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Design of 1,2-dioxines with anti-*Candida* activity: aromatic substituted 1,2-dioxines

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Abstract

In an ongoing effort to rationally design new antimicrobials, 47 new 1,2-dioxines have been synthesised. Broad antifungal structure–activity relationships governing aromatically substituted epoxy-1,2-dioxines **2** and **3** and their parent 1,2-dioxines **1** were assessed primarily against the pathogenic yeast, *Candida albicans*, with haemolytic activity of selected examples also reported.

Keywords: Antifungal; 1,2-Dioxine; *Candida*; Epoxy-1,2-dioxine; Haemolytic activity

1. Introduction

New effective antifungal agents are urgently required, due to evolving resistance of fungal pathogens to existing drugs. These resistant pathogens are 'selected' through increased immune deficiency within our population, a result of our ageing population and the increased numbers of surgical procedures (including transplantations) or chemotherapies, requiring immune suppression. There is further need for effective antifungals with reduced toxicity to humans.

Previously we have screened a wide range of 1,2-dioxines and epoxy-1,2-dioxines with aliphatic (cyclic and acyclic) substituents in combination with hydroxyl and ester functional groups about the dioxine ring.[1a,b] These prior studies have yielded promising lead compounds and generated a wealth of structure–activity data for monocyclic 1,2-dioxines and epoxy-1,2-dioxines. During this process we tested the antifungal activity of the bis aromatically substituted 1,2-dioxine and its corresponding epoxy-1,2-dioxine, Figure 1.

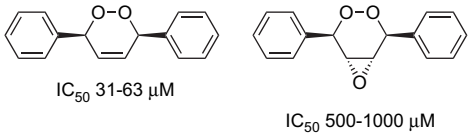

Figure 1. Previously tested bis aromatic 1,2-dioxine and epoxy-1,2-dioxine.

This simple aromatically substituted 1,2-dioxine gave an IC_{50} value of 31–63 μM.[1a] In order to elaborate upon this promising result we embarked on synthesising and testing a series of aromatic substituted 1,2-dioxines. Due to synthetic difficulties and solubility problems we chose to investigate primarily mono-substituted aromatic 1,2-dioxines, whose parent 1,3-butadienes were simple to construct through the reaction of a chosen benzaldehyde and allyltriphenylphosphonium bromide.

2. Results and discussion

1,2-Dioxines **1a–q** were synthesised from the appropriate 1,3-butadiene through the photosensitised cycloaddition of singlet oxygen.[2] Epoxidation is achieved through the treatment

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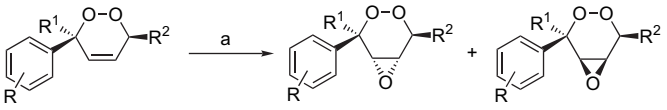
of 1,2-dioxines with *m*-chloroperbenzoic acid (*m*-CPBA) in good yield,[3] generating isomers **2** and **3**, Scheme 1.



1a: R = 2-OMe, R^1 = R^2 = H
1b: R = 3-OMe, R^1 = R^2 = H
1c: R = R^1 = R^2 = H
1d: R = 2-F, R^1 = R^2 = H
1e: R = 3-F, R^1 = R^2 = H
1f: R = 4-F, R^1 = R^2 = H
1g: R = 2-Cl, R^1 = R^2 = H
1h: R = 3-Cl, R^1 = R^2 = H
1i: R = 4-Cl, R^1 = R^2 = H
1j: R = 2-Br, R^1 = R^2 = H
1k: R = 3-Br, R^1 = R^2 = H
1l: R = 4-Br, R^1 = R^2 = H
1m: R= 3,5-Br, R^1 = R^2 = H
1n: R = 3-I, R^1 = R^2 = H
1o: R = H, R^1 = Ph, R^2 = H
1p: R = R^1 = H, R^2 = Me
1q: R = R^1 = H, R^2 = *c*-C_6H_{11}

Scheme 1. Reagents: (a) *m*-CPBA.

From the data presented in Table 1, some general trends can be observed about the antifungal activities of the 1,2-dioxines **1** and the corresponding *trans* (**2**) and *cis* (**3**) epoxy-1,2-dioxine structures against *Candida albicans*. It is apparent that the parent 1,2-dioxines **1** are more active than the corresponding epoxides—without exception. Also there appears to be a marginal increase in activity moving from *trans* epoxy-1,2-dioxine to the *cis* isomer, however, generally the activities are similar.

For the 1,2-dioxines **1**, the position and type of aromatic substituent (R) appear important. The *ortho* substituted 1,2-dioxines were generally the least active followed by *meta*, with *para* being the most active except in the R=Br series. For both the *ortho* and *meta* substituted compounds the following substituent trend was established: H, F<Cl, OMe
I (*meta* only), with R=Br appearing to have the optimum combination of size and/or electro-negativity from the substituents studied. It is interesting to note that for the *para* substituted compounds, there was no change in activity with the change of substituent (all had IC_{50}=31–63 μM).

The addition of an aliphatic (cyclic **1q** or acyclic **1p**) substituent at R^2 had no effect on antifungal activity of 1,2-dioxine or epoxy-1,2-dioxine over the hydrogen substituted series (**1c**, **2c**, **3c**). Similarly, addition of an aromatic group at R^1 had little effect on antifungal activity.

The greatest activity observed was for compound **1k**, the *meta*-bromophenyl 1,2-dioxine with an IC_{50} of 5–10 μM. Unexpectedly, the activity of compound **1m**, the 3,5-dibromophenyl 1,2-dioxine, was slightly decreased (16–31 μM) from **1k**. Having this 3,5-substitution was expected to slightly increase activity due to the conformational locking of bromine. The antifungal activity of **1k** is the best of all compounds screened in this study and our previous two studies.[1a,b] Compound **1k** was therefore further screened against *Candida krusei* and *Candida tropicalis*. The results are presented in Table 2.

Table 1
Growth inhibition of *C. albicans* exposed to 1,2-dioxine compounds

Endoperoxide	IC_{50} (μM)	trans Epoxide	IC_{50} (μM)	cis Epoxide	IC_{50} (μM)
1a	63–125	**2a**	>1000	**3a**	—
1b	63–125	**2b**	250–500	**3b**	—
1c	250–500	**2c**	250–500	**3c**	500–1000
1d	250–500	**2d**	500–1000	**3d**	500–1000
1e	250–500	**2e**	500–1000	**3e**	500–1000
1f	31–63	**2f**	500–1000	**3f**	500–1000
1g	125–250	**2g**	250–500	**3g**	500–1000
1h	63–125	**2h**	500–1000	**3h**	250–500
1i	31–63	**2i**	500–1000	**3i**	250–500
1j	63–125	**2j**	500–1000	**3j**	250–500
1k	5–10	**2k**	250–500	**3k**	250–500
1l	31–63	**2l**	125–250	**3l**	250–500
1m	16–31	**2m**	125–250	**3m**	250–500
1n	31–63	—	—	—	—
1o	125–250	**2o**	500–1000	—	—
1p	250–500	**2p**	>1000	**3p**	—
1q	250–500	**2q**	500–1000	**3q**	>1000

2a, **3a**, **2b** and **3b** were analysed as a 4:1 mixture.

Table 2
A comparison of growth inhibition of *Candida* strains exposed to 1,2-dioxine **1k** compared with some commercial compounds

Compound	IC_{50} against *C. albicans* (μM)	IC_{50} against *C. tropicalis* (μM)	IC_{50} against *C. krusei* (μM)
Amphotericin B	0.5	0.1–0.4	0.2–0.4
Ketoconazole	250–500	11.8–47	100–200
Nystatin	250–500	100–200	100–200
Fluconazole	0.8	1.6	209
1k	5–10	31–63	4–8

The results show that the activity of **1k** is far superior to nystatin and ketoconazole against *C. albicans*, however, it is still 10-fold less active than amphotericin B. Compound **1k** appears active against all of the strains tested; most importantly it is very active against *C. krusei* compared to fluconazole, to which the strain is relatively insensitive.

To determine the potential of the compounds as orally administered agents, an erythrocyte lysis assay on a selection of 1,2-dioxines and '*trans*' epoxy-1,2-dioxines was conducted with an upper concentration limit of the IC_{50} assay (1 mM) (Table 3). This is a measure of whether or not the compounds will cause red blood cells to rupture.

Table 3
The % haemolysis of erythrocytes at 1 mM of 1,2-dioxine or epoxy-1,2-dioxine

Endoperoxide	% Haemolysis	trans Epoxide	% Haemolysis
1b	8	**2b**	1
1c	58	**2c**	1
1k	100	**2k**	3
1l	81	**2l**	2

It is apparent from the results above that parent 1,2-dioxines tended to be quite haemolytic except for the OMe substituted **1b**. The epoxidation of the 1,2-dioxines leads to a significant decrease in the haemolytic activity of the compounds. This observation is consistent with their much reduced

antifungal activity. Given that the IC_{50}s of the compounds tested in the haemolysis assays are much lower than the upper limit of 1 mM at which the assay was carried out, the potential of compounds such as **1k** as an oral antifungal should not be ruled out. Further testing would be required to assess the haemolytic activity of **1k** at lower concentrations. The haemolysis results may not be important if the compounds are to be applied as topical antifungal agents only.

3. Conclusion

A series of novel substituted aromatic 1,2-dioxines and their epoxide derivatives have been successfully synthesised and antifungal activity assessed against *C. albicans*. Broad structure–activity relationships were determined with epoxide derivatives in all cases showing reduced activity when compared to their parent 1,2-dioxines. Lead compound **1k** was then assessed against *C. tropicalis* and *C. krusei* showing good activity against *C. krusei* which is insensitive to fluconazole. We feel that compound **1k** and possibility derivatives thereof may be good candidates for further evaluation, especially given **1k**'s apparent broad spectrum activity. Moreover other compounds tested may represent good candidates for topical applications as haemolytic activity is not necessarily detrimental to being a good candidate.

4. Experimental

4.1. General biological methods

Yeast strains were maintained on solidified YEPD (1% yeast extract, 2% peptone, 2% glucose, 1.5% agar) and stored at 4 °C. Cells were prepared as fresh inoculations in liquid YEPD at 35 °C, 24 h prior to their utilisation. *Candida* strains employed in this study were the clinical isolates, *C. albicans* JRW #5, *C. krusei* WM 03,204, and the American Type Culture Collection strain *C. tropicalis* 750.

1,2-Dioxine compounds were prepared as 100 mM ethanolic stock solutions. Dimethylsulfoxide was used to aid the solubilisation of amphotericin B (Sigma, St. Louis, MO, USA) and fluconazole (Pfizer Pharmaceuticals, New York, NY, USA). Ketoconazole (Sigma, St. Louis, MO, USA) was solubilised in methanol. Nystatin suspension (Sigma, St. Louis, MO, USA) and amphotericin B stocks were stored at −80 °C. Other stocks were stored at 4 °C until required. DMSO, ethanol and methanol comprised <1% of the total test volume. Growth curves were determined using concentrations of DMSO, ethanol and methanol equal to those present in test solutions to verify that they did not inhibit the growth of *Candida*.

Yeast was grown to log phase and diluted in YEPD to achieve a starting optical density at A_{595} of 0.2–0.4 in order to examine growth inhibition immediately after addition of compounds. The yeast inocula (100 μL) were then added to each well of a 96-well microplate (Nunc, Wiesbaden, Germany). Drugs and endoperoxide compounds were then added as twofold serial dilutions down from 1 mM concentrations. A growth control was included in the same microplate. The microplate was incubated in a microplate shaker at 35 °C, and the A_{595} was measured at the time of compound addition and 2 h later using a microplate reader (Labsystem Multiscan Ascent). Each sample was assayed in triplicate. Absorbance values were averaged and plotted against the drug and compound concentration, and the concentration required to inhibit 50% growth (IC_{50}) was calculated.

4.2. General synthetic methods

Solvents were dried by appropriate methods wherever needed. Thin-layer chromatography (TLC) used aluminium sheets coated with silica gel 60 F_{254} (40×80 mm) from Merck, visualised under 254 nm light or developed in vanillin or permanganate dip. Flash chromatography was conducted using Merck silica gel 60 of particle size 0.040–0.063 mm. Melting points were taken on a Reichert Thermovar Kofler apparatus and are uncorrected. Infrared spectra were recorded on an ATI Mattson Genesis series FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Varian Gemini 2000 (200 MHz), Varian Gemini 2000 (300 MHz) or Varian INOVA (600 MHz) instrument, using TMS (0 ppm) and $CDCl_3$ (77.0 ppm) as internal standards. Electron impact mass spectra (EIMS) were recorded at 70 eV. Crystal structures were determined on a Bruker AXS SMART CCD. All yields reported refer to isolated material judged to be homogeneous by TLC and NMR spectrometry.

4.3. General procedure for the synthesis of 1,2-dioxines *1a–q*[2]

A solution of the appropriate parent 1,3-butadiene in CH_2Cl_2 (30 mL/g) was photolysed with 3×500 W halogen lamps in the presence of Rose Bengal bis(triethylammonium) salt (100 mg) and oxygen for 6–9 h. The reaction was performed in a Pyrex flask fitted with an external cooling jacket. The solution was concentrated in vacuo and the resulting residue purified by flash chromatography. In all cases starting diene was reclaimed from the photolysis reactions as the other major product. The following 1,2-dioxines are known: **1c**,[2] **1i**,[4] **1o**,[4] **1p**,[2] **1q**.[5] The following 1,2-dioxines were prepared.

4.3.1. ±3-(2-Methoxyphenyl)-3,6-dihydro-1,2-dioxine (*1a*)

Yield: 360 mg, 6%; colourless oil; R_f 0.39 (1:19 ethyl acetate/hexane); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.40–7.28 (m, 2H), 6.98–6.88 (m, 2H), 6.19–6.05 (m, 3H), 4.74–4.58 (m, 2H), 3.85 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 157.4, 129.8, 129.0, 127.1, 125.7, 124.4, 120.4, 110.7, 74.5, 69.9, 55.6; IR (neat): 1601, 1589, 1493, 1464, 1248, 1050, 1030 cm^{-1}; MS *m/z* (EI^+): 192 (M^+, 60), 174 (43), 160 (100), 145 (19), 135 (77), 91 (16); HRMS (EI^+) $(M)^+$ found 192.0789; $(M)^+$ calcd for $C_{11}H_{12}O_3$ 192.0786.

4.3.2. ±3-(3-Methoxyphenyl)-3,6-dihydro-1,2-dioxine (*1b*)

Yield: 960 mg, 17%; colourless oil; R_f 0.37 (1:9 ethyl acetate/hexane); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.33–7.24 (m, 1H), 6.99–6.85 (m, 3H), 6.18 (dddd, *J*=10.3, 2.2, 2.2,

2.2 Hz, 1H), 6.09 (dddd, J=10.3, 2.2, 2.2, 2.2 Hz, 1H), 5.59 (dddd, J=2.2, 2.2, 2.2, 2.2 Hz, 1H), 4.76 (dddd, J=16.3, 2.2, 2.2, 2.2 Hz, 1H), 4.58 (dddd, J=16.3, 2.2, 2.2, 2.2 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.7, 138.7, 129.5, 126.8, 124.8, 120.7, 114.5, 113.9, 80.5, 69.9, 55.2; IR (neat): 1602, 1588, 1489, 1455, 1284, 1047, 760 cm^{-1}; MS *m/z* (EI$^+$): 192 (M$^+$, 44), 174 (50), 160 (100), 145 (22), 135 (39), 92 (17); HRMS (EI$^+$) (M)$^+$ found 192.0782; (M)$^+$ calcd for $C_{11}H_{12}O_3$ 192.0786.

*4.3.3. ±3-(2-Fluorophenyl)-3,6-dihydro-1,2-dioxine (**1d**)*

Yield: 720 mg, 12%; colourless oil; R_f 0.34 (2:3 CH_2Cl_2/hexane); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.48–7.24 (m, 2H), 7.17–7.01 (m, 2H), 6.19 (dddd, J=10.3, 2.6, 2.6, 2.0 Hz, 1H), 6.08 (dddd, J=10.3, 2.0, 2.0, 1.6 Hz, 1H), 5.92 (dddd, J=2.0, 2.0, 2.0, 2.0 Hz, 1H), 4.68–4.64 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 160.8 (d, J=247.4 Hz), 130.3 (d, J=8.4 Hz), 129.7 (d, J=3.4 Hz), 125.8, 125.2, 124.7 (d, J=13.7 Hz), 124.0 (d, J=3.8 Hz), 115.5 (d, J=21.7 Hz), 79.9 (d, J=3.5 Hz), 69.8; IR (neat): 1616, 1588, 1489, 1457, 1231, 1035, 996 cm^{-1}; MS *m/z* (EI$^+$): 180 (M$^+$, 10), 162 (98), 148 (100), 133 (20), 123 (25), 95 (15); HRMS (ESI) (M+Na)$^+$ found 203.0482; (M+Na)$^+$ calcd for $C_{10}H_9O_2FNa$ 203.0484.

*4.3.4. ±3-(3-Fluorophenyl)-3,6-dihydro-1,2-dioxine (**1e**)*

Yield: 1.12 g, 23%; colourless oil; R_f 0.31 (2:3 CH_2Cl_2/hexane); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.39–7.26 (m, 1H), 7.20–6.96 (m, 3H), 6.18 (dddd, J=10.3, 2.2, 2.2, 1.6 Hz, 1H), 6.08 (dddd, J=10.3, 2.2, 2.2, 1.6 Hz, 1H), 5.56 (dddd, J=2.2, 2.2, 2.2, 2.2 Hz, 1H), 4.70 (dddd, J=16.8, 2.2, 2.2, 1.6 Hz, 1H), 4.60 (dddd, J=16.8, 2.2, 2.2, 1.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 162.8 (d, J=245.1 Hz), 139.9 (d, J=6.9 Hz), 130.0 (d, J=8.0 Hz), 126.2, 125.2, 124.0 (d, J=3.05 Hz), 115.6 (d, J=20.9 Hz), 115.2 (d, J=21.7 Hz), 79.8 (d, J=1.9 Hz), 69.8; IR (neat): 1616, 1592, 1488, 1449, 1265, 1140, 1035 cm^{-1}; MS *m/z* (EI$^+$): 180 (M$^+$, 24), 162 (36), 148 (100), 133 (15), 123 (13), 95 (15); HRMS (ESI) (M+Na)$^+$ found 203.0483; (M+Na)$^+$ calcd for $C_{10}H_9O_2FNa$ 203.0484.

*4.3.5. ±3-(4-Fluorophenyl)-3,6-dihydro-1,2-dioxine (**1f**)*

Yield: 2.25 g, 31%; colourless planks; mp 30–31 °C; R_f 0.30 (2:3 CH_2Cl_2/hexane); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.41–7.31 (m, 2H), 7.11–6.98 (m, 2H), 6.18 (dddd, J=10.2, 2.2, 2.2, 2.2 Hz, 1H), 6.07 (dddd, J=10.2, 2.2, 2.2, 2.2 Hz, 1H), 5.58 (dddd, J=2.2, 2.2, 2.2, 2.2 Hz, 1H), 4.72 (dddd, J=16.6, 2.2, 2.2, 2.2 Hz, 1H), 4.57 (dddd, J=16.6, 2.2, 2.2, 2.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 163.0 (d, J=246.2 Hz), 133.0 (d, J=3.1 Hz), 130.4 (d, J=8.4 Hz), 126.6, 125.1, 115.4 (d, J=21.7 Hz), 79.8, 69.8; IR (Nujol): 1604, 1509, 1225, 1158, 1060, 996, 839 cm^{-1}; MS *m/z* (EI$^+$): 180 (M$^+$, 10), 162 (4), 148 (100), 133 (9), 123 (14), 95 (8). Anal. Calcd for $C_{10}H_9O_2F$: C, 66.66; H, 5.03. Found: C, 66.78; H, 4.81.

*4.3.6. ±3-(2-Chlorophenyl)-3,6-dihydro-1,2-dioxine (**1g**)*

Yield: 540 mg, 9%; colourless oil; R_f 0.29 (2:3 CH_2Cl_2/hexane); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.52–7.45 (m, 1H), 7.43–7.35 (m, 1H), 7.31–7.21 (m, 2H), 6.21 (dddd, J=10.2, 2.2, 2.2, 1.6 Hz, 1H), 6.11 (dddd, J=10.2, 2.2, 2.0, 1.6 Hz, 1H), 6.04 (dddd, J=2.2, 2.2, 2.2, 2.2 Hz, 1H), 4.69–4.66 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 135.1, 133.9, 129.8, 129.7, 129.6, 126.8, 125.8, 125.2, 76.9, 69.8; IR (neat): 1593, 1573, 1474, 1440, 1253, 1035, 757 cm^{-1}; MS *m/z* (EI$^+$): 198 (M$^+$, ^{37}Cl, 1), 196 (M$^+$, ^{35}Cl, 4), 178 (6), 164 (68), 139 (25), 129 (100), 111 (13); HRMS (EI$^+$) (M)$^+$ found 196.0292; (M)$^+$ calcd for $C_{10}H_9O_2{}^{35}Cl$ 196.0291.

*4.3.7. ±3-(3-Chlorophenyl)-3,6-dihydro-1,2-dioxine (**1h**)*

Yield: 1.12 g, 19%; colourless oil; R_f 0.26 (2:3 CH_2Cl_2/hexane); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38–7.37 (m, 1H), 7.32–7.25 (m, 3H), 6.18 (dddd, J=10.5, 2.4, 2.4, 2.4 Hz, 1H), 6.08 (dddd, J=10.5, 2.4, 2.4, 2.4 Hz, 1H), 5.53 (dddd, J=2.4, 2.4, 2.4, 2.4 Hz, 1H), 4.68 (dddd, J=16.8, 2.4, 2.4, 2.4 Hz, 1H), 4.61 (dddd, J=16.8, 2.4, 2.4, 2.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 139.4, 134.3, 129.7, 128.8, 128.4, 126.5, 126.0, 125.2, 79.7, 69.8; IR (neat): 1598, 1575, 1477, 1430, 1248, 1035, 785 cm^{-1}; MS *m/z* (EI$^+$): 198 (M$^+$, ^{37}Cl, 6), 196 (M$^+$, ^{35}Cl, 17), 178 (28), 164 (68), 139 (27), 129 (100), 111 (20); HRMS (EI$^+$) (M)$^+$ found 196.0291; (M)$^+$ calcd for $C_{10}H_9O_2{}^{35}Cl$ 196.0291.

*4.3.8. ±3-(2-Bromophenyl)-3,6-dihydro-1,2-dioxine (**1j**)*

Yield: 320 mg, 6%; colourless oil; R_f 0.48 (1:9 ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (dd, J=7.8, 1.5 Hz, 1H), 7.48 (dd, J=7.8, 1.2 Hz, 1H), 7.30 (ddd, J=7.8, 7.5, 1.2 Hz, 1H), 7.19 (ddd, J=7.8, 7.5, 1.5 Hz, 1H), 6.21 (dddd, J=10.4, 3.0, 3.0, 2.4 Hz, 1H), 6.11 (dddd, J=10.4, 2.4, 2.0, 2.0 Hz, 1H), 6.01 (dddd, J=2.4, 2.4, 2.4, 2.4 Hz, 1H), 4.69–4.66 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.7, 133.1, 130.1, 129.9, 127.4, 125.9, 125.2, 124.2, 79.2, 69.9; IR (neat): 1591, 1571, 1467, 1441, 1186, 1025, 999 cm^{-1}; MS *m/z* (EI$^+$): 242 (M$^+$, ^{81}Br, 6), 240 (M$^+$, ^{79}Br, 6), 210 (40), 208 (41), 155 (6), 129 (100); HRMS (EI$^+$) (M)$^+$ found 239.97889; (M)$^+$ calcd for $C_{10}H_9O_2{}^{79}Br$ 239.97895.

*4.3.9. ±3-(3-Bromophenyl)-3,6-dihydro-1,2-dioxine (**1k**)*

Yield: 760 mg, 14%; colourless oil; R_f 0.42 (1:9 ethyl acetate/hexane); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.58–7.44 (m, 2H), 7.36–7.19 (m, 2H), 6.21 (dddd, J=10.3, 2.2, 2.2, 2.2 Hz, 1H), 6.08 (dddd, J=10.3, 2.2, 2.2, 2.2 Hz, 1H), 5.54 (dddd, J=2.2, 2.2, 2.2, 2.2 Hz, 1H), 4.72 (dddd, J=16.6, 2.2, 2.2, 2.2 Hz, 1H), 4.63 (dddd, J=16.6, 2.2, 2.2, 2.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 139.7, 131.9, 131.4, 130.1, 127.1, 126.1, 125.4, 122.6, 79.8, 69.9; IR (neat): 1596, 1569, 1474, 1427, 1190, 1060, 998 cm^{-1}; MS *m/z* (EI$^+$): 242 (M$^+$, ^{81}Br, 11), 240 (M$^+$, ^{79}Br, 11), 210 (84), 208 (89), 183 (27), 155 (12), 129 (100); HRMS (EI$^+$) (M)$^+$ found 239.97892; (M)$^+$ calcd for $C_{10}H_9O_2{}^{79}Br$ 239.97859.

*4.3.10. ±3-(4-Bromophenyl)-3,6-dihydro-1,2-dioxine (**1l**)*

Yield: 1.24 g, 27%; colourless flakes; mp 75–76 °C; R_f 0.36 (1:9 ethyl acetate/hexane); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.53–7.46 (m, 2H), 7.31–7.23 (m, 2H), 6.20 (dddd, J=10.3, 2.2, 2.2, 2.2 Hz, 1H), 6.07 (dddd, J=10.3, 2.2, 2.2, 2.2 Hz, 1H), 5.55 (dddd, J=2.2, 2.2, 2.2, 2.2 Hz, 1H), 4.72 (dddd,

J=16.7, 2.2, 2.2, 2.2 Hz, 1H), 4.61 (dddd, *J*=16.7, 2.2, 2.2, 2.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 136.4, 131.7, 130.1, 126.3, 125.2, 123.0, 79.8, 69.9; IR (Nujol): 1587, 1570, 1410, 1256, 1057, 994 cm^{-1}; MS *m/z* (EI^+): 242 (M^+, ^{81}Br, 28), 240 (M^+, ^{79}Br, 29), 210 (50), 208 (51), 185 (100), 183 (98), 129 (88). Anal. Calcd for $C_{10}H_9O_2Br$: C, 49.82; H, 3.76. Found: C, 49.91; H, 3.68.

4.3.11. ±3-(3,5-Dibromophenyl)-3,6-dihydro-1,2-dioxine (**1m**)

Yield: 710 mg, 27%; colourless oil; R_f 0.42 (2:3 CH_2Cl_2/hexane); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.64 (dd, *J*=1.8, 1.8 Hz, 1H), 7.47 (dd, *J*=1.8, 0.5 Hz, 2H), 6.22 (dddd, *J*=10.3, 2.8, 2.2, 2.2 Hz, 1H), 6.07 (dddd, *J*=10.3, 28, 2.2, 2.2 Hz, 1H), 5.43 (ddddd, *J*=2.2, 2.2, 2.2, 2.2, 0.5 Hz, 1H), 4.71 (dddd, *J*=16.6, 2.8, 2.2, 2.2 Hz, 1H), 4.62 (dddd, *J*=16.6, 2.8, 2.2, 2.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 141.5, 134.2, 130.1, 125.9, 125.2, 123.0, 78.9, 69.9; IR (neat): 1585, 1557, 1424, 1191, 1060, 1035, 858 cm^{-1}; MS *m/z* (EI^+): 322 (M^+, ^{81}Br^{81}Br, 13), 320 (M^+, ^{81}Br^{79}Br, 27), 318 (M^+, ^{79}Br^{79}Br, 15), 288 (30), 128 (100), 75 (25); HRMS (ESI) $(M+Na)^+$ found 340.8785; $(M+Na)^+$ calcd for $C_{10}H_8O_2{}^{79}Br_2Na$ 340.8789.

4.3.12. ±3-(3-Iodophenyl)-3,6-dihydro-1,2-dioxine (**1n**)

Yield: 340 mg, 28%; colourless oil; R_f 0.29 (2:3 CH_2Cl_2/hexane); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.73 (dd, *J*=1.7, 1.7 Hz, 1H), 7.68 (ddd, *J*=7.8, 1.7, 1.2 Hz, 1H), 7.36 (ddd, *J*=7.8, 1.7, 1.2 Hz, 1H), 7.10 (dd, *J*=7.8, 7.8 Hz, 1H), 6.20 (dddd, *J*=10.3, 2.2, 2.2, 1.8 Hz, 1H), 6.08 (dddd, *J*=10.3, 2.2, 2.2, 1.8 Hz, 1H), 5.51 (dddd, *J*=2.2, 2.2, 2.2, 2.2 Hz, 1H), 4.72 (dddd, *J*=16.6, 2.2, 2.2, 1.8 Hz, 1H), 4.62 (dddd, *J*=16.6, 2.2, 2.2, 1.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 139.6, 137.8, 137.3, 130.2, 127.7, 126.1, 125.3, 94.3, 79.7, 69.9; IR (neat): 1590, 1566, 1471, 1422, 1059, 997, 781 cm^{-1}; MS *m/z* (EI^+): 288 (M^+, 7), 272 (45), 271 (100), 257 (53), 256 (16), 145 (32), 130 (54). Anal. Calcd for $C_{10}H_9O_2I$: C, 41.69; H, 3.15. Found: C, 41.93; H, 3.13.

4.4. General procedure for the synthesis of epoxy-1,2-dioxines **2a–m,o–q** and **3a–m,q**[3]

To a solution of 1,2-dioxine **1** (1 equiv) in CH_2Cl_2 (20 mL/g) was added 70% *m*-chloroperbenzoic acid (2 equiv), and the reaction was stirred at ambient temperature until complete by TLC. Dichloromethane was then added and the solution extracted with satd $Na_2S_2O_3$ followed by $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered and the volatiles removed in vacuo. The crude epoxides were purified by column chromatography. The following epoxy-1,2-dioxines are known: **2c**,[3] **3c**,[3] **2o**,[6] **2p**,[3] **3p**,[3] **2q**,[5] **3q**.[5] The following epoxy-1,2-dioxines were prepared.

4.4.1. ±(1aS,2R,5aS)-2-(2-Methoxyphenyl)perhydrooxireno[2,3-d][1,2]dioxine (**2a**)

Yield: 402 mg, 74%; colourless oil; R_f 0.43 (1:3 ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.31 (m, 2H), 6.99–6.91 (m, 2H), 5.70 (br s, 1H), 4.56 (dd, *J*=13.7, 1.6 Hz, 1H), 4.40 (dd, *J*=13.8, 0.6 Hz, 1H), 3.86 (s, 3H), 3.58 (ddd, *J*=4.4, 0.9, 0.6 Hz, 1H), 3.47 (dd, *J*=4.4, 1.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.0, 130.3, 128.9, 127.9, 120.6, 110.9, 76.9, 69.3, 55.5, 53.8, 48.7; IR (neat): 1603, 1590, 1495, 1464, 1250, 1036, 785 cm^{-1}; MS *m/z* (EI^+): 208 (M^+, 39), 176 (3), 147 (9), 135 (100), 131 (26), 119 (21), 107 (19); HRMS (EI^+) $(M)^+$ found 208.0738; $(M)^+$ calcd for $C_{11}H_{12}O_4$ 208.0736.

4.4.2. ±(1aR,2R,5aR)-2-(2-Methoxyphenyl)perhydrooxireno[2,3-d][1,2]dioxine (**3a**)

Yield: 107 mg, 19%; colourless oil; R_f 0.34 (1:3 ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57–7.53 (m, 1H), 7.36–7.30 (m, 1H), 7.01–6.89 (m, 2H), 5.83 (br s, 1H), 4.58 (ddd, *J*=13.9, 1.1, 0.6 Hz, 1H), 4.39 (dd, *J*=13.9, 3.9 Hz, 1H), 3.87 (s, 3H), 3.61 (ddd, *J*=4.5, 3.9, 1.1 Hz, 1H), 3.58 (ddd, *J*=4.5, 1.4, 0.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.8, 129.9, 128.9, 124.1, 120.8, 110.4, 73.6, 70.1, 55.5, 50.9, 50.6; IR (neat): 1602, 1589, 1494, 1464, 1291, 1026, 757 cm^{-1}; MS *m/z* (EI^+): 208 (M^+, 81), 176 (1), 147 (13), 135 (100), 131 (39), 119 (36), 107 (35); HRMS (EI^+) $(M)^+$ found 208.0731; $(M)^+$ calcd for $C_{11}H_{12}O_4$ 208.0736.

4.4.3. ±(1aS,2R,5aS)-2-(3-Methoxyphenyl)perhydrooxireno[2,3-d][1,2]dioxine (**2b**)

Yield: 387 mg, 74%; colourless oil; R_f 0.38 (1:3 ethyl acetate/hexane); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.37–7.25 (m, 1H), 7.01–6.88 (m, 3H), 5.35 (br s, 1H), 4.57 (ddd, *J*=13.7, 1.5, 0.4 Hz, 1H), 4.41 (ddd, *J*=13.7, 0.9, 0.4 Hz, 1H), 3.82 (s, 3H), 3.58 (ddd, *J*=4.4, 1.0, 0.4 Hz, 1H), 3.50 (dddd, *J*=4.4, 1.5, 0.9, 0.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 160.1, 137.2, 130.1, 120.2, 114.8, 113.7, 81.4, 69.5, 55.5, 53.7, 48.9; IR (neat): 1603, 1587, 1493, 1456, 1287, 1157, 1037 cm^{-1}; MS *m/z* (EI^+): 208 (M^+, 100), 176 (3), 161 (11), 147 (13), 135 (64), 121 (10), 109 (13); HRMS (EI^+) $(M)^+$ found 208.0740; $(M)^+$ calcd for $C_{11}H_{12}O_4$ 208.0736.

4.4.4. ±(1aR,2R,5aR)-2-(3-Methoxyphenyl)perhydrooxireno[2,3-d][1,2]dioxine (**3b**)

Yield: 97 mg, 19%; colourless oil; R_f 0.32 (1:3 ethyl acetate/hexane); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.37–7.27 (m, 1H), 7.14–7.06 (m, 2H), 7.02–6.89 (m, 1H), 5.36 (br s, 1H), 4.61 (ddd, *J*=14.0, 1.3, 0.8 Hz, 1H), 4.39 (dd, *J*=14.0, 4.2 Hz, 1H), 3.82 (s, 3H), 3.66 (ddd, *J*=4.4, 4.2, 1.3 Hz, 1H), 3.53 (ddd, *J*=4.4, 1.1, 0.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.8, 136.3, 129.6, 120.8, 115.2, 113.8, 79.7, 70.1, 55.3, 51.1, 50.6; IR (neat): 1601, 1585, 1494, 1462, 1265, 1158, 1064 cm^{-1}; MS *m/z* (EI^+): 208 (M^+, 56), 176 (5), 161 (15), 136 (28), 135 (100), 121 (13), 109 (21); HRMS (EI^+) $(M)^+$ found 208.0739; $(M)^+$ calcd for $C_{11}H_{12}O_4$ 208.0736.

4.4.5. ±(1aS,2R,5aS)-2-(4-Methoxyphenyl)perhydrooxireno[2,3-d][1,2]dioxine (**2c**)

Yield: 415 mg, 75%; colourless solid; mp 93–94 °C; R_f 0.38 (1:3 ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.30 (m, 2H), 6.94–6.90 (m, 2H), 5.32 (br s, 1H), 4.56 (dd, *J*=13.4, 1.5 Hz, 1H), 4.39 (ddd, *J*=13.4, 0.6, 0.6 Hz, 1H),

3.81 (s, 3H), 3.58 (ddd, J=4.3, 0.9, 0.6 Hz, 1H), 3.51 (ddd, J=4.3, 1.5, 0.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.3, 129.5, 127.6, 114.2, 81.0, 69.1, 55.3, 53.6, 48.7; IR (Nujol): 1610, 1583, 1515, 1249, 1180, 1028, 800 cm^{-1}; MS m/z (EI$^+$): 208 (M$^+$, 39), 176 (19), 149 (18), 135 (89), 73 (88), 57 (64), 43 (100). Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.46; H, 5.81. Found: C, 63.36; H, 5.86.

*4.4.6. ±(1aR,2R,5aR)-2-(4-Methoxyphenyl)perhydro-oxireno[2,3-d][1,2]dioxine (**3c**)*

Yield: 110 mg, 20%; colourless oil; R_f 0.30 (1:3 ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51–7.45 (m, 2H), 6.94–6.89 (m, 2H), 5.31 (br s, 1H), 4.59 (ddd, J=13.9, 1.2, 0.9 Hz, 1H), 4.37 (dd, J=13.9, 4.5 Hz, 1H), 3.81 (s, 3H), 3.65 (ddd, J=4.5, 4.2, 1.2 Hz, 1H), 3.49 (ddd, J=4.2, 0.9, 0.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.4, 130.4, 126.9, 114.0, 79.4, 70.1, 55.3, 51.1, 50.6; IR (neat): 1607, 1581, 1497, 1236, 1174, 1056, 821 cm^{-1}; MS m/z (EI$^+$): 208 (M$^+$, 23), 176 (16), 147 (14), 136 (36), 135 (81), 77 (100); HRMS (EI$^+$) (M)$^+$ found 208.0739; (M)$^+$ calcd for $C_{11}H_{12}O_4$ 208.0736.

*4.4.7. ±(1aS,2R,5aS)-2-(2-Fluorophenyl)perhydro-oxireno[2,3-d][1,2]dioxine (**2d**)*

Yield: 384 mg, 72%; colourless oil; R_f 0.18 (1:1 CH_2Cl_2/hexane); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.49–7.32 (m, 2H), 7.22–7.05 (m, 2H), 5.59 (br s, 1H), 4.56 (dd, J=13.7, 1.8 Hz, 1H), 4.42 (ddd, J=13.7, 0.6, 0.4 Hz, 1H), 3.6 (ddd, J=4.3, 0.6, 0.4 Hz, 1H), 3.53 (ddd, J=4.3, 1.8, 0.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 160.6 (d, J=248.2 Hz), 131.1 (d, J=8.4 Hz), 130.1 (d, J=3.8 Hz), 124.4 (d, J=3.4 Hz), 122.7 (d, J=13.7 Hz), 115.9 (d, J=21.6 Hz), 76.6 (d, J=1.6 Hz), 69.4, 52.8 (d, J=3.1 Hz), 48.7; IR (neat): 1618, 1589, 1494, 1456, 1233, 1037, 930 cm^{-1}; MS m/z (EI$^+$): 196 (M$^+$, 60), 164 (48), 138 (27), 135 (29), 123 (100), 109 (59), 95 (35); HRMS (ESI) (M+Na)$^+$ found 219.0431; (M+Na)$^+$ calcd for $C_{10}H_9O_3FNa$ 219.0433.

*4.4.8. ±(1aR,2R,5aR)-2-(2-Fluorophenyl)perhydro-oxireno[2,3-d][1,2]dioxine (**3d**)*

Yield: 108 mg, 20%; colourless oil; R_f 0.29 (1:1 CH_2Cl_2/hexane); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.68–7.58 (m, 1H), 7.42–7.28 (m, 1H), 7.22–7.03 (m, 1H), 5.74 (br d, J=1.2 Hz, 1H), 4.57 (ddd, J=13.8, 1.3, 0.8 Hz, 1H), 4.41 (dd, J=13.8, 3.8 Hz, 1H), 3.64 (ddd, J=4.3, 3.8, 1.3 Hz, 1H), 3.58 (ddd, J=4.3, 1.2, 0.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 160.2 (d, J=246.6 Hz), 130.6 (d, J=8.4 Hz), 129.6 (d, J=3.1 Hz), 124.4 (d, J=3.4 Hz), 122.7 (d, J=13.7 Hz), 115.2 (d, J=21.3 Hz), 72.9 (d, J=3.8 Hz), 70.0, 50.9, 50.5 (d, J=1.5 Hz); IR (Nujol): 1618, 1589, 1494, 1456, 1234, 1035, 990 cm^{-1}; MS m/z (EI$^+$): 196 (M$^+$, 100), 164 (47), 138 (13), 135 (14), 123 (85), 109 (35), 95 (24); HRMS (ESI) (M+Na)$^+$ found 219.0432; (M+Na)$^+$ calcd for $C_{10}H_9O_3FNa$ 219.0433.

*4.4.9. ±(1aS,2R,5aS)-2-(3-Fluorophenyl)perhydro-oxireno[2,3-d][1,2]dioxine (**2e**)*

Yield: 413 mg, 72%; colourless solid; mp 54–55 °C; R_f 0.14 (1:1 CH_2Cl_2/hexane); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.44–7.32 (m, 1H), 7.22–7.02 (m, 3H), 5.36 (br s, 1H), 4.55 (ddd, J=13.8, 1.6, 0.4 Hz, 1H), 4.42 (ddd, J=13.8, 0.8, 0.4 Hz, 1H), 3.57–3.49 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 162.8 (d, J=245.8 Hz), 137.9 (d, J=7.2 Hz), 130.4 (d, J=8.0 Hz), 123.4 (d, J=3.5 Hz), 116.1 (d, J=20.9 Hz), 114.7 (d, J=22 Hz), 80.4 (d, J=1.9 Hz), 69.3, 52.9, 48.7; IR (Nujol): 1618, 1593, 1491, 1449, 1273, 1022, 989 cm^{-1}; MS m/z (EI$^+$): 196 (M$^+$, 6), 164 (3), 138 (13), 124 (29), 123 (100), 109 (28), 95 (78). Anal. Calcd for $C_{10}H_9O_3F$: C, 61.22; H, 4.62. Found: C, 61.31; H, 4.49.

*4.4.10. ±(1aR,2R,5aR)-2-(3-Fluorophenyl)perhydro-oxireno[2,3-d][1,2]dioxine (**3e**)*

Yield: 116 mg, 20%; colourless oil; R_f 0.19 (1:1 CH_2Cl_2/hexane); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.42–7.33 (m, 1H), 7.31–7.22 (m, 2H), 7.13–7.01 (m, 1H), 5.35 (br d, J=1.2 Hz, 1H), 4.57 (ddd, J=13.9, 1.3, 0.6 Hz, 1H), 4.38 (dd, J=13.9, 4.1 Hz, 1H), 3.65 (ddd, J=4.4, 4.1, 1.3 Hz, 1H), 3.53 (ddd, J=4.4, 1.2, 0.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 162.5 (d, J=245.1 Hz), 137.0 (d, J=7.2 Hz), 129.8 (d, J=8.0 Hz), 123.8 (d, J=3.0 Hz), 115.9 (d, J=20.9 Hz), 115.2 (d, J=22.4 Hz), 78.8 (d, J=1.9 Hz), 69.8, 50.8, 50.2; IR (Nujol): 1617, 1592, 1491, 1449, 1272, 1143, 992 cm^{-1}; MS m/z (EI$^+$): 196 (M$^+$, 100), 164 (20), 135 (23), 125 (32), 123 (72), 109 (35), 95 (46). Anal. Calcd for $C_{10}H_9O_3F$: C, 61.22; H, 4.62. Found: C, 61.33; H, 4.56.

*4.4.11. ±(1aS,2R,5aS)-2-(4-Fluorophenyl)perhydro-oxireno[2,3-d][1,2]dioxine (**2f**)*

Yield: 406 mg, 74%; colourless solid; mp 69.5–70.5 °C; R_f 0.14 (1:1 CH_2Cl_2/hexane); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.45–7.34 (m, 2H), 7.16–7.04 (m, 2H), 5.36 (br s, 1H), 4.57 (dd, J=13.6, 1.4 Hz, 1H), 4.42 (ddd, J=13.6, 0.6, 0.6 Hz, 1H), 3.56 (ddd, J=4.3, 1, 0.6 Hz, 1H), 3.54–3.50 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 163.2 (d, J=247.4 Hz), 131.5 (d, J=3.0 Hz), 129.9 (d, J=8.4 Hz), 115.9 (d, J=21.7 Hz), 80.7, 69.3, 53.3, 48.7; IR (Nujol): 1608, 1515, 1423, 1226, 1022, 987 cm^{-1}; MS m/z (EI$^+$): 196 (M$^+$, 5), 164 (2), 149 (21), 138 (11), 123 (100), 109 (27), 95 (52). Anal. Calcd for $C_{10}H_9O_3F$: C, 61.22; H, 4.62. Found: C, 61.47; H, 4.67.

*4.4.12. ±(1aR,2R,5aR)-2-(4-Fluorophenyl)perhydro-oxireno[2,3-d][1,2]dioxine (**3f**)*

Yield: 108 mg, 20%; colourless flakes; mp 89.5–90.5 °C; R_f 0.18 (1:1 CH_2Cl_2/hexane); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.58–7.47 (m, 2H), 7.13–7.00 (m, 2H), 5.33 (br s, 1H), 4.57 (ddd, J=13.9, 1.3, 0.8 Hz, 1H), 4.37 (dd, J=13.9, 4.2 Hz, 1H), 3.65 (ddd, J=4.4, 4.2, 1.2 Hz, 1H), 3.49 (ddd, J=4.4, 1.0, 0.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 163.3 (d, J=247.0 Hz), 130.8 (d, J=3.2 Hz), 130.6 (d, J=8.4 Hz), 115.5 (d, J=21.3 Hz), 79.0, 70.0, 51.1, 50.5; IR (Nujol): 1603, 1510, 1417, 1226, 1034, 987 cm^{-1}; MS m/z (EI$^+$): 196 (M$^+$, 38), 164 (2), 138 (8), 125 (64), 123 (100), 109 (33), 95 (91). Anal. Calcd for $C_{10}H_9O_3F$: C, 61.22; H, 4.62. Found: C, 61.43; H, 4.64.

*4.4.13. ±(1aS,2R,5aS)-2-(2-Chlorophenyl)perhydro-oxireno[2,3-d][1,2]dioxine (**2g**)*

Yield: 346 mg, 74%; colourless oil; R_f 0.16 (1:1 CH_2Cl_2/hexane); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.50–7.40 (m, 2H), 7.37–

7.25 (m, 2H), 5.75 (br s, 1H), 4.59 (dd, J=13.8, 1.4 Hz, 1H), 4.42 (ddd, J=13.8, 0.4, 0.4 Hz, 1H), 3.57 (ddd, J=4.3, 0.4, 0.4 Hz, 1H), 3.52 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 133.4, 133.2, 130.2, 130.0, 129.1, 127.0, 78.4, 69.4, 53.1, 48.7; IR (neat): 1595, 1574, 1476, 1441, 1244, 1038, 928 cm^{-1}; MS *m/z* (EI$^+$): 214 (M$^+$, ^{37}Cl, 24), 212 (M$^+$, ^{35}Cl, 79), 180 (44), 141 (68), 139 (100), 131 (51), 77 (70); HRMS (ESI) (M+Na)$^+$ found 235.0134; (M+Na)$^+$ calcd for $C_{10}H_9O_3{}^{35}ClNa$ 235.0138.

4.4.14. ±(1aR,2R,5aR)-2-(2-Chlorophenyl)perhydrooxireno[2,3-d][1,2]dioxine (**3g**)

Yield: 86 mg, 18%; colourless oil; R_f 0.21 (1:1 CH_2Cl_2/hexane); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.68–7.58 (m, 1H), 7.43–7.35 (m, 1H), 7.33–7.25 (m, 2H), 5.84 (br d, J=0.8 Hz, 1H), 4.59 (ddd, J=14.0, 1.2, 1.2 Hz, 1H), 4.39 (dd, J=14.0, 4.2 Hz, 1H), 3.65 (ddd, J=4.4, 4.2, 1.2 Hz, 1H), 3.62 (ddd, J=4.4, 1.2, 0.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 133.2, 132.9, 130.0, 129.6, 129.4, 127.1, 75.9, 70.0, 51.2, 49.9; IR (neat): 1595, 1574, 1475, 1442, 1280, 1034, 917 cm^{-1}; MS *m/z* (EI$^+$): 214 (M$^+$, ^{37}Cl, 31), 212 (M$^+$, ^{35}Cl, 97), 180 (44), 141 (65), 139 (100), 131 (24), 77 (67); HRMS (ESI) (M+Na)$^+$ found 235.0134; (M+Na)$^+$ calcd for $C_{10}H_9O_3{}^{35}ClNa$ 235.0138.

4.4.15. ±(1aS,2R,5aS)-2-(3-Chlorophenyl)perhydrooxireno[2,3-d][1,2]dioxine (**2h**)

Yield: 403 mg, 74%; colourless oil; R_f 0.23 (1:1 CH_2Cl_2/hexane); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.42–7.32 (m, 3H), 7.31–7.28 (m, 1H), 5.34 (br s, 1H), 4.55 (dd, J=13.8, 1.8 Hz, 1H), 4.43 (ddd, J=13.8, 0.6, 0.6 Hz, 1H), 3.54 (ddd, J=4.2, 0.6, 0.6 Hz, 1H), 3.52 (ddd, J=4.2, 1.8, 0.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 137.5, 134.7, 130.1, 129.3, 127.9, 126.0, 80.5, 69.3, 52.9, 48.7; IR (neat): 1599, 1575, 1479, 1433, 1195, 1036, 843 cm^{-1}; MS *m/z* (EI$^+$): 214 (M$^+$, ^{37}Cl, 30), 212 (M$^+$, ^{35}Cl, 90), 180 (34), 141 (55), 139 (100), 131 (22), 111 (56); HRMS (ESI) (M+Na)$^+$ found 235.0133; (M+Na)$^+$ calcd for $C_{10}H_9O_3{}^{35}ClNa$ 235.0138.

4.4.16. ±(1aR,2R,5aR)-2-(3-Chlorophenyl)perhydrooxireno[2,3-d][1,2]dioxine (**3h**)

Yield: 107 mg, 20%; colourless oil; R_f 0.28 (1:1 CH_2Cl_2/hexane); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.53 (dd, J=1.2, 1.2 Hz, 1H), 7.40 (ddd, J=7.8, 1.2, 1.2 Hz, 1H), 7.35 (ddd, J=7.8, 1.2, 1.2 Hz, 1H), 7.32 (dd, J=7.8, 7.8 Hz, 1H), 5.33 (br d, J=1.2 Hz, 1H), 4.57 (ddd, J=13.8, 1.2, 1.2 Hz, 1H), 4.39 (dd, J=13.8, 4.2 Hz, 1H), 3.66 (ddd, J=4.2, 4.2, 1.2 Hz, 1H), 3.53 (ddd, J=4.2, 1.2, 1.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 136.9, 134.5, 129.8, 129.3, 128.6, 126.5, 79.0, 70.0, 51.0, 50.4; IR (neat): 1600, 1575, 1478, 1424, 1195, 1035, 843 cm^{-1}; MS *m/z* (EI$^+$): 214 (M$^+$, ^{37}Cl, 21), 212 (M$^+$, ^{35}Cl, 64), 180 (19), 141 (69), 139 (91), 111 (59), 77 (100); HRMS (ESI) (M+Na)$^+$ found 235.0134; (M+Na)$^+$ calcd for $C_{10}H_9O_3{}^{35}ClNa$ 235.0138.

4.4.17. ±(1aS,2R,5aS)-2-(4-Chlorophenyl)perhydrooxireno[2,3-d][1,2]dioxine (**2i**)

Yield: 451 mg, 76%; colourless oil; R_f 0.18 (1:1 CH_2Cl_2/hexane); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.42–7.30 (m, 4H), 5.35 (br s, 1H), 4.56 (dd, J=13.9, 1.3 Hz, 1H), 4.42 (ddd, J=13.9, 0.8, 0.6 Hz, 1H), 3.56–3.5 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 135.2, 134.1, 129.2, 129.1, 80.5, 69.3, 53.0, 48.7; IR (neat): 1598, 1494, 1423, 1410, 1091, 1016, 929 cm^{-1}; MS *m/z* (EI$^+$): 214 (M$^+$, ^{37}Cl, 23), 212 (M$^+$, ^{35}Cl, 69), 180 (31), 141 (64), 139 (100), 131 (15), 77 (43). Anal. Calcd for $C_{10}H_9O_3Cl$: C, 56.49; H, 4.27. Found: C, 56.75; H, 4.20.

4.4.18. ±(1aR,2R,5aR)-2-(4-Chlorophenyl)perhydrooxireno[2,3-d][1,2]dioxine (**3i**)

Yield: 113 mg, 19%; colourless solid; mp 81–82 °C; R_f 0.26 (1:1 CH_2Cl_2/hexane); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.51–7.43 (m, 2H), 7.41–7.33 (m, 2H), 5.33 (br d, J=1.1 Hz, 1H), 4.57 (ddd, J=14.0, 1.3, 0.6 Hz, 1H), 4.38 (dd, J=14.0, 4.2 Hz, 1H), 3.66 (ddd, J=4.4, 4.2, 1.3 Hz, 1H), 3.50 (ddd, J=4.4, 1.1, 0.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 135.3, 133.5, 129.9, 128.8, 79.0, 70.0, 51.1, 50.4; IR (Nujol): 1596, 1493, 1411, 1096, 1016, 909 cm^{-1}; MS *m/z* (EI$^+$): 214 (M$^+$, ^{37}Cl, 23), 212 (M$^+$, ^{35}Cl, 87), 180 (31), 141 (91), 139 (100), 131 (43), 77 (61). Anal. Calcd for $C_{10}H_9O_3Cl$: C, 56.49; H, 4.27. Found: C, 56.66; H, 4.13.

4.4.19. ±(1aS,2R,5aS)-2-(2-Bromophenyl)perhydrooxireno[2,3-d][1,2]dioxine (**2j**)

Yield: 235 mg, 69%; colourless solid; mp 67.5–68.5 °C; R_f 0.21 (1:1 CH_2Cl_2/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (dd, J=7.8, 1.5 Hz, 1H), 7.43 (dd, J=7.8, 1.2 Hz, 1H), 7.34 (ddd, J=7.8, 7.5, 1.2 Hz, 1H), 7.24 (ddd, J=7.8, 7.5, 1.5 Hz, 1H), 5.74 (br s, 1H), 4.59 (dd, J=13.7, 1.5 Hz, 1H), 4.42 (br d, J=13.7 Hz, 1H), 3.56 (ddd, J=4.5, 0.6, 0.6 Hz, 1H), 3.50 (ddd, J=4.5, 1.5, 0.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.7, 132.7, 130.3, 129.9, 127.7, 123.0, 78.2, 70.0, 51.3, 49.9; IR (Nujol): 1590, 1570, 1441, 1243, 1023, 975, 836 cm^{-1}; MS *m/z* (EI$^+$): 258 (M$^+$, ^{81}Br, 23), 256 (M$^+$, ^{79}Br, 24), 224 (9), 183 (29), 117 (44), 77 (83), 44 (100). Anal. Calcd for $C_{10}H_9O_3Br$: C, 46.72; H, 3.52. Found: C, 46.62; 3.48.

4.4.20. ±(1aR,2R,5aR)-2-(2-Bromophenyl)perhydrooxireno[2,3-d][1,2]dioxine (**3j**)

Yield: 78 mg, 23%; colourless oil; R_f 0.27 (1:1 CH_2Cl_2/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (dd, J=7.8, 1.4 Hz, 1H), 7.58 (dd, J=7.8, 1.2 Hz, 1H), 7.37 (ddd, J=7.8, 7.4, 1.2 Hz, 1H), 7.23 (ddd, J=7.8, 7.4, 1.4 Hz, 1H), 5.82 (br s, 1H), 4.61 (br d, J=13.7 Hz, 1H), 4.40 (dd, J=13.7, 3.9 Hz, 1H), 3.68–3.63 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.1, 133.3, 130.4, 129.1, 127.6, 123.0, 80.3, 69.4, 53.2, 48.7; IR (neat): 1593, 1568, 1473, 1439, 1278, 1024, 990 cm^{-1}; MS *m/z* (EI$^+$): 258 (M$^+$, ^{81}Br, 38), 256 (M$^+$, ^{79}Br, 39), 224 (15), 185 (82), 131 (100), 117 (37), 77 (57); HRMS (EI$^+$) (M)$^+$ found 255.9744; (M)$^+$ calcd for $C_{10}H_9O_3{}^{79}Br$ 255.9735.

4.4.21. ±(1aS,2R,5aS)-2-(3-Bromophenyl)perhydrooxireno[2,3-d][1,2]dioxine (**2k**)

Yield: 395 mg, 74%; colourless oil; R_f 0.19 (1:1 CH_2Cl_2/hexane); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.59–7.49 (m, 2H), 7.38–7.23 (m, 2H), 5.33 (br s, 1H), 4.57 (dd, J=13.4,

1.2 Hz, 1H), 4.43 (dd, J=13.4, 0.6 Hz, 1H), 3.57–3.50 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 137.8, 132.3, 130.8, 130.4, 126.5, 122.9, 80.4, 69.4, 52.9, 48.7; IR (neat): 1596, 1569, 1477, 1428, 1192, 1074, 841 cm^{-1}; MS *m/z* (EI$^+$): 258 (M^+, ^{81}Br, 83), 256 (M^+, ^{79}Br, 85), 224 (23), 185 (100), 183 (89), 157 (44), 131 (33); HRMS (EI$^+$) $(M)^+$ found 255.97396; $(M)^+$ calcd for $C_{10}H_9O_3{}^{79}Br$ 255.97351.

*4.4.22. ±(1aR,2R,5aR)-2-(3-Bromophenyl)perhydro-oxireno[2,3-d][1,2]dioxine (**3k**)*

Yield: 111 mg, 21%; colourless oil; R_f 0.26 (1:1 CH_2Cl_2/hexane); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.70–7.66 (m, 1H), 7.55–7.40 (m, 2H), 7.30–7.21 (m, 1H), 5.33 (br s, 1H), 4.58 (br d, J=14.0 Hz, 1H), 4.39 (dd, J=14.0, 4.0 Hz, 1H), 3.66 (dd, J=4.2, 4.0 Hz, 1H), 3.53 (dd, J=4.2, 1.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 137.2, 132.3, 131.5, 130.1, 127.0, 122.6, 79.0, 70.0, 51.1, 50.4; IR (neat): 1596, 1569, 1476, 1425, 1191, 1034, 990 cm^{-1}; MS *m/z* (EI$^+$): 258 (M^++2, 47), 256 (M^+, 48), 224 (13), 185 (72), 183 (49), 131 (60), 77 (100); HRMS (EI$^+$) $(M)^+$ found 255.9742; $(M)^+$ calcd for $C_{10}H_9O_3{}^{79}Br$ 255.9735.

*4.4.23. ±(1aS,2R,5aS)-2-(4-Bromophenyl)perhydro-oxireno[2,3-d][1,2]dioxine (**2l**)*

Yield: 410 mg, 73%; colourless solid; mp 70–71 °C; R_f 0.20 (1:1 CH_2Cl_2/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58–7.51 (m, 2H), 7.32–7.25 (m, 2H), 5.34 (br s, 1H), 4.56 (dd, J=13.7, 1.4 Hz, 1H), 4.43 (ddd, J=13.7, 0.8, 0.6 Hz, 1H), 3.56–3.49 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.5, 132.0, 129.5, 123.3, 80.5, 69.3, 52.9, 48.6; IR (Nujol): 1591, 1575, 1408, 1242, 1073, 1013, 987 cm^{-1}; MS *m/z* (EI$^+$): 258 (M^++2, 19), 256 (M^+, 20), 224 (3), 185 (100), 183 (86), 131 (65), 77 (33). Anal. Calcd for $C_{10}H_9O_3Br$: C, 46.72; H, 3.53. Found: C, 46.97; H, 3.33.

*4.4.24. ±(1aR,2R,5aR)-2-(4-Bromophenyl)perhydro-oxireno[2,3-d][1,2]dioxine (**3l**)*

Yield: 109 mg, 19%; colourless solid; mp 92.5–94.5 °C; R_f 0.27 (1:1 CH_2Cl_2/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56–7.49 (m, 2H), 7.44–7.36 (m, 2H), 5.32 (br d, J=1.2 Hz, 1H), 4.58 (ddd, J=13.9, 1.3, 0.8 Hz, 1H), 4.39 (dd, J=13.9, 4.2 Hz, 1H), 3.66 (ddd, J=4.4, 4.2, 1.3 Hz, 1H), 3.51 (ddd, J=4.4, 1.2, 0.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.0, 13.8, 30.2, 123.5, 79.1, 70.0, 51.1, 50.4; IR (Nujol): 1592, 1491, 1403, 1243, 1071, 1012, 996 cm^{-1}; MS *m/z* (EI$^+$): 258 (M^++2, 28), 256 (M^+, 29), 224 (2), 185 (63), 183 (43), 131 (100), 77 (44). Anal. Calcd for $C_{10}H_9O_3Br$: C, 46.72; H, 3.53. Found: C, 47.00; H, 3.57.

*4.4.25. ±(1aS,2R,5aS)-2-(3,5-Dibromophenyl)perhydro-oxireno[2,3-d][1,2]dioxine (**2m**)*

Yield: 332 mg, 62%; colourless oil; R_f 0.21 (1:1 CH_2Cl_2/hexane); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.69 (dd, J=1.8, 1.8 Hz, 1H), 7.50 (dd, J=1.8, 0.5 Hz, 2H), 5.29 (br s, 1H), 4.56 (dd, J=13.8, 1.8 Hz, 1H), 4.45 (ddd, J=13.8, 0.8, 0.6 Hz, 1H), 3.55 (ddd, J=4.2, 0.8, 0.6 Hz, 1H), 3.50 (ddd, J=4.3, 1.8, 0.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 139.3, 134.8, 129.5, 123.4, 79.6, 69.5, 52.4, 48.8; IR (neat): 1588, 1557, 1424, 1194, 1036, 860 cm^{-1}; MS *m/z* (EI$^+$): 338 (M^+, ^{81}Br^{81}Br, 48), 336 (M^+, ^{81}Br^{79}Br, 100), 334 (M^+, ^{79}Br^{79}Br, 49), 304 (18), 263 (98), 211 (37), 209 (37), 156 (25), 102 (31); HRMS (ESI) $(M+Na)^+$ found 356.8739; $(M+Na)^+$ calcd for $C_{10}H_8O_3{}^{79}Br_2Na$ 356.8738.

*4.4.26. ±(1aR,2R,5aR)-2-(3,5-Dibromophenyl)perhydro-oxireno[2,3-d][1,2]dioxine (**3m**)*

Yield: 93 mg, 17%; colourless solid; mp 108.5–110.5 °C; R_f 0.29 (1:1 CH_2Cl_2/hexane); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.68 (dd, J=1.8 Hz, 1H), 7.61 (dd, J=1.8, 0.6 Hz, 2H), 5.29 (br d, J=1.4 Hz, 1H), 4.55 (ddd, J=13.9, 1.2, 0.4 Hz, 1H), 4.40 (dd, J=13.9, 3.7 Hz, 1H), 3.66 (ddd, J=4.3, 3.7, 1.2 Hz, 1H), 3.54 (ddd, J=4.3, 1.4, 0.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 138.7, 134.8, 130.0, 123.1, 78.3, 69.9, 51.0, 50.2; IR (Nujol): 1588, 1557, 1423, 1187, 1037, 862 cm^{-1}; MS *m/z* ($^+$EI): 338 (M^+, ^{81}Br^{81}Br, 39), 336 (M^+, ^{81}Br^{79}Br, 86), 334 (M^+, ^{79}Br^{79}Br, 42), 304 (9), 263 (100), 211 (65), 209 (66), 156 (29), 102 (53); HRMS (ESI) $(M+Na)^+$ found 356.8739; $(M+Na)^+$ calcd for $C_{10}H_8O_3{}^{79}Br_2Na$ 356.8738.

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Supplementary data

Experimental details for diene precursors to 1,2-dioxines **4m**,**n** and **5m**,**n** and ^{1}H or ^{13}C NMR spectra for **1**–**3d**, **1**–**3h**, **1**–**3l**, **1**–**3m** and **1n**. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 648695 (**1l**), 648694 (**2l**) and 648693 (**3l**). Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.11.071.

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