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A Method for the Synthesis of 2,3-Disubstituted 2,3-Dihydrobenzofurans

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Summary. The synthesis of 2,3-disubstituted 2,3-dihydrobenzofuran diastereomers is described. The key step in the reaction sequence is the chemoselective reduction of a *tert*. alcohole with *tert.*-butylamine-borane/$AlCl_3$. The relative configuration of the substituents on the dihydrofurane moiety was assigned *via* NMR spectroscopy.

Keywords. 2,3-Dihydrobenzofuranes; *t*-Butylamine borane; Propafenone; Antiarrhythmic; MDR modulator.

Introduction

As a result of the Cardiac Arrhythmia suppression Trial [1], the world of antiarrhythmic drugs has changed to a large extent. Apart from other factors, extensive studies on the mode of action have become a major prerequisite for the development of new drugs in this field. Recently we have described the synthesis of a new benzofurane type antiarrhythmic agent (**1**) which is structurally related both to propafenone (**2**) and phenylethanolamin drugs such as sotalol [2]. Compound **1** has revealed remarkable differences in the kinetics of recovery of sodium channels from block [3] when compared to **2**. In addition, it has shown to act as a modulator of multidrug resistance in human tumor cells [4]. Following our substrate modelling approach, we decided to synthesize the corresponding dihydrobenzofuranes **3** as substrates for further structure-activity relationship studies. Reduction of the double bond would generate two additional centers of chirality, thus leading to 8 stereoisomers with remarkable differences in the relative positions of their pharmakophoric groups (nitrogen and phenyl). Pharmacological testing of all possible stereoisomers might provide interesting insights both into the structure of the sodium channel binding site and the steric requirements of binding to P-glycoprotein, a membrane protein responsible for clinical resistance to cytostatic drugs [5].

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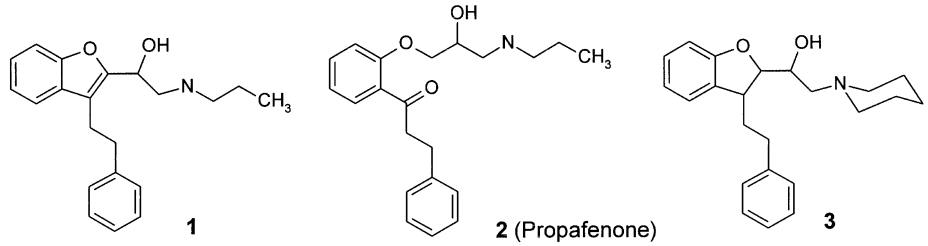
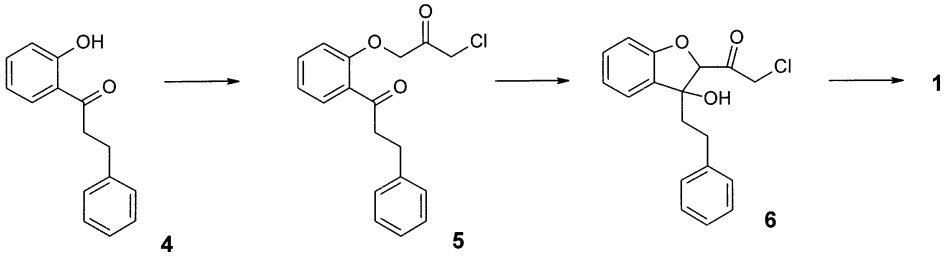


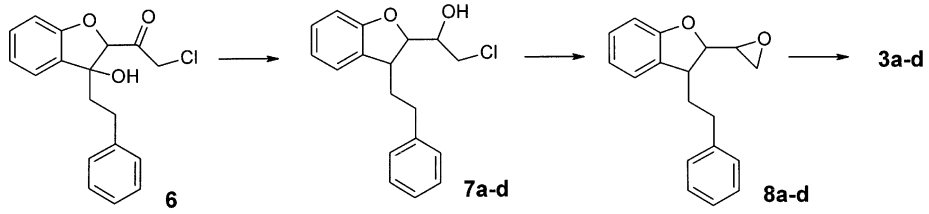
Results and Discussion

Various established methods for the synthesis of functionalized 2,3-dihydrobenzofurans [6] failed to yield the target compounds [7]. Thus, chemoselective reduction of the *tert*. alcohole **6** was attempted, which is the key intermediate in the currently used method for the preparation of **1** (Scheme 1) and other structurally related compounds. The reaction sequence includes alkylation of 1-(2-hydroxyphenyl)-3-phenyl-1-propanone (**4**) with epichlorohydrine, nucleophilic ring opening by addition of HCl, oxidation of the secondary alcohol with *DCC/DMSO* to yield **5**, cyclization with silica gel to yield **6**, dehydratization with phosphoric acid, nucleophilic displacement of chlorine by a suitable amine, and reduction of the keto group [8].

Attempts to use established approaches for reduction of tertiary (benzylic) alkoholes – such as HI/red phosphorus, catalytic hydrogenation, acylation/desacetylation as well as reaction with triethylsilane/$AlCl_3$ – in all cases resulted in dehydratization yielding the corresponding benzofuran [8]. In the reaction of **6** with triethylsilane/$BF_3 \cdot Et_2O$ also the oxo group was removed, and the corresponding 2-chloroethyl-benzofuran was obtained [8]. Recently, *Lau et al.* have described the reductive deoxygenation of aryl aldehydes and ketones using *tert*-butylamine-borane in the presence of aluminum chloride [9]. Application of this system [10] on the reduction of **6** gave chlorohydrine **7** as the main product. Not only deoxygenation of the tertiary benzylic alcohol to the alkane, but also reduction of the chloroacetyl group to a chlorohydrine had occured. This result suggests a remarkable selectivity of the reagent useful for reduction of various types of alcoholes. Although there is evidence that the educt **6** is of *cis* configuration [11], a mixture of the four possible racemic diastereomers of **7** was obtained in the reaction which could be separated by a combination of flash chromatography and medium pressure column chromatography.



Scheme 1



Scheme 2

Reaction of **7** with sodium methoxide gave the distereomeric epoxides **8a–d** which were converted to the desired aminoethanols **3a–d** using piperidine in methanol (Scheme 2).

Assignment of the relative configuration of the substituents on the dihydrofuran moiety in **3a–d**, **7a–d**, and **8a–d** was achieved by means of NMR spectroscopy (see Table 1). Considering vicinal coupling constants $^3J_{(H\text{-}2,H\text{-}3)}$ in 2,3-dihydrobenzofurans, $^3J_{cis}$ may be expected to be larger than $^3J_{trans}$ [12]. With **7**, this coupling constant turned out to be 4.2 and 6.1 Hz for **7b** and **7d**, respectively, whereas isomers **7a** and **7c** showed greater values (**7a**: 7.5 Hz, **7c**: 8.3 Hz), thus giving a strong hint for *trans*-configuration of **7b** and **7d** and *cis*-configuration of **7a** and **7c**. These assignment were confirmed by NOE difference experiments. With species **7a** and **7c**, irradiation of H-2 resonance resulted in a marked NOE (~10%) on the signal of H-3. Reversely, irradiating H-3 led to a comparable enhancement of the H-2 multiplet, indicating spatial closeness of the involved protons and thus *cis*-configuration. In contrast, similar experiments with **7b** and **7d** revealed only small NOEs in accordance with *trans*-position of H-2 and H-3. In addition, discrimination of *cis*- and *trans*-isomers was possible on basis of ^{13}C chemical shifts. Due to the shielding effect of a *cis*-located carbon atom in γ-position (γ-effect) [13], the signals of CH(OH) and Ph-CH_2-CH_2- in isomers **7a** and **7c** exhibited an upfield shift in comparison to the corresponding resonances in **7b** and **7d** [14]. Almost identical influences on shift values and coupling constants were observed for derivatives **8a–d** and **3a–d**.

Compounds **3a–d** are presently under evaluation for multidrug-resistance modulating activity. All four isomers appear to be less active than propafenone and the corresponding benzofurane **1** with only slight differences between the diastereoisomers. This suggests that a planar orientation of the substituents might

Table 1. Selected NOE data and chemical shifts (δ/ppm) of compounds **7a–d**

	7a	**7b**	**7c**	**7d**
δ(H-2)	4.49	4.45	4.82	4.65
δ(H-3)	3.39	3.51	3.45	3.46
^3J(H-2/H-3)	7.5	4.2	8.3	6.1
NOE(H-/H-)	~11%	~2%	~10%	~2%
δ(CH(OH))	69.09	72.14	70.70	73.05
δ(Ph-CH_2-CH_2-)	30.90	37.47	31.50	36.65

be necessary for good chemosensitizing activity. A full evaluation of the pharmacology of these novel dihydrobenzofuranes will be reported elsewhere.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Plus 300 spectrometer. ^{1}H spectra were referenced to *TMS* ^{13}C spectra to $CDCl_3$ ($\delta = 77.0$). Infrared spectra were measured on a Perkin Elmer Spectrum 1000 FT-IR spectrometer. High resolution mass spectra were recorded on a Finnigan MAT 8230 spectrometer (*A. Nikiforov*, Institute of Organic Chemistry, University of Vienna). Flash chromatography was carried out on Merck silica gel 60, TLC on plastic sheets (Merck silica gel 60 F_{254}).

2-Chloro-1-(3-(2-phenyl-ethyl)-2,3-dihydro-2-benzofuryl)-ethanol (**7a–d**; $C_{18}H_{19}ClO_2$)

A suspension of 1.32 g (9.90 mmol) $AlCl_3$, dried under vacuum, in 20 cm^3 dry CH_2Cl_2 was cooled to 0°C with an ice-water bath. 1.70 g boran-*tert.*-butylamin-complex (19.54 mmol) were added, and the mixture was stirred under an argon atmosphore at 0°C for 30 min. A solution of 1.0 g (3.16 mmol) **6** [8] in 10 cm^3 dry CH_2Cl_2 was added dropwise, and the reaction mixture was stirred at 0°C for 2 h. 20 cm^3 of cold 0.1 *N* HCl were added, and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with 0.1 *N* HCl, H_2O, and brine, dried over Na_2SO_4 and concentrated under vacuum to give 1 g of crude product. A preliminary purification *via* flash chromatography (100 g silica gel, petroleum ether/diethyl ether (90:10 → 85:15)) afforded in order of elution the chlorohydrines **7a** (0.021 g, 2.2%), **7b** (0.076 g, 7.9%), **7c** (0.053 g, 5.5%), and **7d** (0.088 g, 9.2%) as pale oils. Additionally, the three couples of mixtures **7a+b**, **7b+c**, and **7c+d** were obtained giving in total 0.605 g (63%) of **7**. Besides this compound, 0.128 g (14%) of 1-chloro-2-(3-(2-phenyl-ethyl)-2-benzofuryl)-ethane [8] were isolated. The mixtures were further separated through a combination of flash chromatographies, and the yields, considering also the remaining mixtures, were 2.8–3.3%, 17.3–20.0%, 12.9–18.5%, and 24.3–26.6% respectively which means approximately a ratio of 1:6:5:8 for **7a**:**7b**:**7c**:**7d.**

7a (*cis*): ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 1.68–1.81 (m, 1H, –CH_a–Bz), 2.20–2.31 (m, 1H, -CH_b-Bz), 2.41 (d, 1H, $J = 5.8$ Hz, -OH), 2.61–2.71 (m, 1H, -CH_a-Ph) 2.77–2.87 (m, 1H, -CH_b-Ph), 3.35–3.43 (m, 1H, H-3), 3.81 (dd, 1H, $J = 6.6$, 11.3 Hz, -CH_a-Cl), 4.02 (dd, 1H, $J = 2.6$, 11.3 Hz, -CH_b-Cl), 4.15–4.23 (m, 1H, -C*H*(OH)-), 4.49 (dd, 1H, $J = 7.5$, 9.4 Hz, H-2), 6.80 (d, 1H, $J = 7.9$ Hz, arom H), 6.91 (t, 1H, $J = 7.3$ Hz, arom H), 7.14–7.20 (m, 4H, arom H), 7.25–7.30 (m, 3H, arom H) ppm; ^{13}C NMR ($CDCl_3$, δ, 75.4 MHz): 30.90 (-CH_2-Bz), 32.92 (-CH_2-Ph), 43.10 (C-3), 49.44 (-CH_2-Cl), 69.09 (-CH(OH)-), 85.25 (C-2), 109.92, 120.82, 125.43, 125.93, 128.38, 128.42, 131.37, 141.77, 158.57 (arom C) ppm; IR (KBr): $\nu = 3555$ (s, O-H), 3027 2923 (s, C-H), 1594 (m, arom C-H), 1476 (s, aliph C-H), 1228 (s, C-O), 753 (s, arom C-H) cm^{-1}; HRMS (70 eV): 302.107 ($\pm$5 ppm) (M^+, 19.7), 226.1 (6.0), 223.1 (39.7), 149.0 (55.1), 121.0 (35.4), 91.0 (100.0), 74.0 (72.8), 57.0 (81.0).

7b (*trans*): ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 2.00 (dt, 2H, $J = 6.6$, 8.1 Hz, -CH_2-Bz), 2.36 (s, 1H, -OH), 2.64–2.82 (m, 2H, -CH_2-Ph), 3.51 (dt, 1H, $J = 4.2$, 6.4 Hz, H-3), 3.74–3.85 (m, 3H, -CH_2-Cl-C*H*(OH)-), 4.45 (dd, 1H, $J = 4.2$, 7.1 Hz, H-2), 6.78 (d, 1H, $J = 7.9$ Hz, arom H), 6.89 (t, 1H, $J = 7.3$ Hz, arom H), 7.11–7.30 (m, 7H, arom H) ppm; ^{13}C NMR ($CDCl_3$, δ, 75.4 MHz): 32.72 (-CH_2-Ph), 37.7 (-CH_2-Bz), 44.16 (C-3), 47.53 (-CH_2-Cl), 72.14 (-CH(OH)-), 86.99 (C-2), 109.57, 120.95, 124.90, 125.95, 128.33, 128.39, 128.41, 129.75, 141.56, 158.73 (arom C) ppm; IR (KBr): $\nu = 3456$ (s, O-H), 3026 2925 (s, C-H), 1597 (m, arom C-H), 1479 (s, aliph C-H), 1235 (s, C-O), 751 (s, arom C-H), cm^{-1}; HRMS (70 eV): 302.107 ($\pm$5 ppm) (M^+, 21.0), 226.0 (13.6), 223.1 (33.1), 149.0 (15.6), 121.0 (44.5), 91.0 (100.0), 74.0 (32.7), 57.0 (15.9).

7c (*cis*): ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 1.98–2.20 (m, 2H, -CH_2-Bz), 2.32 (d, 1H, $J = 6.6$ Hz, -OH), 2.67–2.77 (m, 1H, -CH_a-Ph), 2.84–2.94 (m, 1H, -CH_b,-Ph), 3.45 (dt, 1H, $J = 6.4$, 8.3 Hz, H-3),

3.68 (d, 2H, $J = 6.0$ Hz, -CH_2-Cl), 4.09–4.21 (m, 1H, -C*H*(OH)-), 4.82 (dd, 1H, $J = 3.2$, 8.3 Hz, H-2), 6.84 (d, 1H, $J = 7.9$ Hz, arom H), 6.91 (t, 1H, $J = 7.3$ Hz, arom H), 7.12–7.32 (m, 7H, arom H); ^{13}C NMR ($CDCl_3$, δ, 75.4 MHz): 31.50 (-CH_2-Bz), 34.08 (-CH_2-Ph), 43.12 (C-3), 45.93 (-CH_2-Cl), 70.70 (-CH(OH)-), 84.20 (C-2), 109.57, 120.99, 124.59, 126.13, 128.35, 128.54, 128.75, 131.28, 141.38, 158.61 (arom C); IR (KBr): $\nu = 3444$ (s, O-H), 3026 2925 (s, C-H), 1596 (m, arom C-H), 1478 (s, aliph C-H), 754 (s, arom C-H) cm^{-1}; HRMS (70 eV): 302.107 ($\pm$5 ppm) (M^+, 8.3), 226.0 (30.0), 223.1 (16.2), 149.0 (26.1), 121.0 (99.9), 91.0 (100.00), 74.0 (77.2), 57.0 (25.1)

7d (*trans*): 1H NMR ($CDCl_3$, δ, 300 MHz): 1.94–2.17 (m, 2H, -CH_2-Bz), 2.38 (d, 1H, $J = 6.8$ Hz, -OH), 2.65–2.82 (m, 2H, -CH_2-Ph), 3.46 (dt, 1H, $J = 6.1$, 6.8 Hz, H-3), 3.59–3.74 (m, 2H, -CH_2-Cl), 3.79–3.87 (m, 1H, -C*H*(OH)-), 4.65 (dd, 1H, $J = 3.6$, 6.1 Hz, H-2), 6.80 (d, 1H, $J = 7.9$ Hz, arom H), 6.89 (t, 1H, $J = 7.5$ Hz, arom H), 7.11–7.31 (m, 7H, arom H) ppm; ^{13}C NMR ($CDCl_3$, δ, 75.4 MHz): 32.87 (-CH_2-Ph), 36.65 (-CH_2-Bz) 43.21 (C-3), 45.28 (-CH_2-Cl), 73.05 (-CH(OH)-), 87.20 (C-2), 109.56, 121.04, 124.42, 126.09, 128.26, 128.41, 128.70, 130.12, 141.25, 158.83 (arom C) ppm; IR (KBr): $\nu = 3431$ (s, O-H), 3027, 2924 (s, C-H), 1597 (m, arom C-H), 1480 (s, aliph C-H), 1235 (s, C-O), 750 (s, arom C-H) cm^{-1}; HRMS (70 eV): 302.107 ($\pm$5 ppm) (M^+, 14.6), 226.0 (41.5), 223.1 (21.9), 149.1 (19.2), 121.1 (95.6), 91.0 (100.0), 77.0 (25.6), 57.0 (11.9).

1,2-Epoxy-1-(3-(2-phenyl-ethyl)-2,3-dihydro-2-benzofuryl)-ethane (**8a–d**; $C_{18}H_{18}O_2$)

0.120 g of **7a** (0.39 mmol) were dissolved in 1.5 cm^3 of MeOH and treated under magnetic stirring with a solution of 9 mg Na (0.39 mmol) in 1.5 cm^3 of MeOH. The reaction mixture was stirred at room temperature for 1 h, diluted with Et_2O, and washed with saturated $NaHCO_3$ solution. The organic phase was dried over Na_2SO_4 and concentrated to dryness. The residue (0.113 g) was purified *via* flash chromatography (34 g silica gel, petroleum ether/diethyl ether (90:10)) to give 0.046 g (44%) of **8a** (*cis*) as a colorless oil.

^{1}H NMR ($CDCl_3$, δ, 300 MHz): 1.98–2.11 (m, 1H, -CH_a-Bz), 2.17–2.29 (m, 1H, -CH_b-Bz), 2.80–2.88 (m, 3H, -CH_2-Ph, epoxide-CH_a-), 2.93 (dd, 1H, $J = 4.9$, 4.0 Hz, epoxide -CH_b-), 3.24 (ddd, 1H, $J = 2.8$, 3.7, 6.7 Hz, bf-CH(O)-), 3.56 (dt, 1H, $J = 7.5$, 7.7 Hz, H-3), 4.38 (dd, 1H, $J = 7.5$, 7.9 Hz, H-2), 6.82 (d, 1H, $J = 7.9$ Hz, arom H), 6.91 (t, 1H, $J = 7.4$ Hz, arom H), 7.13–7.32 (m, 7H, arom H) ppm; ^{13}C NMR ($CDCl_3$, δ, 75.4 MHz): 31.89 (-CH_2-Bz), 33.79 (-CH_2-Ph), 43.86 (C-3), 46.25 (epoxide-CH_2-), 49.32 (bf-CH(O)-), 86.02 (C-2), 109.71, 120.88, 124.85, 126.02, 128.39, 128.43, 128.47, 130.54, 141.61, 158.7 (arom C) ppm; IR (KBr); $\nu = 3026$, 2926 (s, C-H), 1596 (m, arom C-H), 1477 (s, aliph C-H), 1230 (s, C-O), 752 (s, arom C-H) cm^{-1}; HRMS (70 eV): 266.131 ($\pm$5 ppm) (M^+, 42.4), 235.0 (54.4), 149.0 (57.3), 131.0 (56.3), 91.0 (100.0), 77.0 (37.3), 74.0 (14.8), 57.0 (52.3).

8b, **8c,** and **8d** were prepared from **7b** (0.153 g, 0.51 mmol), **7c** (0.132 g, 0.44 mmol), and **7d** (0.178 g, 0.59 mmol), respectively, in the same manner as described for **8a**.

8b (*trans*): Yield: 0.117 g (87%); colorless oil; ^{1}H NMR ($CDCl_3$, δ, 300 MHz):1.92–2.14 (m, 2H, -CH_2-Bz), 2.72–2.79 (m, 3H, -CH_2-Ph, epoxide-CH_a-), 2.85 (dd, 1H, $J = 4.5$, 4.7 Hz, epoxide-CH_b), 3.09 (ddd, 1H, $J = 2.7$, 4.6, 5.3 Hz, bf-CH(O)-), 3.42 (dt, 1H, $J = 5.3$, 7.7 Hz, H-3), 4.33 (dd, 1H, $J = 5.1$, 5.3 Hz, H-2) 6.81 (d, 1H, $J = 8.1$ Hz, arom H), 6.89 (t, 1H, $J = 7.4$ Hz, arom H), 7.12–7.31 (m, 7H, arom H) ppm; ^{13}C NMR ($CDCl_3$, δ,75.4 MHz); 32.89 (-CH_2-Ph), 37.03 (-CH_2-Bz), 44.92 (C-3), 45.57 (epoxide-CH_2-), 52.75 (bf-CH(O)-), 87.26 (C-2), 109.60, 120.87, 124.66, 126.01, 128.36, 128.46, 128.49, 129.79, 141.33, 158.94 (arom C) ppm; IR (KBr): $\nu = 3027$, 2925 (s, C-H), 1597 (m, arom C-H), 1479 (s, aliph C-H), 1236 (s, C-O), 751 (s, arom C-H) cm^{-1}; HRMS (70 eV): 266.131 ($\pm$5 ppm) (M^+, 29.8), 235.1 (77.1), 149.0 (15.1), 131.1 (49.5), 91.0 (100.0), 77.0 (26.7), 74.0 (20.3), 57.0 (15.1).

8c (*cis*) Yield: 0.058 g (50%); colorless oil; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 2.01–2.18 (m, 2H, -CH_2-Bz), 2.68–2.74 (m, 1H, -CH_a-Ph), 2.77 (dd, 1H, $J = 2.8$, 5.0 Hz, epoxide-CH_a-), 2.83–2.89 (m, 1H,-CH_b-Ph), 2.92 (dd, 1H, $J = 4.2$, 4.7 Hz, epoxide-CH_b-), 3.30 (ddd, 1H, $J = 2.8$, 3.8, 6.6 Hz,

bf-CH(O)-), 3.49 (dt, 1H, $J = 7.2$, 8.1 Hz, H-3), 4.39 (dd, 1H, $J = 6.6$, 8.1 Hz, H-2) 6.85 (d, 1H, $J = 8.3$ Hz, arom H), 6.89 (t, 1H, $J = 7.3$ Hz, arom H), 7.13–7.32 (m, 7H, arom H) ppm; ^{13}C NMR ($CDCl_3$, δ, 75.4 MHz): 32.17 (-CH_2-Bz), 33.99 (-CH_2-Ph), 43.85 (C-3), 44.11 (epoxide-CH_2-), 50.56 (bf-CH(O)-), 86.56 (C-2), 109.89, 120.67, 124.61, 126.14, 128.28, 128.50, 128.54, 130.46, 141.36, 158.88 (arom C) ppm; IR (KBr): $v = 3026$ 2927 (s, C-H), 1595 (m, arom C-H), 1477 (s, aliph C-H), 1230 (s, C-O), 753 (s, arom C-H) cm^{-1}; HRMS (70 eV): 266.131 ($\pm$5 ppm) (M^+, 6.4), 235.2 (5.6), 149.0 (13.5), 131.1 (7.9), 91.0 (16.7), 77.0 (12.0), 74.0 (100.0), 57.0 (9.7).

8d (*trans*): Yield: 0.065 g (42%); colorless oil; ^{1}H NMR ($CDCl_3$, δ, 300 MHz); 1.93–2.12 (m, 2H, -CH_2-Bz), 2.66–2.76 (m, 2H, -CH_2-Ph), 2.79 (dd, 1H, $J = 2.6$, 4.9 Hz, epoxide-CH_a-), 2.85 (dd, 1H, $J = 4.3$, 4.9 Hz, epoxide-CH_b-), 3.17 (ddd, 1H, $J = 2.7$, 3.9, 5.9 Hz, bf-CH(O-), 3.41 (dt, 1H, $J = 5.8$, 7.1 Hz, H-3), 4.31 (t, 1H, $J = 5.8$ Hz, H-2), 6.83 (d, 1H, $J = 7.9$ Hz, arom H), 6.88 (t, 1H, $J = 7.5$ Hz, arom H), 7.12–7.32 (m, 7H, arom H) ppm; ^{13}C NMR ($CDCl_3$, δ, 75.4 MHz): 33.05 (-CH_2-Ph), 36.72 (-CH_2-Bz), 44.21 (C-3), 44.24 (epoxide -CH_2-), 53.25 (bf-CH(O)-), 87.99 (C-2), 109.74, 120.72, 124.35, 126.12, 128.26, 128.52, 129.63, 141.18, 159.05 (arom C) ppm; IR (KBr); $v = 3026$ 2925 (s, C-H), 1597 (m, arom C-H), 1479 (s, arom C-H), 1234 (s, C-O), 751 (s, arom C-H) cm^{-1}; HRMS (70 eV): 266.131 ($\pm$5 ppm) (M^+, 3.1), 235.1 (5.7), 149.0 (3.5), 131.1 (3.6), 91.0 (9.3), 77.0 (8.2), 74.0 (100.0), 57.0 (3.3).

1-(3-(2-Phenyl-ethyl)-2,3-dihydro-2-benzofuryl)-2-(1-piperidyl)-ethanol (**3a–d**; $C_{23}H_{29}NO_2$)

A solution of 0.040 g epoxide **8a** (0.15 mmol) in 2 cm^3 of distilled piperidine was refluxed for 30 h. The mixture was evaporated to dryness, and the residue was purified *via* flash chromatography (5 g silica gel, CH_2Cl_2/MeOH/NH_4OH_{conc} (970/30/1)) to give the amine **3a** (*cis*) (0.038 g, 72%) as a yellow oil.

^{1}H NMR ($CDCl_3$, δ, 300 MHz): 1.44-1.49 (m, 2H, 1 piperidyl -CH_2-), 1.58–1.62 (m, 4H, 2 piperidyl -CH_2-), 1.68–1.81 (m, 1H, -CH_a-Bz), 2.27–2.54 (m, 4H, -CH_b-Bz, 1 piperidyl -N-CH_2-, -CH_a-N-), 2.63–2.88 (m, 5H, 1 piperidyl-N-CH_2-, -CH_b-N-, -CH_2-Ph), 3.39 (ddd, 1H, $J = 4.5$, 7.3, 10.5, H-3), 4.02 (dt, 1H, $J = 3.4$, 9.8 Hz, -C*H*(OH)-), 3.9–4.2 (1H, -OH), 4.35 (dd, 1H, $J = 7.5$, 9.2 Hz, H-2), 6.79 (d, 1H, $J = 7.9$ Hz, arom H), 6.89 (dt, 1H, $J = 0.9$, 7.5 Hz, arom H), 7.11–7.29 (m, 7H, arom H) ppm; ^{13}C NMR ($CDCl_3$, δ, 75.4 MHz): 24.07, 25.94 (3 piperidyl-CH_2-), 31.12 (-CH_2-Bz), 33.10 (-CH_2-Ph), 43.58 (C-3), 54.62 (2 piperidyl -N-CH_2-), 60.42 (-CH_2-N-), 67.64 (-CH(OH)-), 89.74 (C-2), 109.31, 120.43, 124.65, 125.81, 128.13, 128.33, 128.45, 130.20, 141.81, 159.30 (arom C) ppm; IR (KBr): $v = 3400$ (s, O-H), 2935 (s, C-H), 1596 (m, arom C-H) 1476 1459 (s, aliph C-H), 1299 (s, C-O), 753 (s, arom C-H) cm^{-1}; HRMS (70 eV): 351.220 ($\pm$5 ppm) (M^+, 2.1), 149.1 (3.5), 128.1 (17.9), 98.1 (100.0), 84.0 (7.9), 91.0 (35.7), 55.0 (22.1).

3b, **3c**, and **3d** were prepared from **8b** (0.091 g, 0.34 mmol), **8c** (0.045 g, 0.17 mmol), and **8d** (0.040 g, 0.15 mmol), respectively in the same manner as described for **3a**.

3b (*trans*): Yield: 0.100 g (83%); yellow oil; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 1.41–1.46 (m, 2H, 1 piperidyl -CH_2-), 1.52–1.67 (m, 4H, 2 piperidyl -CH_2-), 1.95–2.04 (m, 2H, -CH_2-Bz), 2.31–2.60 (m, 6H, 2 piperidyl -N-CH_2-, -CH_2-N-), 2.70–2.77 (m, 2H, -CH_2-Ph), 3.48 (dt, 1H, $J = 5.3$, 6.2 Hz, H-3), 3.4–3.6 (1H, -OH), 3.71 (ddd, 1H, $J = 3.8$, 6.4, 10.0 Hz, 1H, -C*H*(OH)-), 4.41 (dd, 1H, $J = 4.9$, 6.4 Hz, H-2), 6.78 (d, 1H, $J = 7.9$ Hz, arom H), 6.86 (dt, 1H, $J = 0.9$, 7.5 Hz, arom H), 7.09–7.30 (m, 7H, arom H) ppm; ^{13}C NMR ($CDCl_3$, δ, 75.4 MHz): 24.15, 26.05 (3 piperidyl -CH_2-), 32.76 (-CH_2-Ph), 37.56 (-CH_2-Bz), 43.87 (C-3), 54.63 (2 piperidyl-N-CH_2-), 60.43 (-CH_2-N-), 67.65 (-CH(OH)-), 89.75 (C-2), 109.32, 120.44, 124.66, 125.82, 128.14, 128.34, 130.21, 141.82, 159.31 (arom C) ppm; IR (KBr): $v = 3350$ (s, O-H), 2934 2855 (s, C-H), 1598 (m, arom C-H), 1497, 1480 (s, aliph C-H), 1236 (s, C-O), 750 (s, arom C-H) cm^{-1}; HRMS (70 eV): 351.220 ($\pm$5 ppm) (M^+, 3.5), 149.0 (33.9), 128.1 (6.5), 98.1 (100.0), 91.0 (17.3), 84.0 (68.8), 55.0 (22.3).

3c (*cis*) Yield: 0.024 g (47%); yellow oil; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 1.43–1.50 (m, 2H, 1 piperidyl -CH_2-), 1.56–1.70 (m, 4H, 2 piperidyl-CH_2-), 1.96–2.21 (m, 2H, -CH_2-Bz), 2.39–2.44 (m,

3H, 1 piperidyl-N-CH_2-, -CH_a-N-), 2.63–2.73 (M, 4H, 1 piperidyl-N-CH_2-, -CH_a-Ph, -CH_b-N-) 2.89 (ddd, 1H, $J = 5.5$, 9.6, 14.5 Hz, -CH_b-Ph), 3.33 (dt, 1H, $J = 5.5$, 8.3 Hz, H-3), 3.4–3.9 (1H, -OH), 4.11 (ddd, 1H, $J = 3.8$, 7.9, 10.0 Hz, -C*H*(OH)-), 4.42 (dd, 1H, $J = 4.5$, 8.1 Hz, H-2), 6.86 (d, 1H, $J = 7.3$ Hz, arom H), 6.87 (dt, 1H, $J = 0.6$, 8.3 Hz, arom H), 7.11–7.32 (m, 7H, arom H) ppm; ^{13}C NMR ($CDCl_3$, δ, 75.4 MHz): 23.97, 25.73 (3 piperidyl-CH_2-), 31.23 (-CH_2-Bz), 33.83 (-CH_2-Ph), 43.07 (C-3), 54.68 (2 piperidyl -N-CH2-), 61.24 (-CH_2-N-), 65.49 (-CH(OH)-), 86.74 (C-2), 109.57, 120.32, 124.34, 125.94, 128.08, 128.42, 128.44, 131.55, 141.74, 159.26 (arom C) ppm; IR (KBr): $v = 3308$ (s, O-H), 2933 2854 (s, C-H), 1596 (m, arom C-H), 1478 1458 (s, aliph C-H), 1231 (s, C-O), 751 (s, arom C-H) cm^{-1}; HRMS (70 eV): 351.220 ($\pm$5 ppm) (M^+, 2.5), 149.0 (77.9), 128.1 (16.2), 98.1 (100.0), 91.0 (37.0), 84.1 (13.7), 55.0 (29.0).

3d (*trans*): Yield: 0.045 g (100%); yellow oil: ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 1.41–1.48 (m, 2H, 1 piperidyl-CH_2-), 1.53–1.61 (m, 4H, 2 piperidyl-CH_2-), 1.91–2.12 (m, 2H, -CH_2-Bz), 2.31–2.39 (m, 3H, 1 piperidyl-N-CH_2-, -CH_a-N-), 2.54–2.84 (m, 5H, 1 piperidyl-N-CH_2-, -CH_b-N-, -CH_2-Ph), 3.18–3.33 (m, 1H, -OH), 3.53 (dt, 1H, $J = 6.2$, 6.4 Hz, H-3), 3.81 (dt, 1H, $J = 3.8$, 10.3 Hz, -C*H*(OH)-), 4.38 (dd, 1H, $J = 4.3$, 5.8 Hz, H-2), 6.80 (d, 1H, $J = 7.9$ Hz, arom H), 6.85 (dt, 1H, $J = 0.8$, 7.3 Hz, arom H), 7.09–7.30 (m, 7H, arom H) ppm; ^{13}C NMR ($CDCl_3$, δ, 75.4 MHz): 24.18, 26.01 (3 piperidyl-CH_2-), 32.97 (-CH_2-Ph), 37.19 (-CH_2-Bz), 43.02 (C-3), 54.61 (2 piperidyl-N-CH_2), 60.20 (-CH_2-N-), 68.10 (-CH(OH)-), 88.98 (C-2), 109.35, 120.38, 124.30, 125.96, 128.17, 128.31, 128.44, 130.43, 141.68, 159.49 (arom C) ppm; IR (KBr); $v = 3369$ (s, O-H), 2934, 2855 (s, C-H), 1598 (m, arom C-H), 1480 1460 (s, aliph C-H), 1236 (s, C-O), 750 (s, arom C-H) cm^{-1}; HRMS (70 eV): 351.220 ($\pm$5 ppm) (M^+, 5.5), 149.0 (18.3), 128.2 (11.6), 98.1 (100.0) 91.0 (28.8), 84.0 (9.4), 55.0 (20.6).

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