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Iodo- and bromo-enolcyclization of 2-(2-propenyl)cyclohexanediones and 2-(2-propenyl)cyclohexenone derivatives using iodine in methanol and pyridinium hydrobromide perbromide in dichloromethane

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α-Allylcyclohexane-1,3-diones undergo one-pot iodine–methanol promoted iodocyclization and oxidative aromatization to afford variously substituted 2-iodomethyltetrahydrobenzofuran-4-ones (minor) and 2-iodomethyl-4-methoxydihydrobenzofuran derivatives (major). On the other hand, the α-allyl-1,3-cyclohexanediones react with pyridinium hydrobromide perbromide in dichloromethane to afford mixtures of 2-bromomethyltetrahydrobenzofuran-4-ones (major) and 3-bromomethyltetrahydrobenzopyran-5-ones (minor). The prepared products and their derivatives were characterized using a combination of NMR, FT-IR and mass spectroscopic techniques.

Introduction

Dihydrofuran and furan moieties constitute important chemical units in a large number of naturally occurring substances obtained from plants and marine organisms.[1] Although several methods have been developed for the synthesis of substituted dihydrobenzofurans and benzofurans,[1,2] due to their importance as pharmaceutical, flavor, insecticidal and fish antifeedant agents,[2e,3] development of simple and efficient methods for their construction remains a challenge. Kibayashi and coworkers have previously reported a one-step synthesis of 4-aminodihydrobenzofurans and 4-hydroxyindoles *via* mercury(II) acetate-promoted dehydrogenation–heteromercuration of 2-allyl-3-aminocyclohexenones.[4] Iodoenolcyclization of 2-allylphenol using $SnCl_4$–I_2 in dichloromethane[5a] or I_2–EPZ-10[5b] has been reported to afford the 2-iodomethyl-2,3-dihydrobenzofurans, which are important precursors for the synthesis of benzofurans. Iodine–sodium bicarbonate mixture in dichloromethane, on the other hand, has recently been shown to promote electrophilic cyclization of α-allyl-β-cyclohexanediones to afford the 2-iodomethyltetrahydrobenzofuran-4-ones in good yields.[6a] Huang *et al.*[6b] recently prepared these derivatives *via* polymer-supported selenium-induced electrophilic cyclization of α-(2-propenyl)-1,3-cyclohexanediones and subsequent cleavage of the selenium linkers with CH_3I–NaI in DMF. Electrophilic reagents such as *p*-methoxyphenyltellurium trichloride[2,6] and phenylselenenyl bromide[2,5,6] have also been used before to promote cyclization of α-allyl-β-cyclohexanediones to tetrahydrofuranone derivatives. Although several methods have been described in literature for the construction of 2-iodomethyltetrahydrobenzofuranone moiety,[2e,6,7] corresponding data for the synthesis of 2-bromomethyl derivatives are considerably less documented. Recourse to literature revealed only one example for the synthesis of 2-bromomethyl-6,6-dimethyltetrahydrobenzofuran-4-one (15%) involving the use of rhodium(II)-catalyzed reaction of 2-diazo-5,5-dimethylcyclohexane-1,3-dione with allyl bromide.[2e]

Only a limited number of methods exist in literature for the direct aromatization of cyclohexenone moiety of tetrahydrobenzofuran-4-ones to dihydrobenzofuran derivatives.[1c,2b] Yamaguchi and coworkers[2b] previously dehydrogenated the 4-oxo-4,5,6,7-tetrahydrobenzofuran-2-carboxylic acid to 4-hydroxybenzofuran-2-carboxylic acid using copper(II) bromide in refluxing methanol. Lee and Morehead,[1c] on the other hand, used DDQ in dioxane on 5-acetyl-4-oxo-4,5,6,7-tetrahydrobenzofuran and 4-oxo-4,5,6,7-tetrahydrobenzofuran-5-carboxylate, the products of which were in turn converted to *O*-methylated derivatives using iodomethane in acetone in the presence of potassium carbonate. In 1980 Tamura and Yoshimoto reported the aromatization of cyclohexenones using iodine in methanol under reflux.[8] We have also applied these reaction conditions before to 3-(phosphonoalkyl)cyclohexenones and have prepared a series of benzylphosphonic esters substituted in the aromatic ring with a methoxy group.[9] In a cognate study we subjected the 3-(phosphonoalkyl)cyclohexenones to pyridinium tribromide in acetic acid to afford phenol derivatives bearing 3-phosphonoalkyl moiety.[9] A pyridinium tribromide and sodium bicarbonate mixture in THF has been shown by Trost *et al*. to promote bromolactonization in the synthesis of picrotoxinin.[10] The main objective of this investigation was to study new halocyclization reactions of 2-(2-propenyl)cyclohexanediones with iodine or pyridinium tribromide, in order to assess the regioselectivity of the reactions and the possibility to obtain direct one-pot aromatization of the resulting adducts. The results have been then extended also to some special 2-(2-propenyl)cyclohexenones. Herein we describe the outcome of these reactions and further studies of chemical transformation of the resulting products.

Results and discussion

The readily accessible 2-(2-propenyl)cyclohexane-1,3-diones **1** were subjected to iodine (2 equiv.) in methanol under reflux. Two products were isolated by column chromatography and were found by NMR (^{1}H and ^{13}C), IR and mass spectroscopic techniques to correspond to the previously reported 2-iodomethyl-3,5,6,7-tetrahydrobenzofuran-4-ones **2** (minor) and the 2-iodomethyl-4-methoxy-2,3-dihydrobenzofurans **3** (major) described here for the first time (Scheme 1). Products **3a,b,d** are the result of initial hemiacetal formation from **2** followed by dehydration and spontaneous oxidative aromatization. In the case of 6,6-dimethyl-1,3-cyclohexanedione derivative **1c** we isolated from the cooled reaction mixture a crystalline product characterized as the benzofuran-4-one **2c**. The ^{1}H- and ^{13}C NMR spectral data of product **2c** compare favourably with data reported in the literature for the compound that was previously described by Lee *et al.*[2e] as liquid and by Ferraz *et al.*[6a] and Huang *et al.*[6b] as oil. Its experimentally determined accurate *m*/*z* value ($C_{12}H_{15}O_2I$: 306.0116) represents the closest fit consistent

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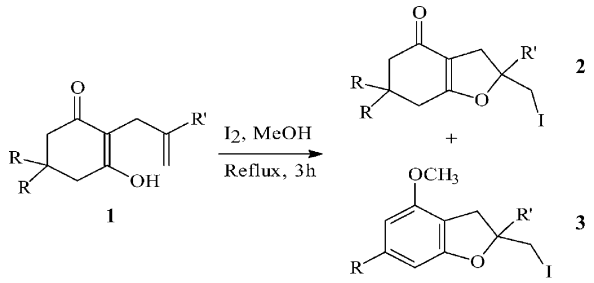


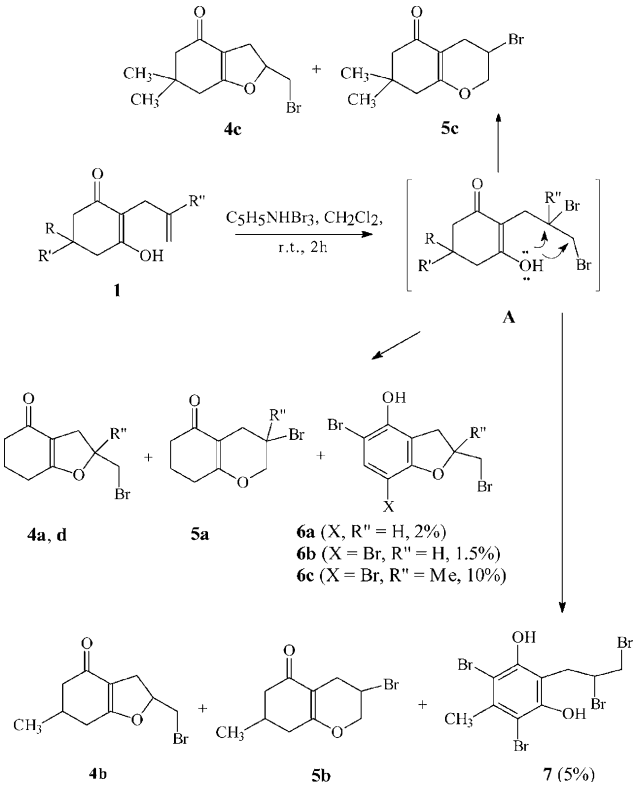
	R, R	R'	% Yield of **2**	% Yield of **3**
a	H, H	H	14	75
b	H, CH_3	H	20	70
c	CH_3, CH_3	H	80	-
d	H, H	CH_3	23	60

Scheme 1

with the assigned structure. However, the efficient preparation of compounds of general formula **2** through iodocyclization reaction was already described previously.[6,2e]

Prompted by the scant attention paid in the literature to the bromoenolcyclization of α-allyl-1,3-dicarbonyl compounds, in the second part of this investigation we subjected systems **1** to pyridinium tribromide in dichloromethane at room temperature to afford mixtures of products characterized as the corresponding 2-bromomethyltetrahydrobenzofuran-4-ones **4** (major) and 3-bromotetrahydrobenzopyran-5-ones **5** (minor) (Scheme 2). In the case of substrates **1a** and **d** we also isolated traces of the 2-bromomethyl-4-hydroxy-2,3-dihydrobenzofuran derivatives **6** substituted with bromine at either C-5 (**6a**) or C-5 and C-7 (**6b** and **6c**). Products **6** are the result of oxidative aromatization of the cyclohexenone moiety of **4** followed by halogenation of the aromatic ring. On the other hand, from the crude mixture of **1b** we also isolated from silica gel column a product characterized using a combination of spectroscopic techniques as the 5,6-dibromo-2-(2,3-dibromopropyl)-5-methyl-1,3-benzenediol **7** (5%). The latter is presumably the result of initial halogenation of the propenyl moiety followed by oxidative aromatization of the ring to a 5-methylresorcinol derivative which then undergoes further bromination at C-5 and C-7. Whereas iodocyclization of α-allylcyclohexanediones leads exclusively to *exo*-cyclized derivatives according to Baldwin's rules,[11] bromoenolcyclization on the other hand gives both the *exo*-**2** and *endo*-cyclized products **3**. Halocyclization reactions of 1,ω-alkenones using Br_2 are known to be much faster and non-selective than the I_2 reactions and their product mixtures often contain 1,2-dibromides and bromosolvates as well as cyclized material.[12] Additionally, it is also known that neighbouring group participation in internal displacements leading to three-membered halonium ions by iodine is 1000–3000 fold better than the corresponding bromine participation.[12]

Although the involvement of a bromonium ion cannot be completely ruled out, the above reaction in our opinion proceeds through a 2-(2,3-dibromopropyl)-1,3-cyclohexanedione intermediate to form both the *endo*- and *exo*-cyclic derivatives. It has been demonstrated in literature that variously substituted allylic alcohols react with bromine in dichloromethane to afford the 1,2-dibromoalcohols, which can be isolated and then cyclized under basic conditions to the corresponding 3-bromotetrahydrobenzofuran derivatives.[13] This literature observation, at least in our opinion, provides further support for the envisaged involvement of the 2-(2,3-dibromopropyl)-1,3-cyclohexanedione intermediate **A** in the proposed mechanism.



	R, R'	R"	% Yield **4**	% Yield **5**
a	H, H	H	40	15
b	H, CH_3	H	44	8
c	CH_3, CH_3	H	50	10
d	H, CH_3	CH_3	54	-

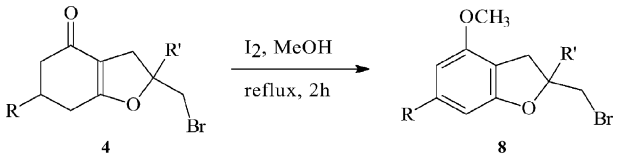
Scheme 2

Tetrahydrobenzofuranone and tetrahydropyranone moieties contain several potential reactive centers for further studies of chemical transformation. Systems **4a,b,d** and **5a,b** were subjected to iodine (1.5–2 equiv.) in refluxing methanol to afford the corresponding 2-bromomethyl-4-methoxydihydrobenzofurans **8a–c** and 3-bromo-5-methoxydihydrobenzopyran **9a,b** all described here for the first time (Scheme 3).

To further demonstrate the versatility of the iodine–methanol mixture in the construction of diversely functionalized benzofuran derivatives, we prepared the 3-phosphonylmethyl-2-(2-propenyl)-2-cyclohexenone derivative **10a**[14] and its previously undescribed 5-methyl derivative **10b** and subjected them to the above reaction conditions to afford the corresponding 2-iodomethyl-2,3-dihydrobenzofuran derivatives **11a** and **b** as sole products, respectively (Scheme 4). Under similar reaction conditions, the 3-(phosphonoalkyl)cyclohexenones bearing no substituent at position 2 previously afforded the benzylphosphonic esters substituted in the aromatic ring with methoxy group.[9] The mechanism of formation of **11** presumably involves initial iodocyclization of the hemiacetal followed by expulsion of methanol to form a conjugated diene which then undergoes oxidative aromatization.

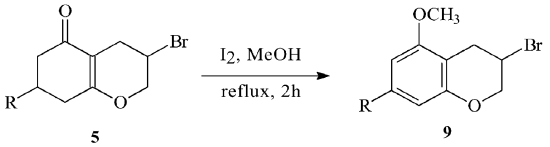
The 2-iodomethyl-4-methoxydihydrobenzofuran derivatives **3a–c** undergo Arbuzov reaction when heated with triethyl phosphite to afford the corresponding hitherto unknown phosphonate derivatives **12** in moderate yields (Scheme 5).

Systems **3a,b** and **11a,b** were subjected to DBU in toluene under reflux to afford the corresponding benzofuran derivatives



4 8

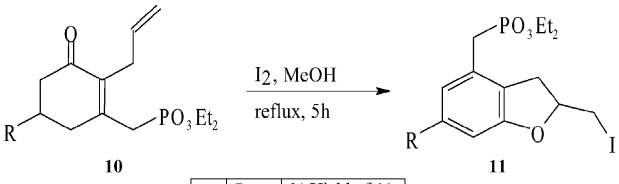
	R, R'	% Yield **8**
a	H, H	72
b	CH_3, H	65
c	H, CH_3	86



5 9

	R	% Yield **9**
a	H	85
b	CH_3	89

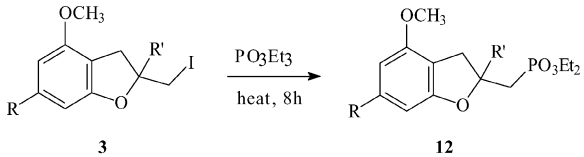
Scheme 3



10 11

	R	% Yield of **11**
a	H	69
b	CH_3	65

Scheme 4



3 12

	R	R'	% Yield **12**
a	H	H	66
b	CH_3	H	55
c	H	CH_3	69

Scheme 5

13 (Scheme 6). These products are easily distinguished from the corresponding precursors by the presence of the methyl and olefinic proton signals in their ^{1}H NMR spectra in the region δ 2.40–2.50 ppm and δ 6.00–6.50 ppm, respectively.

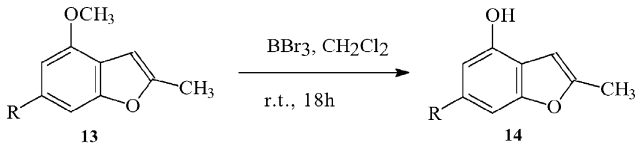
Further functional group modification was made on the 4-methoxy-2-methylbenzofurans **13a,b** through demethylation using boron tribromide in dichloromethane to afford the corresponding 4-hydroxy-2-methylbenzofurans **14a,b** (Scheme 7) which are useful intermediates in the synthesis of biologically active furoquinolinedione derivatives.[15]

In conclusion, the combined electrophilic and oxidative properties associated with iodine were exploited to construct diversely substituted tetrahydrobenzofuranones and dihydrobenzofuran derivatives. Pyridinium tribromide in dichloromethane, on the other hand, provides an effective medium

3, 11 13

Substr.	R	R'	% Yield of **13**
3a	H	OCH_3	72 (**13a**)
3b	CH_3	OCH_3	93 (**13b**)
11a	H	$CH_2PO_3Et_2$	85 (**13c**)
11b	CH_3	$CH_2PO_3Et_2$	60 (**13d**)

Scheme 6



13 14

	R	% Yield **14**
a	H	91
b	CH_3	80

Scheme 7

for the bromoenolcyclization of α-allylcyclohexane-1,3-diones to afford tetrahydrobenzofuranones and tetrahydrobenzopyranones. Whereas electrophilic reagents such as iodine,[1,2,5] *p*-methoxyphenyltellurium trichloride[2,6] and phenylselenenyl bromide[2,5,6] promote *exo*-cyclization of α-allyl-β-cyclohexanediones to tetrahydrofuranone derivatives in accordance with Baldwin's rules,[11] bromocyclization is nonselective and it affords both the *exo*- and *endo*-cyclized derivatives.

Experimental

Solvents and commercially available reagents were purified by conventional methods before use. Reactions involving organolithium reagents were carried out in an atmosphere of dry nitrogen using oven-dried glassware. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. For column chromatography, Merck kieselgel 60 (0.063–0.200 mm) was used as the stationary phase. NMR spectra were obtained as $CDCl_3$ solutions using Varian Mercury 300 MHz NMR spectrometer and the chemical shifts are quoted relative to the solvent peaks (δ_H 7.25 and δ_C 77.0 ppm). ^{31}P NMR chemical shift values are given relative to 85% H_3PO_4 as external standard. FT-IR spectra were recorded neat (powder or oil) using a FTS 7000 Series Digilab Win-IR Pro spectrometer. Low- and high-resolution mass spectra were recorded at an ionization potential of 70 eV using a Micromass Autospec-TOF (double focusing high resolution) instrument. Substrates **1a–d**[16] and **10a**[14] were prepared according to the procedures described in the respective literature.

Preparation of diethyl {[(5-methyl-2-(propen-2-yl)-3-oxo]methyl}phosphonate 10b

n-Butyl lithium (1.6 M solution in hexane; 1.3 mol equiv.) was diluted with THF (3 mL per mmol of diethyl methylphosphonate) and cooled to −65 °C. To this solution was added dropwise with stirring a solution of diethyl methylphosphonate (1 mol equiv.) in THF (1 mL per mmol of phosphonate) and the mixture was stirred at this temperature for 30 min. A solution of 3-chloro-5-methyl-2-(2-propenyl)-2-cyclohexenone (1 mol equiv.) in THF (1 mL per mmol of electrophile) was then added and the reaction mixture was stirred at −65 °C for 30 min. The

mixture was allowed to warm to room temperature and after stirring for 1 h at this temperature, the mixture was quenched with 20% aqueous sulfuric acid. The product was extracted with chloroform and the combined organic layers were sequentially washed with water, brine and dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the residue was purified by column chromatography R_F (3 : 2 EtOAc–hexane, v/v) 0.27, to afford **10b** as an oil (50%); δ_H (300 MHz, $CDCl_3$) 1.04 (3H, d, *J* 6.0 Hz), 1.31 (6H, dt, *J* 1.8 and 7.1 Hz), 2.02–2.31 (3H, m), 2.47–2.63 (2H, m), 2.81 (2H, ddd, *J* 14.1 and 24.2 Hz), 3.04–3.21 (2H, m), 4.04–4.16 (4H, m), 4.91 (1H, dddd, *J* 1.8, 3.6 and 6.6 Hz), 4.96 (1H, t, *J* 1.8 Hz), 5.66–5.79 (1H, m); δ_C (75 MHz, $CDCl_3$) 16.4 (d, J_{CP} 6.0 Hz), 21.0, 29.1, 29.6, 33.3 (d, J_{CP} 134.0 Hz), 40.2 (d, J_{CP} 2.0 Hz), 45.8, 62.2 (t, J_{CP} 6.0 Hz), 114.8, 135.3, 135.2 (d, J_{CP} 8.0 Hz), 149.4 (d, J_{CP} 11.1 Hz), 198.3 (d, J_{CP} 3.2 Hz); δ_P 25.6; ν_{max}/cm^{-1} 964.3, 1022.8, 1241.1, 1664.6; MS (EI) *m*/*z* 300 (M^+, 45.1), 162 (100), 147 (33.0). HRMS (EI) calculated for $C_{15}H_{25}O_4P$: 300.1490. Found: 300.1491.

General procedure for iodocyclization of 1

A stirred mixture of **1** (1 equiv.) and iodine (2 equiv.) in methanol (5 mL per mmol of allylcyclohexenone) was boiled under reflux for 3 h. The solvent was evaporated under reduced pressure and the residue was taken up into chloroform. The organic solution was sequentially washed with saturated aqueous sodium thiosulfate, sodium bicarbonate and brine and then dried (Na_2SO_4). The mixture was filtered, evaporated under reduced pressure and the residue was purified by column chromatography.

2-Iodomethyl-3,5,6,7-tetrahydrobenzofuran-4(2*H*)-one 2a and 2-iodomethyl-4-methoxy-2,3-dihydrobenzofuran 3a. Reaction of **1a** with I_2–MeOH followed by column chromatography (3 : 2 toluene–EtOAc, v/v) yielded two products **3a** and **2a** in sequence.

3a (R_F 0.86), oil (75%); δ_H (300 MHz, $CDCl_3$) 2.96 (1H, dd, *J* 6.6 and 15.9 Hz), 3.30 (1H, dd, *J* 3.9 and 10.5 Hz), 3.33 (1H, dd, *J* 3.6 and 11.7 Hz), 3.42 (1H, dd, *J* 5.1 and 10.2 Hz), 3.82 (3H, s), 4.86–4.95 (1H, m), 6.57 (1H, d, *J* 6.0 Hz), 6.60 (1H, d, *J* 5.7 Hz), 7.09 (1H, t, *J* 8.4 Hz); δ_C (75 MHz, $CDCl_3$) 9.0, 33.6, 55.4, 82.2, 102.8, 103.2, 112.7, 129.2, 156.4, 160.3; ν_{max}/cm^{-1} 760.8, 1084.3, 1234.4, 1462.0, 1606.7; MS (EI) *m*/*z* 290 (M^+, 100), 163 (68.3), 147 (26.0), 91 (29.2). HRMS (EI) calculated for $C_{10}H_{11}O_2I$: 289.9804. Found: 289.9803.

2a (R_F 0.29), solid (14%), mp 71–73 °C (Lit.[2e,6] 72–74 °C); δ_H (300 MHz, $CDCl_3$) 2.03 (2H, quint., *J* 6.6 and 9.4 Hz), 2.33 (2H, t, *J* 6.5 Hz), 2.40–2.46 (2H, m), 2.58 (1H, ddt, *J* 2.0, 6.7 and 14.8 Hz), 2.97 (1H, ddt, *J* 2.0, 10.2 and 14.8 Hz), 3.33 (2H, dddd, *J* 6.0, 8.3 and 14.8 Hz), 4.77–4.87 (1H, m); δ_C (75 MHz, $CDCl_3$) 8.25, 21.6, 23.8, 32.5, 36.4, 83.4, 112.9, 176.6, 195.4; ν_{max}/cm^{-1} 937.4, 1222.9, 1403.4, 1614.2.

2-Iodomethyl-6-methyl-3,5,6,7-tetrahydrobenzofuran-4(2*H*)-one 2b and 2-iodomethyl-4-methoxy-6-methyl-2,3-dihydrobenzofuran 3b. Reaction of **1b** with I_2–MeOH followed by column chromatography (3 : 2 toluene–EtOAc, v/v) yielded two products **3b** and **2b** in sequence.

3b (R_F 0.96), oil (70%); δ_H (300 MHz, $CDCl_3$) 2.29 (3H, s), 2.91 (1H, dd, *J* 6.6 and 15.6 Hz), 3.27 (1H, dd, *J* 9.9 and 15.0 Hz), 3.31 (1H, dd, *J* 7.5 and 9.9 Hz), 3.41 (1H, dd, *J* 5.1 and 10.2 Hz), 3.80 (3H, s), 4.83–4.92 (1H, m), 6.24 (1H, s), 6.27 (1H, s); δ_C (75 MHz, $CDCl_3$) 9.2, 22.0, 33.4, 55.3, 82.3, 103.4, 104.2, 109.7, 139.8, 156.1, 160.4; ν_{max}/cm^{-1} 978.0, 1094.3, 1220.9, 1336.7, 1602.9; MS (EI) *m*/*z* 304 (M^+, 100), 177 (68.0), 28 (72.5). HRMS (EI) calculated for $C_{11}H_{13}O_2I$: 303.9960. Found: 303.9969.

2b (R_F 0.37), (Equal mixture of diastereomers by ^{13}C NMR), oil (20%); δ_H (300 MHz, $CDCl_3$) 1.09 (3H, dd, *J* 1.6 and 6.5 Hz), 2.00–2.59 (4H, m), 2.90–3.00 (1H, m), 3.32 (2H, dd, *J* 5.7 and 6.9 Hz), 4.76–4.86 (1H, m); δ_C (75 MHz, $CDCl_3$) 8.2, 8.3, 20.9, 21.0, 29.6, 29.8, 31.7, 31.8, 32.3, 32.4, 44.9, 83.5, 83.6, 112.4, 112.5, 176.2, 176.3, 194.9, 194.8; ν_{max}/cm^{-1} 1044.1, 1206.0, 1400.8, 1630.7.

2-Iodomethyl-6,6-dimethyl-3,5,6,7-tetrahydrobenzofuran-4(2*H*)-one 3c. The product which crystallised from the cooled reaction mixture of **1c** with I_2–MeOH was filtered, washed with ice-cold ethanol and dried to afford pure **3c**, solid (80%) mp 151–154 °C; δ_H (300 MHz, $CDCl_3$ + 0.5% DMSO-d_6) 0.87 (3H, s), 0.88 (3H, s), 1.99 (2H, s), 2.08 (2H, s), 2.34 (1H, ddt, *J* 1.8, 6.7 and 14.8 Hz), 2.74 (1H, ddt, *J* 1.9, 10.0 and 14.8 Hz), 3.16 (2H, dd, *J* 1.6 and 5.3 Hz), 4.56–4.65 (1H, m); δ_C (75 MHz, $CDCl_3$ + 0.5% DMSO-d_6) 8.7, 27.9, 28.3, 31.9, 33.5, 37.0, 50.2, 82.8, 110.7, 175.5, 194.0; ν_{max}/cm^{-1} 1036.8, 1217.1, 1401.6, 1629.8; MS (EI) *m*/*z* 306 (M^+, 75.5), 254 (80.0), 250 (51.5), 179 (100), 123 (45.0), 28 (74.0). HRMS (EI) calculated for $C_{12}H_{15}O_2I$: 306.0117. Found: 306.0116.

2-Iodomethyl-2-methyl-3,5,6,7-tetrahydrobenzofuran-4(2*H*)-one 2d and 2-iodomethyl-4-methoxy-2-methyl-2,3-dihydrobenzofuran 3d. Reaction of **1d** with I_2–MeOH followed by column chromatography (3 : 2 toluene–EtOAc, v/v) yielded products **3d** and **2d** in sequence.

3d (R_F 0.96), oil (60%); δ_H (300 MHz, $CDCl_3$) 1.66, 2.98 (1H, d, *J* 15.9 Hz), 3.25 (1H, d, *J* 15.9 Hz), 3.42 (2H, s), 3.82 (3H, s), 6.40 (1H, d, *J* 3.6 Hz), 6.43 (1H, d, *J* 3.0 Hz), 7.09 (1H, t, *J* 7.8 Hz); δ_C (75 MHz, $CDCl_3$) 15.6, 26.2, 38.7, 55.3, 87.1, 102.9, 103.0, 113.0, 129.2, 156.6, 159.7; ν_{max}/cm^{-1} 760.3, 1086.4, 1246.0, 1462.0, 1605.6; MS (EI) *m*/*z* 304 (M^+, 100), 177 (70.0), 163 (28.0). HRMS (EI) calculated for $C_{11}H_{13}O_2I$: 303.9960. Found: 303.9960.

2d (R_F 0.36), oil (23%); δ_H (300 MHz, $CDCl_3$) 159 (3H, s), 2.02 (2H, quint., *J* 6.3 and 10.1 Hz), 2.33 (2H, t, *J* 6.9 Hz), 2.38–2.44 (1H, m), 2.66 (1H, tt, *J* 1.5 and 15.0 Hz), 2.85 (1H, tt, *J* 2.1 and 14.7 Hz), 3.34 (1H, *J* 10.5 Hz), 3.38 (1H, d, *J* 10.2 Hz); δ_C (75 MHz, $CDCl_3$) 14.5, 21.6, 23.9, 26.2, 36.4, 37.7, 89.4, 112.8, 175.7, 195.6; ν_{max}/cm^{-1} 1000.9, 1179.0, 1399.5, 1626.6; MS (EI) *m*/*z* 292 (M^+, 53.0), 165 (100), 43 (59.0). 39 (93.8). HRMS (EI) calculated for $C_{10}H_{13}O_2I$: 291.9960. Found: 291.9960.

General procedure for bromocyclization of 1

A stirred mixture of 2-allyl-1,3-cyclohexanedione **1** (1 equiv.) and pyridinium tribromide (1.2–1.5 equiv.) in dichloromethane (2.5 mL per mmol of **1**) was stirred at room temperature for 1 h. The reaction mixture was poured into ice-cold solution of saturated aqueous Na_2CO_3 and the product was extracted into chloroform. The combined chloroform solutions were washed with brine, dried (Na_2SO_4), filtered, evaporated under reduced pressure and the residue was purified by column chromatography.

2-Bromomethyl-3,5,6,7-tetrahydrobenzofuran-4(2*H*)-one 4a, 3-bromo-2,3,4,6,7,8-hexahydro-1-benzopyran-5(5*H*)-one 5a, 5-bromo-2-bromomethyl-4-hydroxy-2,3-dihydrobenzofuran 6a and 5,7-dibromo-2-bromomethyl-4-hydroxy-2,3-dihydrobenzofuran 6b. Reaction of **1a** with pyridinium tribromide followed by column chromatography (3.5 : 1.5 hexane–EtOAc, v/v) yielded products **6a,6b,5a** and **4a** in sequence.

6a (R_F 0.71), oil (2%); δ_H (300 MHz, $CDCl_3$) 3.11 (1H, dd, *J* 6.3 and 16.2 Hz), 3.38 (1H, dd, *J* 9.3 and 16.2 Hz), 3.54 (1H, dd, *J* 6.6 and 10.5 Hz), 3.59 (1H, dd, *J* 4.8 and 10.7 Hz), 5.01–5.10 (1H, m), 5.55 (1H, s), 6.32 (1H, d, *J* 8.4 Hz), 7.19 (1H, dd, *J* 0.6 and 8.5 Hz); δ_C (75 MHz, $CDCl_3$) 32.3, 34.3, 82.4, 101.1, 103.6, 112.6, 131.2, 148.8, 160.3; ν_{max}/cm^{-1} 791.2, 1031.2, 1259.5, 1452.4, 1607.4, 3489.2; MS (EI) *m*/*z* 308 (M^+, 100), 306 (48.5), 227 (31.5), 148 (81.5), 134 (77.4). HRMS (EI) calculated for $C_9H_8O_2{}^{79}Br_2$ 305.8891. Found: 305.8893.

6b (R_F 0.62), oil (1.5%); δ_H (300 MHz, $CDCl_3$) 3.24 (1H, dddd, *J* 0.9, 6.6 and 16.2 Hz), 3.47 (1H, dddd, *J* 0.9, 9.5 and 16.2 Hz), 3.53 (1H, dd, *J* 7.2 and 10.5 Hz), 3.64 (1H, dd, *J* 4.5 and 10.5 Hz), 5.10–5.19 (1H, m), 5.53 (1H, s), 7.37 (1H, t, *J* 1.8 Hz); δ_C (75 MHz, $CDCl_3$) 33.3, 33.8, 82.6, 93.6, 101.6,

113.3, 133.0, 148.3, 157.4; ν_{max}/cm^{-1} 717.5, 964.4, 1039.9, 1155.4, 1263.3, 1316.3, 1442.8, 1611.2, 3488.0; *m/z* 388 (100), 384 (M$^+$, 34.0), 307 (55.5), 228 (60.5), 226 (53.0), 147 (33.4). HRMS (EI) calculated for $C_9H_7O_2{}^{79}Br_3$: 383.7996. Found: 383.7996.

5a (R_F 0.29), oil (15%); δ_H (300 MHz, $CDCl_3$) 2.03 (2H, quint., *J* 6.9 and 9.8 Hz), 2.32 (2H, dt, *J* 3.6 and 6.5 Hz), 2.40–2.46 (2H, m), 3.42 (1H, dd, *J* 8.1 and 9.5 Hz), 3.64–3.73 (1H, m), 3.73 (1H, dd, *J* 3.0 and 10.2 Hz), 4.46 (1H, dd, *J* 5.4 and 9.9 Hz), 4.60 (1H, t, *J* 9.9 Hz); δ_C (75 MHz, $CDCl_3$) 21.6, 24.0, 35.3, 36.4, 36.6, 41.8, 77.5, 113.9, 179.5, 195.1; ν_{max}/cm^{-1} 935.9, 1182.2, 1236.6, 1401.6, 1623.4; MS (EI) *m/z* 230 (M$^+$, 25.0), 151 (56.0), 137 (58.5), 130 (44.5), 41 (42.5), 28 (85.0). HRMS (EI) calculated for $C_9H_{11}O_2{}^{79}Br$: 229.9942. Found: 229.9945.

4a (R_F 0.14), solid (40%), m.p. 82–84 °C; δ_H (300 MHz, $CDCl_3$) 2.03 (2H, quint., *J* 6.3 and 9.8 Hz), 2.34 (2H, t, *J* 6.3 Hz), 2.44 (2H, t, *J* 6.3 Hz), 2.67 (1H, dd, *J* 6.9 and 15.0 Hz), 2.97 (1H, dd, *J* 10.2 and 14.4 Hz), 3.37 (2H, d, *J* 6.7 Hz), 4.96–5.02 (1H, m); δ_C (75 MHz, $CDCl_3$) 21.6, 23.7, 30.8, 34.2, 36.4, 83.2, 112.9, 176.9, 195.4; ν_{max}/cm^{-1} 950.9, 1226.2, 1404.6, 1615.3; MS (EI) *m/z* 230 (M$^+$, 41.0), 204 (77.0), 151 (100), 81 (25.5). HRMS (EI) calculated for $C_9H_{11}O_2{}^{79}Br$: 229.9942. Found: 229.9943.

2-Bromomethyl-6-methyl-3,5,6,7-tetrahydrobenzofuran-4(2*H*)-one 4b, 3-bromo-2,3,4,6,7,8-hexahydro-7-methyl-1-benzopyran-5(5*H*)-one 5b and 4,6-dibromo-2-(2,3-dibromopropyl)-5-methyl-1,3-benzenediol 7. Reaction of **1b** with pyridinium tribromide followed by column chromatography (3.5 : 1.5 hexane–EtOAc, v/v) yielded products **7**,**5b** and **4b** in sequence.

7 (R_F 0.85), solid (5%), m.p. 130–132 °C; δ_H (300 MHz, $CDCl_3$) 2.55 (3H, s), 3.35 (1H, dd, *J* 8.4 and 14.1 Hz), 3.55 (1H, dd, *J* 5.4 and 14.1 Hz), 3.73 (1H, dd, *J* 7.5 and 10.8 Hz), 3.84 (1H, dd, *J* 5.4 and 10.7 Hz), 4.55–4.65 (1H, m), 5.82 (1H, s); δ_C (75 MHz, $CDCl_3$) 24.3, 33.3, 37.1, 51.0, 104.7, 110.2, 135.7, 150.5; ν_{max}/cm^{-1} 883.4, 1076.3, 1161.7, 1244.1, 1316.4, 1387.7, 1599.0, 3440.5; MS (EI) *m/z* 478 (M$^+$, 31.4), 297 (50.5), 295 (100), 293 (54.5). HRMS (EI) calculated for $C_{10}H_{10}O_2{}^{79}Br_3$ 477.7414. Found: 477.7416.

5b (R_F 0.37), (equal mixture of diastereomers by ^{13}C NMR), oil (8%); δ_H (300 MHz, $CDCl_3$) 1.10 (3H, dd, *J* 2.4 and 6.5 Hz), 2.00–2.20 (2H, m), 2.22–2.35 (1H, m), 2.40–2.53 (2H, m), 3.44 (1H, dddd, *J* 8.4, 10.0 and 11.4 Hz), 3.63–3.72 (1H, m), 3.42 (1H, dd, *J* 2.4 and 10.2 Hz), 4.47 (1H, dddd, *J* 5.4, 6.6 and 9.5 Hz), 4.61 (1H, dt, *J* 3.1 and 10.1 Hz); δ_C (75 MHz, $CDCl_3$) 20.8, 20.9, 29.7, 29.8, 31.9, 32.0, 35.3, 35.4, 41.6, 41.7, 45.0, 45.2, 77.6, 77.8, 113.4, 113.7, 179.0, 179.3, 194.7; MS (EI) *m/z* 244 (M$^+$, 39.2), 204 (25.0), 165 (53.0), 151 (100), 109 (26.2), 69 (27.0), 53 (32.6), 41 (43.0), 39 (50.8). HRMS (EI) calculated for $C_{10}H_{13}O_2Br$: 244.0099. Found: 244.0098.

4b (R_F 0.20), (equal mixture of diastereomers by ^{13}C NMR), oil (44%); δ_H (300 MHz, $CDCl_3$) 1.11 (3H, d, *J* 6.3 Hz), 2.03–2.23 (2H, m), 2.25–2.36 (1H, m), 2.47 (2H, *J* 3.6 and 16.5 Hz), 2.68 (1H, dd, *J* 6.9 and 14.7 Hz), 2.98 (1H, *J* 10.6 and 14.7 Hz), 3.51 (2H, dd, *J* 5.4 and 6.6 Hz), 4.97–5.06 (1H, m); δ_C (75 MHz, $CDCl_3$) 20.8, 20.9, 29.7, 29.8, 31.9, 32.0, 35.3, 35.4, 41.6, 41.7, 45.0, 45.2, 77.6, 77.8, 113.4, 113.7, 179.0, 179.3, 194.7; ν_{max}/cm^{-1} 1210.9, 1394.5, 1610.6; MS (EI) *m/z* 244 (M$^+$, 34.0), 202 (77.0), 165 (100), 140 (31.0), 41 (31.8). HRMS (EI) calculated for $C_9H_{11}O_2{}^{79}Br$: 244.0099. Found: 244.0099.

2-Bromomethyl-6,6-dimethyl-3,5,6,7-tetrahydrobenzofuran-4(2*H*)-one 4c and 3-bromo-2,3,4,6,7,8-hexahydro-7,7-dimethyl-1-benzopyran-5(5*H*)-one 5c. Reaction of **1c** with pyridinium tribromide followed by column chromatography (3.5 : 1.5 hexane–EtOAc, v/v) yielded products **5c** and **4c** in sequence.

5c (R_F 0.43), oil (10%); δ_H (300 MHz, $CDCl_3$) 1.09 (3H, s), 1.10 (3H, s), 2.20 (2H, s), 2.28 (2H, d, *J* 0.6 Hz), 3.52 (1H, dd, *J* 8.1 and 11.1 Hz), 3.69 (1H, dd, *J* 3.0 and 9.9 Hz), 3.65–3.75 (1H, m), 4.48 (1H, dd, *J* 5.4 and 9.9 Hz), 4.61 (1H, t, *J* 9.9 Hz); δ_C (75 MHz, $CDCl_3$) 28.2, 29.1, 35.5, 37.8, 41.5, 51.0, 77.5, 112.5, 178.5, 194.4; MS (EI) *m/z* 258 (M$^+$, 29.5), 204 (37.0), 202 (40.0), 179 (47.0), 165 (100), 123 (51.5). HRMS (EI) calculated for $C_{11}H_{15}O_2{}^{79}Br$: 258.0255. Found: 258.0256.

4c (R_F 0.29),[6] oil (50%); δ_H (300 MHz, $CDCl_3$) 1.09 (6H, s), 2.21 (2H, s), 2.29 (2H, t, *J* 1.8 Hz), 2.69 (1H, ddt, *J* 1.8, 6.6 and 14.8 Hz), 2.98 (1H, ddt, *J* 1.8, 10.5 and 14.4 Hz), 3.49 (1H, dd, *J* 4.8 and 9.9 Hz), 3.54 (1H, dd, *J* 4.8 and 9.9 Hz), 5.01 (1H, doublet of quint., *J* 3.9, 5.4 and 8.1 Hz); δ_C (75 MHz, $CDCl_3$) 28.5, 28.8, 30.6, 34.1, 34.5, 37.5, 50.8, 83.2, 111.4, 175.8, 194.7; ν_{max}/cm^{-1} 1216.9, 1400.3, 1631.8; MS (EI) *m/z* 258 (M$^+$, 42.3), 204 (95.5), 202 (100), 179 (87.6), 53 (28.7), 41 (36.5). HRMS (EI) calculated for $C_9H_{11}O_2{}^{79}Br$: 258.0255. Found: 258.0256.

2-Bromomethyl-2-methyl-3,5,6,7-tetrahydrobenzofuran-4(2*H*)-one 4d and 5,7-dibromo-2-bromomethyl-4-hydroxy-2-methyl-2,3-dihydrobenzofuran 6d. Reaction of **1d** with pyridinium tribromide followed by column chromatography (3.5 : 1.5 hexane–EtOAc, v/v) yielded products **6d** and **4d** in sequence.

6d (R_F 0.74), oil (10%), δ_H (300 MHz, $CDCl_3$) 1.67 (3H, s), 3.09 (1H, dd, *J* 0.9 and 16.2 Hz), 3.47 (1H, dd, *J* 0.9 and 16.7 Hz), 3.54 (1H, s), 3.56 (1H, s), 7.37 (1H, t, *J* 0.9 Hz); δ_C (75 MHz, $CDCl_3$) 25.4, 38.8, 38.9, 89.5, 93.8, 101.3, 113.6, 133.0, 148.3, 156.8; ν_{max}/cm^{-1} 1001.4, 1182.3, 1400.4, 1627.2; MS (EI) *m/z* 402 (63.0), 398 (M$^+$, 20.5), 242 (100), 240 (91.5), 63 (47.4), 39 (86.5). HRMS (EI) $C_{10}H_9O_2{}^{79}Br_3$: 397.9942. Found: 397.9942.

4d (R_F 0.24), oil (54%); δ_H (300 MHz, $CDCl_3$) 1.53 (3H, s), 2.01 (2H, quint., *J* 6.3 and 9.5 Hz), 2.31 (2H, t, *J* 6.9 Hz), 2.37–2.43 (2H, m), 2.61 (1H, dd, *J* 1.8 and 14.9 Hz), 2.88 (1H, tt, *J* 1.5 and 15.0 Hz), 3.44 (1H, d, *J* 11.1 Hz), 3.48 (1H, d, *J* 10.8 Hz); δ_C (75 MHz, $CDCl_3$) 21.5, 23.8, 25.3, 36.3, 36.5, 39.3, 89.6, 112.6, 175.7, 195.5; ν_{max}/cm^{-1} 1001.4, 1182.3, 1400.4, 1627.2; MS (EI) *m/z* 244 (M$^+$, 22.0), 165 (100), 137 (27.0), 41 (53.5), 39 (50.8). HRMS (EI) $C_{10}H_{13}O_2{}^{79}Br$: 244.0099. Found: 244.0098.

General procedure for oxidative aromatization of 4 and 5 using iodine

A stirred mixture of **4** or **5** (1 equiv.) and iodine (2 equiv.) in methanol (5 mL per mmol of **4** or **5**) was boiled under reflux for 2 h. The solvent was evaporated under reduced pressure and the residue was taken up into chloroform. The organic solution was sequentially washed with saturated aqueous sodium thiosulfate, sodium bicarbonate and brine and then dried (Na_2SO_4). The mixture was filtered, evaporated under reduced pressure and the residue was purified by column chromatography.

2-Bromomethyl-4-methoxy-2,3-dihydrobenzofuran 8a. Reaction of **4a** with I_2–MeOH followed by column chromatography R_F (toluene) 0.70, yielded **8a**, oil (72%); δ_H (300 MHz, $CDCl_3$) 3.04 (1H, dd, *J* 6.3 and 15.9 Hz), 3.31 (1H, dd, *J* 9.3 and 16.1 Hz), 3.50 (1H, dd, *J* 6.6 and 10.5 Hz), 3.59 (1H, dd, *J* 5.2 and 10.4 Hz), 3.82 (3H, s), 5.02 (1H, m, *J* 1.5, 2.7, 5.4 and 8.6 Hz), 6.42 (1H, d, *J* 8.4 Hz), 6.46 (1H, d, *J* 8.4 Hz), 7.10 (1H, t, *J* 8.1 Hz); δ_C (75 MHz, $CDCl_3$) 32.0, 34.6, 55.3, 81.8, 102.7, 103.2, 112.6, 129.3, 156.5, 160.3; ν_{max}/cm^{-1} 761.5, 1084.8, 1232.5, 1462.0, 1606.7; MS (EI) *m/z* 242 (M$^+$, 100), 163 (80.0), 149 (96.5), 147 (49.0), 107 (69.8), 91 (85.2), 77 (49.0). HRMS (EI) calculated for $C_{10}H_{11}O_2{}^{79}Br$: 241.9942. Found: 241.9943.

2-Bromomethyl-4-methoxy-5-methyl-2,3-dihydrobenzofuran 8b. Reaction of **4b** with I_2–MeOH followed by column chromatography R_F (toluene) 0.72, yielded **8b**, oil (65%); δ_H (300 MHz, $CDCl_3$) 2.30 (3H, s), 2.99 (1H, dd, *J* 6.3 and 15.8 Hz), 3.26 (1H, dd, *J* 9.3 and 15.6 Hz), 3.48 (1H, dd, *J* 6.9 and 10.4 Hz), 3.56 (1H, dd, *J* 5.4 and 10.5 Hz), 4.95–5.05 (1H, m), 6.24 (1H, s), 6.29 (1H, s); δ_C (75 MHz, $CDCl_3$) 22.0, 31.9, 34.7, 55.3, 81.9, 103.4, 104.3, 109.6, 139.9, 156.1, 160.4, 166.6; ν_{max}/cm^{-1} 810.1, 987.2, 1094.9, 1220.9, 1336.9, 1603.1; MS (EI) *m/z* 256 (M$^+$, 100), 177 (85.6), 163 (85.0), 121 (69.0), 105 (71.4), 91 (80.0). HRMS (EI) calculated for $C_{11}H_{13}O_2{}^{79}Br$: 256.0099. Found: 256.0099.

2-Bromomethyl-4-methoxy-2-methyl-2,3-dihydrobenzofuran 8c. Reaction of **4d** with I_2–MeOH followed by column chromatography R_F (3.5 : 1.5 hexane–EtOAc v/v) 0.85, yielded **8c**, oil (86%); δ_H (300 MHz, $CDCl_3$) 1.62 (3H, s), 2.96 (1H, d, *J* 15.9 Hz), 3.29 (1H, d, *J* 15.9 Hz), 3.53 (2H, s), 3.82 (3H, s), 6.41 (1H, d, *J* 4.8 Hz), 6.44 (1H, d, *J* 4.2 Hz), 7.09 (1H, t, *J* 8.1 Hz); δ_C (75 MHz, $CDCl_3$) 25.3, 37.7, 39.8, 55.3, 87.5, 102.9, 103.0, 112.9, 129.3, 156.6, 159.7; ν_{max}/cm^{-1} 761.1, 1053.5, 1089.9, 1249.9, 1462.0, 1606.4; MS (EI) *m/z* 256 (M^+, 81.0), 177 (83.5), 163 (100), 135 (40.0), 39 (41.5). HRMS (EI) calculated for $C_{11}H_{13}O_2{}^{79}Br$: 256.0099. Found: 256.0098.

3-Bromo-5-methoxy-3,4-dihydro-2*H*-1-benzopyran 9a. Reaction of **5a** with I_2–MeOH followed by column chromatography R_F (toluene) 0.69, yielded analytically pure **9a**, oil (85%); δ_H (300 MHz, $CDCl_3$) 3.39 (1H, t, *J* 9.9 Hz), 3.82 (3H, s), 3.86 (1H, ddd, *J* 0.9, 3.3 and 9.9 Hz), 3.91–4.01 (1H, m), 4.53 (1H, dd, *J* 5.1 and 9.6 Hz), 4.62 (1H, dt, *J* 0.9 and 9.3 Hz), 6.40 (1H, dd, *J* 0.6 and 8.3 Hz), 6.45 (1H, dd, *J* 0.6 and 8.9 Hz), 7.12 (1H, dt, *J* 0.6 and 8.2 Hz); δ_C (75 MHz, $CDCl_3$) 34.8, 43.8, 55.7, 77.8, 103.4, 103.7, 114.5, 131.0, 157.4, 162.0; ν_{max}/cm^{-1} 773.6, 1083.4, 1238.4, 12271.1, 1455.8, 1606.5; MS (EI) *m/z* 242 (M^+, 66.0), 163 (90.5), 149 (100), 91 (75.5). HRMS (EI) calculated for $C_{10}H_{11}O_2{}^{79}Br$: 2412.9942. Found: 2412.9942.

3-Bromo-5-methoxy-7-methyl-3,4-dihydro-2*H*-1-benzopyran 9b. Reaction of **5b** with I_2–MeOH followed by column chromatography R_F (toluene) 0.73, yielded analytically pure **9b**, solid (89%), m.p. 83–85 °C; δ_H (300 MHz, $CDCl_3$) 2.29 (3H, s), 3.35 (1H, t, *J* 10.2 Hz), 3.80 (3H, s), 3.81–3.93 (2H, m), 4.51 (1H, dd, *J* 5.0 and 9.6 Hz), 4.61 (1H, dt, *J* 0.9 and 9.2 Hz), 6.22 (1H, s), 6.27 (1H, d, *J* 0.3 Hz); δ_C (75 MHz, $CDCl_3$) 22.1, 34.6, 43.3, 55.2, 76.3, 103.9, 104.0, 111.2, 141.3, 156.6, 161.7; ν_{max}/cm^{-1} 812.7, 1097.9, 1219.0, 1456.3, 1597.1; MS (EI) *m/z* 256 (M^+, 30.0), 177 (100), 163 (68.0); HRMS (EI) calculated for $C_{11}H_{13}O_2{}^{79}Br$: 256.0099. Found: 256.0099.

General procedure for iodocyclization of 10

A stirred mixture of **10** (1 equiv.) and iodine (2 equiv.) in methanol (5 mL per mmol of **10**) was boiled under reflux for 5 h. The solvent was evaporated under reduced pressure and the residue was taken-up into chloroform. The organic solution was sequentially washed with saturated aqueous sodium thiosulfate, sodium bicarbonate and brine and then dried (Na_2SO_4). The mixture was filtered, evaporated under reduced pressure and the residue was purified by column chromatography to afford pure **11**.

4-[(Diethoxyphosphonyl)methyl]-2-iodomethyl-2,3-dihydrobenzofuran 11a. Reaction of **10a** with I_2–MeOH followed by column chromatography R_F (EtOAc) 0.57, yielded **11a**, oil (69%); δ_H (300 MHz, $CDCl_3$) 1.25 (6H, dt, *J* 3.0 and 7.1 Hz), 2.26 (3H, s), 3.01 (2H, d, *J* 21.9 Hz), 3.31 (2H, dd, *J* 7.2 and 9.9 Hz), 3.41 (2H, dd, *J* 4.5 and 10.1 Hz), 4.81–4.91 (1H, m), 3.95–4.08 (4H, m), 6.49 (1H, s), 6.60 (1H, d, *J* 0.6 Hz); δ_C (75 MHz, $CDCl_3$) 9.0, 16.4 (d, J_{CP} 5.7 Hz), 31.7 (d, J_{CP} 138.3 Hz), 35.2, 62.2 (t, J_{CP} 6.6 Hz), 81.6, 108.2 (d, J_{CP} 3.7 Hz), 122.4 (d, J_{CP} 5.7 Hz), 126.0 (d, J_{CP} 6.5 Hz), 128.4 (d, J_{CP} 3.5 Hz), 128.6, 138.6 (d, J_{CP} 3.4 Hz), 159.2; δ_P 27.2; ν_{max}/cm^{-1} 960.6, 1022.1, 1049.6, 1234.4, 1454.3, 1597.2; MS (EI) *m/z* 410 (M^+, 72.0), 283 (72.2), 269 (42.0), 145 (100), 28 (88.0). HRMS (EI) calculated for $C_{14}H_{20}O_4IP$: 410.0143. Found: 410.0143.

4-[(Diethoxyphosphonyl)methyl]-2-iodomethyl-6-methyl-2,3-dihydrobenzofuran 11b. Reaction of **10b** with I_2–MeOH followed by column chromatography R_F (EtOAc) 0.60, yielded **11b**, oil (65%); δ_H (300 MHz, $CDCl_3$) 1.25 (6H, dt, *J* 3.0 and 7.1 Hz), 2.26 (3H, s), 3.01 (2H, d, *J* 21.9 Hz), 3.31 (2H, dd, *J* 7.2 and 9.9 Hz), 3.41 (2H, dd, *J* 4.5 and 10.1 Hz), 4.81–4.91 (1H, m), 3.95–4.08 (4H, m), 6.49 (1H, s), 6.60 (1H, d, *J* 0.6 Hz); δ_C (75 MHz, $CDCl_3$) 9.2, 16.4 (d, J_{CP} 6.0 Hz), 21.4, 31.6 (d, J_{CP} 138.0 Hz), 34.9, 62.1 (t, J_{CP} 6.5 Hz), 81.7, 108.9 (d, J_{CP} 4.0 Hz), 122.9 (d, J_{CP} 6.6 Hz), 123.2 (d, J_{CP} 5.6 Hz), 127.9 (d, J_{CP} 10.0 Hz), 138.6 (d, J_{CP} 3.4 Hz), 159.3 (d, J_{CP} 3.4 Hz); δ_P 27.5; ν_{max}/cm^{-1} 960.9, 1020.9, 1234.1, 1597.1; MS (EI) *m/z* 424 (M^+, 100), 297 (64.0), 283 (31.5), 159 (96.0), 145 (44.0). HRMS (EI) calculated for $C_{15}H_{22}O_4IP$: 424.0300. Found: 424.0301.

Arbuzov's reaction of 3 with triethyl phosphite to form 12. General procedure

A stirred mixture of **3** (1 equiv.) and triethyl phosphite (4 equiv.) was heated under reflux for 8 h. The crude mixture was purified by column chromatography to afford pure **12**.

2-[(Diethoxyphosphono)methyl]-4-methoxy-2,3-dihydrobenzofuran 12a. Reaction of **3a** with triethyl phosphite followed by column chromatography R_F (3 : 2 toluene–EtOAc, v/v) 0.19, afforded pure **12a**, oil (66%); δ_H (300 MHz, $CDCl_3$) 1.29–1.37 (6H, m), 2.15 (1H, dd, *J* 7.5 and 18.3 Hz), 2.20 (1H, dd, *J* 7.5 and 18.3 Hz), 2.36 (1H, dd, *J* 6.3 and 18.8 Hz), 2.41 (1H, dd, *J* 6.0 and 18.6 Hz), 2.95 (1H, dd, *J* 7.2 and 15.9 Hz), 3.34 (1H, dd, *J* 9.0 and 15.8 Hz), 4.03–4.22 (4H, m), 5.02–5.15 (1H, m), 6.38 (1H, d, *J* 4.2 Hz), 6.41 (1H, d, *J* 3.9 Hz), 7.06 (1H, t, *J* 8.1 Hz); δ_C (75 MHz, $CDCl_3$) 16.4 (d, J_{CP} 2.3 Hz), 32.4 (d, J_{CP} 129.2 Hz), 33.9, 55.3, 61.8 (dd, J_{CP} 6.5 and 17.6 Hz), 78.4, 102.7, 103.1, 113.1, 129.1, 156.5, 160.1; δ_P 27.5; ν_{max}/cm^{-1} 762.6, 951.5, 1021.9, 1234.4, 1464.0, 1606.7; MS (EI) *m/z* 300 (M^+, 59.5), 152 (100), 125 (94.5), 108 (37.0), 97 (44.0), 29 (29.9). HRMS (EI) calculated for $C_{14}H_{21}O_5P$: 300.1127. Found: 300.1127.

2-[(Diethoxyphosphono)methyl]-4-methoxy-6-methyl-2,3-dihydrobenzofuran 12b. Reaction of **3b** with triethyl phosphite followed by column chromatography R_F (3 : 2 toluene–EtOAc, v/v) 0.14, afforded pure **12b**, oil (55%); δ_H (300 MHz, $CDCl_3$) 1.33 (6H, tt, *J* 3.3 and 7.1 Hz), 2.15 (1H, dddd, *J* 7.5, 15.0 and 18.3 Hz), 2.28 (3H, s), 2.37 (1H, dddd, *J* 6.0, 15.0 and 18.6 Hz), 2.90 (1H, dd, *J* 6.9 and 15.6 Hz), 3.29 (1H, dd, *J* 9.0 and 15.6 Hz), 3.78 (3H, s), 4.02–4.21 (4H, m), 5.01–5.13 (1H, m), 6.22 (1H, s), 6.24 (1H, s); δ_C (75 MHz, $CDCl_3$) 16.4 (dd, J_{CP} 2.6 and 5.8 Hz), 21.9, 33.1 (d, J_{CP} 138.0 Hz), 33.7 (d, *J* 7.7 Hz), 55.3, 61.8 (dd, J_{CP} 6.5 and 18.5 Hz), 78.5, 104.1, 103.4, 110.1, 139.7, 156.1, 160.1; δ_P 27.6; ν_{max}/cm^{-1} 762.3, 958.9, 1022.8, 1242.2, 1462.0, 1606.5; MS (EI) *m/z* 314 (M^+, 68.0), 175 (50.0), 152 (100), 125 (90.5), 97 (40.5). HRMS (EI) calculated for $C_{15}H_{23}O_5P$: 314.1283. Found: 314.1283.

2-[(Diethoxyphosphono)methyl]-4-methoxy-2-methyl-2,3-dihydrobenzofuran 12c. Reaction of **3d** with triethyl phosphite followed by column chromatography R_F (3 : 2 toluene–EtOAc, v/v) 0.19, afforded pure **12c**, oil δ_H (300 MHz, $CDCl_3$) 1.31 (6H, tt, *J* 4.5 and 7.1 Hz), 1.62 (3H, s), 2.31 (2H, d, *J* 19.2 Hz), 2.95 (1H, d, *J* 15.9 Hz), 3.34 (1H, d, *J* 15.9 Hz), 3.79 (3H, s), 4.01–4.16 (4H, m), 6.36 (1H, d, *J* 1.8 Hz), 6.39 (1H, d, *J* 2.4 Hz); 7.06 (1H, t, *J* 8.4 Hz); δ_C (75 MHz, $CDCl_3$) 16.3 (d, J_{CP} 6.3 Hz), 27.4 (d, *J* 3.5 Hz), 37.3 (d, J_{CP} 137.2 Hz), 39.5 (d, *J* 4.8 Hz), 55.3, 61.6 (t, J_{CP} 6.2 Hz), 86.5, 102.8, 102.9, 113.5, 129.0, 156.7, 159.3; δ_P 26.9; ν_{max}/cm^{-1} 763.1, 960.4, 1023.7, 1244.1, 1464.7, 1606.8; MS (EI) *m/z* 314 (M^+, 90.8), 175 (127.0), 152 (100), 125 (88.0), 108 (32.9). HRMS (EI) calculated for $C_{15}H_{23}O_5P$: 314.1283. Found: 314.1283.

General procedure for the dehydrohalogenation of 3 and 11

A stirred solution of the iodomethyl derivative **3** or **11** (1 equiv.) in toluene (5 mL per mmol of iodo derivative) was treated with DBU (3 equiv.). The mixture was refluxed for 18 h, cooled and then quenched with water. The solution was extracted with chloroform and the combined organic extracts were washed with saturated ammonium chloride solution, dried (Na_2SO_4), filtered and then evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to afford the product.

4-Methoxy-2-methylbenzofuran 13a[2a]. Reaction of **3a** with DBU followed by column chromatography R_F (toluene) 0.76, yielded **13a**, oil (74%); δ_H (300 MHz, $CDCl_3$) 2.44 (3H, d, *J* 1.0 Hz), 3.92 (3H, s), 6.45 (1H, d, *J* 1.0 Hz), 6.62 (1H, d, *J* 8.0 Hz), 7.05 (1H, d, *J* 7.8 Hz), 7.13 (1H, t, *J* 7.8 Hz); δ_C (75 MHz, $CDCl_3$) 14.0, 55.5, 99.9, 103.1, 104.1, 119.1, 123.6, 152.7, 153.9, 155.9.

4-Methoxy-2,6-dimethylbenzofuran 13b. Reaction of **3b** with DBU followed by column chromatography R_F (toluene) 0.81, yielded **13b**, solid (93%), m.p. 54–56 °C; δ_H (300 MHz, $CDCl_3$) 2.41 (3H, d, *J* 0.9 Hz), 2.44 (3H, s), 3.90 (3H, s), 6.39 (1H, d, *J* 0.9 Hz), 6.46 (1H, s), 6.86 (1H, d, *J* 0.6 Hz); δ_C (75 MHz, $CDCl_3$) 14.0, 22.0, 55.5, 99.6, 104.3, 104.7, 116.5, 134.0, 152.2, 153.2, 156.2; ν_{max}/cm^{-1} 804.3, 825.5, 1211.3, 1410.0, 1591.2; HRMS (EI) calculated for $C_{11}H_{12}O_2$: 176.0837. Found: 176.0836.

4-[(Diethoxyphosphono)methyl)]-2-methylbenzofuran 13c. Reaction of **11a** with DBU followed by column chromatography R_F (EtOAc) 0.49, yielded **13c**, oil (85%); δ_H (300 MHz, $CDCl_3$) 1.19 (6H, t, *J* 6.9 Hz), 2.44 (3H, t, *J* 0.9 Hz), 3.32 (2H, *J* 21.6 Hz), 3.89–4.03 (4H, m), 6.49 (1H, t, *J* 1.2 Hz), 7.06–7.11 (1H, m), 7.13 (1H, t, *J* 7.7 Hz), 7.29–7.30 (1H, m); δ_C (75 MHz, $CDCl_3$) 14.1, 16.3 (d, J_{CP} 5.9 Hz), 31.5 (d, J_{CP} 138.6 Hz), 62.1 (d, J_{CP} 6.8 Hz), 101.7, 109.3 (d, J_{CP} 4.0 Hz), 123.1 (d, J_{CP} 3.4 Hz), 123.4 (d, J_{CP} 9.7 Hz), 123.9 (d, J_{CP} 6.8 Hz), 129.5, 154.6, 155.4; δ_P 27.2; ν_{max}/cm^{-1} 791.1, 1013.1, 1084.0, 1258.5; MS (EI) *m/z* 282 (M^+, 72.0), 205 (44.5), 145 (100). HRMS (EI) calculated for $C_{14}H_{19}PO_4$: 282.1021. Found: 282.1021.

4-[(Diethoxyphosphono)methyl)]-2,6-dimethylbenzofuran 13d. Reaction of **11b** with DBU followed by column chromatography R_F (EtOAc) 0.54, yielded **13d**, oil (65%); δ_H (300 MHz, $CDCl_3$) 1.20 (6H, t, *J* 7.2 Hz), 2.41 (3H, d, *J* 3.3 Hz), 3.27 (2H, *J* 21.6 Hz), 3.91–4.00 (4H, m), 6.42 (1H, t, *J* 1.2 Hz), 6.92 (1H, d, *J* 2.4 Hz), 7.09 (1H, s); δ_C (75 MHz, $CDCl_3$) 14.1, 16.3 (d, J_{CP} 5.9 Hz), 16.4, 30.5, 32.4, 62.1 (d, J_{CP} 6.5 Hz), 101.4, 109.8 (d, J_{CP} 4.0 Hz), 122.5, 122.6, 125.2 (d, J_{CP} 6.9 Hz), 126.9 (d, J_{CP} 5.5 Hz), 133.1 (d, J_{CP} 1.3 Hz), 154.9; δ_P 27.4; ν_{max}/cm^{-1} 787.0, 960.9, 1021.8, 1246.0, 1588.4; MS (EI) *m/z* 296 (M^+, 59.3), 159 (100), 28 (28.0). HRMS (EI) calculated for $C_{15}H_{21}PO_4$: 296.1177. Found: 296.1177.

General procedure for the demethylation of 13a and 13b with BBr_3

A stirred solution of **13a** or **b** (1 equiv.) in dichloromethane (5 mL per mmol) at 0 °C was treated dropwise with BBr_3 (1.5 equiv.). The mixture was then allowed to warm to room temperature for 24 h. The mixture was cooled to 0 °C and quenched with ice-cold water and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by column chromatography to afford **14**.

4-Hydroxy-2-methylbenzofuran 14a. Reaction of **13a** with BBr_3 followed by column chromatography R_F (toluene) 0.08, yielded **14a**, oil (91%); δ_H (300 MHz, $CDCl_3$) 2.43 (3H, s), 6.42 (1H, s), 5.10 (1H, br s), 6.58 (1H, dd, *J* 2.4 and 6.2 Hz), 7.01–7.05 (2H, m); δ_C (75 MHz, $CDCl_3$) 14.0, 99.1, 103.9, 107.7, 118.0, 123.7, 148.3, 154.2, 156.3; ν_{max}/cm^{-1} 767.7, 1017.6, 1228.7, 1287.3, 1460.1, 1602.8, 3339.8; HRMS (EI) calculated for $C_9H_8O_2$: 148.0524. Found: 148.0524.

4-Hydroxy-2,6-dimethylbenzofuran 14b. Reaction of **13b** with BBr_3 followed by column chromatography R_F (toluene) 0.11, yielded **14b**, solid (80%), mp 86–88 °C; δ_H (300 MHz, $CDCl_3$) 2.37 (3H, s), 2.40 (3H, d, *J* 0.9 Hz), 4.96 (1H, s), 6.35 (1H, t, *J* 1.1 Hz), 6.42 (1H, s), 6.82 (1H, d, *J* 0.3 Hz); δ_C (75 MHz, $CDCl_3$) 14.0, 21.6, 98.9, 104.3, 109.1, 115.5, 134.2, 147.7, 153.5, 156.7; ν_{max}/cm^{-1} 823.6, 976.0, 1056.7, 1205.8, 1315.4, 1428.5, 1587.6, 3300.9; MS (EI) *m/z* 162 (M^+, 100), 147 (27), 28 (40.5). HRMS (EI) calculated for: $C_{10}H_{11}O_2$ 162.0681. Found: 162.0680.

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