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Study of the interaction of salicyl aldehydes with epichlorohydrin: a simple, convenient, and efficient method for the synthesis of 3,6-epoxy[1,5]dioxocines

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ABSTRACT

An efficient synthetic method for 3,6-epoxy[1,5]dioxocines via the condensation of salicyl aldehydes and epichlorohydrin, using benzyl triethylammonium chloride as catalyst, is described. The use of neutral or electron-deficient salicyl aldehydes in all cases was found to give 3,6-epoxy[1,5]dioxocine derivatives in good yields. The structural features were resolved by IR, NMR spectroscopy, mass spectrometry, and ultimately proved by X-ray crystallographic analysis.

1. Introduction

Epoxides have become very popular in organic synthesis not only as building blocks but also as synthesis intermediates.[1] They can be easily prepared from a variety of substrates and are easily opened under a broad range of conditions giving a wide spectrum of materials. Particularly, O-alkylation reactions of various substituted phenols with epichlorohydrin are of great interest as the products obtained are of value in both industrial and academic applications.[2] Consequently, synthetic methodologies for preparing glycidyl ethers have attracted considerable interest and several methods offering good results have been reported.[2e,3]

The simplest and most popular method for preparation of 3-aryloxy-1,2-epoxypropanes consists of the one-step O-alkylation of the suitable phenol with epichlorohydrin in the presence of a base.[2b,4] Generally, in all the procedures described, the epichlorohydrin is used in a significant excess and the reaction is carried out in an aqueous solution of a base, or in an organic solvent containing pyridine or piperidine.[5,6] Depending on the substituent position and nature of the phenol, it takes 6–20 h at reflux or 24–26 h at room temperature to complete the reaction. However, classical methods possess a number of drawbacks, such as: moderate yields, moderate purity of products, and poor reaction selectivity.[4,5a] These problems may be partially solved by addition of a phase transfer catalyst (PTC) to the aqueous solution of base (K_2CO_3 or similar).[5a,c,f,h,6a,e] However, excellent yields of glycidyl ethers were obtained only when the compounds investigated contained electron-donating groups, while presence of electron-withdrawing ones led to formation of 1-chloro-3-aryloxypropan-2-ols in large amounts as unwanted by-products.[7]

The reaction of epichlorohydrin with compounds possessing the salicyl aldehyde core has not been thoroughly investigated—only a limited number of papers were published to this date.[2b,4b,c]

2. Results and discussion

During our ongoing research program on the study of epichlorohydrin interactions with various substrates, we found that 2-hydroxybenzaldehyde (**1a**) and epichlorohydrin afforded the glycidyl ether **2a** in high yield in the presence of benzyl triethylammonium chloride as a PTC. The reaction was carried out at the reflux temperature (125 °C) of epichlorohydrin and under these conditions reaction duration was 10 min (Scheme 1).

An increase in reaction time resulted in formation of the new product (TLC monitoring, during the course of the reaction, showed two products, one of them gradually fading in favor of the other). Utilizing spectroscopic and elemental analysis data a new compound was identified as 3,4-dihydro-2*H*,6*H*-3,6-epoxy-benzo-[1,5]dioxocine (**3a**). It is apparent that 2-(2-oxiranylmethoxy)-benzaldehyde (**2a**) undergoes intramolecular cyclization, which

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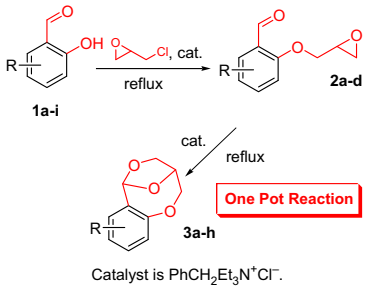


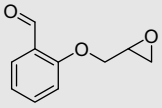
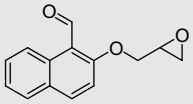
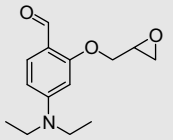
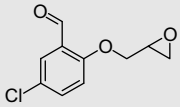
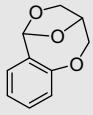
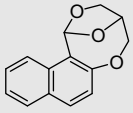
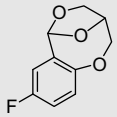
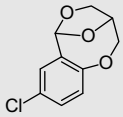
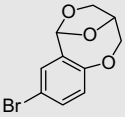
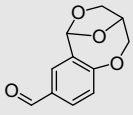
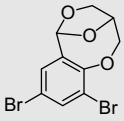
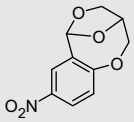
Scheme 1. Reactions of salicyl aldehydes with EPH.

results in the formation of 3,6-epoxy[1,5]dioxocine based polycyclic compound. To generalize the methodology, we investigated a number of different salicyl aldehydes possessing electron-donating or electron-withdrawing substituents. As seen from the results presented in Table 1, this method is most effective for electron-deficient salicyl aldehydes. The reaction time is strongly influenced by the relative strength of the electron-withdrawing group. **1i** with a nitro group, at the *m*-position relative to the carbonyl moiety, reacts in 30 min while halogen containing ones **1d–f** take 20 h. Neutral salicyl aldehydes **1a**, **b** react even slower (60 h); meanwhile, compound **1c**, containing an electron-donating diethylamino moiety, does not form the desired product at all and only glycidyl ether **2c** is obtained. Nonetheless, despite significantly increased reaction times all the products were isolated in good to excellent yields. In order to confirm the assumption that the desired products **3a–h** are obtained via an intramolecular cyclization of corresponding glycidyl ethers, a number of intermediate compounds **2a**, **b**, **d** were isolated and their structures confirmed (Table 1). This relatively simple and easy synthesis method of 3,6-epoxy[1,5]-dioxocine derivatives could be of particular interest in the field of medicinal chemistry, as dioxocine derivatives are important in pharmaceutical and agricultural applications.[8] It is also noteworthy that the variety of functional groups available could make these compounds appealing intermediate materials for the synthesis of other new and important derivatives.

The structures of the goal products are confirmed by the spectral analysis. In Figure 1 a typical example—(3,4-dihydro-2*H*,6*H*-3,6-epoxy-8-nitro-benzo[1,5]dioxocine (**3h**)) is analyzed.

Thus, a singlet of the CH group attached to the phenyl ring appears at 6.05 ppm and can be easily explained by deshielding effects due to its neighboring aromatic fragment and two oxygen atoms. The other aliphatic protons, of the isolated product, yield a set of signals for five not equivalent protons. They were analyzed as two spin–spin systems with one generic proton: AMX and A′M′X. The resonances of CH_2 protons (labeled H_A and H_M in Fig. 1) appear as a triplet and doublet of doublets positioned at 4.01 and 4.30 ppm, respectively (J_{AM}=6.9 Hz, J_{Ax}=6.9 Hz, and J_{Mx}=1.3 Hz). This is due to the coupling with CH (labeled H_x), which in turn is observed as a multiplet at 4.78–4.71 ppm. The A′M′X system, on the other hand, is not typical. $H_{M'}$ appears as a doublet of doublets at 4.43 ppm ($J_{A'M'}$=13.2 Hz, $J_{M'x}$=2.6 Hz), while $H_{A'}$ is observed as a doublet centered at 4.09 ppm. This phenomenon can be explained by the fact that a vicinal coupling constant between protons H_x and $H_{A'}$ is 0 Hz. It means there is no interaction between these two protons, consequently the dihedral angle between vicinal protons H_x and $H_{A'}$ tends to be ca. 90°. MO calculations confirm this assumption, as the dihedral angle for $H_{A'}$–C–C–H_x obtained from MM3 optimized structure is 88°. The crystallographic data showed that the investigated compound 3,4-dihydro-2*H*,6*H*-3,6-epoxy-8-nitro-benzo[1,5]dioxocine (**3h**) was isolated as a mixture of two enantiomers, in which chiral centers have *R*,*S* and *S*,*R* configuration with dihedral angles 93.4° and 96.3° for $H_{(42)}$–$C_{(25)}$–$C_{(20)}$–$H_{(38)}$ and $H_{(49)}$–$C_{(31)}$–$C_{(29)}$–$H_{(48)}$, respectively (Fig. 2).

Table 1
Reaction products, times, and yields

Entry	Product	Time	Yield (%)
2a		10 min	86
2b		15 min	79
2c		15 min	86
2d		15 min	81
3a		60 h	74
3b		60 h	72
3c		20 h	82
3d		20 h	73
3e		20 h	71
3f		10 h	77
3g		30 min	89
3h		30 min	89

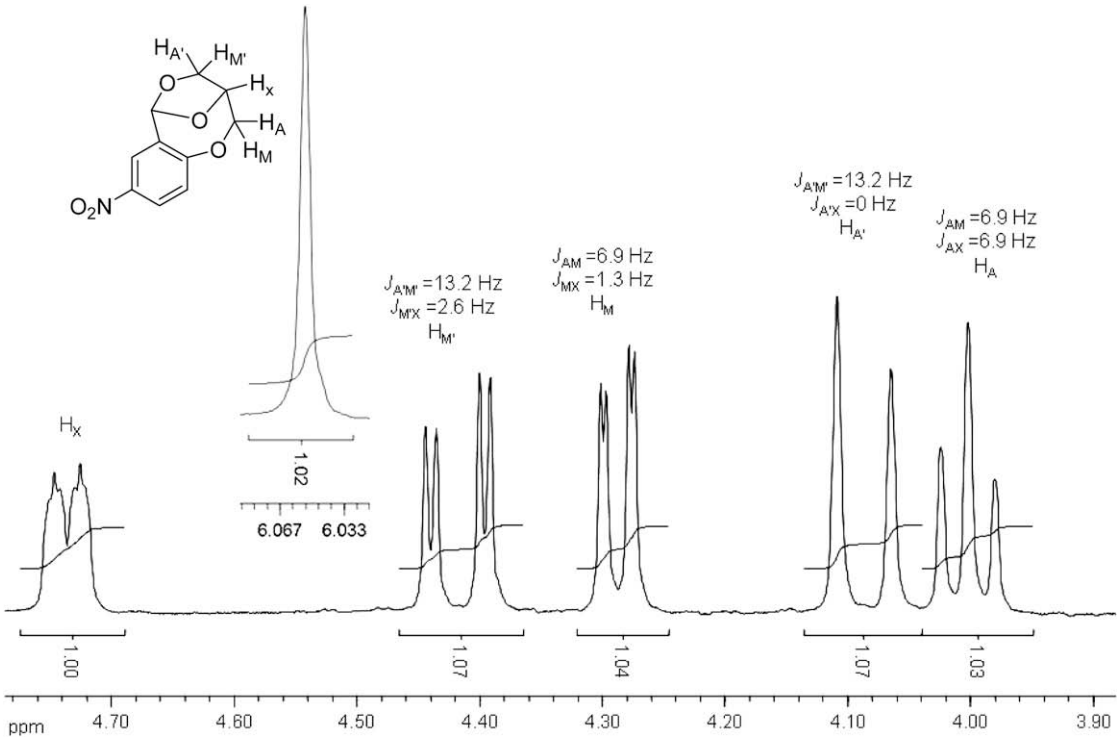


Figure 1. ^{1}H NMR spectra fragment of **3h** (300 MHz, $CDCl_3$).

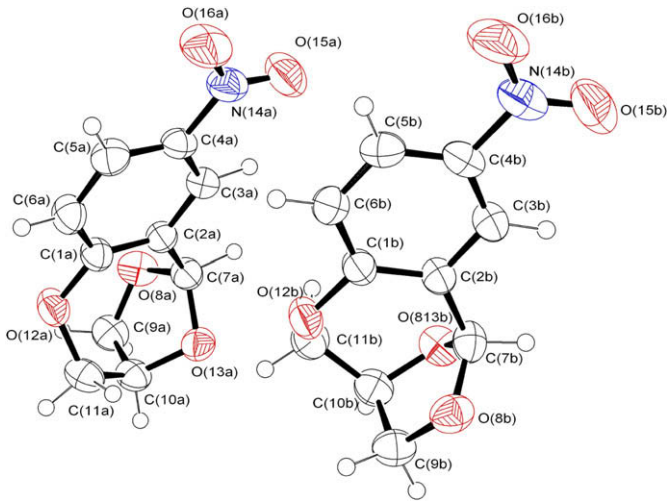


Figure 2. Molecular structure of **3h**. Displacement ellipsoids are drawn at 50% probability level.

3. Conclusion

In summary, we demonstrated that salicyl aldehydes with electron-withdrawing substituents, as well as without any additional functional groups, react with epichlorohydrin in the presence of quaternary ammonium halide (under reflux conditions) yielding 3,6-epoxy[1,5]dioxocine based polycyclic compounds in good yields. The reaction rate is highly dependent on the nature of the substituent. Salicyl aldehydes possessing electron-withdrawing fragments react considerably faster then those with no additional substituents. The strength of the electron-withdrawing moieties is also an important factor. This relatively simple and easy one pot synthesis method of 3,6-epoxy[1,5]dioxocine derivatives could be of particular interest in the field of medicinal chemistry, as dioxocine derivatives are important in the synthesis of biologically active compounds. Furthermore, the variety of functional groups available makes these compounds appealing intermediate materials for the synthesis of other new and important derivatives.

4. Experimental section

4.1. General

All chemicals were purchased from Aldrich and used as received without further purification. The ^{1}H NMR spectra were taken on Varian Unity Inova (300 MHz) and Varian Mercury 200 (500 MHz) spectrometers at room temperature. All the data are given as chemical shifts in δ (ppm), $(CH_3)_4Si$ (TMS, 0 ppm) was used as an internal standard. The course of the reaction products was monitored by TLC on ALUGRAM SIL G/UV254 or Silufol UV-254 plates and developed with I_2 or UV light. Silica gel (grade 62, 60–200 mesh, 150 Å, Aldrich) was used for column chromatography. Elemental analysis was performed with an Exeter Analytical CE-440 Elemental. IR spectroscopy was performed on a Perkin Elmer Spectrum BX II FT-IR System, using KBr pellets or coated on KRS5 discs. Melting points were determined using Electrothermal Mel-Temp melting point apparatus. Mass spectra (MS) were recorded on an Agilent 110 (series MS with VL) apparatus. X-ray crystallography analysis was carried out utilizing Bruker-Nonius Kappa CCD single crystal diffractometer, using Mo Kα radiation (λ=0.71073 Å). Single crystal data was processed using maXus, SIR 97, ORTEP, SHELXL-97 software.

4.2. General procedure for the alkylation of salicyl aldehydes with epichlorohydrin

The corresponding salicyl aldehyde was dissolved in epichlorohydrin, heated to reflux, and then 10 mol % of benzyl triethylammonium chloride was added to the reaction mixture. It was then vigorously stirred at the reflux temperature. After termination of the reaction, the reaction mixture was diluted with

chloroform and washed with distilled water. The organic layer was dried over anhydrous $MgSO_4$, filtered, and solvents were removed.

*4.2.1. 2-(2-Oxiranylmethoxy)benzaldehyde (**2a**).* 2-Hydroxybenzaldehyde (**1a**) (1 g, 8.1 mmol), epichlorohydrin (32 mL; 409 mmol), and benzyl triethylammonium chloride (0.186 g; 0.81 mmol). Reaction duration 10 min (TLC, acetone/*n*-hexane, 1:4). Obtained product was purified by column chromatography using 1:24 acetone/*n*-hexane as the eluent to yield colorless oil (1.25 g, 86%); [Found: C, 67.22; H, 5.80. $C_{10}H_{10}O_3$ requires C, 67.41; H, 5.66%]; R_f (acetone/*n*-hexane, 1:4, v/v) 0.3; ν_{max} (on KRS5 disc) 3072, 3005, 2929, 2867, 2763, 1688, 1599, 1484, 1458, 1396, 1288, 1240, 1024, 841, 760 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 10.48 (d, *J*=0.8 Hz, 1H), 7.80 (ddd, *J*=0.3 Hz, *J*=1.8 Hz, *J*=5.7 Hz, 1H), 7.57–7.49 (m, 1H), 7.05–6.94 (m, 2H), 4.34 (dd, *J*=2.8 Hz, *J*=11.1 Hz, 1H), 4.01 (dd, *J*=5.7 Hz, *J*=11.1 Hz, 1H), 3.40–3.35 (m, 1H), 2.94 (dd, *J*=4.2 Hz, *J*=4.8 Hz, 1H), 2.76 (dd, *J*=2.8 Hz, *J*=4.8 Hz, 1H); δ_C (52 MHz, $CDCl_3$) 189.5, 160.8, 136.0, 128.4, 125.1, 121.3, 112.8, 69.3, 49.9, 44.5; MS (APCI$^+$, 20 V), *m*/*z*: 179 ([M+H]$^+$).

*4.2.2. 2-(2-Oxiranylmethoxy)-1-naphthaldehyde (**2b**).* 2-Hydroxy-1-napthaldehyde (**1b**) (1 g, 5.8 mmol), epichlorohydrin (23 mL, 290 mmol), and benzyl triethylammonium chloride (0.132 g, 0.58 mmol). Reaction duration 15 min (TLC, acetone/*n*-hexane, 7:18). The residue was dissolved in 2-propanol. Obtained crystals were filtered off and washed with 2-propanol to yield (1.1 g, 79%) **2b** as light brown powder, mp: 102–104 °C (recrystallized from 2-propanol); [Found: C, 73.55; H, 5.10. $C_{14}H_{12}O_3$ requires C, 73.67; H, 5.30%]; R_f (acetone/*n*-hexane, 7:18, v/v) 0.36; ν_{max} (KBr) 3064, 2997, 2926, 2878, 2799, 1667, 1618, 1592, 1513, 1268, 1250 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 10.91 (s, 1H), 9.25 (d, *J*=8.5 Hz, 1H), 8.01 (d, *J*=9.2 Hz, 1H), 7.75 (d, *J*=8.1 Hz, 1H), 7.64–7.56 (m, 1H), 7.45–7.37 (m, 1H), 7.23 (d, *J*=9.2 Hz, 1H), 4.48 (dd, *J*=2.9 Hz, *J*=11.2 Hz, 1H), 4.16 (dd, *J*=5.7 Hz, *J*=11.2 Hz, 1H), 3.45–3.38 (m, 1H), 2.94 (t, *J*=4.5 Hz, 1H), 2.79 (dd, *J*=2.6 Hz, *J*=4.5 Hz, 1H); δ_C (52 MHz, $CDCl_3$) 191.6, 162.7, 137.4, 131.3, 129.8, 128.7, 128.1, 124.9, 124.8, 117.0, 113.5, 70.1, 49.8, 44.3; MS (APCI$^+$, 20 V), *m*/*z*: 229 ([M+H]$^+$).

*4.2.3. 4-Diethylamino-2-(2-oxiranylmethoxy)benzaldehyde (**2c**).* 4-Diethylamino-2-hydroxybenzaldehide (**1c**) (2.5 g, 12.9 mmol), epichlorohydrin (50 mL, 647 mmol), and benzyl triethylammonium chloride (0.359 g, 1.29 mmol). Reaction duration 15 min (TLC, acetone/*n*-hexane, 1:4). The residue was dissolved in diethyl ether. Obtained crystals were filtered off and washed with diethyl ether to yield (2.5 g, 86%) **2c** white powder, mp: 62–63 °C (recrystallized from diethyl ether); [Found: C, 67.38; H, 7.59; N, 5.42. $C_{14}H_{19}NO_3$ requires C, 67.45; H, 7.68; N, 5.62%]; R_f (acetone/*n*-hexane, 1:4, v/v) 0.18; ν_{max} (KBr) 3058, 3015, 2980, 2957, 2921, 1655, 1273, 870 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 10.18 (s, 1H), 7.72 (d, *J*=9 Hz, 1H), 6.31 (dd, *J*=2.3 Hz, *J*=9 Hz, 1H), 6.11 (d, *J*=2.3 Hz, 1H), 4.34 (dd, *J*=3 Hz, *J*=11.2 Hz, 1H), 4.05 (dd, *J*=5.6 Hz, *J*=11.2 Hz, 1H), 3.47–3.36 (m, 5H), 2.95 (t, *J*=4.5 Hz, 1H), 2.81 (dd, *J*=2.7 Hz, *J*=4.5 Hz, 1H), 1.22 (t, *J*=7.1 Hz, 6H); δ_C (52 MHz, $CDCl_3$) 186.8, 162.9, 153.7, 130.4, 114.2, 104.7, 93.6, 69.0, 50.1, 44.7, 44.6, 12.4; MS (APCI$^+$, 20 V), *m*/*z*: 250 ([M+H]$^+$).

*4.2.4. 5-Chloro-2-(2-oxiranylmethoxy)benzaldehyde (**2d**).* 5-Chloro-2-hydroxybenzaldehyde (**1d**) (1 g, 6.4 mmol), epichlorohydrin (25 mL, 320 mmol), and benzyl triethylammonium chloride (0.142 g, 0.64 mmol). Reaction duration 20 min (TLC, acetone/*n*-hexane, 1:4). Obtained colorless oil was purified by column chromatography using 1:24 acetone/*n*-hexane as the eluent and crystallized upon standing to yield (1.1 g, 81%) **2d** as white powder, mp: 35–36 °C; [Found: C, 56.55; H, 4.18. $C_{10}H_9ClO_3$ requires C, 56.49; H, 4.27%]; R_f (acetone/*n*-hexane, 1:4, v/v) 0.3; ν_{max} (KBr) 3101, 3070, 2999, 2927, 2886, 1678, 1268, 1250 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 10.44 (s, 1H), 7.78 (d, *J*=2.7 Hz, 1H), 7.48 (dd, *J*=2.7 Hz, *J*=8.9 Hz, 1H), 6.97 (d, *J*=8.9 Hz, 1H), 4.41 (dd, *J*=2.7 Hz, *J*=11.4 Hz, 1H), 4.03 (dd, *J*=5.9 Hz, *J*=11.4 Hz, 1H), 3.43–3.37 (m, 5H), 2.95 (t, *J*=4.2 Hz, 1H), 2.78 (dd, *J*=2.6 Hz, *J*=4.2 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 188.1, 159.1, 135.3, 127.9, 126.9, 125.9, 114.4, 69.7, 49.7, 44.3; MS (APCI$^+$, 20 V), *m*/*z*: 213 ([M+H]$^+$).

*4.2.5. 3,4-Dihydro-2H,6H-3,6-epoxy-benzo[1,5]dioxocine (**3a**).* 2-Hydroxybenzaldehyde (**1a**) (1 g, 8.1 mmol), epichlorohydrin (32 mL, 409 mmol), and benzyl triethylammonium chloride (0.186 g, 0.81 mmol). Reaction duration 60 h (TLC, acetone/*n*-hexane, 1:4). Obtained product was purified by column chromatography using 1:24 acetone/*n*-hexane as the eluent to yield yellow oil (1.08 g, 74%); [Found: C, 67.53; H, 5.57. $C_{10}H_{10}O_3$ requires C, 67.41; H, 5.66%]; R_f (acetone/*n*-hexane, 1:4, v/v) 0.36; ν_{max} (on KRS5 disc) 3057, 2965, 2923, 2896, 1221, 1105 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.28–7.18 (m, 2H), 7.08–6.97 (m, 2H), 6.03 (s, 1H), 4.68–4.62 (m, 1H), 4.34–4.23 (m, 2H), 4.04–3.95 (m, 2H); δ_C (75 MHz, $CDCl_3$) 156.4, 132.7, 129.9, 128.4, 122.7, 121.1, 106.1, 75.5, 73.6, 65.7; MS (APCI$^+$, 20 V), *m*/*z*: 179 ([M+H]$^+$).

*4.2.6. 3,4-Dihydro-1H,3H-3,6-epoxy-naphtho[2,1-b][1,5]dioxocine (**3b**).* 2-Hydroxy-1-napthaldehyde (**1b**) (1 g, 5.8 mmol), epichlorohydrin (23 mL, 290 mmol), and benzyl triethylammonium chloride (0.132 g, 0.58 mmol). Reaction duration 60 h (TLC, acetone/*n*-hexane, 1:4). Obtained product was purified by column chromatography using 1:24 acetone/*n*-hexane as the eluent to yield yellow oil (0.95 g, 72%); [Found: C, 73.61; H, 5.36. $C_{14}H_{12}O_3$ requires C, 73.67; H, 5.30%]; R_f (acetone/*n*-hexane, 1:4, v/v) 0.33; ν_{max} (on KRS5 disc) 3059, 2964, 2923, 2892, 1231, 1116 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.18 (d, *J*=8.6 Hz, 1H), 7.81 (d, *J*=8.1 Hz, 1H), 7.74 (d, *J*=8.8 Hz, 1H), 7.56–7.47 (m, 1H), 7.43–7.35 (m, 1H), 7.25 (d, *J*=8.8 Hz, 1H), 7.16 (s, 1H), 4.75–4.68 (m, 1H), 4.42–4.33 (m, 2H), 4.12–3.98 (m, 2H); δ_C (75 MHz, $CDCl_3$) 155.6, 131.6, 130.2, 130.0, 128.6, 126.9, 125.4, 124.2, 121.8, 121.4, 100.0, 75.5, 73.9, 66.7; MS (APCI$^+$, 20 V), *m*/*z*: 229 ([M+H]$^+$).

*4.2.7. 8-Fluoro-3,4-dihydro-2H,6H-3,6-epoxy-benzo[1,5]dioxocine (**3c**).* 5-Fluoro-2-hydroxybenzaldehyde (**1d**) (1 g 7.14 mmol), epichlorohydrin (28 mL, 357 mmol), and benzyl triethylammonium chloride (0.16 g, 0.714 mmol). Reaction duration 20 h (TLC, acetone/*n*-hexane, 1:4). Obtained product was purified by column chromatography using 1:24 acetone/*n*-hexane as the eluent to yield colorless oil (1.15 g, 82%); [Found: C, 61.30; H, 4.63. $C_{10}H_9FO_3$ requires C, 61.23; H, 4.62%]; R_f (acetone/*n*-hexane, 1:4, v/v) 0.33; ν_{max} (on KRS5 disc) 3062, 2964, 2921, 2898, 1258, 1112, 952, 834 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.06–6.98 (m, 1H), 6.97–6.88 (m, 2H), 5.95 (s, 1H), 4.71–4.65 (m, 1H), 4.37–4.23 (m, 2H), 4.03–3.95 (m, 2H); δ_C (75 MHz, $CDCl_3$) 156.2, 152.5 (d, *J*=2.8 Hz), 134.3 (d, *J*=6.1 Hz), 122.4 (d, *J*=7.9 Hz), 116.2 (d, *J*=22.7 Hz), 115.1 (d, *J*=23.6 Hz), 105.3 (d, *J*=1.4 Hz), 75.8, 73.6, 65.9; MS (APCI$^+$, 20 V), *m*/*z*: 197 ([M+H]$^+$).

*4.2.8. 8-Chloro-3,4-dihydro-2H,6H-3,6-epoxy-benzo[1,5]dioxocine (**3d**).* 5-Chloro-2-hydroxybenzaldehyde (**1e**) (1 g 6.39 mmol), epichlorohydrin (25 mL, 320 mmol), and benzyl triethylammonium chloride (0.14 g, 0.639 mmol). Reaction duration 20 h (TLC, acetone/*n*-hexane, 1:4). Obtained product was purified by column chromatography using 1:24 acetone/*n*-hexane as the eluent to yield colorless oil (0.99 g, 73%); [Found: C, 56.55; H, 4.33. $C_{10}H_9ClO_3$ requires C, 56.49; H, 4.27%]; R_f (acetone/*n*-hexane, 1:4, v/v) 0.45; ν_{max} (on KRS5 disc) 3058, 2964, 2934, 2897, 1259, 1114, 935, 833 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.23–7.17 (m, 2H), 7.02–6.97 (m, 1H), 5.95 (s, 1H), 4.70–4.64 (m, 1H), 4.33–4.24 (m, 2H), 4.03–3.94 (m, 2H); δ_C

(75 MHz, $CDCl_3$) 155.1, 134.3, 129.5, 128.2, 127.6, 122.6, 105.3, 75.6, 73.7, 65.8; MS ($APCI^+$, 20 V), *m*/*z*: 213 ($[M+H]^+$).

*4.2.9. 8-Bromo-3,4-dihydro-2H,6H-3,6-epoxy-benzo[1,5]dioxocine (**3e**).* 5-Bromo-2-hydroxybenzaldehyde (**1f**) (1 g 4.97 mmol), epichlorohydrin (19.5 mL, 248 mmol), and benzyl triethylammonium chloride (0.11 g, 0.49 mmol). Reaction duration 20 h (TLC, acetone/*n*-hexane, 1:4). Obtained product was purified by column chromatography using 1:24 acetone/*n*-hexane as the eluent to yield colorless oil (0.91 g, 71%); [Found: C, 46.65; H, 3.58. $C_{10}H_9BrO_3$ requires C, 46.72; H, 3.53%]; R_f (acetone/*n*-hexane, 1:4, v/v) 0.42; ν_{max} (on KRS5 disc) 3057, 2964, 2923, 2897, 1259, 1114, 933, 834 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.36–7.30 (m, 2H), 6.96–6.90 (m, 1H), 5.93 (s, 1H), 4.69–4.63 (m, 1H), 4.33–4.24 (m, 2H), 4.02–3.95 (m, 2H); δ_C (75 MHz, $CDCl_3$) 155.6, 134.8, 132.5, 131.1, 123.0, 115.0, 105.2, 75.6, 73.7, 65.8; MS ($APCI^+$, 20 V), *m*/*z*: 258 ($[M+H]^+$).

*4.2.10. 8-Formyl-3,4-dihydro-2H,6H-3,6-epoxy-benzo[1,5]dioxocine (**3f**).* 4-Hydroxyisophthalaldehyde (**1g**) (1 g, 6.66 mmol), epichlorohydrin (26 mL, 333 mmol), and benzyl triethylammonium chloride (0.15 g, 0.666 mmol). Reaction duration 10 h (TLC, acetone/*n*-hexane, 1:4). The residue was dissolved in diethyl ether. Obtained crystals were filtered off and washed with small amount of diethyl ether to yield (1.05 g, 77%) **3f** as yellow powder, mp: 101.5–103 °C (recrystallized from diethyl ether); [Found: C, 64.14; H, 4.81. $C_{11}H_{10}O_4$ requires C, 64.08; H, 4.89%]; R_f (acetone/*n*-hexane, 1:4, v/v) 0.21; ν_{max} (KBr) 3048, 2981, 2959, 2904, 1692, 1254, 1111, 952, 835 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 9.92 (s, 1H), 7.82–7.74 (m, 2H), 7.20 (d, *J*=7.9 Hz, 1H), 6.12 (s, 1H), 4.75–4.69 (m, 1H), 4.42 (dd, *J*=2.6 Hz, *J*=13.2 Hz, 1H), 4.31 (dd, *J*=1.3 Hz, *J*=6.8 Hz, 1H), 4.10 (d, *J*=13.2 Hz, 1H), 4.00 (t, *J*=6.8 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 190.4, 161.8, 133.4, 131.8, 131.2, 130.0, 122.1, 105.5, 75.2, 74.2, 65.6; MS ($APCI^+$, 20 V), *m*/*z*: 207 ($[M+H]^+$).

*4.2.11. 8,10-Dibromo-3,4-dihydro-2H,6H-3,6-epoxy-benzo[1,5]dioxocine (**3g**).* 3,5-Dibromosalicylaldehyde (**1h**) (1 g 3.57 mmol), epichlorohydrin (14 mL, 178 mmol), and benzyl triethylammonium chloride (0.08 g, 0.357 mmol). Reaction duration 30 min (TLC, acetone/*n*-hexane, 1:4). The residue was dissolved in diethyl ether. Obtained crystals were filtered off and washed with small amount of diethyl ether to yield (1.07 g, 89%) **3g** as white powder, mp: 105–107 °C (recrystallized from diethyl ether); [Found: C, 35.68; H, 2.34. $C_{10}H_8Br_2O_3$ requires C, 35.75; H, 2.40%]; R_f (acetone/*n*-hexane, 1:4, v/v) 0.42; ν_{max} (KBr) 3070, 2950, 2903, 2892, 1257, 1112 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.67 (s split, *J*=2.3 Hz, 1H), 7.32 (s split, *J*=2.3 Hz, 1H), 5.96 (s, 1H), 4.76–4.69 (m, 1H), 4.43 (dd, *J*=2.6 Hz, *J*=13.3 Hz, 1H), 4.38 (dd, *J*=1.3 Hz, *J*=6.5 Hz, 1H), 4.08–3.97 (m, 2H); δ_C (75 MHz, $CDCl_3$) 152.5, 135.8, 135.6, 130.5, 116.8, 115.2, 105.1, 75.6, 74.1, 66.1; MS ($APCI^+$, 20 V), *m*/*z*: 337 ($[M+H]^+$).

*4.2.12. 3,4-Dihydro-2H,6H-3,6-epoxy-8-nitro-benzo[1,5]dioxocine (**3h**).* 2-Hydroxy-5-nitrobenzaldehyde (**1i**) (3 g, 18 mmol), epichlorohydrin (70 mL, 898 mmol), and benzyl triethylammonium chloride (0.4 g, 1.8 mmol). Reaction duration 30 min (TLC, acetone/*n*-hexane, 1:4). The light yellow residue was dissolved in 2-propanol and obtained crystals filtered off to yield (3.56 g, 89%) **3h** as white powder, mp: 145.5–146 °C (recrystallized from toluene); [Found: C, 53.91; H, 4.07; N, 6.35. $C_{10}H_9NO_5$ requires C, 53.82; H, 4.06; N 6.28%]; R_f (acetone/*n*-hexane, 1:4, v/v) 0.27; ν_{max} (KBr) 3107, 3073, 2968, 2940, 2901, 1586, 1255, 1096 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.16–8.09 (m, 2H), 7.18–7.11 (m, 1H), 6.08 (s, 1H), 4.77–4.70 (m, 1H), 4.42 (dd, *J*=2.6 Hz, *J*=13.2 Hz, 1H), 4.29 (dd, *J*=1.3 Hz, *J*=6.9 Hz, 1H), 4.09 (d, *J*=13.2 Hz, 1H), 4.00 (t, *J*=6.9 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 161.8, 142.3, 133.3, 125.4, 124.1, 122.0, 104.8, 75.0, 74.3, 65.6; MS ($APCI^+$, 20 V), *m*/*z*: 225 ($[M+H]^+$).

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 739499. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.07.093.

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