Aust. J. Chem., 1995, **48**, 515–529

A Synthetic Approach to (±)-Tridentoquinone

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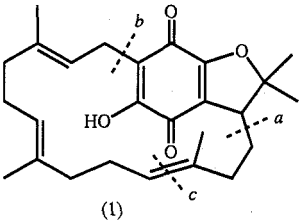
Abstract

Synthesis of the ansa-bridged benzofuranquinone (±)-tridentoquinone (±)-(1) is approached by construction of a C_4 methyl ketone chain at the 3-position of 6-bromo-4,5,7-trimethoxy-2,2-dimethyl-2,3-dihydrobenzofuran (10) and alkylation at its 6-position leading after modification to a dimethyl C_{10} aldehydic chain. Closure of the ansa bridge by McMurry coupling of the aldehyde and ketone groups of the intermediate (33) with $C_8K/TiCl_3$ appears to occur, but in poor yield and with uncertain stereochemistry, and the synthesis has not been completed.

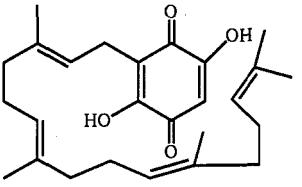
Introduction

The edible European mushroom *Suillus tridentinus* contains several orange and orange-red compounds including grevillin-B, grevillin-C, and tridentoquinone (1).[1] The species *S. bovinus* contains a benzoquinone, bovinone,[2] which when arbitrarily drawn as in (2) can be seen to be plausibly related to tridentoquinone (2) by biosynthetic cyclization. Indeed, Steglich and his coworkers have attempted biosynthetic experiments aimed at the conversion of bovinone (2) or its terminal epoxide into tridentoquinone, so far without success.[3] We report here our progress towards synthesis of tridentoquinone.

We were attracted to the unusual ansa-bridged structure of tridentoquinone as a synthetic target because it offered an interesting combination of isoprenoid



(1)



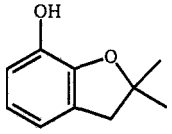
(2)

[1] Besl, H., Hecht, H.-J., Luger, P., Pasupathy, V., and Steglich, W., *Chem. Ber.*, 1975, **108**, 3675.
[2] Beaumont, P. C., and Edwards, R. L., *J. Chem. Soc. C*, 1969, 2398.
[3] Steglich, W., personal communication to R.F.C.B., 1993; biosynthetic work is continuing.

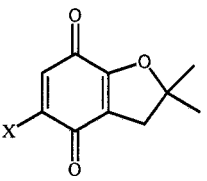
Manuscript received 3 November 1994 0004-9425/95/030515$05.00

and quinonoid chemistry, with many promising disconnections possible in the retrosynthetic analysis.

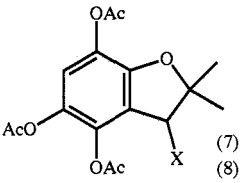
We finally based our approach on the commercial availability of 2,2-dimethyl-2,3-dihydrobenzofuran-7-ol (3); this implied the addition of chains to the benzofuran ring at disconnection points marked *a* and *b* in (1), and a further disconnection point in the ansa chain. For the last we chose to use disconnection *c*, which fixed the nature of the final reaction leading to ring closure. With C_4 and dimethyl C_{10} chains in position and bearing suitably placed carbonyl groups, the ansa ring might be closed by McMurry coupling with low-valent titanium[4,5] to form the double bond marked *c* in (1). Tridentoquinone contains one chiral centre, but it has not proved possible to introduce chiral selectivity into the sequence and all the compounds described are racemic.



(3)



(4) X = H
(5) X = OH
(6) X = OMe



(7) X = H
(8) X = Br

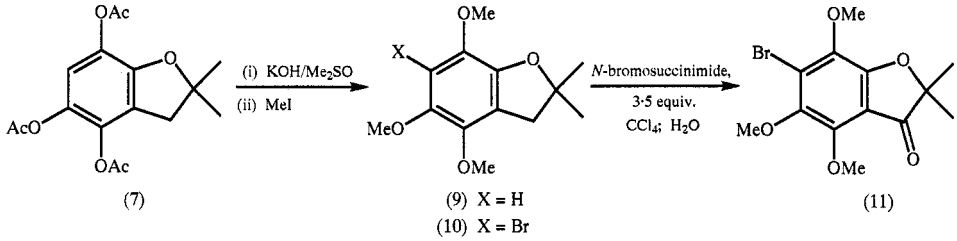
Synthesis of 6-Bromo-4,5,7-trimethoxy-2,2-dimethyl-2,3-dihydrobenzofuran-3-one (11)

The title benzofuranone (11) was a key intermediate because it contains (i) a carbonyl group suitable for adding a chain at C 3, (ii) bromine at C 6 well placed between two methoxy groups for lithiation by exchange and subsequent alkylation with a second chain, and (iii) methoxy groups which might be oxidatively removed at C 4 and C 7 to form a 4,7-quinone. Oxidation of the benzofuranol (3) (Aldrich) with Fremy's salt gave the quinone (4) which had been used previously in our mycorrhizin A work.[6] Thiele–Winter acetoxylation[7] of the quinone (4) with acetic anhydride and sulfuric acid at −10° gave the 4,5,7-triacetate (7) in 75% yield. The orientation of acetate addition (at C 5) was assigned following the work of Friess *et al.*[8] on the corresponding reaction of 2-methoxybenzoquinone; this showed that an electron-donating substituent at C 2 directed acetate addition to C 5. In quinone (4) the electron donor is the dihydrofuran ring oxygen.

Bromination of the triacetate (7) with *N*-bromosuccinimide in carbon tetrachloride afforded the 3-bromo derivative (8) (71%), but attempted further bromination to a 3,3-dibromo compound failed, as did attempted Kornblum oxidation[9] of (8) with dimethyl sulfoxide. Replacement of the acetoxy groups of (7) with methoxy groups was effected in one pot in 85% yield with powdered potassium

[4] McMurry, J. E., *Acc. Chem. Res.*, 1983, **16**, 405.
[5] McMurry, J. E., *Chem. Rev.*, 1989, **89**, 1513.
[6] Brown, R. F. C., Fallon, G. D., Gatehouse, G. M., Jones, C. M., and Rae, I. D., *Aust. J. Chem.*, 1982, **35**, 1665.
[7] McOmie, J. F. W., and Blatchly, J. M., *Org. React.*, 1972, **19**, 3.
[8] Friess, S. L., Soloway, A. H., Morse, B. K., and Ingersoll, W. C., *J. Am. Chem. Soc.*, 1952, **74**, 1305.
[9] Kornblum, N., Powers, J. W., Anderson, G. J., Jones, W. J., Larson, H. O., Levand, O., and Weaver, W. M., *J. Am. Chem. Soc.*, 1957, **79**, 6562.

hydroxide in dimethyl sulfoxide, followed by addition of methyl iodide (Scheme 1). The trimethoxy compound (9), an oil, could be oxidized with ceric ammonium nitrate in aqueous acetonitrile to the 5-methoxy 4,7-quinone (6) (74%) and this in turn could be demethylated with boron tribromide at −78° to the 5-hydroxy 4,7-quinone (5). The yield of crude (5) was satisfactory but that of pure material was poor (9%). Nevertheless, this sequence demonstrated that use of the three methoxy groups as protecting groups for the hydroxyquinone portion of the tridentoquinone molecule was a valid tactic.



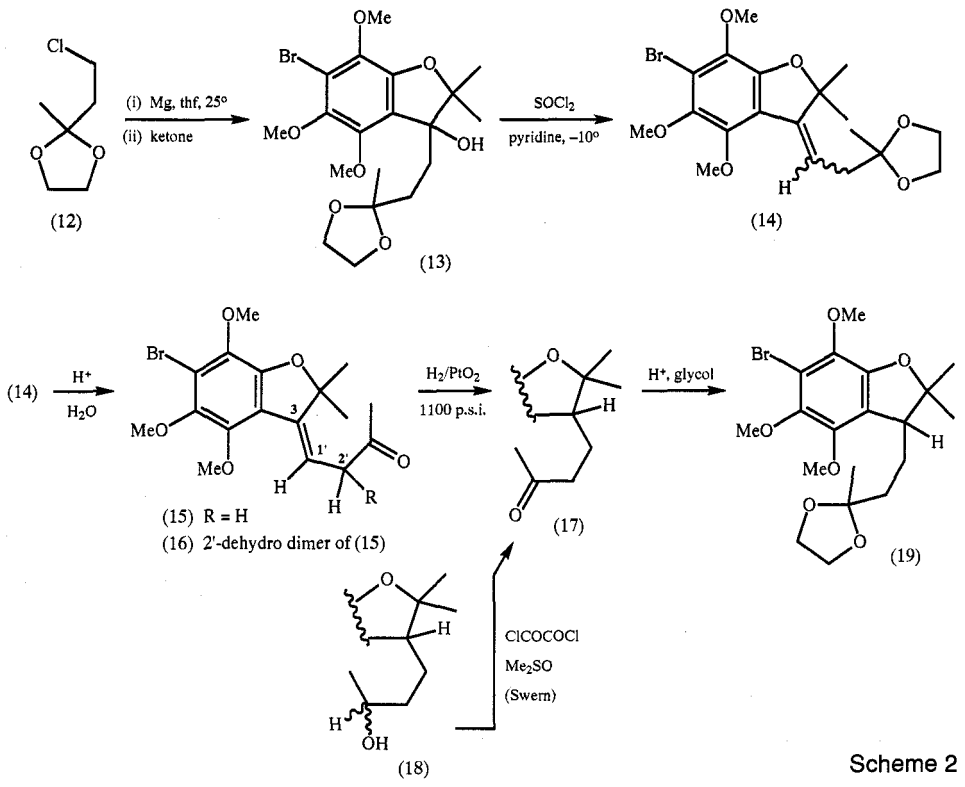
Scheme 1

Treatment of the trimethoxy compound (9) with 1·1 equiv. of *N*-bromosuccinimide led to the 6-bromo derivative (10) (67%) by electrophilic attack. With 3·5 equiv. of *N*-bromosuccinimide in boiling carbon tetrachloride further radical attack occurred to give an oil considered to be the crude 3,3,6-tribromo derivative. Hydrolysis of this oil in aqueous acetone (18 h, room temperature) gave the crystalline 6-bromobenzofuran-3-one (11), m.p. 82–82·5°, in 98% yield. The infrared spectrum of (11) showed strong absorption at 1717 cm^{-1}.

Attachment of the C_4 Chain to give 6-Bromo-3-(3,3-ethylenedioxybutyl)-4,5,7-trimethoxy-2,2-dimethyl-2,3-dihydrobenzofuran

We chose to add the C_4 chain by use of the Grignard reagent formed from 1-choro-3,3-ethylenedioxybutane (12), a halide readily obtainable from methyl vinyl ketone.[10] Generation of Grignard reagents in this system is somewhat capricious; rearrangement has been reported[11,12] and in some unsuccessful runs we obtained dimeric material. In runs where the temperature could be kept below 25°,[13] use of a threefold excess of magnesium activated with 1,2-dibromoethane was successful, and addition of the bromobenzofuranone (11) to the Grignard reagent in tetrahydrofuran (thf) gave the benzofuranol (13), bearing the required C_4 chain, in 90% yield. Dehydration of this tertiary alcohol occurred partially on attempted distillation, but could be effected more satisfactorily with thionyl chloride and pyridine at −10° (Scheme 2). The product was a mixture of *E* and *Z* isomers (1 : 3·5) of the alkene (14) (92%); the assignment of the *Z* stereochemistry of the major product was based on deshielding of the olefinic proton (δ 6·5 *v.* 5·4) by the aromatic ring.

[10] Gil, G., *Tetrahedron Lett.*, 1984, **25**, 3805.
[11] Feugeas, C., *Bull. Soc. Chim. Fr.*, 1963, 2568.
[12] Giusti, G., *Bull. Soc. Chim. Fr.*, 1972, 753.
[13] Ponaras, A. A., *Tetrahedron Lett.*, 1976, 3105.



Scheme 2

The next step needed was hydrogenation of the alkene (14) to give a saturated chain. We had hoped to achieve this under conditions which might have permitted chiral reduction of a single geometric isomer. In practice we were unable to reduce this sterically congested C=C bond cleanly with either chemical or catalytic methods. Lithium and ethylenediamine[14] mainly attacked the aromatic ring, diimide gave no reduction, and a range of low and high pressure, medium temperature catalytic hydrogenations failed. During about a year of experimentation we had some success with the combination $H_2/PtO_2/EtOAc/HClO_4/80°/50$ p.s.i., but this gave the alcohol (18) accompanied by its acetate, its ethyl ether, and what appeared to be a 3-butyl derivative of benzofuran (10). These experiments are not reported here; attempts to reduce (14) directly were finally abandoned.

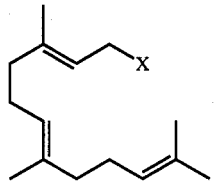
Hydrolysis of the acetal function of alkene (14) was achieved with 2 M sulfuric acid and acetone to give the unconjugated enone (15) (53%). The yield was somewhat reduced by concurrent formation of a dehydro dimer (16) by oxidation of C 2′ of (15). Enone (15) proved to be a single stereoisomer, assigned *Z*-stereochemistry on chemical shift and n.O.e. evidence. It was successfully hydrogenated under severe conditions ($H_2/PtO_2/EtOAc/80°/1100$ p.s.i.) to give the saturated ketone (17) (81%) accompanied by the secondary alcohol (18) (14%). More of the ketone could be obtained by Swern oxidation of the secondary alcohol (18). Reprotection of the carbonyl group of (17) with ethylene glycol

[14] Markgraf, J. H., Staley, S. W., and Allen, T. R., *Synth. Commun.*, 1989, **19**, 1471.

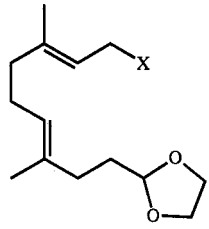
and toluenesulfonic acid gave the saturated acetal (19) which we had signally failed to make by direct hydrogenation.

Attachment of the C_{12} Chain at C6 of the Bromobenzofuran (19)

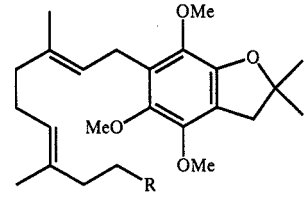
The dimethyl C_{10} chain running from *b* to *c* of structure (1) might in principle be constructed by a two-carbon extension of geranyl compounds (C_{10}) or by cleavage of three carbons from farnesol (21) or derivatives (C_{15}). We chose the C_{15} approach and, in the first instance, we attempted to use as an alkylating agent the allylic bromide (25), obtained via the alcohol (24) and the acetate (23) derived from van Tamelen terminal oxidation and cleavage of farnesyl acetate (20).[15–19] The alcohol (24) with triphenylphosphine and carbon tetrabromide yielded the crude bromide (25) in *c.* 87% yield, but this bromide was unstable and very susceptible to hydrolysis, and was used shortly after preparation.



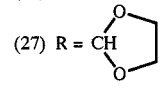
(20) X = OAc
(21) X = OH
(22) X = Br



(23) X = OAc
(24) X = OH
(25) X = Br



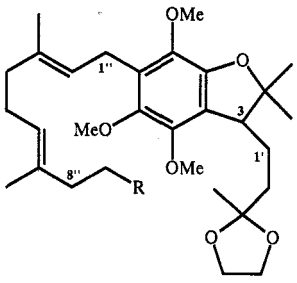
(26) R = CH=CMe$_2$ (6-farnesyl compound)



The conditions used for alkylation were established through model experiments. The trimethoxybenzofuran (9) in ether was lithiated with butyllithium with careful regulation of temperature (−78°; 0°; −78°), and the allylic bromide and catalytic amount of Li_2CuCl_4 in tetrahydrofuran were added, also at −78° (the method of Schmid *et al.*[20]). Farnesyl bromide gave the 6-farnesyl compound (26) in 43% yield, with 50% recovery of starting material (9), but under the same conditions the bromide (25) bearing an acetal function failed to give any alkylation product (27). The reason for this failure is still uncertain, but it led us to modify tactics by introducing a C_{15} (farnesyl) chain at C6 of the benzofuran system and applying van Tamelen oxidation and cleavage to the resulting 6-farnesylbenzofuran.

In the final series of experiments the bromobenzofuran (19), bearing the protected C_4 chain, was lithiated by exchange with butyllithium, and the 6-lithio derivative was alkylated with farnesyl bromide (2 equiv.) in the presence of Li_2CuCl_4. The 6-farnesyl derivative (28) was obtained in 33% yield, with 67% recovery of the benzofuran C_4 system as the debrominated compound (32). Now

[15] Sharpless, K. B., Hanzlik, R. P., and van Tamelen, E. E., *J. Am. Chem. Soc.*, 1968, **90**, 209.
[16] Hanzlik, R. P., *Org. Synth.*, 1977, **56**, 112.
[17] van Tamelen, E. E., *Acc. Chem. Res.*, 1968, **1**, 111.
[18] Sakai, T., and Mori, K., *Agric. Biol. Chem.*, 1986, **50**, 177.
[19] Stenberg, V. I., and Kubik, D. A., *J. Org. Chem.*, 1974, **39**, 2815.
[20] Schmid, R., Antoulas, S., Rüttimann, A., Schmid, M., Vecchi, M., and Weiser, H., *Helv. Chim. Acta*, 1990, **73**, 1276.

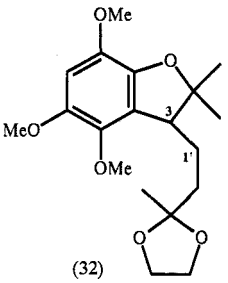


(28) R = CH=CMe$_2$

(29) R = CH(Br)–C(OH)(Me)–Me

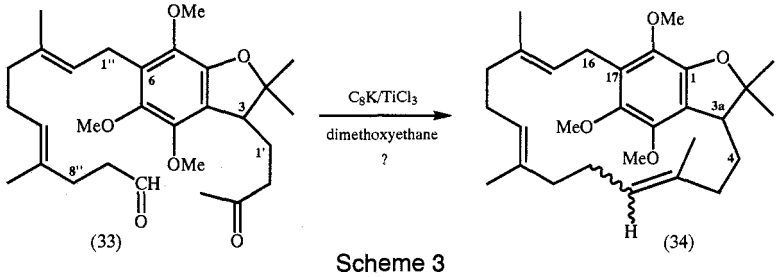
(30) R = CH(epoxide)–C(Me)(Me)

(31) R = CHO



(32)

van Tamelen oxidation of the 6-farnesyl compound (28) with *N*-bromosuccinimide in aqueous tetrahydrofuran gave the bromohydrin (29) (55%) with some recovery of starting material. The bromohydrin was cyclized with potassium carbonate in methanol to the epoxide (30) in 60% yield. The epoxide was hydrated and cleaved in one step by treatment with periodic acid dihydrate in tetrahydrofuran and ether at 0°; the crude product, mainly (31), had undergone some loss of the ethylenedioxy protecting group on the C_4 chain, and this hydrolysis was completed with 2 M sulfuric acid and acetone. In this way the keto aldehyde (33) (52%) was obtained as a colourless film which had the correct composition $C_{29}H_{42}O_6$ as determined by high-resolution mass spectrometry. Its infrared spectrum showed broad absorption at 1717 cm^{-1} (2×CO) and anomalous hydroxyl absorption at 3429 cm^{-1}, and the ^1H n.m.r. spectrum showed reduced intensity for the aldehyde proton although other signals were as expected. The ^{13}C n.m.r. spectrum was fully consistent with structure (33) although unidentified impurity signals were seen for the product of one run. We speculate that the anomalous features of the infrared and ^1H n.m.r. spectra may be due to partial hydration or condensation reactions of the aldehyde.



(33) (34)

Scheme 3

Attempted Cyclization of Keto Aldehyde (33) (Scheme 3)

The keto aldehyde (33) was used in an attempted McMurry cyclization. Low-valent titanium was generated in 1,2-dimethoxyethane under argon by reduction of titanium trichloride with potassium graphite.[21] The efficacy of the reagent was tested with benzophenone, which gave tetraphenylethene in 88% yield (lit.[21] 89–91%). For the cyclization attempt a 0·01 M solution of the keto aldehyde (33)

[21] Clive, D. L. J., Zhang, C., Murthy, K. S. K., Hayward, W. D., and Daigneault, S., *J. Org. Chem.*, 1991, **56**, 6447.

in dimethoxyethane was added by syringe pump over 20 h to a refluxing slurry of the titanium reagent in dimethoxyethane. The product formed under these high dilution conditions consisted of a group of polar materials and a more mobile fraction (t.l.c.). The latter was isolated by chromatography as a colourless film which showed a strong molecular ion at m/z 454 corresponding to the composition of the cyclized product (34), $C_{29}H_{42}O_4$. This composition was confirmed by high-resolution mass spectrometery. The yield of this fraction from 96 mg of keto aldehyde (33) was 10 mg (11%). Although it was apparently homogeneous on t.l.c., its ^{1}H n.m.r. spectrum showed a poorly resolved C=C–H region and a methoxyl region which contained at least eight lines. Further, there was a weak aromatic proton signal which suggested some reductive demethoxylation of the aromatic ring, although the rather clean mass spectrum failed to confirm this.

Formation of both E and Z isomers of the new double bond in the macrocycle (34) is to be expected and could give rise to up to six signals from the olefinic protons and up to six from the methoxy groups. A preference for the required E stereochemistry has generally been found in the synthesis of 10-membered and larger rings by McMurry coupling.[22–24] If the complexity of the methoxyl region of the fraction is substantially due to E/Z isomerism this stereochemical preference cannot be very marked in the present reaction.

We conclude that cyclized products (34) were present in the fraction obtained, but that separation of individual compounds would require more sophisticated chromatographic methods than those used above. Other methods of generation of the McMurry titanium reagent might produce a more useful yield of cyclized material, but unfortunately funds were not available to permit further work on this project.

Experimental

Melting points are uncorrected. Microanalyses were performed by National Analytical Laboratories, Melbourne. Infrared spectra were recorded with either Jasco IRA-1 or Perkin–Elmer 1600 FT-IR spectrophotometers, and ultraviolet spectra of solutions in 95% ethanol with a Hitachi 150-20 instrument. In most cases strong or structurally significant infrared bands are reported. ^{1}H n.m.r. spectra were measured at 200 MHz with a Bruker AC200 spectrometer, and ^{13}C n.m.r. spectra were measured at 50·3 or 75·5 MHz with Bruker AC200 or AM300 spectrometers. ^{13}C n.m.r. signals were assigned to CH_n groups by use of DEPT or JMODXH sequences. Assignment of carbon signals in isoprenoid compounds was based on the published assignments of the spectrum of (E,E)-farnesol.[25]

Low-resolution mass spectra were measured at 70 eV with a V.G. Micromass 7070F or a V.G. Trio 1 spectrometer; the former was used for accurate mass measurements. Most mass spectra have been edited to show only the molecular ion, strong high-mass peaks and the base peak.

Bulb-to-bulb distillations were carried out with a Büchi GKR-50 oven. Merck Kieselgel 60 (No. 9385, 230–400 mesh) was used for column chromatography, and Polygram silica gel/UV254 precoated plastic sheets for thin-layer chromatography (t.l.c.). Compounds were detected under ultraviolet light, by exposure to iodine or ammonia vapour, and by spraying with vanillin (1·5%) in ethanol/H_2SO_4 (95:5) followed by heating.

[22] McMurry, J., Matz, J. R., Kees, K. L., and Bock, P. A., *Tetrahedron Lett.*, 1982, **23**, 1777.
[23] McMurry, J. E., Rico, J. G., and Shih, Y., *Tetrahedron Lett.*, 1989, **30**, 1173.
[24] McMurry, J. E., and Rico, J. G., *Tetrahedron Lett.*, 1989, **30**, 1169.
[25] Jautelat, M., Grutzner, J. B., and Roberts, J. D., *Proc. Natl Acad. Sci. U.S.A.*, 1970, **65**, 288.

In most of the following experiments crude products were isolated after addition of water by extraction with dichloromethane or diethyl ether, but descriptions of the washing and drying procedures have been omitted as repetitive. Generally the combined organic extracts were washed with aqueous $NaHCO_3$ (when appropriate), water or brine, then dried ($MgSO_4$ or K_2CO_3) and evaporated (rotary evaporator below 50°).

2,2-Dimethyl-2,3-dihydrobenzofuran-4,5,7-triyl Triacetate (7)

A solution of 2,2-dimethyl-2,3-dihydrobenzofuran-4,7-dione (4) (400 mg, 2·25 mmol) in acetic anhydride (35 ml) was stirred and cooled to −10°. Concentrated sulfuric acid (5 drops) was then added at 30 min intervals until thin-layer chromatography showed the absence of starting material. The reaction mixture was then allowed to warm to room temperature and was stirred for a further 18 h. Sodium bicarbonate was added and the reaction mixture was cautiously poured onto crushed ice and sodium bicarbonate. Extraction with dichloromethane (×3), and evaporation of the washed ($NaHCO_3$) and dried (Na_2SO_4) extract gave a yellow-brown oil (0·78 g) which partially crystallized on cooling. Trituration with diethyl ether gave the crude triacetate (7) as an off-white solid (0·63 g) which was recrystallized from diethyl ether to afford *4,5,7-triacetate* (7) (0·54 g, 75%) as a colourless solid, m.p. 145° (Found: C, 59·2; H, 5·5. $C_{16}H_{18}O_7$ requires C, 59·6; H, 5·6%). ν_{max} (KBr) 1760s(br) cm^{-1} (ArOAc). ^1H n.m.r. δ ($CDCl_3$) 6·77, s, H6; 2·95, s, H3; 2.29, s, $COCH_3$; 2·25, s, $COCH_3$×2; 1·48, s, CH_3×2. ^{13}C n.m.r. δ 168·5, 168·0, 167·1, CO×3; 148·6, 136·7, 134·6, 131·2, 122·9, C3a,4,5,7,7a; 116·3, C6; 89·8, C2; 41·4, C3; 28·1, CH_3×2; 20·7, 20·5, 20·4, $COCH_3$×3. Mass spectrum: *m/z* 322 (M, 4%), 280 (9), 238 (21), 196 (100), 177 (9), 69 (9).

The crude solid obtained by trituration with diethyl ether could also be purified by sublimation (130°/2×10^{-4} mmHg).

3-Bromo-2,2-dimethyl-2,3-dihydrobenzofuran-4,5,7-triyl Triacetate (8)

The triacetate (7) (250 mg, 0·776 mmol) and *N*-bromosuccinimide (148 mg, 0·832 mmol) in carbon tetrachloride (20 ml) were heated at reflux and irradiated with a Philips sunlamp. After 3·5 h, thin-layer chromatography indicated a higher R_F spot but still showed the presence of starting material (7). Additional *N*-bromosuccinimide (50 mg, 0·28 mmol) was added and irradiation was continued for 2 h. The cooled suspension was filtered, and the filtrate was evaporated.

Trituration of the semisolid residue with diethyl ether afforded in three crops *3-bromo-2,2-dimethyl-2,3-dihydrobenzofuran-4,5,7-triyl triacetate* (8) (220 mg, 71%) as colourless needles, m.p. 135° (Found: M^+, 400·015±0·004. $C_{16}H_{17}{}^{79}BrO_7$ requires M^+, 400·016). ν_{max} (KBr) 1768s(br) cm^{-1} (ArOAc). ^1H n.m.r. δ ($CDCl_3$) 6·94, s, H6; 5·26, s, H3; 2·33, 2·29, 2·26, 3×s, $COCH_3$×3; 1·70, 1·49, 2×s, CH_3×2. ^{13}C n.m.r. δ 168·2, 167·7, 166·9, CO×3; 148·0, 136·6, 135·5, 131·8, 123·0, C3a,4,5,7,7a; 119·1, C6; 90·7, C2; 55·9, C3; 26·7, 26·2, CH_3×2; 20·6, 20·5, 20·4, $COCH_3$×3. Mass spectrum: *m/z* 402, 400 (M, <1%), 196 (58), 194 (100). The bromo triacetate (8) darkened rapidly at room temperature and slowly at 0°.

4,5,7-Trimethoxy-2,2-dimethyl-2,3-dihydrobenzofuran (9)

A degassed solution of 2,2-dimethyl-2,3-dihydrobenzofuran-4,5,7-triyl triacetate (7) (500 mg, 1·55 mmol) in dry dimethyl sulfoxide (25 ml) was added via cannula to a suspension of powdered potassium hydroxide (860 mg, 15·3 mmol) in dry dimethyl sulfoxide (5 ml). The mixture was stirred at room temperature for 18 h under an atmosphere of nitrogen. Methyl iodide (0·61 ml, 9·8 mmol) was then injected via syringe, and the reaction mixture was stirred for a further 10 min.

Dilution with water, and extraction with diethyl ether gave an oil (329 mg), which on bulb-to-bulb distillation (130°/0·2 mmHg) gave *4,5,7-trimethoxy-2,2-dimethyl-2,3-dihydrobenzofuran* (9) (313 mg, 85%) as a pale yellow oil (Found: C, 65·2; H, 7·5. $C_{13}H_{18}O_4$ requires C, 65·5; H, 7·6%). ν_{max} (film) 2971s, 2934s, 2838m, 1617m, 1498s, 1454s, 1434s cm^{-1}. ^1H n.m.r. δ ($CDCl_3$) 6·43, s, H6; 3·84, 3·82, 3·81, 3×s, OCH_3×3; 3·06, s, H3; 1·50, s, CH_3×2. ^{13}C n.m.r. δ 145·8, 141·8, 140·0, 139·6, 120·6, C3a,4,5,7,7a; 99·7, C6; 87·7, C2; 60·4, 57·5, 56·6, OCH_3×3; 41·4, C3; 28·2, CH_3×2. Mass spectrum: *m/z* 238 (M, 100%), 223 (33), 191 (63), 162 (14).

5-Methoxy-2,2-dimethyl-2,3-dihydrobenzofuran-4,7-dione (6)

A solution of ceric ammonium nitrate (1·76 g, 3·18 mmol) in water (4 ml) was added dropwise over 25 min to a stirred solution of the trimethoxybenzofuran (9) (316 mg, 1·33 mmol) in acetonitrile (10 ml). The solution was stirred for 19 h at room temperature, the acetonitrile was evaporated and the aqueous residue was extracted with dichloromethane. The extract yielded a dark red semisolid (212 mg). Column chromatography (alumina, 1:1 light petroleum/ethyl acetate) gave *5-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran-4,7-dione* (6) (204 mg, 74%) which was recrystallized from light petroleum as orange needles, m.p. 190–191° (Found: C, 63·6; H, 6·1. $C_{11}H_{12}O_4$ requires C, 63·5; H, 5·8%). ν_{max} (KBr) 1662s, 1650s, 1624m, 1583s cm^{-1}. λ_{max} (EtOH) 298 nm (log ϵ 3·84). ^1H n.m.r. δ ($CDCl_3$) 5·60, s, H6; 3·84, s, OCH_3; 2·87, s, H3; 1·55, s, $CH_3\times2$. ^{13}C n.m.r. δ ($CDCl_3$) 180·0, 178·5, C4,7; 161·0, 158·6, 117·6, C3a,5,7a; 104·1, C6; 93·2, C2; 56·8, OCH_3; 39·4, C3; 28·3, $CH_3\times2$. Mass spectrum: *m/z* 208 (M, 33%), 193 (24), 180 (25), 165 (36), 69 (100).

5-Hydroxy-2,2-dimethyl-2,3-dihydrobenzofuran-4,7-dione (5)

A solution of boron tribromide in dichloromethane (1·0 M, 0·98 ml, 0·98 mmol) was added via syringe to a cooled (−78°) and stirred solution of the methoxy quinone (6) (68 mg, 0·33 mmol) in dichloromethane (7 ml), and the mixture was allowed to warm to room temperature over 1·5 h. The solution was then extracted with 10% sodium bicarbonate solution (10 ml), and the red aqueous extract was acidified (pH = 1; 1 M HCl). Continuous extraction of the aqueous phase with dichloromethane over 12 h, and subsequent rotary evaporation of the extract afforded crude hydroxy quinone (5) (91 mg) as an orange solid. Recrystallization from light petroleum/dichloromethane gave in low yield *5-hydroxy-2,2-dimethyl-2,3-dihydrobenzofuran-4-7-dione* (5) (6 mg, 9%) as orange needles, m.p. 127–128° (Found: C, 61·7; H, 5·4. $C_{10}H_{10}O_4$ requires C, 61·9; H, 5·2%). ν_{max} (KBr) 3309s, 1624s, 1594s, 1358s, 1336s, 1190s cm^{-1}. λ_{max} (EtOH) 294 (log ϵ 4·08), 498 nm (2·95). ^1H n.m.r. δ ($CDCl_3$) 8·15, br s, exch. D_2O, OH; 6·05, s, H6; 2·72, s, H3; 1·29, s, $CH_3\times2$. ^{13}C n.m.r. (C4,7 not observed) δ ($CDCl_3$) 157·1, C7a; 113·4, C3a; 103·1, C6; 94·3, C2; 72·8, C5; 36·1, C3; 29·5, $CH_3\times2$. Mass spectrum: *m/z* 194 (M, 44%), 179 (35), 154 (74), 151 (31), 69 (100).

6-Bromo-4,5,7-trimethoxy-2,2-dimethyl-2,3-dihydrobenzofuran (10)

N-Bromosuccinimide (452 mg, 2·54 mmol) was added to a stirred solution of the trimethoxybenzofuran (9) (549 mg, 2·31 mmol) in carbon tetrachloride (50 ml). After 18 h at room temperature additional *N*-bromosuccinimide (50 mg, 0·28 mmol) was added and the mixture was heated to reflux for 1 h, cooled and then filtered. The filtrate yielded a red-brown oil (866 mg) which on column chromatography (silica gel, 4:1 light petroleum/ethyl acetate) afforded *6-bromo-4,5,7-trimethoxy-2,2-dimethyl-2,3-dihydrobenzofuran* (10) (488 mg, 67%) as a light yellow oil (Found: C, 49·5; H, 5·5. $C_{13}H_{17}BrO_4$ requires C, 49·2; H, 5·4%). ν_{max} (film) 2972s, 2936s, 2871m, 2837m, 1600m, 1471s, 1450s, 1413s cm^{-1}. ^1H n.m.r. δ ($CDCl_3$) 3·87, 3·86, 3·80, 3×s, $OCH_3\times3$; 3·01, s, H3; 1·50, s, $CH_3\times2$. ^{13}C n.m.r. δ ($CDCl_3$) 147·4, 145·9, 143·2, 137·1, 119·6, 111·1, C3a,4,5,6,7,7a; 88·4, C2; 60·8, 60·22, 60·17, $OCH_3\times3$; 40·9, C3; 28·0, $CH_3\times2$. Mass spectrum: *m/z* 318, 316 (M, 100%), 303 (66), 301 (71).

6-Bromo-4,5,7-trimethoxy-2,2-dimethyl-2,3-dihydrobenzofuran-3-one (11)

N-Bromosuccinimide (1·94 g, 10·9 mmol) was added to a stirred solution of 4,5,7-trimethoxy-2,2-dimethyl-2,3-dihydrobenzofuran (9) (742 mg, 3·12 mmol) in carbon tetrachloride (25 ml). The mixture was heated at reflux and irradiated with a 450 W projection lamp for 3 h, and then left to stir for 18 h at room temperature. Examination of a sample by ^1H n.m.r. showed that a 3,6-dibromo compound (δ 3-CHBr 5·25) was still present. The mixture was irradiated and heated at reflux for a further 1·5 h before being cooled in ice, filtered, and evaporated to an orange oil (crude tribromo compound). The oil was dissolved in acetone (30 ml); the solution was diluted with water (20 ml), and stirred for 18 h at room temperature. The acetone was then removed in vacuum and the aqueous residue was extracted with dichloromethane (×3). The combined extract was evaporated to give a light orange oil (1·06 g) which solidified

on standing. Column chromatography (silica gel, 3:1 light petroleum/ethyl acetate) afforded *6-bromo-4,5,7-trimethoxy-2,2-dimethyl-2,3-dihydrobenzofuran-3-one* (11) (1·01 g, 98%) as a pale yellow solid that could be used without further purification, m.p. 82·0–82·5° (Found: C, 47·2; H, 4·5. $C_{13}H_{15}BrO_5$ requires C, 47·2; H, 4·6%). ν_{max} (film) 1717 cm^{-1} (C=O). ^1H n.m.r. δ ($CDCl_3$) 4·09, 3·97, 3·84, 3×s, OCH_3×3; 1·50, s, CH_3×2. ^{13}C n.m.r. δ ($CDCl_3$) 200·7, C 3; 159·0, 146·5, 143·7, 139·1, 124·0, 112·5, C 3a,4,5,6,7,7a; 88·7, C 2; 62·3, 61·4, 60·8, OCH_3×3; 23·2, CH_3×2. Mass spectrum: *m/z* 332, 330 (M, 100%), 317, 315 (52), 289 (13), 287 (16).

1-Chloro-3,3-ethylenedioxybutane (12)

This halide was prepared by the method A of Gil[10] from methyl vinyl ketone (1·66 ml, 19·9 mmol), ethylene glycol (2·22 ml, 39·8 mmol) and trimethylsilyl chloride (5·57 ml, 43·9 mmol) in dichloromethane (10 ml). This gave the chloride (12) as a colourless liquid (2·28 g, 76%), b.p. 70°/20 mm. ^1H n.m.r. δ ($CDCl_3$) 4·00–3·85, m, OCH_2CH_2O; 3·58, t, *J* 8·0 Hz, CH_2Cl; 2·17, t, *J* 8·0 Hz, CH_2; 1·34, s, CH_3. Mass spectrum: *m/z* (M absent); 137, 135 (10, 32%), M − CH_3; 87 (100).

6-Bromo-3-(3,3-ethylenedioxybutyl)-4,5,7-trimethoxy-2,2-dimethyl-2,3-dihydrobenzofuran-3-ol (13)

Under an atmosphere of nitrogen, 1,2-dibromoethane (0·24 ml, 2·8 mmol) was added to a stirred suspension of magnesium turnings (1·03 g, 42·3 mmol) in anhydrous tetrahydrofuran (8 ml). After the initial exothermic reaction had subsided, 1-chloro-3,3-ethylenedioxybutane (12) (2·12 g, 14·1 mmol) and 1,2-dibromoethane (0·24 ml, 2·8 mmol) in dry tetrahydrofuran (5 ml) were added dropwise over 55 min below 25°. The reaction mixture was then stirred at room temperature for 18 h before being filtered under nitrogen into a stirred solution of 6-bromo-4,5,7-trimethoxy-2,2-dimethyl-2,3-dihydrobenzofuran-3-one (11) (1·55 g, 4·68 mmol) in anhydrous tetrahydrofuran (8 ml). The mixture was stirred at room temperature for 24 h, then quenched by the addition of saturated ammonium chloride solution (10 ml) and water (10 ml). Extraction with diethyl ether yielded crude alcohol (13) (2·1 g) which was purified by column chromatography (silica gel, 1:1 light petroleum/ethyl acetate) to give the *title benzofuranol* (13) (1·89 g, 90%) as a colourless oil (Found: M^+, 446·094±0·004. $C_{19}H_{27}{}^{79}BrO_7$ requires M^+, 446·094). ν_{max} (film) 3449s(br) cm^{-1} (OH). ^1H n.m.r. δ ($CDCl_3$) 4·00, s, OCH_2CH_2O; 3·98, 3·93, 3·86, 3×s, OCH_3×3; 3·30–2·90, br s, exch. D_2O, OH; 2·50–2·15, m, 1H, H 1′; 2·05–1·70, m, 3H, H 1′,2′; 1·46, 1·42, 2×s, CH_3×2; 1·34, s, H 4′. ^{13}C n.m.r. δ ($CDCl_3$) 146·7, 146·2, 144·2, 138·2, 125·8, 113·0, C 3a,4,5,6,7,7a; 109·9, C 3′; 93·0, C 2; 82·9, C 3; 64·7, OCH_2CH_2O; 61·2, 60·7, 60·4, OCH_3×3; 33·0, C 2′; 29·5, C 1′; 23·9, C 4′; 23·0, 22·7, *gem* CH_3×2. Mass spectrum: *m/z* 448, 446 (M, 5%), 333, 331 (12), 288, 286 (11), 87 (100). Attempted purification of the title alcohol (13) by distillation (200°/10^{-3} mmHg) resulted in partial decomposition to alkene (14).

6-Bromo-3-(3,3-ethylenedioxybutylidene)-4,5,7-trimethoxy-2,2-dimethyl-2,3-dihydrobenzofuran (14)

To a cooled solution (−50°) of the hydroxy acetal (13) (45 mg, 1·0 mmol) in anhydrous pyridine (3 ml) was added freshly distilled thionyl chloride (0·11 ml, 1·5 mmol). The mixture was then stirred at −10° for 3 h before being poured onto ice (30 g), and extracted with diethyl ether (×3). The combined organic extract was washed with water (×2), dried (K_2CO_3) and evaporated to a yellow oil (45 mg). Column chromatography (silica gel, 2:1 light petroleum/ethyl acetate) then yielded 6-bromo-3-(3,3-ethylenedioxybutylidene)-4,5,7-trimethoxy-2,2-dimethyl-2,3-dihydrobenzofuran (14) (41 mg, 92%), a colourless oil, as a mixture of *E* and *Z* isomers (1:3·5 by ^1H n.m.r.). ν_{max} (film 2927s, 2854m, 1588w, 1472s, 1415s, 1376w, 1263m, 1118m, 1054s cm^{-1}. ^1H n.m.r. δ ($CDCl_3$) 6·46, t, *J* 8·0 Hz, H 1′ of *Z* isomer; 5·36, t, *J* 7·4 Hz, H 1′ of *E* isomer; 4·00, s, OCH_2CH_2O; 3·89, 3·87, 3·82, 3×s, OCH_3×3; 3·02, d, *J* 7·4 Hz, H 2′ of *E* isomer; 2·62, d, *J* 8·0 Hz, H 2′ of *Z* isomer; 1·62, s, CH_3×2; 1·40, s, H 4′. Mass spectrum: *m/z* 430, 428 (M, <1%), 415, 413 (M − CH_3, <1), 343, 341 (<1), 333, 331 (<1), 87 (100). This alkene was unstable and was used promptly after isolation.

*(Z)-6-Bromo-4,5,7-trimethoxy-2,2-dimethyl-3-(3-oxobutylidene)-2,3-dihydrobenzofuran (15)**

Crude 6-bromo-3-(3,3-ethylenedioxybutylidene)-4,5,7-trimethoxy-2,2-dimethyl-2,3-dihydrobenzofuran (14) (1·75 g, 3·91 mmol) in acetone (10 ml) containing 2 M sulfuric acid (8 ml) was stirred at room temperature for 18 h. The mixture was then neutralized with 2 M sodium hydroxide solution, and the acetone was removed in vacuum. Extraction with diethyl ether yielded an orange-brown oil (1·26 g). Column chromatography (silica gel, 1·5:1 light petroleum/ethyl acetate) of this oil gave first a dimeric fraction and later the monomeric enone (15). The dimeric fraction (70 mg) crystallized on stirring with light petroleum to give 3,4-bis[(6-bromo-4,5,7-trimethoxy-2,2-dimethyl-2,3-dihydrobenzofuran-3-ylidene)methyl]hexane-2,5-dione (16) as a pale yellow solid, m.p. 198–200°. ^{1}H n.m.r. δ ($CDCl_3$) 6·12, apparent dd, J 9·6, 2·4 Hz, C=CH×2; 4·13, apparent dd, J 9·3, 2·8 Hz, COCH–CHCO; 3·84, 3·81, 3·73, 3×s, OCH_3×6; 2·30, s, $COCH_3$×2; 1·79, s, CH_3×2; 1·60, s, CH_3×2. ^{13}C n.m.r. δ ($CDCl_3$) 207·8, CO×2; 148·5, 146·6, 146·1, 143·8, 138·0, 118·0, (C 3a′,4′,5′,6′,7′,7a′)×2; 117·1, C=CH×2; 114·1, C 3′×2; 89·2, C 2′×2; 60·8, 60·5, 60·0, OCH_3×6; 54·9, CO**C**H**C**HCO; 29·7, COCH_3×2; 28·7, 28·0, CH_3×4. Mass spectrum: (c.i. positive mode): m/z 771, 769, 767 (M+1; 1, 2, 1%), 387 (59), 385 (100).

Further elution then afforded *(Z)-6-bromo-4,5,7-trimethoxy-2,2-dimethyl-3-(3-oxobutylidene)-2,3-dihydrobenzofuran* (15) (806 mg, 53%), as a pale yellow oil (Found: C, 52·8; H, 5·6. $C_{17}H_{21}BrO_5$ requires C, 53·0; H, 5·5%). ν_{max} (film). 1711s (C=O), 1588m cm^{-1}. ^{1}H n.m.r. δ ($CDCl_3$) 6·58, t, J 8·1 Hz, H 1′; 3·92, 3·87, 3·82, 3×s, OCH_3×3; 3·41, d, J 8·1 Hz, H 2′; 2·25, s, H 4′; 1·61, s, CH_3×2. ^{13}C n.m.r. δ ($CDCl_3$) 205·5, C 3′; 148·5, 146·0, 144·6, 144·3, 137·7, 118·9, C 3a,4,5,6,7,7a; 113·5, C 1′; 113·2, C 3; 89·4, C 2; 60·9, 60·5, 60·0, OCH_3×3; 43·2, C 2′; 29·7, C 4′; 27·0, CH_3×2. Mass spectrum: m/z 386, 384 (M, 43%), 343, 341 (100), 328, 326 (14), 313, 311, (21). ^{1}H n.O.e. difference measurements were made on enone (15) and the following n.O.e. effects were observed: irrad. CH_3 (δ 1·61) → +5·8% at H 2′ (δ 3·41); irrad. H 1′ (δ 6·58) → +2·4% at OMe (δ 3·92). These interactions were confirmed by a two-dimensional (NOESY) experiment, and are consistent with *Z*-stereochemistry.

6-Bromo-4,5,7-trimethoxy-2,2-dimethyl-3-(3-oxobutyl)-2,3-dihydrobenzofuran (17) †

Enone (15) (360 mg) in ethyl acetate (10 ml) was hydrogenated over PtO_2 at 1100 p.s.i. and 80° for 8 h with magnetic stirring in a 100 ml glass-lined autoclave. The crude product (368 mg) on column chromatography (silica gel, 2:1 light petroleum/ethyl acetate) first gave *6-bromo-4,5,7-trimethoxy-2,2-dimethyl-3-(3-oxobutyl)-2,3-dihydrobenzofuran* (17) (289 mg, 81%) as a pale yellow oil (Found: C, 52·4; H, 5·9. $C_{17}H_{23}BrO_5$ requires C, 52·7; H, 6·0%). ν_{max} (film) 1715m (C=O), 1678m, 1593m cm^{-1}. ^{1}H n.m.r. δ ($CDCl_3$) 3·86, 3·83, 3·82, 3×s, OCH_3×3; 3·10, dd, J 8·3, 5·4 Hz, H 3; 2·50, t, with fine splitting, J 7·4 Hz, H 2′; 2·14, s, H 4′, superimposed on 2·15–1·85, m, 1H, H 1′; 1·85–1·55, m, 1H, H 1′; 1·50, s, CH_3; 1·36, s, CH_3. ^{13}C n.m.r. δ ($CDCl_3$) 208·4, C 3′; 146·9, 146·7, 144·0, 138·1, 124·7, 111·6, C 3a,4,5,6,7,7a; 90·9, C 2; 61·0, OCH_3×2; 60·5, OCH_3; 48·1, C 3; 40·5, C 2′; 30·0, C 4′; 28·3, CH_3; 24·1, C 1′; 22·2, CH_3. Mass spectrum: m/z 388, 386 (M, 71%), 330, 328 (100), 315, 313 (44).

Further elution then afforded *6-bromo-3-(3-hydroxybutyl)-4,5,7-trimethoxy-2,2-dimethyl-2,3-dihydrobenzofuran* (18) (52 mg, 14%) as a pale yellow oil (Found: M^+, 390·087±0·002. $C_{17}H_{25}{}^{81}BrO_5$ requires M^+, 390·087). ν_{max} (film) 3406s(br) cm^{-1} (OH). ^{1}H n.m.r. δ ($CDCl_3$) 3·88, 3·86, 3·81, 3×s, OCH_3×3, superimposed on 4·00–3·70, m, H 3′; 3·09, t, J 5·7 Hz, H 3; 1·49, 1·40, 2×s, CH_3×2, superimposed on 2·10–1·35, m, H 1′,2′, OH; 1·19, dd, J 6·2, 1·6 Hz, H 4′. ^{13}C n.m.r. δ ($CDCl_3$) 146·8, 146·7, 143·8, 137·8, 124·8, 111·4, C 3a,4,5,6,7,7a; 90·7, C 2; 68·2, C 3′; 60·9, 60·8, 60·5, OCH_3×3; 49·7, C 3; 36·8, 36·7, C 2′; 28·9, CH_3; 26·4, 26·1, C 1′; 23·7, 23·5, C 4′; 22·3, CH_3. Mass spectrum: m/z 390, 388 (M, 100, 94%). Swern

* Best name for indexing purposes is (*Z*)-4-(6-bromo-4,5,7-trimethoxy-2,2-dimethyl-2,3-dihydrobenzofuran-3-ylidene)butan-2-one.

† Best names for indexing of compounds (17) and (18): 4-(6-bromo-4,5,7-trimethoxy-2,2-dimethyl-2,3-dihydrobenzofuran-3-yl)butan-2-one (17) and 4-(6-bromo-4,5,7-trimethoxy-2,2-dimethyl-2,3-dihydrobenzofuran-3-yl)butan-2-ol (18).

oxidation[26] of alcohol (18) with oxalyl chloride and dimethyl sulfoxide in dichloromethane at −78° gave the ketone (17) (80%). More conveniently, the mixture of (17) and (18) could be oxidized without prior separation to give (17) in comparable total yield.

6-Bromo-3-(3,3-ethylenedioxybutyl)-4,5,7-trimethoxy-2,2-dimethyl-2,3-dihydrobenzofuran (19)

A mixture of 6-bromo-4,5,7-trimethoxy-2,2-dimethyl-3-(3-oxobutyl)-2,3-dihydrobenzofuran (17) (213 mg, 0·55 mmol), ethylene glycol (0·03 ml, 0·6 mmol) and *p*-toluenesulfonic acid (*c.* 5 mg) in benzene (15 ml) was heated at reflux with a Dean–Stark water separator for 18 h. Neutralization ($NaHCO_3$) and evaporation yielded a yellow oil (256 mg). Column chromatography (silica gel, 1·5:1 light petroleum/ethyl acetate) afforded *6-bromo-3-(3,3-ethylenedioxybutyl)-4,5,7-trimethoxy-2,2-dimethyl-2,3-dihydrobenzofuran* (19) (234 mg, 99%) as a pale yellow oil (Found: M^+, 432·098±0·004. $C_{19}H_{27}{}^{81}BrO_6$ requires M^+, 432·097). ν_{max} (film) 2977m, 2937m, 2876w, 1594w, 1470s, 1413s, 1371w, 1254w, 1121m, 1054s, 979m, 862m, 804w cm^{-1}. ^1H n.m.r. δ ($CDCl_3$) 3·89, 3·86, 3·80, 3×s, OCH_3×3, superimposed on 4·05–3·70, m, OCH_2CH_2O; 3·08, t with fine splitting, *J* 5·6 Hz, H 3; 1·49, 1·39, 2×s, CH_3×2, and 1·31, s, C 4′, superimposed on 1·95–1·25, m, H 1′,2′. ^{13}C n.m.r. δ ($CDCl_3$) 146·7×2, 143·8, 137·6, 124·6, 111·3, C 3a,4,5,6,7,7a; 109·9, C 3′; 90·6, C 2; 64·7, OCH_2CH_2O; 60·8, 60·7, 60·4, OCH_3×3; 49·5, C 3; 36·5, C 2′; 28·9, CH_3; 24·3, C 1′; 23·8, C 4′; 22·2, CH_3. Mass spectrum: *m/z* 432, 430 (M, 6%), 417, 415 (2), 330 (12), 328 (10), 115 (26), 87 (100), 71 (22).

(E,E)-*10,10-Ethylenedioxy-3,7-dimethyldeca-2,6-dien-1-ol (24)*

Potassium carbonate (3·00 g, 21·7 mmol) was added to a solution of acetoxy acetal (23)[15,19] (370 mg, 1·31 mmol) in methanol (40 ml). The mixture was stirred at room temperature for 18 h, filtered, and evaporated. Extraction with dichloromethane gave a pale yellow oil (360 mg). Column chromatography (silica gel, 2:1 → 1:1 light petroleum/ethyl acetate) yielded (E,E)-*10,10-ethylenedioxy-3,7-dimethyldeca-2,6-dien-1-ol* (24) (308 mg, 98%) as a pale yellow oil (Found: C, 69·8; H, 9·9. $C_{14}H_{24}O_3$ requires C, 70·0; H, 10·1%). ν_{max} (film) 3406s(br), 1140s, 1032s cm^{-1}. ^1H n.m.r. δ ($CDCl_3$) 5·40, t with fine splitting, *J* 6·9 Hz, H 2; 5·15, br t, *J* ≈ 6 Hz, H 6; 4·85, t, *J* 4·9 Hz, H 10; 4·14, d, *J* 6·8 Hz, H 1; 4·05–3·80, m, OCH_2CH_2O; 2·20–2·00, m, H 4,5,8; 1·67, 1·61, 2×s, CH_3×2, superimposed on 1·90–1·60, m, H 9, OH. ^{13}C n.m.r. δ ($CDCl_3$) 139·2, C 3; 134·4, C 7; 124·0, C 2; 123·5, C 6; 104·2, C 10; 64·7, OCH_2CH_2O; 59·2, C 1; 39·3, 33·7, 32·3, 26·1, C 4,5,8,9; 16·1, CH_3×2. Mass spectrum: *m/z* 240 (M, <1%), 99 (47), 93 (100), 86 (83), 73 (100).

(E,E)-*1-Bromo-10,10-ethylenedioxy-3,7-dimethyldeca-2,6-diene (25)*

A solution of triphenylphosphine (59 mg, 0·22 mmol) in anhydrous diethyl ether (3 ml) was added dropwise to a cooled (0°) and stirred solution of the hydroxy acetal (24) (53 mg, 0·22 mmol) and carbon tetrabromide (74 mg, 0·22 mmol) in anhydrous diethyl ether (3 ml). The reaction mixture was heated at reflux for 1 h, then cooled in ice, and diluted with pentane to precipitate triphenylphosphine oxide. The suspension was filtered, and evaporation of the filtrate afforded crude (*E,E*)-1-bromo-10,10-ethylenedioxy-3,7-dimethyldeca-2,6-diene (25) (58 mg, 87%) as a colourless oil, which was used immediately after isolation. ^1H n.m.r. (contaminated with Ph_3PO/Ph_3P) δ ($CDCl_3$) 5·43, t with fine splitting, *J* 7·1 Hz, H 2; 5·10–4·95, m, H 6; 4·75, t, *J* 4·8 Hz, H 10; 3·92, d with fine splitting, *J* 8·4 Hz, H 1, superimposed on 3·95–3·65, m, OCH_2CH_2O; 2·15–1·85, m, H 4,5,8; 1·62, 1·52, 2×s, CH_3×2, superimposed on 1·75–1·45, m, H 9. ^{13}C n.m.r. δ ($CDCl_3$) 143·2, C 3; 132·7, C 7; 123·3, C 2; 120·3, C 6; 104·0, C 10; 64·6, OCH_2CH_2O; 39·1, C 1; 33·6, 32·1, 29·4, 25·8, C 4,5,8,9; 15·9, 15·7, CH_3×2.

An aqueous workup caused hydrolysis of the bromide (25) to give the starting alcohol (24).

Lithiation and Alkylation of 4,5,7-Trimethoxy-2,2-dimethyl-2,3-dihydrobenzofuran (9)

(i) *With* (E,E)-*farnesyl bromide.* Butyllithium (2·4 M, 0·29 ml, 0·70 mmol) was added dropwise to a cooled (−78°) and stirred suspension of trimethyl ether (9) (166 mg, 0·697 mmol) in anhydrous diethyl ether (5 ml) under nitrogen. The reaction mixture was warmed to 0°

[26] Mancuso, A. J., and Swern, D., *Synthesis*, 1981, 165.

over 1 h before being recooled to −78°. A degassed and cooled (−78°) solution of Li_2CuCl_4 [27] (0·10 M in tetrahydrofuran, 0·17 ml, 0·017 mmol) and (*E*,*E*)-farnesyl bromide (Aldrich) (22) (0·38 ml, 1·40 mmol) in diethyl ether (3 ml) was then added and the mixture was stirred at −78°. After 1·5 h, the mixture was warmed to room temperature and stirred for a further 2·5 h. The reaction mixture was then quenched with 2 M hydrochloric acid (5 ml), and extracted with diethyl ether (×3). The combined organic extract was evaporated to give a light brown oil (552 mg). Column chromatography (silica gel, 9:1 light petroleum/ethyl acetate) firstly gave unreacted (*E*,*E*)-farnesyl bromide (22) (170 mg), identified by its infrared spectrum. Further elution afforded (E,E)-*4,5,7-trimethoxy-2,2-dimethyl-6-(3,7,11-trimethyldodeca-2,6,10-trienyl)-2,3-dihydrobenzofuran* (26) [128 mg, 42%; 88% based on the recovery of starting material (9)] as a pale yellow oil (Found: M^+, 442·308±0·004. $C_{28}H_{42}O_4$ requires M^+, 442·308). ^{1}H n.m.r. δ ($CDCl_3$) 5·30–5·00, m, H 2′,6′,10′; 3·84, 3·80, 3·75, 3×s, OCH_3×3; 3·33, d, *J* 6·9 Hz, H 1′; 3·02, s, H 3; 2·20–1·85, m, H 4′,5′,8′,9′; 1·78, 1·67, 1·58, 1·57, 4×s, =C–CH_3×4; 1·48, s, *gem* CH_3×2. ^{13}C n.m.r. δ ($CDCl_3$) 147·0, 145·4, 143·6, 137·7, 134·9, 134·5, 131·2, 128·0, 117·5, C 3a,4,5,6,7,7a,3′,7′,11′; 124·4, 124·3, 123·7, C 2′,6′,10′; 87·5, C 2; 61·1, 60·1, 59·9, OCH_3×3; 41·2, C 3; 39·8, 39·7, C 4′,8′; 28·2, *gem* CH_3×2; 26·7, 26·6, C 5′,9′; 25·7, =C($\mathbf{C}H_3$)$_2$; 23·6, C 1′; 16·1, 16·0, internal =C–$\mathbf{C}H_3$×2. Mass spectrum: *m/z* 442 (M, 19%), 274 (10), 251 (42), 236 (20), 69 (100). Alternatively, the product (26) could be purified by bulb-to-bulb distillation (200–205°/0·01 mmHg). Continued elution yielded unreacted trimethoxybenzofuran (9) (88 mg).

(ii) *Attempted alkylation with* (E,E)-*1-bromo-10,10-ethylenedioxy-3,7-dimethyldeca-2,6-diene (25).* The trimethyl ether (9) (120 mg, 0·504 mmol) in diethyl ether (5 ml) was lithiated as described in (i) above with butyllithium (2·5 M, 0·22 ml, 0·55 mmol). The crude bromo acetal (25) (306 mg, *c.* 1 mmol) and Li_2CuCl_4 (0·1 M in tetrahydrofuran, 0·28 ml) in diethyl ether (3 ml) were added at −78°, and the reaction was completed and worked up as in (i). The ^{1}H n.m.r. spectrum of the crude product (464 mg) showed mainly the starting materials (9) and (25).

(E,E)-*3-(3,3-Ethylenedioxybutyl)-4,5,7-trimethoxy-2,2-dimethyl-6-(3,7,11-trimethyldodeca-2,6,10-trienyl)-2,3-dihydrobenzofuran (28)*

Butyllithium (2·5 M, 0·13 ml, 0·33 mmol) was added via syringe to a cooled (−78°) and stirred solution of 6-bromo-3-(3,3-ethylenedioxybutyl)-4,5,7-trimethoxy-2,2-dimethyl-2,3-dihydrobenzofuran (19) (124 mg, 0·287 mmol) in anhydrous diethyl ether (4 ml) under an argon atmosphere. The cooling bath was removed and the mixture was brought to 0–10° over 45 min. The aryllithium solution was then recooled (−78°) and treated with a degassed and cooled (−78°) solution of (*E*,*E*)-farnesyl bromide (22) (0·16 ml, 0·59 mmol) and Li_2CuCl_4 [27] (0·10 M in tetrahydrofuran, 0·09 ml, 0·009 mmol) in anhydrous diethyl ether (2 ml). The reaction mixture was stirred at −78° for 1 h and then allowed to warm to room temperature over 2 h. Stirring was continued at ambient temperature for a further 40 h after which time t.l.c. showed no starting material and two new components. The reaction mixture was then quenched with water (5 ml), and extracted with diethyl ether to give a yellow oil (317 mg).

Column chromatography (silica gel, 2:1 light petroleum/ethyl acetate) first gave unreacted farnesyl bromide (22) (112 mg). Further elution afforded (E,E)-*3-(3,3-ethylenedioxybutyl)-4,5,7-trimethoxy-2,2-dimethyl-6-(3,7,11-trimethyldodeca-2,6,10-trienyl)-2,3-dihydrobenzofuran* (28) [53 mg, 33%; 99% based on recovery of reduced starting material (32)] as a pale yellow oil (Found: M^+, 556·376±0·005. $C_{34}H_{52}O_6$ requires M^+, 556·376). ν_{max} (film) 2980s, 2932s, 1474m, 1451m, 1418s, 1376m, 1060s, 1013m cm^{-1}. ^{1}H n.m.r. δ ($CDCl_3$) 5·30–5·00, m, H 2″,6″,10″; 3·85, 3·78, 3·74, 3×s, OCH_3×3, superimposed on 4·05–3·75, m, OCH_2CH_2O; 3·32, d, *J* 6·8 Hz, H 1″; 3·15–3·00, apparent m, H 3; 1·78, s, internal =C–CH_3, 1·67, s, terminal =C–CH_3, and 1·59, s, internal =C–CH_3 and terminal =C–CH_3, superimposed on 2·30–1·55, m, H 1′,2′,4″,5″,8″,9″; 1·46, 1·39, 2×s, *gem* CH_3×2; 1·31, s, C 4′–H_3. ^{13}C n.m.r. δ ($CDCl_3$) 146·0, 144·2, 138·1, arom. C×3; 134·9, 134·5×2, C 3″,7″,11″; 131·22, 128·0, arom. C×2; 124·4, 124·3, 123·7, C 2″,6″,10″; 122·3, arom. C; 110·1, C 3′; 89·6, C 2; 64·6, OCH_2CH_2O; 60·9, 60·3, 60·2, OCH_3×3; 49·7, C 3; 39·8, 39·7, C 4″,8″; 36·7, C 2′; 29·1, *gem* CH_3; 26·7, 26·6, C 5″,9″; 25·7, terminal =C–$\mathbf{C}H_3$×2; 24·5, C 1′; 23·8, C 4′; 23·6, C 1″; 22·3, *gem* CH_3;

[27] Nunomoto, S., *J. Org. Chem.*, 1983, **48**, 1912.

16·1, internal =C–CH_3×2. Mass spectrum: *m/z* 556 (M, 20%), 263 (24), 249 (15), 115 (30), 87 (100), 69 (94).

Continued elution yielded *3-(3,3-ethylenedioxybutyl)-4,5,7-trimethoxy-2,2-dimethyl-2,3-dihydrobenzofuran* (32) (68 mg, 17%) as a colourless film (Found: M^+, 352·189±0·003. $C_{19}H_{28}O_6$ requires M^+, 352·189). ν_{max} (film) 2976s, 1618w, 1496s, 1453m, 1434m, 1370m, 1346m, 1254s, 1224s, 1129m, 1055s cm^{-1}. ^1H n.m.r. δ ($CDCl_3$) 6·42, s, H6; 3·84, 3·82, 2×s, OCH_3×2, superimposed on 4·00–3·70, m, OCH_3, OCH_2CH_2O; 3·11, t, *J* 5·8 Hz, H3; 1·95–1·55, m, H1′,2′; 1·50, 1·39, 2×s, CH_3×2; 1·30, s, C4′–H_3. ^{13}C n.m.r. δ ($CDCl_3$) 146·1, 140·7, 140·6, 139·9, 125·1, C3a,4,5,7,7a; 110·1, C3′; 99·5, C6; 89·7, C2; 64·7, OCH_2CH_2O; 60·7, 57·2, 56·4, OCH_3×3; 49·8, C3; 36·4, C2′; 29·0, CH_3; 24·4, C1′; 23·8, C4′; 22·2, CH_3. Mass spectrum: *m/z* 352 (M, 19%), 337 (3), 308 (5), 250 (18), 115 (31), 87 (100), 71 (39).

(E,E)-*6-(10-Bromo-11-hydroxy-3,7,11-trimethyldodeca-2,6-dienyl)-3-(3,3-ethylenedioxybutyl)-4,5,7-trimethoxy-2,2-dimethyl-2,3-dihydrobenzofuran (29)* *

The farnesyl acetal (28) (53 mg, 0·095 mmol) was dissolved in tetrahydrofuran (5 ml), and the solution was cooled to 12°. Distilled water (*c.* 4 ml) was slowly added until the solution became turbid, and the turbidity was then removed by dropwise addition of tetrahydrofuran. *N*-Bromosuccinimide (19 mg, 0·11 mmol) was added and the mixture was stirred at room temperature. After 3 h, t.l.c. and mass spectrometry showed starting material (28) and a lower R_F component (29). Additional *N*-bromosuccinimide (4 mg) was added and the mixture was stirred at room temperature for an additional 0·5 h. The mixture was then extracted with diethyl ether, and evaporation afforded a yellow oil (75 mg). Column chromotography (silica gel, 1:1 light petroleum/ethyl acetate) initially gave unreacted farnesyl acetal (28) (22 mg). Further elution then gave the title bromohydrin (29) [34 mg, 55%; 93% allowing for recovery of starting material (28)] as a pale yellow oil. ν_{max} (film) 3451s(br), 1060s cm^{-1}. ^1H n.m.r. δ ($CDCl_3$) 5·20, br t, $J \approx 7$ Hz, H2″,6″; 3·85, 3·78, 3·74, 3×s, OCH_3×3, superimposed on 4·00–3·70, m, OCH_2CH_2O, H10″; 3·32, d, *J* 6·8 Hz, H1″; 3·15–3·00, apparent m, H3; 1·78, 1·58, 2×s, internal =C–CH_3×2; 1·46, 1·39, 2×s, *gem* CH_3×2; 1·34, 1·32, 1·31, 3×s, terminal =C–CH_3×2 and C4′–H_3, superimposed on 2·40–1·15, m, H1′,2′,4″,5″,8″,9″, OH. ^{13}C n.m.r. δ ($CDCl_3$) 146·0, 144·1, 138·1, 134·3×2, 132·9, 127·9, 122·3, C3a,4,5,6,7,7a,3″,7″; 126·0, 123·8, C2″,6″; 110·1, C3′; 89·6, C2; 72·4, C11″; 70·9, C10″; 64·6, OCH_2CH_2O; 60·8, 60·2, 60·1, OCH_3×3; 49·7, C3; 39·7, 38·1, =C–CH_2×2; 36·7, C2′; 32·1, =C–CH_2; 29·1×2, terminal =C–CH_3 and *gem* CH_3; 26·6, =C–CH_2; 25·8, terminal =C–CH_3; 24·4, C1′; 23·8, C4′; 23·6, C1″; 22·3, *gem* CH_3; 16·1, 15·8, internal =C–CH_3×2. Mass spectrum: *m/z* (M absent), 573 (M − Br, 3%), 572 (M − HBr, 8), 263 (21), 249 (15), 115 (24), 87 (100), 71 (51), 69 (31).

(E,E)-*6-(10,11-Epoxy-3,7,11-trimethyldodeca-2,6-dienyl)-3-(3,3-ethylenedioxybutyl)-4,5,7-trimethoxy-2,2-dimethyl-2,3-dihydrobenzofuran (30)*

Potassium carbonate (500 mg, 3·62 mmol) was added to a stirred solution of the bromohydrin (29) (34 mg, 0·052 mmol) in methanol (10 ml). The mixture was stirred for 19 h at room temperature, filtered, and evaporated. Water and diethyl ether were added, and the ether extract yielded the *title epoxide* (30) (18 mg, 60%) as a colourless film (Found: M^+, 572·372±0·006. $C_{34}H_{52}O_7$ requires M^+, 572·371). ν_{max} (film) 2964s, 2933s, 1474s, 1451s, 1418s, 1378m, 1260m, 1119m, 1060s, 1013m cm^{-1}. ^1H n.m.r. δ 5·35–5·00, m, H2″,6″; 4·00–3·90, m, OCH_2CH_2O; 3·85, 3·78, 3·74, 3×s, OCH_3×3; 3·31, d, *J* 6·6 Hz, H1″; 3·20–3·00, apparent m, H3; 2·69, t, *J* 6·3 Hz, H10″; 1·78, 1·60, 2×s, internal =C–CH_3×2, superimposed on 2·30–1·50, m, H1′,2′,4″,5″,8″,9″; 1·46, 1·39, 2×s, *gem* CH_3×2; 1·31, s, C4′–H_3; 1·29, 1·25, 2×s, terminal =C–CH_3×2. Mass spectrum: *m/z* 572 (M, 7%), 263 (38), 249 (26), 115 (35), 87 (100), 71 (45).

* (*E,E*)-3-Bromo-12-[3-(3,3-ethylenedioxybutyl)-4,5,7-trimethoxy-2,2-dimethyl-2,3-dihydrobenzofuran-6-yl]-2,6,10-trimethyldodeca-6,10-dien-2-ol.

(E,E)-4,5,7-Trimethoxy-2,2-dimethyl-6-(3,7-dimethyl-10-oxodeca-2,6-dienyl)-3-(3-oxobutyl)-2,3-dihydrobenzofuran (33) *

A solution of periodic acid dihydrate (7·0 mg, 0·031 mmol) in tetrahydrofuran (1 ml) was added dropwise to a stirred solution of the epoxy acetal (30) (18 mg, 0·031 mmol) in diethyl ether (2 ml) at 0°. After 2·3 h, the reaction mixture was diluted with water, and extracted with diethyl ether to give a yellow film (18 mg) which showed two major components by t.l.c. Infrared, ^{1}H n.m.r. and mass spectra showed that the mixture consisted of the aldehyde acetal (31) and the keto aldehyde (33) resulting from deprotection. The oil was dissolved in acetone (3 ml) and 2 M sulfuric acid (2 ml) and stirred at room temperature for 24 h, after which time t.l.c. showed only one component. Neutralization with $NaHCO_3$, evaporation of acetone, and extraction with diethyl ether then afforded the *title keto aldehyde* (33) (8 mg, 52%) as a colourless film (Found: M^+, 486·297±0·005. $C_{29}H_{42}O_6$ requires M^+, 486·298). ν_{max} (film) 3429m (OH?), 1717s(br), 1612w, 1474s, 1450s, 1418s, 1370s, 1262s, 1160m, 1142m, 1116m, 1060s, 1013s cm^{-1}. ^{1}H n.m.r. δ ($CDCl_3$) 9·72, t, *J* 1·8 Hz, 0·3H, H 10″; 5·30–5·00, m, H 2″,6″; 3·78, s, OCH_3×2; 3·76, s, OCH_3; 3·32, t, *J* 6·5 Hz, H 1″; 3·07, dd, *J* 8·2, 5·4 Hz, H 3; 2·13, s, C 4′–H_3, superimposed on 2·60–1·90, m, H 2′,4″,5″,8″,9″; 1·77, 1·59, 2×s, =C–CH_3×2, and 1·48, 1·36, 2×s, *gem* CH_3×2, superimposed on 1·85–1·25, m, H 1′. ^{13}C n.m.r. δ ($CDCl_3$) 208·7, C 3′; 202·7, C 10″; 146·1, 144·3, 138·4, arom. C×3; 134·2×2, C 3″,7″; 132·9, 128·1, arom. C×2; 125·4, 123·8, C 2″,6″; 122·4, arom. C; 89·8, C 2; **77·2, extra CH**; 60·9, 60·4, 60·1, OCH_3×3; 48·0, C 3; 42·1, C 9″; 40·7, C 2′; 39·6, 31·8, CH_2×2; 29·9, C 4′; **29·7, extra CH_2**; 28·3, *gem* CH_3; 26·5, =C–CH_2; 24·2, C 1′; 23·6, C 1″; 22·2, *gem* CH_3; 16·1, =C–CH_3×2. (The impurity peaks printed in **bold**, were seen only for the product of one run.) Mass spectrum: *m/z* 486 (M, 63%) 428 (15), 321 (28), 305 (11), 263 (45), 249 (28), 125 (37), 107 (29), 93 (50), 81 (50), 69 (43), 55 (100).

*Attempted Preparation of 18,19,20-Trimethoxy-3,3,6,10,14-pentamethyl-3a,4,5,8,9,12,13,16-octahydro-3*H*-1,17-methenocyclooctadeca[c]furan (34)*

Freshly prepared potassium graphite (C_8K)[28] (454 mg, 3·36 mmol) and titanium(III) chloride (244 mg, 1·58 mmol) were successively weighted into a 100 ml Schlenk flask in a dry box under an atmosphere of argon. Dry and degassed dimethoxyethane (20 ml) was added via cannula, and the suspension was heated at reflux for 2 h under an atmosphere of argon. A solution of the keto aldehyde (33) (96 mg, 0·020 mmol) in anhydrous dimethoxyethane (20 ml) was then added to the refluxing slurry of titanium reagent by syringe pump over 20 h. Stirring and heating at reflux were continued for a further 3 h. The mixture was then cooled to room temperature and filtered under an atmosphere of argon through a pad of Celite contained in a sintered funnel. The pad was repeatedly washed with anhydrous diethyl ether, and the combined filtrate was evaporated to give a yellow oil (124 mg). Thin-layer chromatography (3:1 ethyl acetate/light petroleum) of the crude product showed multiple components with R_F values of *c.* 0·50 and a less polar component with R_F 0·80. Column chromatography (silica gel, light petroleum) firstly afforded the less polar fraction as a colourless film (10 mg, 11%) which appeared homogeneous on t.l.c. and showed some spectroscopic features consistent with the title macrocyclic structure (34) (Found: M^+, 454·310±0·008. $C_{29}H_{42}O_4$ requires M^+, 454·308). ν_{max} (film) 2924s, 2853s, 1474m, 1418m, 1062m cm^{-1}. ^{1}H n.m.r. spectrum: no CHO signal; δ ($CDCl_3$) 7·2–7·4, weak aromatic signal; 4·8–5·3, m, CH×3; 3·7–3·9, eight lines, 9H, OCH_3; the upfield region was complex. Mass spectrum: *m/z* 454 (M, 29%), 249 (15), 125 (25), 111 (48), 97 (83), 95 (94), 71 (96), 57 (100).

Acknowledgments

This work was carried out during tenure of an Australian Postgraduate Research Award (to A.J.R.), and maintenance in 1990–91 was assisted by an Australian Research Council Small Grant.

* (*E*,*E*)-4,8-Dimethyl-10-[4,5,7-trimethoxy-2,2-dimethyl-3-(3-oxobutyl)-2,3-dihydrobenzofuran-6-yl]deca-4,8-dienal.

[28] Boldrini, G. P., Savoia, D., Tagliavini, E., Trombini, C., and Umani-Ronchi, A., *J. Organomet. Chem.*, 1985, **280**, 307.