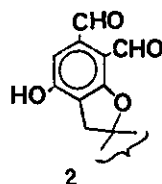
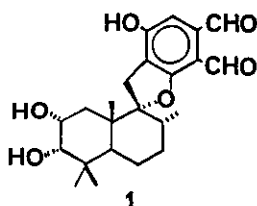


FORMATION OF 2,2-SPIRO-SUBSTITUTED 2,3-DIHYDROBENZOFURANS.

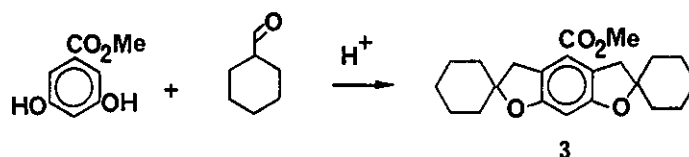
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Abstract - Routes from substituted resorcinols to spiro-substituted dihydrobenzofurans are described. Whilst use of acid-catalysed condensations between a resorcinol and an aldehyde only gave low yields of dihydrobenzofurans and lacked regiocontrol, use of a nucleophilic aromatic substitution approach was successful.

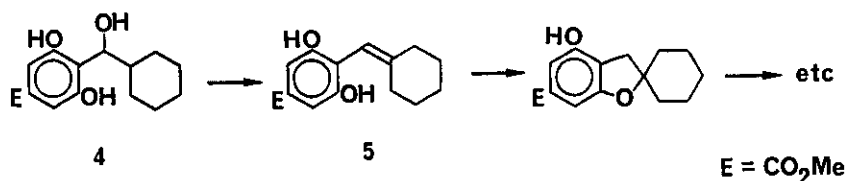
The interesting complement inhibitor, K-76 (1) and its congeners,² have been the subject of two elegant synthetic studies.^{3,4}



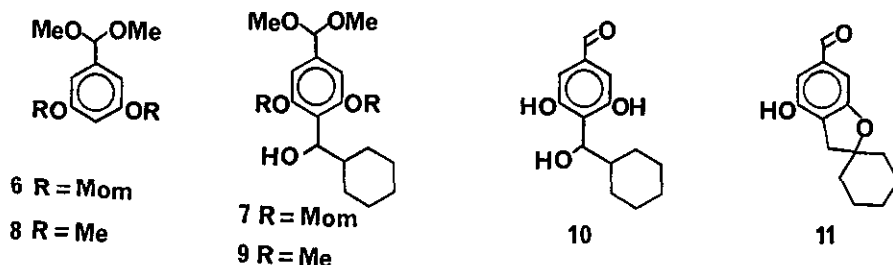
A novel feature of this molecule is the spiro-substituted benzofuran moiety (2) and in order to find a simple route to some analogues of K-76 some model studies on the formation of this system have been carried out. One possibility involves the direct condensation of aldehydes with appropriately substituted resorcinols.⁵ Thus condensation of methyl 3,5-dihydroxybenzoate with cyclohexanecarboxaldehyde in toluene, using sulphuric acid as catalyst under Dean and Stark conditions, afforded a complex mixture of products from which only one compound could be readily isolated (16%). This proved to be a symmetrical 1:2 adduct, identified as the 2,6-disubstituted resorcinol ether (3).



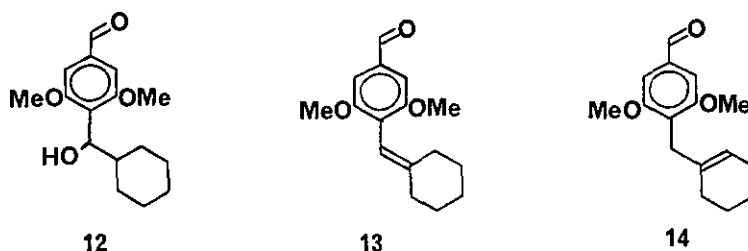
Using a variety of alternative acid catalysts neither improved the yield of the adduct (3) nor provided any discrete monosubstituted products. The orientation of substitution in compound (3) is in agreement with the empirical 'ortho-effect' rule.⁶ We initially assumed that the condensation had proceeded via the alcohol intermediate (4), (Scheme), followed by dehydration to the olefin (5) and intramolecular addition of the phenol after protonation of the latter, although later results indicated that a hydride shift may occur, *vide infra*.



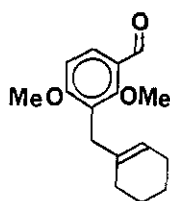
Since no 4-monosubstituted resorcinols of the desired type, *cf.* (2), were isolated, a modified approach was utilized in which the protected bis-methoxymethoxybenzaldehyde (6) was first lithiated, this occurring selectively at the required position 4, and the anion reacted with cyclohexanecarboxaldehyde to give the alcohol (7), followed by the removal of the protecting groups to produce the trihydroxybenzaldehyde (10). Treatment of this alcohol with a variety of dehydrating agents gave complex mixtures but use of tosic acid in toluene did produce some of the required benzofuran (11), more closely related to the eventual target (2) but again only in low yield.



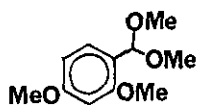
The corresponding dimethoxybenzaldehyde (12) was also prepared, via compounds (8) and (9), and the behaviour of this to the acid dehydration conditions examined. The isolated product was not the anticipated styrene (13) but instead the endocyclic olefin (14). Presumably steric hindrance by the ortho-methoxy groups disfavors the former; the endocyclic olefin is favored with respect to the alicyclic ring system.⁷ Formation of this olefin most likely occurred by a hydride shift rather than intermediate formation of the (unstable) styrene intermediate. A similar process might occur in the dihydroxy series described above. A further indication of steric hindrance to styrene formation was obtained when attempts to produce olefins of the type (13) by Wittig condensation of the components failed to give any of the desired product.



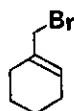
As an alternative to the foregoing, inefficient routes the possibility of nucleophilic aromatic substitution was explored. The perceived advantage of this route was to avoid the time-consuming selective protection and deprotection sequences needed to distinguish between the two resorcinol oxygens used in the previous syntheses.^{3,4}



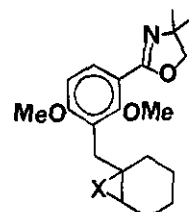
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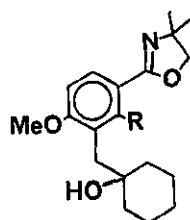


18 X = double bond

19 X = O

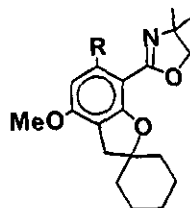
The olefin (15), prepared by reaction of the protected 2,4-dimethoxybenzaldehyde (16) with the bromide (17), could be oxidised to the acid and protected as the oxazoline (18).⁸ Subsequent epoxidation gave the epoxide (19). Reduction of the latter with one equivalent of lithium aluminium hydride gave the required alcohol (20), although the use of an excess of the hydride reagent gave both reduction of the epoxide group and reductive elimination of the 2-methoxy substituent to give the product (21); the oxazoline group is stable to lithium aluminium hydride.⁹ Formation of the over-reduction product (21) gave an indication of the greater susceptibility of the 2-position to nucleophilic attack and no removal of the 4-methoxyl group was observed.

Treatment of the alcohol (20) with sodium hydride in THF¹⁰ promoted nucleophilic displacement of the methoxyl group to give a 69% yield of the spiro-2,3-dihydrobenzofuran (22). This was ideally suited for introduction of the final aromatic ring substituent by directed aromatic substitution.¹¹ Thus treatment with butyllithium in THF at -30°C followed by quenching with dimethylformamide gave the aldehyde (23); the differentiation between the aldehyde and



20 R = OMe

21 R = H

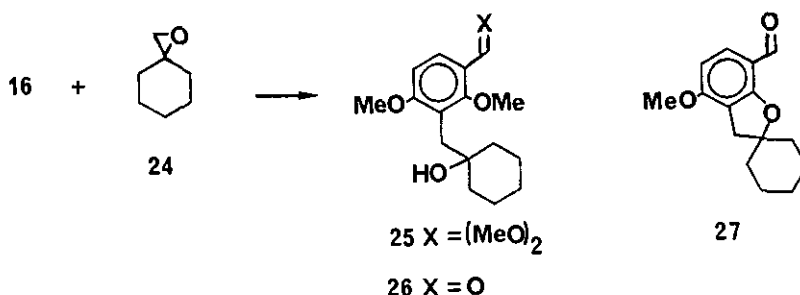


22 R = H

23 R = CHO

carboxylic substituents potentially allows for further selective transformations of these groups.

In subsequent studies we found that we could dispense with the oxazoline protecting group. Thus reaction of the anion from (16) with the epoxide (24) and removal of the acetal protecting group from the intermediate (25) gave the alcohol (26) in overall 50% yield. Treatment of this alcohol with an equivalent of sodium hydride in THF afforded the spiro-compound (27) in 94% yield.



The use of this strategy is currently being applied to a synthesis of the natural product K-76 and its congeners.

EXPERIMENTAL

Mps were determined on a Kofler hot-stage apparatus and are uncorrected. Ir spectra were obtained from chloroform solutions recorded on a Perkin Elmer 1420 spectrophotometer. ^1H Nmr spectra were recorded using a Varian EM360A (60MHz) spectrometer, a Jeol FX90Q (90 MHz) spectrometer, or a Bruker AM400 (400MHz) spectrometer using deuteriochloroform as solvent and tetramethylsilane as internal reference. ^{13}C Nmr spectra were determined either on the Jeol FX90Q (22.5 MHz) using deuteriochloroform as solvent and tetramethylsilane as internal reference.

Accurate mass measurements were determined using an AEI-Kratos MS9/50 spectrometer. Elemental

analyses were determined by the Microanalytical Laboratory, School of Chemistry, University of Leeds.

Reactions were monitored by thin layer chromatography (tlc) using glass plates precoated with Merck Kieselgel 60 GF₂₅₄. Reaction product mixtures were usually processed by chromatography through Merck silica gel (60G) under slight pressure; solvent mixtures are cited in ratios of volumes before mixing. Generally reaction solvents were removed, after drying over anhydrous sodium sulphate, under reduced pressure using a rotary evaporator. Solvents were dried and distilled following standard procedures before use.¹² Light petroleum refers to the fraction of boiling range 30-40°C; ether refers to diethyl ether. All reactions involving air-sensitive materials were conducted under an atmosphere of dry, oxygen-free nitrogen. The term brine refers to saturated aqueous sodium chloride solution. Small scale distillations were conducted using a bulb-to-bulb distillation oven under reduced pressure.

4-Methoxycarbonyl-2,3,5,6-tetrahydrobenzo[1,2-b:5,4-b']difuran-2,6-bispirocyclohexane (3).-

Methyl 3,5-dihydroxybenzoate (0.5 g, 3 mmol) and cyclohexanecarboxaldehyde (0.5 g, 4.5 mmol) were heated in refluxing toluene (50 ml) in the presence of conc. H₂SO₄ (0.5 ml) using a Dean and Stark apparatus to remove water. After 4 h the reaction mixture was cooled, washed with water and the solvent removed before chromatographing the residue, using ether - light petroleum (1:1) as eluant. The major fraction was the title compound, isolated as a crystalline solid (0.17 g, 16%), mp (from MeOH) 131-132°C; $\tilde{\nu}_{\text{max}}$ 1708, 1597 and 1450 cm⁻¹; δ (¹H, 90 MHz) 1.2 - 2.0 (20 H, m, CH₂), 3.16 (4 H, s, ArCH₂), 3.86 (3H, s, Me), 6.37 (1 H, s, ArH); δ (¹³C, 22.5 MHz) 22.97 (CH₂), 25.19 (CH₂), 37.27 (CH₂), 42.36 (CH₂), 51.47 (Me), 89.17 (C), 96.81 (aromatic CH), 119.83 (C-O), 123.14 (C), 159.65 (C-O), 167.07 (CO). (Found: C, 73.9; H, 7.8; C₂₂H₂₆O₄ requires C, 74.1; H, 7.9%.)

4-(Cyclohexylhydroxymethyl)-3,5-bis(methoxymethoxy)-1-(dimethoxymethyl)benzene (7).- Butyllithium

(8.8 ml, 1.5 M solution in hexane, 13.2 mmol) was added dropwise to a solution of the acetal (6)³ (3.0 g, 11 mmol) in dry THF (60 ml) at -30°C. The solution was warmed to -20°C over 40 min and then to 0°C over 20 min before recooling, to -78°C and adding cyclohexanecarboxaldehyde (1.6 ml, 13 mmol) dropwise. The temperature of the reaction was maintained at -78°C for 1 h before

allowing it to warm to room temperature and quenching with saturated ammonium chloride solution (200 ml) and extracted with chloroform (4 x 70 ml). The combined extracts were dried (MgSO_4) and evaporated. the residue was chromatographed, using ether - light petroleum (2:3) as eluant, to yield the title compound as a pale yellow oil (3.24 g, 76%), bp $185^\circ\text{C}/0.3$ mm Hg; ν_{max} (film) 3570, 1611, 1587, 1155 and 1045 cm^{-1} ; δ (^1H , 90MHz) 0.8 - 2.0 (11 H, m, CH and CH_2), 2.3 (1 H, m, CH), 3.32 (6 H, s, 2 x MeO), 3.48 (6 H, 2 x MeO), 4.82 (1 H, broad t, J 8 Hz, collapses to d with D_2O , CHOH), 5.21 (4 H, s, 2 x OCH_2O), 5.29 (1 H, s, $\text{CH}(\text{OMe})_2$), 6.87 (2 H, s, ArH). (Found: C, 62.6; H, 8.4%. m/z 384.2139. $\text{C}_{20}\text{H}_{32}\text{O}_7$ requires C, 62.5%; H, 8.4%, M^+ 384.2148.)

4-(Cyclohexylhydroxymethyl)-3,5-dihydroxybenzaldehyde (10).- The acetal (7) (2.25 g, 5.9 mmol) was dissolved in 1M HCl in THF (1:3, 80 ml) and stirred for 1 h at room temperature before pouring into water (150 ml) and extracting with chloroform (4 x 70 ml). The combined chloroform extracts were dried and the solvent removed to afford an oil (1.93 g, 98%). A sample of this (1.1 g) was immediately added to a solution of 4M aqueous sulphuric acid in THF (1:1, 35 ml) before heating to reflux for 3 h. The solution was cooled, neutralised with a saturated aqueous solution of sodium hydrogen carbonate solution and extracted with chloroform (4 x 50 ml). The combined organic extracts were washed with brine (200 ml), dried and the solvent removed. The residue was chromatographed, using ether - light petroleum (1:3) as eluant, to give the title alcohol (0.59 g, 72%) as a crystalline solid, mp $75 - 77^\circ\text{C}$ (ethanol); ν_{max} 3610, 3330, 1695, and 1590 cm^{-1} ; δ (^1H , 90 MHz)(CDCl_3 - d_6 -DMSO) 1.0 - 2.0 (11 H, m, CH, CH_2), 5.06 (1 H, t, J 6 Hz, collapses to d on exchange with D_2O , CHOH), 5.32 (1H, broad d, J 5 Hz, exchanged by D_2O , OH), 6.84 (2 H, s, ArH), 9.27 (2H, broad s, exchanged by D_2O , ArOH), 9.77 (1 H, s, CHO). (Found: C, 62.4; H, 7.5; $\text{C}_{14}\text{H}_{18}\text{O}_4 \cdot \text{H}_2\text{O}$ requires C, 62.7; H, 7.5%.)

2,3-Dihydro-4-hydroxybenzo[b]fura-6-carboxaldehyde-2-spirocyclohexane (11).-

A solution of the alcohol (10) (100 mg, 0.4 mmol) and tosic acid (10 mg) in toluene (5 ml) was heated to reflux for 1 h, before cooling and quenching with a saturated aqueous solution of sodium hydrogen carbonate (10 ml). The toluene layer was separated, the aqueous layer extracted with chloroform (4 x 5 ml) and the combined organic layers dried. The solvent was removed to give a residue that was immediately chromatographed, using ether - light petroleum (1:3) as eluant, to afford the title compound (5 mg, 5%) as a gum, ν_{max} 3590, 3300, 1694, 1593, 1443,

and 1332 cm^{-1} ; δ (^1H , 90 MHz) 0.7 - 2.0 (10 H, m, CH_2), 2.95 (2 H, s, ArCH_2), 5.21 (1H, broad s, exchanged by D_2O , ArOH), 6.85 (2 H, s, ArH), 9.80 (1 H, s, CHO). (Found: M^+ 232.1098; $\text{C}_{14}\text{H}_{16}\text{O}_3$ requires M^+ 232.1099.)

1,3-Dimethoxy-5-(dimethoxymethyl)benzene (8).—Tosic acid (0.16 g) was added to a chilled solution of 3,5-dimethoxybenzaldehyde (1.9 g, 11.4 mmol) in dry methanol (35 ml). After stirring at 0°C for 2.5 h a saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, water (80 ml) added and the mixture extracted with ether (4 x 70 ml). The combined extracts were dried, filtered and evaporated. The residue was chromatographed through silica gel, using ether - light petroleum (1:3) as the eluant to give the title acetal (8) as an amber oil (2.32 g, 92%), bp $115^\circ\text{C}/0.3\text{ mm Hg}$; ν_{max} 1600, 1463, 1156 and 1055 cm^{-1} ; δ (^1H , 60 MHz) 3.38 [6 H, s, $(\text{MeO})_2\text{CH}$], 3.84 (6 H, s, ArOMe), 5.36 [1 H, s, $(\text{MeO})_2\text{CH}$], 6.49 (1 H, m, ArH), 6.68 (2 H, m, ArH). (Found: C, 62.2; H, 7.5; $\text{C}_{11}\text{H}_{16}\text{O}_4$ requires C, 62.2; H, 7.6%.)

4-(Cyclohexylhydroxymethyl)-3,5-dimethoxy-1-(dimethoxymethyl)benzene (9).—Butyllithium (15 ml, 1.5 M solution in hexane, 22.5 mmol) was added dropwise to a solution of the acetal (8) (4.0 g, 19 mmol) in dry THF (60 ml) cooled to -30°C . The temperature of the solution was allowed to warm to 0°C over 1 h before recooling to -78°C and adding cyclohexanecarboxaldehyde (2.8 ml, 23 mmol) dropwise. After a further 1 h at -78°C the solution was allowed to warm to room temperature and poured into a saturated aqueous ammonium chloride solution. The mixture was extracted with chloroform (4 x 70 ml), the combined extracts dried, filtered and evaporated and the residue chromatographed through silica gel, using ether - light petroleum (1:2) as eluant, to afford the title alcohol as a crystalline solid (3.79 g, 62%), mp $60 - 62^\circ\text{C}$ (from ether); ν_{max} 3545, 1590, 1450, 1415, 1353, 1150, 1050 and 1007 cm^{-1} ; δ (^1H , 90 MHz) 0.8 - 1.4 (6 H, m, CH_2), 1.4 - 2.0 (4 H, m, CH_2), 2.0 - 2.3 (1 H, m, CH), 3.33 [6 H, s, $(\text{MeO})_2\text{CH}$], 3.52 ([1H,d,J 11.6 Hz, exchanged by D_2O , HO), 3.83 (6 H, s, ArOMe), 4.79 (1 H, dd, J 11.6, 8.7 Hz, collapses to d, J 8.7 Hz with D_2O , CHOH). (Found: C, 66.5, H, 8.7; $\text{C}_{18}\text{H}_{26}\text{O}_5$ requires C, 66.6; H, 8.7%.)

4-(Cyclohexylhydroxymethyl)-3,5-dimethoxybenzaldehyde (12).—The acetal (9) (3.88 g, 12 mmol) was dissolved in 1M aqueous HCl in THF (1:3, 30 ml) and the solution stirred at room temperature for 1 h. The solution was then poured into distilled water (200 ml) and extracted with chloroform (4

x 80 ml), the combined extracts dried, filtered and evaporated and the residue crystallised from aqueous ethanol to give the title aldehyde (3.23 g, 97%), mp 132-134°C; $\bar{\nu}_{\max}$ 3560, 1692, 1583, 1461, 1420, 1310 and 1112 cm^{-1} ; δ (^1H , 90 MHz) 0.8 - 2.0 (10 H, m, CH_2), 2.0 - 2.3 (1 H, m, CH), 3.46 (1 H, d, J 11.8 Hz, exchanged by D_2O , OH), 3.91 (6 H, s, ArOMe), 4.85 (1 H, dd, J 11.8, 8.7 Hz, collapses to d, J 8.7 Hz on exchange with D_2O , CHOH), 7.08 (2 H, s, ArH), 9.91 (1 H, s, CHO). (Found: C, 68.8; H, 8.0; $\text{C}_{16}\text{H}_{22}\text{O}_4$ requires C, 69.0; H, 8.0%.)

4-(Cyclohex-1-en-1-ylmethyl)-3,5-dimethoxybenzaldehyde (14).- The aldehyde (12) (3.2 g, 11.5 mmol) and tosic acid (51 mg) were dissolved in dry toluene (150 ml) and the resulting solution heated to reflux for 24 h. The reaction mixture was poured into a saturated aqueous sodium hydrogen carbonate solution (200 ml) and the organic layer separated. The aqueous layer was extracted with chloroform (4 x 100 ml), the combined organic layers washed with brine and then dried, filtered and evaporated. The residue was chromatographed, using ether - light petroleum (1:12) as eluant to afford the title olefin (2.09 g, 70%) as a colourless solid, mp 82 - 83°C (from ether); $\bar{\nu}_{\max}$ 1688, 1585, 1455, 1420, 1383, 1340, 1190, 1168 and 1040 cm^{-1} ; δ (^1H , 90 MHz) 1.35 - 1.75 (4 H, m, CH_2), 1.75 - 2.05 (4 H, m, CH_2), 3.31 (2 H, s, ArCH_2), 3.86 (6 H, s, ArOMe), 5.17 (1 H, m, vinylic H), 7.06 (2 H, s, ArH), 9.91 (1 H, s, CHO). (Found: C, 73.6; H, 8.0; $\text{C}_{16}\text{H}_{20}\text{O}_3$ requires C, 73.8; H, 7.7%.)

1,3-Dimethoxy-4-(dimethoxymethyl)benzene (16).- Amberlyst-15 (H^+) resin (2.25 g) was added to a chilled solution of 2,4-dimethoxybenzaldehyde (9.00 g, 54 mmol) and trimethyl orthoformate (28.8 g, 271 mmol) in dry THF (250 ml). The reaction mixture was stirred vigorously for 2 h at 0 - 5°C, filtered and the solvent removed. The residue was rapidly distilled (bulb oven) to give the title acetal (9.54 g, 83%), bp 130°C / 0.2 mm Hg; $\bar{\nu}_{\max}$ 1615, 1593, 1508, 1467, 1160 and 1050 cm^{-1} ; δ (^1H , 60 MHz) 3.34 [6 H, s, $(\text{MeO})_2\text{CH}$], 3.83 (6 H, s, ArOMe), 5.61 [1 H, s, $(\text{MeO})_2\text{CH}$], 6.51 (2 H, m, ArH), 7.46 (1 H, m, ArH). (Found: C, 62.4; H, 7.6; $\text{C}_{11}\text{H}_{16}\text{O}_4$ requires C, 62.3; H, 7.6%.)

1-(Bromomethyl)cyclohex-1-ene (17).- Methyl sulphide (6.25 ml, 0.1 mol) was added dropwise to a stirred solution of N-bromosuccinimide (14.8 g, 55 mmol) in dichloromethane (750 ml) at -5°C. After 1 h at 0°C the suspension was cooled to -20°C and 1-(hydroxymethyl)cyclohex-1-ene¹³ (6.2 g, 55 mmol) added. The mixture was then stirred at 0°C for 1 h, poured into brine and the

aqueous phase extracted with ether (2 x 100 ml) before the organic extracts were combined, dried and the solvent carefully removed to yield the title bromide as a pale yellow liquid, $\nu_{\max}$ 3010 and 1438 cm^{-1} . This was used without further purification.

3-(Cyclohex-1-en-1-ylmethyl)-2,4-dimethoxybenzaldehyde (15).— Butyllithium (18 ml, 1.54 M solution in hexane, 27.7 mmol) was added dropwise to a chilled (-40°C) solution of the acetal (16) (4.5 g, 21 mmol) in dry THF (150 ml) and the temperature allowed to rise over 1 h to -5°C and added to a suspension of copper (I) bromide - dimethyl sulphide complex (5.24 g, 25.5 mmol) in THF (150 ml) at -30°C . The mixture was allowed to warm to 0°C and stirred for 1 h before adding the bromide (17) (4.5 g, 26 mmol), keeping the temperature below 0°C . After a further 1 h the mixture was poured into a saturated aqueous ammonium chloride solution (400 ml) and the mixture extracted with chloroform (3 x 200 ml). The organic extract was washed with brine, dried and the solvent removed before chromatographing the residue, using ether - light petroleum (1:3) as eluant. The title olefin (4.15 g, 75%) was obtained as an oil, bp (bulb oven) $150^{\circ}\text{C}/0.3$ mm Hg; $\nu_{\max}$ 1677, 1591, 1463, 1280, and 1095 cm^{-1} ; δ (^1H , 90 MHz) 1.4 - 2.1 (8H, m), 3.85 (3H, s, ArOMe), 3.87 (3 H, s, ArOMe), 5.16 (1 H, m, vinylic H), 6.77 (1 H, d, J 8.7 Hz, 5-H), 7.77 (1 H, d, J 8.7 Hz, 4-H), 10.21 (1 H, s, CHO). (Found: C, 73.6; H, 7.8. $\text{C}_{16}\text{H}_{20}\text{O}_3$ requires C, 73.8; H, 7.7%.)

3-(Cyclohex-1-en-1-ylmethyl)-2,4-dimethoxy-1-(4,5-dihydro-4',4'-dimethyloxazol-2'-yl)benzene (18).— The aldehyde (15) (1.9 g) was oxidised with silver oxide (8.5 g) in ethanol (75 ml) under standard conditions¹⁴ to afford the corresponding acid (1.56 g, 77%). A sample of the acid (612 mg, 2.2 mmol) was reacted with 2-amino-2-methyl-1-propanol (218 mg, 2.4 mmol) in the presence of dicyclohexylcarbodiimide (504 mg, 2.4 mmol) and 1-hydroxybenzotriazole (330 mg, 2.4 mmol) in dry THF (15 ml) at room temperature for 0.5 h before workup in the usual manner,¹⁵ to give 3-(cyclohex-1-en-1-ylmethyl)-2,4-dimethoxy-1-[N-(1,1-dimethyl-2-hydroxyethyl)carbamoyl]-benzene (766 mg, 99%), m.p. $96 - 98^{\circ}\text{C}$; $\nu_{\max}$ 3360, 1633, 1595, 1538, 1274 and 1093 cm^{-1} . (Found: C, 69.1; H, 8.4; N, 4.3; $\text{C}_{20}\text{H}_{29}\text{NO}_4$ requires C, 69.1; H, 8.4; N, 4.0%.)

The amido-alcohol (766 mg, 2.21 mmol) in benzene (15 ml) was treated with thionyl chloride (1.5 ml, excess) at room temperature. The solution was stirred for 2 h before pouring into ether

- hexane (1:1, 200 ml). The mixture was then evaporated under reduced pressure and the residual oil treated with aqueous 3M NaOH solution, until basic, and extracted with ether (4 x 50 ml). The organic extract was dried, filtered and evaporated to give the title_oxazoline (646 mg, 89%) as an oil, ν_{max} 1645, 1596, 1278, and 1095 cm^{-1} . (Found: m/z 329.1988; $\text{C}_{20}\text{H}_{27}\text{NO}_3$ requires M^+ 329.1991.)

Epoxidation of the Oxazoline (18).- A solution of 3-chloroperbenzoic acid (1.76 g, 8.1 mmol) in dichloromethane (15 ml) was added dropwise at 0°C to a solution of the oxazoline (2.68 g, 8.1 mmol) in dichloromethane (100 ml). The solution was stirred at 0°C for 5 min and then at room temperature for 20 min. The unreacted oxidant was destroyed with a little aqueous sodium sulphite solution and the mixture washed with water (100 ml) and brine (100 ml) before drying, filtering and evaporating. The residue was chromatographed, using ether - light petroleum (1:1) as eluant, to afford the epoxide (19) (2.39 g, 95%) as a yellow oil; ν_{max} 1644, 1597, 1488, 1462, 1280, and 1107 cm^{-1} ; δ (^1H , 60MHz), 0.1 - 1.5 (4 H, m, CH_2), 1.39 (6 H, s, Me_2), 1.5 - 2.25 (4 H, m, CH_2), 2.81 (1 H, d, J 14 Hz, ArCHH), 3.19 (1 H, d, J 14 Hz, ArCHH), 2.99 (1 H, m, 2"-H), 3.80 (3 H, s, ArOMe), 3.84 (3 H, s, ArOMe), 4.10 (2 H, s, 5'-H), 6.79 (1 H, d, J 9 Hz, Ar-H), 7.72 (1 H, d, J 9 Hz, ArH). (Found: m/z 345.1928; $\text{C}_{20}\text{H}_{27}\text{NO}_4$ requires M^+ 345.1940.)

Reduction of the Epoxide (19).- Lithium aluminium hydride (0.74 ml, 1M solution in THF, 74 mmol) was added dropwise to the epoxide (212 mg, 0.61 mmol) in THF (1 ml) at room temperature and the mixture stirred for 1.5 h before quenching with water and dilute sodium hydroxide solution. The mixture was filtered and then extracted with ether (10 ml), before drying and removal of solvent to leave 3-(1-hydroxycyclohexan-1-yl)methyl-2,4-dimethoxy-1-(4,5-dihydro-4,4-dimethyloxazol-2-yl)benzene (20) (213 mg, 100%); ν_{max} 3530, 1643, 1600, 1488, 1465, 1280, and 1097 cm^{-1} ; δ (^1H , 60MHz) 1.39 (6H, s, Me_2), 1.53 (10 H, broad s, cyclohexyl H), 2.95 (2 H, s, ArCH_2), 3.26 (1 H, s, OH), 3.82 (3 H, s, ArOMe), 3.90 (3 H, s, ArOMe), 4.12 (2 H, s, 5'-H), 6.75 (1 H, d, J 9 Hz, ArH), 7.77 (1 H, d, J 9 Hz, ArH). (Found: m/z 347.2087. $\text{C}_{20}\text{H}_{29}\text{NO}_4$ requires M^+ 347.2097.)

When the reduction was carried out in the presence of an excess of lithium aluminium hydride (>2.5 eq.) a mixture of the above alcohol and the over-reduction product (21) formed, ratio

1.4:1 respectively. The compound (21) was isolated as a colourless oil (25%), $\bar{\nu}_{\max}$ 3535, 1645, 1608, 1505, 1357, 1252, and 910 cm^{-1} ; δ (^1H , 60 MHz) 1.37 (6 H, s, Me_2), 1.50 (10 H, broad s, cyclohexyl H), 2.42 (1 H, s, OH), 2.85 (2 H, s, ArCH_2), 3.87 (3 H, s, ArOMe), 4.08 (2 H, s, 5'-H), 6.90 (1 H, m, ArH), 7.83 (2 H, m, ArH). (Found: m/z 317.1990; M^{+} requires 317.1991.)

2,3-Dihydro-4-methoxy-7-(4,5-dihydro-4,4-dimethyloxazol-2-yl)benzo[b]furan-6-carboxaldehyde-2-spirocyclohexane (22).— Sodium hydride (28 mg, 1.2 mmol) suspended in THF (10 ml) was stirred with the alcohol (20) (200 mg, 0.6 mmol) in THF (10 ml) at reflux for 16 h. The mixture was cooled and poured into brine before extraction with ether (3 x 20 ml). The combined extracts were dried, filtered, evaporated and the residue chromatographed, using ether - light petroleum (1:1) as eluant to give the title compound (125 mg, 69%), mp 110–111°C (from water-methanol); $\bar{\nu}_{\max}$ 1636, 1622, 1505, 1430, 1284, and 1102 cm^{-1} ; δ (^1H , 400 MHz) 1.35 (6 H, s, Me_2), 1.40 – 1.54 (4 H, m, CH_2), 1.67 – 1.75 (2 H, m, CH_2), 1.75 – 1.85 (2 H, m, CH_2), 1.84 – 1.93 (2 H, m, CH_2), 2.86 (2 H, d, J 0.5 Hz, ArCH_2), 3.84 (3 H, s, ArOMe), 4.09 (2 H, s, 5'-H), 6.39 (1 H, d, J 8.8 Hz, 5-H), 7.71 (1 H, dt, J 8.8, 0.5 Hz, 4-H). (Found: C, 72.2; H, 7.8; N, 4.5; $\text{C}_{19}\text{H}_{25}\text{NO}_3$ requires C, 72.3; H, 8.0; N, 4.4%.)

2,3-Dihydro-4-methoxy-7-(4,5-dihydro-4,4-dimethyloxazol-2-yl)benzo[b]furan-6-carboxaldehyde-2-spirocyclohexane (23).— Butyllithium (0.6 ml, 1.54M solution in hexane, 0.92 mmol) was added dropwise to a solution of the spiro-2,3-dihydrobenzofuran (22) (200 mg, 0.63 mmol) in THF (7 ml) at -40°C . After 1 h the stirred solution was warmed to -30°C for a further 0.5 h, cooled to -78°C and dry DMF (0.1 ml, 1.29 mmol) added. After 1 h at -78°C the reaction mixture was warmed to room temperature and quenched with an aqueous saturated solution of ammonium chloride (20 ml) and extracted with ether (3 x 20 ml). The organic extract was dried, filtered and evaporated and the residue chromatographed, using ether - light petroleum (1:1) as eluant, to give the title aldehyde (112 mg, 51%) as a pale yellow oil, $\bar{\nu}_{\max}$ 1690, 1655, 1605, 1323, 1145 and 910 cm^{-1} ; δ (^1H , 60 MHz) 1.41 (6 H, s, Me_2), 1.00 – 2.30 (10 H, cyclohexyl H), 2.93 (2 H, s, ArCH_2), 3.90 (3 H, s, ArOMe), 4.16 (2 H, s, 5'-H), 7.05 (1 H, s, ArH), 10.33 (1 H, s, CHO). (Found: m/z 343.1790. $\text{C}_{20}\text{H}_{25}\text{NO}_4$ requires M^{+} 343. 1784.)

Reaction of Compound (16) with the Epoxide (24).— Butyllithium (6.14 ml, 1.54 M solution in hexane, 9.5 mmol) was added dropwise to a chilled (-40°C) solution of the acetal (2.01 g, 9.5

mmol) in THF (30 ml) and the solution allowed to warm to -5°C over 1.5 h, before adding HMPA (3.4 ml, 19 mmol) and the epoxide (24)¹⁶ (0.96 g, 8.5 mmol). The mixture was heated to reflux for 2 h, cooled and quenched with a saturated aqueous solution of ammonium chloride (30 ml) before extraction with chloroform (3 x 30 ml). The organic extract was dried, filtered and evaporated and the residue chromatographed, using ether - light petroleum (1:6) as eluant, to afford 2,6-dimethoxy-3-(dimethoxymethyl-1-[(1-hydroxycyclohexyl)methyl]benzene (25) (1.43 g, 51%) as a viscous oil, bp (bulb oven) $175^{\circ}\text{C}/0.1$ mm Hg; $\bar{\nu}_{\text{max}}$ 3505, 1603, 1485, 1462, 1434, 1365, 1273, and 1095 cm^{-1} . (Found: C, 66.6; H, 8.7; $\text{C}_{18}\text{H}_{28}\text{O}_8$ requires C, 66.6; H, 8.7%.)

3-(1-Hydroxycyclohex-1-yl)methyl-2,4-dimethoxybenzaldehyde (26).- The acetal (25) (1.19 g, 3.7 mmol) was treated with Amberlyst 15 (H^{+}) resin (255 mg) in water (0.55 ml) in acetone (30 ml) at room temperature for 45 min, before filtering and evaporating the filtrate. The residue was chromatographed, using ether as eluant, to give the title aldehyde (0.98 g, 96%) as a pale yellow oil, $\bar{\nu}_{\text{max}}$ 3540, 1675, 1587, 1275, 1255, and 1094 cm^{-1} ; δ (^1H , 90 MHz) 1.49 (10 H, m, cyclohexyl H), 2.89 (2 H, s, ArCH_2), 2.89 (1 H, s, exchanged by D_2O , OH), 3.88 (3 H, s, ArOMe), 3.91 (3 H, s, ArOMe), 6.7 (1 H, d, J 8.8 Hz, 5-H), 7.75 (1H, d, J 8.8Hz, 6-H), 10.19 (1 H, s, CHO). (Found: C, 68.9; H, 8.0; $\text{C}_{18}\text{H}_{22}\text{O}_4$ requires C, 69.0; H, 8.0%.)

2,3-Dihydro-4-methoxybenzo[b]furan-7-carboxaldehyde-2-spirocyclohexane (27).- Sodium hydride (17 mg, 60% in oil, 0.42 mmol) was added to a solution of the aldehyde (26) (52 mg, 0.2 mmol) in dry THF (8 ml) and the mixture heated at 60°C for 17 h. The reaction mixture was then poured into brine and extracted with chloroform (3 x 15 ml). The combined extracts were dried, filtered and evaporated and the residue chromatographed, using ether - light petroleum (1:7) as eluant, to give the title ether (44 mg, 94%) as a viscous oil, $\bar{\nu}_{\text{max}}$ 1670, 1611, 1586, 1435, 1285, 1257, and 1096 cm^{-1} ; δ (^1H , 400 MHz) 1.50 (4 H, m, CH_2), 1.68 - 1.73 (2 H, m, CH_2), 1.77 - 1.82 (2 H, m, CH_2), 1.86 - 1.91 (2 H, m, CH_2), 2.88 (2 H, d, J 0.7 Hz, ArCH_2), 3.89 (3 H, s, ArOMe), 6.46 (1 H, dt, J 8.8, 0.7 Hz, 5-H), 7.64 (1 H, dd, J 8.8, 0.6 Hz, 6-H), 10.10 (1 H, d, J 0.6 Hz, CHO). (Found: C, 73.2; H, 7.4; $\text{C}_{18}\text{H}_{18}\text{O}_3$ requires C, 73.2; H, 7.4%.)

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