New entry to a *cis*-fused bicyclic ring system by a [2,3]sigmatropic rearrangement *via* cyclic allylsulfonium ylides. Synthesis of the *cis*-2-oxa-9-vinyldecalin skeleton

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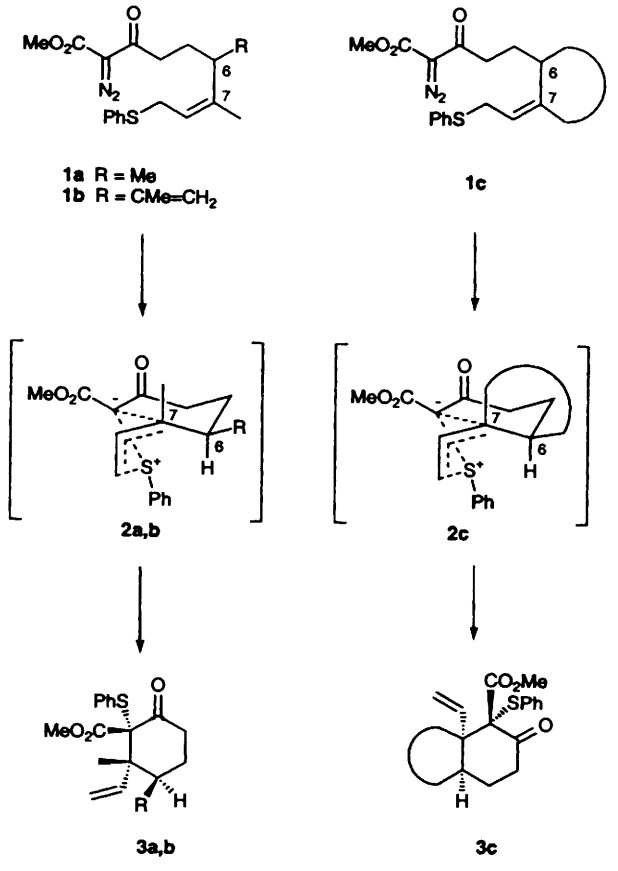
Rhodium(II) acetate-catalysed cyclisation of methyl 2-diazo-5-[2-methoxy-5-(2-phenylsulfanylethylidene)tetrahydro-2*H*-pyran-4-yl]-3-oxopentanoate **4** proceeded in a stereoselective fashion to provide in a high yield *cis*-2-oxa-9-vinyldecalin derivative **5**, the basic AB ring skeleton of vernolepin, by a [2,3]sigmatropic rearrangement *via* a nine-membered cyclic allyl sulfonium ylide.

Carbocyclic construction is a widely investigated subject in synthetic organic chemistry, and a variety of methodologies for this purpose have been reported to date.[1] The carbene insertion cyclisation starting with acyclic α-diazo esters[2] is one of these methodologies, and from the viewpoint of utility and reaction mechanism, we have studied analogous rhodium(II)-catalysed cyclisations starting with acyclic α-diazomalonates and α-diazo-β-keto esters possessing an allyl sulfide function at the terminal position, so that a variety of stereoselective syntheses of contiguously substituted lactones[3] and cyclohexanones[4] by a [2,3]sigmatropic rearrangement *via* cyclic sulfonium ylides have been achieved.

Recently, we have demonstrated that in the [2,3]sigmatropic rearrangement of nine-membered allylsulfonium ylides, the alkyl substituents (R) at the C-6 position of the α-diazo-β-keto esters **1a,b** control the stereochemistry of the transition state **2a,b** wherein the alkyl group and olefin methyl group at the C-7 position are oriented equatorially and axially, respectively, in a six-membered ring part, thus producing stereoselectively, as the sole product, cyclohexanones **3a,b** with a *trans*-disposition between the alkyl and the newly formed vinyl groups.[5] These findings indicate that the monocyclic α-diazo-β-keto ester **1c**, in which the C-6–C-7 bond constitutes a ring, could provide stereoselectively the *cis*-fused bicyclic compound **3c** by a [2,3]sigmatropic rearrangement of cyclic allylsulfonium ylide **2c**. In this study, we show an enantioselective synthesis of the *cis*-2-oxa-9-vinyldecalin skeleton in connection with the construction of *cis*-fused bicyclic ring systems, *i.e.* preparation of the precursor, tetrahydropyran **4** possessing vicinal *cis*-allyl sulfide and α-diazo-β-keto ester functions, and an enantioselective synthesis of *cis*-2-oxa-9-vinyldecalin derivative **5** starting from **4**. In practice, 2-methoxytetrahydropyran **4** was adopted as the target precursor, since the product **5** has the AB ring skeleton of vernolepin **6**,[6] the well-known elemanolide possessing cytotoxic and antitumour activity,[7] and the acetal function in the A ring is synthetically equivalent to a δ-lactone function which constitutes one of the characteristics of the elemanolide **6**.



Results and discussion

We chose (−)-limonene oxide **7** as the chiral source, and planned to prepare the acetal **14** as the first synthetic intermediate leading to the target precursor **4**, because its structure definitely allows the chemical transformation of the 3-oxobutyl and exocyclic methylene groups to the α-diazo-β-keto ester and allyl sulfide functions, respectively, as shown below.

The synthetic route to the acetal **14** is shown in Scheme 1. According to the well-established procedures,[8] epoxide ring-opening of **7** was carried out with aqueous base to give the diastereoisomeric diol **8**, whose 1,2-diol function was protected as the acetonide. Chemical transformation of the isopropenyl group into a 1-(hydroxymethyl)ethenyl one was performed by oxidation of the resulting acetonide **9** with *m*-chloroperbenzoic acid (MCPBA) followed by epoxide ring-opening of the resulting epoxide **10** with diethylaluminium 2,2,6,6-tetramethylpiperidinide,[9] giving the allyl alcohol **11**. Deprotection of **11** provided the triol **12** in 60% overall yield from **7**. Oxidative 1,2-diol cleavage of **12** with lead tetraacetate proceeded by initial generation of the keto aldehyde with concomitant intramolecu-

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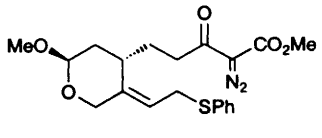

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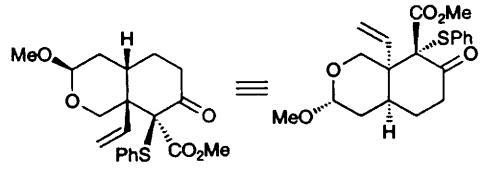

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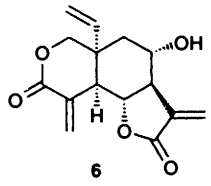

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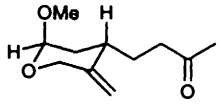
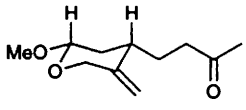
lar hemiacetalisation to give the keto hemiacetal **13** in 88% yield. Acetalisation of **13** with trimethyl orthoformate gave the requisite acetal **14** as a separable mixture (a *ca.* 2:1 ratio) of epimers with respect to the methoxy group.

From ^{1}H NMR studies, the stereochemistry of the acetal protons in the major isomer **14a** and the minor isomer **14b** were established to be equatorial and axial, respectively, on the basis of a broad singlet at δ 4.7 for the former and a doublet of doublets ($J_{a,a}$ 7.5 and $J_{a,e}$ 3.0 Hz) at δ 4.60 for the latter, these assignments indicating the stereostructures of **14a,b** as depicted.



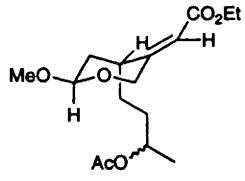
14a



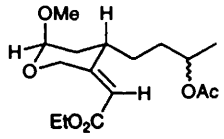
14b

The major isomer **14a** of the above diastereoisomeric mixture was subjected to the subsequent experiment, since stereochemical fixation of the acetal hydrogen atom at this stage is effective not only for simplification of further reaction products, but also for the assignment of their stereostructures.

Before oxidative transformation of the exocyclic methylene group in **14a** into a ring carbonyl function, with which the Peterson olefination will be carried out, the ketone in the side chain was converted into an acetoxy group; reduction of **14a** with sodium boranuide ($NaBH_4$) provided the diastereoisomeric alcohol **15**, which was acetylated, giving the acetate **16** in nearly quantitative overall yield. Ozonolysis of **16** under conventional reaction conditions afforded the keto acetal **17** in a high yield. Then, the Peterson olefination[10] of **17** with the lithium enolate of ethyl trimethylsilylacetate proceeded cleanly to provide in 79% yield a separable mixture of unsaturated esters, *E*-isomer **18a** and *Z*-isomer **18b** in a *ca.* 2:1 ratio. Stereochemical assignment of these olefination products was easily performed from ^{1}H NMR studies; the chemical shift of the methylene protons adjacent to the ring ether oxygen of **18b** shows considerable deshielding by the proximate carbonyl group, compared with that of **18a** [δ 4.42 (1 H) and 5.14 (1 H) in **18b**, and δ 4.22 (2 H) in **18a**]. Interestingly, the acetal proton in **18b** occurs at δ 4.78 as a doublet of doublets (*J* 3.6 and 3.6 Hz), while that in **18a** occurs at δ 4.60 as a doublet of doublets ($J_{a,a}$ 8.0 and $J_{a,e}$ 4.3 Hz), these results indicate the stereochemistry of the acetal hydrogen atom to be equatorial in **18b** and axial in **18a**. The findings of the ^{1}H NMR studies indicate orientation of the 3-acetoxybutyl chain of **18a** as axial, arising from the A^{1,3}-strain.[11] Therefore, the stereostructures of **18a,b** were surmised as depicted.



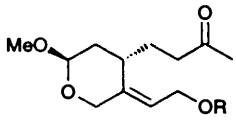
18a



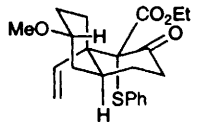
18b

The *E*-isomer **18a** was used for further reactions, since in the cyclisation step, the stereochemical requirement leading to the proposed transition state **2c** would be satisfied only with the *syn*-olefin structure in the precursor **1c**.[12] The *E*-isomer **18a** was reduced with diisobutylaluminium hydride (DIBAH) to give the diol **19**, and *via* regioselective acetylation, the acetoxy ketone **21** was obtained by oxidation of the hydroxy acetate **20** with pyridinium dichromate (PDC).

The main remaining task for the synthesis of the key intermediate was the transformation of the 3-oxobutyl chain in **21** into the α-diazo-β-keto ester function. According to Mander's procedure,[13] the lithium enolate of **21** was prepared with lithium diisopropylamide (LDA) under kinetically controlled conditions and trapped with methyl cyanoformate to produce the bis-β-keto ester **22**. In this reaction, both attempted regioselective generation of the lithium enolate of the methyl ketone and regioselective methoxycarbonylation at this enolate were unsuccessful, and the malonylation reaction always occurred concomitantly. Eventually, the bis-ester **22** was obtained in 73% yield by the use of 2.5 equiv. of both LDA and the Mander reagent. Attempted methoxycarbonylation of the allyl alcohol **25** and *tert*-butyldimethylsilyl (TBDMS) ether **26**,



25 R = H
26 R = TBDMS



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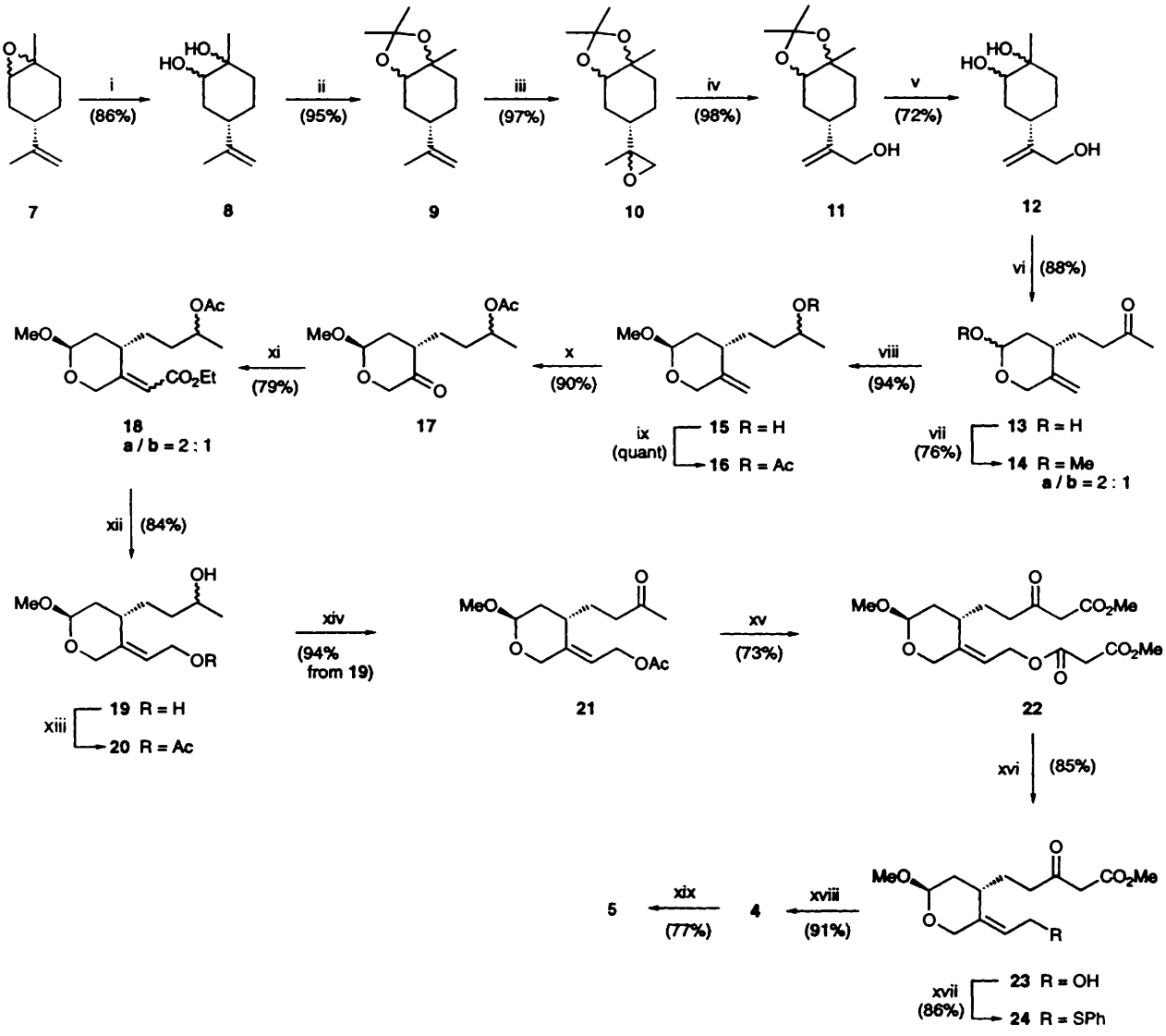
both readily available from **21**, were also unsuccessful. However, preparation of the allyl alcohol **23** was successfully carried out in 88% yield by methanolysis of **22** with potassium carbonate in methanol. The desired key intermediate **4** was obtained from **22** in 78% overall yield with displacement of the hydroxy group of **23** by a phenylsulfanyl group, followed by a diazo transfer reaction[14] of the resulting sulfide **24** with tosyl azide.

Finally, construction of the *cis*-fused bicyclic ring skeleton starting from **4** was cleanly performed under our standard reaction conditions, wherein treatment with rhodium(II) acetate (0.01 mol equiv.) in refluxing benzene produced the *cis*-2-oxa-9-vinyldecalin derivative **5** in 77% yield. No isomer of **5** could be detected in spite of a careful inspection of the reaction mixture. The stereochemistry of the two substituents, the phenylsulfanyl and methoxycarbonyl groups, was surmised, as depicted, on the basis of the favourable conformation of the transition state **2c**. A doublet of doublets (δ 4.64, $J_{a,a}$ 9.0 and $J_{a,e}$ 3.6 Hz) due to the acetal proton in the ^{1}H NMR spectrum of **5** shows the hydrogen atom to be axial, the findings suggesting the conformation of **5** to be of nonsteroid-type, as shown in **27**. This result accounts for the fact that our proposed transition state **2c** is product-like.



Scheme 1 *Reagents and conditions:* i, 30% KOH, aq. DMSO; ii, $MeC(OMe)=CH_2$, PPTS, CH_2Cl_2; iii, MCPBA, CH_2Cl_2; iv, 2,2,6,6-tetramethylpiperidine, BuLi, Et_2AlCl, toluene; v, HCl(g), MeOH, acetone; vi, $Pb(OAc)_2$, toluene; vii, $CH(OMe)_3$, PPTS, THF; viii, **14a**, $NaBH_4$, MeOH; ix, Ac_2O, py; x, O_3, CH_2Cl_2, MeOH, −78 °C then Me_2S; xi, **18a**, LDA, $Me_3SiCH_2CO_2Et$, THF, −78 °C; xii, DIBAH, THF, −30 °C; xiii, Ac_2O (1 equiv.), py; xiv, PDC, molecular sieves 4 Å, CH_2Cl_2; xv, LDA (2.5 equiv.), $NCCO_2Me$ (2.5 equiv.), HMPA, THF, −78 °C; xvi, K_2CO_3, MeOH; xvii, PhSSPh, Bu_3P, THF, reflux; xviii, TsN_3, Et_3N, MeCN, 45 °C, 2 days; xix, $Rh_2(OAc)_4$ (0.01 equiv.), PhH, 80 °C

Conclusions

As part of the stereoselective construction of *cis*-fused bicyclic ring systems, in the present study, a search for synthesis of *cis*-2-oxa-9-vinyldecalin derivative was carried out, and it was demonstrated that the [2,3]sigmatropic rearrangement of the nine-membered cyclic allylsulfonium ylide arising from the treatment of **4** with catalytic amount of rhodium(II) acetate proceeded in the stereoselective fashion predicted by our aforementioned consideration to give **5** as the only product *via* the product-like transition state **2c**. The main features of this type of annulation reaction are not only stereoselective construction of a quaternary carbon at an angular position, but also utility of the newly formed vinyl group in organic synthesis in that a vinyl group could be easily converted into methyl and hydoxymethyl groups which are found as the angular constituent in many natural products.

Experimental

Melting points are uncorrected. ^1H NMR spectra were recorded at 90 MHz. *J* Values are given in Hz. $[\alpha]_D$ Values are given in units of 10^{-1} deg cm^2 g^{-1}. (−)-Limonene oxide, a mixture of *cis* and *trans* isomers, is commercial material (Aldrich). All organic solvents were purified and dried using standard procedures. All reactions were carried out under dry N_2 or Ar atmosphere with the use of standard procedures for the exclusion of moisture except for those under aqueous reaction conditions. Extracts from the aqueous work-up of the reaction mixtures were washed successively with water and brine, and dried ($MgSO_4$). Column and flash column chromatography were performed on 70–230 and 230–400 mesh silica gel (Merck), respectively, and Kieselgel GF_{254} was employed for preparative thin-layer chromatography (TLC). Solvents for elution are shown in parentheses. Ether refers to diethyl ether.

2-[(5*S*)-2,2,7a-Trimethylhexahydro-1,3-benzodioxol-5-yl]prop-2-enol 11

To a stirred solution of (−)-limonene oxide **7** (138 g, 0.91 mol) in dimethyl sulfoxide (DMSO)(300 cm^3) was added at room temperature aqueous KOH (30%; 1000 cm^3, 4.55 mol), and stirring was continued for 18 h at 110 °C. After cooling to room temperature, the reaction mixture was carefully neutralised at

0 °C with concentrated HCl, and the product was extracted with ether–CH_2Cl_2 (2:1). Evaporation followed by recrystallization of the crystalline residue (methanol–H_2O) gave the *diol* **8** (133g, 86%) as crystals, mp 86–87 °C (hexane–ether); $\nu_{max}(CHCl_3)/cm^{-1}$ 3600, 3450, 1030 and 890; $\delta_H(CDCl_3)$ 1.28 (3 H, s), 1.72 (3 H, s), 1.4–2.8 (9 H, m), 3.62 (1 H, br s) and 4.74 (2 H, s).

A mixture of **8** (33.6 g, 0.197 mol), 2-methoxypropene (42.5 g, 0.590 mol), pyridinium toluene-*p*-sulfonate (PPTS) (5.0 g, 0.02 mol) and CH_2Cl_2 (300 cm^3) was stirred at room temperature for 2 h and then quenched with aqueous $NaHCO_3$, and washed successively with water and brine. Evaporation of the solvent left an oil which was purified by distillation [150 °C (oil bath), 15 Torr] to give the *acetonide* **9** (39.2 g, 95%) as an oil (Found: C, 74.0; H, 10.6. $C_{13}H_{22}O_2$ requires C, 74.24; H, 10.55%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3020 and 1390; $\delta_H(CDCl_3)$ 1.14 (3 H, s), 1.30 (3 H, s), 1.44 (3 H, s), 1.6–2.3 (6 H, m), 2.46 (1 H, br s), 3.54 (1 H, dd, *J* 12.0, 3.6) and 4.84 (2 H, br s).

A mixture of **9** (23.0 g, 0.10 mol), *m*-chloroperbenzoic acid (MCPBA)(80% purity; 35.0 g, 0.16 mol) and CH_2Cl_2 (300 cm^3) was stirred at 0 °C for 3 h, and filtered through a small bed of Celite 545. The filtrate was washed successively with aqueous K_2CO_3, water and brine, and dried. Evaporation of the solvent followed by purification of the residue by chromatography on silica gel (hexane–EtOAc, 20:1) gave the *epoxide* **10** (23.6 g, 97%) as an oil (Found: C, 69.2; H, 10.1. $C_{13}H_{22}O_3$ requires C, 68.99; H, 9.80%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1120, 1100 and 850; $\delta_H(CDCl_3)$ 1.16 (3 H, s), 1.38 (6 H, s), 1.50 (3 H, s), 1.6–2.3 (7 H, m), 2.58 and 2.77 (1 H, m each) and 3.5–3.8 (1 H, m).

To a stirred solution of 2,2,6,6-tetramethylpiperidine (283 mg, 2.0 mmol) in toluene (6 cm^3) was added at 0 °C a solution of butyllithium in hexane (1.49 mol dm^{-3}; 1.35 cm^3, 2.0 mmol). After being stirred briefly, a solution of diethylaluminium chloride in hexane (1.0 mol dm^{-3}; 2.0 cm^3, 2.0 mmol) was added dropwise, and at the same time a solution of **10** (113 mg, 0.5 mmol) in toluene (2 cm^3) was added. After stirring for an additional 30 min, aqueous NH_4Cl was added and the solid was filtered through a small bed of Celite 545. The organic layer was separated and dried. Removal of the solvent followed by chromatography of the residue on silica gel (hexane–EtOAc, 1:1) gave the *title compound* **11** (112 mg, 98%) as an oil (Found: C, 69.1; H, 9.9. $C_{13}H_{22}O_3$ requires C, 68.99; H, 9.80%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3520 and 915; $\delta_H(CDCl_3)$ 1.18 (3 H, s), 1.34 (3 H, s), 1.50 (3 H, s), 1.6–2.2 (7 H, m), 2.75 (1 H, br s), 3.62 (1 H, dd, *J* 12.6, 3.6), 4.16 (2 H, br s), 5.10 (1 H, s) and 5.24 (1 H, s).

4-[(4*S*)-2-Hydroxy-5-methylidenetetrahydro-2*H*-pyran-4-yl]-butan-2-one 13

To a stirred solution of **11** (9.6 g, 42.5 mmol) in acetone (30 cm^3) was added at 0 °C a methanolic HCl solution (saturated, 20 cm^3). The reaction mixture was stirred for 8 h at room temperature, neutralised with stirring by the addition of K_2CO_3 (s) and then filtered through a small column of Celite 545. Evaporation of the solvent left a residue which was purified by chromatography on silica gel (EtOAc) to give the triol **12** (3.34 g, 72%) as a viscous oil (Found: C, 64.5; H, 9.9. $C_{10}H_{18}O_3$ requires C, 64.49; H, 9.74%).

A mixture of **12** (1.31 g, 7.03 mmol), lead tetraacetate (3.59 g, 7.73 mmol) and toluene (150 cm^3) was stirred at room temperature for 2 h. To the reaction mixture was added $MgSO_4$ (7.0 g) and stirring was continued for an additional 20 h. The reaction mixture was filtered through a short silica gel column (ether–EtOAc, 1:1), and the filtrate was concentrated. Purification of the residue by chromatography on silica gel (hexane–EtOAc, 1:2) gave the *title compound* **13** (1.13 g, 88%) as an oil (Found: C, 65.0; H, 8.7. $C_{10}H_{16}O_3$ requires C, 65.19; H, 8.76%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3450, 1720 and 915; $\delta_H(CDCl_3)$ 1.0–2.0 (5 H, m), 2.08 (3 H, s), 2.52 (2 H, t, *J* 7.2), 3.96 (1 H, d, *J* 12.6), 4.2–4.6, (1 H, m), 4.82 (1 H, s), 4.96 (1 H, s) and 5.0–5.4 (1 H, m).

4-[(2*R*,4*S*)-2-Methoxy-5-methylidenetetrahydro-2*H*-pyran-4-yl]butan-2-one 14a and its epimer 14b

A mixture of **13** (1.13 g, 6.15 mmol), trimethyl orthoformate (10.0 cm^3, 92.3 mmol), PPTS (309 mg, 1.23 mmol) and tetrahydrofuran (THF) (15 cm^3) was stirred at room temperature for 1 h, and then poured into aqueous $NaHCO_3$, and extracted with CH_2Cl_2. Removal of the solvent followed by purification of the residue by chromatography on silica gel (hexane–EtOAc, 3:1) gave a mixture of the *title compounds* **14a,b** (Found: C, 66.6; H, 9.2. $C_{11}H_{18}O_3$ requires C, 66.64; H, 9.15%), which were separated by HPLC (hexane–EtOAc, 5:2), giving the *title compound* **14a** (618 mg, 51%) and its *epimer* **14b** (309 mg, 25%).

14a: Oil; $[\alpha]_D^{18}$ +137.2 (*c* 2.87 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1710, 1655, 1130 and 910; $\delta_H(CDCl_3)$ 1.2–2.1 (5 H, m), 2.14 (3 H, s), 2.50 (2 H, t, *J* 7.2), 3.40 (3 H, s), 3.86 (1 H, d, *J* 12.6), 4.24 (1 H, d, *J* 12.6), 4.7–4.8 (1 H, br s), 4.78 (1 H, s) and 4.92 (1 H, s).

14b: Oil; $[\alpha]_D^{18}$ −107.8 (*c* 2.36 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1710, 1655, 1125 and 910; $\delta_H(CDCl_3)$ 1.4–2.1 (5 H, m), 2.14 (3 H, s), 2.46 (2 H, t, *J* 7.2), 3.40 (3 H, s), 3.85 (1 H, d, *J* 12.6), 4.30 (1 H, d, *J* 12.6), 4.60 (1 H, dd, *J* 7.5, 3.0), 4.80 (1 H, s) and 4.92 (1 H, s).

(4*S*,6*R*)-4-(3-Acetoxybutyl)-6-methoxytetrahydro-2*H*-pyran-3-one 17

A mixture of **14a** (558 mg, 2.81 mmol) and sodium boranuide ($NaBH_4$) (53 mg, 1.40 mmol) and methanol (11 cm^3) was stirred at 0 °C for 15 min and then quenched with aqueous NH_4Cl. The product was extracted with ether–CH_2Cl_2 (3:1). Concentration of the extracts left an oil which was filtered through a short silica gel column (hexane–EtOAc, 3:1) to give the *alcohol* **15** (529 mg, 94%) as an oil (Found: C, 66.2; H, 10.3. $C_{11}H_{20}O_3$ requires C, 65.97; H, 10.07%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3475, 1125, 1050 and 910; $\delta_H(CDCl_3)$ 1.20 (3 H, d, *J* 7.2), 1.3–2.1 (5 H, m), 2.3–2.7 (1 H, br s), 3.40 (3 H, s), 3.6–3.9 (1 H, br s), 3.86 (1 H, d, *J* 10.8), 4.24 (1 H, d, *J* 10.8), 4.7–4.9 (1 H, br s), 4.78 (1 H, s) and 4.90 (1 H, s).

A mixture of **15** (530 mg, 2.65 mmol), acetic anhydride (2.5 cm^3) and pyridine (5 cm^3) was stirred at 0 °C for 18 h. Methanol (5 cm^3) was added and stirring was continued for an additional 1 h. The reaction mixture was diluted with water and extracted with ether. The combined extracts were washed successively with aqueous $CuSO_4$, water and brine and dried. Evaporation of the solvent followed by filtration of the residue through a short silica gel column (hexane–ether, 2:1) gave the *acetate* **16** (632 mg, quant.) as an oil (Found: C, 65.0; H, 8.7. $C_{13}H_{20}O_4$ requires C, 64.98; H, 8.37); $\nu_{max}(CHCl_3)/cm^{-1}$ 1730, 1655, 1130, 1055 and 910; $\delta_H(CDCl_3)$ 1.24 (3 H, d, *J* 7.2), 1.4–2.5 (5 H, m), 2.06 (3 H, s), 3.42 (3 H, s), 3.86 (1 H, d, *J* 10.8), 4.26 (1 H, d, *J* 10.8), 4.76 (1 H, s), 4.92 (1 H, s) and 4.6–5.0 (1 H, m).

Ozone was bubbled through a solution of **16** (1.79 g, 7.4 mmol) in CH_2Cl_2–methanol (3:1, 360 cm^3) at −78 °C until the medium turned pale blue. Excess ozone was purged by N_2 and then dimethyl sulfide (5 cm^3) was added. The reaction mixture was stirred for 2 h, and then washed successively with water and brine, and dried. Evaporation of the solvent followed by purification of the residue by chromatography on silica gel (hexane–EtOAc, 3:1) gave the *title compound* **17** (1.62 g, 90%) as an oil (Found: C, 59.3; H, 8.5. $C_{12}H_{20}O_5$ requires C, 59.00; H, 8.25%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1730 and 1150; $\delta_H(CDCl_3)$ 1.24 (3 H, d, *J* 7.2), 1.4–2.4 (5 H, m), 2.04 (3 H, s), 2.5–3.0 (1 H, m), 3.48

(3 H, s), 3.86 (1 H, d, *J* 15.1), 4.18 (1 H, d, *J* 15.1) and 4.7–5.0 (2 H, m).

Ethyl [(*E*,4*S*,6*R*)-4-(3-acetoxybutyl)-6-methoxytetrahydro-2*H*-pyran-3-ylidene]acetate 18a and its *Z*-isomer 18b

To a stirred solution of diisopropylamine (354 mg, 3.50 mmol) in THF (7 cm^3) was added at −78 °C a solution of butyllithium in hexane (1.58 mol dm^{-3}; 2.2 cm^3, 3.50 mmol) and stirring was continued for 30 min. To the reaction mixture was added a solution of ethyl trimethylsilylacetate (561 mg, 3.50 mmol) in THF (1.5 cm^3). After stirring for 30 min, hexamethylphosphoramide (HMPA) (627 mg, 3.50 mmol) followed by a solution of **17** (428 mg, 1.75 mmol) in THF (8 cm^3) was added, and stirring was continued for an additional 30 min. The reaction mixture was quenched with aqueous NH_4Cl, and the product was extracted with ether. Evaporation of the solvent followed by purification of the residue by HPLC (hexane–EtOAc, 3:1) gave the *title compound* **18a** (289 mg, 53%) and its *Z-isomer* **18b** (145 mg, 26%).

18a: Oil (Found: C, 61.3; H, 8.5. $C_{16}H_{26}O_6$ requires C, 61.13; H, 8.34%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1720 and 1650; $\delta_H(CDCl_3)$ 1.24 (3 H, d, *J* 7.2), 1.30 (3 H, t, *J* 7.2), 1.4–2.0 (6 H, m), 2.06 (3 H, s), 3.44 (3 H, s), 3.7 (1 H, br s), 4.18 (2 H, q, *J* 7.2), 4.22 (2 H, s), 4.60 (1 H, dd, *J* 8.0, 4.3), 4.9 (1 H, m) and 5.68 (1 H, s).

18b: Oil (Found: C, 61.3; H, 8.5. $C_{16}H_{26}O_6$ requires C, 61.13; H, 8.34%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1725 and 1655; $\delta_H(CDCl_3)$ 1.24 (3 H, d, *J* 7.2), 1.32 (3 H, t, *J* 7.2), 1.4–2.0 (6 H, m), 2.06 (3 H, s), 2.5 (1 H, br s), 3.42 (3 H, s), 4.18 (2 H, q, *J* 7.2), 4.42 (1 H, d, *J* 14.4), 4.78 (1 H, dd, *J* 3.6, 3.6), 4.9 (1 H, m), 5.14 (1 H, d, *J* 14.4) and 5.64 (1 H, br s).

4-[(*Z*,2*R*,4*S*)-5-(2-Acetoxyethylidene)-2-methoxytetrahydro-2*H*-pyran-4-yl]butan-2-one 21

To a stirred solution of **18a** (289 mg, 0.92 mmol) in THF (18 cm^3) was added at −30 °C a solution of diisobutylaluminium hydride (DIBAH) in hexane (1.0 mol dm^{-3}; 5.5 cm^3, 5.5 mmol) and stirring was continued for an additional 30 min. A small amount of aqueous NH_4Cl was added dropwise until the aluminium compound solidified, and the whole was dried over $MgSO_4$. Filtration through a bed of Celite 545, followed by evaporation of the filtrate left an oil, chromatography of which on silica gel (EtOAc) gave the *diol* **19** (177 mg, 84%) as an oil (Found: C, 62.4; H, 9.5. $C_{12}H_{22}O_4$ requires C, 62.58; H, 9.63%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3450 and 1060; $\delta_H(CDCl_3)$ 1.4–2.4 (8 H, m), 2.8 (1 H, br s), 3.46 (3 H, s), 3.6–4.6 (1 H, m), 4.0–4.4 (3 H, m), 4.70 (1 H, dd, *J* 7.9, 3.6) and 5.56 (1 H, t, *J* 7.2).

A mixture of **19** (115 mg, 0.50 mmol), acetic anhydride (52 mg, 0.51 mmol) and pyridine (2 cm^3) was stirred at 0 °C for 18 h. Methanol (2 cm^3) was added and the reaction mixture was stirred for 1 h, diluted with water, and extracted with ether. The combined extracts were washed successively with aqueous $CuSO_4$, water and brine and dried. Removal of the solvent left the *allyl acetate* **20** (130 mg) as an oil. To a stirred suspension of pyridinium dichromate (PDC) (563 mg, 1.49 mmol), molecular sieves 4 Å (280 mg) and CH_2Cl_2 (5 cm^3) was added a solution of the above oil **20** in CH_2Cl_2 (0.5 cm^3), and stirring was continued for an additional 2 h. The reaction mixture was filtered through a short silica gel column (EtOAc) and the filtrate was concentrated to give an oil, which was purified by chromatography on silica gel (hexane–EtOAc, 2:1) to give the *title compound* **21** (126 mg, 93%) as an oil; $[\alpha]_D^{18}$ −6.53 (*c* 1.23 in $CHCl_3$) (Found: C, 61.9; H, 8.2. $C_{14}H_{22}O_5$ requires C, 62.20; H, 8.20%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1730, 1710 and 1160; $\delta_H(CDCl_3)$ 1.6–2.0 (4 H, m), 2.10 (3 H, s), 2.18 (3 H, s), 2.48 (2 H, t, *J* 7.2), 2.7–3.0 (1 H, m), 3.48 (3 H, s), 4.0–4.3 (2 H, m), 4.5–4.8 (3 H, m) and 5.52 (1 H, t, *J* 7.2).

Methyl 5-((*Z*,2*R*,4*S*)-2-methoxy-5-{5-[2-(methoxycarbonylacetoxy)ethylidene]}tetrahydro-2*H*-pyran-4-yl)-3-oxopentanoate 22

To a stirred solution of diisopropylamine (44 mg, 0.43 mmol) in THF (0.8 cm^3) was added at −78 °C a solution of butyllithium in hexane (1.55 mol dm^{-3}; 0.28 cm^3, 0.43 mmol). After being stirred for 30 min, a solution of **21** (47 mg, 0.17 mmol) in THF (1 cm^3) was added and, after stirring for 1 h, HMPA (78 mg, 0.43 mmol) followed by methyl cyanoformate (37 mg, 0.43 mmol) were added, and stirring was continued for an additional 30 min. The reaction mixture was quenched with aqueous NH_4Cl and the product was extracted with ether. The oily residue obtained by removal of the solvent was chromatographed on silica gel (hexane–EtOAc, 1:2) to give the *title compound* **22** (47 mg, 73%) as an oil; $[\alpha]_D^{18}$ +3.88 (*c* 1.61 in $CHCl_3$) (Found: C, 54.2; H, 7.2. $C_{17}H_{26}O_9$ requires C, 54.54; H, 7.00%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1750, 1730 and 1060; $\delta_H(CDCl_3)$ 1.6–2.2 (5 H, m), 2.60 (2 H, t, *J* 7.2), 3.42 (2 H, s), 3.46 (3 H, s), 3.48 (2 H, s), 3.76 (6 H, s), 4.16 (2 H, br s), 4.70 (1 H, dd, *J* 7.2, 3.6), 4.6–4.8 (2 H, m) and 5.52 (1 H, t, *J* 7.2).

Methyl 5-[(*Z*,2*R*,4*S*)-2-methoxy-5-(2-phenylsulfanylethylidene)tetrahydro-2*H*-pyran-4-yl]-3-oxopentanoate 24

A mixture of **22** (11 mg, 0.03 mmol), K_2CO_3 (4 mg, 0.03 mmol) and methanol (0.5 cm^3) was stirred at room temperature for 1 h. Aqueous NH_4Cl was added and the product was extracted with CH_2Cl_2. The oily residue obtained by evaporation of the solvent was purified by preparative TLC (EtOAc) to give the *allyl alcohol* **23** (6 mg, 88%) as an oil; $[\alpha]_D^{18}$ +21.3 (*c* 0.76 in $CHCl_3$) (Found: C, 59.0; H, 8.0. $C_{14}H_{22}O_6$ requires C, 58.72; H, 7.75%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3500, 1755, 1725 and 1055; $\delta_H(CDCl_3)$ 1.4–2.0 (5 H, m), 2.62 (2 H, t, *J* 7.2). 3.46 (2 H, d, *J* 3.6), 3.48 (3 H, s), 3.78 (3 H, s), 4.1–4.4 (4 H, m). 4.70 (1 H, dd, *J* 9.0, 4.3) and 5.62 (1 H, t, *J* 7.2).

A mixture of **23** (14 mg, 0.05 mmol), diphenyl disulfide (33 mg, 0.15 mmol), tributylphosphine (30 mg, 0.15 mmol) and THF (1 cm^3) was gently refluxed for 6 h with stirring. After cooling to room temperature, water was added and the product was extracted with CH_2Cl_2. The combined extracts were washed successively with aqueous NaOH, water and brine and dried. Evaporation of the solvent followed by purification of the residue by preparative TLC (hexane–EtOAc, 1:1) gave the *title compound* **24** (16 mg, 86%) as an oil; $[\alpha]_D^{17}$ −8.25 (*c* 1.03 in $CHCl_3$) (Found: C, 63.5; H, 7.0; S, 8.5. $C_{20}H_{26}O_5S$ requires C, 63.66; H, 6.93; S, 8.45%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1750, 1725 and 1050; $\delta_H(CDCl_3)$ 1.4–2.0 (5 H, m), 2.58 (2 H, t, *J* 7.2), 3.46 (3 H, s), 3.49 (2 H, s), 3.76 (3 H, s), 4.1–4.2 (2 H, br s), 4.66 (1 H, dd, *J* 9.0, 3.6), 5.54 (1 H, t, *J* 7.9) and 7.2–7.5 (5 H, m).

Methyl 2-diazo-5-[(*Z*,2*R*,4*S*)-2-methoxy-5-(2-phenylsulfanylethylidene)tetrahydro-2*H*-pyran-4-yl]-3-oxopentanoate 4

A mixture of **24** (16 mg, 0.043 mmol), toluene-*p*-sulfonyl azide (13 mg, 0.065 mmol), triethylamine (35 mg, 0.086 mmol) and acetonitrile (0.5 cm^3) was stirred at 45 °C for 48 h. After cooling to room temperature, water was added and the product was extracted with ether. The combined extracts were washed successively with aqueous acetic acid, water, aqueous $NaHCO_3$, water and brine and dried. Removal of the solvent followed by purification of the residue by preparative TLC (hexane–EtOAc, 3:1) gave the *title compound* **4** (16 mg, 91%) as an oil; $[\alpha]_D^{17}$ −8.23 (*c* 1.12 in $CHCl_3$) (Found: C, 59.7; H, 6.1; N, 7.1; S, 8.0. $C_{20}H_{24}N_2O_5S$ requires C, 59.38; H, 5.98; N, 6.93; S, 7.93%); $\nu_{max}(CHCl_3)/cm^{-1}$ 2150, 1725, 1650 and 1150; $\delta_H(CDCl_3)$ 1.4–2.0 (5 H, m), 2.86 (2 H, t, *J* 7.2), 3.42 (1 H, d, *J* 7.2), 3.46 (3 H, s), 3.62 (1 H, d, *J* 7.2), 4.12 (2 H, br s), 4.68 (1 H, dd, *J* 9.0, 3.6), 5.52 (1 H, t, *J* 7.2) and 7.2–7.5 (5 H, m).

Methyl (3*R*,4a*S*,8*S*,8a*R*)-3-methoxy-7-oxo-8-phenylsulfanyl-8a-vinyloctahydro-1*H*-2-benzopyran-8-carboxylate 5

A mixture of **4** (16 mg, 0.039 mmol), rhodium acetate (0.16 mg, 3.9×10^{-4} mmol), and benzene (1.6 cm^3) was stirred at room temperature for 30 min, and then at 80 °C for 30 min. After cooling to room temperature, the reaction mixture was filtered through a short silica gel column (EtOAc), and the filtrate was concentrated to leave a crystalline residue. Purification by preparative TLC (hexane–EtOAc, 3:2) gave the *title compound* **5** (12 mg, 77%) as crystals, mp 165–166 °C; $[\alpha]_D^{15}$ +42.7 (*c* 0.15 in $CHCl_3$) (Found: C, 64.0; H, 6.5; S, 8.55. $C_{20}H_{24}O_5S$ requires C, 63.80; H, 6.43; S, 8.52%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1728, 1710 and 1073; $\delta_H(CDCl_3)$ 1.2–2.4 (7 H, m), 3.64 (3 H, s), 3.70 (3 H, s), 4.06 (2 H, s), 4.64 (1 H, dd, *J* 9.0, 3.6), 5.38 (1 H, dd, *J* 17.1, 1.8), 5.56 (1 H, dd, *J* 10.8, 1.8), 5.92 (1 H, dd, *J* 17.1, 10.8) and 7.1–7.5 (5 H, m).

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