess of bromoacetaldehyde diethylacetal was removed *in vacuo* (0.3 mmHg) and the residue purified by chromatography, eluting with petroleum (b.p. 60–80 °C) - ethyl acetate (5:1) followed by petroleum (b.p. 60–80 °C) - dichloromethane (1:1) followed by petroleum (b.p. 60–80 °C) - ether (10:3), which gave the *title compound* (*R,R*)-**3c** (11.5 mg, 46%) as an oil (*M* + NH_4^+, 392.1224. $C_{20}H_{27}BrNO_2$ requires 392.1226); δ_H 0.75 (6 H, s, 2 x Me), 1.95–2.15 (4 H, m, 2 x CH_2Ar), 3.69 (2 H, d, *J* 3.5 Hz, $BrCH_2$), 5.17 (1 H, d, *J* 8.5 Hz, OCHAr), 5.21 (1 H, d, *J* 8.5 Hz, OCHAr), 5.73 (1 H, t, *J* 3.5 Hz, $BrCH_2CH$), 7.02 (2 H, br d, *J* *ca.* 7.5 Hz, 3,3'-ArH), 7.15–7.30 (4 H, m, 4,4',5,5'-ArH), 7.58 (1 H, d, *J* 7.5 Hz, 6-ArH), 7.78 (1 H, d, *J* 7.5 Hz, 6'-ArH); m/z 394 [M + NH_4^+ (^{81}Br), 59%], 392 [M + NH_4^+ (^{79}Br), 55], 270 (20), 161 (100).

(R,R)-4,5-bis(2-Ethylphenyl)-2-methylene-1,3-dioxolane **1c**

A stirred solution of the bromoacetal (*R,R*)-**3c** (11.5 mg, 0.031 mmol) in dry THF (0.5 ml) at 0 °C under argon was treated with solid potassium *t*-butoxide (10.3 mg, 0.092 mmol). After 3 min the mixture was treated with a solution of Aliquat® 336[30] (25 mg, 0.062 mmol) in THF (0.5 ml). After 2 h at 0 °C the dehydrobromination was complete and the reaction mixture was evaporated, diluted with ether and filtered through a small column containing basic alumina (*ca.* 0.7 g) to remove the catalyst and excess of base. The filtrate was evaporated and the residue, containing (*R,R*)-**1c** (*ca.* 90%), used without further purification in the cycloaddition with the aldehyde **4**.

3,3-Dimethyl-5-(4,4-dimethyl-1-cyclohexenyl)-6-oxo-1-cyclohexene-1-carbaldehyde **48**

Potassium (15.6 g, 0.4 mol) was dissolved in *t*-butanol (300 ml) and the resulting solution treated with 4,4-dimethylcyclohexanone (12.6 g, 0.1 mol) in *t*-butanol (*ca.* 40 ml).[10,35] The mixture was heated to 50 °C and ethyl formate (29.6 g, 0.4 mol) then added dropwise over 45 min. The mixture turned yellow and was left stirring overnight at 50 °C. It was then treated with glacial acetic acid (40 ml) and the mixture poured into water (*ca.* 300 ml) and extracted with ether (4 x 150 ml). The combined ethereal extract was washed with saturated aq. sodium hydrogen carbonate (3 x 150 ml) and water (200 ml), dried and evaporated to an oily orange liquid (13.09 g). T.l.c. showed the presence of at least two products, but the mixture was used without purification. A solution of phenylselenenyl chloride (17.09 g, 89 mmol) in dichloromethane (200 ml) was cooled to 0 °C and treated with dry pyridine (7.39 g, 93.5 mmol). The mixture was then stirred for *ca.* 0.5 h and treated with the orange liquid (13.09 g) in dichloromethane (40 ml). After stirring for 0.75 h the mixture was extracted with 3 M hydrochloric acid (200 ml). The organic layer was then cooled back to 0 °C, stirred and treated with 30%

hydrogen peroxide (8 ml). Additional portions of 30% hydrogen peroxide (8, 8, 9 ml) were added at intervals of 10, 20 and 30 min respectively, and the mixture was then stirred for a further 3 h. Water (150 ml) was then added and the organic layer was separated and washed with saturated aq. sodium hydrogen carbonate (3 x 100 ml) and water (100 ml), dried and evaporated to give an orange liquid (12.22 g). Chromatography over silica gel (300 g), eluting with petroleum and ethyl acetate (4:1), gave the aldehyde **4** (4.99 g, 33%) and a second product identified as the aldehyde **48** (1.95 g, 15%). The latter was rechromatographed to give the *title compound* **48** (1.139 g, 9%) as a yellow solid (*M* + NH_4^+, 278.2131. $C_{17}H_{28}NO_2$ requires 278.2120); ν_{max} (Nujol) 1706, 1685 cm^{-1}; δ_H (assigned using a COSY spectrum) 0.87 (3 H, s, CH_3), 0.92 (3 H, s, CH_3), 1.21 (3 H, s, CH_3), 1.24 (3 H, s, CH_3), 1.31–1.44 (2 H, m, 5'-H_2), 1.72–1.84 (2 H, m, 6'-H_2), 1.79 (1 H, ddd, $J_{3,5}$ 2, $J_{5,6}$ 4.5, $J_{5,5}$ 14 Hz, 5-H_{eq}), 1.90–1.94 (2 H, m, 3'-H_2), 2.06 (1 H, t, *J* 14 Hz, 5-H_{ax}), 3.14 (1 H, dd, *J* 4.5, 14 Hz, 6-H_{ax}), 5.43 (1 H, br. s, 2'-H), 7.37 (1 H, d, *J* 2 Hz, 3-H), 9.99 (1 H, s, CHO); δ_C 198.2 (C-1), 189.9 (CHO), 164.2 (C-3), 133.4 (C-1' or C-2), 131.8 (C-2 or C-1'), 124.9 (C-2'), 51.5 (C-6), 40.7 (*C-3'), 39.2 (*C-6'), 35.4 (*C-5), 34.0 (C-4), 29.9 (4-CH_3), 28.5 (4-CH_3), 28.5 (C-4'), 27.7 (4'-CH_3), 24.9 (4'-CH_3), 24.0 (C-5') (*assignments tentative); m/z 278 (M + NH_4^+, 100%); m/z (EI, peaks ≥) 260 (M^+, 18%), 204 (100), 175 (29), 148 (68), 124 (22), 107 (27), 96 (27), 95 (21), 93 (38), 91 (31), 80 (20), 79 (52), 77 (30), 67 (30).

*rel(3R,4aS,7R)-3-Ethoxy-3,4,4a,5,6,7-hexahydro-5,5-dimethyl-7-(4,4-dimethyl-1-cyclohexenyl)-8H-2-benzopyran-8-one (±)-***49**

A solution of the aldehyde **48** (50 mg, 0.19 mmol) in dichloromethane (2 ml) and ethoxyethene (5 ml) was stirred at room temperature for 3 days, after which t.l.c. indicated that the heterodiene had been consumed. The mixture was evaporated to dryness to give *the title compound* **49** (61 mg, 96%) as a pale yellow solid (***M*⁺**, 332.2352. $C_{21}H_{32}O_3$ requires 332.2351); ν_{max} (Nujol) 1671, 1593, 1146 cm^{-1}; δ_H 0.78 (3 H, s, CH_3), 0.85 (3 H, s, CH_3), 0.88 (3 H, s, CH_3), 0.97 (3 H, s, CH_3), 1.22 (3 H, t, *J* 7 Hz, CH_3CH_2O), 1.26–1.42 (2 H, m, 5'-H_2), 1.54–2.03 (8 H, m, 4-H_2, 6-H_2, 3'-H_2, 6'-H_2), 2.59 (1 H, ddd, *J* 2, 6, 12 Hz, 4a-H), 3.00 (1 H, dd, *J* 6.5, 10 Hz, 7-H_{ax}), 3.57 (1 H, dq, *J* 7, 9.5 Hz, $OCHCH_3$), 3.96 (1 H, dq, *J* 7, 9.5 Hz, $OCHCH_3$), 4.97 (1 H, dd, *J* 2, 10 Hz, 3-H), 5.26 (1 H, br. s, 2'-H), 7.42 (1 H, d, *J* 2 Hz, 1-H); m/z (EI, peaks ≥25%), 332 (M^+, 41%), 260 (29), 204 (81), 177 (36), 175 (27), 148 (72), 125 (25), 121 (33), 109 (53), 107 (51), 105 (61), 97 (40), 95 (48), 93 (59), 91 (72), 81 (48), 79 (92), 77 (67), 69 (82), 67 (63), 57 (35), 56 (100).

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