Synthesis of Paniculides B and C

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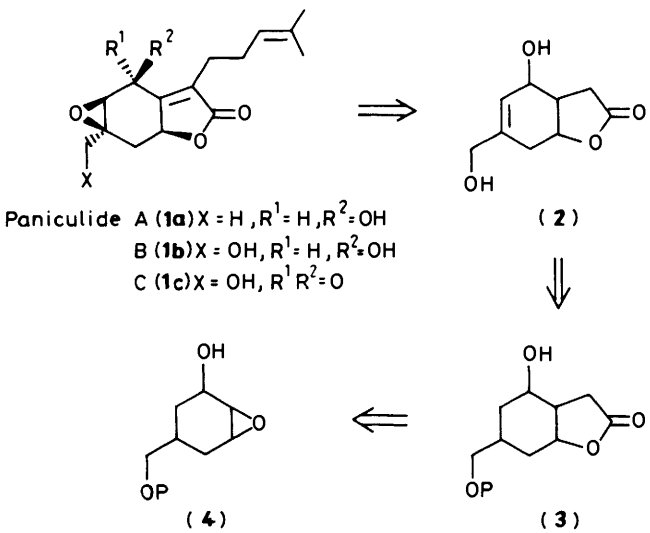
A stereoselective approach to the paniculide skeleton is reported utilising an approach based on the dilithioacetate opening of an α-hydroxy epoxide. Two isomeric α-hydroxy epoxides were prepared from 3,5-dimethoxy-1,4-dihydrobenzyl methoxymethyl ether which, in turn, was obtained from 3,4,5-trimethoxybenzoic acid. Reaction of the *trans*-epoxy alcohol proceeded with high regio- and stereo-control to yield a *cis*-fused δ-butyrolactone. A similar reaction with the analogous *cis*-epoxy alcohol gave the *trans*-lactone in low yield but with excellent regioselectivity. Following oxidation of the hydroxy group in the cis-fused lactone, a double bond was introduced into the cyclohexane ring *via* a seleniation – oxidative elimination protocol. The regioselectivity in this case was 8:1 in favour of the required enone. Reduction of this enone with lithium triethylborohydride proceeded in a highly stereoselective manner to give two alcohols in the ratio 98:2, the major (desired) epimer being derived *via* hydride attack from the least hindered α-face. Finally, epoxidation of the allylic alcohol derivative with *m*-chloroperbenzoic acid gave two epoxy lactones in a highly stereoselective manner in the ratio 95:5. The derivative in which the δ-butyrolactone, hydroxy, and epoxide groups were all *cis* could be readily converted into paniculides B and C.

Three highly oxygenated lactones, paniculides A (**1a**), B (**1b**), and C (**1c**), were isolated in 1968 by Overton and co-workers from callus cultures derived from hypocotyl and stem tissues of *Andrographis paniculata* Nees (Acanthaceae).[1,2] The absolute configuration of paniculide B (**1b**) has been determined by *X*-ray crystal determination of the bis-*p*-bromobenzoate.[3] Two alternative strategies have been utilised in the synthesis of the paniculides.[4,5] The first successful synthesis utilised a [2 + 2] cycloaddition of a cyclohexenone with 1,1-diethoxyethylene to generate a bicyclic ketone; this was subsequently transformed into paniculide A (**1a**) in twelve steps which included a Beyer–Villiger oxidation and concomitant epoxidation to form a mixture of two epoxy lactones.[6]



Scheme 1.

The other synthesis involved reaction between 3-phenylthio-4-vinylfuran-2(5*H*)-one and ketones in which a 1,6-conjugate addition was followed by an aldol-type cyclisation; the synthesis of paniculide A involved 15 steps (with an overall yield of 0.2%). We now report our own studies in this field based on the retrosynthetic analysis described (Scheme 1). We envisaged that regiospecific opening of the epoxide (**4**) with dilithioacetate and subsequent cyclisation would yield the hydroxy lactone (**3**). Regiospecific introduction of unsaturation (**2**) would then be followed by a stereoselective epoxidation. We have now demonstrated that these transformations can be achieved with a high degree of regio- and stereo-control.

Results and Discussion

Synthesis of Epoxides.—It was anticipated that epoxy alcohols (**11**) and (**12**) would serve as the key intermediates for the synthesis of the butyrolactone skeleton and that these intermediates could both be derived from the common intermediate (**8**). The starting point for the syntheses was 3,4,5-trimethoxybenzoic acid which underwent Birch reduction to yield 3,5-dimethoxy-1,4-dihydrobenzoic acid (**5**) in 97% yield[7] (Scheme 2). Lithium aluminium hydride reduction of the carboxy group (95%)[7] and protection of the resulting hydroxy group as the methoxymethyl (MOM) ether[8] (**6b**) proceeded in excellent yield (92%). Treatment with toluene-*p*-sulphonic acid (PTSA) in ethanol yielded the vinylogous ester (**7a**) and subsequent hydrolysis with aqueous potassium hydroxide yielded the dione (**7b**). Lithium aluminium hydride reduction proceeded smoothly to furnish the corresponding allylic alcohol (**8**) in an overall yield of 60% from (**5**).

It was anticipated that vanadyl acetylacetonate-catalysed t-butyl hydroperoxide oxidation of the allylic alcohol (**8**) would yield the *cis*-epoxy alcohol (**12**).[9] In fact the only product isolated (in 90% yield) was found to be the ketone (**13**). This result yielded some information as to the relative stereochemistry of the ring substituents. Sharpless and Verhoeven[10] observed, in a similar oxidation reaction, that the relative stereochemistry of the substituents was crucial to the course of the reaction. It has been reported that the epoxidation reactions require a quasi-axial hydroxy group for optimal interaction with the olefinic π-orbital.[11] In the case of conformationally 'fixed' allylic alcohols where such a desirable geometry cannot

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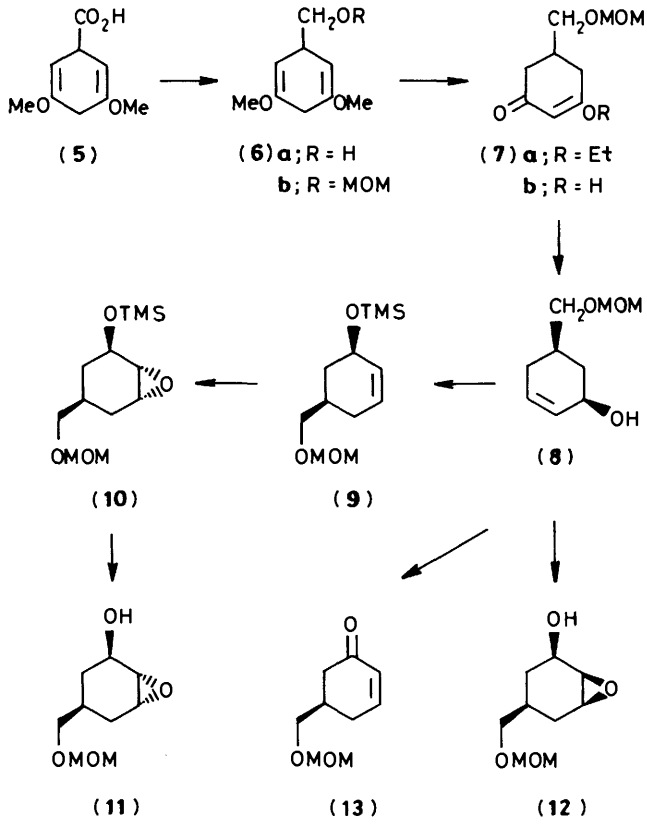


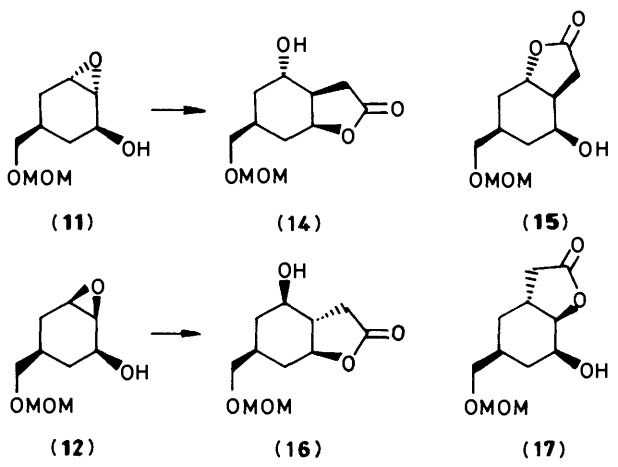
Scheme 2. MOM = $-CH_2OMe$. TMS = $SiMe_3$

be obtained, direct oxidation of the equatorial secondary alcohol can occur. The diequatorial relationship of the substituents in compound (**8**) could not be confirmed by its spectral characteristics but would be consistent with reduction of the dione (**7b**) proceeding *via* axial attack of hydride from the least hindered face. Further evidence for this assignment was obtained at a later stage in the synthesis.

Protection of the alcohol as the trimethylsilyl (TMS) ether (**9**) followed by epoxidation (**10**) with *m*-chloroperbenzoic acid (MCPBA) at 0 °C and subsequent hydrolysis yielded a mixture of *trans*- and *cis*-α-hydroxy epoxides (**11**) and (**12**) in the ratio 99:1 and an overall yield of 90%. In contrast, directed epoxidation of the allylic alcohol (**8**) gave a 12:1 mixture of the *cis*- and *trans*-α-hydroxy epoxides (**12**) and (**11**) in 70% yield; these two epoxides were easily separated by flash chromatography.*

Synthesis of the δ-Butyrolactone Skeleton.—The next stage in the synthesis utilised the directing effect of an α-hydroxy group in the dilithioacetate opening of an epoxide.[12] Thus treatment of the *trans*-α-hydroxy epoxide (**11**) with 5 mol equiv. of dilithioacetate in a mixture of 1,2-dimethoxyethane (DME) and hexamethylphosphoramide (HMPA) afforded the *cis*-lactone (**14**). The reaction proceeded with excellent regioselectivity and no products derived from the C-3 ring opening of the epoxide were observed. Following the initial ring opening, acid-catalysed cyclisation could take place *via* either alcohol to yield either the *cis* (**14**) or *trans*- (**15**) lactone (Scheme 3). Exclusive formation of the more stable *cis*-lactone (**14**) was observed in a yield of 56% (93% yield based on consumed starting material).

* A similar approach was previously undertaken by C. G. Chavdarian and C. H. Heathcock, *Synth. Commun.*, 1976, **6**, 277.



Scheme 3.

The *cis*-stereochemistry of the ring junction of the product (**14**) could not be confirmed by examination of the 100 MHz ^1H n.m.r. spectrum; however, the stereochemistry could be confirmed at a subsequent stage in the synthesis.

It is interesting that, in a similar reaction, the *cis*-epoxy alcohol (**12**) under identical conditions gave a 15% yield (75% based on consumed starting material) of the *trans*-lactone (**16**). Although proceeding in low yield, the reaction was entirely regioselective, there being no evidence for attack at C-3 of the epoxide to yield the lactone (**17**). The poor reactivity of the epoxide (**12**) could be attributable to two factors: (a) the *trans*-hydroxy group is better placed for directing attack and (b) attack at C-2 requires a pseudo-equatorial opening of the epoxide. The *cis*-ring junction of compound (**14**) ensured that the concave nature of the molecule should provide a high degree of stereocontrol in subsequent reactions.

Introduction of Unsaturation into the Cyclohexane Ring.—It was hoped that the olefinic double bond could be introduced into the cyclohexyl ring *via* the seleniation–oxidative elimination protocol developed by Sharpless.[13] Accordingly, oxidation with pyridinium chlorochromate (PCC) on alumina gave the ketone (**18**) in 80% yield. Treatment of the ketone (**18**) with benzeneselenenyl chloride in ethyl acetate proceeded smoothly to yield two unstable components. These were not normally isolated but were immediately subjected to treatment with hydrogen peroxide to achieve convenient *syn*-elimination of the selenoxide. Two components, (**19**) (85%) and (**20**) (10%), were isolated from the reaction mixture and the structural assignment of compound (**19**) was confirmed by examination of the ^1H n.m.r. spectra.

In the 100 MHz ^1H n.m.r. the broad singlet at δ 6.39 was attributed to the proton on C-5 and the multiplet at δ 5.01—5.16 was assigned to the methine proton on C-7a. Irradiation of the signal at δ 5.28—5.04 caused simplification of the signal at δ 2.80 assigned to the allylic protons on C-7. Irradiation of the signal at δ 2.80 removed the allylic coupling to the signal at δ 6.39 and caused collapse of the multiplet at δ 5.28—5.04 to a doublet (J 5 Hz). The coupling of 5 Hz between the protons on C-7a and C-5 is consistent with the assigned *cis*-ring junction.[14,15]

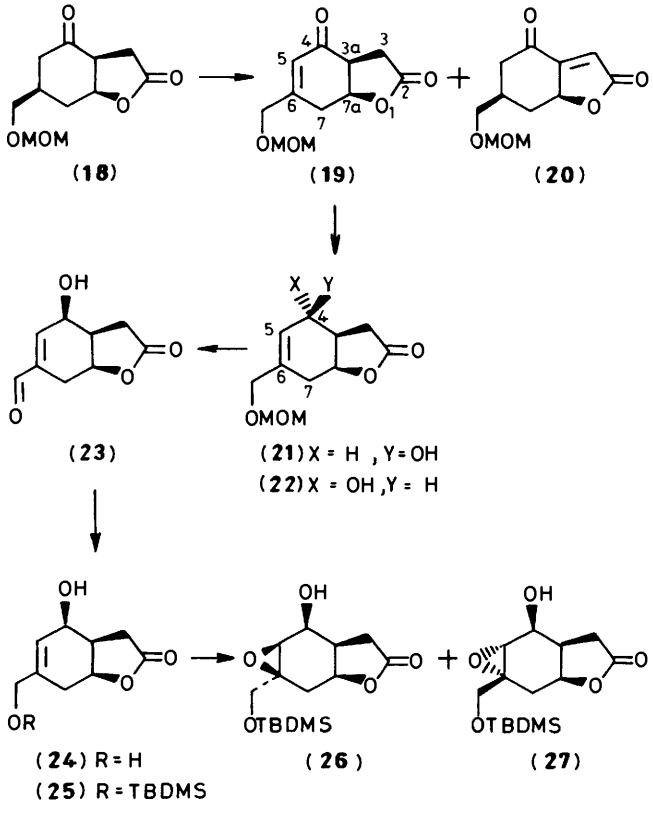
Reduction of Enone.—Treatment of the enone (**19**) with sodium borohydride in methanol in the presence of cerium(III) chloride[16] at 0 °C gave a 2:1 mixture of the two epimeric alcohols (**21**) and (**22**) in a combined yield of 76%. In contrast, the reduction of the enone (**19**) with lithium triethylborohydride proceeded in a highly stereoselective manner to give a 92% yield

of the two alcohols (**21**), a white crystalline solid, m.p. 64—65 °C (ethyl acetate–pentane) and (**22**) in the ratio 98:2, the major (desired) epimer (**21**) being derived *via* hydride attack from the least hindered α-face. The stereochemistry of the C-4 hydroxy group was confirmed by examination of the 100 MHz ^{1}H n.m.r. spectrum; irradiation of the olefinic signal at δ 6.01 caused collapse of the signal at δ 5.08—4.88, assigned to the proton on C-4, to a doublet (*J* 5 Hz) thus confirming the *cis* relationship with the bridgehead proton.

Epoxidation

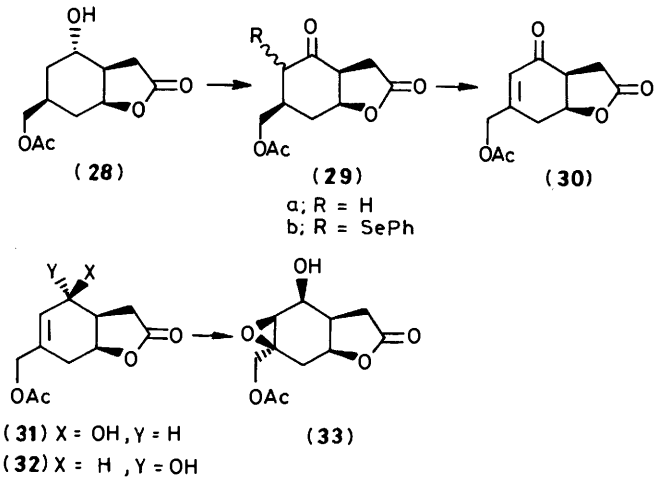
At this stage in the studies, it was decided to replace the MOM protecting group of (**21**) by the t-butyldimethylsilyl group. This was for two reasons. First, MOM deprotection usually requires fairly vigorous conditions and these might have caused problems if left until after epoxidation. Secondly, a synthesis of the paniculides by Smith and Richmond[6] was reported in the literature and conversion of compound (**21**) into the epoxide (**26**) would consititute a formal synthesis of paniculides B and C.

Treatment of the enol (**21**) with 2 mol equiv. of a 24% solution of hydrobromic acid in DME at 50 °C gave a single component which was identified as (**23**) by spectroscopic evidence and which was isolated as an unstable white crystalline solid.[17] This was immediately treated with 1 mol equiv. of sodium borohydride and cerium(III) chloride in methanol at 0 °C to yield the corresponding unstable diol (**24**) in 91% yield. Protection of the primary alcohol with t-butyldimethylsilyl chloride gave the required silyl ether (**25**). The final step in the synthetic sequence required the stereoselective epoxidation of the double bond. Treatment of (**25**) with MCPBA in dry methylene dichloride at −15 °C proceeded in 81% yield in a highly stereoselective manner to yield a mixture of two epoxy lactones (**26**) and (**27**) in the ratio of 95:5 (Scheme 4). As anticipated the major isomer (**26**) was that derived *via* C4-hydroxy-directed epoxidation. The epoxide (**26**) has been demonstrated to be readily converted into paniculides B and C.[6]



Scheme 4. TBDMS = $-SiMe_2Bu^t$

Transesterification.—In an alternative approach it was also demonstrated that lactone (**28**) was readily available from the acid-catalysed transesterification of compound (**14**). Thus, following the reaction of epoxide (**11**) with dilithioacetate, the reaction mixture was acidified to pH 1 and the product isolated by continuous extraction with ethyl acetate; lactone (**28**) was isolated in *ca.* 50% yield together with unchanged epoxy alcohol (**11**) (30%). Complete purification of lactone (**28**) from traces of HMPA proved difficult so oxidation with PCC on alumina was carried out directly to yield keto lactone (**29a**) in *ca.* 70% yield. Following phenylseleniation–oxidative elimination the enone (**30**) was isolated as the sole product in 85% yield. Reduction of the ketone (**30**) with either freshly prepared zinc borohydride or cerium(III) chloride–sodium borohydride both gave mixtures of the epimeric alcohols (**31**) and (**32**) in the ratios 3:1 and 2:1 respectively. However, reduction with lithium triethylborohydride at −80 °C gave a 94% yield of (**31**) and (**32**) in the ratio 98:2. Epoxidation with MCPBA as before using slow addition of the oxidant and low temperatures again proceeded in a highly stereoselective manner to yield a single product in 67% yield. This was identified as the epoxide (**33**) (Scheme 5).



Scheme 5.

Experimental

I.r. spectra were recorded on a Perkin-Elmer 157G spectrophotometer and ^{1}H n.m.r. spectra on a Varian XL-100 (100 MHz) or a Hitachi-Perkin-Elmer R-24B (60 MHz) spectrometer using $CDCl_3$ as solvent. Mass spectra were measured in a Kratos MS 30 instrument using either electron impact (e.i.) or chemical ionisation (c.i.) modes. T.l.c. was carried out using pre-coated silica gel plates [Merck Keiselgel 60F (255)] and flash chromatography was performed according to the procedure of Still *et al.*[18] using Macherey–Nagal Kieselgel 60 (230—400 mesh). All solvents were dried and distilled before use. Light petroleum refers to the fraction boiling between 40—60 °C.

3,5-*Dimethoxy*-1,4-*dihydrobenzyl Methoxymethyl Ether* (**6b**).—Chloromethyl methyl ether (66 g, 0.82 mol) was added dropwise to a stirred solution of 3,5-dimethoxy-1,4-dihydrobenzyl alcohol (**6a**) (69.07 g, 0.41 mol) in methylene dichloride (270 ml) and *N*-ethyldi-isopropylamine (157 g, 1.23

mol) at 0 °C under an atmosphere of nitrogen. After the addition, the reaction mixture was allowed to warm to room temperature and was stirred at room temperature for 3 days. The reaction mixture was diluted with water (200 ml) and extracted with diethyl ether (3 × 200 ml). The combined extracts were then dried ($CaSO_4$) and the solvent was removed at reduced pressure. The residue was then distilled at reduced pressure to yield 3,5-dimethoxy-1,4-dihydrobenzyl methoxymethyl ether (**6b**) as an oil, b.p. 92 °C at 0.05 mmHg (82.4 g, 94%); $\nu_{max.}$ 2 960, 1 630s, and 1 130s cm^{-1}; δ_H (100 MHz) 4.68 (2 H, d, *J* 5 Hz, 2 × CH=), 4.65 (2 H, s, OCH_2O), 3.57 (6 H, s, 2 × CH_3), 3.38 (5 H, br s, CH_2O and CH_2OCH_3), 3.19 (1 H, m, $CHCH_2O$), and 2.78 (2 H, d, *J* 7 Hz, CH_2).

3-*Ethoxy*-5-(*methoxymethoxymethyl*)*cyclohex*-2-*enone* (**7a**).—PTSA (120 mg) was added to a solution of compound (**6b**) (12 g, 56 mmol) in ethanol (100 ml) at room temperature. The resulting solution was stirred for 1 h and then diluted with ether (200 ml) and washed with water (50 ml). The organic phase was dried ($MgSO_4$) and the solvent was evaporated off at reduced pressure to yield a yellow oil. Distillation gave pure enone (**7a**) as an oil, b.p. 150 °C at 0.8 mmHg (11.88 g, 99%); $\nu_{max.}$ 2 960s, 1 690s (C=O), and 1 620m cm^{-1}; δ_H (100 MHz) 5.35 (1 H, s, =CHCO), 4.60 (2 H, s, OCH_2O), 3.90 (2 H, q, *J* 6 Hz, OCH_2CH_3), 3.48 (2 H, br s, CH_2OMOM), 3.35 (1 H, s, OCH_3), 2.4 (5 H, m, 2 × CH_2 and CH), and 1.40 (3 H, t, *J* 6 Hz, OCH_2CH_3); *m/z* 155 (21%), 154 (1.6), 109 (4), 81 (16), 77 (5), and 45 (100).

5-(*Methoxymethoxymethyl*)*cyclohexane*-1,3-*dione* (**7b**).—To a flask charged with the enone (**7a**) (0.1 g, 0.5 mmol) was added 1M-aqueous potassium hydroxide (5 ml). The reaction mixture was warmed to 50 °C and stirred vigorously. After 15 min the reaction was observed to be complete by t.l.c. [silica gel; Et_2O–EtOH (1:1)]. The resulting solution was neutralised with 0.5M-hydrochloric acid and then saturated with sodium chloride and extracted with ethyl acetate (3 × 50 ml). The combined extracts were dried (Na_2SO_4) and the solvent was removed at reduced pressure to yield a pale yellow solid. Recrystallisation from ethyl acetate afforded 5-(*methoxymethoxymethyl*)*cyclohexane*-1,3-*dione* (**7b**), m.p. 68—70 °C (93 mg, 100%); $\nu_{max.}$ 3 500s, 2 960s, 1 700s, and 1 650w cm^{-1}; δ_H (100 MHz) (*inter alia*) 6.25 (1 H, br s, OH), 5.5 (1 H, br s, CH=), 4.6 (2 H, s, OCH_2O), 3.5 (2 H, d, *J* 5 Hz, CH_2OMOM), 2.6 (2 H, m, 4-H_2), and 2.4 (3 H, m, CH_2CO and CH) (Found: (c.i.) MNH_4^+, 204.2521. $C_9H_{18}NO_4$ requires *m/z* 204.2481).

cis-5-(*Methoxymethoxymethyl*)*cyclohex*-2-*enol* (**8**).—5-(Methoxymethoxymethyl)cyclohexane-1,3-dione (**7b**) (28 g, 0.15 mol) was added to a stirred suspension of lithium aluminium hydride (6.5 g, 0.17 mol) in diethyl ether (200 ml) at 0 °C. The resulting mixture was stirred for 30 min at 0 °C and then for 16 h at reflux. The reaction mixture was then cooled to room temperature, the organic phase was decanted into ice–water (800 ml), and the solid residue was washed with diethyl ether (2 × 50 ml). The combined organic layers were washed successively with a 20% aqueous solution of Rochelle salt (100 ml) and saturated brine (100 ml) and dried (Na_2SO_4). The solvent was evaporated off at reduced pressure to yield an oil, distillation of which gave 5-(*methoxymethoxymethyl*)*cyclohex*-2-*enol* (**8**) as an oil, b.p. 89 °C at 0.1 mmHg (17.12 g, 70%); $\nu_{max.}$ 3 390s, 1 650m, and 1 050s cm^{-1}; δ_H (100 MHz) (*inter alia*) 5.85 (1 H, br s, OH), 5.72 (2 H, m, CH=CH), 4.62 (2 H, s, OCH_2O), 4.20 (1 H, m, CHOH), 3.45 (2 H, d, *J* 5 Hz, CH_2OMOM), 3.35 (3 H, s, CH_3), and 2.70 (2 H, m, CH_2) [Found: (M^+ – CH_2OCH_3), 127.0685. $C_7H_{11}O_2$ requires *m/z* 127.0759]; *m/z* 111 (1%), 95 (2.4), 67 (3), and 45 (19).

5-(*Methoxymethoxymethyl*)*cyclohex*-2-*enone* (**13**).—A solution of 5-(methoxymethoxymethyl)cyclohex-2-enol (**8**) (0.5 g, 2.9 mmol) in benzene was added dropwise to a stirred solution of vanadyl acetylacetonate (3 mg, 0.01 mmol) in dry benzene (10 ml) under nitrogen. A soltution of tertiary butyl hydroperoxide (0.31 g, 3.48 mmol; as a 4M solution in benzene) was then added dropwise. The reaction mixture was stirred at room temperature for 16 h, during which time a colour change from green to orange occurred. The reaction mixture was added to saturated aqueous sodium sulphite (5 ml) and extracted with diethyl ether (3 × 10 ml). The combined organic extracts were passed through Florisil to yield a clear solution which was dried (Na_2SO_4) and the solvent was removed at reduced pressure. Purification by medium-pressure chromatography (elution with ether) yielded 5-(methoxymethoxymethyl)cyclohex-2-enone (**13**) as an oil (0.44 g, 90%) $\nu_{max.}$ 2 960s and 1 680s cm^{-1} (C=O); δ_H (100 MHz) 6.9 (1 H, m, CH=CHCO), 5.9 (1 H, d, *J* 9 Hz, =CHCO), 4.55 (2 H, s, OCH_2O), 3.45 (2 H, d, *J* 5 Hz, CH_2OMOM), 3.30 (3 H, s, OCH_3), and 2.60—2.10 (5 H, m, 2 × CH_2 and CH); *m/z* 170 (0.1%), 125 (6), 109 (4), 108 (4), 68 (14), and 45 (100).

c-2,3-*Epoxy*-c-5-(*methoxymethoxymethyl*)*cyclohexan*-r-1-*ol* (**12**).—To a stirred solution of *cis*-5-(methoxymethoxymethyl)-cyclohex-2-enol (**8**) (0.5 g, 2.9 mmol) in methylene dichloride (20 ml) under nitrogen at 0 °C was added a solution of MCPBA (0.62 g, 3 mmol) in methylene dichloride (20 ml) dropwise during 1 h. The resultant solution was stirred at 0 °C for 24 h. Filtration of the reaction mixture followed by washing of the filtrate with saturated aqueous sodium sulphite (3 ml) yielded a colourless solution. The methylene dichloride layer was dried ($MgSO_4$) and the solvent was removed at reduced pressure to give an oil. Flash chromatography [diethyl ether–ethyl acetate (9:1)] yielded the required c-2,3-*epoxy*-c-5-(*methoxymethoxymethyl*)*cyclohexan*-r-1-*ol* (**12**) (0.38 g, 70%) as an oil, b.p. 86 °C at 15 mmHg (Found: C, 57.6; H, 8.45. $C_9H_{16}O_4$ requires C, 57.4; H, 8.6%); $\nu_{max.}$ 3 410m (OH) and 2 920m cm^{-1}; δ_H (100 MHz) 4.55 (2 H, s, OCH_2O), 4.01 (1 H, m, CHOH), 3.31 (3 H, s, OCH_3), 3.30 (2 H, m, 2- and 3-H), 3.20 (2 H, d, *J* 5 Hz, CH_2OMOM), and 2.10—1.20 (6 H, m, 2 × CH_2, CH, and OH); *m/z* 143 (M^+ – 45, 1%), 126 (1.2), 125 (21.5), 96 (8), 81 (10.8), 69 (22), and 45 (100). A small quantity of the isomer (**11**) was also isolated from the reaction mixture (ratio 12:1); the spectral characteristics of this sample were identical with those for the authentic specimen isolated later.

cis-5-(*Methoxymethoxymethyl*)*cyclohex*-2-*enyl Trimethylsilyl Ether* (**9**).—To a stirred solution of *cis*-5-(methoxymethoxymethyl)cyclohex-2-enol (**8**) (10.0 g, 58 mmol) in dry diethyl ether (200 ml) under nitrogen at room temperature was added slowly a mixture of trimethylsilyl chloride (8.8 ml, 69.6 mmol) and dry triethylamine (10.5 ml, 75.4 mmol). The reaction mixture was stirred vigorously at room temperature for 8 h. The reaction was quenched by dilution with ice–water (60 ml) and light petroleum (150 ml). The organic layer was separated, washed successively with ice–hydrochloric acid (5%; 50 ml), saturated aqueous sodium hydrogen carbonate (5%; 100 ml), and saturated aqueous sodium chloride (50 ml) and dried (Na_2SO_4). Concentration gave the TMS ether (**9**) as a pale yellow oil. Distillation gave a compound (**9**) as a colourless oil, b.p. 94 °C at 0.2 mmHg (13.33 g, 94%); δ_H (60 MHz) 5.65 (2 H, m, CH=CH), 4.65 (2 H, m, OCH_2O), 4.2 (1 H, m, CHO), 3.45 (2 H, br s, CH_2OMOM), 3.35 (3 H, s, OCH_3), 2.25—1.2 (5 H, m), and 0.05 (9 H, s, $SiMe_3$); $\nu_{max.}$ 2 980s and 1 050 cm^{-1} (s, C–O, ether); *m/z* 229 (M^+ – CH_3, 0.6%), 199 (2.8), 181 (1), 169 (3.7), 93 (2.5), 73 (11.7), and 45 (8.5).

t-2,3-*Epoxy*-c-5-(*methoxymethoxymethyl*)*cyclohex*-r-1-*yl Trimethysilyl Ether* (**10**).—To a stirred solution of compound

(**9**) (13.3 g, 54.6 mmol) in dry chloroform (300 ml) under nitrogen at −14 °C was added dropwise a solution of MCPBA (12.2 g, 73 mmol) in chloroform (100 ml) during 3 h. The mixture was stirred at −14 °C for a further 1 h before the flask and contents were allowed to warm to room temperature. The reaction was quenched after 5 h at room temperature when the mixture was poured into ice–saturated aqueous sodium sulphite (50 ml). The organic layer was separated and washed successively with ice–aqueous sodium hydrogen carbonate (3 × 50 ml), water (3 × 20 ml), and brine (20 ml). Drying (Na_2SO_4) followed by concentration yielded a pale yellow oil (97%). Gas chromatography of this oil showed two components in the ratio 99:1. The components were separated by careful flash chromatography [light petroleum–diethyl ether (4:1)]. The major component was identified on the basis of its spectral characteristics as *t*-2,3-epoxy-*c*-5-(methoxymethoxymethyl)-cyclohex-*r*-1-yl trimethylsilyl ether (**10**), δ_H (100 MHz) (*inter alia*) 4.52 (2 H, m, 2- and 3-H), 2.20—0.90 (5 H), 0.10 (9 H, s, $SiMe_3$); $\nu_{max.}$ 2 960s, 1 260s, and 1 050s cm^{-1}; *m/z* 215 (9.6%), 183 (5.4), 125 (5), 116 (6.1), 89 (12.6), 73 (42.75), 69 (12), and 45 (100).

The minor component was hydrolysed using the method outlined below and the product was identified as *c*-2,3-epoxy-*c*-5-(methoxymethoxymethyl)cyclohexan-*r*-1-ol (**12**) by comparison of the spectra with those previously obtained for this compound.

t-2,3-*Epoxy*-c-5-(*methoxymethoxymethyl*)*cyclohexan*-r-1-*ol* (**11**).—A solution of the trimethylsilyl ether (**10**) (19 g, 73 mmol) in methanol (300 ml) and saturated aqueous ammonium chloride (200 ml) was stirred at room temperature for 2 h, whereupon it was diluted with water (200 ml). The methanol was removed at reduced pressure and the aqueous phase was saturated with ammonium sulphate and then extracted with chloroform (3 × 150 ml), the combined extracts were washed with brine (100 ml) and dried over magnesium sulphate. Evaporation of the solvent gave a yellow oil (18.1 g). Purification by flash chromatography [diethyl ether–ethanol (19:1)] yielded the desired t-2,3-*epoxy*-c-5-(*methoxymethoxymethyl*)*cyclohexan*-r-1-*ol* (**11**) (17.8 g, 100%), b.p. 90 °C at 15 mmHg, as an oil (Found: C, 57.4; H, 8.1. $C_9H_{16}O_4$ requires C, 57.4; H, 8.6%); $\nu_{max.}$ 3 400 and 2 925 cm^{-1}; δ_H (100 MHz) 4.60 (2 H, s, OCH_2O), 4.21 (1 H, m, C*H*OH), 3.40 (2 H, m, 2- and 3-H), 3.34 (3 H, s, OCH_3), 3.25 (2 H, d, *J* 5 Hz, CH_2OMOM), and 2.15—1.15 (6 H, m); *m/z* 143 (M^+ − 45, 24.9%), 126 (21.9), 125 (41.55), 109 (2.5), 95 (33.6), 81 (39.2), 69 (55), and 45 (100).

rel-(3aR,4S,6S,7aS)-4-*Hydroxy*-6-(*methoxymethoxymethyl*)-3a,4,5,6,7,7a-*hexahydrobenzo*[b]*furan*-2(3H)-*one* (**14**).—To a stirred solution of di-isopropylamine (5.9 ml, 42.4 mmol) in dry DME (80 ml) at −50 °C under nitrogen was added n-butyllithium (1.6M in hexane; 26.5 ml, 42.4 mmol). The resultant pale yellow solution was stirred at −50 °C for 1 h prior to the addition of dry acetic acid (1.28 g, 21.2 mmol) in DME (10 ml). The white suspension was then stirred at 50 °C for 1¾ h. After this time the reaction mixture was cooled to −38 °C and a solution of the *trans*-epoxy alcohol (**11**) (0.4 g, 2.12 mmol) in DME (20 ml) and HMPA (3.8 g, 10 mol equiv., 21.2 mmol) was added during 30 min. The reaction mixture was stirred at −38 °C for 30 min before being allowed to warm to room temperature. The reaction mixture was then heated to 55 °C for 24 h and then cooled to 10 °C and water (15 ml) was added. The organic solvents were removed (rotary evaporator) and the aqueous layer was washed with diethyl ether (20 ml). The aqueous phase was cooled to −10 °C and acidified to pH 3 with cold conc. hydrochloric acid. Saturation with sodium chloride was followed by continuous extraction with ethyl acetate for 24 h. The organic phase was separated and dried (Na_2SO_4), and the solvent was evaporated off at reduced pressure to yield a red oil. Residual acetic acid was removed by azeotropic distillation with dry toluene (70 ml). The resultant oil was then dissolved in benzene (100 ml) and PTSA (100 mg) was added. This solution was stirred at reflux beneath a phase-separating head (charged with activated 4Å molecular sieves) for 4½ h. Evaporation of the solvent and purification by flash chromatography (ethyl acetate) yielded the *title compound* (**14**) (0.27 g, 56%) (Found: C, 57.4; H, 7.9. $C_{11}H_{18}O_5$ requires C, 57.4; H, 7.9%); $\nu_{max.}$ 3 500, 2 960, 1 770s (lactone), and 1 040 cm^{-1}; δ_H (100 MHz) 4.90—4.70 (1 H, m, C*H*OH), 4.61 (2 H, s, OCH_2O), 4.16—4.02 (1 H, m, CHOCO), 3.50—3.40 (2 H, d, *J* 6 Hz, CH_2OMOM), 3.38 (3 H, s, OCH_3), 2.74—2.30 (3 H, m, $CHCH_2CO_2$), 2.28—2.10 (1 H, br s, OH, D_2O-exchanged), and 1.90—1.20 (5 H, m); *m/z* 185 (M^+ − 45, 0.85%), 167 (2.05), 138 (12.7), 111 (8.2), 95 (14.3), 69 (25.7), and 45 (100). Unchanged starting material (0.1 g, 25%) was also recovered.

rel-(3aS,6R,7aS)-6-(*Methoxymethoxymethyl*)-3,3a,5,6,7,7a-*hexahydrobenzo*[b]*furan*-2,4-*dione* (**18**).—To a stirred solution of compound (**14**) (1.0 g, 4 mmol) in dry methylene dichloride (80 ml) under nitrogen at room temperature was added PCC (1.12 g) on alumina (4.48 g, 1.2 mol equiv., 5.2 mmol). The resulting reaction mixture was stirred at room temperature for 24 h. Diethyl ether (70 ml) was then added and the reaction mixture was filtered through Celite (5.0 g). The amber coloured solution was concentrated (rotary evaporator) and the resulting orange oil was immediately purified by flash chromatography [diethyl ether–ethyl acetate (1:1)]. The only product isolated was rel-(3aS,6R,7aS)-6-(*methoxymethoxymethyl*)-3,3a,5,6,7,7a-*hexahydrobenzo*[b]*furan*-2,4-*dione* (**18**) which was obtained as an oil (0.8 g, 81%), $\nu_{max.}$ 2 940, 2 870m, 1 770s (lactone), 1 720 (ketone), 1 100m, and 1 040s cm^{-1}; δ_H (100 MHz) 5.15—4.80 (1 H, m, CHOCO), 4.50 (2 H, s, OCH_2O), 3.50—3.35 (2 H, d, *J* 5 Hz, CH_2OMOM), 3.30 (3 H, s, OCH_3), 3.25—3.20 (1 H, m, CHCO), 2.90—2.40 (4 H, m, CH_2CO and CH_2CO_2), and 1.80—1.50 (3 H, m); *m/z* (c.i.) (Found: MNH_4^+, 246.2808. $C_{11}H_{20}NO_5$ 246.2857).

6-(*Methoxymethoxymethyl*)-3,3a,7,7a-*tetrahydro*-cis-*benzo*-[b]*furan*-2,4-*dione* (**19**).—To a stirred solution of compound (**18**) (500 mg, 2.2 mmol) in dry ethyl acetate (40 ml) under nitrogen at room temperature was added dropwise a solution of benzeneselenenyl chloride (0.5 g, 1.2 mol equiv., 2.6 mmol) in ethyl acetate (10 ml). The resultant red solution was stirred at room temperature overnight during which time the colour changed from red to yellow. Water (25 ml) was added and the organic phase was separated and washed again with water (10 ml). The organic phase was collected and immediately combined with tetrahydrofuran (THF) (50 ml). The reaction mixture was cooled to 0 °C and hydrogen peroxide (0.49 ml, 5.76 mmol; 30% w/w) was added dropwise. The temperature of the reaction mixture was maintained at 0 °C throughout the addition of the peroxide and for a further 1 h upon completion of the addition. After this time water (5 ml) was added and the reaction mixture was poured into ethyl acetate (105 ml). The aqueous layer was drawn off and the organic layer was washed with saturated aqueous sodium hydrogen carbonate (10 ml). Drying (Na_2SO_4) of the extract followed by concentration (rotary evaporator) yielded a pale brown oil. Flash chromatography [ethyl acetate–diethyl ether (1:1.2)] led to the isolation of compound (**20**) (49 mg, 10%) and 6-(methoxymethoxymethyl)-3,3a,7,7a-tetrahydro-*cis*-benzo[b]furan-2,4-dione (**19**) as an oil (406 mg, 82%), $\nu_{max.}$ 2 970m, 2 860m, 1 760s (lactone), 1 710s (ketone), and 1 100 cm^{-1}; δ_H (100 MHz) 6.4—6.38 (1 H, d, *J* 2 Hz, CH=), 5.28—5.04 (1 H, ddd, *J* 2, 5, and 13 Hz, CHOCO), 4.65 (2 H, s, OCH_2O), 3.64—3.56 (2 H, d, *J* 5 Hz, CH_2OMOM), 3.38 (3 H, s, OCH_3), and 2.9—1.8 (5 H, m).

rel-(3aR,4R,7aS)-4-*Hydroxy*-6-(*methoxymethoxymethyl*)-3a,4,7,7a-*tetrahydrobenzo*[b]*furan*-2(3H)-*one* (**21**).—To a stirred solution of 6-(methoxymethoxymethyl)-3,3a,7,7a-tetrahydro-*cis*-benzo[*b*]furan-2,4-dione (**19**) (370 mg, 1.6 mmol) in THF (20 ml) at −80 °C under nitrogen was added dropwise lithium triethylborohydride (1.6 ml, 1.6 mmol, 1 mol equiv.; 1M solution in THF). The temperature of the reaction mixture was maintained at −80 °C during the addition of the reducing agent. Upon completion of the addition the reaction mixture was allowed to warm to room temperature overnight. Water (5 ml) was added and the organic solvents were removed (rotary evaporator). The aqueous residue was then saturated with sodium chloride and exhaustively extracted with ethyl acetate (3 × 25 ml). The combined extracts were then dried (Na_2SO_4) and the solvent was removed (rotary evaporator) to yield an oil which crystallised on storage at −20 °C. The product was shown by analytical high-pressure liquid chromatography (h.p.l.c.) to be a 98:2 mixture of the lactone (**21**) and a second component. Recrystallisation from warm ethyl acetate–pentane yielded rel-3aR,4R,7aS)-4-*hydroxy*-6-(*methoxymethoxymethyl*)-3a,4,6,7a-*tetrahydrobenzo*[b]*furan*-2(3H)-*one* (**21**) as white needles (343 mg, 92%), m.p. 64—65 °C (Found: C, 57.6; H, 7.05. $C_{11}H_{16}O_5$ requires C, 57.9; H, 7.1%); $\nu_{max.}$ 3 500m (OH), 2 970m, 2 860m, 1 760s (CO), and 1 640 cm^{-1}; δ_H (100 MHz) (*inter alia*) 6.07—5.96 (1 H, m, CH=bond), 5.08—4.88 (1 H, m, C*H*OH), 4.68 (2 H, s, OCH_2O), 4.22—4.06 (1 H, m, CHOCO), 4.05 (s, 2H, CH_2OMOM), 3.42 (3 H, s, OCH_3), 2.98—2.74 (1 H, m, C*H*CH_2CO_2), 2.71—2.60 (3 H, m, CH_2CO_2 and OH), and 2.41—2.36 (2 H, d, *J* 5 Hz, $CH_2$7-H_2); *m/z* 210 (*M* − 18, 0.2%), 165 (17.8), 121 (5.5), 97 (7), 91 (8.55), 79 (7.4), 55 (14.8), and 45 (100).

rel-(3aR,4R,7aS)-6-*Formyl*-4-*hydroxy*-3a,4,7,7a-*tetrahydrobenzo*[b]*furan*-2(3H)-*one* (**23**).—To a stirred solution of *rel*-(3a*R*,4*R*,7a*S*)-4-hydroxy-6-(methoxymethoxymethyl)-3a,4,-7,7a-tetrahydrobenzo[*b*]furan-2(3*H*)-one (**21**) (70 mg, 0.3 mmol) in DME (25 ml) at 50 °C under argon was added a 24% solution of hydrobromic acid (0.14 ml, 2 mol equiv. of HBr; 24% solution in water). The reaction was monitored by t.l.c. (ethyl acetate as developer). After 20 min at 50 °C a more polar product was the sole component in the reaction mixture (by t.l.c.). The reaction mixture was cooled to room temperature and extracted with ethyl acetate (3 × 50 ml). The combined organic extracts were washed once with brine (20 ml) and dried (Na_2SO_4). Removal of the organic solvent (rotary evaporator) gave a semi-solid, and 'flash' chromatography (elution with ethyl acetate) led to the isolation of the title compound (**23**) as an unstable off-white crystalline solid (44 mg, 80%), m.p. 68—70 °C); $\nu_{max.}$ 3 400 (OH), 2 970s, 1 760s (CO), 1 680s (CHO), and 1 050 cm^{-1}; δ_H (100 MHz) 9.51 (1 H, s, CHO), 6.98—6.83 (1 H, m, =CH), 4.98—4.80 (1 H, dd, *J* 5 and 9 Hz, C*H*OH), 4.22—4.10 (1 H, m, C*H*OCO), 2.90—2.82 (1 H, m, C*H*CH_2CO_2), 2.80—2.60 (4 H, m, 7- and 3-H_2), 2.50 (1 H, br s, OH, D_2O-exchanged); *m/z* 182 (M^+, 0.1%), 164 (1.8), 135 (1.5), 107 (3), 98 (2.9), 69 (1.7), 58 (100), 55 (3.1), and 39 (2.9).

rel-(3aR,4R,7aS)-4-*Hydroxy*-6-*hydroxymethyl*-3a,4,7,7a-*tetrahydrobenzo*[b]*furan*-2(3H)-*one* (**24**).—*rel*-(3a*R*,4*R*,7a*S*)-6-formyl-4-hydroxy-3a,4,7,7a-tetrahydrobenzo[*b*]furan-2(3H)-one (**23**) (30 mg, 0.16 mmol) in methanol (10 ml) at 0 °C under nitrogen was added cerium(III) chloride heptahydrate (59 mg, 0.16 mmol, 1 mol equiv.). The resultant solution was stirred for 5 min prior to the addition of sodium borohydride (6.6 mg, 0.176 mmol, 1.1 mol equiv.). The reaction mixture was then stirred at 0 °C for a further 5 min before the addition of water (2 ml). Extraction with ethyl acetate (3 × 20 ml) followed by washing of the combined extracts with brine (50 ml), drying (Na_2SO_4), and concentration (rotary evaporator) led to the isolation of a pale yellow oil. This oil was unstable to 'flash' silica and storage. The spectral data were recorded on the unpurified material (27.5 mg, crude yield 91%); $\nu_{max.}$ 3 500s (OH) 2 960s, 1 760s (CO), 1 250s, and 1 050s cm^{-1}; δ_H (60 MHz) 5.90—5.65 (1 H, m, CH=), 4.90—4.55 (2 H, m, C*H*OH and C*H*OCO), 4.15—3.98 (2 H, br s, CH_2OH), 3.30 (1 H, br m, OH), 2.95—2.85 (1 H, m, C*H*CH_2CO_2), 2.68—2.38 (5 H, br m, CH_2C=C, OH, and CH_2CO_2).

'One-pot' Preparation of rel-(3aR,4R,7aS)-6-(*t-Butyldimethylsilyloxymethyl*)-4-*hydroxy*-3a,4,7,7a-*tetrahydrobenzofuran*-2(3H)-*one* (**25**).—To a stirred solution of compound (**21**) (200 mg, 0.8 mmol) in DME (45 ml) at 50 °C under argon was added a 24% solution of hydrobromic acid (0.46 ml, 2 mol equiv. of HBr). After being stirred for 20 min at 50 °C the reaction mixture was cooled to room temperature. The products were extracted into ethyl acetate (2 × 50 ml) and evaporation of the combined extracts gave a pale yellow semi-solid. Methanol (30 ml) was added together with cerium(III) chloride heptahydrate (295 mg, 0.8 mmol, 1 mol equiv.). The resultant mixture was cooled to 0 °C and sodium borohydride (30 mg, 0.8 mmol, 1 mol equiv.) was added in small portions. After 5 min at 0 °C, the mixture was treated with water (3 ml) and the products were extracted with ethyl acetate (2 × 50 ml). Drying (Na_2SO_4) of the extracts followed by concentration yielded a rose-pink coloured oil (116 mg, 72% crude yield), which was immediately dissolved in dimethylformamide (20 ml) and the solution was stirred and cooled to 0 °C under nitrogen. Imidazole (0.11 g, 1.6 mmol, 2 mol equiv.) and t-butyldimethylsilyl chloride (0.11 g, 0.8 mmol, 1 mol equiv.) were added and the mixture was stirred at 0 °C for 1 h. After this time the reaction flask and contents were allowed to warm to room temperature and were then stirred for a further 24 h. The reaction mixture was then diluted with ether (150 ml) and the ether extract was washed successively with water (30 ml) and brine (30 ml). Drying (Na_2SO_4) of the extract followed by concentration (rotary evaporator) and purification by flash chromatography [diethyl ether–ethyl acetate (2:1)] led to the isolation of *rel*-(3a*R*,4-*R*,7a*S*)-benzo[*b*]furan-2(3H)-one (**25**) [152 mg, 81% from (**21**)] as an oil, $\nu_{max.}$ 3 500 (OH), 1 770s, 1 640m, 1 250m, and 1 050 cm^{-1}; δ_H (100 MHz) 5.80—5.64 (1 H, br s, CH=), 4.82—4.65 (2 H, br m, C*H*OH and CHOCO), 4.06—3.98 (2 H, br s, C*H*$_2$OR), 2.85—2.60 (1 H, br m, C*H*CH_2CO_2), 2.59—2.50 (2 H, m, CH_2CO_2), 2.40—2.30 (3 H, m, CH_2C= and OH), 0.89 (9 H, s, Bu^t), and 0.04 (6 H, s, 2 × CH_3Si); *m/z* 280 (M^+ − 18, 0.4%), 223 (0.2), 166 (1.8), 135 (2.1), 134 (3.4), 91 (3.2), 79 (3.0), 74 (100), and 57 (2.7).

rel-(3aR,4S,5S,6S,7aS)-6-(*t-Butyldimethylsilyloxymethyl*)-5,6-*epoxy*-4-*hydroxybenzo*[b]*furan*-2(3H)-*one* (**26**).—To a stirred solution of *rel*-(3a*R*,4*R*,7a*S*)-6-(t-butyldimethylsilyloxymethyl)-4-hydroxy-3a,4,7,7a-tetrahydrobenzo[*b*]furan-2(3*H*)-one (**25**) (20 mg, 0.08 mmol) in dry methylene dichloride (5 ml) at −15 °C was added sodium hydrogen carbonate (6 mg, anhydrous). To the resultant suspension was added purified MCPBA (7 mg, 0.08 mmol, 1 mol equiv.) in small portions during 3 h. The resultant suspension was stirred at −15 °C for 62 h. The reaction was monitored by t.l.c. (developer diethyl ether). After the reaction was complete, the reaction mixture was washed successively with saturated aqueous sodium sulphite (5 ml), 5% aqeuous sodium hydrogen carbonate (5 ml), and brine (5 ml) and dried (Na_2SO_4). Evaporation of the solvent gave an oil. Analytical h.p.l.c. [methanol–water (70:30)] using a reverse-phase column with refractive index detection indicated that two components were present in the ratio 95:5. Flash chromatography (diethyl ether) yielded a single, oily component (17 mg, 81%). After storage at −25 °C the product was observed to crystallise. Recrystallisation from diethyl

ether–pentane yielded the *cis*-epoxy alcohol (**26**) as white needle-like crystals, m.p. 86—87 °C (lit.,[6] 87—88 °C). The product was identified on the basis of its spectroscopic characteristics as *rel*-(3a*R*,4*S*,5*S*,7a*S*)-6-(butyldimethylsilyloxymethyl)-5,6-epoxy-4-hydroxy-3a,4,5,6,7,7a-hexahydrobenzo[*b*]furan-2(3*H*)-one (**26**), $\nu_{max.}$ 3 500 (OH), 2 900, 1 755s (CO), 1 450, 1 100s, and 1 050s cm^{-1}; δ_H (100 MHz) 4.78 (1 H, dd, *J* 5.5, and 9 Hz, C*H*OH), 4.40 (1 H, v br m, CHOCO), 3.66 (2 H, AB quartet, J_{AB} 12 Hz, CH_2OR), 3.32—3.20 (1 H, s, 5-H), 3.14—2.86 (2 H, m, OH and $CHCH_2CO_2$), 2.62—2.28 (3 H, complex m, CH_2CO_2, and 7-H), 2.18—2.00 (1 H, dd, *J* 5 and 16 Hz, 7-H), and 0.94 (9 H, s, Bu^t), 0.01 (6 H, s, Me_2Si); *m/z* 241 (M^+ − 73, 2.1%), 223 (0.8), 181 (4.3), 151 (0.4), 107 (2.6), 91 (0.9), 72 (2.7), and 57 (1.7).

rel-(3aS,4R,6S,7aS)-4-*Hydroxy*-6-(*methoxymethoxymethyl*)-3a,4,5,6,7,7a-*hexahydrobenzo*[b]*furan*-2(3H)-*one* (**16**).—The procedure for reaction of the *cis*-epoxy alcohol (**12**) with dilithioacetate followed exactly that used for the *trans*-epoxy alcohol (**11**); the *title compound* (**16**) was obtained (73 mg, 15%) (Found: C, 57.6; H, 7.8. $C_{11}H_{18}O_5$ requires C, 57.4; H, 7.9%); $\nu_{max.}$ 3 500, 2 960, 1 765s, and 1 050m, cm^{-1}; δ_H (100 MHz) 4.64 (2 H, s, OCH_2O), 3.99—3.60 (2 H, m, C*H*OH and CHOCO), 3.56—3.52 (2 H, d, *J* 6 Hz, CH_2O), 3.4 (3 H, s, OCH_3), 2.89—2.00 (4 H, m, OH, CH_2CO_2, and CH), and 1.68—1.2 (5 H, m); *m/z* 185 (M^+ − 45, 4%), 167 (4), 138 (4), 111 (2), 95 (4), 75 (22), and 45 (100). Unchanged starting material (80%) was also recovered.

rel-(3aR,4S,6S,7aS)-6-*Acetoxymethyl*-4-*hydroxy*-3a,4,5,6,7,7a-*hexahydrobenzo*[b]*furan*-2(3H)-*one* (**28**).—The *trans*-epoxy alcohol (**11**) was treated with dilithioacetate as described previously except that the final crude product was acidified to pH 1 with conc. hydrochloric acid. Continuous extraction with ethyl acetate for 24 h yielded *rel*-(3a*R*,4*S*,-6*S*,7a*S*)-6-acetoxymethyl-4-hydroxy-3a,4,5,6,7,7a-hexahydrobenzo[*b*]furan-2(3*H*)-one (**28**), contaminated with HMPA which could not be removed by flash chromatography.

rel-(3aS,6R,7aS)-6-*Acetoxymethyl*-3,3a,5,6,7,7a-*hexahydrobenzo*[b]*furan*-2,4-*dione* (**29a**).—To a stirred solution of the crude alcohol (**28**) (1.0 g) in methylene dichloride (50 ml) was added PCC on alumina (1.96 g, 2 mol equiv.). The resulting suspension was stirred at room temperature for 36 h after which time the reaction mixture was diluted with diethyl ether (50 ml) and the inorganic residues were removed by filtration through a short column of silica. Removal of the solvents at reduced pressure yielded a dark yellow oil which was purified by flash chromatography (ethyl acetate) to yield rel-(3aS,6R,7aS)-6-*acetoxymethyl*-3,3a,5,6,7,7a-*hexahydrobenzo*[b]*furan*-2,4-*dione* (**29a**) as an oil (0.86 g, 70%), $\nu_{max.}$ 2 940, 1 780s (lactone), 1 740s (acetate), and 1 720s cm^{-1} (ketone); δ_H (100 MHz; $CDCl_3$) 5.1—4.9 (1 H, m, CHOCO), 4.05 (2 H, d, *J* 5 Hz, CH_2OAc), 3.4—3.2 (1 H, m, $CHCH_2CO_2$), 3.0—2.2 (4 H, m, CH_2CO and CH_2CO_2), 2.05 (3 H, s, CH_3CO), 1.8—1.2 (3 H, m, $CHCH_2OAc$ and CH_2) [Found: M^+, 226.2303 (2%). $C_{11}H_{14}O_5$ requires *M*, 226.2313]; *m/z* 183 (26), 165 (7), 121 (8), 91 (6), 85 (3), 77 (5), and 43 (100).

rel-(3aS,5R,6S,7aS)-6-*Acetoxymethyl*-5-*phenylseleno*-3,3a,5,6,7,7a-*hexahydrobenzo*[b]*furan*-2,4-*dione* (**29b**).—Ketone (**29**) (190 mg, 0.84 mmol) was treated with benzeneselenenyl chloride (0.192 g, 1.0 mmol) as described previously for the reaction of compound (**18**) except that aqeuous work-up and purification by flash chromatography (diethyl ether) gave *rel*-(3a*S*,5*R*,6*S*,7a*S*)-6-acetoxymethyl-5-phenylseleno-3,3a,5,6,7,7a-hexahydrobenzo[*b*]furan-2,4-dione (214 mg, 67%) as an unstable yellow oil, $\nu_{max.}$ 3 025, 2 960, 1 780s (lactone), 1 740 (acetate), 1 715 (ketone), 1 590m, and 1 510 cm^{-1}; δ_H (100 MHz) 7.65—7.25 (5 H, m, Ph), 5.15—4.8 (1 H, q, *J* 6 Hz, CHOCO), 4.3—4.15 (2 H, d, *J* 5 Hz, CH_2OAc), 3.75—3.5 (1 H, d, *J* 6 Hz, PhSeC*H*), 3.47—3.17 (1 H, m, $CHCH_2CO_2$), 2.75—2.15 (4 H, m), 1.93 (3 H, s, CH_3CO), and 1.8—1.5 (1 H, $CHCH_2OAc$); *m/z* 380 (M^+, 2%), 337 (1), 180 (8), 164 (1), 95 (16), 81 (1), 77 (5), and 43 (100).

cis-6-*Acetoxymethyl*-3,3a,7,7a-*tetrahydrobenzo*[b]*furan*-2,4-*dione* (**30**).—Oxidation/elimination of *rel*-(3a*S*,5*R*,6*S*,7a*S*)-6-acetoxymethyl-5-phenylseleno-3,3a,5,6,7,7a-hexahydrobenzo-[*b*]furan-2,4-dione (100 mg, 0.26 mmol) as described for the preparation of compound (**19**) yielded cis-6-*acetoxymethyl*-3,3a,7,7a-*tetrahydrobenzo*[b]*furan*-2,4-*dione* (**30**) as an oil (50 mg, 85%), $\nu_{max.}$ 2 920, 1 760 (lactone), 1 720s (acetate), 1 670s (ketone), and 1 220s cm^{-1}; δ_H (100 MHz) 6.17 (1 H, s, HC=), 5.1 (1 H, m, CHOCO), 4.7 (2 H, br s, CH_2OAc), 3.2 (1 H, m, $CHCH_2CO_2$), 2.99—2.68 (4 H, m, CH_2C= and CH_2CO_2), and 2.17 (3 H, s, CH_3CO) [Found: M^+, 224.2155 (1%). $C_{11}H_{12}O_5$ requires *M*, 224.2153]; *m/z* 181 (24), 166 (17), 136 (5), 82 (14), and 43 (92).

rel-(3aR,4R,7aS)-6-*Acetoxymethyl*-4-*hydroxy*-3a,4,7,7a-*tetrahydrobenzo*[b]*furan*-2(3H)-*one* (**31**).—Enone (**30**) (200 mg, 1 mmol) was treated with lithium triethylborohydride (1.14 ml, 1.14 mmol; 1M solution in THF) as described for the preparation of compound (**21**) to yield a 98:2 mixture, and purification by flash chromatography (ethyl acetate) was required to yield *rel*-(3a*R*,4*R*,7a*S*)-6-acetoxymethyl-4-hydroxy-3a,4,7,7a-tetrahydrobenzo[*b*]furan-2(3*H*)-one (**31**) as an oil, $\nu_{max.}$ 3 300s (OH), 1 765s (lactone), and 1 740s cm^{-1}; (acetate); δ_H (100 MHz) 6.01—5.9 (1 H, m, CH=), 5.02—4.84 (1 H, m, CHOCO), 4.6 (2 H, s, CH_2OAc), 4.0 (2 H, d, *J* 7 Hz, CH_2C=), 3.12—2.91 (1 H, m, $CHCH_2CO_2$), 2.74—2.40 (2 H, m, CH_2CO_2), and 2.08 (3 H, s, CH_3CO); *m/z* 183 (1%), 165 (11), 91 (6), 60 (6), 55 (28), and 43 (18).

rel-(3aR,4S,5S,6S,7aS)-6-*Acetoxymethyl*-5,6-*epoxy*-4-*hydroxy*-3a,4,5,6,7,7a-*hexahydrobenzo*[b]*furan*-2(3H)-*one* (**33**).—To a stirred solution of the hydroxy lactone (**31**) (50 mg, 4.5 mmol) in methylene dichloride (10 ml) at −5 °C was added dropwise a solution of MCPBA (0.9 g, 5.4 mmol) in methylene dichloride (10 ml) during 3 h. The resultant solution was stirred at −5 °C for 64 h, after which time the reaction mixture was poured into cold saturated aqueous sodium sulphite (5 ml). The organic phase was separated and washed successively with 5% aqueous sodium hydrogen carbonate (5 ml) and brine (5 ml) and dried (Na_2SO_4). Evaporation of the solvent at reduced pressure gave an oil (58 mg), which was purified by flash chromatography [diethyl ether–ethyl acetate (6:1)] to give rel-(3aR,4S,5S,6S,7aS)-6-*acetoxymethyl*-5,6-*epoxy*-4-*hydroxy*-3a,4,5,6,7,7a-*hexahydrobenzo*[b]*furan*-2(3H)-*one* (**33**) as an oil (36 mg, 67%), $\nu_{max.}$ 3 600m, 1 760s (lactone), 1 750 (acetate), 1 250s, and 1 100m cm^{-1}; δ_H (100 MHz) 4.75 (1 H, dd, *J* 6 and 9 Hz, CHOCO), 4.3 (1 H, br s, C*H*OH), 4.65—4.59 (2 H, dd, *J* 12 and 3 Hz, CH_2OAc), 3.32 (1 H, d, *J* 5 Hz, 5-H), 3.18—2.95 (3 H, m, $CHCH_2CO$ and CH_2CO), 2.62—2.12 (3 H, m, CH_2CHOCO and OH), and 2.02 (3 H, s, CH_3CO); *m/z* (c.i.) [Found: (M + NH_4), 260.2688. $C_{11}H_{18}NO_6$ requires *m/z*, 260.2694].

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