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Asymmetric synthesis of (*S*)-bufuralol and a propafenone analogue

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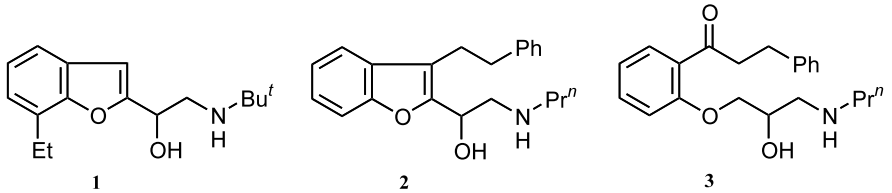
Abstract—Asymmetric synthesis of (*S*)-bufuralol of 87% ee from 3-ethyl-2-hydroxybenzaldehyde, via the reduction of 2-bromo-1-(7-ethylbenzofuran-2-yl)ethanone with (−)-*B*-chlorodiisopinocampheylborane as the key step, followed by cyclization of the product bromohydrin to the corresponding epoxide and treatment with *tert*-butylamine, is described. (*S*)-1-(3-Phenethylbenzofuran-2-yl)-2-propylaminoethanol of 73% ee, a propafenone analogue, was prepared following the same approach.

1. Introduction

Benzofuran derivatives have been the subject of increased interest in recent years due to their diverse biological activities.[1] For example, they act as inhibitors of 5-lipoxygenase,[2] cyclooxygenase-2,[3] and β-amyloid (Aβ) aggregations,[4] antagonists for the brain CB1 receptor,[5] the central and peripheral $GABA_B$-receptor,[6] the angiotensin II receptor,[7] and the oxytocin (OT) hormone.[8]

Among these derivatives, β-amino alcohols play an important role showing antiarrhythmic,[9] enzyme inhibitory,[9b,10] antihypertensive,[11] and β-andrenoacceptor blocking activity.[12] Bufuralol **1**, the most studied compound of this class, proved effective for treatment of hypertension,[11] is a potent non selective β-adrenergic receptor antagonist,[12] an inhibitor of testosterone 6β-hydroxylase,[10] and is widely used in studies of cytochrome P450.[13] 1-(3-Phenethylbenzofuran-2-yl)-2-propylaminoethanol **2**, a propafenone **3** analogue, shows antiarrhythmic activity, but in contrast to **3** lacks β-adrenoacceptor blocking activity.[9b]

Synthetic approaches to racemic **1** and **2** have been described, and the racemates have been resolved.[9,12a,14] However, asymmetric syntheses of **1** and **2** have not been reported. Recently, we have developed an enantioselective synthesis of model benzofuryl β-amino alcohols,[15] using as a key reaction the reduction of the corresponding α-bromo ketones with (−)-*B*-chlorodiisopinocampheylborane ((−)-DIP-Cl).[16] Following this approach, here we wish to report on the first asymmetric synthesis of **1** and **2** (Fig. 1).



1 **2** **3**

Figure 1.

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2. Results and discussion

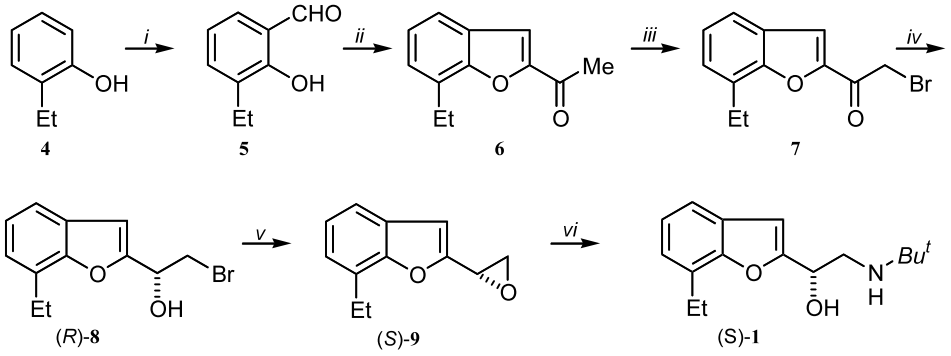
3-Ethyl-2-hydroxybenzaldehyde **5** is a convenient precursor for the synthesis of **1**. However, the reported methods for its preparation furnish the compound only in low to moderate yields.[17] Consequently, we developed a convenient procedure starting from 2-ethylphenol **4**, involving a modified Casiraghi formylation,[18] producing **5** in 72% yield. The aldehyde was transformed into 1-(7-ethylbenzofuran-2-yl)ethanone **6** by the reaction with chloroacetone and cyclization (Scheme 1). Bromination of **6** with pyridinium tribromide gave bromo ketone **7**, easily isolated by crystallization.

The reduction of **7** with (–)-DIP-Cl at −25°C furnished the corresponding bromohydrin (*R*)-**8** of 87% ee. The enantiomeric excess was determined by GC analysis on a chiral capillary column and comparison with the racemate prepared by the reduction of **7** with lithium tetrahydridoaluminate. The bromohydrin was transformed into an unstable epoxide (*S*)-**9**. Attempts to purify the epoxide by column chromatography failed. Racemic **9** was also reported to be unstable.[19] Consequently, the crude epoxide was treated with *tert*-butylamine, and (*S*)-**1** of 87% ee was isolated as its hydrochloride. Enantiomeric excess was determined by GC analysis of (*S*)-**1** on a chiral capillary column. Absolute configuration was established by comparing the sign of rotation with (*S*)-**1**·HCl, prepared by resolution of an authentic racemic sample (F. Hoffmann-La Roche Ltd.) as reported in the literature.[12,20]

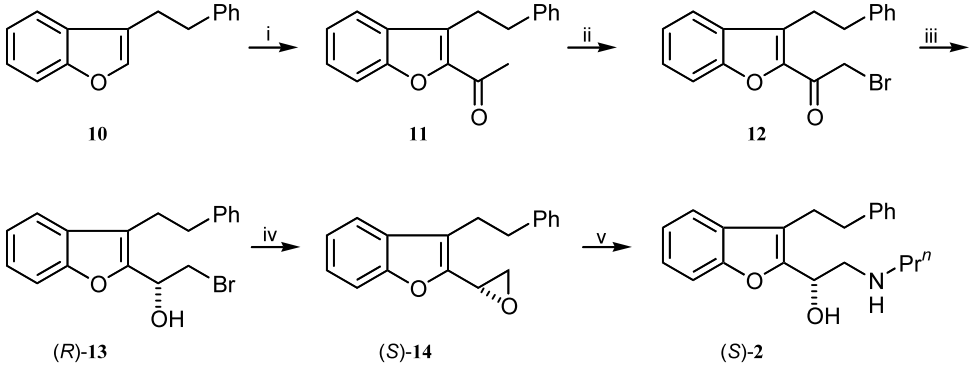
Racemic **2** was first synthesized from (3-phenethylbenzofuran-2-yl)methanone by the reduction of its cyanhydrin and alkylation of the product amino alcohol.[9a] The second synthesis of **2** involving the sequence **10**→**11**→**12** (Scheme 2), followed by the reduction of **12** with lithium tetrahydridoaluminate, chromatographic resolution of racemic **13** derivatized with (+)-NOE-lactol® dimer, and treatment with *n*-propylamine, afforded both enantiomers of **2**.[9b]

We also followed the same sequence, modifying the isolation procedure of **11**, and the reagent in the next step. Thus, acetylation of **10** gave a dark-brown oil, and isolation of **11** required several triturations with methanol, and final chromatographic purification. Bromination of **11** with a stoichiometric amount of bromine afforded a mixture of **12**, unreacted **11**, and 2,2-dibromo-1-(3-phenethylbenzofuran-2-yl)ethanone, which was difficult to separate. This difficulty was circumvented by bromination of **11** with pyridinium tribromide producing **12** cleanly in 62% yield.

The reduction of **12** with (–)-DIP-Cl furnished (*R*)-**13** of 73% ee, determined by HPLC analysis on a chiral column and comparison with the racemate prepared by the reduction of **12** with lithium tetrahydridoaluminate. Treatment of (*R*)-**13** with sodium hydride in tetra-



Scheme 1. *Reagents and conditions*: (i) HCHO, NEt_3, $MgCl_2$, MeCN; (ii) $ClCH_2COCH_3$, K_2CO_3, MeCN; (iii) $C_5H_6NBr_3$, AcOH; (iv) (–)-DIP-Cl, THF; (v) NaH, THF; (vi) *t*-$BuNH_2$.



Scheme 2. *Reagents and conditions*: (i) Ac_2O, $BF_3{\cdot}OEt_2$; (ii) $C_5H_6NBr_3$, AcOH; (iii) (–)-DIP-Cl, THF; (iv) NaH, THF; (v) *n*-$PrNH_2$.

hydrofuran furnished the corresponding epoxide (*S*)-**14**. Attempts to purify it by chromatography on silica gel and on alumina failed. The crude (*S*)-**14** was treated with *n*-propylamine and (*S*)-**2** was isolated as hydrochloride of 73% ee, determined by HPLC analysis on a chiral column. Its configuration was assigned by transformation into the tartrate salt and comparing the sign of rotation with reported data.[9b]

3. Conclusion

Asymmetric synthesis of (*S*)-**1** of 87% ee and (*S*)-**2** of 73% ee has been achieved employing as a key step the reduction of **7** and **12** with (−)-DIP-Cl, respectively. Similarly, the reduction of the model 2-bromo-1-(benzofuran-2-yl)ethanone with (−)-DIP-Cl, leads to the corresponding β-amino alcohol of *S*-configuration.[15] A convenient synthesis of **5**, the precursor of both racemic and optically active **1**, has been developed.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 and a Bruker AMX 300 spectrometers. GC analyses were performed on a Hewlett-Packard chromatograph provided with a flame ionization detector and a chiral column Supelco Beta DEX 325, 30 m×0.25 mm. HPLC analyses were carried out with a liquid chromatography system model LC-5B, Laboratorni Pristroje, Praha, equipped with chiral columns: Daicel Chiracel OJ, 10 μm, 25 cm×4.6 mm, and Daicel Chiracel OD-H 5 μm, 25 cm×4.6 mm. Rotations were measured on a Lot-Oriel S-2 automatic polarimeter.

4.2. Materials

Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl. Acetonitrile was distilled from calcium hydride. Triethylamine was distilled from lithium tetrahydridoaluminate. (−)-DIP-Cl of >99% ee was a commercial product (Aldrich).

4.3. 3-Ethyl-2-hydroxybenzaldehyde, 5

Paraformaldehyde (16.21 g, 540 mmol) was added in small portions to a solution of 2-ethylphenol **4** (9.77 g, 80 mmol), magnesium chloride (11.42 g, 120 mmol), and triethylamine (30.36 g, 300 mmol) in acetonitrile (100 mL) at rt. The mixture was refluxed for 5 h, stirred for 12 h at rt, and acidified with a 5% hydrochloric acid (ca 200 mL). The mixture was extracted with diethyl ether (2×100 mL), the extract was dried with magnesium sulphate and the product was isolated by distillation, 8.63 g, 72% yield, bp 55–57°C/1 mmHg; lit.[17b] bp 117–118°C/28 mmHg. ^{13}C NMR ($CDCl_3$): δ 13.62 (CH_3), 22.19 (CH_2), 119.48 (CH), 120.12 (C), 131.34 (CH), 132.68 (C), 136.21 (CH), 159.66 (C), 196.76 (CO).

4.4. 1-(7-Ethylbenzofuran-2-yl)ethanone, 6

Chloroacetone (10.03 g, 110 mmol) was added dropwise to a mixture of **5** (15.02 g, 100 mmol), anhydrous potassium carbonate (13.82 g, 100 mmol), and acetonitrile (70 mL) at 35°C. The mixture was refluxed for 5 h and cooled to rt. The precipitated solid was filtered off and washed with acetonitrile (10 mL). The product was isolated from the filtrate by distillation, 14.66 g, 78% yield, bp 103–105°C/0.5 mmHg, mp 54–56°C, lit.[17a] mp 54.5°C. ^{1}H NMR ($CDCl_3$): δ 1.34 (t, $J=8.0$ Hz, 3H), 2.61 (s, 3H), 3.00 (q, $J=8.0$ Hz, 2H), 7.19–7.33 (m, 2H), 7.49 (s, 1H), 7.27 (dd, $J=7.4$ Hz, $J=1.7$ Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 13.97 (CH_3), 22.69 (CH_2), 26.45 (CH_3), 113.19 (CH), 120 (CH), 124.05 (CH), 126.75 (C), 127.13 (CH), 128.96 (C), 152.46 (C), 154.38 (C), 188.69 (CO).

4.5. 2-Bromo-1-(7-ethylbenzofuran-2-yl)ethanone, 7

Pyridinium tribromide (11.20 g, 35 mmol) was added in portions to a stirred solution of **6** (5.30, 28 mmol) in acetic acid (100 mL) at 50–55°C, and stirring was continued for 4 h. Water (100 mL) was added and the mixture was extracted with diethyl ether (2×100 mL), the combined extract was washed with a saturated solution of sodium hydrogencarbonate (5×30 mL), water (20 mL), and dried with anhydrous magnesium sulphate. The solvent was removed and the product was crystallized from petroleum ether, 5.09 g, 69% yield, mp 58–60°C. ^{1}H NMR ($CDCl_3$): δ 1.38 (t, $J=7.5$ Hz, 3H), 2.99 (q, $J=7.5$ Hz, 2H), 4.46 (s, 2H, CH_2Br), 7.24–7.35 (m, 2H), 7.56 (dd, $J=6$ Hz, $J=1$ Hz, 1H), 7.65 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 13.92 (CH_3), 22,74 (CH_2), 30.22 (CH_2), 114.99 (CH), 120.86 (CH), 124.41 (CH), 126.58 (C), 127.83 (CH), 129.03 (C), 149.93 (C), 154.61 (C), 182.24 (CO). Anal. calcd for $C_{12}H_{11}BrO_2$: C, 53.96; H, 4.15. Found: C, 53.81; H, 4.11%.

4.6. (*R*)-(−)-2-Bromo-1-(7-ethylbenzofuran-2-yl)ethanol, (*R*)-8

A solution of **7** (4.00 g, 15 mmol) in tetrahydrofuran (10 mL) was added dropwise to a stirred mixture of (−)-DIP-Cl (5.58 g, 17 mmol) in tetrahydrofuran (10 mL) at −25°C under nitrogen, and stirring was continued for 4 h, and then for 20 h at rt. Tetrahydrofuran was removed, diethyl ether (80 mL) was added, followed with diethanolamine (2.10 g, 20 mmol). The mixture was stirred for 2 h at rt. White precipitate which was formed was filtered off and washed with diethyl ether (10 mL). The solvent was removed from the filtrate and the product was isolated by column chromatography on silica gel (petroleum ether/diethyl ether, 4:1), 2.56 g, 64% yield, $[\alpha]_D^{20}=-31.7$ (*c* 8.84, $CHCl_3$). GC analysis on a Supelco Beta-DEX 325, 30 m×0.25 mm, column showed 87% ee. Racemic **8**, prepared by the reduction of **7** with lithium tetrahydridoaluminate, was also analyzed. ^{1}H NMR ($CDCl_3$): δ 1.34 (t, $J=7.5$ Hz, 3H), 2.70 (d, $J=6.0$ Hz, 1H, OH), 2.92 (q, $J=7.5$ Hz, 2H), 3.80 (dd, $J=10.5$ Hz, $J=6.5$ Hz, 1H, CH_2Br), 3.87 (dd, $J=10.5$ Hz, $J=4.4$ Hz, 1H, CH_2Br), 5.11 (dd, $J=6.5$ Hz, $J=4.4$

Hz, 1H), 6.76 (d, $J=1$ Hz, 1H), 7.10–7.23 (m, 2H), 7.40 (dd, $J=7.5$ Hz, $J=1.8$ Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 14.06 (CH_3), 22.78 (CH_2), 36.58 (CH_2), 68.18 (CH), 104.34 (CH), 118.72 (CH), 123.17 (CH), 123.75 (CH), 127.42 (C), 127.77 (C), 153.41 (C), 155.03 (C). Anal. calcd for $C_{12}H_{13}BrO_2$: C, 53.55; H, 4.87. Found: C, 53.60; H, 4.82%.

4.7. (*S*)-7-Ethyl-2-oxiranyl-benzofuran, (*S*)-9

A solution of (*R*)-**8** (2.20 g, 8 mmol) in tetrahydrofuran (10 mL) was added dropwise to a stirred suspension of sodium hydride (0.60 g, 25 mmol) in tetrahydrofuran (10 mL), at rt, under nitrogen, and stirring was continued for 24 h. Solids were filtered off and washed with diethyl ether (10 mL). Solvents were removed and the crude epoxide was obtained as a red oil, 1.71 g. ^{1}H NMR ($CDCl_3$): δ 1.34 (t, $J=7.6$ Hz, 3H), 2.92 (q, $J=7.6$ Hz, 2H), 3.24 (dd, $J=5.5$ Hz, $J=4.2$ Hz, 1H), 3.37 (dd, $J=5.5$ Hz, $J=2.6$ Hz, 1H), 4.02 (ddd, $J=4.1$ Hz, $J=2.6$ Hz, $J=0.4$ Hz, 1H), 6.80 (d, $J=0.4$ Hz, 1H), 7.09–7.20 (m, 2H), 7.38 (ddt, $J=6.8$ Hz, $J=2.0$ Hz, $J=0.2$ Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 14.02 (CH_3), 22.71 (CH_2), 46.67 (CH), 48.27 (CH_2), 106.46 (CH), 118.44 (CH), 123.07 (CH), 123.84 (CH), 127.59 (C), 127.78 (C), 152.51 (C), 153.51 (C).

4.8. (*S*)-2-*tert*-Butylamino-1-(7-ethylbenzofuran-2-yl)-ethanol, (*S*)-1

A mixture of (*S*)-**9** (1.89 g, 10 mmol) and *tert*-butylamine (7.31 g, 100 mmol) was placed in an autoclave for 6 h at 55°C. After cooling to rt, excess of *tert*-butylamine was removed under vacuum, diethyl ether (50 mL) and water (10 mL) was added, and the mixture was stirred for 15 min. The organic layer was separated, washed with water (5 mL), and dried with magnesium sulphate. Ether was evaporated and 2.03 g of a red oil was obtained. GC analysis on a Supelco Beta-DEX 325, 30 m×0.25 mm, column showed 87% ee. An authentic sample of racemic **1** was also analyzed.

MTPA derivative. Derivatization with (*S*)-(+)-MTPA–Cl.[21] ^{1}H NMR ($CDCl_3$): δ 1.10 (s, 9H, CH_3), 1.29 (t, $J=7.6$ Hz, 3H, CH_3), 2.86 (q, $J=7.6$ Hz, 2H, CH_2), 3.23 (d, $J=5.6$ Hz, 1H, NCH_2), 3.34 (d, $J=7.6$ Hz, 1H, NCH_2), 3.58 (q, $J=1.0$ Hz, 3H, OCH_3), 6.20 (dd, $J=7.6$ Hz, $J=5.6$ Hz, 1H, OCH), 6.72 (s, 1H), 7.1–7.58 (m, 8H). The spectrum indicated 88% ee.

*Hydrochlorid*e. Hydrogen chloride was passed through a solution of (*S*)-**1** (1.31 g, 5.0 mmol) in diethyl ether at 0°C. A white precipitate which was formed was filtered off and crystallized from acetone, 0.55 g, 37% yield, mp 121–123°C, $[\alpha]_D^{20}=-39.5$ (*c* 1.00, EtOH), 87% ee; lit.[12a] mp 122–123°C; lit.[20a] $[\alpha]_D^{20}=-43.5$, (*c* 0.6, EtOH), 96% ee. ^{1}H NMR ($CDCl_3$): δ 1.30 (t, $J=7.6$ Hz, 3H), 1.53 (s, 9H), 2.89 (q, $J=7.6$ Hz, 2H), 3.32 (dd, $J=12.0$ Hz, $J=10.2$ Hz, 1H, NCH_2), 3.46 (dd, $J=12.0$ Hz, $J=2.6$ Hz, 1H, NCH_2), 5.59 (dd, $J=10.2$ Hz, $J=2.6$ Hz, 1H), 5.90 (bs, 1H, OH), 6.77 (d, $J=0.8$ Hz, 1H), 7.09–7.17 (m, 2H), 7.32 (dd, $J=7.0$ Hz, $J=2.0$ Hz, 1H), 8.30 (bs, 1H), 10.07 (bs, 1H); ^{13}C NMR ($CDCl_3$): δ 14.00 (CH_3), 22.60 (CH_2), 25.92 (3×CH_3), 46.47 (CH_2), 57.82 (C), 63.85 (CH), 104.50 (CH), 118.72 (CH), 123.09 (CH), 123.60 (CH), 127.44 (C),127.70 (C), 153.46 (C), 154.77 (C).

4.9. 1-(3-Phenethylbenzofuran-2-yl)ethanone, 11

A mixture of 3-phenethylbenzofuran **10**[9a] (20.00 g, 90 mmol), acetic anhydride (43 mL), and boron trifluoride etherate (1.2 mL) was stirred at 50°C for 10 h. Water (100 mL) was added and stirring was continued for 12 h at rt. The mixture was extracted with diethyl ether (3×50 mL), the combined extract was washed with a saturated solution of sodium hydrogencarbonate (5×30 mL), water (2×30 mL), and dried with magnesium sulphate. Ether was removed, and a dark brown viscous liquid was triturated several times with methanol. Methanol was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (petroleum ether/diethyl ether, 9:1), 10.85 g, 46% yield, mp 85–87°C, lit.[9b] mp 85–87°C. ^{1}H NMR ($CDCl_3$): δ 2.61 (s, 3H), 2.93–3.01 (m, 2H), 3.35–3.41 (m, 2H), 7.15–7.35 (m, 6H), 7.45–7.60 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 26.40 (CH_3), 27.75 (CH_2), 35.81 (CH_2), 112.17 (CH), 121.56 (CH), 123.22 (CH), 126.05 (CH), 127.98 (C), 128.03 (CH), 128.33 (2×CH), 128.54 (2×CH), 128.65 (C), 141.42 (C), 148.09 (C), 154.00 (C), 191.13 (CO).

4.10. 2-Bromo-1-(3-phenethylbenzofuran-2-yl)ethanone, 12

Pyridinium tribromide (16.26 g, 50 mmol) was added in portions to a stirred solution of **11** (12.00 g, 40 mmol) in acetic acid (150 mL) at 50–55°C, and stirring was continued for 4 h. Water (150 mL) was added and the mixture was extracted with diethyl ether (2×100 mL). The combined extract was washed with saturated solution of sodium hydrogencarbonate (5×30 mL), water (2×30 mL), and dried with magnesium sulphate. Ether was removed and the product was isolated by column chromatography on silica gel (petroleum ether/diethyl ether, 1:1), 9.46 g, 62% yield, mp 64–66°C, lit.[9b] mp 65–67°C. ^{1}H NMR ($CDCl_3$): δ 2.93–3.01 (m, 2H), 3.36–3.44 (m, 2H), 4.54 (s, 2H, CH_2Br), 7.15–7.40 (m, 3H), 7.47–7.62 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 26.51 (CH_2), 32.14 (CH_2Br), 35.65 (CH_2), 112.34 (CH), 121.74 (CH), 123.60 (CH), 126.16 (CH), 128.37 (2×CH), 128.40 (C), 128.54 (2×CH), 128.86 (CH), 131.09 (C), 141.12 (C), 145.81 (C), 154.32 (C), 183.62 (CO).

4.11. (*R*)-(−)-2-Bromo-1-(3-phenethylbenzofuran-2-yl)ethanol, (*R*)-13

A solution of **12** (4.08 g, 12 mmol) in tetrahydrofuran (10 mL) was added to a stirred suspension of (−)-DIP-Cl) (4.25 g, 13 mmol) in tetrahydrofuran (10 mL) at −25°C under nitrogen, stirring was continued for 8 h, and then for 18 h at rt. Tetrahydrofuran was removed under vacuum, diethyl ether (40 mL) was added, followed with diethanolamine (1.51 g, 14.4 mmol). The same workup as described in Section 4.6, gave the product, 2.31 g, 56% yield, $[\alpha]_D^{20}=-12.4$ (*c* 8.03,

$CHCl_3$), 73% ee, determined by HPLC analysis: Daicel Chiracel OJ 10 μm, 25 cm×4.6 mm column, *n*-hexane/isopropanol, 9:1. Racemic **13**, prepared by the reduction of **12** with lithium tetrahydridoaluminate, was also analyzed. ^{1}H NMR ($CDCl_3$): δ 1.80 (d, $J=4.0$ Hz, 1H, OH), 2.94–3.10 (m, 4H), 3.18 (dd, $J=10.4$ Hz, $J=5.2$ Hz, 1H, CH_2Br), 3.56 (dd, $J=10.4$ Hz, $J=8.2$ Hz, 1H, CH_2Br), 4.64 (dd, $J=8.2$ Hz, $J=5.4$ Hz, 1H), 7.00–7.09 (m, 2H), 7.20–7.40 (m, 5H), 7.41–7.52 (m, 1H), 7.53–7.69 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 25.62 (CH_2), 34.87 (CH_2Br), 35.58 (CH_2), 66.62 (CH), 111.52 (CH), 116.92 (C), 119.68 (CH), 122.60 (CH), 124.83 (CH), 126.36 (CH), 128.39 (C), 128.49 (2×CH), 128.75 (2×CH), 141.18 (C), 150.03 (C), 154.21 (C). Anal. calcd for $C_{18}H_{17}BrO_2$: C, 62.62; H, 4.97. Found: C, 62.57; H, 4.81%.

4.12. (*S*)-2-Oxiranyl-3-phenethylbenzofuran, (*S*)-14

A solution of (*R*)-**13** (2.00 g, 5.8 mmol) in tetrahydrofuran (10 mL) was added to a stirred suspension of sodium hydride (0.60 g, 25 mmol) in tetrahydrofuran (10 mL) at rt under nitrogen, and the mixture was stirred for 20 h at rt. Solids were filtered off and washed with diethyl ether (15 mL). Solvents were removed from the filtrate and the crude product was obtained as a brown–red oil, 1.79 g. ^{1}H NMR ($CDCl_3$): δ 2.98–3.17 (m, 5H), 3.31 (dd, $J=5.4$ Hz, $J=2.8$ Hz, 1H), 3.68 (dd, $J=4.2$ Hz, $J=2.8$ Hz, 1H), 7.08–7.20 (m, 2H), 7.21–7.38 (m, 5H), 7.39–7.47 (m, 1H), 7.50–7.57 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 25.47 (CH_2), 36.13 (CH_2), 45.04 (CH), 47.68 (CH_2), 111.36 (CH), 119.26 (CH), 119.97 (C), 122.49 (CH), 124.78 (CH), 126.19 (CH), 128.40 (2×CH), 128.59 (2×CH), 128.83 (C), 141.13 (C), 147.52 (C), 154.07 (C).

4.13. (*S*)-(−)-1-(3-Phenethylbenzofuran-2-yl)-2-propylaminoethanol hydrochloride, (*S*)-2·HCl

A mixture of (*S*)-**14** (1.48 g, 5.6 mmol) and *n*-propylamine (20 mL) was placed in a autoclave for 20 h at 70°C. After cooling to rt, excess of *n*-propylamine was removed under vacuum, diethyl ether (20 mL) was added, and hydrogen chloride was passed through the solution. White precipitate which was formed was filtered off and crystallized from ethyl acetate, 0.62 g, 31% yield, mp 144–146°C, $[\alpha]_D^{20}=-58.05$ (*c* 4.33, $CHCl_3$), 73% ee, determined by HPLC analysis: Daicel Chiracel OD-H 5 μm, 250 cm×4.6 mm column, *n*-hexane/isopropanol, 95:5. ^{1}H NMR ($CDCl_3$): δ 0.94 (t, $J=7.2$ Hz, 3H), 1.85 (sext., $J=7.2$ Hz, 2H), 2.30 (dd, $J=12.4$ Hz, $J=2.8$ Hz, 1H, NCH_2), 2.80–3.10 (m, 6H, NCH_2, 2×CH_2), 3.23 (dd, $J=12.4$ Hz, $J=10.8$ Hz, 1H, NCH_2), 5.20 (bs, 1H, OH), 5.29 (dd, $J=10.8$ Hz, $J=2.8$ Hz, 1H), 7.00–7.38 (m, 8H), 7.45–7.57 (m, 1H), 8.60 (bs, 1H), 9.60 (bs, 1H); ^{13}C NMR ($CDCl_3$): δ 11.13 (CH_3), 19.26 (CH_2), 25.25 (CH_2), 35.48 (CH_2), 50.00 (CH_2), 50.98 (CH_2), 61.35 (CH), 111.33 (CH), 116.77 (C), 119.89 (CH), 122.57 (CH), 124.72 (CH), 125.87 (CH), 128.40 (2×CH), 128.43 (C), 129.04 (2×CH), 141.34 (C), 149.69 (C), 154.19 (C). Anal. calcd for $C_{21}H_{26}NO_2Cl$: C, 70.08; H, 7.28; N, 3.89, Cl, 9.85. Found: C, 69.65; H, 7.19; N, 3.94, Cl, 9.64%.

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