An Enantioconvergent Route to Carbocyclic Nucleosides (−)-Aristeromycin and (−)-Neplanocin A *via* the Asymmetric Diels–Alder Reaction

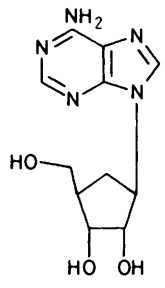
Yoshitsugu Arai, Yoshikazu Hayashi, Masatoshi Yamamoto, Hiromitsu Takayema, and Toru Koizumi*

Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Sugitani 2630, Toyama 930-01, Japan

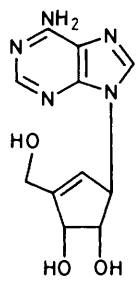
The asymmetric Diels–Alder reaction of (S_S)-menthyl-3-(2-pyridylsulphinyl)acrylate (**4**) with cyclopentadiene gave almost a pure single diastereoisomeric cycloadduct. The cycloadduct was then converted into the central intermediate (+)-(**3**) which was involved in the synthesis of both (−)-aristeromycin and (−)-neplanocin A. Similarly, the Diels–Alder adduct of (R_S)-menthyl-3-(2-pyridylsulphinyl)acrylate (**6**) with cyclopentadiene was transformed into the lactone (**3**) with the same absolute configuration. Namely, an enantioconvergent synthesis of (**3**) starting from each of the diastereoisomeric sulphoxides (**4**) and (**6**) has been achieved.

Aristeromycin (**1**), a carbocyclic nucleoside, was first synthesized in racemic form out of biological interest.[1] (−)-Enantiomer was later isolated from *S. citricolor* n. sp.[2] Neplanocin A (**2**), the dehydro derivative of aristeromycin, was isolated from *Ampullariella regularis*.[3] Neplanocins and aristeromycin exhibit remarkable antitumour activity.[4] Therefore, many reports concerned with the racemic synthesis of these carbocylic nucleosides[5] and their congeners[6] have appeared in the literature.

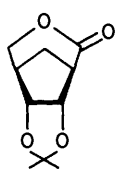
To date, there have been some successful enantioselective syntheses of (−)-neplanocin A[7–9] and (−)-aristeromycin.[7,10,11] The first enantioselective synthesis of the carbocylic nucleosides (**1**) and (**2**) was reported by Ohno and co-workers.[7] The construction of the chiral cyclopentane ring was accomplished by oxidative cleavage of the chiral bicyclo-[2.2.1]heptene precursor which was obtained by enzymatic hydrolysis of a racemic diester. The choice of the chiral intermediate (**3**) in their total synthesis originated from the



(**1**)



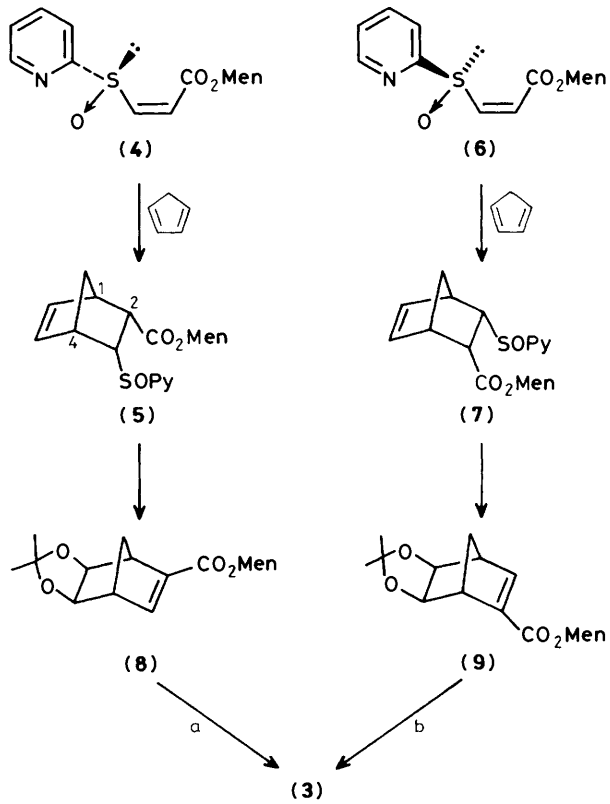
(**2**)



(**3**)

previous studies on the racemic synthesis developed by Just.[12] Other approaches relied on the use of chiral cyclopentane derivatives starting from D-ribose[8] or D-erythrose.[10] Johnson *et al.* reported the synthesis *via* an asymmetric hydrolysis of the *meso* 2,4-diacetylcyclopentene derivative.[9] A synthesis involving a resolution step of the racemic intermediate was also reported.[11]

In order to find an efficient route to the chiral bicyclo[2.2.1]heptane system, we investigated an asymmetric Diels–Alder reaction. In a preliminary communication,[13] we described the asymmetric Diels–Alder reaction of (S_S)-menthyl 3-(2-pyridylsulphinyl)acrylate (**4**)[14,†] with cyclopentadiene, which gave the cycloadduct (**5**) with high diastereoselectivity, and its application to the synthesis of Ohno's intermediate (+)-(**3**)[7] (Scheme 1, route a).



Scheme 1. Men = menthyl; Py = 2-pyridyl

Our approach to the synthesis of the lactone (**3**) with the same absolute configuration, beginning from (R_S)-menthyl 3-(2-pyridylsulphinyl)acrylate (**6**), is outlined in Scheme 1 (route b); the Diels–Alder reaction of compound (**6**) with cyclopentadiene

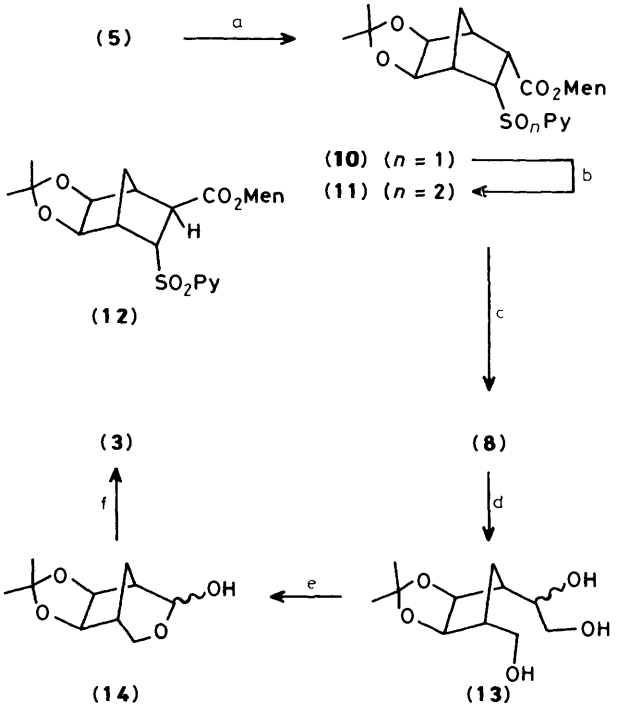
† The symbol (S_S) given in this text expresses that the chirality at sulphur is *S* configuration.

gives the cycloadduct (**7**), and the adduct is transformed into the lactone (**3**) *via* the ester (**9**).

In this paper we describe, in detail, an enantioconvergent route to (−)-aristeromycin and (−)-neplanocin A *via* the esters (**8**) and (**9**).

Results and Discussion

The Diels–Alder reaction of the sulphoxide (**4**) with cyclopentadiene in the presence of a Lewis acid (Et_2AlCl, −78 °C, 3 h) gave the cycloadduct (**5**) as almost a single diastereoisomer in 96% yield. The *endo* stereochemistry of the product (**5**) was determined by the coupling constants ($J_{2,3}$ 9 and $J_{3,4}$ 4 Hz) of 3-H with the bridgehead 4-H and with 2-H in the n.m.r. spectrum. The diastereoisomeric excess (d.e.) was shown to be no less than 96% as judged by n.m.r. and h.p.l.c. analysis. *cis*-Hydroxylation of compound (**5**) with catalytic osmium tetroxide (room temperature, 12 h)[15] and subsequent acetonide formation [2,2-dimethoxypropane, acetone, toluene-*p*-sulphonic acid (TSA)] furnished the sulphoxide (**10**) and the sulphone (**11**) in 64 and 22% yield, respectively (Scheme 2). The

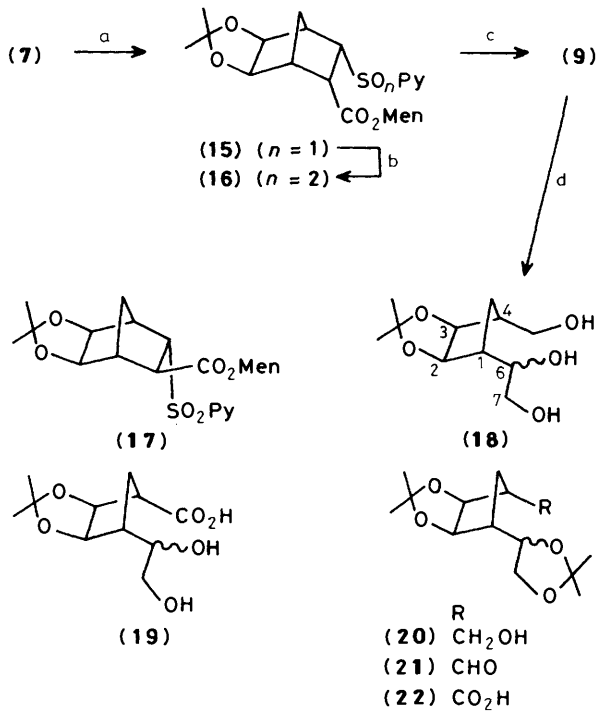


Scheme 2. *Reagents:* a, OsO_4 (cat.), Me_3NO; $Me_2C(OMe)_2$, TSA (cat.); b, MCPBA; c, DBU, DMSO–Et_2O; d, O_3, CH_2Cl_2; Me_2S; $LiAlH_4$, THF; e, $NaIO_4$, THF–water; f, CrO_3·2Py, CH_2Cl_2

product ratio was dependent on reaction time and/or amounts of oxidants used. Exposure of the sulphoxide (**10**) to *m*-chloroperbenzoic acid afforded the sulphone (**11**) in quantitative yield. The sulphone (**11**) was treated with 1,5-diazabicyclo-[5.4.0]undec-7-ene (DBU) to give the unsaturated ester (**8**) in 61% yield, along with the epimerised sulphone (**12**) (26%). Attempts to suppress the formation of (**12**) were unsuccessful.

Following the procedure of Just,[12] the ester (**8**) was transformed into the chiral lactone (**3**). Ozonolysis of the ester (**8**) (O_3, MeOH; Me_2S, −70 °C) followed by reduction with lithium aluminium hydride gave the triol (**13**). Cleavage of the diol group in compound (**13**) with sodium metaperiodate produced the lactol (**14**) as an anomeric mixture. Using this 'one-pot' procedure, the lactol (**14**) was obtained in 60% overall yield from intermediate (**8**). Collins oxidation[16] of the lactol (**14**) afforded Ohno's lactone (**3**), $[\alpha]_D^{25}$ +46.7° (lit.,[7] $[\alpha]_D^{25}$ +44.4°), in 73% yield. The i.r. spectrum of (**3**) was superimposable with that of an authentic sample.[7]

The Diels–Alder reaction of the sulphoxide (**6**) with cyclopentadiene proceeded, with high diastereoselectivity, to afford the *endo* adduct (**7**) in 93% yield. The d.e. of the cycloadduct (**7**) was shown to be >96% by n.m.r. spectroscopy and its absolute stereochemistry could be deduced (as depicted in Scheme 1) based upon our proposal of the reaction mechanism.[17] By treating the product (**7**) as described above for the adduct (**5**), the intermediate (**9**) was obtained *via* compounds (**15**) and (**16**) in 55% yield (Scheme 3). The epimerised sulphone (**17**) was also produced in the elimination step as a by-product (29%).



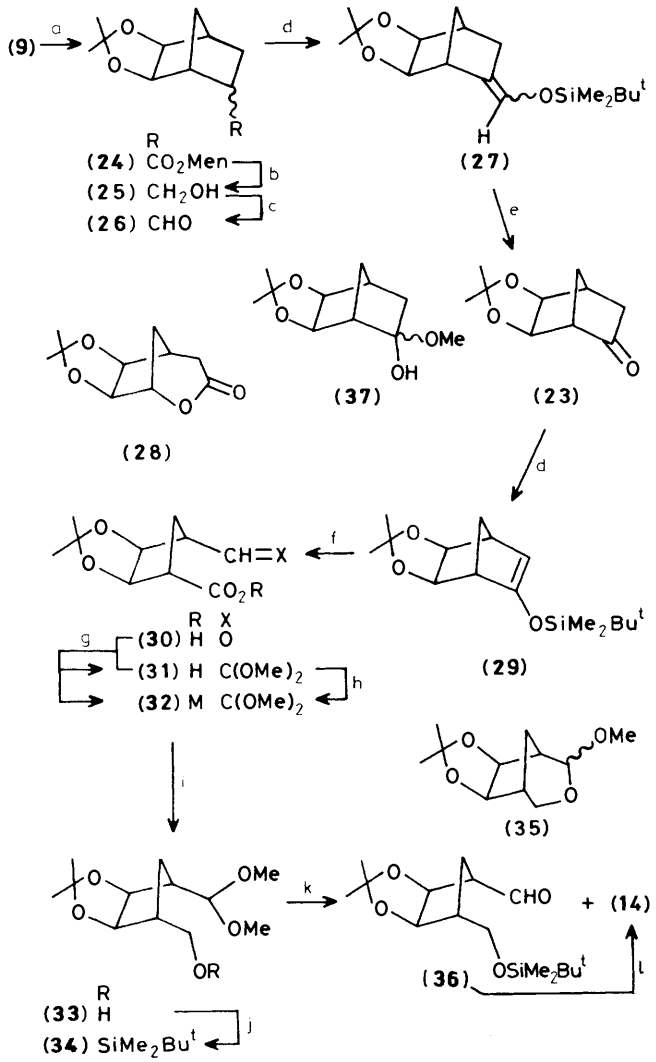
Scheme 3. *Reagents:* a, OsO_4 (cat.), Me_3NO; $Me_2C(OMe)_2$, TSA (cat.); b, MCPBA; c, DBU, DMSO; d, O_3, MeOH; Me_2S; $LiAlH_4$, THF

Our initial approach to the lactone (**3**) relied on the conversion of the triol (**18**), derived from the ester (**9**), into the carboxylic acid (**19**). We expected that oxidative cleavage of the diol (**19**) with sodium metaperiodate followed by reduction with sodium borohydride would give the desired lactone (**3**).

Indeed, ozonolysis of the ester (**9**) and subsequent reduction ($LiAlH_4$) afforded the triol (**18**) in 43% isolated yield as a diastereoisomeric mixture. Protection of the diol group in the triol (**18**) was accomplished with 2,2-dimethoxypropane [dimethylformamide (DMF), TSA, room temperature, 18 h][18] to give the acetonide (**20**) in 72% yield. After Collins oxidation of compound (**20**) (66%), the resulting aldehyde (**21**) was subjected to oxidation with potassium permanganate in a buffered medium[19] to give the carboxylic acid (**22**) in moderate yield. In order to synthesize the lactone (**3**), the acetonide groups on the C-6 and -7 positions in the diacetonide (**22**) needed to be deprotected selectively. A variety of reagents [70% AcOH–tetrahydrofuran (THF),[20] 0.8% H_2SO_4–MeOH[21] or $FeCl_3$–silica gel[22]] were used for this purpose; however, we were unable to obtain the desired mono acetonide (**19**) in substantial yield.

We then turned our attention to the preparation of the ketone (**23**), starting from the ester (**9**). The racemic ketone (**23**) has been transformed into an intermediate (**31**), used in the synthesis of carbocyclic nucleoside analogues, by Cookson *et al.*[23]

Hydrogenation of the ester (**9**) over Pd gave the saturated ester (**24**) in 92% yield (Scheme 4). The ester (**24**) was obtained



Scheme 4. *Reagents*: a, H_2, Pd–C, EtOH; b, $LiAlH_4$, Et_2O; c, PCC, molecular sieves 4A; d, TBDMSOTf, Et_3N; e, O_3, MeOH–CH_2Cl_2; Me_2S; TSA (cat.), acetone; f, O_3, MeOH–CH_2Cl_2; Me_2S; g, Dowex 50W-X8, MeOH; h, $Me_2C(OMe)_2$; i, CH_2N_2, Et_2O–MeOH; i, $LiAlH_4$, THF; j, TBDMSCl, imidazole, DMF; k, TSA (cat.), acetone; l, 70% AcOH THF (1:1)

as an inconsequential mixture of *endo* and *exo* epimers (>98:2). Reduction of the saturated ester (**24**) with lithium aluminium hydride in ether followed by oxidation with pyridinium chlorochromate (PCC)[24] gave the aldehyde (**26**) derived from the alcohol (**25**) in 82% yield. The aldehydic protons of compound (**26**) in the n.m.r. spectrum showed the *endo* isomer (9.83) contaminated with a small amount of its epimer (9.69). From the above result, it was assumed that epimerisation of the carbonyl did not occur during the oxidation. Conversion of the aldehyde (**26**) into the ketone (**23**) was carried out as follows. Treatment of compound (**26**) with dimethyl-t-butylsilyl trifluoromethanesulphonate (triflate)[25] furnished the unstable enol ether (**27**) as a 1:1 mixture of *E* and *Z* isomers. Careful ozonolysis of the ether (**27**) at −78 °C for 15 min gave the desired ketone (**23**) as a major product. The minor product was assumed to be the hemiacetal of (**23**) [(**37**), see Experimental section]. Without separation, this mixture was then treated with a catalytic amount of TSA at room temperature for 12 h to give the ketone (**23**) in 76% combined yield. Passing ozone through the mixture over a prolonged period of time resulted in low yields of the ketone (**23**) and in the formation of lactones such as (**28**) and (−)-(**3**). The spectral data of the ketone (**23**) were identical with those reported[23] except for chiroptical properties.

Conversion of the chiral ketone (**23**) into the ester (**32**) was carried out by modification of the method of Cookson. The reaction of the ketone (**23**) with dimethyl-t-butylsilyl triflate gave the enol ether (**29**) in excellent yield. Ozonolysis of the ester (**29**) in methanol–dichloromethane and subsequent treatment with dimethyl sulphide gave a mixture of the carboxylic acids (**30**) and (**31**) in a ratio of 1:16. This mixture was directly used for acetalisation (Dowex 50W-X8, H^+ form) followed by esterification (CH_2N_2), which afforded the methyl ester (**32**) in 60% yield from the ketone (**23**). The acetal (**32**) was treated with $LiAlH_4$ to give the alcohol (**33**) in excellent yield. Attempts to convert the alcohol (**33**) into the desired hemiacetal (**14**) by using a variety of reagents (pyridinium toluene-*p*-sulphonate,[26] TSA,[23] or AcOH–water[20]) were unsuccessful, resulting in the exclusive formation of the methyl acetate (**35**) which was assumed to be a 1:1 anomeric mixture (OMe, δ 3.36 and 3.44). Despite considerable effort, it was difficult to convert the acetal (**35**) into the desired acetal (**14**); using a variety of reagents for demethylation gave a complex mixture of products, presumably resulting from the decomposition of compound (**36**).

The alcohol (**33**) was then protected as the silyl ether (**34**) and deprotection of the acetal moiety with TSA afforded a mixture of compounds (**14**) and (**36**) in a ratio of *ca.* 2:5, together with a small amount of the acetal (**35**). The crude mixture was treated with 70% acetic acid to produce the hemiacetal (**14**) (71% combined yield) which was subjected to Collins oxidation to give Ohno's lactone (**3**), $[\alpha]_D^{25}$ +44.1°, in 48% yield from the silyl ether (**34**).

Hence, a synthesis of the optically pure lactone, a central intermediate in Ohno's synthesis of (−)-aristeromycin and (−)-neplanocin A, has been achieved in an enantioconvergent way starting from the sulphoxide (**4**) and its diastereoisomer (**6**).

Experimental

M.p.s were taken with a YANACO micro melting-point apparatus and are uncorrected. B.p.s are also uncorrected. I.r. spectra were measured as films, on KBr discs, or in chloroform solution on a JASCO A-102 spectrophotometer. ^1H N.m.r. spectra were recorded on a JEOL PMX-60 (60 MHz) spectrometer, a Varian XL-200 (200 MHz) spectrometer, or a JEOL GX-270 (270 MHz) spectrometer with deuteriochloroform as solvent; *J* values in Hz. Tetramethylsilane was used as internal standard. Mass spectra were recorded with a JEOL JMS-D 200 spectrometer. Optical rotations were measured on a JASCO DIP-140 digital polarimeter.

All organometallic and low temperature reactions were carried out in oven-dried glassware under a slight positive pressure of argon. All solvents were distilled prior to use. Dry THF was freshly distilled from lithium aluminium hydride, and dry dichloromethane was distilled from phosphorus pentaoxide and stored with molecular sieves 4A. Ether refers to diethyl ether, and light petroleum refers to the fraction with b.p. 30—60 °C. Column chromatography was performed with Nakarai Chemicals 70—230 mesh silica gel. Silyl compounds obtained were purified with Mallinckrodt 7087 silica gel.

Wako's pre-coated thin-layer silica $PF70_{254}$ plates were used for monitoring the reactions. Visualisation of t.l.c. plates was achieved by u.v. and/or by phosphomolybdic acid. Medium-pressure liquid chromatography (m.p.l.c.) was performed with an FMI pump on Nakarai Chemicals 230—400 mesh silica gel. Analytical h.p.l.c. was carried out on a Waters Associates 6000 A pump or a Shimadzu LC-6A pump by using a 5μ-Develosil 60 column and monitoring at 254 nm. Peak ratios on h.p.l.c. were measured with a Shimadzu integrator (Chromatopac C-R3A).

(S$_S$)(Z)-Menthyl 3-(2-Pyridylsulphinyl)acylate (**4**) *and* *(R$_S$)(Z)-Menthyl 3-(2-Pyridylsulphinyl)acrylate* (**6**).—Triethylamine (10 drops) was added to a solution of (−)-menthyl propiolate[27] [4.92 g, 23.7 mmol, $[\alpha]_D^{23}$ −81° (*c* 1.0, $CHCl_3$)] in dry dimethyl sulphoxide (DMSO) (50 ml) and dry dichloromethane (50 ml) was added at −75 °C. 2-Mercaptopyridine (2.76 g, 24.9 mmol) in dry dichloromethane (25 ml) was added dropwise and the temperature was allowed to rise slowly to −30 °C over 1 h. The reaction mixture was diluted with dichloromethane (200 ml) and the organic layer was washed with saturated aqueous sodium hydrogen carbonate (150 ml). The aqueous layer was re-extracted with dichloromethane (2 × 200 ml). The combined organic layers (*ca.* 800 ml) were washed with saturated brine and dried ($MgSO_4$). The dichloromethane was removed to give a red–brown oil (*ca.* 58 g). Column chromatography of the oil with hexane–ether (2:1) as eluant afforded the sulphide (7.25 g, 95%) which was shown to be a mixture of *Z*- and *E*-isomers by n.m.r. spectroscopy. Purification of the crude product by recrystallisation with hexane gave the pure (*Z*)-sulphide as colourless needles (5.19 g, 68%), m.p. 72—73 °C (Found: C, 67.9; H, 7.9; N, 4.4. $C_{18}H_{25}NO_2S$ requires C, 67.68; H, 7.82; N, 4.38%); $\nu_{max.}$(KBr) 1 680 and 1 580 cm^{-1}; δ_H(200 MHz) 0.8—2.2 (18 H, m, 3 × Me, 3 × CH_2, 3 × CH), 4.82 (1 H, dt, *J* 11 and 4, OCH), 6.08 (1 H, d, *J* 10, HC=), 7.14 (1 H, m, ArH), 7.34 (1 H, m, ArH), 7.62 (1 H, td, *J* 8 and 2, ArH), 8.55 (1 H, d, *J* 10, SCH=), and 8.56 (1 H, m, ArH).

A solution of *m*-chloroperbenzoic acid (80% purity; 17.7 g, 82 mmol) in dry dichloromethane (100 ml) was added dropwise to a solution of the crude sulphide (25.0 g, 78 mmol; *E*:*Z* = 85:13) in dry dichloromethane (200 ml) at −70 °C. After addition the temperature was allowed to rise slowly to 0 °C over 3 h. The reaction mixture was then diluted with dichloromethane and the organic layer was washed with diluted aqueous sodium thiosulphate, saturated aqueous sodium hydrogen carbonate, and dried ($MgSO_4$). The solvent was evaporated to afford a yellow oil (41.9 g). Purification by chromatography (ether) afforded the sulphoxide (22.94 g, 88%) as a diastereoisomeric mixture. The sulphoxide was dissolved in hexane–ether (4:1; 70 ml) and the solution was cooled to −20 °C in a refrigerator for 5 days. The precipitate obtained as an oily solid was collected and recrystallisation from hexane–ether afforded the pure sulphoxide (**4**) (5.92 g, 23%) as colourless needles, m.p. 93 °C (Found: C, 64.55; H, 7.4; N, 3.9. $C_{18}H_{25}NO_3S$ requires C, 64.48; H, 7.46; N, 4.18%); $[\alpha]_D^{24}$ +258 °C (*c* 0.77, $CHCl_3$); d.e. >99%; $\nu_{max.}$(KBr) 1 725, 1 200, 1 040, and 1 030 cm^{-1}; δ_H(200 MHz) 0.79 (C H, d, *J* 7, Me), 0.89 (3 H, d, *J* 7, Me), 0.92 (3 H, d, *J* 7, Me), 0.98—2.10 (9 H, m, 3 × CH_2, 3 × CH), 4.85 (1 H, dt, *J* 11 and 4, CHO), 6.39 (1 H, d, *J* 10, CH=), 6.87 (1 H, d, *J* 10, SCH=), 7.42 (1 H, ddd, *J* 7.5, 5, and 1.5, ArH), 7.92 (1 H, dt, *J* 7.5 and 1.5, ArH), 8.03 (1 H, d, *J* 7.5, ArH), and 8.69 (1 H, dm, *J* 5, ArH).

The mother liquor was concentrated and the residue purified by m.p.l.c. (hexane–propan-2-ol, 9:1) to afford the pure sulphoxide (**6**) (2.63 g, 10%) as a colourless prisms, m.p. 72—74 °C (Found: C, 64.75; H, 7.6; N, 4.15. $C_{18}H_{25}NO_2S$ requires C, 64.48; H, 7.46; N, 4.18%); $[\alpha]_D^{24}$ −394 °C (*c* 0.84, $CHCl_3$); d.e. >99%; $\nu_{max.}$(KBr) 1 720 cm^{-1}; δ_H(200 MHz) 0.74 (3 H, d, *J* 7, Me), 0.89 (3 H, d, *J* 7, Me), 0.92 (3 H, d, *J* 7, Me), 0.90—2.20 (9 H, m, 3 × CH_2, 3 × CH), 4.82 (1 H, dt, *J* 9 and 4, OCH), 6.40 (1 H, d, *J* 10, CH=), 6.91 (1 H, d, *J* 10, SCH=), 7.42 (1 H, ddd, *J* 8, 5, and 1.5, ArH), 7.92 (1 H, dt, *J* 8 and 1.5, ArH), 8.03 (1 H, d, *J* 8, ArH), and 8.70 (1 H, d, *J* 5, ArH). The later fractions contained a mixture of the sulphoxides (**4**) and (**6**), which were inseparable by recrystallisation.

The diastereoisomeric excesses of the crystalline compounds (**4**) and (**6**) were estimated by the peak ratios of the ^1H n.m.r. spectrum [6.87 for (**4**) and 6.91 for (**6**)].

(+)-(1R,S$_S$)-Menthyl 3-endo-(2-Pyridylsulphinyl)bicyclo[2.2.1]hept-5-ene-2-endo-carboxylate (**5**).—Diethylaluminium chloride (1M solution in hexane; 6.6 ml, 6.6 mmol) was added to a stirred solution of the sulphoxide (**4**) [2.0 g, 6 mmol, $[\alpha]_D^{24}$ +264° (*c* 1.02, $CHCl_3$] in dry dichloromethane (50 ml) at −70 °C over 5 min and the mixture was stirred for 15 min. Freshly distilled cyclopentadiene (10 ml, 120 mmol) was then added and the solution was stirred for 3 h at −70 °C. The reaction mixture was poured on to cold 5% aqueous sodium carbonate (50 ml) and the aqueous layer was neutralised with 5% hydrochloric acid. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 × 80 ml). The combined extracts were washed with saturated brine and dried ($MgSO_4$). The solvent was removed and the residue was chromatographed on silica gel (hexane and then ethyl acetate). Early fractions contained dicyclopentadiene. Further elution with ethyl acetate yielded the cycloadduct (**5**) (2 975 g, 96%) as white plates, m.p. 141—142 °C (from hexane) (Found: C, 68.85; H, 7.7; N, 3.4. $C_{23}H_{31}NO_3S$ requires C, 68.78; H, 7.78; N, 3.49%); $[\alpha]_D^{25}$ +41.9° (*c* 1.0, $CHCl_3$); $\nu_{max.}$(KBr) 1 730 and 1 575 cm^{-1}; δ_H(270 MHz) 0.440 (3 H, d, *J* 7, Me), 0.717 (3 H, d, *J* 7, Me), 0.796 (3 H, d, *J* 7, Me), 0.65—1.85 (11 H, m, 4 × CH_2, 3 × CH), 3.264 (1 H, br s, 4-H), 3.358 (1 H, dd, *J* 9 and 3.5, $CHCO_2$), 3.419 (1 H, br s, 1-H), 4.118 (1 H, dd, *J* 9 and 3, CHSO), 4.366 (1 H, td, *J* 11 and 4.5, CHO), 6.127 (1 H, dd, *J* 5.5 and 3, CH=), 6.568 (1 H, dd, *J* 5.5 and 3, CH=), and 7.24—8.53 (4 H, m, ArH).

The diastereoisomeric excess (d.e.) of the product (**5**) was shown to be >96% by h.p.l.c. analysis (Develosil, hexane–ethyl acetate 7:1) and by 270 MHz n.m.r. spectroscopy.

(−)-(1S)-Menthyl 5-exo,6-exo-(Isopropylidenedioxy)-3-endo-(2-pyridylsulphonyl)bicyclo[2.2.1]heptane-2-endo-carboxylate (**11**).—Osmium tetroxide (0.1M solution in t-butyl alcohol; 0.25 ml, 0.025 mmol) was added to a solution of the sulphoxide (**5**) (609 mg, 1.52 mmol) and trimethylamine *N*-oxide dihydrate (1.27 g, 11.4 mmol) in acetone (10 ml) and water (1 ml). The reaction mixture was stirred for 20 h at room temperature. Filtration and evaporation to dryness gave a black oil (747 mg). This oil was dissolved in a mixture of acetone (20 ml) and 2,2-dimethoxypropane (3 ml) with a catalytic amount of TSA and heated under reflux for 3 h. The solution was concentrated and the residue was diluted with chloroform (30 ml). The organic phase was washed with water, saturated brine, and dried ($MgSO_4$). The solvent was evaporated and the residue was purified by chromatography with hexane–ethyl acetate (4:1) to give the sulphone (**11**) (163 mg, 22%) as colourless needles, m.p. 147—149 °C (from ethyl acetate–light petroleum) (Found: C, 63.55; H, 7.65; N, 2.8. $C_{26}H_{37}NO_6S$ requires C, 63.52; H, 7.59; N, 2.85%); $[\alpha]_D^{25}$ −1.14° (*c* 1.0, $CHCl_3$); $\nu_{max.}$(KBr) 1 720 and 1 070 cm^{-1}; δ_H(270 MHz) 0.760 (3 H, d, *J* 7, Me), 0.861 (2 × 3 H, d, *J* 7, 2 × Me), 1.329 (3 H, s, Me), 1.457 (3 H, s, Me), 2.060 (1 H, d, *J* 10.8, 7-H), 0.8—2.0 (10 H, m, 3 × CH_2, 4 × CH), 2.88 (1 H, br, 1- or 4-H), 2.71 (1 H, br, 4- or 1-H), 3.194 (1 H, dd, *J* 11.7 and 4.2, $CHCO_2$), 4.637 (1 H, dt, *J* 10.8 and 4.4, OCH), 4.789 (1 H, dd, *J* 11.7 and 4.4, $CHCO_2$), 4.829 (1 H, d, *J* 5.5, OCH), 5.202 (1 H, d, *J* 5.5, OCH), and 7.50—8.69 (4 H, m, ArH). Further elution with ethyl acetate gave the sulphoxide (**10**) (465 mg, 64%), as colourless prisms, m.p. 162—164 °C (from ethyl acetate–light

petroleum) (Found: C, 65.95; H, 7.8; N, 2.8. $C_{26}H_{37}NO_5S$ requires C, 65.66; H, 7.84; N, 2.94%); $[\alpha]_D^{25}$ +13.1° (*c* 1.1, $CHCl_3$); $\nu_{max.}$(KBr) 1 730, 1 570, and 1 030 cm^{-1}; δ_H(270 MHz) 0.768 (3 H d, *J* 7, Me), 0.851 (3 H, d, *J* 6.5, Me), 0.895 (3 H, d, *J* 7, Me), 1.238 (1 H, d, *J* 11, 7-H), 1.318 (3 H, s, Me), 1.454 (3 H, s, Me), 0.7—1.8 (9 H, m, 3 × CH_2, 3 × CH), 1.9 (1 H, m, CH), 2.050 (1 H, d, *J* 11, 7-H), 2.726 (1 H, br, 1- or 4-H), 2.818 (1 H, br, 4- or 1-H), 3.241 (1 H, dd, *J* 11 and 5, $HCCO_2$), 3.675 (1 H, dd, *J* 11 and 4, $HCSO_2$), 4.372 (1 H, d, *J* 5, OCH), 4.603 (1 H, td, *J* 11 and 4, OCH), 5.103 (1 H, d, *J* 5, OCH), and 7.3—8.6 (4 H, m, ArH). The osmylation, conducted at room temperature for 3 days, and subsequent acetonidation resulted in the formation of compounds (**10**):(**11**) in a ratio of *ca.* 2:1.

m-Chloroperbenzoic acid (80% purity; 116 mg, 0.54 mmol) in dry dichloromethane (4 ml) was added to a solution of the sulphoxide (**10**) (214 mg, 0.45 mmol) in dry dichloromethane (5 ml) and the mixture was stirred at room temperature for 1 h. After work-up, purification of the crude product by recrystallisation gave the sulphone (**11**) (218 mg, 99%).

(−)-(1S)-*Menthyl* 5-exo,6-exo-(*Isopropylidenedioxy*)*bicyclo*[2.2.1]*hept*-2-*ene*-2-*carboxylate* (**8**).—A mixture of the sulphone (**11**) (219 mg, 0.45 mmol), dry DMSO (0.8 ml), DBU (0.2 ml) was heated at 55 °C for 3 h. Purification of the crude mixture by chromatography with hexane–ethyl acetate (5:1) gave the α,β-unsaturated ester (**8**) (95 mg, 61%), as a colourless oil (Found: M^+, 348.2258. $C_{21}H_{32}O_4$ requires *M*, 348.2298); $[\alpha]_D^{25}$ −18.1° (*c* 2.9, $CHCl_3$); $\nu_{max.}$(film) 1 710, 1 600, and 1 260 cm^{-1}; δ_H(270 MHz) 0.760 (3 H, d, *J* 7, Me), 0.893 (3 H, d, *J* 7, Me), 0.905 (3 H, d, *J* 6.5, Me), 1.353 (3 H, s, Me), 1.501 (3 H, s, Me), 0.71—2.09 (11 H, m, 4 × CH_2, 3 × CH), 2.950 (1 H, br s, 4-H), 3.170 (1 H, br s, 1-H), 4.273 (2 H, s, 2 × OCH), 4.718 (1 H, td, *J* 11 and 4.5, OCH), and 6.922 (1 H, d, *J* 3.5, 3-H). Further elution with ethyl acetate gave the epimerised sulphone (**12**) (56 mg, 26%), as a white solid, m.p. 138—139 °C (ethyl acetate–light petroleum) (Found: C, 63.8; H, 7.85; N, 2.6. $C_{26}H_{37}NO_6S$ requires C, 63.52; H, 7.59; N, 2.85%); $\nu_{max.}$(KBr) 1 720 and 1 070 cm^{-1}; δ_H(270 MHz) 0.655 (3 H, d, *J* 7, Me), 0.860 (3 H, d, *J* 6.5, Me), 0.876 (3 H, d, *J* 7. Me), 1.347 (3 H, s, Me), 1.452 (3 H, s, Me), 0.75—1.77 (10 H, m, 3 × CH_2, 3 × CH, 7-H), 1.941 (1 H, d, *J* 9.5, 7-H), 2.621 (1 H, s, 1-H), 2.918 (1 H, d, *J* 5.5, 2-H), 3.188 (1 H, br d, *J* 4, 4-H), 4.256 (1 H, dd, *J* 5.5 and 4, 3-H), 4.396 (1 H, d, *J* 5, OCH), 4.507 (1 H, td, *J* 11 and 4.5, OCH), 5.106 (1 H, d, *J* 5, OCH), and 7.50—8.69 (4 H, m, ArH).

(1S,5R)-2-*Hydroxy*-6-exo,7-exo-(*isopropylidenedioxy*)-3-*oxobicyclo*[3.2.1]*octane* (**14**).—Ozone in oxygen was passed through a solution of the ester (**8**) (100 mg, 0.29 mmol) in dry dichloromethane (6 ml) at −70 °C until a pale blue colour was evident. After the excess of ozone in the mixture was purged with nitrogen, dimethyl sulphide (0.2 ml, 3 mmol) was added and the temperature was allowed to rise to ambient temperature. The solvent was evaporated and the residue (*ca.* 120 mg) was dissolved in dry THF (25 ml) with lithium aluminium hydride (100 mg, 2.6 mmol) at 5 °C for 1 h. The excess of reducing reagent was destroyed with water and the suspension was neutralised with 2% hydrochloric acid (*ca.* 20 ml). As indicated in the literature of the racemic synthesis of the lactone (**3**),[12] isolation by chromatography gave low yields of the triol (**13**). After filtration, sodium *m*-periodate (66 mg, 0.3 mmol) was added in three portions to the filtrate containing the triol (**13**). The reaction mixture was stirred at room temperature for 0.5 h. The aqueous phase was extracted with chloroform (4 × 20 ml) and the combined organic layer was washed with saturated brine and dried ($MgSO_4$). The solvent was evaporated and the residue purified by chromatography with hexane–ethyl acetate (2:1) to give the hemiacetal (**14**) of a white solid (22 mg, 60%) as an anomeric mixture in a ratio of 1:1, m.p. 94—97 °C; $\nu_{max.}$($CHCl_3$) 3 400, 1 450, and 1 375 cm^{-1}; δ_H(270 MHz) 1.350 (3 H, s, Me), 1.460 (3 H, s, Me), 1.8—2.3 (4 H, m, CH_2, 2 × CH), 2.488 (1/2 H, d, *J* 3, α-anomeric OH), 2.800 (1/2 H, d, *J* 5, β-anomeric OH), 3.500 (1/2 H, dt, *J* 10.5 and 2.5, α-anomeric 4-H), 3.585 (1/2 H, d, *J* 11, β-anomeric 4-H), 3.791 (1/2 H, dt, *J* 11 and 2.5, β-anomeric 4-H), 3.997 (1/2 H, dd, *J* 10.5 and 1, α-anomeric 4-H), 4.549 (1 H, B of ABq, *J* 5, α- and β-anomeric 6- or 7-H), 4.629 (1/2 H, A of ABq, *J* 5, α-anomeric 7- or 6-H), 4.732 (1/2H, A of ABq, *J* 5, β-anomeric 7- or 6-H), 4.765 (1/2 H, d, *J* 5, β-anomeric 2-H), and 5.062 (1/2 H, t, *J* 3, α-anomeric 2-H). Recrystallisation from hexane gave an analytical sample, m.p. 97—99 °C (Found: C, 59.7; H, 7.95. $C_{10}H_{16}O_4$ requires C, 59.98; H, 8.05%), which showed to be an anomeric mixture of 2:1 (α:β) by n.m.r. spectroscopy. The crude anomeric mixture was used in the next step without recrystallisation.

(+)-(1R,5S)-6-exo,7-exo-(*Isopropylidenedioxy*)-2-*oxo*-3-*oxabicyclo*[3.2.1]*octane* (**3**).—Collins reagent [prepared from chromic trioxide (46 mg, 0.46 mmol) and dry pyridine (0.1 ml, 1.2 mmol) in dry dichloromethane (2 ml)] was added to a solution of the hemiacetal (**14**) (22 mg, 0.11 mmol) in dry dichloromethane (5 ml). The reaction mixture was stirred at room temperature for 1 h. The organic layer was separated by decantation and the residue was diluted with water (10 ml). The aqueous phase was extracted with dichloromethane (3 × 20 ml) and the combined organic extracts were washed with 10% aqueous sodium hydrogen carbonate (3 × 70 ml), 5% hydrochloric acid (70 ml), saturated brine, and dried ($MgSO_4$). The solvent was evaporated to give a white solid which crystallised from hexane–dichloromethane to give the lactone (**3**) (16 mg, 73%) as white needles, m.p. 140—143 °C (sublimed) (Found: C, 60.6; H, 7.1. $C_{10}H_{14}O_4$ requires C, 60.59; H, 7.12%); $[\alpha]_D^{25}$ +46.7° (*c* 0.48, $CHCl_3$) (lit. $[\alpha]_D^{25}$ +44.4° (*c* 1.0, $CHCl_3$); $\nu_{max.}$(KBr) 1 740 cm^{-1}; δ_H(270 MHz) 1.329 (3 H, s, Me), 1.475 (3 H, s, Me), 1.882 (1 H, d, *J* 12, 8-H), 2.269 (1 H, dtd, *J* 12, 5, and 2, 8-H), 2.464 (1 H, br, 5-H), 3.006 (1 H, dd, *J* 5 and 1, 1-H), 4.194 (1 H, ddd, *J* 11, 2, and 0.5, 4-H), 4.336 (1 H, dd, *J* 11 and 4, 4-H), 4.587 (1 H, dd, *J* 5 and 1, 6-H), and 4.654 (1 H, dd, *J* 5 and 1, 7-H).

(−)-(1S,R_S)-*Menthyl* 3-endo-(2-*Pyridylsulphinyl*)*bicyclo*[2.2.1]*hept*-5-*ene*-2-endo-*carboxylate* (**7**).—Diethylaluminium chloride (1M in hexane; 13 ml, 13 mmol) was added to a stirred solution of the sulphoxide (**6**) (4.011 g, 12 mmol), $[\alpha]_D^{23}$ −378° (*c* 0.69, $CHCl_3$) in dry dichloromethane (60 ml) at −70 °C over 5 min. After an additional 20 min, freshly distilled cyclopentadiene (20 ml, 240 mmol) was added dropwise for 15 min and the mixture was stirred for 4 h at −70 °C. According to the work-up as described for the sulphoxide (**5**), the cycloadduct (**7**) was obtained as a colourless oil (4.46 g, 93%), $[\alpha]_D^{26}$ −92° (*c* 2.2, $CHCl_3$), d.e. >96%. Crystallisation from pentane gave an analytical sample, m.p. 82—84 °C (Found: C, 68.75; H, 7.9; N, 3.3. $C_{23}H_{31}NO_3S$ requires C, 68.79; H, 7.78; N, 3.49%); $[\alpha]_D^{27}$ −135° (*c* 1.3, $CHCl_3$); $\nu_{max.}$(film) 1 730, 1 570, 1 450, and 1 180 cm^{-1}; δ_H(270 MHz) 0.440 (3 H, d, *J* 7, Me), 0.717 (3 H, d, *J* 7, Me), 0.796 (3 H, d, *J* 6.5, Me), 0.65—1.85 (11 H, m, 4 × CH_2, 3 × CH), 3.264 (1 H, br s, 1- or 4-H), 3.358 (1 H, dd, *J* 9 and 3.5, $HCCO_2$), 3.419 (1 H, br s, 4- or 1-H), 4.118 (1 H, dd, *J* 9 and 3, HCSO), 4.366 (1 H, td, *J* 11 and 4.5, HCO), 6.127 (1 H, dd, *J* 5.5 and 3, CH=), 6.568 (1 H, dd, *J* 5.5 and 3, CH=), and 7.24—8.53 (4 H, m, ArH).

(−)-(1R)-*Menthyl* 5-exo,6-exo-(*Isopropylidenedioxy*-3-endo-(2-*pyridinylsulphonyl*)*bicyclo*[2.2.1]*heptane*-2-endo-*carboxylate* (**16**).—Osmium tetraoxide (0.1M solution in t-butyl alcohol; 0.6 ml, 0.06 mmol) was added to a solution of the sulphoxide (**6**) (4.815 g, 12 mmol), $[\alpha]_D^{23}$ −378° (*c* 0.69, $CHCl_3$) and trimethylamine *N*-oxide dihydrate (13.3 g, 120 mmol) in acetone (40 ml) and water (1 ml) at room temperature. The reaction

mixture was stirred for 3 h. Filtration and evaporation to dryness gave a black oil. This oil was dissolved in a mixture of acetone (90 ml) and 2,2-dimethoxypropane (18 ml) with TSA (20 mg) and the mixture was heated under reflux for 3 h. The solution was concentrated and the residue was diluted with chloroform (100 ml). The organic layer was washed with water, saturated aqueous sodium hydrogen carbonate, 1% hydrochloric acid, saturated brine, and dried ($MgSO_4$). The solvent was evaporated and the residue was purified by chromatography with hexane–ethyl acetate (4:1) to give the sulphone (**16**) (845 mg). Recrystallisation from hexane–ethyl acetate afforded colourless prisms (708 mg, 12%), m.p. 208.5—209 °C (Found: C, 63.5; H, 7.65; N, 2.7. $C_{26}H_{37}NO_6S$ requires C, 63.52; H, 7.59; N, 2.85%); $[\alpha]_D^{26}$ −74° (*c* 0.49, $CHCl_3$); $\nu_{max.}$(KBr) 1 740, 1 590, 1 160, and 1 015 cm^{-1}; δ_H(270 MHz) 0.671 (3 H, d, *J* 7, Me), 0.856 (3 H, d, *J* 7, Me), 0.943 (3 H, d, *J* 6, Me), 1.466 (3 H, s, Me), 1.593 (3 H, s, Me), 0.8—2.1 (11 H, m, 4 × CH_2, 3 × CH), 2.712 (1 H, br d, *J* 4, 1- or 4-H), 2.891 (1 H, br d, *J* 4, 4- or 1-H), 3.185 (1 H, dd, *J* 11.5 and 4, $HCCO_2$), 4.651 (1 H, td, *J* 11 and 4.5, HCO), 4.686 (1 H, d, *J* 5.5, OCH), 4.708 (1 H, dd, *J* 11.5 and 4, $HCSO_2$), 5.257 (1 H, d, *J* 5.5, OCH), and 7.5—8.70 (4 H, m, ArH).

Further elution with ethyl acetate gave (−)-(R_S)-*menthyl* 5-exo,6-exo-(*isopropylidenedioxy*)-3-endo-(2-*pyridylsulphinyl*)-*bicyclo*[2.2.1]*heptane*-2-*carboxylate* (**15**) (4.224 g, 74%) as a colourless prisms, m.p. 221—224 °C (from ethyl acetate–light petroleum) (Found: C, 65.5; H, 7.7; N, 2.8. $C_{26}H_{37}NO_5S$ requires C, 65.66; H, 7.84; N, 2.94%); $[\alpha]_D^{27}$ −90° (*c* 1.1, $CHCl_3$); $\nu_{max.}$(KBr) 1 720, 1 570, 1 190, 1 065, and 1 040 cm^{-1}; δ_H(270 MHz) 0.524 (3 H, d, *J* 7, Me), 0.819 (3 H, d, *J* 7, Me), 0.891 (3 H, d, *J* 6.5, Me), 1.343 (3 H, s, Me), 1.468 (3 H, s, Me), 0.75—1.95 (10 H, m, 3 × CH_2, 3 × CH, HC*H*), 2.062 (1 H, d, *J* 11, 7-H), 2.749 (1 H, br d, *J* 4, 1- or 4-H), 2.888 (1 H, br d, *J* 4, 4- or 1-H), 3.307 (1 H, dd, *J* 11 and 4.5, HCSO), 3.823 (1 H, dd, *J* 11 and 4, $HCCO_2$), 4.266 (1 H, d, *J* 4.5, OCH), 4.532 (1 H, td, *J* 11 and 4.5, OCH), 5.100 (1 H, d, *J* 4.5, OCH), and 7.32—8.56 (5 H, m, ArH). The sulphoxide (**15**) was converted into the sulphone (**16**) with *m*-chloroperbenzoic acid as described above for the sulphone (**11**) quantitatively. A prolonged period of hydroxylation (16 h) gave compounds (**15**) and (**16**) in 35 and 47% yield, respectively.

(−)-(1R)-*Menthyl* 5-exo,6-exo-(*Isopropylidenedioxy*)*bicyclo*-[2.2.1]*hept*-2-*ene*-2-*carboxylate* (**9**).—A mixture of the sulphone (**16**) (750 mg, 1.58 mmol), dry DMSO (2 ml) and DBU (1 ml) was heated at 55 °C for 4 h. Purification of the crude mixture by chromatography with hexane–ethyl acetate (5:1) gave the unsaturated ester (**9**) (367 mg, 67%) as a colourless oil (Found: M^+, 348.2329. $C_{21}H_{32}O_4$ requires *M*, 348.2301); $[\alpha]_D^{26}$ −92.5 °C (*c* 4.15, $CHCl_3$); $\nu_{max.}$(film) 1 710 and 1 605 cm^{-1}; δ_H(270 MHz) 0.763 (3 H, d, *J* 7, Me), 0.891 (3 H, d, *J* 7, Me), 0.900 (3 H, d, *J* 6.5, Me), 1.356 (3 H, s, Me), 1.499 (3 H, s, Me), 0.81—2.08 (11 H, m, 4 × CH_2, 3 × CH), 2.952 (1 H, br s, 4-H), 3.153 (1 H, s, 1-H), 4.278 (2 H, ABq, *J* 5, 2 × OCH), 4.706 (1 H, td, *J* 11 and 4.5, OCH), and 6.915 (1 H, d, *J* 3, CH=). Further elution with ethyl acetate gave the epimerised sulphone (**17**) (214 mg, 29%) as white needles, m.p. 197—198 °C (from ethyl acetate–light petroleum) (Found: C, 63.8; H, 7.7; N, 2.7. $C_{26}H_{37}NO_6S$ requires C, 63.52; H, 7.59; N, 2.85%); $\nu_{max.}$(KBr) 1 720 and 1 070 cm^{-1}; δ_H(270 MHz) 0.667 (3 H, d, *J* 7, Me), 0.866 (3 H, d, *J* 7, Me), 0.897 (3 H, d, *J* 6.5, Me), 1.353 (3 H, s, Me), 1.463 (3 H, s, Me), 0.78—1.81 (10 H, m, 3 × CH_2, 3 × CH, *H*CH), 1.946 (1 H, d, *J* 10, 7-H), 2.611 (1 H, s, 1-H), 2.940 (1 H, d, *J* 5.5, 2-H), 3.011 (1 H, br d, *J* 4, 4-H), 4.219 (1 H, dd, *J* 5.5 and 4, 3-H), 4.390 (1 H, d, *J* 5.5, OCH), 4.500 (1 H, td, *J* 11 and 4, OCH), 5.100 (1 H, d, *J* 5.5, OCH), and 7.51—8.71 (4 H, m, ArH).

(1S,4S)-[2β,3β-*Isopropylidenedioxy*-4α-(*hydroxymethyl*)-*cyclopent*-1α-*yl*]*ethylene Glycol* (**18**).—A solution of the α,β-unsaturated ester (**9**) (270 mg, 0.77 mmol) in dry methanol (20 ml) at −70 °C was treated with ozone in oxygen until a pale blue colour was evident. After the excess of ozone was purged with nitrogen, dimethyl sulphide (0.5 ml) was added and the temperature was allowed to rise to room temperature. The solvent was evaporated to dryness and the crude mixture was diluted with dry THF (8 ml). Lithium aluminium hydride (200 mg, 5.3 mmol) was added in several portions to the mixture at 0 °C. The mixture was stirred at that temperature for 6 h, then diluted with ether (10 ml), followed by a minimal amount of water (8 drops) with caution. Anhydrous $MgSO_4$ (*ca.* 0.5 g) was added, the precipitate filtered off, and the filtrate concentrated. The crude mixture was dissolved in a small amount of methanol and the solution was separated on a silica gel column. Elution with chloroform–methanol (8:1) gave the triol (**18**) (77 mg, 43%) as a diastereoisomeric mixture (Found: M^+, 232.1298. $C_{11}H_{20}O_5$ requires *M*, 232.1309); $\nu_{max.}$(film) 3 350 cm^{-1}; δ_H(270 MHz) 1.313, 1.325 (total 3 H, 2 × s, diastereoisomeric Me), 1.503, 1.508 (total 3 H, 2 × s, diastereoisomeric Me), 1.2—2.4 (4 H, m, CH_2, 2 × CH), and 3.5—4.6 (10 H, m, 2 × CH_2, 2 × CH, 3 × OH).

(−)-(1R)-*Menthyl* 5-exo,6-exo-(*Isopropylidenedioxy*)*bicyclo*-[2.2.1]*heptane*-2-α/β-*carboxylate* (**24**).—A mixture of the ester (**9**) (795 mg, 2.3 mmol) and 10% Pd–C (45 mg) in ethanol (30 ml) was stirred vigorously under hydrogen at 1 atm for 4 h. The mixture was filtered through a short plug of Celite and the filtrate was concentrated to give the ester (**24**) (735 mg, 92%) as a white solid, which was shown to be almost a single *endo*-isomer by n.m.r. spectroscopy. Recrystallisation from heptane afforded the pure *endo*-isomer of (**24**) as colourless needles, m.p. 78—79 °C (Found: C, 72.2; H, 9.4. $C_{21}H_{34}O_4$ requires C, 71.96; H, 9.78%); $[\alpha]_D^{23}$ −68.4° (*c* 1.01, $CHCl_3$); $\nu_{max.}$(KBr) 1 720 cm^{-1}; δ_H(270 MHz) 0.755 (3 H, d, *J* 7, Me), 0.893 (3 H, d, *J* 7, Me), 0.912 (3 H, d, *J* 6.4, Me), 1.190 (1 H, dt, *J* 10.4 and 1.4, 7-H), 1.276 (3 H, s, Me), 1.441 (3 H, s, Me), 0.8—2 (12 H, m, 4 × CH_2, 3 × CH, *H*CH), 2.305 (1 H, d, *J* 4.8, 1- or 4-H), 2.582 (1 H, d, *J* 4.2, 4- or 1-H), 2.730 (1 H, dt, *J* 11 and 5, 2-H), 4.048 (1 H, dd, *J* 5 and 1, HOC), 4.084 (1 H, d, *J* 5, HOC), and 4.685 (1 H, td, *J* 11 and 4.4, HCO). A mixture of *endo*- and *exo*-isomers was used in the next step.

(+)-(1R)-5-exo,6-exo-(*Isopropylidenedioxy*)*bicyclo*[2.2.1]-*heptan*-2α/β-*ylmethanol* (**25**).—The ester (**24**) (720 mg, 2.05 mmol) in dry ether (25 ml) was added dropwise to a suspension of lithium aluminium hydride (245 mg, 6.5 mmol) in dry ether (10 ml) at 5 °C. The reaction mixture was stirred at room temperature for 1 h. The cooled mixture was carefully diluted with cold water until gas evolution ceased. Anhydrous $MgSO_4$ (*ca.* 0.5 g) was added and the mixture was stirred for 2 min. The mixture was filtered and the filtrate was evaporated to dryness. The residue was chromatographed on silica gel with hexane–ethyl acetate (4:1) to result in recovery of menthol. Further elution with hexane–ethyl acetate (1:1) gave the alcohol (**25**) (377 mg, 93%). The n.m.r. spectrum indicated the presence of a small amount (< 5%) of the *exo* alcohol (4.007 due to 5- or 6-H). Crystallisation from hexane gave the pure *endo* alcohol (**25**), m.p. 86—87 °C (Found: C, 66.6; H, 9.25. $C_{11}H_{18}O_3$ requires C, 66.64; H, 9.15%); $[\alpha]_D^{23}$ +11.6° (*c* 0.92, $CHCl_3$); $\nu_{max.}$(KBr) 3 550 and 3 325 cm^{-1}; δ_H(270 MHz) 0.563 (1 H, dq, *J* 13 and 2.4, 3-H), 1.141 (1 H, dt, *J* 10.4 and 1.4, 7-H), 1.290 (3 H, s, Me), 1.448 (3 H, s, Me), 1.68—1.81 (3 H, m, CH_2, CH), 2.106 (1 H, m, CH), 2.261 (1 H, d, *J* 5, 1- or 4-H), 2.376 (1 H, d, *J* 3.8, 4- or 1-H), 3.54 (2 H, m, CH_2), 3.970 (1 H, *J* 5.5, 5- or 6-H), and 4.303 (1 H, d, *J* 5.5, 6- or 5-H). The crude mixture contaminated with a small amount of the *exo*-isomer (**25**) was used in the next step.

(+)-(1R)-5-exo,6-exo-(*Isopropylidenedioxy*)*bicyclo*[2.2.1]-*heptane*-2α/β-*carbaldehyde* (**26**).—The alcohol (**25**) (155 mg,

0.78 mmol) in dry dichloromethane (5 ml) was added in one portion at room temperature to a vigorously stirred mixture of PCC (735 mg, 3.4 mmol) and molecular sieves 4A (1/16 pellets, 900 mg) in dry dichloromethane (16 ml) and the reaction mixture was stirred for 2 h. The dark mixture was then diluted with ether (15 ml) and the organic layer was filtered through a short plug of Florisil. This work-up was repeated three times and the filtrates were concentrated to give the aldehyde (**26**) (136 mg, 88%) as a colourless oil, b.p. 57—60 °C (bath temperature)/0.02 mmHg (Found: $M^+ - 15$ 181.0862. $C_{10}H_{13}O_3$ requires $M - 15$, 181.0863); $[\alpha]_D^{23}$ +29.6° (*c* 1.08, $CHCl_3$); $\nu_{max.}$ 2 720 and 1 720 cm^{-1}; δ_H(270 MHz) 1.23 (1 H, m, overlapping with Me signal), 1.248 (3 H, s, Me), 1.438 (3 H, s, Me), 1.58 (2 H, m, CH_2), 1.885 (1 H, dd, *J* 10.5 and 1.4, 7-H), 2.353 (1 H, d, *J* 2.6, 2-H), 2.78 (2 H, m, 1- and 4-H), 4.013 (2 H, s, 2 × OCH), and 9.832 (1 H, s, CHO). The product after distillation was contaminated with a small amount (<2%) of the *exo* aldehyde, the aldehydic portion of which was at 9.692 (d, *J* 1) in the n.m.r. spectrum.

(−)-(1R)-(2E/Z)-(*Dimethyl-t-butylsiloxyethylidene*)-5-exo,6-exo-(*isopropylidenedioxy*)*bicyclo*[2.2.1]*heptane* (**27**).—Triethylamine (0.144 ml, 1.04 mmol) was added at room temperature to a solution of the aldehyde (**26**) (136 mg, 0.69 mmol) in dry dichloromethane (2 ml). Dimethyl-t-butylsilyl-trifluoromethane sulphonate (TBDMSOTf) (0.300 ml, 1.31 mmol) was added *via* a syringe and the reaction mixture was stirred for 30 min. After diluting with pentane (10 ml), the organic layer was washed successively with cold dilute aqueous sodium hydrogen carbonate (10 ml), dried ($MgSO_4$), and the solvent was evaporated to afford a red oil. Purification by chromatography on silica gel (Mallinckrodt 7087) with hexane–ethyl acetate (9:1) gave a mixture of the *E*- and *Z*-isomers of (**27**) in a ratio of 1:1, as a colourless oil (207 mg, 96%), b.p. 77—80 °C (bath temperature)/0.02 mmHg (Found: $M^+ - 15$, 310.1965. $C_{17}H_{30}O_3Si$ requires $M - 15$, 319.1966); $[\alpha]_D^{23}$ −47° (*c* 0.4, $CHCl_3$); $\nu_{max.}$(film) 1 690 cm^{-1}; δ_H(270 MHz) 0.105 (3 H, s, SiMe), 0.108 (3 H, s, SiMe), 0.904 (3 H, s, $SiCMe_3$), 0.915 (2 × 3 H, s, 2 × $SiCMe_3$), 1.276 (3/2 H, s, Me), 1.289 (3/2 H, s, Me), 1.448 (3/2 H, s, Me), 1.458 (3/2 H, s, Me), 1.6—2.1 (4 H, m, 2 × CH_2), 2.356 (1 H, br s, 1- or 4-H), 2.619 (1/2 H, s, 4- or 1-H), 3.176 (1/2 H, 2, 4- or 1-H), 4.04 (2 H, m, 2 × OCH), 6.110 (1/2 H, s, CH=), and 6.282 (1/2 H, t, *J* 2.2, CH=).

(−)-(1S)-5-exo,6-exo-(*Isopropylidenedioxy*)*bicyclo*[2.2.1]-*heptan*-2-*one* (**23**).—Ozone in oxygen was bubbled through a stirred solution of the silyl ether (**27**) (236 mg, 0.76 mmol) in dry methanol–dry dichloromethane (10 ml, 4:1) at −70 °C until a pale blue colour was evident. After the excess of ozone was purged with nitrogen, dimethyl sulphide (0.500 ml) was added at that temperature. The temperature was allowed to rise to room temperature and the solvent was removed to give a crude oil (*ca.* 250 mg). The crude material contained a certain amount of the hemiacetal (**37**), the structure of which was deduced by n.m.r. and i.r. spectroscopy: $\nu_{max.}$(film) 3 350 cm^{-1}; δ_H(270 MHz) 1.324 (3 H, s, Me), 1.457 (3 H, s, Me), 0.9—1.1 (4 H, m, 2 × CH_2), 2.35 (1 H, bt, 1- or 4-H), 2.60 (1 H, m, 4- or 1-H), 3.291 (3 H, s, OMe), 4.159 (1 H, d, *J* 5.5, HCO), 4.519 (1 H, d, *J* 5.5, HCO), and 8.20 (1 H, br, OH).

The crude product was thus treated with a catalytic amount of TSA in acetone (3 ml) for 12 h at room temperature. The solvent was evaporated to dryness. Purification by chromatography with hexane–ethyl acetate (1:1) gave the ketone (**23**) (106 mg, 76%) as colourless needles, m.p. 101—103 °C (from hexane) (Found: C, 65.95; H, 7.6. $C_{10}H_{14}O_3$ requires C, 65.91; H, 7.74%); $[\alpha]_D^{23}$ −100° (*c* 0.65, $CHCl_3$), the spectral data of which were identical with those previously reported except for the chiroptical properties.[23,28] If dichloromethane was used as a single solvent for this reaction, the yields of the ketone (**23**) were reduced (~39%); two by-products were also obtained, one being an enantiomer of (**3**) {$[\alpha]_D^{23}$ −36° (*c* 0.88, $CHCl_3$)} and other the δ-lactone (**28**) [$\nu_{max.}$ 1 750 cm^{-1}; δ_H(60 MHz) 1—2.5 (5 H, m, 2 × CH_2, CH), 1.30 (3 H, s, Me), 1.43 (3 H, s, Me), 3.37 (1 H, br, OCH), 4.07 (1 H, d, *J* 5, HCO), and 4.43 (1 H, d, *J* 5, HCO)].

(+)-(1S)-2-(*Dimethyl-t-butylsiloxy*-5-exo,6-exo-(*isopropylidenedioxy*)*bicyclo*[2.2.1]*hept*-2-*ene* (**29**).—Triethylamine (0.055 ml, 0.39 mmol) was added to a solution of the ketone (**23**) (37 mg, 0.2 mmol) in dry dichloromethane (1 ml) at room temperature. TBDMSOTf (0.080 ml, 0.35 mmol) was added and the mixture was stirred for 1 h. After diluting with pentane (10 ml), the organic layer was washed successively with cold dilute aqueous sodium hydrogen carbonate and dried ($MgSO_4$), and the solvent was evaporated to afford a red oil. Purification by chromatography with hexane–ethyl acetate (5:1) gave the silyl enol ether (**29**) (58 mg, 98%) as a colourless oil, b.p. 86—90 °C (bath temperature)/0.15 mmHg (Found: M^+, 296.1827. $C_{18}H_{28}O_3Si$ requires M, 296.1807); $[\alpha]_D^{23}$ +14.5° (*c* 0.48, $CHCl_3$); $\nu_{max.}$ 1 615 cm^{-1}; δ_H(270 MHz) 0.128 (3 H, s, SiMe), 0.151 (3 H, s, SiMe), 0.913 (9 H, m, $SiCMe_3$), 1.364 (3 H, s, Me), 1.474 (3 H, s, Me), 1.787 (1 H, dt, *J* 8.8 and 1.5, 7-H), 1.928 (1 H, d, *J* 8.8, 7-H), 2.44 (1 H, br s, 1- or 4-H), 2.65 (1 H, br s, 4- or 1-H), 4.335 (1 H, d, *J* 5.6, OCH), 4.443 (1 H, d, *J* 3.2, CH=), and 4.629 (1 H, d, *J* 3.2, 3-H).

(+)-(1S,4R)-*Methyl*-4α-*Dimethoxymethyl*-2α,3α-(*isopropylidenedioxy*)*cyclopentane*-1α-*carboxylate* (**32**).—Ozone in oxygen was bubbled through a solution of the silyl enol ether (**29**) (70 mg, 0.24 mmol) in dry methanol (4 ml) and dry dichloromethane (1 ml) at −70 °C until a pale blue colour was evident. After work-up, the n.m.r. spectrum of an aliquot of the crude product, which was purified by chromatography on silica gel with chloroform–methanol (8:1), showed to be a 1:1.6 mixture of (**30**) and (**31**). δ_H(270 MHz) 9.770 [0.38 H, s, CHO for (**30**)], 3.358 [1.85 H, s, OMe for (**31**)], and 3.363 [1.85 H, s, OMe for (**31**)].

The crude mixture of compounds (**30**) and (**31**) was dissolved in 2,2-dimethoxypropane (2 ml) containing dry methanol (0.5 ml) and the mixture was cooled to −10 °C. Dowex 50W-X8 cation exchange resin (30 mg) was added, and the suspension was stirred at −10 °C for 2 days, then filtered and concentrated. The n.m.r. spectrum of an aliquot of the crude product, which was purified by chromatography with hexane–ethyl acetate (3:1), showed to be a *ca.* 1:2 mixture of the compounds (**31**) and (**32**).

The crude mixture of the carboxylic acids (**31**) and (**32**) was diluted with dry methanol (2 ml) and treated with ethereal diazomethane to give the ester (**32**) [45 mg, 69% from (**29**)] as a colourless oil, b.p. 140—144 °C (bath temperature)/0.3 mmHg (Found: M^+, 274.1436. $C_{13}H_{22}O_6$ requires M, 274.1416); $[\alpha]_D^{23}$ +27° (*c* 2.1, $CHCl_3$); $\nu_{max.}$(film) 1 740 cm^{-1}; δ_H(270 MHz) 1.318 (3 H, s, Me), 1.499 (3 H, s, Me), 1.894 (1 H, dt, *J* 13.5 and 9, 5-H), 2.251 (1 H, dt, *J* 13.5 and 7.5, 5-H), 2.44 (1 H, m, 4-H), 2.887 (1 H, ddd, *J* 9, 7.5, and 5, 1-H), 3.357 (3 H, s, OMe), 3.370 (3 H, s, OMe), 3.712 (3 H, s, OMe), 4.239 (1 H, d, *J* 6, 6-H), 4.538 (1 H, dd, *J* 6.5 and 3.5, 3-H), and 4.817 (1 H, dd, *J* 6.5 and 5, 2-H).

Cookson *et al.* reported that ozonolysis of compound (**29**) and subsequent treatment with Dowex 50G-X8 cation exchange resin gave exclusively the carboxylic acid (**31**).[23] Although we have repeated the literature reaction [(**29**) ⟶ (**31**)], we obtained the ester (**32**) in addition to the carboxylic acid (**31**).

(−)-(1R,4R)-4α-*Dimethoxymethyl*-2β,3β-(*isopropylidenedioxy*)*cyclopentylmethanol* (**33**).—The ester (**32**) (97 mg, 0.35 mmol) was added dropwise to a suspension of lithium aluminium hydride (40 mg, 1.05 mmol) in dry THF (3 ml) at

5 °C. The reaction mixture was stirred at room temperature for 30 min and then diluted with water until the gas evolution of hydrogen ceased. After diluting with ether (10 ml), anhydrous $MgSO_4$ (*ca.* 0.5 g) was added and the suspension was stirred for 2—3 min. The precipitate was filtered off and the filtrate was concentrated. Purification by chromatography with hexane–ethyl acetate (1:2) gave the alcohol (**33**) (81 mg, 93%) as a colourless oil, b.p. 103—105 °C (bath temperature)/0.02 mmHg (Found: $M^+ - 15$, 231.1227. $C_{11}H_{19}O_5$ requires $M - 15$, 231.1232); $[\alpha]_D^{23}$ −6.6° (*c* 1.1, $CHCl_3$); $\nu_{max.}$(film) 3 450 cm^{-1}; δ_H(270 MHz) 1.316 (3 H, s, Me), 1.39 (1 H, m, CH), 1.508 (3 H, s, Me), 2.055 (1 H, dt, *J* 13 and 7.5, CH), 2.23 (1 H, m, CH), 2.44 (1 H, m, CH), 3.369 (3 H, s, OMe), 3.402 (3 H, s, OMe_3), 3.68 (2 H, m, OCH_2), 4.278 (1 H, d, *J* 6.5, 6-H), 4.357 (1 H, dd, *J* 7 and 5, 2- or 3-H), and 4.465 (1 H, dd, *J* 7 and 5, 3- or 2-H).

(+)-(1R,4R)-4-(*Dimethyl-t-butylsiloxymethyl*)-2β,3β-(*isopropylidenedioxy*)*cyclopentane*-β-*carbaldehyde Dimethyl Acetal* (**34**).—A mixture of imidazole (26 mg, 0.38 mmol) and dimethyl-t-butylsilyl chloride (28 mg, 0.19 mmol) in dry DMF (1 ml) containing a catalytic amount of 4-dimethylaminopyridine was stirred at room temperature. The alcohol (**33**) (31 mg, 0.13 mmol) in dry DMF (0.5 ml) was added to the mixture and the solution was stirred for 12 h. The crude mixture was purified by chromatography with hexane–ethyl acetate (7:1) to give the silyl ether (**34**) (32 mg, 73%) as a colourless oil (Found: $M^+ - 15$, 345.2132. $C_{17}H_{33}O_5Si$ requires $M - 15$, 345.2097); $[\alpha]_D^{23}$ +1.2° (*c* 0.3, $CHCl_3$); $\nu_{max.}$(film) 1 460, 1 380, and 1 370 cm^{-1}; δ_H(270 MHz) 0.043 (3 H, s, SiMe), 0.046 (3 H, s, SiMe), 0.889 (9 H, s, $SiCMe_3$), 1.306 (3 H, s, Me), 1.420 (1 H, dd, *J* 13.2 and 10.7, 5-H), 1.497 (3 H, s, Me), 2.010 (1 H, dt, *J* 13.2 and 7.3, 5-H), 2.18 (1 H, m, CH), 2.39 (1 H, m, CH), 3.348 (3 H, s, OMe), 3.392 (3 H, s, OMe), 3.606 (1 H, dd, *J* 10.2 and 5.6, HC*H*OSi), 3.676 (1 H, dd, *J* 10.2 and 4.5, HC*H*OSi), 4.256 (1 H, d, *J* 7.0, C*H*OMe), 4.318 (1 H, dd, *J* 6.8 and 5, OCH), and 4.398 (1 H, dd, *J* 6.8 and 5, OCH).

(+)-*Lactone* (**3**) *from the Dienophile* (**6**).—A pinch of TSA monohydrate was added to a solution of the acetal (**34**) (36 mg, 0.1 mmol) in dry acetone (1 ml) and the mixture was stirred at room temperature for 1 h. At this stage the n.m.r. spectrum of an aliquot did not show a signal at 4.256 for the methine proton attached to the two methoxy groups in the acetal (**34**). Instead, it indicated the presence of the aldehydic proton (9.715) and the formation of the hemiacetal (**14**). It was difficult to monitor the reaction by t.l.c. because the R_F value of compound (**36**) was fairly similar to that of compound (**34**).

(1S,4S)-4-(*Dimethyl-t-butylsiloxymethyl*)-2β,3β-(*isopropylidenedioxy*)*cyclopentane*-1β-*carbaldehyde* (**36**), as a colourless oil (Found: $M^+ - 15$, 345.2132. $C_{17}H_{33}O_5Si$ requires $M - 15$, 345.2097); $\nu_{max.}$($CHCl_3$) 2 730 and 1 720 cm^{-1}; δ_H(270 MHz) 0.031 (3 H, s, SiMe), 0.070 (3 H, s, SiMe), 0.877 (3 × 3 H, m, $SiCMe_3$), 1.329 (3 H, s, Me), 1.488 (3 H, s, Me), 1.9—2.0 (1 H, m, CH), 2.2—2.4 (2 H, m, 2 × CH), 2.85 (1 H, m, CH), 3.527 (2 H, d, *J* 5.0, CH_2O), 4.459 (1 H, dd, *J* 6 and 2.5, OCH), 4.898 (1 H, dd, *J* 6 and 4, OCH), and 9.715 (1 H, s, CHO).

The reaction mixture was concentrated and the residue was filtered through a short plug of silica gel with hexane–ethyl acetate (1:2). The filtered solution was concentrated and the residue was dissolved in THF (10 drops) and 70% aqueous acetic acid (10 drops). The mixture was then stirred at room temperature for 12 h. The solvent was evaporated and the residue was purified by chromatography with hexane–ethyl acetate (1:1). Initial fractions contained the acetal (**35**) (6.4 mg, 30%). The later fractions contained the lactol (**14**) (12.6 mg, 67%) which was identical with that derived from the dienophile (**4**). Oxidation of the hemiacetal (**14**) (11.2 mg, 0.06 mmol) with Collins reagent gave the lactone (**3**) (7.9 mg, 71%) as a white solid; $[\alpha]_D^{23}$ +44.1° (*c* 0.22, $CHCl_3$), identical with (m.p., i.r., n.m.r., and t.l.c.) that prepared from the sulphoxide (**4**).

Acknowledgements

This work was financially supported by the Sankyo Foundation of Life Science. We thank Professor M. Ohno (Tokyo) for providing the spectroscopic data and for helpful discussions.

References

1 Y. F. Shealy and J. D. Clayton, *J. Am. Chem. Soc.*, 1966, **88**, 3885.
2 T. Kusaka, H. Yamamoto, M. Shibata, M. Muroi, T. Kishi, and K. Mizuno, *J. Antibiot.*, 1968, **21**, 255.
3 M. Hayashi, S. Yaginuma, H. Yoshioka, and K. Nakatsu, *J. Antibiot.*, 1981, **34**, 675.
4 S. Yaginuma, N. Muto, M. Tsujino, Y. Sudate, M. Hayashi, and M. Otani, *J. Antibiot.*, 1981, **34**, 359.
5 For recent racemic synthesis, see: A. K. Saksena, *Tetrahedron Lett.*, 1980, **21**, 133; M. Jung, G. Offenbächer, and J. Rétey, *Helv. Chim. Acta*, 1983, **66**, 1915.
6 R. J. Suhadolnik, 'Nucleoside Antibiotics,' Wiley-Interscience, New York, 1970; R. Marumoto, Y. Yoshioka, Y. Furukawa, and M. Honjo, *Chem. Pharm. Bull.*, 1976, **24**, 2624; R. Vince and S. Daluge, *J. Med. Chem.*, 1977, **20**, 612; R. Vince and S. Daluge, *J. Org. Chem.*, 1978, **43**, 2311; R. C. Cermak and R. Vince, *Tetrahedron Lett.*, 1981, **22**, 2331; A. K. Saksena and A. K. Ganguly, *ibid.*, p. 5227; J. A. Montgomery, S. J. Clayton, H. J. Thomas, W. M. Shannon, G. Arnett, A. J. Bodner, I.-K. Kion, G. L. Cantoni, and P. K. Chiang, *J. Med. Chem.*, 1982, **25**, 626; D. R. Borcherding, S. A. Scholtz, and R. T. Borchardt, *J. Org. Chem.*, 1987, **52**, 5457.
7 M. Arita, K. Adachi, Y. Ito, H. Sawai, and M. Ohno, *J. Am. Chem. Soc.*, 1983, **105**, 4049.
8 M.-I. Lim and V. E. Marquez, *Tetrahedron Lett.*, 1983, **24**, 5559; C. K. H. Tseng and V. E. Marquez, *ibid.*, 1985, **26**, 3669.
9 J. R. Medich, K. B. Kunnen, and C. R. Johnson, *Tetrahedron Lett.*, 1987, **28**, 4131.
10 K. Tadano, M. Hoshino, S. Ogawa, and T. Suami, *Tetrahedron Lett.*, 1987, **28**, 2741.
11 G. V. B. Madhavan and J. C. Martin, *J. Org. Chem.*, 1986, **51**, 1287.
12 G. Just, G. Reader, and B. Chalard-Faure, *Can. J. Chem.*, 1976, **54**, 849.
13 Y. Arai, Y. Hayashi, M. Yamamoto, H. Takayama, and T. Koizumi, *Chem. Lett.*, 1987, 185.
14 For a preliminary communication of the preparation of the dienophiles (**4**) and (**6**) and its highly asymmetric Diels–Alder reaction with furan, see: H. Takayama, A. Iyobe, and T. Koizumi, *J. Chem. Soc., Chem. Commun.*, 1986, 771.
15 V. VanRheenen, R. C. Kelly, and D. Y. Cha, *Tetrahedron Lett.*, 1976, 1973.
16 J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 1968, 3363.
17 T. Koizumi, I. Hakamada, and E. Yoshii, *Tetrahedron Lett.*, 1984, **25**, 87; T. Koizumi, Y. Arai, H. Takayama, K. Kuriyama, and M. Shiro, *Tetrahedron Lett.*, 1987, **28**, 3689.
18 M. E. Evans, F. W. Parrish, and L. Long, Jr., *Carbohydr. Res.*, 1967, **3**, 453.
19 A. Abiko, J. C. Roberts, T. Takemasa, and S. Masamune, *Tetrahedron Lett.*, 1986, **27**, 4537.
20 H. Ohrui and S. Emoto, *Agric. Biol. Chem.*, 1976, **40**, 2267.
21 S. Manna, J. Viala, P. Yadagiri, and J. R. Falck, *Tetrahedron Lett.*, 1986, **27**, 2679.
22 K. S. Kim, Y. H. Song, B. H. Lee, and C. S. Hahn, *J. Org. Chem.*, 1986, **51**, 404.
23 R. C. Cookson, P. J. Dudfield, and D. I. C. Scopes, *J. Chem. Soc., Perkin Trans. 1*, 1986, 393.
24 J. Herscovici, M.-J. Egron, and K. Antonakis, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1967.
25 L. N. Mander and S. P. Sethi, *Tetrahedron Lett.*, 1984, **25**, 5953.
26 M. Miyashita, A. Yoshikoshi, and P. A. Grieco, *J. Org. Chem.*, 1977, **42**, 3772; R. Sterzycki, *Synthesis*, 1979, 724.
27 H. R. Pfaendler, J. Gosteli, and R. B. Woodward, *J. Am. Chem. Soc.*, 1979, **101**, 6306.
28 A. K. Saksena, A. T. McPhail, and K. D. Onan, *Tetrahedron Lett.*, 1981, **22**, 2067.

Received 31*st December* 1987; *Paper* 7/2276