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ENANTIOSELECTIVE SYNTHESIS OF 2- AND 3-BENZOFURYL β-AMINO ALCOHOLS

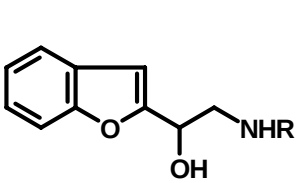
Marek Zaidlewicz*, Aldona Chechłowska, Andrzej Prewysz-Kwinto, and Andrzej Wojtczak
E-mail: zaidlevi@chem.uni.torun.pl

Faculty of Chemistry, Nicolaus Copernicus University, 87–100 Toruń, Poland

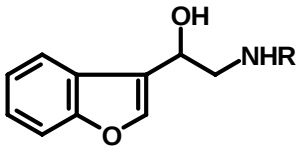
Abstract – Enantioselective reduction of 2- and 3-bromoacetylbenzofurans with (–)-*B*-chlorodiisopinocampheylborane produced the corresponding bromohydrins which were transformed into (*S*)-(benzofuran-2-yl)oxirane of 72% ee and (*S*)-(benzofuran-3-yl)oxirane of 71% ee, respectively. The epoxides treated with primary alkylamines gave the corresponding (*S*)-1-(benzofuran-2- and -3-yl)-2-(alkylamino)ethanols.

In spite of a long history of studies on the synthesis of benzofuran derivatives, enantioselective approaches to these compounds and preparation of enantiomers *via* resolution of racemates is the subject of current interest, justified by their diverse pharmacological activity.[1-5] Among these derivatives, amino alcohols play an important role showing antiarrhythmic,[6,7] enzyme inhibitiory,[5,7] antihypertensive,[8] and β-adrenoacceptor blocking activity.[9] For example, bufuralol, a derivative of **1** proved effective for treatment of hypertension,[10] is a potent nonselective β-adrenergic receptor antagonist with partial β_2 agonist preperties,[9,11] and an inhibitor of testosterone 6β-hydroxylase.[5]

The aim of this study was an enantioselective synthesis of β-amino alcohols (**1)** and (**2)** using as a key reaction the reduction of the corresponding bromo ketones with (–)-*B*-chlorodiisopinocampheylborane ((–)-DIP-Cl).[12,13]

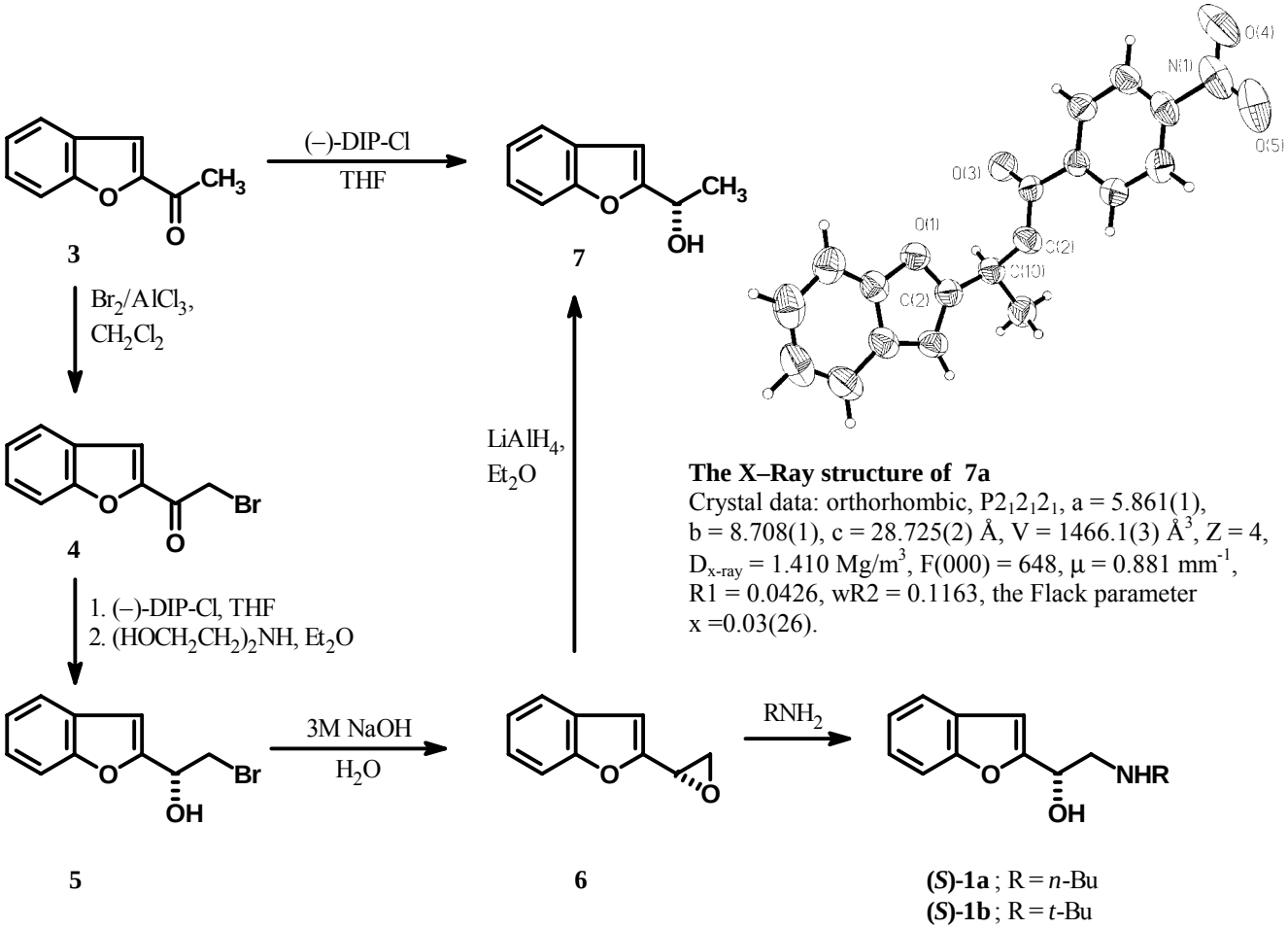


1; R = alkyl



2; R = alkyl

A readily available 2-acetylbenzofuran (**3**) was the starting material for the synthesis of β-amino alcohols (**1a, 1b)** (Scheme 1). Bromination of **3** with bromine / aluminum chloride gave bromo ketone (**4**) in good yield. Enantioselective reduction of **4** with (**–**)-DIP-Cl afforded bromohydrin (**5**) which was transformed into epoxide (**6**) of 70% ee. The (*S*)–configuration of the epoxide was correlated with (*S*)-1-(benzofuran-2-yl)ethanol (**7**)[14] by the reduction of **6** with lithium aluminum hydride and comparison of the sign of rotation. Alcohol (**7**) of 91% ee was independently prepared by the reduction of **3** with (**–**)-DIP-Cl. The X-Ray analysis of its *p*-nitrobenzoate (**7a**) is shown on Scheme 1. Epoxide (**6**) was treated with *n*-butyl- and *tert*-butylamine to give the corresponding amino alcohols ((***S***)-**1a,** (***S***)-**1b**).[15]

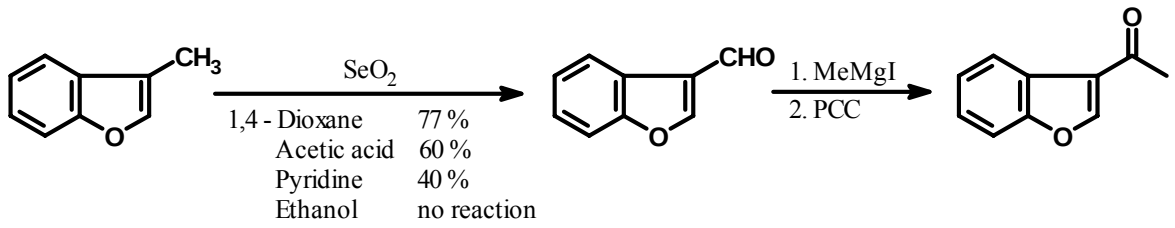


The X–Ray structure of 7a
Crystal data: orthorhombic, $P2_12_12_1$, a = 5.861(1), b = 8.708(1), c = 28.725(2) Å, V = 1466.1(3) Å^3, Z = 4, $D_{x\text{-}ray}$ = 1.410 Mg/m^3, F(000) = 648, μ = 0.881 mm^{-1}, R1 = 0.0426, wR2 = 0.1163, the Flack parameter x =0.03(26).

Scheme 1

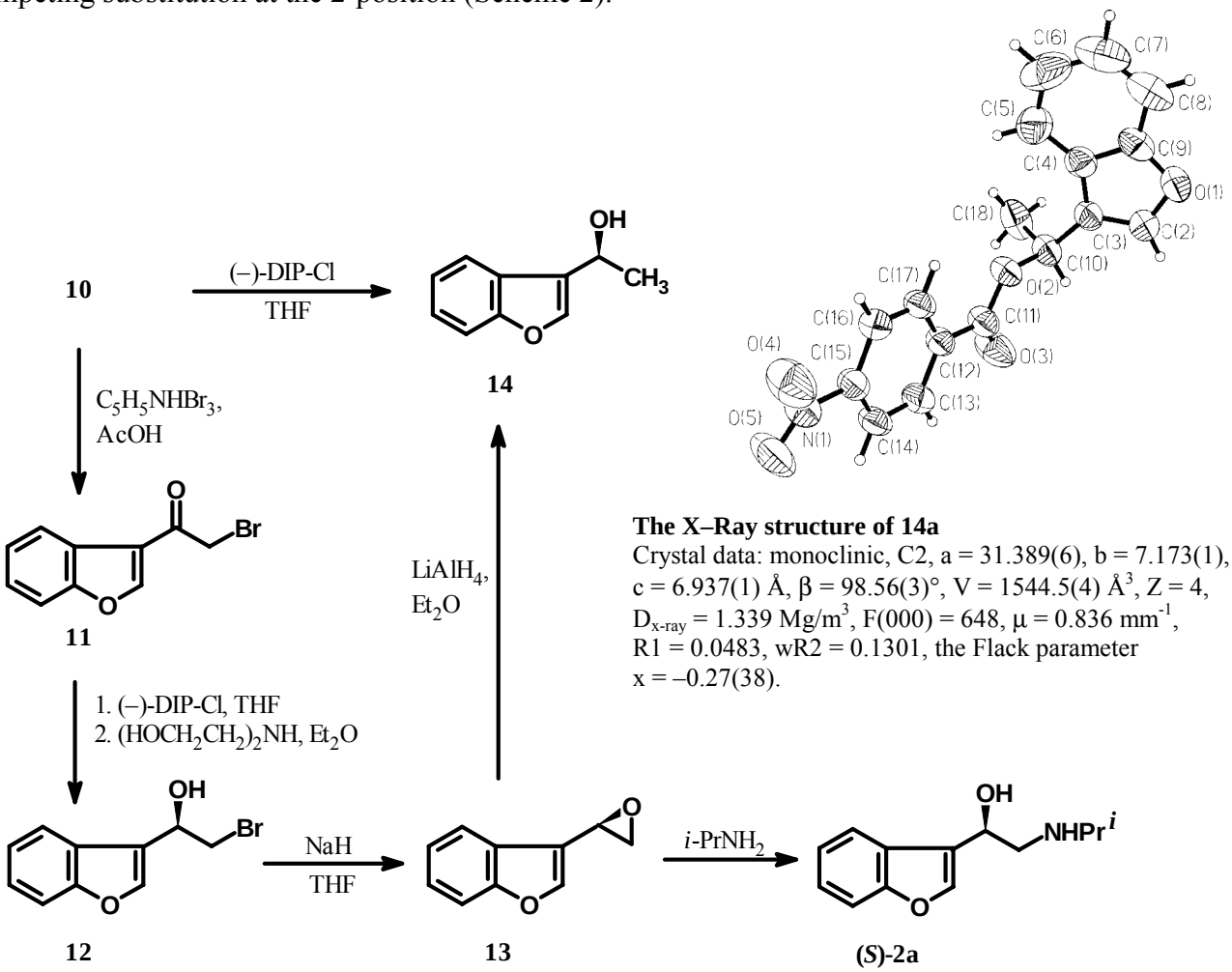
3-Acetylbenzofuran (**10**), the starting material for the synthesis of 1-(benzofuran-3-yl)-2-(isopropyl-amino)ethanol (Scheme 2), is not so readily available as its isomer (**3**). The literature procedures involve several steps and the overall yield of **10** is low.[16] Considering other possibilities we focused on 3-formyl-benzofuran (**9**) as an intermediate. Since the reported syntheses of **9** require several steps, we decided to study the oxidation of a readily available 3-methylbenzofuran (**8**) with selenium dioxide. Surprisingly, no

oxidation product was formed after refluxing the reagents in ethanol for several hours. Fortunately, in dioxane **9** was produced cleanly in 77% yield. Treatment with methylmagnesium iodide followed by oxidation of the crude product alcohol with pyridinium chlorochromate afforded **10** in 60% yield.



8 **9** **10**

Bromination of **10** with pyridinium tribromide proceeded regioselectively to give bromo ketone (**11**) with no competing substitution at the 2-position (Scheme 2).



The X–Ray structure of 14a
Crystal data: monoclinic, C2, a = 31.389(6), b = 7.173(1), c = 6.937(1) Å, β = 98.56(3)°, V = 1544.5(4) Å^3, Z = 4, $D_{x\text{-}ray}$ = 1.339 Mg/m^3, F(000) = 648, μ = 0.836 mm^{-1}, R1 = 0.0483, wR2 = 0.1301, the Flack parameter x = –0.27(38).

Scheme 2

The bromo ketone was reduced with (**–**)-DIP-Cl to bromohydrin (**12**), which was treated with sodium hydride in tetrahydrofuran to give (*S*)-epoxide (**13**) of 71% ee. Its configuration was correlated with (*S*)-1-

(benzofuran-3-yl)ethanol (**14**) prepared by the reduction of **10** with (**–**)-DIP-Cl. The absolute configuration of **14** was established by the X-Ray analysis of its *p*-nitrobenzoate (**14a**). Epoxide (**13**) was treated with isopropylamine to give amino alcohol ((***S***)-**2a**). A small amount of its regioisomer (~5 %) present in the crude reaction product was removed by crystallization.

In conclusion, the enantioselective reduction of α-bromo ketones (**4**) and (**11**) with (**–**)-DIP-Cl provides a convenient access to the corresponding β-amino alcohols. The reaction sequence leading to these products employs simple reagents, does not require tedious separations, and can be scaled up to larger quantities. Convenient syntheses of 3-formyl- and 3-acetylbenzofuran, which in general are more difficult to prepare as compared to the corresponding 2-substituted derivatives, have been developed. These compounds can serve as useful intermediates in transformations leading to other 3-substituted benzofurans.

EXPERIMENTAL

^{1}H, ^{13}C, and ^{11}B NMR spectra were recorded on a Varian Gemini 200 instrument. IR spectra were recorded on a Perkin Elmer 200 spectrophotometer. X-Ray structures were determined using a Kuma KM4 diffractometer with Cu Kα radiation. GC analyses were performed on a Chrom 5 chromatograph provided with a flame ionisation detector and two columns: 2 m x 4 mm, OV-17 on Chromosorb G AW DMCS 80-100 mesh, and 3 m x 4 mm, 15% Carbowax 20M on Chromosorb W NAW 80-100 mesh. A Hewlett-Packard chromatograph was provided with a flame ionisation detector and two capillary columns: SPB-5, 30 m x 0.32 mm, and Supelcowax-10, 30 m x 0.32 mm. Preparative GC separations were carried out using a GCHF 18.3 chromatograph provided with a column 1 m x 10 mm, 20% Carbowax 20M on Chromosorb W 60-80 mesh. HPLC analyses were carried out with a liquid chromatography system model LC-5B, Laboratorni Pristroje, Praha, equipped with a Daicel Chiralcel OJ column 25 cm x 4.6 mm and a precolumn 5 cm x 4.6 mm. Rotations were measured on a Lot-Oriel S-2 automatic polarimeter. Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl. 2-Acetylbenzofuran (**3**),[17] 2-bromoacetylbenzofuran (**4**)[18] and 3-methylbenzofuran (**8**)[19] were prepared according to the literature. (**–**)-*B*-Chlorodiisopinocampheylborane ((–)-DIP-Cl) was a commercial product (Aldrich).

(*S*)-(–)-(Benzofuran-2-yl)oxirane (6)

A mixture of (**–**)-DIP-Cl (8.71 g, 27.1 mmol) and tetrahydrofuran (40 mL) was cooled to –30 °C under nitrogen and a solution of **4** (5.88 g, 24.6 mmol) in tetrahydrofuran (15 mL) was slowly added. The mixture was stirred at this temperature for 3 h, and then at –5 °C for 24 h. The ^{11}B NMR spectrum indicated no signal at δ 32 corresponding to DIP-Cl. The solvent was removed under vacuum and ether

(30 mL) was added, followed with diethanolamine (5.65 g, 53.7 mmol). The mixture was stirred for 2 h at rt. The precipitated solid was filtered off and washed with ether (2x10 mL). The combined ether solution was dried over magnesium sulfate. Solvent was removed under vacuum and crude **5** (11.60 g) was obtained. A mixture of 3M sodium hydroxide (87 mmol, 29 mL), ether–pentane (1 : 1) (150 mL) and the crude **5** was stirred for 3 h at rt. The organic layer was separated, and the aqueous phase was extracted with ether (3x10 mL). The combined ether solution was dried over magnesium sulfate. Solvent was removed and **6** was isolated by distillation, bp 81–84 °C/0.6 mmHg, (1.67 g, 42%). An analytical sample was isolated by preparative GC, $[\alpha]_D^{20}$ –31.86° (c 25.24, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 3.21 (1H, dd, *J*=5.4 Hz, *J*=4.0 Hz, CH), 3.36 (1H, dd, *J*=5.4 Hz, *J*=2.6 Hz, CH), 4.00 (1H, dd, *J*=4.0 Hz, *J*=2.6 Hz, CH), 6.80 (1H, s, CH_{Ar}), 7.15–7.35 (2H, m, CH_{Ar}), 7.40–7.60 (2H, m, CH_{Ar}).^{13}C NMR ($CDCl_3$) δ: 46.51 (CH), 48.17(CH_2), 106.40, 111.25, 120.91, 122.89, 124.65, 127.91, 152.80, 154.80. *Anal.* Calcd for $C_{10}H_8O_2$: C, 74.99; H, 5.03. Found: C, 74.68; H, 5.00.

For determining the enantiomeric excess, a solution of **6** (0.40 g, 2.5 mmol) in ether (2 mL) was added dropwise to a solution of lithium aluminum hydride (0.10 g, 2.6 mmol) in ether (3 mL). The mixture was stirred for 0.5 h at rt. Water (1 mL) was slowly added and the mixture was stirred for 0.5 h. Precipitated solid was filtered off and washed with ether (10 mL). The ether solution was dried over magnesium sulfate, and **7** was isolated by distillation (0.36 g, 90%), bp 109–110 °C/ 1 mmHg, $[\alpha]_D^{20}$ –25.40° (c 10.38, $CHCl_3$), 70% ee (by comparison of the sign of rotation with a sample of **7** prepared as described below).

(*S*)-(–)-1-(Benzofuran-2-yl)ethanol (7)

A solution of **3** (3.20 g, 20.0 mmol) in THF (20 mL) was slowly added to a mixture of (–)-DIP-Cl (7.70 g, 24.0 mmol) and THF (25 mL) at –30 °C under nitrogen. The mixture was stirred at this temperature for 3 h and then at rt for 24 h. The ^{11}B NMR spectrum indicated no signal at δ 32 corresponding to DIP-Cl. The solvent was removed under vacuum and ether (20 mL) was added, followed with diethanolamine (5.01 g, 47.6 mmol). The mixture was stirred for 2 h at rt. The precipitated solid was filtered off and washed with ether (2x10 mL). The combined ether solution was dried over magnesium sulfate. The product was isolated by distillation, (1.48 g, 46%), bp 106–108 °C/1.2 mmHg. An analytical sample was purified by preparative GC, $[\alpha]_D^{20}$ –33.27° (c 10.17, $CHCl_3$). HPLC analysis, Daicel Chiralcel OJ column, *n*–hexane/isopropanol (9 : 1) showed 91% ee. lit.[14] **(*R*)-7**, $[\alpha]_D^{20}$ +19.99° (c 1.21, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 1.64 (3H, d, *J*=4.4 Hz, CH_3), 2.92 (1H, br s, OH), 5.00 (1H, q, *J*=4.4 Hz, CH), 6.60 (1H, s, CH_{Ar}), 7.20–7.35 (2H, m, CH_{Ar}), 7.45–7.55 (2H, m, CH_{Ar}). ^{13}C NMR ($CDCl_3$) δ: 21.28 (CH_3), 63.97 (CH), 101.66, 111.08, 120.95, 122.64, 124.01, 128.06, 154.65, 160.19. *Anal.* Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.20. Found: C, 74.02; H, 6.18. *p*-Nitrobenzoate (**7a**), mp 59–60 °C (from *n*-hexane). ^{1}H NMR

($CDCl_3$) δ: 1.85 (3H, d, *J*=4.4 Hz, CH_3), 6.38 (1H, q, *J*=4.4 Hz, CH), 6.80 (1H, s, CH_{Ar}), 7.20–7.35 (2H, m, CH_{Ar}), 7.45–7.60 (2H, m, CH_{Ar}), 8.21–8.29 (4H, m, CH_{Ar}). ^{13}C NMR ($CDCl_3$) δ: 18.21 (CH_3), 67.03 (CH), 104.93, 111.42, 121.36, 123.01, 123.50 (2CH), 124.85, 127.68, 130.88 (2CH), 135.46, 150.63, 154.92, 155.11, 163.84 (C=O). *Anal.* Calcd for $C_{17}H_{13}NO_5$: C, 65,59; H, 4.21; N, 4.49. Found: C, 65.38; H, 4.10; N, 4.45. The crystal data and the X-Ray structure are given on Scheme 1.

(*S*)-(–)-1-(Benzofuran-2-yl)-2-(*n*-butylamino)ethanol ((*S*)-1a). Typical procedure

A solution of **6** (1.00 g, 6.25 mmol) in *n*–butylamine (5 mL) was placed in an autoclave and kept at 100 °C for 3 h. Excess of *n*–butylamine was removed and the product was crystallized from cyclohexane (1.20 g, 83%), mp 51–53 °C, $[\alpha]_D^{20}$ –30.88° (c 10.00, THF). ^{1}H NMR ($CDCl_3$) δ: 0.90 (3H, t, *J*=7.0 Hz, CH_3), 1.25–1.55 (4H, m, CH_2), 2.65 (2H, t, *J*=6.8 Hz, CH_2), 2.75 (2H, br s, OH, NH), 3.02 (1H, dd, *J*=12.0 Hz, *J*=4.8 Hz, CH_2N), 3.10 (1H, dd, *J*=12.0 Hz, *J*=6.8 Hz, CH_2N), 4.87 (1H, dd, *J*=6.8 Hz, *J*=4.8 Hz, CH-O), 6.70 (1H, s, CH_{Ar}), 7.15–7.30 (2H, m, CH_{Ar}), 7.40–7.60 (2H, m, CH_{Ar}). ^{13}C NMR ($CDCl_3$) δ: 13.89 (CH_3), 20.29 (CH_2), 32.06 (CH_2), 49.24 (CH_2), 53.29 (CH_2), 66.02 (CH), 102.89, 111.09, 120.86, 122.63, 123.88, 128.09, 154.73, 158.40. *Anal.* Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.00; H; 8.02, N; 5.89.

(*S*)-(–)-1-(Benzofuran-2-yl)-2-(*tert*-butylamino)ethanol ((*S*)-1b)

Yield (0.91 g, 61%), mp 149–151 °C (from cyclohexane). $[\alpha]_D^{20}$ –30.36° (c 10.00, THF). ^{1}H NMR ($CDCl_3$) δ: 1.07 (9H, s, CH_3), 2.70 (2H, br s, OH, NH), 2.98 (1H, dd, *J*=11.6 Hz, *J*=6.2 Hz, CH_2), 3.05 (1H, dd, *J*=11.6 Hz, *J*=4.8 Hz, CH_2), 4.80 (1H, dd, *J*=6.2 Hz, *J*=4.8 Hz, CH), 6.70 (1H, s, CH_{Ar}), 7.15–7.30 (2H, m, CH_{Ar}), 7.40–7.60 (2H, m, CH_{Ar}). ^{13}C NMR ($CDCl_3$) δ: 29.13 (CH_3), 46.40 (CH_2), 50.32 (C), 66.74 (CH), 102.88, 111.08, 120.81, 122.62, 123.79, 128.27, 154.89, 158.76. *Anal.* Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.00; H, 8.20; N, 5.89.

3-Formylbenzofuran (9)

A mixture of **8** (10.02 g, 75.8 mmol) and selenium dioxide (9.70 g, 87.4 mmol) in dry 1,4-dioxane (100 mL) was refluxed for 48 h. Black precipitate was filtered off and the product was isolated by distillation, (8.62 g, 77%), bp 68–69 °C/0.4 mmHg, mp 37–38 °C. lit.,[20] bp 72–74 °C/2 mmHg, mp 38–39 °C.

^{1}H NMR ($CDCl_3$) δ: 7.30–7.50 (2H, m, CH_{Ar}), 7.50–7.60 (1H, m, CH_{Ar}), 8.15–8.22 (1H, m, CH_{Ar}), 8.26 (1H, s, CH_{Ar}), 10.17 (1H, s, CHO). ^{13}C NMR ($CDCl_3$) δ: 111.66, 122.60, 122.94, 123.01, 124.86, 126.28, 155.31, 155.48, 184.77 (C=O).

3-Acetylbenzofuran (10)

A solution of **9** (8.50 g, 58.2 mmol) in ether (25 mL) was slowly added with stirring at 0 °C to a solution of methylmagnesium iodide, prepared from magnesium (1.70 g, 69.9 mmol) and iodomethane (9.94 g, 70.0 mmol), in ether (40 mL). The mixture was left overnight at rt and a saturated ammonium chloride solution (15 mL) was slowly added. The organic layer was separated and the aqueous layer was extracted

with ether (3x20 mL). The combined ether solution was washed with brine (10 mL) and dried over magnesium sulfate. Solvent was removed, dichloromethane (50 mL) was added, and the solution was slowly added to PCC (21.39 g, 99.2 mmol) in dichloromethane (75 mL) at 20–25 °C. The mixture was stirred at rt for 10 h, diluted with ether (100 mL), and stirred for 1 h. Precipitated solid was filtered off and washed with ether (2x25 mL). The combined solution was dried over magnesium sulfate. Solvent was removed and the product was isolated by distillation, (6.80 g, 77%), bp 78–80 °C/0.5 mmHg. lit.,[16] bp 60–70 °C/0.3 mmHg. ^{1}H NMR ($CDCl_3$) δ: 2.50 (3H, s, CH_3), 7.30–7.40 (2H, m, CH_{Ar}), 7.45–7.52 (1H, m, CH_{Ar}), 8.17 (1H, m, CH_{Ar}), 8.20–8.25 (1H, m, CH_{Ar}). ^{13}C NMR ($CDCl_3$) δ: 27.86 (CH_3), 111.30, 122.46, 122.69, 124.04, 124.36, 125.46, 151.16, 155.50, 192.78 (C=O).

3-Bromoacetylbenzofuran (11)

To a solution of **10** (6.09 g, 38.0 mmol) in acetic acid (60 mL), pyridinium tribromide (14.58 g, 45.6 mmol) was slowly added at 45–50 °C. The mixture was stirred at this temperature for 0.5 h and then at rt for 1 h. Precipitated solid was filtered off and dissolved in ether (50 mL). The solution was washed with saturated bicarbonate solution (3x10 mL) and dried over magnesium sulfate. Solvent was removed and the product was crystallized from carbon tetrachloride, (3.59 g, 60%), mp 135–136 °C. ^{1}H NMR ($CDCl_3$) δ: 4.32 (2H, s, CH_2), 7.35–7.46 (2H, m, CH_{Ar}), 7.50–7.60 (1H, m, CH_{Ar}), 8.15–8.30 (1H, m, CH_{Ar}), 8.39 (1H, s, CH_{Ar}). ^{13}C NMR ($CDCl_3$) δ: 31.35 (CH_2), 111.58, 119.55, 122.82, 124.02, 124.85, 126.04, 151.72, 155.60, 186.50 (C=O). *Anal.* Calcd for $C_{10}H_7O_2Br$: C, 50.24; H, 2.95. Found: C, 50.00, H, 2.89.

(*S*)-(+)-(Benzofuran-3-yl)oxirane (13)

A mixture of (–)-DIP-Cl (8.45 g, 26.0 mmol) and tetrahydrofuran (30 mL) was cooled to –30 °C under nitrogen and a solution of **11** (5.03 g, 21.0 mmol) in tetrahydrofuran (20 mL) was slowly added. The mixture was stirred at this temperature for 2 h and then at rt for 24 h. The ^{11}B NMR spectrum indicated no signal at δ 32 corresponding to DIP-Cl. Workup carried out as described for **5** gave 9.37 g of crude **12.** To a mixture of sodium hydride (4.37 g, 182.1 mmol) and tetrahydrofuran (50 mL), a solution of the crude **12** (9.20 g, 38.2 mmol) was slowly added with vigorous stirring at rt. Stirring was continued for 3 h, and the solid material was filtered off, and **13** was isolated by distillation, (2.63 g, 78%), bp 70–74 °C/0.3 mmHg. An analytical sample was isolated by preparative GC, $[\alpha]_D^{20}$ +12.26° (c 36.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 3.16–3.19 (2H, m, CH_2), 4.05 (1H, dd, *J*=3.2 Hz, *J*=3.0 Hz, CH), 7.20–7.40 (2H, m, CH_{Ar}), 7.47–7.55 (1H, m, CH_{Ar}), 7.55–7.70 (1H, m, CH_{Ar}), 7.65 (1H, s, CH_{Ar}). ^{13}C NMR ($CDCl_3$) δ: 46.32 (CH), 48.26 (CH_2), 111.62, 118.23, 120.12, 122.89, 124.72, 126.02, 142.95, 155.63. *Anal.* Calcd for $C_{10}H_8O_2$: C, 74.99; H, 5.03. Found: C, 74.90; H, 5.00.

For determining the enantiomeric excess, a solution of **13** (0.45 g, 2.8 mmol) in ether (2 mL) was reduced with lithium aluminum hydride (0.12 g, 3.2 mmol) in ether (2 mL), as described above for **6**, to give **14**

isolated by distillation, (0.40 g, 89%), bp 81–82 °C/0.1 mmHg, $[\alpha]_D^{20}$ –20.28° (c 11.34, $CHCl_3$), 71% ee (by comparison of the sign of rotation with **14** prepared as described below).

(*S*)-(–)-1-(Benzofuran-3-yl)-2-(isopropylamino)ethanol ((*S*)-2a)

A solution of **13** (1.00 g, 6.25 mmol) in isopropylamine (10 mL) was placed in an autoclave and kept at 100 °C for 3 h. Excess of isopropylamine was removed and the product was crystallized from cyclohexane, (0.75 g, 55%), mp 92–93 °C, $[\alpha]_D^{20}$ –46.27° (c 10.15, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 1.09 (6H, dd, *J*=6.2 Hz, *J*=1.0 Hz, CH_3), 2.10–2.65 (2H, br s, NH, OH), 2.87 (1H, septet, *J*=6.2 Hz, CH), 2.93 (1H, dd, *J*=12.0 Hz, *J*=8.0 Hz, CH_2), 3.10 (1H, dd, *J*=12.0 Hz, *J*=4.0 Hz, CH_2), 4.94 (1H, ddd, *J*=8.2 Hz, *J*=4.0 Hz, *J*=1.0 Hz, CH), 7.18–7.37 (2H, m, CH_{Ar}), 7.46–7.55 (1H, m, CH_{Ar}), 7.60 (1H, d, *J*=1.0 Hz, CH_{Ar}), 7.62–7.70 (1H, m, CH_{Ar}). ^{13}C NMR ($CDCl_3$) δ: 23.09 (CH_3), 23.28 (CH_3), 48.73(CH), 52.49 (CH_2), 65.66 (CH), 111.64, 120.39, 122.44, 122.54, 124.40, 126.25, 141.66, 155.78. *Anal.* Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.11; H, 7.68; N, 6.25.

(*S*)-(–)-1-(Benzofuran-3-yl)ethanol (14)

A solution of **10** (1.62 g, 10.1 mmol) in tetrahydrofuran (10 mL) was slowly added to a mixture of (–)-DIP-Cl (3.88 g, 12.1 mmol) and tetrahydrofuran (10 mL) at –30 °C under nitrogen. The mixture was stirred at this temperature for 24 h. ^{11}B NMR spectrum indicated no signal at δ 32 corresponding do DIP-Cl. Workup carried as described for **7** gave the product which was isolated by distillation, (1.14 g, 69.5%), bp 80–82 °C/0.1 mmHg. An analytical sample was further purified by preparative GC, $[\alpha]_D^{20}$ –20.76° (c 10.91, EtOH). HPLC analysis, Daicel Chiralcel OJ column, *n*–hexane/isopropanol (9 : 1) showed 90% ee. ^{1}H NMR ($CDCl_3$) δ: 1.64 (3H, d, *J*=4.4 Hz, CH_3), 2.10 (1H, s, OH), 5.14 (1H, q, *J*=4.4 Hz, CH), 7.22–7.34 (2H, m, CH_{Ar}), 7.47–7.50 (1H, m, CH_{Ar}), 7.55 (1H, m, CH_{Ar}), 7.69–7.72 (1H, m, CH_{Ar}).^{13}C NMR ($CDCl_3$) δ: 23.25 (CH_3), 62.96 (CH), 111.50, 120.40, 122.48, 124.36, 125.06, 126.02, 140.66, 155.62. *Anal.* Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: C, 74.00, H, 6.10. *p*-Nitrobenzoate (**14a**) mp 81–83 °C (from ethanol). ^{1}H NMR ($CDCl_3$) δ: 1.86 (3H, d, *J*=4.4 Hz, CH_3), 6.47 (1H, q, *J*=4.4 Hz, CH), 7.24–7.40 (2H, m, CH_{Ar}), 7.48–7.54 (1H, m, CH_{Ar}), 7.69–7.74 (1H, m, CH_{Ar}), 7.72 (1H, s, CH_{Ar}), 8.19–8.29 (4H, m, CH_{Ar}). ^{13}C NMR ($CDCl_3$) δ: 20.30 (CH_3), 66.82 (CH), 111.87, 120.20, 120.73, 123.00, 123.53 (2CH), 124.80, 125.76, 130.75 (2CH), 135.65, 142.36, 150.58, 155.67, 164.00 (C=O). *Anal.* Calcd for $C_{17}H_{13}NO_5$: C, 65,59; H, 4.21; N, 4.49. Found: C, 65.38; H, 4.10; N, 4.33. The crystal data and the X-Ray structure are shown on Scheme 2.

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