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Synthesis of cicerfuran, an antifungal benzofuran, and some related analogues

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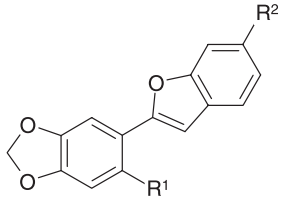
Abstract—Routes were investigated for the synthesis of cicerfuran, a hydroxylated benzofuran from wild chickpea implicated in resistance to Fusarium wilt, and some of its analogues. A novel method is described for the synthesis of oxygenated benzofurans by epoxidation and cyclisation of 2′-hydroxystilbenes. The stilbene intermediates required could be synthesised by palladium-catalysed coupling of styrenes with mono-oxygenated aryl halides but not with di-oxygenated aryl halides. Stilbenes corresponding to the latter were synthesised by Wittig reactions.

1. Introduction

Benzofurans and their analogues constitute a major group of naturally-occurring compounds that are of particular interest because of their biological activity and role in plant defence systems.[1] The hydroxylated benzofuran cicerfuran (**1a**, Fig. 1) was first obtained from the roots of a wild species of chickpea, *Cicer bijugum*, and reported to be a major factor in the defence system against Fusarium wilt.[2]



1a R^1=OMe, R^2=OH
1b R^1=H, R^2=H
1c R^1=OMe, R^2=H
1d R^1=Me, R^2=H
1e R^1=H, R^2=OH
1f R^1=Me, R^2=OH

Figure 1. Structures of cicerfuran (**1a**) and analogues (**1b–f**).

Several methodologies are available for the synthesis of simple benzofurans[3] but less attention has been given to the synthesis of hydroxylated benzofurans. Methodologies reported to date for the synthesis of natural hydroxylated benzofurans involve formation of a C–C bond between benzofuran and a substituted aryl halide,[4] arylation of a benzofuranone,[5] cyclisation of an arylbenzylketone,[6] coupling of cuprous acetylides with aryl halides,[7] Sonogashira coupling of terminal acetylenes with aryl halides,[8] coupling of a diphenylketone with the lithium salt of trimethylsilyldiazomethane[9] and use of an intramolecular Wittig reaction.[10]

Recently, the first synthesis of cicerfuran (**1a**) was reported by Sonogashira coupling of 2-methoxy-4,5-methylenedioxyphenylacetylene with dioxygenated aryl halides.[11] Our study employs an alternative strategy for the production of both cicerfuran and related analogues and was developed independently of the work of Novak and colleagues.[11] The essential features (Scheme 1) are palladium-catalysed coupling of a styrene and a 2-hydroxyaryl halide to generate a stilbene, followed by epoxidation, cyclisation and dehydration.

Two analogues (**1c**, **1d**) of cicerfuran (**1a**) were synthesised successfully by this method, but the palladium coupling step did not proceed with the dioxygenated aryl halides that are required for synthesis of cicerfuran itself (Scheme 1, R_2=OH). Palladium-catalysed coupling of the more reactive aryl acetylenes[12–14] with 2-iodophenol proceeded well to give two analogues (**1b**, **1c**) of cicerfuran directly. Use of this approach, essentially as described by Novak

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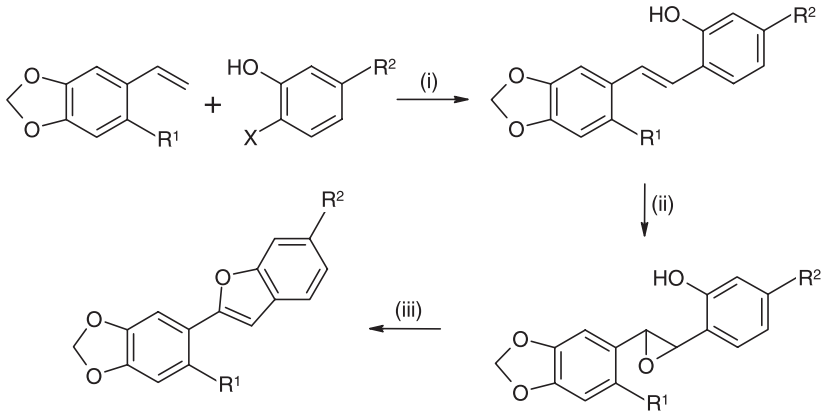


Scheme 1. Reagents and conditions: (i) palladium catalyst; (ii) epoxidation; (iii) mild acid.

et al.[11] gave cicerfuran (**1a**) only in low yields. Returning to the original synthetic plan, the stilbene required was synthesised by a Wittig reaction between 2-methoxy-4,5-methylenedioxybenzyltriphenylphosphonium bromide and 2,4-di-*tert*-butyldimethylsiloxy-benzaldehyde. Epoxidation and cyclisation gave an alternative route to cicerfuran (**1a**) in quantities sufficient for further biological assays. In addition, the synthetic and natural cicerfuran were compared directly and shown to have identical spectroscopic and chromatographic properties, confirming the proposed structure for the natural compound. Two further analogues (**1e**, **1f**) of cicerfuran were prepared by this route but were not characterised fully due to decomposition during the purification.

2. Results and discussion

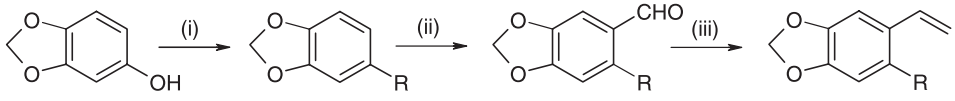
2.1. Synthesis of benzofurans via palladium-catalysed coupling of styrenes and aryl halides

2.1.1. Synthesis of styrenes. Styrene precursors for use in palladium-catalysed coupling (Scheme 1) were styrene itself (**5**) and methylenedioxystyrenes (**6a–c**) prepared from the corresponding benzaldehydes (**4a–c**) by a Wittig reaction with methyltriphenylphosphonium bromide and *n*-butyllithium (Scheme 2). 3,4-Methylenedioxystyrene (**6a**) was obtained in 97% yield from piperonal (3,4-methylenedioxybenzaldehyde) (**4a**).

Sesamol (3,4-methylenedioxyphenol) (**2**) was *O*-methylated using sodium hydroxide and dimethylsulphate to give anisole **3a** in 99% yield. Formylation[15] of **3a** gave benzaldehyde **4b** in 90% yield as shown in Scheme 2. The benzaldehyde **4b** was then converted to the desired styrene **6b** by a Wittig reaction in 98% yield.

2-Methyl-4,5-methylenedioxybenzaldehyde (**4c**) was similarly obtained in 96% yield by formylation of commercially-available 3,4-methylenedioxytoluene (**3b**) and 2-methyl-4,5-methylenedioxyphenyl-ethene (**6c**) was obtained in 96% yield via a Wittig reaction of **4c** under the same reaction conditions (Scheme 2).

2.1.2. Palladium-catalysed coupling of styrenes with aryl halides. Palladium-catalysed reactions are among the most frequently used methods for carbon–carbon bond formation and have been applied to synthesis of both natural and non-natural compounds.[16–19] Experiments were carried out to optimise the reaction conditions for the palladium-catalysed coupling of styrenes **5** and **6a** with simple aryl halides and then with multioxygenated aryl halides (Scheme 3, Table 1).

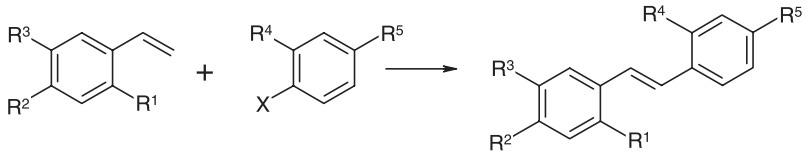


3a R=OMe (99%)
3b R=Me

4a R=H
4b R=OMe (90%)
4c R=Me (96%)

6a R=H (97%)
6b R=OMe (98%)
6c R=Me (96%)

Scheme 2. Reagents and conditions: (i) NaOH, $(CH_3)_2SO_4$; (ii) α,α-dichloromethylmethyl ether, $TiCl_4$; (iii) *n*-BuLi, THF, methyltriphenylphosphonium bromide.



5, 6a-c **7a-k** **8a-j**

Scheme 3. Palladium-catalysed coupling of styrenes with aryl halides.

Table 1. Palladium-catalysed coupling of styrenes with aryl halides

Styrene (**5**)				Aryl halide (**7**)				Solvent	Cat	Temperature (°C)	Time	Stilbene product (%)
	R_1	R_2	R_3		X	R_4	R_5					
5	H	H	H	**7a**	I	H	H	Et_3N	—	100	24 h	**8a** (60%)
5	H	H	H	**7b**	I	OH	H	Et_3N	B	100	13 h	**8b** (50%)
5	H	H	H	**7d**	I	H	OMe	Et_3N	B	100	3 days	**8c** (65%)
5	H	H	H	**7e**	I	OMe	OMe	DMA	B	130	4 days	**8d** (31%)
5	H	H	H	**7f**	Cl	OH	OH	DMA	A	130	5 days	—
5	H	H	H	**7g**	Cl	OAc	OAc	DMA	A	130	4 days	—
5	H	H	H	**7h**	Br	OH	OH	DMA	A	130	4 days	—
5	H	H	H	**7i**	Br	OAc	OAc	DMA	A	130	4 days	—
6a	H	OCH_2O		**7a**	I	H	H	Et_3N	—	100	18 h	**8e** (50%)
6a	H	OCH_2O		**7b**	I	OH	H	Et_3N	B	100	18 h	**8f** (42%)
6a	H	OCH_2O		**7c**	I	OAc	H	Et_3N	B	100	18 h	**8g** (49%)
6a	H	OCH_2O		**7d**	I	H	OMe	Et_3N	B	100	5 h	**8h** (60%)
6b	OMe	OCH_2O		**7b**	I	OH	H	Et_3N	B	100	5 h	**8i** (68%)
6b	OMe	OCH_2O		**7j**	I	OH	OH	Et_3N	B	100	5 h	—
6b	OMe	OCH_2O		**7k**	I	OAc	OAc	Et_3N	B	100	5 h	—
6c	Me	OCH_2O		**7b**	I	OH	H	Et_3N	B	100	5 h	**8j** (54%)

Catalyst (Cat) was palladium acetate with triphenylphosphine (A) or tri-*o*-tolylphosphine (B).

Palladium acetate with either triphenylphosphine or tri-*o*-tolylphosphine was used as catalyst and the different ligands had no obvious effect on yield. However, the solvent used for the coupling reaction was found to be important. Styrene (**5**) polymerised at temperatures above 100 °C when triethylamine was used as solvent, but with dimethylacetamide and sodium acetate no polymerisation of **5** was observed at temperatures above 120 °C.

After optimisation of the conditions for palladium-catalysed coupling using simple styrenes **5** and **6a** (Scheme 3) two stilbenes 1-(2-methoxy-4,5-methylenedioxyphenyl)-2-(2-hydroxyphenyl)ethene (**8i**) and 1-(2-methyl-4,5-methylenedioxyphenyl)-2-(2-hydroxyphenyl)ethene (**8j**) were obtained in 68 and 54% yield by palladium-catalysed coupling of 2-iodophenol (**7b**) with styrenes **6b** and **6c**, respectively. Two equivalents of 2-iodophenol were used for the coupling to ensure complete reaction of the styrene. The stilbenes were shown to be the *E* isomers by ^{1}H NMR spectroscopy.

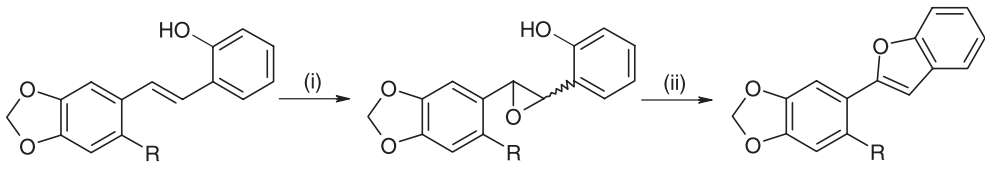
Stilbenes **8i** and **8j** were epoxidised with 3-chloroperbenzoic acid in dichloromethane (Scheme 4). Stilbene **8j** underwent sequential epoxidation and cyclisation under these conditions to give 2-(2-methyl-4,5-methylenedioxyphenyl)benzofuran (**1d**, Fig. 1) in 50% yield after stirring overnight. The same process applied to **8i** resulted in complete decomposition. Thus, the epoxide **9a** was isolated and then subjected to acid-catalysed ring-opening, cyclisation and dehydration with *p*-toluenesulphonic acid in chloroform to give 2-(2-methoxy-4,5-methylenedioxyphenyl)benzofuran (**1c**, Fig. 1). The 2-methoxy group in **1c** makes this benzofuran much less stable to acid than **1d** with the 2-methyl group.

As indicated in Table 1, palladium-catalysed coupling of styrenes could be carried out with aryl halides having one oxygenated functionality. However, introduction of a second oxygenated functionality deactivated the halide towards nucleophilic substitution, and several unsuccessful attempts were made to couple styrene **6b** with 4-iodoresorcinol (**7j**). The reaction still failed after acetylation of the hydroxyl groups which was expected to increase the reactivity of the halide.

2.2. Synthesis of benzofurans via palladium-catalysed coupling of acetylenes with aryl halides

Palladium catalysed coupling of terminal acetylenes with *o*-hydroxy aryl halides is reported to give the benzofurans in a single step reaction.[12–14] As aryl acetylenes are more reactive in palladium-catalysed coupling than the corresponding styrenes,[20] it was considered that this approach might be more successful with the multioxygenated aryl halides required for synthesis of cicerfuran and its analogues (Scheme 5).

2.2.1. Synthesis of acetylenes. 3,4-Methylenedioxyphenylethyne (**10b**) was obtained in 56% yield by bromination of the corresponding styrene **6a**, synthesised previously, with bromine in dichloromethane at 0 °C followed by dehydrohalogenation with potassium *t*-butoxide and 18-crown-6 ether. Similar treatment of 2-methoxy-3,4-methylenedioxystyrene (**6b**) resulted in bromination of the aryl ring. However, bromination in chloroform at room temperature then at 40 °C, followed by dehydrohalogenation gave acetylene **10c** in 51% yield. The use of chloroform rather

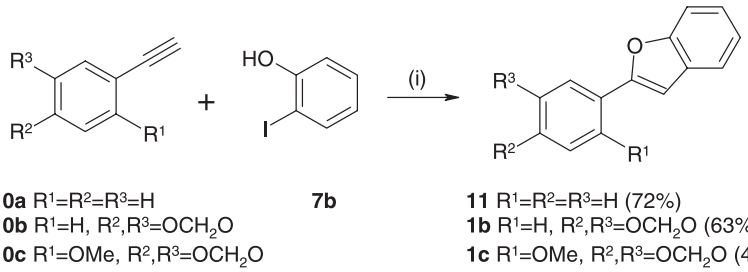


8i R=OMe
8j R=Me

9a R=OMe (67%)
9b R=Me

1c R=OMe (76%)
1d R=Me (50%)

Scheme 4. Reagents and conditions: R=Me (i), (ii) 3-CPBA, DCM; R=OMe (i) 3-CPBA, DCM; (ii) *p*TSA, $CHCl_3$.



Scheme 5. Reagents and conditions: (i) $Pd(Ph_3P)_2Cl_2$, CuI, Et_3N, DMF.

than dichloromethane was reported to enhance the bromination of styrenes.[21]

2.2.2. Palladium-catalysed coupling of aryl acetylenes. Three arylbenzofurans, **11**, **1b** and **1c**, were synthesised by palladium-catalysed coupling of acetylenes **10a–c** with 2-iodophenol (**7b**) as shown in Scheme 5. While this approach worked well with the monohydroxyaryl iodide **7b**, attempts to couple acetylene (**10c**) with 4-iodoresorcinol (**7j**) were unsuccessful.

Acetylation of the hydroxyl groups was expected to make the aryl halide more reactive to nucleophilic attack, and the synthesis of cicerfuran was therefore attempted by palladium-catalysed coupling[7] of acetylene (**10c**) with the diacetate of iodoresorcinol (**7k**), as shown in Scheme 6.

Iodoresorcinol (**7j**) was obtained in 70% yield by reaction of resorcinol with iodine monochloride, and was acetylated with acetic anhydride and pyridine to give the diacetate **7k**. Coupling of **7k** with acetylene **10c** was carried out in DMF in the presence of $Pd(PPh_3)_2Cl_2$, CuI, and diisopropylamine at 60 °C. The diarylacetylene **12** was 15% of the total reaction mixture as shown by GC-MS analysis. The other major products were 2-methoxy-4,5-methylenedioxybenzene, a decomposition product of acetylene **10c**, and diacetoxybenzene formed by reduction of **7k**. Acetylene **12** could not be isolated by flash chromatography, and the crude product was used for the further reaction. Deacetylation of **12** with anhydrous potassium carbonate in methanol was followed by cyclisation to give cicerfuran (**1a**). However, this was present as only 5% of the mixture by GC–MS and attempted isolation by chromatography on silica gel was unsuccessful.

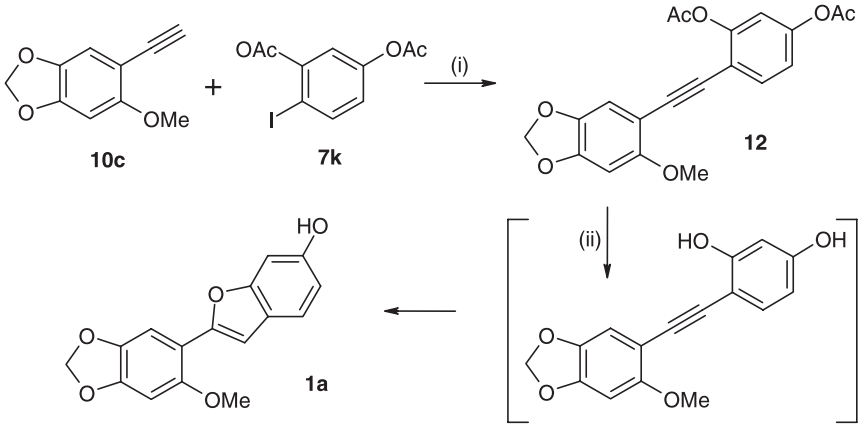
Novak et al.[11] used a similar approach to synthesise cicerfuran and also noted the instability of the acetylenic intermediates.

2.3. Synthesis of cicerfuran via the Wittig reaction

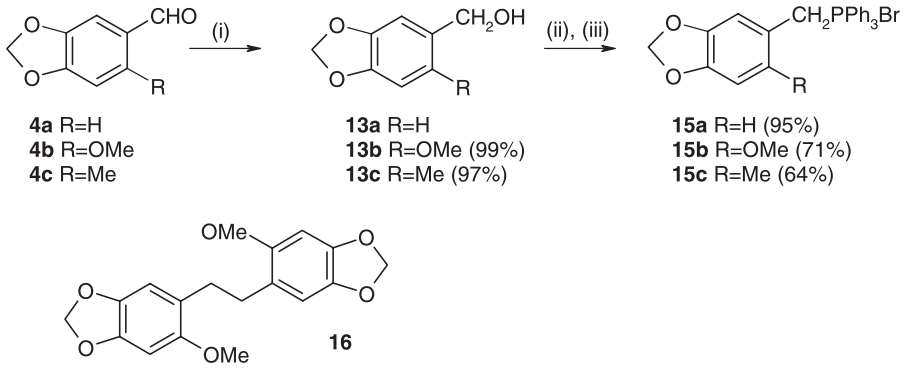
Returning to the original reaction scheme (Scheme 1), the stilbenes with the multioxygenated functionalities required for synthesis of cicerfuran and analogues were synthesised by a Wittig reaction, an olefination reaction relatively independent of the nature of the substituents on the moieties to be coupled. The hydroxyl groups were protected as *tert*-butyldimethylsiloxy (TBDMS) derivatives during the Wittig coupling.

For synthesis of the required phosphonium salts **15a–c**, benzaldehydes **4a–c** were reduced to the corresponding benzyl alcohols **13a–c** with sodium borohydride in ethanol (Scheme 7). For the reduction of 2-methoxy-4,5-methylenedioxybenzaldehyde (**4b**) the volume of ethanol was found to be critical. When solvent was used at 0.1 g of benzaldehyde mL^{-1} ethanol, 1,2-di-(2-methoxy-4,5-methylenedioxyphenyl)ethane (**16**) was formed. When the concentration of benzaldehyde was halved, benzyl alcohol (**13b**) was obtained in 96% yield and only 2% of dimer **16** was found in the reaction mixture.

For the conversion of benzyl alcohols **13a**,**c** to the corresponding triphenylphosphonium bromides **15a**,**c**, a two-step procedure[22] was initially used. This involved



Scheme 6. Reagents and conditions: (i) $Pd(Ph_3P)_2Cl_2$, CuI, $(iPr)_2NH$, DMF; (ii) K_2CO_3, MeOH. Intermediates and product were not purified or fully characterised.



Scheme 7. Reagents and conditions: (i) $NaBH_4$, MeOH; (ii) PBr_3, toluene; (iii) PPh_3.

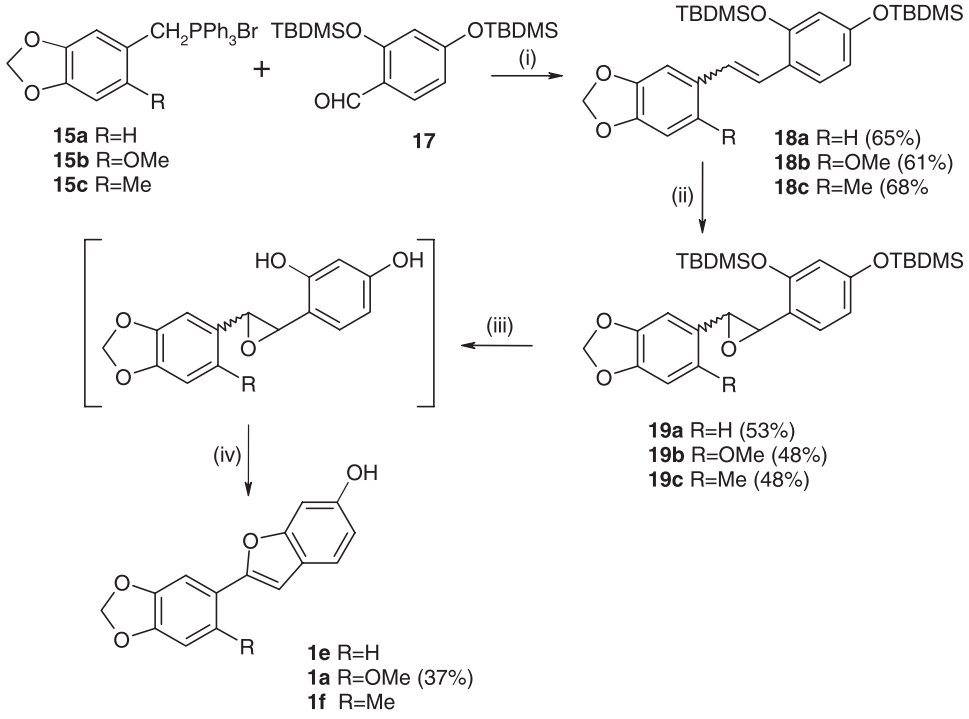
bromination with 1.2 equiv of phosphorus tribromide in dichloromethane, isolation of the bromides **14a**,**c** and conversion to the phosphonium bromides **15a**,**c** with triphenylphosphine in refluxing toluene. However, attempted bromination of 2-methoxy-4,5-methylenedioxybenzyl alcohol (**13b**) in dichloromethane gave the dimer **16** in 73% yield (Scheme 7).

The method was improved by bromination of benzyl alcohol **13b** with 0.5 equiv of phosphorous tribromide in toluene. After aqueous workup and drying, the toluene solution was refluxed directly with triphenylphosphine and phosphonium salt **15b** was obtained in 71% yield. Use of this procedure gave phosphonium bromide **15a** in 95% overall yield and **15c** in 64% overall yield (Scheme 7).

Phosphonium bromides **15a–c** and benzaldehyde **17** were coupled by Wittig reactions. Use of butyllithium as base was unsuccessful, but sodium hexamethyldisilazide in THF gave the desired stilbenes **18a–c**. Analyses by GC and TLC indicated these were approximately 1:1 mixtures of the *E* and *Z* isomers (Scheme 8).

The stilbenes **18a–c** were epoxidised with 3-chloroperbenzoic acid in dichloromethane (Scheme 8). Yields were low presumably due to the instability of the epoxides **19a–c**. There was also removal of TBDMS groups by the 3-chlorobenzoic acid and formation of the *tert*-butyldimethylsilyl ester of 3-chlorobenzoic acid was confirmed by GC–MS.

Conventional methods for removing the TBDMS protecting groups with tetrabutyl ammonium fluoride or mild acid[7,23,24] led to decomposition of the desired products. A more neutral deprotection procedure[25] using cupric chloride in acetone–water (95/5) under gentle reflux for 24–48 h was successful and the crude products were immediately cyclised with a few crystals of *p*-toluenesulphonic acid in chloroform (Scheme 8).



Scheme 8. Reagents and conditions: (i) NaHMDS, THF; (ii) 3-CPBA, DCM; (iii) $CuCl_2$, acetone, water; (iv) pTSA, $CHCl_3$.

The dihydroxyepoxides and final products were highly acid sensitive. Traces of 3-chlorobenzoic acid from the epoxidation greatly reduced yields, and significant decomposition was observed during flash chromatography on silica gel. Cicerfuran (**1a**) was obtained in 37% yield from the protected stilbene, but the two analogues **1d** and **1e** could not be isolated by chromatography on silica gel due to decomposition, even though they were shown to be present by GC–MS at 16 and 10% of the reaction mixture, respectively.

2.4. Comparison of synthetic and natural cicerfuran

Cicerfuran was isolated from roots of wild chickpea, *C. bijugum* as described previously.[2] The natural and synthetic compounds were shown to have identical chromatographic retention times on GC using a non-polar column and on HPLC using a reversed phase column. They also had the same UV spectra as recorded online by HPLC coupled with diode array detection, the same EI mass spectrum in GC-MS, and identical ^{1}H and ^{13}C NMR spectra.

3. Conclusions

Cicerfuran (**1a**), an antifungal agent isolated from roots of wild chickpea,[2] has been synthesised from sesamol (3,4-methylenedioxyphenol) (**2**) in seven steps and 37% overall yield. The route involved epoxidation and cyclisation of a dihydroxystilbene intermediate. Two analogues (**1e**, **1f**) were also prepared and characterised by GC–MS. Although they could be recovered in small quantities by HPLC for some bioassays [20] their instability meant it was not possible to isolate enough for NMR analysis. The intermediate stilbenes were synthesised by a Wittig reaction. These could not be synthesised by palladium-catalysed coupling of appropriate styrenes and dioxygenated aryl halides, as originally planned, because of deactivation of the halides to nucleophilic attack. The limitations of this approach have been explored and two deoxy analogues (**1c**, **1d**) of cicerfuran were synthesised by this route in good yield. As reported previously,[20] the more reactive aryl acetylenes could be used in palladium-catalysed coupling with dihydroxy-aryl halides if the hydroxyl groups are converted to the more electron-withdrawing acetoxy functions.

Both the benzofurans (**1a–f**) and the corresponding stilbene intermediates synthesised here have been shown to have antifungal and antibacterial activities[20,26] and details of these will be reported separately.

4. Experimental

4.1. General

Thin layer chromatography was performed using Merck 60F-254 aluminium sheets and compounds were visualised under UV light. Gas chromatograms were recorded on a Carlo Erba Strumentazione HRGC with fused silica capillary column (25 m×0.32 mm i.d.) coated with either polar CP Wax 52CB (Carbowax 20 M equiv, Chrompack) or non polar CPSil 5CB (methyl silicone, Chrompack) and flame ionisation detection. Split injection was used with the injector at 220 °C and detector at 250 °C. Typical oven temperature programmes were 60 °C for 2 min then at 10 °C/min–250 °C for the polar column and 280 °C for the non-polar. GC–MS analyses were carried out on a Hewlett–Packard HP 6890 GC System linked directly to a HP 5973 mass selective detector operated in electron impact (EI) mode at 70 eV. A fused silica capillary column (25 m× 0.22 mm i.d.) coated with non polar HP-MS5, split/splitless injector and helium carrier gas (1 mL min^{-1}) were used with oven temperature programme as above. High resolution mass spectra were provided by the EPSRC National Mass Spectrometry Service Centre, Chemistry Department, University of Wales, Swansea, UK. HPLC was carried out with a Waters 600E pump, Waters 996 photodiode array detector and Waters 717 autosampler with Spherisorb 5ODS analytical column (250 mm×4.6 mm i.d.). The binary solvent system consisted of 2% acetic acid in water (A) with 2% acetic acid in acetonitrile with 70% A at $t=0$ min, 50% A at $t=20$ min and 30% A at $t=30$ min. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Jeol EX270 spectrometer at 270 and 67.5 MHz, respectively or a Bruker Avance 400 MHz instrument. Spectra acquired in $CDCl_3$ were referenced to TMS and those in DMSO-d_6 to internal solvent resonances at δ_H 2.50 and δ_C 39.50 ppm. IR spectra were recorded as thin films (liquids), nujol mulls or solutions in ethanol-free chloroform (solids) on a Perkin–Elmer 298 grating spectrophotometer. Melting points were recorded in open capillary tubes in a heating block. Silica gel (230–400 mesh) was used for flash chromatography.

4.2. Synthesis of styrenes (6a–c)

4.2.1. 3,4-Methylenedioxyanisole (3a). A solution of 3,4-methylenedioxyphenol (sesamol) (6.0 g, 43.5 mmol) in water (30 mL) was treated with sodium hydroxide (1.7 g, 43.5 mmol) while the flask was kept in an ice bath. The reaction mixture was stirred for 15 min after which dimethyl sulphate (6.3 g, 43.5 mmol) was added dropwise. The reaction mixture was then heated under reflux for 1 h, allowed to cool down to room temperature and extracted with diethyl ether (3×100 mL). The extract was washed with 2 M NaOH (100 mL), dried, filtered and concentrated. The crude product was purified by flash chromatography and pure anisole (**3a**) obtained as an amber oil in 99% yield (6.6 g); IR (film) ν_{max}: 2905, 2860, 2720, 1585, 1565, 1458, 1441, 1200, 1155, 1133, 1088, 995 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.42 (m, 3H), 5.88 (s, 2H), 3.72 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.3, 148.4, 141.6, 107.9, 104.7, 101.1, 97.5, 56.0; MS *m/z* (% relative intensity, ion): 152(100, $[M]^+$), 137(100), 121(5), 107(50), 79(50), 69(5), 63(10), 51(30).

4.3. General method for formylation

α,α-Dichloromethylmethyl ether (2 equiv) was added dropwise via syringe to a stirred solution of anisole **3a** or 3,4-methylenedioxytoluene (**3b**) (37.3 mmol) in DCM (50 mL) at 0 °C. After stirring for 15 min titanium tetrachloride solution (1.2 equiv) in DCM (50 mL) was added dropwise via a dropping funnel. On complete addition, the reaction mixture was allowed to warm to room temperature and stirring continued for 1 h.

The reaction mixture was poured into ice-cold water (100 mL) and extracted with diethyl ether (3×100 mL) and ethyl acetate (3×100 mL). The combined organic extracts were washed with brine (1×100 mL), aqueous $NaHCO_3$ (3×100 mL), dried and passed through silica gel. The eluent was concentrated under vacuum and the crude product purified by flash chromatography.

4.3.1. 2-Methoxy-4,5-methylenedioxybenzaldehyde (4b). Light yellow crystals (90%), mp 108–110 °C; IR (nujol mull) ν_{max}: 1625, 1584, 1466, 1385, 1338, 1230, 1201, 1165, 1123, 1110, 1043, 995 cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.27 (s, 1H), 7.25 (s, 1H), 6.53 (s, 1H), 5.99 (s, 2H), 3.87 (s, 3H); MS *m/z* (% relative intensity, ion): 180(100, $[M]^+$), 163(20), 149(20), 134(50), 120(25), 107(50), 93(18), 79(35), 69(20), 62(30), 53(60).

4.3.2. 2-Methyl-4,5-methylenedioxybenzaldehyde (4c). Yellow solid (96%), mp 85–88 °C; IR (nujol mull) ν_{max}: 2905, 1641, 1581, 1563, 1460, 1215, 1152, 1111, 1070, 1012, 1001, 961 cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.12 (s, 1H), 7.24 (s, 1H), 6.65 (s, 1H), 5.99 (s, 2H), 2.57 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 189.8, 152.3, 146.6, 138.1, 128.5, 111.2, 108.7, 101.8, 18.8; MS *m/z* (% relative intensity, ion): 163(100, $[M-1]^+$), 155(1), 149(1), 135(40), 123(6), 105(12), 95(1), 86(1), 77(32), 51(36), 40(1).

4.4. General method for synthesis of styrenes

n-Butyl lithium in hexane (29 mmol) was added dropwise to a stirred solution of methyltriphenylphosphonium bromide (30 mmol) in THF (50 mL) at 0 °C. After stirring for 30 min, a cold solution of benzaldehyde **4a–c** (30 mmol) in THF (50 mL) was added dropwise from a dropping funnel to the reaction mixture. The yellow suspension produced was stirred for a further 4 h, then treated with saturated ammonium chloride solution, dried, filtered and concentrated under vacuum. The resulting viscous solution was purified by flash chromatography using hexane as eluent.

4.4.1. 3,4-Methylenedioxyphenylethene (6a). Light yellow oil (97%); IR (film) ν_{max}: 2865, 2800, 2685, 1645, 1581, 1558, 1458, 1440, 1399, 1303, 1202, 1072, 1051, 995 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.94 (br s,1H), 6.83 (dd, J=7.9, 1.5 Hz, 1H), 6.75 (d, J=7.9 Hz, 1H), 6.62 (dd, J=17.6, 10.9 Hz, 1H), 5.95 (s, 2H), 5.57 (d, J=17.6 Hz, 1H), 5.13 (d, J=10.9 Hz, 1H); ^{13}C NMR ($CDCl_3$): 148.2, 136.4, 132.1, 128.7, 121.0, 112.0, 108.2, 105.4, 101.1; MS *m/z* (% relative intensity, ion): 148(100, $[M]^+$), 89(35), 74(5), 63(20), 51(10).

4.4.2. 2-Methoxy-4,5-methylenedioxyphenylethene (6b). Yellow oil (98%); IR (film) ν_{max}: 2860, 2685, 1635, 1458, 1440, 1303, 1202, 995 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.98 (dd, J=17.8, 11.1 Hz, 1H), 6.97 (s, 1H), 6.50 (s, 1H), 5.91 (s, 2H,), 5.53 (dd, J=17.8, 1.2 Hz, 1H), 5.13 (dd, J=11.1, 1.2 Hz,1H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 152.1, 148.4, 141.6, 131.0, 119.6, 111.9, 105.2, 106.2, 94.9, 56.7; MS *m/z* (% relative intensity, ion): 178(80, $[M]^+$), 163(20), 133(100), 105(20), 77(30), 63(15), 53(30); HRMS (EI) *m/z*=178.0624 $[M]^+$, calcd for $C_{10}H_{10}O_3$=178.0625.

4.4.3. 2-Methyl-4,5-methylenedioxyphenylethene (6c). Yellow oil (96%); IR (film) ν_{max}: 2860, 2675, 1581, 1562, 1458, 1440, 1381, 1303, 1202, 1120, 995 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.96 (s, 1H), 6.83 (dd, J=17.3, 10.9 Hz, 1H), 6.59 (s, 1H), 5.86 (s, 2H), 5.48 (d, J=17.3 Hz, 1H), 5.15 (d, J=10.9 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 147.1, 146.1, 134.2, 130.0, 129.3, 113.1, 110.2, 105.1, 100.8, 19.5; MS *m/z* (% relative intensity, ion): 162(100 $[M]^+$), 147(5), 131(37), 115(2), 103(38), 91(19), 77(18), 63(9), 51(18); HRMS (EI) *m/z*=162.0675 $[M]^+$, calcd for $C_{10}H_{10}O_2$=162.0672.

4.5. Palladium-catalysed coupling of styrenes 5, 6a–c with aryl halides (Table 1)

To a stirred solution of aryl halide (10 mmol) and styrene **5**, **6a–c** (15 mmol) in dimethyl acetamide or triethylamine (20 mL) as indicated in Table 1, was added palladium acetate (28 mg, 0.12 mmol) and triphenylphosphine (68 mg, 0.25 mmol) or tri-*o*-tolylphosphine (80 mg, 0.26 mmol). The reaction mixture was stirred at room temperature for 1 h and then heated at the required temperature as shown in Table 1. After completion the reaction was quenched by addition of water (50 mL), extracted with diethyl ether (3×50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was then purified by flash chromatography.

4.5.1. 1,2-Diphenylethene (8a). ^1H NMR ($CDCl_3$): δ 7.55–7.49 (br s, 4H), 7.40–7.33 (br s, 4H) 7.30–7.26 (br s, 2H), 7.11 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 128.7, 127.6, 126.5; MS *m/z* (% relative intensity, ion): 180(100 $[M^+]$), 165(30), 102(2), 77(10), 51(15); (identical to commercially-available material).

4.5.2. 1-(2-Hydroxyphenyl)-2-phenylethene (8b). ^1H NMR ($CDCl_3$): δ 7.55–7.50 (m, 3H), 7.38–7.32 (m, 2H), 7.36 (d, J=16.5 Hz, 1H), 7.26 (m, 1H), 7.15 (td, J=7.8, 1.5 Hz, 1H), 7.12 (d, J=16.5 Hz, 1H), 6.95 (td, J=7.8, 1.5 Hz, 1H), 6.80 (dd, J=7.8, 1.5 Hz, 1H) 1.59 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 153.0, 137.7, 130.2, 128.7, 127.6, 127.2, 126.6, 124.8, 123.0, 121.2, 115.9; MS *m/z* (% relative intensity, ion): 196(100, $[M]^+$), 179(15), 165(33), 152(22), 139(7), 128(7), 118(11), 106(1), 98(7), 89(15), 76(7), 63(6), 51(6), 41(1).[27]

4.5.3. 1-(4-Methoxyphenyl)-2-phenylethene (8c). IR ($CHCl_3$) ν_{max}: 3000, 2830, 1610, 1510, 1310, 1300, 1250, 1180, 1150, 1055, 970, 960 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.51–7.43 (m, 4H), 7.37–7.31 (m, 2H), 7.26–7.20 (m, 1H), 7.07 (d, J=15.4 Hz, 1H), 6.97 (d, J=15.4 Hz, 1H), 6.93–6.87 (m, 2H), 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 128.7, 128.2, 127.7, 127.2, 126.6, 126.3, 114.2, 55.3; MS *m/z* (% relative intensity, ion): 210(90, $[M]^+$), 177(20), 162(100), 134(2), 114(2), 100(2), 87(2), 65(2) 52(2).[28]

4.5.4. 1-(2,4-Dimethoxyphenyl)-2-phenylethene (8d). ^1H NMR ($CDCl_3$): δ 7.51–7.48 (m, 3H), 7.40, (d, J=15.3 Hz, 1H), 7.35–7.29 (m, 2H), 7.23–7.16 (m, 1H), 7.0 (d, J=15.3 Hz, 1H), 6.42–6.52 (m, 2H), 3.85 (s, 3H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 160.5, 158.0, 138.3, 128.5, 127.2, 127.0, 126.9, 126.3, 123.3, 105.0, 98.5, 55.5; MS *m/z* (% relative intensity, ion): 240(100, $[M]^+$), 225(5), 209(7),

197(21), 182(16), 165(64), 153(27), 139(13), 121(20), 104(21), 91(20), 76(13), 63(10), 51(10).[27]

4.5.5. 1-(3,4-Methylenedioxyphenyl)-2-phenylethene (8e). IR ($CHCl_3$) ν_{max}: 2900, 1605, 1495, 1450, 1360, 1255, 1100, 1040, 960, 935, 870, 610 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.46 (dt, J=7.2, 1.5 Hz; 2H), 7.33 (tt, J=7.2, 1.5 Hz, 2H), 7.22 (tt, J=7.2, 1.5 Hz, 1H), 7.05 (d, J=1.5 Hz, 1H), 7.01 (d, J=16.3 Hz, 1H), 6.92 (dd, J=8.5, 1.5 Hz, 1H), 6.91 (d, J=16.3 Hz, 1H), 6.78 (d, J=8.5 Hz, 1H), 5.93 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 148.2, 147.3, 137.4, 131.9, 128.7, 128.4, 127.4, 127.0, 126.3, 121.5, 108.4, 105.6, 101.1; MS *m/z* (% relative intensity, ion): *m/z* 224(100, $[M]^+$), 193(15), 165(85), 139(13), 115(10), 82(10), 63(10).[29]

4.5.6. 1-(3,4-Methylenedioxyphenyl)-2-(2-hydroxyphenyl)ethene (8f). ^1H NMR ($CDCl_3$): δ 7.94 (dd, J=8.2, 1.5 Hz, 1H,), 7.23 (d, J=8.2 Hz, 1H), 7.16–7.05 (m, 3H), 6.99–6.90 (m, 2H), 6.79 (d, J=8.2 Hz, 2H), 5.96 (s, 2H), 1.70 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 152.9, 148.1, 147.3, 132.2, 129.8, 128.4, 127.1, 124.8, 121.5, 121.3, 121.1, 115.9, 108.4, 105.7, 101.1; MS *m/z* (% relative intensity, ion): 240(100 $[M]^+$), 225(5), 211(7), 193(7), 181(36), 165(18), 152(38), 139(5), 122(7), 105(3), 91(15), 76(16), 63(13), 51(7), 40(1); HRMS (EI) *m/z*: 240.0852 $[M]^+$ ($C_{15}H_{12}O_3$ requires 240.0786).

4.5.7. 1-(3,4-Methylenedioxyphenyl)-2-(2-acetoxyphenyl)ethene (8g). White solid, mp 68–70 °C; IR (nujol mull) ν_{max}: 1701, 1581, 1460, 1442, 1333, 1210, 1187, 1175,1135, 1045, 1001, 982 cm^{-1}; MS *m/z* (% relative intensity, ion): 282(51, $[M]^+$), 265(1), 240(100), 211(4), 181(24), 152(37), 131(53), 103(4), 86(1), 63(20).

4.5.8. 1-(3,4-Methylenedioxyphenyl)-2-(4-methoxyphenyl)ethene (8h). White solid, mp 139–141 °C; IR ($CHCl_3$) ν_{max}: 2900, 2840, 1610, 1510, 1590, 1450, 1360, 1310, 1285, 1255, 1180, 1040, 960, 935, 850, 825, 610 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.41 (dt, J=8.9, 2.0 Hz, 2H), 7.03 (d, J=1.5 Hz, 1H), 6.92–6.82 (m, 5H), 6.81 (d, J=8.2 Hz, 1H), 5.94 (s, 2H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 159.2, 148.3, 147.2, 132.4, 130.2, 127.5, 126.6, 126.3, 121.0, 114.1, 108.4, 105.4, 101.1, 55.3; MS *m/z* (% relative intensity, ion): 254(100, $[M]^+$), 223(5), 181(20), 152(50), 127(50), 98(10), 76(10), 51(10).[30]

4.5.9. 1-(2-Methoxy-4,5-methylenedioxyphenyl)-2-(2-hydroxyphenyl)ethene (8i). To a stirred solution of 2-iodophenol (**7b**) (0.99 g, 4.5 mmol) in triethylamine (10 mL) was added styrene **6b** (0.8 g, 4.5 mmol), palladium acetate (28 mg, 0.12 mmol) and tri-*o*-tolylphosphine (80 mg, 0.26 mmol). The reaction mixture was stirred at room temperature for 1 h and then the temperature was increased to 100 °C. After 4 h of heating, a further equivalent of **7b** (0.99 g, 4.5 mmol) was added and stirring was continued for a further 16 h. The reaction was monitored by following the disappearance of styrene **6b** by TLC and GC. On completion, the reaction was quenched by addition of water (50 mL) and extracted with ethyl acetate (50 mL) and diethyl ether (3×50 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography and stilbene **8i** was obtained as yellow solid in 68% yield (810 mg), mp 137–139 °C; IR ($CHCl_3$) ν_{max}: 3680, 3300, 3000, 2890, 1625, 1600, 1590, 1400, 1485, 1430, 1320, 1290, 1260, 1170, 1160, 1040, 1015,975, 940, 870, 840 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.51 (dd, J=7.7, 1.5 Hz, 1H), 7.40 (d, J=16.6 Hz, 1H), 7.14 (d, J=16.6 Hz, 1H), 7.13–7.08 (m, 2H), 6.94–6.89 (m, 1H), 6.79 (d, J=7.2 Hz, 1H), 6.53 (s, 1H), 5.93 (s, 2H), 5.15 (br s, 1H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 152.8, 152.7, 147.7, 141.8, 128.2, 127.1, 125.4, 124.6, 121.0, 121.0, 119.6, 115.8, 105.3, 101.3, 95.0, 56.8; MS *m/z* (% relative intensity, ion): 270(100, $[M]^+$), 255(5), 227(40), 197(20), 181(50), 169(20), 152(15), 133(20), 115(20), 105(5), 91(10), 77(10), 63(10), 53(2); HRMS (EI) *m/z* 271.0965 $[M+H]^+$, calcd for $C_{16}H_{15}O_4$ 271.0970.

4.5.10. 1-(2-Methyl-4,5-methylenedioxyphenyl)-2-(2-hydroxyphenyl)ethene (8j). To a stirred solution of 2-iodophenol (**7b**) (6.6 g, 30 mmol) in triethylamine (50 mL) was added styrene **6c** (3.42 g, 21 mmol), palladium acetate (31 mg, 0.13 mmol) and tri-*o*-tolylphosphine (85 mg, 0.27 mmol). The reaction mixture was stirred for 1 h at room temperature and then the temperature increased to 100 °C. After 4 h of heating, a further equivalent of 2-iodophenol (**7b**) was added and stirring continued for 16 h. The reaction was monitored by following the disappearance of styrene (**6d**) by TLC and GC. After completion, the reaction was quenched by adding water (50 mL) and extracted with ethyl acetate (1×50 mL) and diethyl ether (3×50 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was then purified by flash chromatography and stilbene **8j** was obtained as a white solid (2.77 g, 54%), mp 147–149 °C; IR ($CHCl_3$) ν_{max}: 3600, 3300, 3000, 2890, 1610, 1505, 1485, 1460, 1370, 1320, 1255, 1170, 1045, 970, 940, 875 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.48 (dd, J=7.9, 1.7 Hz, 1H), 7.26 (d, J=16.3 Hz, 1H), 7.13 (td, J=7.9, 1.7, 1H), 7.12 (s, 1H), 7.08 (d, J=16.3 Hz, 1H), 6.94 (td, J=7.9, 0.7 Hz, 1H), 6.81 (dd, J=7.9, 1.5 Hz, 1H), 6.66 (s, 1H), 5.94 (s, 2H), 2.33 (s, 3H), 1.58 (br s, 1H,); ^{13}C NMR ($CDCl_3$): δ 152.9, 146.9, 130.9, 129.9, 129.9, 128.4, 127.9, 127.3, 125.1, 122.4, 121.1, 115.9, 110.4, 105.2, 100.9, 19.8; MS *m/z* (% relative intensity, ion): 254(100, $[M]^+$), 239(27), 225(7), 209(8), 195(13), 181(15), 165(27), 152(33), 135(13), 115(13), 102(8), 89(15), 77(13), 63(12), 51(14), 40(5); HRMS (EI) *m/z* 254.0937 $[M]^+$, calcd for $C_{16}H_{14}O_3$ 254.0943.

4.6. Epoxidation and acid-catalysed cyclisation of stilbenes

4.6.1. 1-(2-Methoxy-4,5-methylenedioxyphenyl)-2-(2-hydroxyphenyl)ethene oxide (9a). 3-Chloroperbenzoic acid (276 mg, 2 equiv) was added stepwise to a stirred solution of stilbene **8i** (220 mg, 0.8 mmol) in DCM (10 mL) at 0 °C. After addition, the reaction mixture was warmed to 35 °C and stirring continued for 2 h. The reaction was quenched by the addition of water (50 mL) and extracted with DCM. The combined organic extracts were dried and concentrated under vacuum and purified by flash chromatography. The epoxide **9a** was obtained as a yellow solid (150 mg, 67%), mp 118–122 °C; IR ($CHCl_3$) ν_{max}: 3520, 3080, 2900, 1580, 1490, 1430, 1280, 1260, 1170, 1080,

1040, 940, 910 cm^{-1}; MS *m/z* (% relative intensity, ion): 286(21, $[M]^+$), 268(100), 253(60), 239(1), 225(60), 207(2), 195(15), 179(5), 167(30), 151(40), 139(70), 126(10), 112(15), 99(10), 87(10), 78(10), 69(20), 53(40), 44(50).

4.6.2. 2-(2-Methoxy-4,5-methylenedioxyphenyl)benzofuran (1c). To a stirred solution of epoxide **9a** (50 mg, 0.17 mmol) in chloroform (10 mL), a few crystals of *p*-toluenesulphonic acid were added. The reaction was stirred at 40 °C for 1 h and then quenched by the addition of water (50 mL), extracted with chloroform (3×30 mL) and the extracts washed with aqueous sodium bicarbonate solution. Benzofuran **1c** was obtained as a white solid in 76% yield (35 mg), mp 114–116 °C; IR ($CHCl_3$) ν_{max}: 2900, 1630, 1580, 1510, 1490, 1450, 1380, 1260, 1180, 1160, 1145, 1045, 1030, 940, 910, 880, 845 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.53–7.52 (m, 3H), 7.23–7.20 (m, 3H), 6.60 (s, 1H), 5.96 (s, 2H), 3.91 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 153.6, 152.8, 152.3, 148.4, 141.6, 138.3, 130.2, 123.7, 122.4, 120.7, 112.2, 106.4, 104.6, 101.5, 94.7, 56.3: MS *m/z* (% relative intensity, ion): 268(100, $[M]^+$), 253(90), 239(2), 225(50), 209(3), 195(15), 181(5), 167(20), 155(15), 139(60), 131(15), 112 (20), 99(10), 87(12), 79(2), 69(10), 53(40), 44(10); HRMS (EI) *m/z* 268.0729 $[M]^+$, calcd for $C_{16}H_{12}O_4$ 268.0736.

4.6.3. 2-(2-Methyl-4,5-methylenedioxyphenyl)benzofuran (1d). To a stirred solution of stilbene (**8j**) (2 g, 7.8 mmol) in DCM (10 mL), 3-chloroperbenzoic acid (2 g, 12 mmol) was added. The reaction mixture was stirred overnight at 35 °C. The reaction was quenched by the addition of water (50 mL) and extracted with DCM. The combined organic extracts were dried, filtered and concentrated under vacuum. The crude product was purified by flash chromatography and pure benzofuran **1d** was obtained as a white solid in 50% yield (1.0 g), mp 73–76 °C; IR ($CHCl_3$) ν_{max}: 2900, 1625, 1510, 1490, 1460, 1375, 1250, 1170, 1090, 1045, 940, 870 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.58 (dd, J=7.4, 1.2 Hz, 1H), 7.50 (br d, J=7.9 Hz, 1H), 7.32 (s, 1H), 7.31–7.20 (m, 2H), 6.77 (br s, 2H), 5.98 (s, 2H), 2.49 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 155.4, 154.1, 147.7, 146.0, 130.4, 129.3, 124.0, 122.8, 122.7, 120.7, 111.2, 111.0, 108.1, 104.3, 101.2, 21.8; MS *m/z* (% relative intensity, ion): 252(100, $[M]^+$), 221(9), 207(10), 194(18), 181(8), 165(40), 152(5), 139(11), 126(15), 115(8), 82(10), 63(5), 51(5), 44(2); HRMS (EI) *m/z* 252.0783 $[M]^+$, calcd for $C_{16}H_{12}O_3$ 252.0786).

4.7. Synthesis of benzofurans via palladium-catalysed coupling of acetylenes with aryl halides

4.7.1. 4-Iodoresorcinol (7j). Iodine monochloride was added to a stirring solution of resorcinol (0.68 g, 6.25 mmol) in diethyl ether (7 mL) at room temperature. After stirring for 1 h the reaction was quenched by adding water (30 mL) and excess iodine monochloride was destroyed by adding Na_2SO_3 (1 g, 7.9 mmol). The aqueous phase was extracted with diethyl ether (3×50 mL). The combined organic extracts were dried, filtered and concentrated under vacuum and the crude product was purified by flash chromatography. 4-Iodoresorcinol (**7j**) was obtained as a colourless oil in 70% yield (1.1 g); ^1H NMR ($CDCl_3$): δ 7.44 (d, J=8.6 Hz, 1H), 6.52 (d, J=2.7 Hz, 1H), 6.24 (dd, J=8.6, 2.7 Hz, 1H); ^{13}C NMR($CDCl_3$): δ 157.8, 145.1, 138.3, 110.4, 107.7, 102.6; MS *m/z* (% relative intensity, ion): 236(100, M^+), 227(1), 219(1), 207(2), 195(1), 187(1), 179(1), 165(1), 152(1), 144(1), 135(1), 127(62), 118(5), 119(6), 96(1), 81(19), 69(10), 61(1), 53(14).[8]

4.7.2. 2,4-Diacetoxyiodobenzene (7k). To a stirring solution of 4-iodoresorcinol (**7j**) (0.57 g, 2.4 mmol) in acetic anhydride (1.6 g, 20 mmol), pyridine (2 g, 20 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 1 h, quenched by adding water (30 mL) and extracted with diethyl ether (3×50 mL). The extracts were washed with 2 N HCl (50 mL), dried, filtered and concentrated under vacuum. The crude product was purified by flash chromatography to give diacetate **7k** as a colourless oil (0.58 g, 76%); IR (film): ν_{max} 3000, 2940, 2905, 2850, 1731, 1670, 1562, 1540, 1453, 1430, 1329, 1253, 1142, 1105, 1081, 995 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.78 (d, J=8.7 Hz, 1H), 6.97 (brs, 1H), 6.79 (m, 1H), 2.33 (s, 3H), 2.25 (s, 3H); MS *m/z* (% relative intensity, ion): 320(19, M^+), 294(1), 278(62), 254(1), 236(100), 207(5), 179(1), 151(8), 127(10), 108(10), 81(10), 51(8).

4.7.3. 3,4-Methylenedioxyphenylethyne (10b). Bromine (1.4 mL, 27.5 mmol) dissolved in DCM (25 mL) was added dropwise to a stirring solution of 3,4-methylenedioxyphenylethene (**6a**) (3.7 g, 25 mmol) in DCM (25 mL) at 0 °C. The ice bath was removed after the complete addition of bromine and the reaction mixture was kept stirring for 1 h. The excess bromine was destroyed by adding 10% sodium thiosulphate solution. The organic phase was dried, filtered and concentrated under vacuum. Potassium *t*-butoxide (6.25 g, 55 mmol) and 18-crown-ether (200 mg, 0.76 mmol) were suspended in cyclohexane (50 mL) and crude brominated styrene was added to this suspension. The resultant slurry was refluxed for 2 h, then cooled to room temperature and filtered through a thick pad of TLC grade silica gel. The filtrate was dried and concentrated under vacuum. The crude product was purified by flash chromatography and the acetylene **10b** was obtained as yellow oil in a yield of 56% (1 g); IR (film): ν_{max} 3200, 2810, 2010, 1582, 1460, 1441, 1382, 1291, 1202, 1145, 1077, 1049, 995 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.04–6.73 (m, 3H), 5.98 (s, 2H), 3.01 (s, 1H); MS *m/z* (% relative intensity, ion): 146(100, $[M]^+$), 89(20), 73(10), 62(65), 50(20).

4.7.4. 2-Methoxy-4,5-methylenedioxyphenylethyne (10c). Bromine (3.52 g, 22 mmol) dissolved in $CHCl_3$ (30 mL) was added dropwise to a stirred solution of 2-methoxy-4,5-methylenedioxyphenylethene (**6b**) (2.0 g, 11 mmol) in $CHCl_3$ (30 mL) at room temperature. The addition was completed in 1 h at which point the temperature of the reaction mixture was increased to 40 °C and stirring was continued for a further 2 h. Excess bromine was destroyed by the addition of 10% sodium thiosulphate. The organic phase was dried and concentrated under vacuum to give the crude brominated styrene as a yellow solid. Potassium *t*-butoxide (5.0 g, 44 mmol) and 18-crown ether (200 mg, 0.76 mmol) were suspended in cyclohexane (50 mL). The crude brominated styrene was added to this suspension and the resultant slurry was heated under reflux for 1 h. The reaction mixture was cooled to

room temperature and the slurry was passed through a thick pad of silica gel and then concentrated. The crude product was obtained as a yellow oil and was further purified by flash chromatography yielding acetylene **10c** as yellow solid (1.0 g, 51%); ^{1}H NMR ($CDCl_3$): δ 6.88 (s, 1H), 6.51 (s, 1H), 5.94 (s, 2H), 3.85 (s, 3H), 3.23 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 157.5, 150.2, 140.9, 112.5, 102.3, 101.6, 94.4, 80.2, 79.8, 56.6; MS *m/z* (% relative intensity, ion): 176(100, $[M]^+$), 161(73), 131(20), 103(25), 87(20), 75(30), 69(10), 63(10), 53(40), 44(5); HRMS (EI) *m/z* 176.0471 $[M]^+$, calcd for $C_{10}H_8O_3$ 176.0473.

4.8. General method for palladium-catalysed coupling of acetylenes with 2-iodophenol

To a stirred solution of 2-iodophenol (**7b**) (6 mmol) in DMF (15 mL), $Pd(Ph_3P)_2Cl_2$ (0.21 mmol), CuI (0.30 mmol) and Et_3N (12 mmol) were added. The mixture was stirred for 1 h at room temperature. One of the acetylenes **10a–c** (12 mmol) was added to the reaction mixture and stirring continued at room temperature for 1 h after which the temperature was increased to 60 °C and stirring maintained overnight. The mixture was then cooled and poured into water (30 mL) and extracted with DCM (3×30 mL). The combined organic extract was washed with 10% NaOH (30 mL) and water (30 mL), dried and concentrated under vacuum. The products were obtained as yellow solids after flash chromatography and further purified by recrystallisation from aqueous ethanol.

4.8.1. 2-Phenylbenzofuran (11). Light yellow solid (72%); MS *m/z* (% relative intensity, ion): 194(100, $[M]^+$), 165(58), 150(1), 139(13), 126(2), 115(6), 105(1), 97(13), 82(7), 74(2), 63(3), 51(4), 40(1). [12]

4.8.2. 2-(3,4-Methylenedioxyphenyl)benzofuran (1b). (63%), mp 78–80 °C; IR ($CHCl_3$) ν_{max}: 2900, 1620, 1585, 1510, 1490, 1455, 1365, 1320, 1290, 1250, 1170, 1150, 1110, 1040, 935, 870 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.58–7.47 (m, 2H), 7.39 (dd, J=8.2, 1.7 Hz, 1H), 7.32 (d, J=1.7 Hz, 1H), 7.25–7.20 (m, 2H), 6.88 (d, J=8.2 Hz, 2H), 6.00 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 155.9, 154.7, 148.1, 135.6, 129.3, 124.8, 124.0, 122.9, 120.7, 119.2, 111.0, 108.7, 105.5, 101.3, 100.2; MS *m/z* (% relative intensity, ion): 238(100, $[M]^+$), 209(2), 181(20), 152(40), 119(15), 102(5), 86(1), 63(5); HRMS (EI) *m/z* 238.0630 $[M]^+$, calcd for $C_{15}H_{10}O_3$ 238.0630.

4.8.3. 2-(2-Methoxy-4,5-methylenedioxyphenyl)benzofuran (1c). To a stirring solution of 2-iodophenol (**7b**) (0.22 mg, 1 mmol) in DMF (5 mL), $Pd(Ph_3P)_2Cl_2$ (10 mg, 0.05 mmol), CuI (24 mg, 0.03 mmol) and Et_3N (0.3 mL, 2.9 mmol) were added and further stirred for 1 h at room temperature. Acetylene **10c** (200 mg, 1.1 mmol) was added to the reaction mixture and stirred for a further 1 h at room temperature and then the temperature was increased to 60 °C and stirring continued overnight. The mixture was then cooled and poured into water (30 mL) and extracted with DCM (3×30 mL). The combined extracts were washed with 10% NaOH (30 mL) and water (30 mL), dried and concentrated under vacuum. Benzofuran **1c** was obtained as a white solid after flash chromatography and was further purified by recrystallisation from aqueous ethanol (140 mg, 46%), mp 114–116 °C; IR ($CHCl_3$) ν_{max}: 2900, 1630, 1580, 1510, 1490, 1450, 1380, 1260, 1180, 1160, 1145, 1045, 1030, 940, 910, 880, 845 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.53–7.52 (m, 3H), 7.23–7.20 (m, 3H), 6.60 (s, 1H), 5.96 (s, 2H), 3.91 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 153.6, 152.8, 152.3, 148.4, 141.6, 130.2, 123.7, 122.4, 120.7, 112.2, 110.6, 106.4, 104.6, 101.5, 94.7, 56.3; MS *m/z* (% relative intensity, ion): 268(100 $[M]^+$), 253(90), 239(2), 225(50), 209(3), 195(15), 181(5), 167(20), 155(15), 139(60), 131(15), 112(20), 99(10), 87(12), 79(2), 69(10), 53(40), 44(10); HRMS (EI) *m/z* 268.0729 $[M]^+$, calcd for $C_{16}H_{12}O_4$ 268.0736.

4.8.4. 1-(2-Methoxy-4,5-methylenedioxyphenyl)-2-(2,4-diacetoxyphenyl)ethyne (12). A mixture of 2-methoxy-4,5-methylenedioxyphenylethyne (**10c**) (176 mg, 1 mmol), 2,4-diacetoxyiodobenzene (**7k**) (384 mg, 1.2 mmol), $PdCl_2(PPh_3)_2$ (36 mg, 0.06 mmol) and disiopropylamine (0.22 mL, 1.4 mmol) in DMF (6 mL) was stirred at 60 °C for 1 h. Water (30 mL) was added to the reaction mixture which was extracted with ethyl acetate (2×50 mL) and chloroform (2×50 mL). The combined organic extracts were dried, filtered and concentrated under vacuum. The crude product **12** was used without any further purification for the next reaction; MS *m/z* (% relative intensity, ion): 368(50, $[M]^+$), 337(1), 326(26), 310(1), 295(20), 284(75), 269(100), 253(2), 241(27), 225(2), 211(7), 197(6), 183(12), 169(3), 155(10), 139(9), 126(15), 115(10), 99(5), 87(5), 69(18), 55(8), 43(78).

4.8.5. 2-(2-Methoxy-4,5-methylenedioxyphenyl)-6-hydroxybenzofuran (cicerfuran) (1a). Anhydrous potassium carbonate (2.5 equiv) was added to the stirring solution of diarylacetylene **12** in methanol (10 mL). The reaction was stirred for a further 2 h at room temperature and concentrated under vacuum. GC–MS analysis showed cicerfuran (**1a**) as 5% of the mixture which could not be further purified by column chromatography; MS *m/z* (% relative intensity, ion): 284(100, $[M]^+$), 269(90), 253(1), 241(60), 225(2), 211(10), 197(5), 183(15), 171(8), 155(22), 142(37), 134(2), 115(10), 102(11), 91(11), 77(13), 69(20), 53(25), 44(20).[11]

4.9. Synthesis of stilbene intermediates by Wittig reactions

4.9.1. 2,4-Di-*O*-*tert*-butyldimethylsiloxybenzaldehyde (17). *tert*-Butyldimethylsilyl chloride (6.94 g, 40 mmol) was stirred for 10 min in DMF (30 mL). To this stirring solution diisopropylamine (6.94 mL, 40 mmol) was added dropwise and allowed to stir for 10 min. 2,4-Dihydroxybenzaldehyde (3.0 g, 20 mmol) was then added with further stirring for 1 h. The reaction was stopped by addition of water (50 mL) and extracted with a mixture of petroleum ether and diethyl ether (9:1). The organic layer was dried and concentrated yielding benzaldehyde **19** as an oil in 99.8% yield (8.03 g); IR (film): ν_{max} 2870, 2840, 2800, 2775, 1648, 1550, 1535, 1430, 1410, 1345, 1250, 1230, 1210, 1195, 1042 cm^{-1}; MS *m/z* (% relative intensity, ion): 365(1, $[M-H]^+$), 351(5), 309(100), 293(2), 279(2), 265(1), 251(8), 25.8(2), 221(1), 208(1), 195(13), 178(10), 165(6), 149(7), 133(8), 117(5), 104(2), 91(5), 73(50), 57(10), 41(9).

4.10. General method for reduction of benzaldehydes

Sodium borohydride (75 mmol) was added stepwise to stirred solutions of benzaldehydes **4a–c** (50 mmol) in ethanol (200 mL) at 0 °C. After complete addition, the reaction mixture was allowed to warm to room temperature and stirring continued for 2 h. The reaction was quenched by adding water (100 mL), ethanol was removed under reduced pressure and the aqueous phase extracted with dichloromethane (3×100 mL). The combined organic phase was then washed with water (100 mL) and aqueous $NaHCO_3$ (100 mL). The organic extract was dried, filtered and concentrated. The products were recrystallised from diethyl ether/petroleum ether as white solids.

4.10.1. 2-Methoxy-4,5-methylenedioxybenzyl alcohol (13b). White solid (99%), mp 53–55 °C; IR (nujol mull) ν_{max}: 1465, 1235, 1148, 1134, 1110, 1035, 982 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.79 (s, 1H), 6.54 (s, 1H), 5.91 (s, 2H), 4.57 (s, 2H), 3.80 (s, 3H,), 2.27 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 152.7, 147.6, 140.8, 121.3, 109.0, 101.1, 94.4, 61.7, 56.2; MS *m/z* (% relative intensity, ion): 182(100, $[M]^+$), 165(90), 149(23), 135(14), 81(23), 69(23), 53(45), 41(5); HRMS (CI) *m/z* 200.0917 $[M+ NH_4]^+$, calcd for $C_9H_{14}NO_4$ 200.0923.

4.10.2. 2-Methyl-4,5-methylenedioxybenzyl alcohol (13c). Yellow solid (97%) mp 53 °C; IR ($CHCl_3$) ν_{max}: 3590, 2870, 1622, 1510, 1490, 1370, 1260, 1160, 1045, 940, 870 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.94 (s, 1H), 6.68 (s, 1H), 5.67 (s, 2H), 4.36 (s, 2H), 2.29 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 146.0, 145.1, 131.9, 127.9, 109.8, 107.7, 100.2, 57.2, 17.9; MS *m/z* (% relative intensity, ion): 166(100, $[M]^+$), 148(83), 135(30), 123(8), 107(50), 93(30), 77(42), 65(20), 51(33), 44(8).

4.10.3. Two-step synthesis of 3,4-methylenedioxybenzyltriphenylphosphonium bromide (15a). To a stirred solution of 3,4-methylenedioxybenzyl alcohol (piperonyl alcohol) (**13a**) (8.45 g, 55.5 mmol) in CH_2Cl_2 (50 mL) was added phosphorous tribromide (17.98 g, 1.2 equiv) dropwise at 0 °C. When addition was complete, the ice bath was removed and the reaction mixture allowed to stir at room temperature. After stirring for 2 h, bromination was terminated by careful addition of aqueous $NaHCO_3$ at 0 °C. The organic phase was separated, dried and concentrated under vacuum, affording 3,4-methylenedioxybenzyl bromide (**14a**) as a white solid in 67% yield (7.8 g), mp 45–47 °C; ^1H NMR ($CDCl_3$): δ 6.86 (d, J=7.6 Hz, 2H), 6.74 (d, J=7.6 Hz, 1H), 5.96 (s, 2H), 4.52 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 147.9, 147.8, 131.5, 122.7, 109.5, 108.3, 101.3, 34.2; MS *m/z* (% relative intensity, ion): 245(7, $[M]^+$), 229(1), 180(2), 165(100), 151(34), 135(20), 121(15), 107(10), 93(10), 77(20), 53(18), 40(5). To the stirred suspension of 3,4-methylenedioxybenzyl bromide (7.8 g, 36.5 mmol) in toluene (100 mL) was added triphenylphosphine (11.45 g, 1.2 equiv). After stirring for 30 min at room temperature the reaction mixture was heated to reflux for 2 h. After cooling to room temperature the precipitates were filtered and washed with excess diethyl ether. Phosphonium salt **15a** was obtained as a white crystalline solid in 60% yield (16 g), mp 242–244 °C; IR (nujol mull): ν_{max} 2950, 2695, 1574, 1581, 1538, 1455, 1435, 1385, 1332, 1250, 1141, 1108, 1064, 1039, 988 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.78–7.63 (m, 15H), 6.64–6.52 (m, 3H), 5.87 (s, 2H), 5.30 (d, J=13.8 Hz, 2H).

4.10.4. Attempted synthesis of 2-methoxy-4,5-methylenedioxybenzyltriphenylphosphonium bromide (15b). To a stirred solution of 2-methoxy-4,5-methylenedioxybenzyl alcohol (**13b**) (3 g, 16.5 mmol) in CH_2Cl_2 (50 mL) was added phosphorous tribromide dropwise (5.34 g, 1.2 equiv). After stirring for 5 h bromination was terminated by careful addition of aqueous $NaHCO_3$. The organic phase was separated, dried and concentrated under vacuum to give 1,2-di-(2-methoxy-4,5-methylenedioxyphenyl)ethane (**16**) in 73% yield (4 g); ^1H NMR ($CDCl_3$): δ 6.57 (s, 2H), 6.51 (s, 1H), 5.85 (s, 2H), 3.78 (s, 2H), 3.75 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 152.3, 146.1, 140.8, 121.7, 110.1, 100.9, 94.7, 56.5, 29.3.

4.11. Improved method for the synthesis of phosphonium bromides

A solution of phosphorous tribromide (0.5 equiv) in toluene (50 mL) was added dropwise to a stirred solution of piperonyl alcohol (66 mmol) in toluene (100 mL) at 0 °C. After addition, the reaction mixture was allowed to warm to room temperature and the stirring was continued for 30 min. Bromination was terminated by careful addition of aqueous $NaHCO_3$ at 0 °C. The organic phase was separated, dried, filtered and passed through a thick pad of Celite®. To the filtrate (100 mL) was added triphenylphosphine (1.2 equiv). The reaction mixture was stirred for 30 min at room temperature and then heated to reflux for 2 h. After cooling to room temperature, the precipitates were filtered and washed with excess diethyl ether.

4.11.1. 3,4-Methylenedioxybenzyltriphenylphosphonium bromide (15a). White crystalline solid (95%), mp 242–244 °C; IR (nujol mull): ν_{max} 2950, 2695, 1574, 1581, 1538, 1455, 1435, 1385, 1332, 1250, 1141, 1108, 1064, 1039, 988 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.78–7.63 (m, 15H), 6.64–6.52 (m, 3H), 5.87 (s, 2H), 5.30 (d, J=13.8 Hz, 2H).

4.11.2. 2-Methoxy-4,5-methylenedioxybenzyltriphenylphosphonium bromide (15b). White crystalline solid (71%), mp 256–258 °C; IR (nujol mull): ν_{max} 1581, 1538, 1455, 1435, 1355, 1332, 1250, 1142, 1108, 1064, 988 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.81–7.76 (m, 15H), 6.86 (s, 1H), 6.24 (s, 1H), 5.87 (s, 2H), 5.09 (d, J=14.5 Hz, 2H), 3.12 (s, 3H).

4.11.3. 2-Methyl-4,5-methylenedioxytriphenylphosphonium bromide (15c). Light yellow solid (64%); IR (nujol mull): ν_{max} 2950, 1581, 1538, 1455, 1435, 1355, 1332, 1250, 1141, 1108, 1064, 988 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.84–7.64 (m, 15H), 6.55 (d, J=2 Hz, 1H), 6.46 (s, 1H), 5.87 (s, 2H), 5.17 (d, J=14.6 Hz, 2H), 1.55 (s, 3H).

4.12. Synthesis of stilbenes by the Wittig reaction

Sodium hexamethyldisilazide (15 mL of 1 M soln in THF, 15 mmol) was added by syringe to a stirred suspension of phosphonium salt (12.6 mmol) in THF (50 mL) at 0 °C, and

allowed to stir for a further 1 h. 2,4-Di-*tert*-butyldimethylsilyloxybenzaldehyde (**17**) (8 mmol) in THF (50 mL) was then added dropwise using a dropping funnel. After addition, the reaction mixture was allowed to warm to room temperature and stirring was continued for 2 h. The reaction mixture was then washed with aqueous NH_4Cl, filtered, dried and concentrated under vacuum. The crude product was dissolved in 1 mL of diethyl ether and excess petroleum ether added to precipitate the remaining triphenylphosphonium oxide. The filtrate was concentrated under vacuum to give the required product.

4.12.1. 1-(3,4-Methylenedioxyphenyl)-2-(2,4-di-*O*-*tert*-butyldimethylsiloxyphenyl)ethene (18a). Yellow oil (65%); IR (film): ν_{max} 2875, 2843, 2800, 2815, 1560, 1523, 1463, 1450, 1405, 1360, 1211, 1159, 1133, 995 cm^{-1}; MS *m/z* (% relative intensity, ion): 484(60, $[M]^+$), 469(2), 427(50), 411(1), 397(2), 369(8), 351(2), 341(3), 325(2), 305(10), 295(2), 283(1), 263(2), 249(1), 239(5), 223(3), 214(1), 203(8), 185(10), 170(12), 156(10), 145(5), 135(10), 117(10), 105(1), 91(1), 73(100), 59(10), 41(10).

4.12.2. 1-(2-Methoxy-4,5-methylenedioxyphenyl)-2-(2,4-di-*O*-*tert*-butyl-dimethylsiloxyphenyl)-ethene (18b). Yellow oil (61%); MS *m/z* (% relative intensity, ion): 514(60, $[M]^+$), 457(6), 426(4), 400(2), 385(10), 369(2), 351(2), 327(8), 311(8), 281(5), 233(4), 207(12), 185(10), 165(13), 115(2), 89(7), 73(100), 44(50).

4.12.3. 1-(2-Methyl-4,5-methylenedioxyphenyl)-2-(2,4-di-*O*-*tert*-butyldimethylsiloxyphenyl)-ethene (18c). Yellow oil (68%); IR (film) ν_{max}: 2875, 2845, 2809, 2790, 1560, 1523, 1441, 1379, 1211, 1132, 995 cm^{-1}; MS *m/z* (% relative intensity, ion): 498(88, $[M]^+$), 483(2), 441(22), 425(1), 411(2), 383(10), 380(8), 355(5), 326(2), 305(8), 293(10), 281(2), 263(1), 249(5), 217(4), 205(2), 192(6), 177(7), 165(6), 149(16), 135(10), 117(5), 103(5), 91(1), 73(100), 59(16), 41(10).

4.13. Epoxidation of stilbenes

3-Chloroperbenzoic acid (4 mmol) was added portionwise to a stirred solution of stilbene (2.06 mmol) in dichloromethane at 0 °C. After addition, the reaction was allowed to warm to room temperature and stirring continued for 1 h. The reaction was then quenched by addition of water. The organic phase was washed three times with aqueous $NaHCO_3$ dried, filtered and concentrated under vacuum. The crude product was purified by adding excess petroleum ether that resulted in precipitation of 3-chlorobenzoic acid as a white solid. Precipitates were filtered off and the filtrate was concentrated under vacuum and used for the next reaction without further purification.

4.13.1. 1-(3,4-Methylenedioxyphenyl)-2-(2,4-di-*O*-*tert*-butyldimethylsiloxyphenyl)ethene oxide (19a). Yellow oil (53%); MS *m/z* (% relative intensity, ion): 500(3, $[M]^+$), 471(100), 443(13), 415(2), 357(2), 299(1), 179(5), 135(13), 105(2), 73(67), 41(5).

4.13.2. 1-(2-Methoxy-4,5-methylenedioxyphenyl)-2-(2,4-di-*O*-*tert*-butyldimethylsiloxyphenyl)ethene oxide (19b). Yellow oil (48%); MS *m/z* (% relative intensity, ion): 530(2, $[M]^+$), 501(100), 473(5), 457(1), 430(1), 387(7), 355(10), 314(8), 297(1), 281(1), 265(1), 241(3), 222(2), 193(8), 165(13), 135(5), 105(2), 89(1), 73(80), 57(10), 41(10); HRMS (E1) *m/z* 531.2593 $[M+H]^+$, calcd for $C_{28}H_{43}O_6Si_2$ 531.2595.

4.13.3. 1-(2-Methyl-4,5-methylenedioxyphenyl)-2-(2,4-di-*O*-*tert*-butyldimethylsiloxyphenyl)ethene oxide (19c). Yellow oil (48%); MS *m/z* (% relative intensity, ion): 514(2, $[M]^+$), 485(100), 457(10), 429(2), 399(2), 373(3), 351(13), 335(1), 313(2), 297(1), 267(1), 239(2), 214(1), 193(4), 165(4), 149(18), 133(4), 115(2), 91(2), 73(88), 57(6), 41(6).

4.14. Deprotection and acid-catalysed cyclisation

Epoxides (**19a**,**b** and **c**) (1 mmol) were each dissolved in acetone–water (95/5, 10 mL). To this solution was added $CuCl_2 \cdot H_2O$ (2 mmol) and the homogeneous mixture was heated under gentle reflux for 48 h. The solvent was removed under vacuum and the crude product immediately dissolved in chloroform (5 mL) and a few crystals of *p*-toluenesulphonic acid added. The reaction was heated at 35 °C for 1 h to give the required product.

4.14.1. 2-(3,4-Methylenedioxyphenyl)-6-hydroxybenzofuran (1e). The product decomposed completely during the work up and purification process; MS *m/z* (% relative intensity, ion): 254(100, $[M]^+$), 225(4), 207(2), 196(14), 181(1), 168(14), 139(22), 127(18), 112(8), 98(4), 89(4), 75(6), 63(7), 51(3), 41(1).

4.14.2. 2-(2-Methoxy-4,5-methylenedioxyphenyl)-6-hydroxybenzofuran (cicerfuran) (1a). White solid (37%); GC-MS retention time 26.45 min; HPLC retention time 22.5 min, λ_m 285.4, 337.8 nm); IR ($CHCl_3$): ν_{max} 3600, 3300, 3000, 2900, 1630, 1510, 1492, 1450, 1380, 1320, 1275, 1175, 1150, 1120, 1045, 960, 940, 910, 880, 850, 830 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.36 (d, $J=8.4$ Hz, 1H), 7.34 (s, 1H), 7.09 (d, $J=1.0$ Hz, 1H), 6.94 (s, 1H), 6.90 (m, 1H), 6.71 (dd, $J=8.4$, 2.1 Hz, 1H), 6.04 (s, 2H), 3.90 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 155.5, 154.0, 151.8, 150.0, 147.7, 141.0, 121.1, 120.7, 112.1, 111.3, 104.6, 104.3, 101.3, 97.1, 95.5, 56.3; MS *m/z* (% relative intensity, ion): 284(100, $[M]^+$), 269(90), 253(1), 241(30), 232(1), 225(2), 211(6), 195(2), 183(10), 171(10), 162(5), 155(10), 142(30), 134(10), 126(10), 115(6), 102(4), 91(5), 84(2), 77(5), 69(10), 62(5), 53(10), 44(2); HRMS (E1) *m/z* 285.0757 $[M+H]^+$, calcd for $C_{16}H_{13}O_5$ 285.0763.

4.14.3. 2-(2-Methoxy-4,5-methylenedioxyphenyl)-6-hydroxybenzofuran (1f). The product decomposed completely during the work up and purification process; MS *m/z* (% relative intensity, ion): 268(100, $[M]^+$), 251(9), 239(7), 221(7), 207(22), 197(6), 181(17), 165(9), 152(35), 139(14), 126(5), 115(9), 105(17), 91(6), 76(14), 63(10), 51(10).

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References and notes

1. Stevenson, P. C.; Aslam, S. N. The Chemistry of the Genus *Cicer* L. In *Studies in Natural Product Chemistry*; Atta-ur-Rahman, Ed.; Bioactive Compounds; Elsevier: Amsterdam, The Netherlands, 2005; Vol. 33; in press.
2. Stevenson, P. C.; Veitch, N. C. *Phytochemistry* **1998**, *48*, 947.
3. Donnelly, D. M. X.; Meegan, M. J. In Katritzky, A. R., Rees, W. C., Eds.; Comprehensive Heterocyclic Chemistry; Pergamon: Oxford, 1984; Vol. 4, pp 657–712.
4. Mann, I. S.; Widdowson, D. A.; Clough, J. M. *Tetrahedron* **1991**, *47*, 7991.
5. Donnelly, D. M. X.; Finet, J. P.; Kielty, J. M. *Tetrahedron Lett.* **1991**, *32*, 3835.
6. Watanabe, M.; Kawanishi, K.; Furukawa, S. *Chem. Pharm. Bull.* **1991**, *39*, 579.
7. Scannell, R. T.; Stevenson, R. *J. Heterocycl. Chem.* **1980**, *17*, 1727.
8. Hiroya, K.; Suzuki, N.; Yasuhara, A.; Egawa, Y.; Kasano, A.; Sakamoto, T. I. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4339.
9. Kao, C. L.; Chern, J. W. *Tetrahedron Lett.* **2001**, *42*, 1111.
10. McAllister, G. D.; Hartley, R. C.; Dowson, M. J.; Knaggs, A. R. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3453.
11. Novak, Z.; Timari, G.; Kotschy, A. *Tetrahedron* **2003**, *59*, 7509.
12. Kundu, N. G.; Pal, M.; Mahanty, J. S.; De, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2815.
13. Arcadi, A.; Marinelli, E. *Chem. Commun.* **1986**, 749.
14. Torii, S.; Xu, L. H.; Okumoto, H. *Synlett* **1992**, 515.
15. Schuda, P. F.; Price, W. A. *J. Org. Chem.* **1987**, *52*, 1972.
16. Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo, C. A.; Coburn, C. A.; Di Grandi, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2843.
17. Overman, L. E.; Ricca, D. J.; Tran, V. D. *J. Am. Chem. Soc.* **1993**, *115*, 2042.
18. Haberli, A.; Leumann, C. J. *Org. Lett.* **2001**, *3*, 489.
19. Burke, T. R.; Liu, D. G.; Gao, Y. *J. Org. Chem.* **2000**, *65*, 6288.
20. Aslam, S. N. PhD Thesis, University of Greenwich, 2004.
21. Harwood, L. M.; Moody, C. J. *Experimental Organic Chemistry; Principles and Practice*; Blackwell Scientific: Oxford, 1989.
22. Pettit, G. R.; Minardi, M. D.; Boyd, M. R.; Pettit, R. K. *Anti-Cancer Drug Des.* **2000**, *15*, 397.
23. Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
24. Sinhababu, A. K.; Kawase, M.; Borchardt, R. T. *Synthesis—Stuttgart* **1988**, 710.
25. Tan, Z. P.; Wang, L.; Wang, J. B. *Chin. Chem. Lett.* **2000**, *11*, 753.
26. Getti, G.; Aslam, S. N.; Humber, D. P.; Stevenson, P. C.; Cheke, R. A. *Trans. R. Soc. Trop. Med. Hyg.* **2005**, *97*, 627.
27. Ali, M. A.; Tsuda, Y. *Chem. Pharm. Bull.* **1992**, *40*, 1130.
28. McEwen, W. E.; Guzikowski, A. P.; Wolf, A. P. *J. Fluorine Chem.* **1984**, *25*, 169.
29. Witiak, D. T.; Williams, D. R.; Kakodkar, S. V. *J. Org. Chem.* **1974**, *39*, 1242.
30. Prakash, S.; Khan, M. A.; Khan, K. Z.; Zaman, A. *Phytochemistry* **1985**, *24*, 622.