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 intermediates[1] for the synthesis of biologically active naphthofurans,[2] analogs of CCK-A agonists,[3] naphthofuranquinones[4] and 3-hydroxymethylbenzofuran chrysanthemates.[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-propynyloxy)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)

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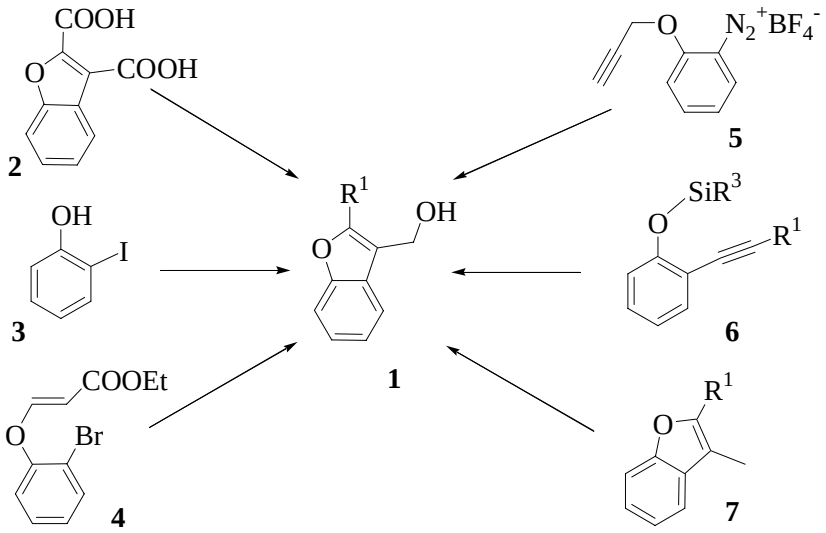
bromination of 2-position protected 3-methylbenzofurans **7** followed by hydrolysis of the intermediate 3-bromomethylbenzofurans[12] (Scheme 1).



Scheme 1

Recently, benzotriazole mediated benzofuran[13] and benzothiophene[14] 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-(1*H*-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.[15] In this case, oxirans **11e–f** were obtained with purity over 90%. The structures of

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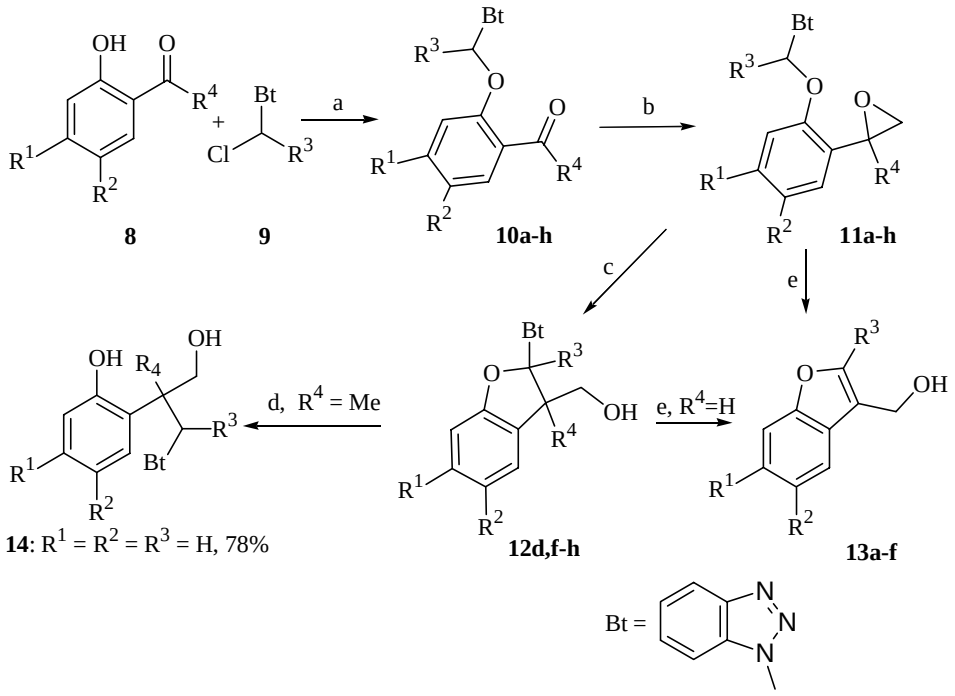
oxirans **11a–h** were supported by their ^{1}H NMR and ^{13}C NMR spectra. Compounds **11e–f** were used in the next step without additional purification.



Scheme 2. For designation of R^1–R^4 see Table 1. a) K_2CO_3, DMF, 50–55 °C, 8–12 h; b) for **11a-d**: $Me_3S^+I^-$, KOBu-*t*, DMSO, 12 h; for **11e-f**: $Me_3S^+I^-$, *n*-Bu_4NI, CH_2Cl_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 ^{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 ^{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.

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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.

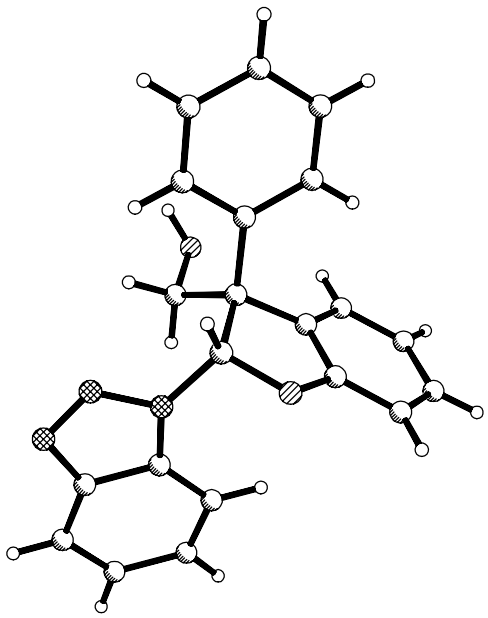

Figure 1. Perspective view of the X-ray structure of **12h-*syn***.

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, 4.04–4.11ppm. 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

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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**

					Yield, %			
	R^1	R^2	R^3	R^4	**10**	**11**	**12**	**13**
a	H	H	H	H	88	65	[a]	85
b	H	H	Me	H	67	63	[a]	77
c	H	Me	H	H	90	70	[a]	71
d	H	Me	Me	H	68	59	56 [b]	78
e	H	Cl	H	H	96	35 (82 [c])	[a]	66
f	MeO	H	H	H	88	81 [c]	81 [b]	76
g	H	H	H	Me	98	85	60	–
h	H	H	H	Ph	92	88	59 [b]	–

[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-dihydro-benzofurans **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.

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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 ^1H (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; ^1H 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 $C_{14}H_{11}N_3O_2$: 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; ^1H 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 $C_{15}H_{13}N_3O_2$: C, 67.40; 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; ^1H 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 $C_{15}H_{13}N_3O_2$: 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 δ 2.18 (d, *J* = 6.1 Hz, 3H), 2.22 (s, 3H), 6.98 (d, *J* = 8.5 Hz, 1H), 7.15 (q, *J* = 6.1 Hz, 1H), 7.19 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.34-7.40 (m, 1H), 7.46-7.51 (m, 1H), 7.55 (d, *J* = 2.1 Hz, 1H), 7.77 (d, *J* = 8.3 Hz, 1H), 8.05 (d, *J* = 8.3 Hz, 1H), 10.50 (s, 1H); ^{13}C NMR δ 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 $C_{16}H_{15}N_3O_2$: 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 δ 6.69 (s, 2H), 7.42-7.52 (m, 3H), 7.56-7.61 (m, 1H), 7.69-7.73 (m, 2H), 8.09 (d, *J* = 8.4 Hz, 1H), 10.28 (s, 1H); ^{13}C NMR δ 74.4, 109.2, 116.5, 120.4, 124.9, 126.8, 128.6, 128.8, 129.0, 132.5, 135.4, 146.2, 156.4, 187.3. Anal. Calcd for $C_{14}H_{10}ClN_3O_2$: 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 δ 3.84 (s, 3H), 6.60 (d, *J* = 8.6 Hz, 1H), 6.69 (s, 2H), 6.94 (s, 1H), 7.39-7.44 (m, 1H), 7.53-7.58 (m, 1H), 7.72-7.76 (m, 2H), 8.06 (d, *J* = 8.2 Hz, 1H), 10.19 (d, *J* = 1.8 Hz, 1H); ^{13}C NMR δ 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 $C_{15}H_{13}N_3O_3$: 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 δ 2.50 (s, 3H), 6.65 (s, 2H), 7.05-7.13 (m, 1H), 7.32 (d, *J* = 8.2 Hz, 1H), 7.37-7.48 (m, 2H), 7.52-7.59 (m, 1H), 7.63-7.68 (m, 2H), 8.09 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR δ 31.4, 74.7, 109.4, 115.2, 120.3, 123.1, 124.7, 128.5, 129.8, 130.5, 132.7, 133.6, 146.3, 154.9, 199.0. Anal. Calcd for $C_{15}H_{13}N_3O_2$: 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 δ 6.46 (s, 2H), 7.08-7.15 (m, 1H), 7.25-7.52 (m, 9H), 7.61 (d, *J* = 7.8 Hz, 2H), 8.00 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR δ 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 $C_{20}H_{15}N_3O_2$: 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.

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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 δ 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 δ 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 $C_{15}H_{13}N_3O_2$: 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 δ 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 δ 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 $C_{16}H_{15}N_3O_2$: 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 δ 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 δ 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, 133.3, 146.2, 152.7. Anal. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.14; H, 5.87; N, 15.08.

1-(Benzotriazol-1-yl)ethyl-4-methyl-2-(2-oxiranyl)phenylether (11d). Yellow oil (59%); ^{1}H NMR δ 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 δ 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, 127.0, 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 $C_{17}H_{17}N_3O_2$: 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 δ 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 δ 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 $C_{15}H_{12}ClN_3O_2$: 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; ^{1}H NMR δ 2.47 (dd, *J* = 5.5 , 2.6 Hz, 1H), 2.84 (dd, *J* = 5.5, 4.2 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* = 2.2 Hz, 1H), 6.97 (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 δ 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 $C_{16}H_{15}N_3O_3$: 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; ^{1}H NMR δ 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 δ 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 $C_{16}H_{15}N_3O_2$: 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; ^{1}H NMR δ 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 δ 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 $C_{21}H_{17}N_3O_2$: 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_4Cl. 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.

[(2*R*,3*R*)-2-(Benzotriazol-1-yl)-2,5-dimethyl-2,3-dihydro-1-benzofuran-3-yl]methanol (12d-*syn*). Yellow needles from ethyl acetate/hexanes (19%), mp 96-98 °C; ^{1}H NMR δ 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 δ 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 $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23. Found: C, 69.01; H, 5.76; N, 14.63.

[(2*R*,3*S*)-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 $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23. Found: C, 68.93; H, 5.80; N, 14.17.

[(2*R*,3*R*)-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 $C_{16}H_{15}N_3O_3$: C, 64.64; H, 5.09; N, 14.13. Found: C, 64.57; H, 5.21; N, 14.25.

[(2*R*,3*S*)-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 $C_{16}H_{15}N_3O_3$: C, 64.64; H, 5.09; N, 14.13. Found: C, 64.57; H, 5.21; N, 14.25.

Crystal data for 12f-*anti*. $C_{16}H_{15}N_3O_3$, FW 297.31, monoclinic, space group $P2_1/n$, *a* = 9.434(3), *b* = 13.842(4), *c* = 10.661(3) Å, *β* = 98.310(4) °, V = 1377.5(6) Å^3, F(000) = 642, Z = 4, T = -105 °C, μ (MoKα) = 0.102 mm^{-1}, D_{calcd} = 1.434 g.cm^{-3}, crystal size 0.88 x 0.80 x 0.73 mm, $2\theta_{max}$ 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).

[(2*R*,3*S*)-2-(Benzotriazol-1-yl)-3-methyl-2,3-dihydro-1-benzofuran-3-yl]methanol (12g-*anti*). Colorless plates from ether/hexanes (60%), mp 136-137 °C; ^{1}H NMR δ 0.95 (s, 3H), 3.51 (br s, 1H), 3.83 (s, 2H), 6.82-6.88 (m, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 7.05-7.11 (m, 1H), 7.20 (br d, *J* = 6.6 Hz, 1H), 7.26-7.37 (m, 4H), 7.98-8.03 (m, 1H); ^{13}C NMR δ 16.0, 52.4, 69.6, 96.1, 109.7, 111.1, 119.8, 122.5, 123.2, 124.2, 128.0, 129.7, 129.9, 131.8, 146.1, 158.1.

Crystal data for 12g-*anti*. $C_{16}H_{15}N_3O_2$, FW 281.31, monoclinic, space group $P2_1/c$, *a* = 10.129(2), *b* = 10.343(3), *c* = 13.246(3) Å, *β* = 97.675(4) °, V = 1375.4(6) Å^3, F(000) = 592, Z = 4, T = -105 °C, μ (MoKα) = 0.092 mm^{-1}, D_{calcd} = 1.359 g.cm^{-3}, crystal size 0.69 x 0.50 x 0.48 mm, $2\theta_{max}$ 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).

[(2*R*,3*R*)-2-(Benzotriazol-1-yl)-3-phenyl-2,3-dihydro-1-benzofuran-3-yl]methanol (12h-*syn*). Colorless prisms from diethyl ether (35%), mp 124-125 °C; ^{1}H NMR δ 2.11 (br s, 1H), 3.75-3.85 (m, 2H), 6.94-7.00 (m, 1H), 7.10 (d, *J* = 8.1 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.28-7.48 (m, 9H), 7.56 (d, *J* = 7.2 Hz, 1H), 7.98-8.04 (m, 1H); ^{13}C NMR δ 60.2, 65.3, 99.5, 110.1, 111.0, 120.1, 122.8, 124.3, 126.4, 127.1, 127.9, 128.2, 128.4, 129.2, 130.1, 132.3, 141.5, 146.0, 158.4.

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Crystal data for 12h-*syn*. $C_{21}H_{17}N_3O_2$, 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) Å^3, 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, $2\theta_{max}$ 53° (CCD area detector, MoKα radiation), 238 parameters, GOF = 1.030, wR(F^2) = 0.0987 (all 3378 data), R = 0.0374 (3014 data with I > 2σI).

[(2*R*,3*S*)-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; ^{1}H 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); ^{13}C 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*. $C_{21}H_{17}N_3O_2$, 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) Å^3, 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, $2\theta_{max}$ 53° (CCD area detector, MoKα radiation), 238 parameters, GOF = 1.034, wR(F^2) = 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 NH_4Cl 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[12]); ^{1}H 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); ^{13}C 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[18]); ^{1}H 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); ^{13}C 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%); ^{1}H 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); ^{13}C 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; ^{1}H 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); ^{13}C 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}H NMR δ 2.70 (br s, 1H), 4.68 (s, 2H), 7.22 (dd, *J* = 8.8, 1.9 Hz, 1H), 7.34 (d, *J* = 8.8 Hz, 1H), 7.52 (s, 1H), 7.56 (d, *J* = 1.9 Hz, 1H); ^{13}C NMR δ 55.3, 112.4, 119.6, 120.0, 124.7, 127.9, 128.3, 143.5, 153.8. Anal. Calcd for $C_9H_7ClO_2$: 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}H NMR δ 2.02 (br s, 1H), 3.83 (s, 3H), 4.76 (s, 2H), 6.88 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.99 (d, *J* = 2.2 Hz, 1H), 7.48 (s, 1H), 7.49 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR δ 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-(1*H*-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-(1*H*-benzotriazol-1-yl)-1-(hydroxymethyl)-1-methylethyl]phenol (110 mg, 78%). Microcrystals from ether (78%), mp 148-149 °C; ^{1}H NMR δ 1.32 (s, 3H), 3.90 (d, *J* = 11.4 Hz, 1H), 3.98 (d, *J* = 11.4 Hz, 1H), 5.05 (d, *J* = 14.5 Hz, 1H), 5.28 (br s, 1H), 5.41 (d, *J* = 14.5 Hz, 1 H), 6.736.80 (m, 1H), 7.00-7.16 (m, 3H), 7.25-7.40 (m, 3H), 7.95 (d, *J* = 7.8 Hz, 1H), 10.12 (br s, 1H); ^{13}C NMR δ 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 $C_{16}H_{17}N_3O_2$: 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

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