Syntheses of 3-hydroxymethyl-2,3-dihydrobenzofurans and 3-hydroxymethylbenzofurans

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Dedicated to Professor A. Varvoglis on his 65th birthday
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Abstract
Reactions of 2-hydroxyphenylmethanones 8 with 1-chloro-1-(benzotriazol-1-yl)alkanes 9 give intermediates 10a–h, which were converted by trimethylsulfonium iodide to oxirans 11a–h. Treatment of 11a–h with LDA gave either 3-hydroxymethyl-2,3-dihydrobenzofurans or 3-hydroxymethylbenzofurans depending on substituents.

Keywords: 3-Hydroxymethylbenzofurans, oxirans

Introduction
3-Hydroxymethylbenzofurans are versatile intermediates1 for the synthesis of biologically active naphthofurans,2 analogs of CCK-A agonists;3 naphthofuranquinones4 and 3-hydroxymethylbenzofuran chrysanthenates.5 3-Hydroxymethylbenzofurans also occur naturally.4,6

Benzofurans undergo electrophilic substitution at the 2-position, and this normally precludes the direct introduction of a 3-substituent. Available methods for the preparation of 3-hydroxymethylbenzofurans 1 include (i) ring syntheses which often involve multi-step reactions,5,7 e.g. via benzofuran-2,3-dicarboxylic acid 2; (ii) Pd-catalyzed heteroannulation of 2-iodophenols 3 with O-silyl protected alkynols,8 or from 3-(2-bromophenoxy)acrylic ester 4;3 (iii) cyclization of 1-[2-(2-propynoxy)phenyl]diazonium salts 5;9 (iv) reaction of O-silyl protected 2-ethynylphenols 6 with aldehydes under TBAF catalysis;10 (v) oxidation of 3-methylbenzofurans 7 with selenium dioxide followed by reduction with LAH;11 and (vi)
bromination of 2-position protected 3-methylbenzofurans 7 followed by hydrolysis of the intermediate 3-bromomethylbenzofurans\(^6\) (Scheme 1).

![Scheme 1](image)

Recently, benzotriazole mediated benzofuran\(^1\) and benzothiophene\(^2\) ring syntheses were reported. We now disclose a related route to 3-hydroxymethylbenzofurans 13 in good overall yields (Scheme 2).

**Results and Discussion**

(2-Hydroxyphenyl)methanones (8) and 1-chloro-1-(1H-benzotriazol-1-yl)alkanes (9) reacted under basic conditions to give alkylated derivatives 10 (Scheme 2) in good yields (Table 1). The structures of compounds 10 were supported by their \(^1\)H NMR and \(^{13}\)C NMR spectra.

Compounds 10a–h were converted to oxirans 11a–h (Scheme 2) by treatment with trimethylsulfonium iodide (3.0 equivalents) and potassium tert-butoxide (3.0 equivalents) in DMSO solution at 0–5 °C. Oxirans 11a–e and 11g–h were purified by column chromatography on silica gel and obtained in 59–88% yields, except for compound 11e which was isolated in only 35% yield. NMR analysis of crude product 11f showed the presence of 70–75% of desired 11f (three characteristic doublet of doublets signals of oxiran ring protons: 2.47 ppm, 2.84 ppm and 3.92 ppm), but chromatographic purification was not possible due to instability on silica gel and alumina. Attempts to use crude product 11f in the next step failed. Compounds 11e–f were prepared in yield 81–82% by reaction of 10e–f with trimethylsulfonium iodide in methylene chloride – 50% aqueous NaOH two phase system with tetrabutylammonium iodide under reflux for 12–48 h.\(^3\) In this case, oxirans 11e–f were obtained with purity over 90%. The structures of
oxirans 11a–h were supported by their \textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectra. Compounds 11e–f were used in the next step without additional purification.

Scheme 2. For designation of R\textsuperscript{1}–R\textsuperscript{4} see Table 1. a) K\textsubscript{2}CO\textsubscript{3}, DMF, 50–55 °C, 8–12 h; b) for 11a–d: Me\textsubscript{3}S\textsuperscript{T}, KOBu\textsubscript{t}, DMSO, 12 h; for 11e–f: Me\textsubscript{3}S\textsuperscript{T}, n-Bu\textsubscript{4}NI, CH\textsubscript{2}Cl\textsubscript{2}–50\% NaOH, reflux; c) LDA, 1 eq., THF, 12–16 h; d) lithium naphthalenide, 3 eq., –40 °C, THF; e) LDA, 2 eq., THF, 12–16 h.

Compounds 11a–h were treated with an equivalent amount of LDA in THF at a temperature ranging from –78 °C to 20 °C. The anion formed by lithiation of the benzotriazole α-carbon in 1-(2-oxiranylphenoxymethyl)-benzotriazoles 11a–h selectively opens the oxiran ring to form 2,3-dihydrobenzofurans 12a–h. To support the reaction pathway proposed in Scheme 2 for benzofurans 13a–f, and to investigate the accessibility of the benzotriazolyl group for substitution in 12a–f, we isolated and characterized compounds 12d-syn, 12d-anti, 12f-syn, and 12f-anti and used them for the preparation of benzofurans 13d, f. We also prepared compound 12g, which was formed exclusively as the anti diastereoisomer. In the case of 12h, we obtained both syn and anti diastereoisomers. The \textsuperscript{1}H NMR spectra of 12d, f–g show no characteristic signals assigned to the oxiranyl rings of compounds 11d, f–h in the range 2.2–4.1 ppm. The \textsuperscript{13}C NMR spectra of 12d, f–g no longer show the carbon signal in 74–84 ppm range, which corresponds to the carbon between the benzotriazole and phenolic oxygen in 11d, f–h. For 12d, f–h new signals in the range 93–104 ppm were assigned to the C2 carbons of the 2,3-dihydrobenzofuran rings.
The structures of diastereoisomers $12f$-anti, $12g$-anti, $12h$-syn and $12h$-anti were unambiguously determined by single crystal X-ray structure determination. Figure 1 shows a perspective view of the molecular structure of a representative example ($12h$-syn), which ascertains both, the structure and relative stereochemistry of this isomer. Interestingly, in each of the four crystal structures determined, the hydroxymethyl substituent participates in an intermolecular hydrogen bond to the N3 nitrogen atom of an adjacent molecule in the solid state.

![Figure 1. Perspective view of the X-ray structure of $12h$-syn.](image)

The signals for the methylene protons of the 3-hydroxymethyl group in $12f$-syn in $^1$H NMR appear as two multiplets at 3.93–4.01 ppm, 4.04–4.11 ppm. The signals for the same protons of $12f$-anti appear as two multiplets at 3.37–3.48 ppm, 3.72–3.82 ppm. The signals for the corresponding protons for the one of the diastereoisomers of $12d$ in the $^1$H NMR spectrum appear as two multiplets at 3.18–3.28 ppm, 3.61–3.69 ppm; the same protons for the second diastereoisomer overlapped in one multiplet at 4.02–4.18 ppm. We assigned the signals at 3.18–3.28 ppm, 3.61–3.69 ppm to the syn-isomer and that at 4.02–4.18 ppm to the anti-isomer. The ratios syn:anti for compounds $12d$, $12f$, and $12h$ were approximately 34:66, 32:68, and 59:41, respectively. The structures of compounds $12d$, $12f$, $12g$ and $12h$ were also supported by their $^1$H NMR and $^{13}$C NMR spectra.

Treatments of 2,3-dihydrobenzofurans $12d$, $12f$ and oxirans $11a$–f with two equivalents of LDA in THF at a temperature ranging from $-78$ °C to 20 °C afford the corresponding 3-hydroxymethylbenzofurans $13a$–f in yields of 66–85%. The structures of compounds $13a$–f were deduced from their $^1$H NMR and $^{13}$C NMR spectra. Unlike $12d$, $12f$ and $11a$–f, the $^1$H NMR spectra of $13a$–f show no characteristic signals for a $N$-substituted benzotriazolyl group (in the
range 7.3–8.1 ppm) or for an oxiranyl ring (in range 2.2–4.1 ppm). The $^{13}$C NMR spectra of 13a–f also no longer show any signal in the range 74–84 ppm, which corresponds to the carbon between the benzotriazole and phenolic oxygen nor any benzotriazole signals at 126–128 ppm, 131–133 ppm and 146–147 ppm, as were assigned for 11a–f.

Table 1. Preparation of intermediates 10, 11, 12 and 3-hydroxymethylbenzofurans 13

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<th>R$^1$</th>
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$^a$ was not prepared. $^b$ two diastereomers. $^c$ yield for Method B (see experimental section).

We also tried to substitute the benzotriazole group in 2-(benzotriazol-1-yl)-2,3-dihydrobenzofurans 12f,g. Compound 12f, when treated with a Grignard reagent (3 eq., benzyl magnesium bromide or isopropyl magnesium bromide) in THF under reflux, unexpectedly gave only the corresponding benzofuran 13f (45%), as the result of benzotriazole elimination. Compound 12g was unreactive to these Grignard reagents. Attempts to use a zinc reagent (3 eq., isopropyl zinc bromide) in THF on 12f were also unsuccessful. In an attempt to substitute benzotriazole with hydrogen, compound 12g was reacted with lithium naphthalenide$^{16}$ (3 eq.) in THF at temperatures ranging from –40 to 20 °C followed by the addition of water. This gave only the product 14. Structure of 14 was deduced from its $^1$H and $^{13}$C NMR spectra, which showed a set of signals characteristic for a N-substituted benzotriazole group, two broad singlets at 5.3 ppm and 10.1 ppm corresponding to the two hydroxy groups and the four doublets corresponding to the two methylene groups, which do not have neighboring protons.

Conclusions

An efficient method for preparation of 3-hydroxymethyl-2,3-dihydrobenzofurans and 3-hydroxymethylbenzofurans has been developed using benzotriazole mediated benzofuran ring closure. The application of this method allows the preparation of the 3-hydroxymethyl-2,3-dihydrobenzofurans 12d,f–h and 3-hydroxymethylbenzofurans 13a–f in good yields, starting from readily available salicylic aldehydes.
Experimental Section

General Procedures. Melting points were determined on a hot-stage apparatus and are uncorrected. NMR spectra were recorded in CDCl$_3$ with TMS as the internal standard for $^1$H (300 MHz) or a solvent as the internal standard for $^{13}$C (75 MHz). Micro elemental analyses were performed on a Carlo Erba EA-1108 elemental analyzer. LDA was used freshly prepared from $n$-butyllithium and di-$iso$-propylamine. Di-$iso$-propylamine was dried over calcium hydride. DMF and DMSO were dried over molecular sieves. Column chromatography was conducted with silica gel 200–425 mesh.

Materials. 1-Benzotriazol-1-ylalkyl chlorides 9 were synthesized according to the previously published procedure: 17 1-(chloromethyl)benzotriazole, colorless prisms from toluene (95%), mp 135–137 °C (136–138 °C$^{17a}$) and 1-(1-chloroethyl)-benzotriazole, yellow oil (53%)$^{17b}$.

General procedure for the preparation of O-alkylated (2-hydroxyphenyl)methanones (10a–h) A mixture of (2-hydroxyphenyl)methanone 8 (20 mmol), 1-benzotriazol-1-ylalkyl chloride 9 (22 mmol) and potassium carbonate (3.6 g, 26 mmol) in DMF (50 mL) was stirred at 40–50 °C for 4 h. Then, the reaction mixture was cooled to 10–15 °C and ice–water (approx. 30–40 mL) was slowly added. The precipitate was filtered off, washed with water and dried in vacuum. The products 10b, 10d were extracted with ethyl acetate, the extract was washed with water, dried over magnesium sulfate and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel.

2-(Benzotriazol-1-ylmethoxy)benzaldehyde (10a). White needles from DMF/water (88%), mp 93–94 °C; $^1$H NMR δ 6.70 (s, 2H), 7.12 (t, $J = 7.5$ Hz, 1H), 7.39–7.47 (m, 2H), 7.52–7.60 (m, 2H), 7.71 (d, $J = 8.2$ Hz, 1H), 7.79 (dd, $J = 7.5$, 1.6 Hz, 1H), 8.08 (d, $J = 8.2$ Hz, 1H), 10.36 (s, 1H); $^{13}$C NMR δ 74.4, 109.4, 114.8, 120.3, 123.2, 124.8, 125.9, 128.6, 129.2, 132.6, 135.9, 146.3, 158.0, 188.7. Anal. Calcd for C$_{14}$H$_{11}$N$_3$O$_2$: C, 66.40; H, 4.38; N, 16.59. Found: C, 66.09; H, 4.19; N, 16.75.

2-[1-(Benzotriazol–1–yl)ethoxy]benzaldehyde (10b). White microcrystals from ethyl acetate/hexanes (67%), mp 90–91 °C; $^1$H NMR δ 2.20 (d, $J = 6.1$ Hz, 3H), 7.02 (t, $J = 7.6$ Hz, 1H), 7.15 (d, $J = 8.4$ Hz, 1H), 7.23 (q, $J = 6.1$ Hz, 1H), 7.32–7.44 (m, 2H), 7.48 (t, $J = 7.7$ Hz, 1H), 7.73–7.82 (m, 2H), 8.05 (d, $J = 8.4$ Hz, 1H), 10.56 (s, 1H); $^{13}$C NMR δ 20.5, 84.1, 110.4, 114.6, 120.1, 122.7, 124.3, 125.5, 128.0, 128.9, 130.6, 135.6, 146.5, 157.5, 188.5. Anal. Calcd for C$_{15}$H$_{13}$N$_3$O$_2$: C, 66.40; H, 4.90; N, 15.72. Found: C, 67.41; H, 4.87; N, 15.94.

2-(Benzotriazol-1-ylmethoxy)-5-methylbenzaldehyde (10c). White microcrystals from DMF/water (90%), mp 80–82 °C; $^1$H NMR δ 2.28 (s, 3H), 6.66 (s, 2H), 7.29–7.36 (m, 2H), 7.38–7.45 (m, 1H), 7.51–7.58 (m, 2H), 7.70 (d, $J = 8.3$ Hz, 1H), 8.07 (d, $J = 8.4$ Hz, 1H), 10.30 (s, 1H); $^{13}$C NMR δ 20.2, 74.7, 109.4, 115.1, 120.2, 124.7, 125.7, 128.5, 129.1, 132.6, 132.9, 136.5,
146.2, 156.0, 188.8. Anal. Calcd for C_{15}H_{13}N_{3}O_{2}: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.12; H, 4.84; N, 15.71.

2-[1-(Benzotriazol-1-yl)ethoxy]-5-methylbenzaldehyde (10d). Oil (68%); \(^1\)H NMR \(\delta 2.18 (d, J = 6.1 \text{ Hz}, 3\text{H}), 2.22 (s, 3\text{H}), 6.98 (d, J = 8.5 \text{ Hz}, 1\text{H}), 7.15 (q, J = 6.1 \text{ Hz}, 1\text{H}), 7.19 (dd, J = 8.5, 2.1 \text{ Hz}, 1\text{H}), 7.34-7.40 (m, 1\text{H}), 7.46-7.51 (m, 1\text{H}), 7.55 (d, J = 2.1 \text{ Hz}, 1\text{H}), 7.77 (d, J = 8.3 \text{ Hz}, 1\text{H}), 8.05 (d, J = 8.3 \text{ Hz}, 1\text{H}), 10.50 (s, 1\text{H}); \(^{13}\)C NMR \(\delta 20.1, 20.7, 84.5, 110.5, 114.9, 120.2, 124.4, 125.4, 128.1, 129.2, 130.8, 132.6, 136.4, 146.6, 155.7, 188.9. Anal. Calcd for C_{16}H_{15}N_{3}O_{2}: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.23; H, 5.58; N, 14.78.

2-(Benzotriazol-1-ylmethoxy)-5-chlorobenzaldehyde (10e). White crystals from DMF/water (96%); mp 121-123 °C; \(^1\)H NMR \(\delta 6.69 (s, 2\text{H}), 7.42-7.52 (m, 3\text{H}), 7.56-7.61 (m, 1\text{H}), 7.69-7.73 (m, 2\text{H}), 8.09 (d, J = 8.4 \text{ Hz}, 1\text{H}), 10.28 (s, 1\text{H}); \(^{13}\)C NMR \(\delta 74.4, 109.2, 116.5, 120.4, 124.9, 126.8, 128.6, 128.8, 132.5, 135.4, 146.2, 156.4, 187.3. Anal. Calcd for C_{14}H_{10}ClN_{3}O_{2}: C, 58.45; H, 3.50; N, 14.61. Found: C, 58.53; H, 3.42; N, 14.68.

2-(Benzotriazol-1-ylmethoxy)-4-methoxybenzaldehyde (10f). White microcrystals from DMF/water (88%); mp 105-106 °C; \(^1\)H NMR \(\delta 3.84 (s, 3\text{H}), 6.60 (d, J = 8.6 \text{ Hz}, 1\text{H}), 6.69 (s, 2\text{H}), 6.94 (s, 1\text{H}), 7.39-7.44 (m, 1\text{H}), 7.53-7.58 (m, 1\text{H}), 7.72-7.76 (m, 2\text{H}), 8.06 (d, J = 8.2 \text{ Hz}, 1\text{H}), 10.19 (s, J = 1.8 \text{ Hz}, 1\text{H}); \(^{13}\)C NMR \(\delta 55.7, 74.2, 100.3, 108.9, 109.4, 119.4, 120.0, 124.7, 128.5, 130.8, 132.5, 146.1, 159.8, 165.8, 187.2. Anal. Calcd for C_{15}H_{13}N_{3}O_{3}: C, 63.60; H, 4.63; N, 14.83. Found: C, 63.76; H, 4.61; N, 14.93.

1-[2-(Benzotriazol-1-ylmethoxy)phenyl]-1-ethanone (10g). White microcrystals from DMF/water (98%); mp 127-128 °C; \(^1\)H NMR \(\delta 2.50 (s, 3\text{H}), 6.65 (d, J = 8.6 \text{ Hz}, 1\text{H}), 6.69 (s, 2\text{H}), 7.05-7.13 (m, 1\text{H}), 7.32 (d, J = 8.2 \text{ Hz}, 1\text{H}), 7.37-7.48 (m, 2\text{H}), 7.52-7.59 (m, 1\text{H}), 7.63-7.68 (m, 2\text{H}), 8.09 (d, J = 8.4 \text{ Hz}, 1\text{H}); \(^{13}\)C NMR \(\delta 31.4, 74.7, 109.4, 115.2, 120.3, 123.1, 124.7, 128.5, 130.5, 132.7, 133.6, 146.3, 154.9, 199.0. Anal. Calcd for C_{15}H_{13}N_{3}O_{2}: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.21; H, 4.98; N, 15.88.

[2-(Benzotriazol-1-ylmethoxy)phenyl] (phenyl)methanone (10h). White microcrystals from DMF/water (92%); mp 99-100 °C (72-74 °C\(^{13b}\)); \(^1\)H NMR \(\delta 6.46 (s, 2\text{H}), 7.08-7.15 (m, 1\text{H}), 7.25-7.52 (m, 9\text{H}), 7.61 (d, J = 7.8 \text{ Hz}, 2\text{H}), 8.00 (d, J = 8.0 \text{ Hz}, 1\text{H}); \(^{13}\)C NMR \(\delta 75.0, 109.8, 115.7, 119.8, 123.1, 124.4, 128.1, 128.2, 129.6, 129.7, 130.6, 131.9, 132.5, 133.0, 137.3, 146.1, 153.5, 195.6. Anal. Calcd for C_{20}H_{15}N_{3}O_{2}: C, 72.94; H, 4.59; N, 12.76. Found: C, 72.83; H, 4.38; N, 12.86.

**General procedure for the preparation of oxirans (11).** Method A for 11a–d and 11g–h

Potassium tert-butoxide (0.9 g, 8 mmol) was added to a stirred solution of the 2-(benzotriazol-1-ylmethoxy)phenylmethanone 10 (2 mmol) and trimethylsulfonium iodide (1.63 g, 8 mmol) in DMSO (20 mL) at 10–15 °C. The reaction mixture was stirred at the same temperature for 1 h, then it was allowed to warm to 20–25 °C and kept at this temperature for 4 h. Then, ice–water was added and the product was extracted with dichloromethane or ethyl acetate. This extract was washed with water, dried over magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel.
**Method B for 11e–f.** A vigorously stirred mixture of 10 (3 mmol) with trimethylsulfonium iodide (0.82 g, 4 mmol) in the presence of tetrabutylammonium iodide (50 mg, 0.13 mmol) in dichloromethane (10 mL) and 50% aqueous NaOH (10 mL) was refluxed under a nitrogen atmosphere for 12–48 h. When 10 was consumed (as monitored by TLC), the product was extracted with dichloromethane. The extract was dried over magnesium sulfate and the solvent was evaporated to give the crude product 11 in approximately 90% purity. These products were used for preparation of compound 12 and 13. The oxiran 11e can be additionally purified by column chromatography on silica gel with a mixture of ethyl acetate–hexanes (1:3).

**1-[[2-(2-Oxiranyl)phenoxy]methyl]-benzotriazole (11a).** White crystals (65%) from diethyl ether, mp 57-58 °C; \(^1\)H NMR \(\delta\) 2.39 (dd, \(J = 5.6, 2.6\) Hz, 1H), 2.83 (dd, \(J = 5.6, 4.2\) Hz, 1H), 3.97 (dd, \(J = 4.2, 2.6\) Hz, 1H), 6.56 (d, \(J = 11.5\) Hz, 1H), 6.60 (d, \(J = 11.5\) Hz, 1H), 6.98-7.08 (m, 2H), 7.22-7.25 (m, 2H), 7.36-7.41 (m, 1H), 7.47-7.52 (m, 1H), 7.59 (d, \(J = 8.2\) Hz, 1H), 8.05 (d, \(J = 8.2\) Hz, 1H); \(^13\)C NMR \(\delta\) 47.6, 50.1, 75.3, 109.4, 114.8, 120.0, 123.5, 124.5, 125.4, 128.0, 128.2, 129.0, 132.7, 146.1, 154.7. Anal. Calcd for C\(_{15}\)H\(_{13}\)N\(_2\)O\(_2\): C, 67.40; H, 4.90; N, 15.72. Found: C, 67.22; H, 5.04; N, 15.48.

**1-[[1-[2-(2-Oxiranyl)phenoxy]ethyl]-benzotriazole (11b).** Colorless oil (63%); \(^1\)H NMR \(\delta\) 2.13 (2.17) (d, \(J = 6.0\) Hz, 3H), 2.31 (2.75) (dd, \(J = 5.6, 2.6\) Hz, 1H), 2.87 (3.18) (dd, \(J = 5.6, 4.2\) Hz, 1H), 4.15 (4.18) (dd, \(J = 4.2, 2.6\) Hz, 1H), 6.90-7.18 (m, 5H), 7.30-7.38 (m, 1H), 7.39-7.50 (m, 1H), 7.65 (7.77) (d, \(J = 8.3\) Hz, 1H), 8.05 (d, \(J = 8.2\) Hz, 1H); \(^13\)C NMR \(\delta\) 20.9, 47.7 (47.9), 50.0 (50.3), 84.4 (85.1), 110.5 (110.6), 113.9 (113.9), 114.9, 120.1 (120.1), 123.0 (123.5), 124.2 (124.3), 125.3 (125.5), 127.2, 127.6 (127.8), 128.9 (128.9), 130.9 (131.2), 146.5 (146.6), 154.3 (154.6). Anal. Calcd for C\(_{16}\)H\(_{13}\)N\(_2\)O\(_2\): C, 68.31; H, 5.37; N, 14.94. Found: C, 68.13; H, 5.54; N, 14.72.

**1-[[4-Methyl-2-(2-oxiranyl)phenoxy]methyl]-benzotriazole (11c).** Colorless oil (70%); \(^1\)H NMR \(\delta\) 2.23 (s, 3H), 2.37 (dd, \(J = 5.6, 2.6\) Hz, 1H), 2.78 (dd, \(J = 5.6, 4.2\) Hz, 1H), 3.92 (dd, \(J = 4.2, 2.6\) Hz, 1H), 6.53 (d, \(J = 11.3\) Hz, 1H), 6.58 (d, \(J = 11.3\) Hz, 1H), 6.85 (d, \(J = 1.5\) Hz, 1H), 7.03 (dd, \(J = 8.3, 1.5\) Hz, 1H), 7.10 (d, \(J = 8.3\) Hz, 1H), 7.36-7.44 (m, 1H), 7.47-7.54 (m, 1H), 7.59 (d, \(J = 8.3\) Hz, 1H), 8.07 (d, \(J = 8.3\) Hz, 1H); \(^13\)C NMR \(\delta\) 20.6, 47.7, 50.2, 75.8, 109.5, 115.2, 120.1, 124.5, 125.8, 127.8, 128.2, 129.5, 132.7, 146.2, 152.7. Anal. Calcd for C\(_{16}\)H\(_{13}\)N\(_2\)O\(_2\): C, 68.31; H, 5.37; N, 14.94. Found: C, 68.14; H, 5.87; N, 15.08.

**1-(Benzoazinol-1-yl)ethyl-4-methyl-2-(2-oxiranyl)phenylether (11d).** Yellow oil (59%); \(^1\)H NMR \(\delta\) 2.12-2.18 (m, 6H), 2.29 (2.75) (dd, \(J = 5.7, 2.6\) Hz, 1H), 2.81 (3.17) (dd, \(J = 5.7, 4.1\) Hz, 1H), 4.09 (4.13) (dd, \(J = 4.1, 2.6\) Hz, 1H), 6.74-7.05 (m, 4H), 7.32-7.50 (m, 2H), 7.65 (7.76) (d, \(J = 8.3\) Hz, 1H), 8.04 (d, \(J = 8.3\) Hz, 1H); \(^13\)C NMR \(\delta\) 20.5, 20.5, 21.0, 47.8, 48.0, 50.1, 50.4, 84.8, 85.6, 110.6, 110.7, 114.3, 115.2, 120.2, 120.2, 124.3, 124.3, 125.7, 126.0, 127.0, 127.6, 127.9, 129.3, 129.5, 131.1, 131.3, 132.8, 133.1, 146.6, 146.7, 152.3, 152.6. Anal. Calcd for C\(_17\)H\(_{17}\)N\(_2\)O\(_2\): C, 69.14; H, 5.80; N, 14.23. Found: C, 69.24; H, 5.62; N, 14.57.

**1-[[4-Chloro-2-(2-oxiranyl)phenoxy]methyl]-benzotriazole (11e).** White microcrystals from diethyl ether (82%), mp 105-107 °C; \(^1\)H NMR \(\delta\) 2.35 (dd, \(J = 5.6, 2.5\) Hz, 1H), 2.82 (dd, \(J = 5.6, 4.1\) Hz, 1H), 3.91 (dd, \(J = 4.1, 2.5\) Hz, 1H), 6.55 (d, \(J = 11.4\) Hz, 1H), 6.60 (d, \(J = 11.4\) Hz, 1H),
7.03 (s, 1H), 7.17-7.20 (m, 2H), 7.38-7.43 (m, 1H), 7.50-7.55 (m, 1H), 7.62 (d, \( J = 8.3 \) Hz, 1H), 8.06 (d, \( J = 8.3 \) Hz, 1H); \(^{13}C\) NMR \( \delta \) 47.2, 50.2, 75.3, 109.3, 116.2, 120.1, 124.6, 125.4, 128.4, 128.7, 128.9, 130.1, 132.6, 146.1, 153.1. Anal. Calcd for C\(_{15}\)H\(_{12}\)ClN\(_3\)O\(_2\): C, 59.71; H, 4.01; N, 13.93. Found: C, 59.65; H, 3.98; N, 13.88.

1-\{5-Methoxy-2-(2-oxiranyl)phenoxy\}methyl-benzotriazole (11f). White powder from diethyl ether (81%), mp 76-78 °C; \(^1H\) NMR \( \delta \) 2.47 (dd, \( J = 5.5, 2.6 \) Hz, 1H), 2.84 (dd, \( J = 5.5, 2.6 \) Hz, 1H), 3.76 (s, 3H), 3.92 (dd, \( J = 4.2, 2.6 \) Hz, 1H), 6.55 (dd, \( J = 8.5, 2.2 \) Hz, 1H), 6.58 (s, 2H), 6.81 (d, \( J = 8.5 \) Hz, 1H), 7.38-7.43 (m, 1H), 7.0-7.55 (m, 1H), 7.63 (d, \( J = 8.2 \) Hz, 1H), 8.07 (d, \( J = 8.4 \) Hz, 1H); \(^{13}C\) NMR \( \delta \) 47.7, 49.9, 55.4, 75.4, 101.7, 108.5, 109.5, 119.8, 120.1, 124.5, 126.4, 128.3, 132.7, 146.2, 155.8, 160.4. Anal. Calcd for C\(_{16}\)H\(_{15}\)N\(_3\)O\(_2\): C, 64.64; H, 5.09; N, 14.13. Found: C, 64.64; H, 5.32; N, 14.14.

1-\{2-(2-Methyl-2-oxiranyl)phenoxy\}methyl-benzotriazole (11g). White microcrystals from DMSO/water (85%), mp 93-94 °C; \(^1H\) NMR \( \delta \) 1.53 (s, 3H), 2.50 (d, \( J = 5.4 \) Hz, 1H), 2.75 (d, \( J = 5.4 \) Hz, 1H), 6.64 (s, 2H), 6.97-7.04 (m, 1H), 7.22-7.28 (m, 2H), 7.33 (d, \( J = 7.3 \) Hz, 1H), 7.38-7.44 (m, 1H), 7.51-7.58 (m, 1H), 7.69 (d, \( J = 8.2 \) Hz, 1H), 8.08 (d, \( J = 8.4 \) Hz, 1H); \(^{13}C\) NMR \( \delta \) 23.0, 54.6, 56.4, 74.6, 109.5, 114.0, 120.2, 123.0, 124.6, 128.0, 128.2, 129.0, 131.3, 132.7, 146.3, 153.6. Anal. Calcd for C\(_{16}\)H\(_{15}\)N\(_3\)O\(_2\): C, 68.31; H, 5.37; N, 14.94. Found: C, 68.25; H, 5.57; N, 14.82.

1-\{2-(2-Phenyl-2-oxiranyl)phenoxy\}methyl-benzotriazole (11h). White microcrystals from DMSO/water (88%), mp 74-75 °C; \(^1H\) NMR \( \delta \) 3.14 (d, \( J = 5.5 \) Hz, 1H), 3.17 (d, \( J = 5.5 \) Hz, 1H), 6.44 (d, \( J = 11.5 \) Hz, 1H), 6.54 (d, \( J = 11.5 \) Hz, 1H), 7.05 (d, \( J = 7.1 \) Hz, 1H), 7.07-7.37 (m, 10H), 7.45 (dd, \( J = 7.6, 1.4 \) Hz, 1H), 7.98-8.04 (m, 1H); \(^{13}C\) NMR \( \delta \) 56.6, 59.3, 74.2, 109.8, 113.9, 119.9, 122.7, 124.4, 125.8, 127.5, 128.1, 128.1, 128.8, 129.8, 130.0, 132.6, 139.9, 146.2, 154.5. Anal. Calcd for C\(_{21}\)H\(_{17}\)N\(_3\)O\(_2\): C, 73.45; H, 4.99; N, 12.24. Found: C, 73.31; H, 5.00; N, 12.23.

**General procedure for the preparation of compounds 12d and 12f–h**

A solution of LDA (2.0 mmol) in THF was added to a stirred solution of oxiran 11 (2.0 mmol) in THF (10 mL) at –78 °C. The reaction mixture was stirred at this temperature for 12 h and then quenched with saturated aqueous NH\(_4\)Cl. The product (mixture of 2 diastereomers) was extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate and evaporated. Diastereoisomers were separated by gradient column chromatography on silica gel using mixtures of ethyl acetate with hexanes.

\[2R,3R\]-2-(Benzotriazol-1-yl)-2,5-dimethyl-2,3-dihydro-1-benzofuran-3-yl]methanol (12dsyn). Yellow needles from ethyl acetate/hexanes (19%), mp 96-98 °C; \(^1H\) NMR \( \delta \) 2.31 (s, 3H), 2.39 (s, 3H), 3.15 (br s, 1H), 3.18-3.28 (m, 1H), 3.61-3.69 (m, 1H), 3.99-4.04 (m, 1H), 6.96 (d, \( J = 8.1 \) Hz, 1H), 7.05 (s, 1H), 7.12 (d, \( J = 8.1 \) Hz, 1H), 7.24-7.35 (m, 2H), 7.46-7.51 (m, 1H), 7.92-7.97 (m, 1H); \(^{13}C\) NMR \( \delta \) 20.8, 29.7, 56.0, 61.1, 103.9, 109.2, 112.9, 119.6, 124.0, 125.1, 126.1, 127.9, 129.8, 131.8, 132.7, 145.7, 154.9. Anal. Calcd for C\(_{17}\)H\(_{17}\)N\(_3\)O\(_2\): C, 69.14; H, 5.80; N, 14.23. Found: C, 69.01; H, 5.76; N, 14.63.
[(2R,3S)-2-(Benzotriazol-1-yl)-2,5-dimethyl-2,3-dihydro-1-benzofuran-3-yl]methanol (12d-anti). Oil (37%). $^1$H NMR δ 2.19 (s, 3H), 2.20 (s, 3H), 3.68 (br s, 1H), 4.02-4.18 (m, 2H), 4.86 (t, $J = 6.0$ Hz, 1H), 6.82 (d, $J = 8.1$ Hz, 1H), 6.93 (br d, $J = 8.1$ Hz, 1H), 7.05 (br s, 1H), 7.28-7.35 (m, 1H), 7.38-7.47 (m, 1H), 7.96 (d, $J = 9.3$ Hz, 2H); $^{13}$C NMR δ 20.7, 22.5, 52.9, 62.1, 104.1, 109.4, 112.7, 119.5, 124.1, 125.8, 126.9, 127.5, 129.4, 131.8, 131.8, 146.2, 154.9. Anal. Calcd for C$_{17}$H$_{15}$N$_3$O$_2$: C, 69.14; H, 5.80; N, 14.23. Found: C, 68.93; H, 5.80; N, 14.17.

[(2R,3R)-2-(Benzotriazol-1-yl)-6-methoxy-2,3-dihydro-1-benzofuran-3-yl]methanol (12f-syn). Sticky oil (26%). $^1$H NMR δ 3.35 (br s, 1H), 3.37-3.48 (m, 1H), 3.72-3.82 (m, 1H), 3.80 (s, 3H), 4.20-4.31 (m, 1H), 6.54 (d, $J = 2.1$ Hz, 1H), 6.59 (dd, $J = 8.2, 2.1$ Hz, 1H), 6.92 (d, $J = 8.0$ Hz, 1H), 7.18-7.32 (m, 3H), 7.43 (d, $J = 8.6$ Hz, 1H), 7.81 (d, $J = 7.8$ Hz, 1H); $^{13}$C NMR δ 47.7, 55.5, 60.2, 92.7, 96.4, 107.8, 110.9, 117.5, 119.5, 124.2, 124.4, 127.9, 132.0, 145.6, 159.4, 161.1. Anal. Calcd for C$_{16}$H$_{15}$N$_3$O$_2$: C, 64.64; H, 5.09; N, 14.13. Found: C, 64.57; H, 5.21; N, 14.25.

[(2R,3S)-2-(Benzotriazol-1-yl)-6-methoxy-2,3-dihydro-1-benzofuran-3-yl]methanol (12f-anti). Colorless prisms from EtOAc/Hexanes (55%), mp 162-164 °C; $^1$H NMR δ 2.26 (t, $J = 5.5$ Hz, 1H), 3.79 (s, 3H), 3.93-4.01 (m, 1H), 4.04-4.11 (m, 1H), 4.29-4.34 (m, 1H), 6.47 (d, $J = 2.2$ Hz, 1H), 6.61 (dd, $J = 8.2, 2.2$ Hz, 1H), 7.20-7.45 (m, 5H), 8.05 (d, $J = 8.1$ Hz, 1H); $^{13}$C NMR δ 49.4, 55.6, 63.9, 92.8, 96.5, 108.2, 110.2, 116.5, 120.2, 124.5, 124.5, 128.1, 131.6, 146.7, 159.7, 161.6. Anal. Calcd for C$_{16}$H$_{15}$N$_3$O$_2$: C, 64.64; H, 5.09; N, 14.13. Found: C, 64.57; H, 5.21; N, 14.25.

Crystal data for 12f-anti. C$_{16}$H$_{15}$N$_3$O$_2$, FW 297.31, monoclinic, space group P2$_1$/n, $a = 9.434$(3), $b = 13.842$(4), $c = 10.661$(3) Å, $\beta = 98.310$(4)°, $V = 1377.5$(6) Å$^3$, F(000) = 642, Z = 4, $T = -105$ °C, $\mu$ (MoKα) = 0.102 mm$^{-1}$, $D_{calc} = 1.434$ g.cm$^{-3}$, crystal size 0.88 x 0.80 x 0.73 mm, 20$_{max}$ 53° (CCD area detector, MoKα radiation), 203 parameters, GOF = 1.03, wR(F$^2$) = 0.0880 (all 2808 data), R = 0.0331 (2556 data with I > 2σI).

Crystal data for 12g-anti. C$_{16}$H$_{15}$N$_3$O$_2$, FW 281.31, monoclinic, space group P2$_1$/c, $a = 10.129$(2), $b = 10.343$(3), $c = 13.246$(3) Å, $\beta = 97.675$(4)°, $V = 1375.4$(6) Å$^3$, F(000) = 592, Z = 4, $T = -105$ °C, $\mu$ (MoKα) = 0.092 mm$^{-1}$, $D_{calc} = 1.359$ g.cm$^{-3}$, crystal size 0.69 x 0.50 x 0.48 mm, 20$_{max}$ 53° (CCD area detector, MoKα radiation), 193 parameters, GOF = 1.057, wR(F$^2$) = 0.1209 (all 2741 data), R = 0.0411 (2087 data with I > 2σI).

Crystal data for 12h-syn. C$_{16}$H$_{15}$N$_3$O$_2$, FW 281.31, monoclinic, space group P2$_1$/c, $a = 10.129$(2), $b = 10.343$(3), $c = 13.246$(3) Å, $\beta = 97.675$(4)°, $V = 1375.4$(6) Å$^3$, F(000) = 592, Z = 4, $T = -105$ °C, $\mu$ (MoKα) = 0.092 mm$^{-1}$, $D_{calc} = 1.359$ g.cm$^{-3}$, crystal size 0.69 x 0.50 x 0.48 mm, 20$_{max}$ 53° (CCD area detector, MoKα radiation), 193 parameters, GOF = 1.057, wR(F$^2$) = 0.1209 (all 2741 data), R = 0.0411 (2087 data with I > 2σI).
Crystal data for 12h-syn. C_{21}H_{17}N_{3}O_{2}, FW 343.38, triclinic, space group P-1, a = 8.308(2), b = 10.206(2), c = 10.689(2) Å, α = 86.529(2), β = 75.967(3), γ = 72.143(2)°, V = 836.8(3) Å³, F(000) = 360, Z = 2, T = -105 °C, μ (MoKα) = 0.090 mm⁻¹, D_calcd = 1.363 g.cm⁻³, crystal size 0.71 x 0.69 x 0.64 mm, 2θ_max 53° (CCD area detector, MoKα radiation), 238 parameters, GOF = 1.030, wR(F²) = 0.0987 (all 3378 data), R = 0.0374 (3014 data with I > 2σI).

[2R,3S]-2-(Benzotriazol-1-yl)-3-phenyl-2,3-dihydro-1-benzofuran-3-yl)methanol (12h-anti). Colorless prisms from diethyl ether (24%), mp 159-160 °C; ¹H NMR δ 2.19 (br s, 1H), 4.25 (d, J = 11.1 Hz, 1H), 4.40-4.50 (m, 1H), 6.78-6.87 (m, 4H), 6.92-6.99 (m, 2H), 7.01-7.12 (m, 2H), 7.15 (d, J = 8.1 Hz, 1H), 7.20-7.27 (m, 1H), 7.42-7.51 (m, 2H), 7.62 (s, 1H), 7.73 (d, J = 7.1 Hz, 1H); ¹³C NMR δ 61.7, 68.9, 97.1, 110.3, 111.7, 119.1, 122.5, 123.9, 125.9, 126.3, 127.0, 127.1, 127.6, 127.7, 130.2, 131.4, 135.2, 145.8, 158.9.

Crystal data for 12h-anti. C_{21}H_{17}N_{3}O_{2}, FW 343.38, triclinic, space group P-1, a = 9.853(2), b = 10.181(2), c = 10.187(2) Å, α = 107.602(2), β = 96.026(2), γ = 115.119(2)°, V = 849.1(3) Å³, F(000) = 360, Z = 2, T = -105 °C, μ (MoKα) = 0.089 mm⁻¹, D_calcd = 1.343 g.cm⁻³, crystal size 0.77 x 0.68 x 0.63 mm, 2θ_max 53° (CCD area detector, MoKα radiation), 238 parameters, GOF = 1.034, wR(F²) = 0.1034 (all 3421 data), R = 0.0373 (3041 data with I > 2σI).

General procedure for the preparation of compounds 13a–f
A solution of LDA (2.0 mmol) in THF was added to a stirred solution of 11 or 12 (0.9 mmol) in THF (10 mL) at −78 °C and the reaction mixture was stirred for 12 h. The reaction temperature was raised to 20–25 °C and the reaction mixture was kept at this temperature for an additional 12 h. Then, the reaction mixture was quenched with saturated aqueous NH₄Cl and the product was extracted with ethyl acetate. The extract was washed with water, dried and evaporated. The product 13 was purified by gradient column chromatography using mixtures of ethyl acetate with hexanes.

1-Benzofuran-3-ylmethanol (13a). White microcrystals from hexanes (85%), mp 45-46 °C (46-47 °C); ¹H NMR δ 2.31 (bs, 1H), 4.75 (s, 2H), 7.21-7.32 (m, 2H), 7.46 (d, J = 8.0 Hz, 1H), 7.53 (s, 1H), 7.62 (d, J = 7.3 Hz, 1H); ¹³C NMR δ 55.7, 111.5, 119.8, 120.3, 122.7, 124.5, 126.6, 142.2, 155.5.

(2-Methyl-1-benzofuran-3-yl)methanol (13b). Yellow needles from hexanes (77%), mp 82-83 °C (83-84 °C); ¹H NMR δ 1.64 (br s, 1H), 2.45 (s, 3H), 4.75 (s, 2H), 7.18-7.28 (m, 2H), 7.36-7.43 (m, 1H), 7.56-7.63 (m, 1H); ¹³C NMR δ 12.0, 55.4, 110.7, 114.2, 119.0, 122.5, 123.6, 128.4, 152.8, 154.0.

(5-Methyl-1-benzofuran-3-yl)methanol (13c). Oil (71%); ¹H NMR δ 2.41 (s, 3H), 2.45 (br s, 1H), 4.71 (s, 2H), 7.06 (dd, J = 8.4, 1.4 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 7.38 (br s, 1H), 7.45 (s, 1H); ¹³C NMR δ 21.2, 55.6, 110.9, 119.6, 120.0, 125.7, 126.7, 132.1, 142.3, 153.9. Anal. Calcd for C_{10}H_{10}O_{2}: C, 74.06; H, 6.21; Found: C, 74.17; H, 6.53.

(2,5-Dimethyl-1-benzofuran-3-yl)methanol (13d). Yellow prisms from hexanes (78%), mp 99-100 °C; ¹H NMR δ 1.47 (bs, 1H), 2.43 (s, 3H), 2.44 (s, 3H), 4.74 (s, 2H), 7.04 (d, J = 7.5 Hz, 1H), 7.27 (d, J = 7.5 Hz, 1H), 7.38 (s, 1H); ¹³C NMR δ 12.1, 21.3, 55.5, 110.2, 114.0, 118.9,
124.7, 128.4, 132.0, 152.4, 152.8. Anal. Calcd for C_{11}H_{12}O_{2}: C, 74.98; H, 6.86; Found: C, 74.99; H, 7.29.

(5-Chloro-1-benzofuran-3-yl)methanol (13e). White crystals from hexanes (66%), mp 68-70 °C; \(^1\text{H NMR}\) \(\delta 2.70 \text{ (br s, 1H), 4.68 (s, 2H), 7.22 (dd, } \text{ } J = 8.8, 1.9 \text{ Hz, 1H), 7.34 (d, } \text{ } J = 8.8 \text{ Hz, 1H), 7.52 (s, 1H), 7.56 (d, } \text{ } J = 1.9 \text{ Hz, 1H); } ^{13}\text{C NMR}\) \(\delta 55.3, 112.4, 119.6, 120.0, 124.7, 127.9, 128.3, 143.5, 153.8.\) Anal. Calcd for C_{9}H_{7}ClO_{2}: C, 59.20; H, 3.86; Found: C, 58.88; H, 3.88.

(6-Methoxy-1-benzofuran-3-yl)methanol (13f). Colorless plates from diethyl ether/hexanes (76%), mp 69-70 °C; \(^1\text{H NMR}\) \(\delta 2.02 \text{ (br s, 1H), 3.83 (s, 3H), 4.76 (s, 2H), 6.88 (dd, } \text{ } J = 8.5, 2.2 \text{ Hz, 1H), 6.99 (d, } \text{ } J = 2.2 \text{ Hz, 1H), 7.48 (s, 1H), 7.49 (d, } \text{ } J = 8.5 \text{ Hz, 1H); } ^{13}\text{C NMR}\) \(\delta 55.6, 55.8, 96.0, 111.8, 120.0, 120.3, 141.3, 141.3, 156.6, 158.2.\) Anal. Calcd for C_{10}H_{10}O_{3}: C, 67.41; H, 5.66; Found: C, 67.04; H, 5.83.

**Procedure for the preparation of 2-[2-(1H-benzotriazol-1-yl)-1-(hydroxymethyl)-1-methylethyl]phenol (14).** A solution of lithium naphthalenide (1.5 mL, 1.5 mmol, 1M in THF; solution was prepared by reaction of lithium (11 mg, 1.5 mmol) with naphthalene (192 mg, 1.5 mmol) in THF (3 mL)) was added dropwise to a stirred solution of [2-(benzotriazol-1-yl)-3-methyl-2,3-dihydro-1-benzofuran-3-yl]methanol 12g (141 mg, 0.5 mmol) in THF (10 ml) at –40 °C (blue color). The reaction mixture was stirred at the same temperature for 30 minutes, and then it was allowed to warm up to 20 °C. The reaction mixture was stirred at same temperature for 90 minutes, and then it was quenched with water and the product was extracted with ethyl acetate. The extract was washed with water, dried and evaporated. The product was purified by column chromatography using a mixture of ethyl acetate with hexanes (1/3 v/v) to give 2-[2-(1H-benzotriazol-1-yl)-1-(hydroxymethyl)-1-methylethyl]phenol (110 mg, 78%). Microcrystals from ether (78%), mp 148-149 °C; \(^1\text{H NMR}\) \(\delta 1.32 \text{ (s, 3H), 3.90 (d, } \text{ } J = 11.4 \text{ Hz, 1H), 3.98 (d, } \text{ } J = 11.4 \text{ Hz, 1H), 5.05 (d, } \text{ } J = 14.5 \text{ Hz, 1H), 5.28 (br s, 1H), 5.41 (d, } \text{ } J = 14.5 \text{ Hz, 1H), 6.73-6.80 (m, 1H), 7.00-7.16 (m, 3H), 7.25-7.40 (m, 3H), 7.95 (d, } \text{ } J = 7.8 \text{ Hz, 1H), 10.12 (br s, 1H); } ^{13}\text{C NMR}\) \(\delta 21.5, 45.4, 51.6, 68.6, 110.1, 118.4, 119.2, 120.3, 124.2, 127.6, 128.0, 128.3, 129.0, 134.2, 144.7, 155.8.\) Anal. Calcd for C_{16}H_{17}N_{3}O_{2}: C, 67.83; H, 6.05; N, 14.83. Found: C, 68.14; H, 6.07; N, 14.83.

**Supporting Information Available**

Crystallography data for compounds 12f-anti, 12g-anti, 12h-syn, and 12h-anti. This material is available on page 237.

**References**


