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Enantioselective reduction of benzofuryl halomethyl ketones: asymmetric synthesis of (*R*)-bufuralol

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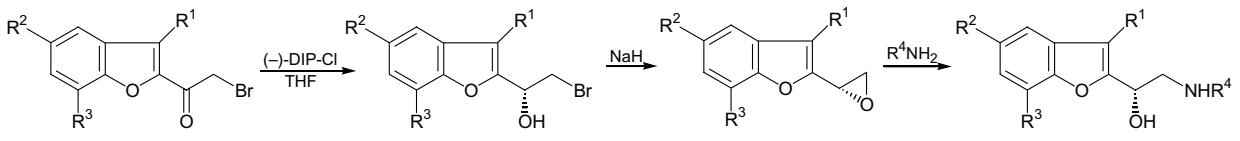
Abstract—Enantioselective reduction of representative 2-(bromoacetyl)- and 2-(chloroacetyl)benzofurans with (−)-*B*-chlorodiisopinocampheylborane and by transfer hydrogenation with formic acid/triethylamine in the presence of RhCl[*R*,*R*-TsDPEN](C$_5$Me$_5$) is described. Transfer hydrogenation of the chloro ketones produced the corresponding chlorohydrins of ⩾95% ee. (*R*)-Bufuralol of 96% ee was prepared from the corresponding chloro ketone by transfer hydrogenation–substitution.

1. Introduction

Recently, we reported the enantioselective synthesis of two important physiologically active benzofuryl β-amino-alcohols, (*S*)-bufuralol (*S*)-**1c** and a propafenone analogue (*S*)-**2c**.[1] Bufuralol is a nonselective β-adrenoceptor blocking agent of comparable potency to propranolol.[2–4] It is also a widely used substrate in studies of cytochrome P450 (CYP) enzymes, and undergoes enantio- and regioselective oxidation in the liver.[5] (*R*)-Bufuralol is a commonly used marker of hepatic CYP 2D6 activity.[6]

The key step in our syntheses of (*S*)-**1c** and (*S*)-**2c** was the reduction of bromo ketones **1** and **2** with (−)-*B*-chlorodiisopinocampheylborane [(−)-DIP-Cl], followed by a sequence of transformations bromohydrin–epoxide–β-amino alcohol (Scheme 1). However, the enantioselectivity of the reduction was only moderate, while the isolation of bromohydrins, (*R*)-**1a** and (*R*)-**2a**, required tedious purification and labile epoxides, (*S*)-**1b** and (*S*)-**2b**, had to be used as crude products for the reaction with amines.

It was clear that improvements in the methodology to achieve higher enantiomeric excess and modification of the approach to avoid the formation of labile epoxides were needed. Considering the first aim, we decided to examine the enantioselective reduction of representative 2-(chloroacetyl)benzofurans with (−)-DIP-Cl and by catalytic transfer hydrogenation introduced recently for the enantioselective reduction of ketones and derivatives.[7–13] For comparison, selected 2-(bromoacetyl)benzofurans were also reduced by transfer hydrogenation.



1 R^1, R^2= H; R^3= Et
2 R^1= CH_2CH_2Ph, R^2, R^3= H

(*R*)-**1a**
(*R*)-**2a**

(*S*)-**1b**
(*S*)-**2b**

(*S*)-**1c** R^4= *t*-Bu
(*S*)-**2c** R^4= *n*-Pr

Scheme 1.

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2. Results and discussion

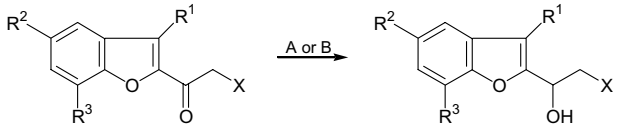
As reported earlier,[14] the reduction of 2-bromo-1-(benzofuran-2-yl)ethanone **3** with (−)-DIP-Cl produced the corresponding bromohydrin (*R*)-**3a** in 77% ee. The 3-methyl derivative **4** was reduced with higher enantioselectivity (88% ee, Table 1), whereas **2**, which had a more sterically demanding 2-phenylethyl substituent at the 3-position, reacted with lower selectivity (73% ee). The 7-ethyl derivative **1** afforded (*R*)-**1a** in 87% ee. The results indicate a moderate enantioselectivity of the reduction of bromo ketones **1**–**4** with (−)-DIP-Cl.

The reduction of unsubstituted chloro ketone **5** with (−)-DIP-Cl produced the corresponding chlorohydrin (*R*)-**5a** in 92% ee (Table 1). The selectivity is considerably higher when compared to the 77% ee obtained in the reduction of the corresponding bromo ketone **3**. Similarly, chloro ketones **6** and **7** were reduced with (−)-DIP-Cl to chlorohydrins (*R*)-**6a** and (*R*)-**7a** with higher enantioselectivity when compared to the reduction of the corresponding bromo ketones **4** and **1** (Table 1). On the other hand, >95% ee was achieved in the reduction of **7**.

While searching for a more selective reducing agent, we turned to the transfer hydrogenation. Complexes of rhodium and ruthenium with various chiral ligands find increasing applications as catalysts for the asymmetric transfer hydrogenation of ketones and derivatives.[7–13] 2-Propanol/potassium hydroxide or formic acid/triethylamine are the hydrogen sources most often used. Avoiding strong alkaline reaction conditions for our product halohydrins, we selected formic acid/triethylamine, 5:2, and RhCl[(*R*,*R*)-TsDPEN](C_5Me_5) catalyst for the reduction of halo ketones **1**–**10**. Reductions were run at room temperature and the reaction progress conveniently monitored by TLC analysis. The product halohydrins were readily isolated by column chromatography. The results are presented in Table 1.

The transfer hydrogenation of unsubstituted chloro ketone **5** produced chlorohydrin (*S*)-**5a** with 97% ee. The enantiomeric excess of chlorohydrins (*S*)-**5a**, (*S*)-**9a** and (*S*)-**10a** was >95% ee. Under the same conditions, the reduction of bromo ketones **1**, **3** and **4** proceeded with slightly lower enantioselectivity as compared to the corresponding chloro ketones **7**, **5** and **6**. The high enantiomeric excess obtained in the transfer hydrogenation of **2**, in contrast to much lower

Table 1. The reduction of halo ketones **1**–**10** with formic acid/triethylamine/RhCl[*R*,*R*-TsDPEN](C_5Me_5) in ethyl acetate, and with (–)-*B*-chlorodiisopinocampheylborane in tetrahydrofuran



1–10 **1a–10a**

Halo ketone					Reducing agent[a]	Time (h)	Product halohydrin		
Compound number	X	R^1	R^2	R^3			Conf.[b] and number	ee[c] (%)	Yield[d] (%)
1	Br	H	H	Et	A	72	(*S*)-**1a**	92	66
					B		(*R*)-**1a**	87[e]	64
2	Br	CH_2CH_2Ph	H	H	A	168	(*S*)-**2a**	96	90
					B		(*R*)-**2a**	73[e]	56
3	Br	H	H	H	A	96	(*S*)-**3a**	91	83
					B		(*R*)-**3a**	77[f]	23
4	Br	Me	H	H	A	72	(*S*)-**4a**	94	57
					B		(*R*)-**4a**	88	35
5	Cl	H	H	H	A	96	(*S*)-**5a**	97	84
					B		(*R*)-**5a**	92	82
6	Cl	Me	H	H	A	72	(*S*)-**6a**	97	76
					B		(*R*)-**6a**	90	94
7	Cl	H	H	Et	A	96	(*S*)-**7a**	98	85
					B		(*R*)-**7a**	98	61
8	Cl	Me	Me	H	A	72	(*S*)-**8a**	98	82
					B		(*R*)-**8a**	92	68
9	Cl	Me	H	Me	A	72	(*S*)-**9a**	96	77
					B		(*R*)-**9a**	86	35
10	Cl	Me	Et	H	A	120	(*S*)-**10a**	97	74

[a] A = HCOOH/NEt_3, 5:2, RhCl[*R*,*R*-TsDPEN](C_5Me_5), ethyl acetate, rt. B = (−)-*B*-Chlorodiisopinocampheylborane (Aldrich), THF, −25 °C, 2 h, rt, 12 h.

[b] Assignments based on the configuration of (*R*)-(−)-**1a**, Ref. 1; (*R*)-(−)-**2a**, Ref. 1 and (*R*)-(−)-**3a**, Ref. 14. Halohydrins with opposite signs of rotation were obtained from reagents A and B.

[c] HPLC or GC analysis on chiral columns as described in Section 4. Racemates were analyzed for comparison.

[d] Isolated yields.

[e] Ref. 1.

[f] Ref. 14.

selectivity in the reduction with (−)-DIP-Cl is noteworthy. In general, transfer hydrogenation of halo ketones **1**–**10** with formic acid/triethylamine/RhCl[*R*,*R*-TsDPEN](C_5Me_5) produced the corresponding halohydrins of higher enantiomeric excess as compared to the reduction with (−)-DIP-Cl. Isolation of the product halohydrins produced by transfer hydrogenation is simpler and the yields are higher.

The high enantiomeric excess obtained for chlorohydrin (*S*)-**7a** prompted us to transform it into (*R*)-bufuralol (*R*)-**1c** (Scheme 2), avoiding cyclization to the labile epoxide. Attempts to substitute the chlorine atom with a *tert*-butylamino group via the reaction of (*S*)-**7a** with *tert*-butylamine in several solvents were unsuccessful. Fortunately, the reaction worked well in ethanol providing (*R*)-**1c** with 96% ee, in 53% yield.

3. Conclusion

A convenient highly enantioselective reduction of benzofuryl chloromethyl ketones by transfer hydrogenation, producing the corresponding chlorohydrins, has been developed. (*R*)-Bufuralol of 96% ee was synthesized via the sequence chloro ketone–β-chlorohydrin–β-amino alcohol, circumventing the intermediate epoxide formation employed in the earlier syntheses.[1–3] The approach can be applied to asymmetric syntheses of other β-amino alcohols.

4. Experimental

4.1. General

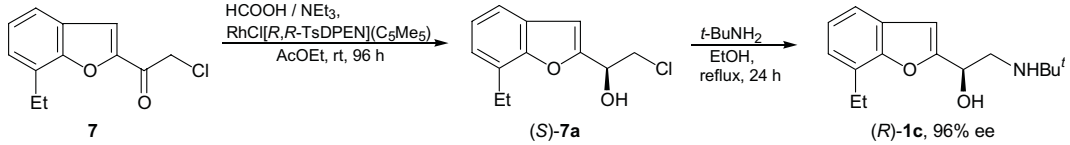
All reactions with air sensitive materials were carried under a nitrogen atmosphere in a glassware kept in an oven at 120 °C for 12 h, assembled hot, and cooled under nitrogen. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 and a Bruker AMX 300 spectrometers. Mass spectra were recorded on a AMD 604 mass spectrometer. IR spectra were recorded on a Perkin–Elmer Spectrum RX I instrument using sodium chloride plates. 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 performed on a Shimadzu VP liquid chromatograph equipped with a $UV_{254\,nm}$ detector and chiral columns: Daicel Chiralcel OJ, 250 × 4.6 mm, 10 μm and Daicel Chiralcel OD-H, 250 × 4.6 mm, 5 μm. Reactions were monitored by TLC using Macherey–Nagel Polygram Sil G/$UV_{254\,nm}$, 0.2 mm plates. Reaction products were purified by column chromatography on silica gel Merck grade 7734, 70–230 mesh. Rotations were measured on an Optical Activity Ltd, PolAAr 3000, automatic polarimeter. Elemental analyses were performed by the Microanalysis Laboratory, Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw, and by the Microanalysis Laboratory, Department of Chemistry, Nicolaus Copernicus University, Toruń.

4.2. Materials

(−)-*B*-Chlorodiisopinocampheylborane [(−)-DIP-Cl], >99% ee, was a commercial product (Aldrich). Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl. Triethylamine was distilled from lithium tetrahydridoaluminate. 3-Methylbenzofuran,[15] 3,5-dimethylbenzofuran,[16] 1-(benzofuran-2-yl)-2-chloroethanone,[17] 1-(benzofuran-2-yl)-2-bromoethanone,[18] 2-bromo-1-(3-methylbenzofuran-2-yl)ethanone,[15] 2-chloro-1-(7-ethylbenzofuran-2-yl)ethanone,[19] 2-bromo-1-(7-ethylbenzofuran-2-yl)ethanone,[1] 2-bromo-1-(3-phenethylbenzofuran-2-yl)ethanone,[1] RhCl[*R*,*R*-TsDPEN]-C_5Me_5),[10] were prepared according to the literature. 3,7-Dimethylbenzofuran, bp 118–120 °C/20 mmHg; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.25 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 6.89–7.11 (m, 2H, 2 × CH), 7.23–7.35 (m, 2H, 2 × CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 7.3 (CH_3), 14.9 (CH_3), 115.6 (C), 118.6 (CH), 121.0 (C), 123.1 (CH), 125.3 (CH), 129.2 (C), 140.3 (CH), 154.8 (C); 5-ethyl-3-methylbenzofuran, bp 51–53 °C/1.5 mmHg; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.25 (t, J = 7.6 Hz, 3H, CH_3), 1.99 (s, 3H, CH_3), 2.62 (q, J = 7.6 Hz, 2H, CH_2), 7.20–7.40 (m, 4H, 4 × CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 8.2 (CH_3), 16.0 (CH_2), 29.0 (CH_2), 111.7 (CH), 115.7 (C), 121.1 (CH), 124.1 (CH), 129.2 (C), 134.9 (C), 140.3 (CH), 151.3 (C), were prepared from 3,7-dimethylbenzofuran-2-yl carboxylic acid[20] and 5-ethyl-3-methylbenzofuran-2-yl carboxylic acid,[21] respectively, by decarboxylation with copper powder in quinoline at reflux for 8 h.

4.3. 2-Chloro-1-(3-methylbenzofuran-2-yl)ethanone 6

Aluminium chloride (4.67 g, 35 mmol) was added in portions to a stirred solution of 3-methylbenzofuran (3.97 g, 30 mmol) and chloroacetyl chloride (3.45 g, 30 mmol) in chloroform (50 mL) at −5 °C and stirring continued for 4 h at room temperature. The mixture was poured into water-ice and acidified with hydrochloric acid. The organic layer was separated and the aqueous layer extracted with chloroform (2 × 15 mL). The combined organic solutions were washed with a saturated solution of sodium hydrogencarbonate (20 mL) and dried with magnesium sulfate. The solvent was



Scheme 2.

removed and the product crystallized from cyclohexane, 3.05 g, 48% yield, mp 97–98 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.65 (s, 3H, CH_3), 4.78 (s, 2H, CH_2Cl), 7.29–7.38 (m, 1H, CH), 7.49–7.55 (m, 2H, 2 × CH), 7.68 (dt, $J = 7.8$, 0.9 Hz, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.5 (CH_3), 46.8 (CH_2), 112.2 (CH), 121.7 (CH), 123.6 (CH), 127.1 (C), 128.9 (C), 129.0 (CH), 146.0 (C), 154.2 (C), 187.7 (CO); MS (70 eV): *m/z* 210 (M+2, 6.6), 208 (M^+, 19.1), 160 (11.0), 159 (100.0), 103 (23.0), 102 (11.9), 77 (22.4), 51 (11.0); IR (KBr): 2935, 1693, 1576, 1397, 1251, 1129, 752. Anal. Calcd for $C_{11}H_9ClO_2$: C, 63.32; H, 4.35; Cl, 16.99. Found: C, 63.34; H, 4.34; Cl, 17.43.

4.4. 2-Chloro-1-(3,5-dimethylbenzofuran-2-yl)ethanone 8

Prepared from 3,5-dimethylbenzofuran following the procedure described for **6**, 36% yield, mp 99–100 °C (from methanol); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.47 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 4.76 (s, 2H, CH_2Cl), 7.30–7.40 (m, 2H, 2 × CH), 7.44–7.45 (m, 1H, CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 9.3 (CH_3), 21.2 (CH_3), 46.6 (CH_2), 111.6 (CH), 121.0 (CH), 126.7 (C), 129.0 (C), 130.5 (CH), 133.2 (C), 146.1 (C), 152.7 (C), 183.6 (CO); MS (70 eV): *m/z* 224 (M+2, 6.2), 222 (M^+, 19.1), 174 (11.9), 173 (100.0), 117 (10.2), 115 (24.5), 91 (11.1); IR (KBr): 2936, 1682, 1575, 1300, 1257, 1129, 722. Anal. Calcd for $C_{12}H_{11}ClO_2$: C, 64.73; H, 4.97; Cl, 15.92. Found: C, 64.94; H, 5.12; Cl, 15.82.

4.5. 2-Chloro-1-(3,7-dimethylbenzofuran-2-yl)ethanone 9

Prepared from 3,7-dimethylbenzofuran following the procedure described for **6**, 48% yield, mp 122–123 °C (from methanol); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.54 (s, 3H, CH_3), 2.63 (s, 3H, CH_3), 4.80 (s, 2H, CH_2Cl), 7.21–7.32 (m, 2H, 2 × CH), 7.48–7.51 (m, 1H, CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 9.5 (CH_3), 14.7 (CH_3), 46.7 (CH_2), 119.0 (CH), 122.4 (C), 123.6 (CH), 127.4 (C), 128.5 (C), 129.5 (CH), 145.8 (C), 153.4 (C), 183.7 (CO); MS (70 eV): *m/z* 224 (M+2, 6.6), 222 (M^+, 20.3), 174 (11.9), 173 (100.0), 117 (11.8), 115 (32.6), 91 (12.0); IR (KBr): 2936, 1689, 1579, 1252, 1124, 783, 751. Anal. Calcd for $C_{12}H_{11}ClO_2$: C, 64.73; H, 4.97; Cl, 15.92. Found: C, 64.34; H, 4.97; Cl, 15.80.

4.6. 2-Chloro-1-(5-ethyl-3-methylbenzofuran-2-yl)ethanone 10

Prepared from 5-ethyl-3-methylbenzofuran following the procedure described for **6**, 53% yield, bp 140–141 °C/1 mmHg, mp 63–64 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (t, $J = 7.6$ Hz, 3H, CH_3), 2.58 (s, 3H, CH_3), 2.77 (q, $J = 7.6$ Hz, 2H, CH_2), 4.75 (s, 2H, CH_2Cl), 7.23–7.48 (m, 3H, 3 × CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 9.4 (CH_3), 15.9 (CH_3), 28.7 (CH_2), 46.6 (CH_2), 111.8 (CH), 119.8 (CH), 126.9 (C), 129.0 (C), 129.5 (CH), 139.8 (C), 146.2 (C), 152.9 (C), 183.6 (CO); MS (70 eV): *m/z* 238 (M+2, 5.7), 236 (M^+, 17.5), 188 (13.6), 187 (100.0), 115 (16.3); IR (KBr): 2974, 1691, 1578, 1382, 1124, 828, 719. Anal. Calcd for $C_{13}H_{13}ClO_2$: C, 65.97; H, 5.53; Cl, 14.98. Found: C, 65.86; H, 5.58; Cl, 14.52.

4.7. (*S*)-(+)-1-(Benzofuran-2-yl)-2-chloroethanol (*S*)-5a. General procedure

To RhCl[*R*,*R*-TsDPEN](C_5Me_5) (1.4 mg, 0.0022 mmol) was added under nitrogen a solution of **5** (0.19 g, 1 mmol) in ethyl acetate (7 mL) and a mixture of formic acid/triethylamine (5:2, 0.3 mL), and the mixture stirred for 96 h at room temperature. The solvent was removed and the product isolated by column chromatography on silica gel (petroleum ether/diethyl ether, 3:2), 0.16 g, as an oil, 84% yield, $[\alpha]_D^{25} = +27.7$ (*c* 3.60, $CHCl_3$), 97% ee, determined by GC analysis on a Supelco Beta-DEX 325, 30 m × 0.25 mm, chiral column; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.79 (br s, 1H, OH), 3.92 (dd, $J = 11.4$, 6.6 Hz, 1H, CH_2Cl), 3.98 (dd, $J = 11.4$, 4.5 Hz, 1H, CH_2Cl), 5.09 (ddd, $J = 6.6$, 4.5, 0.9 Hz, 1H, CH), 6.77 (t, $J = 0.9$ Hz, 1H, CH), 7.21–7.35 (m, 2H, 2 × CH), 7.45–7.48 (m, 1H, CH), 7.55–7.58 (m, 1H, CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 47.5 (CH_2), 68.4 (CH), 104.3 (CH), 111.2 (CH), 121.2 (CH), 122.9 (CH), 124.5 (CH), 127.7 (C), 154.8 (C), 155.1 (C); IR (neat): 3391, 1454, 1253, 1172, 1085, 752. Anal. Calcd for $C_{10}H_9ClO_2$: C, 61.08; H, 4.61; Cl, 18.03. Found: C, 60.80; H, 4.68; Cl, 18.23.

4.8. (*R*)-(−)-1-(Benzofuran-2-yl)-2-chloroethanol (*R*)-5a. General procedure

A solution of **5** (1.95 g, 10 mmol) in tetrahydrofuran (10 mL) was added dropwise to a solution of (−)-DIP-Cl (3.85 g, 12 mmol) in tetrahydrofuran (10 mL) at −25 °C under nitrogen and the mixture stirred for 2 h, and then for 12 h at room temperature. Tetrahydrofuran was removed, diethyl ether (50 mL) was then added, followed by diethanolamine (4.20 g, 40 mmol) and the mixture was stirred for 2 h at room temperature. A white precipitate was filtered off and washed with diethyl ether (2 × 10 mL). The solvent was removed and the product was isolated by distillation, 1.60 g, 82% yield, bp 112–113 °C/1 mmHg, $[\alpha]_D^{20} = -26.0$ (*c* 5.10, $CHCl_3$), 92% ee, determined by GC analysis on a Supelco Beta-DEX 325, 30 m × 0.25 mm, chiral column; ^{1}H, ^{13}C NMR and IR spectra were the same as described above for its enantiomer.

4.9. (*S*)-(+)-2-Bromo-1-(7-ethylbenzofuran-2-yl)ethanol (*S*)-1a

Prepared from **1** following the procedure described for (*S*)-**5a**, isolated by column chromatography on silica gel (petroleum ether/diethyl ether, 3:2), as an oil, 66% yield, $[\alpha]_D^{20} = +33.0$ (*c* 9.35, $CHCl_3$), 92% ee, determined by HPLC analysis on Daicel Chiralcel OD-H, chiral column, *n*-hexane/isopropanol, 95:5; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.34 (t, $J = 7.5$ Hz, 3H, CH_3), 2.70 (d, $J = 6.0$ Hz, 1H, OH), 2.92 (q, $J = 7.5$ Hz, 2H, CH_2), 3.80 (dd, $J = 10.5$, 6.5 Hz, 1H, CH_2Br), 3.87 (dd, $J = 10.5$, 4.4 Hz, 1H, CH_2Br), 5.11 (dd, $J = 6.5$, 4.4 Hz, 1H, CH), 6.76 (d, $J = 1.0$ Hz, 1H, CH), 7.10–7.23 (m, 2H, 2 × CH), 7.40 (dd, $J = 7.5$, 1.8 Hz, 1H, CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0 (CH_3), 22.7 (CH_2), 36.5 (CH_2), 68.1 (CH), 104.3 (CH), 118.7 (CH), 123.1 (CH), 123.7 (CH), 127.4 (C), 127.7 (C), 153.4

(C), 155.0 (C); IR (neat): 3409, 2968, 1426, 1181, 748. Anal. Calcd for $C_{12}H_{13}BrO_2$: C, 53.55; H, 4.87. Found: C, 53.60; H, 4.82.

4.10. (*S*)-(+)-2-Bromo-1-[3-(2-phenylethyl)benzofuran-2-yl]ethanol (*S*)-2a

Prepared from **2** following the procedure described for (*S*)-**5a**, isolated by column chromatography on silica gel (petroleum ether/diethyl ether, 3:2), as an oil, 90% yield, 96% ee, determined by HPLC analysis on Daicel Chiralcel OD-H, chiral column, *n*-hexane/isopropanol, 95:5, and identified by comparison with (*R*)-**2a** prepared earlier[1]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.80 (d, $J = 4.2$ Hz, 1H, OH), 2.99–3.08 (m, 4H, $2 \times CH_2$), 3.19 (dd, $J = 10.5$, 5.4 Hz, 1H, CH_2Br), 3.55 (dd, $J = 10.5$, 8.1 Hz, 1H, CH_2Br), 4.64 (dd, $J = 8.1$, 5.4 Hz, 1H, CH), 7.01–7.04 (m, 2H, $2 \times CH$), 7.20–7.36 (m, 5H, $5 \times CH$), 7.44–7.47 (m, 1H, CH), 7.56–7.60 (m, 1H, CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.6 (CH_2), 34.8 (CH_2), 35.5 (CH_2), 66.6 (CH), 111.5 (CH), 116.9 (CH), 119.6 (CH), 122.6 (CH), 124.8 (CH), 126.3 (CH), 128.3 (C), 128.4 (CH), 128.7 (CH), 141.1 (C), 150.0 (C), 154.2 (C); IR (neat): 3546, 3027, 2926, 1453, 1261, 1199, 1077, 748, 699. Anal. Calcd for $C_{18}H_{17}BrO_2$: C, 62.62; H, 4.97. Found: C, 62.57; H, 4.81.

4.11. (*S*)-(+)-1-(Benzofuran-2-yl)-2-bromoethanol (*S*)-3a

Prepared from **3** following the procedure described for (*S*)-**5a**, isolated by column chromatography on silica gel (petroleum ether/diethyl ether, 3:2), as an oil, 83% yield, $[\alpha]_D^{20} = +15.9$ (*c* 5.03, $CHCl_3$), 91% ee, determined by HPLC analysis on Daicel Chiralcel OD-H, chiral column, *n*-hexane/isopropanol, 98:2; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.83 (br s, 1H, OH), 3.79 (dd, $J = 10.5$, 6.5 Hz, 1H, CH_2Br), 3.86 (dd, $J = 10.5$, 4.7 Hz, 1H, CH_2Br), 5.09 (t, $J = 4.9$ Hz, 1H, CH), 6.76 (t, $J = 0.9$ Hz, 1H, CH), 7.23–7.35 (m, 2H, $2 \times CH$), 7.44–7.51 (m, 1H, CH), 7.54–7.59 (m, 1H, CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 36.4 (CH_2), 68.0 (CH), 104.1 (CH), 111.2 (CH), 121.3 (CH), 122.9 (CH), 124.5 (CH), 127.7 (C), 154.7 (C), 155.3 (C); IR (neat): 3351, 1454, 1367, 1040, 1004, 750. Anal. Calcd for $C_{10}H_9BrO_2$: C, 49.82; H, 3.76. Found: C, 49.51; H, 3.67.

4.12. (*S*)-(+)-2-Bromo-1-(3-methylbenzofuran-2-yl)ethanol (*S*)-4a

Prepared from **4** following the procedure described for (*S*)-**5a**, isolated by column chromatography on silica gel (petroleum ether/diethyl ether, 3:2), as an oil, 57% yield, $[\alpha]_D^{20} = +44.6$ (*c* 3.92, $CHCl_3$), 94% ee, determined by HPLC analysis on Daicel Chiralcel OD-H, chiral column, *n*-hexane/isopropanol, 96:4; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.29 (s, 3H, CH_3), 2.71 (d, $J = 4.8$ Hz, 1H, OH), 3.73 (dd, $J = 10.4$, 5.6 Hz, 1H, CH_2Br), 3.84 (dd, $J = 10.4$, 7.6 Hz, 1H, CH_2Br), 5.11 (dd, $J = 7.6$, 5.6 Hz, 1H, CH), 7.21–7.35 (m, 2H, $2 \times CH$), 7.41–7.53 (m, 1H, CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 7.8 (CH_3), 35.6 (CH_2), 66.9 (CH), 111.2 (CH), 113.8 (C), 119.6 (CH), 122.5 (CH), 124.8 (CH), 129.5 (C), 149.0 (C), 153.9 (C); IR (neat): 3367, 2921, 1455, 1258, 1088, 1039, 746. Anal. Calcd for $C_{11}H_{11}BrO_2$: C, 51.79; H, 4.35. Found: C, 51.66; H, 4.30.

4.13. (*S*)-(+)-2-Chloro-1-(3-methylbenzofuran-2-yl)ethanol (*S*)-6a

Prepared from **6** following the procedure described for (*S*)-**5a**, isolated by column chromatography on silica gel (petroleum ether/diethyl ether, 3:2), as an oil, 76% yield, $[\alpha]_D^{25} = +12.4$ (*c* 3.22, $CHCl_3$), 97% ee, determined by GC analysis on a Supelco Beta-DEX 325, 30 m × 0.25 mm, chiral column; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.30 (s, 3H, CH_3), 2.63 (br s, 1H, OH), 3.86 (dd, $J = 11.1$, 5.4 Hz, 1H, CH_2Cl), 3.98 (dd, $J = 11.1$, 7.8 Hz, 1H, CH_2Cl), 5.10 (t, $J = 6.0$ Hz, 1H, CH), 7.24–7.34 (m, 2H, $2 \times CH$), 7.42–7.45 (m, 1H, CH), 7.49–7.52 (m, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 7.8 (CH_3), 47.1 (CH_2), 67.0 (CH), 111.2 (CH), 113.9 (C), 119.6 (CH), 122.5 (CH), 124.8 (CH), 129.5 (C), 148.8 (C), 153.9 (C); IR (neat): 3351, 2906, 1455, 1367, 1040, 1004, 745. Anal. Calcd for $C_{11}H_{11}ClO_2$: C, 62.71; H, 5.26; Cl, 16.83. Found: C, 62.55; H, 5.39; Cl, 16.78.

4.14. (*S*)-(+)-2-Chloro-1-(7-ethylbenzofuran-2-yl)ethanol (*S*)-7a

Prepared from **7** following the procedure described for (*S*)-**5a**, isolated by column chromatography on silica gel (petroleum ether/diethyl ether, 3:2), as an oil, 85% yield, $[\alpha]_D^{25} = +29.6$ (*c* 5.40, $CHCl_3$), 98% ee, determined by HPLC analysis on Daicel Chiralcel OD-H, chiral column, *n*-hexane/isopropanol, 80:20; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (t, $J = 7.5$ Hz, 3H, CH_3), 2.74 (d, $J = 5.1$ Hz, 1H, OH), 2.93 (q, $J = 7.5$ Hz, 2H, CH_2), 3.93 (dd, $J = 11.4$, 6.6 Hz, 1H, CH_2Cl), 3.99 (dd, $J = 11.4$, 4.2 Hz, 1H, CH_2Cl), 5.10 (dd, $J = 6.6$, 4.2 Hz, 1H, CH), 6.76 (d, $J = 0.9$ Hz, 1H, CH), 7.10–7.20 (m, 2H, $2 \times CH$), 7.40 (dd, $J = 7.5$, 1.5 Hz, 1H, CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0 (CH_3), 22.7 (CH_2), 47.6 (CH_2), 68.5 (CH), 104.4 (CH), 118.7 (CH), 123.1 (CH), 123.7 (CH), 127.4 (C), 127.7 (C), 153.4 (C), 154.7 (C); IR (neat): 3393, 2968, 1427, 1180, 1087, 821, 747. Anal. Calcd for $C_{12}H_{13}ClO_2$: C, 64.15; H, 5.83; Cl, 15.78. Found: C, 64.06; H, 5.91; Cl, 15.57.

4.15. (*S*)-(+)-2-Chloro-1-(3,5-dimethylbenzofuran-2-yl)-ethanol (*S*)-8a

Prepared from **8** following the procedure described for (*S*)-**5a**, isolated by column chromatography on silica gel (petroleum ether/diethyl ether, 3:2), an oil, 82% yield, $[\alpha]_D^{25} = +17.1$ (*c* 5.26, $CHCl_3$), 98% ee, determined by GC analysis on a Supelco Beta-DEX 325, 30 m × 0.25 mm, chiral column; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.26 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 2.67 (br s, 1H, OH), 3.84 (dd, $J = 11.1$, 5.4 Hz, 1H, CH_2Cl), 3.97 (dd, $J = 11.1$, 7.8 Hz, 1H, CH_2Cl), 5.06 (dd, $J = 7.8$, 5.4 Hz, 1H, CH), 7.11 (dd, $J = 8.4$, 1.8 Hz, 1H, CH), 7.26–7.32 (m, 2H, $2 \times CH$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 7.7 (CH_3), 21.2 (CH_3), 47.1 (CH_2), 67.1 (CH), 110.6 (CH), 113.6 (CH), 119.3 (CH), 125.9 ($2 \times CH$), 129.5 (C), 131.9 (C), 148.9 (C), 152.3 (C); IR (neat): 3546, 2921, 1475, 1455, 1266, 1203, 1089, 1057, 834, 801. Anal. Calcd

for $C_{12}H_{13}ClO_2$: C, 64.15; H, 5.83; Cl, 15.78. Found: C, 64.10; H, 5.84; Cl, 15.73.

4.16. (*S*)-(+)-2-Chloro-1-(3,7-dimethylbenzofuran-2-yl)-ethanol (*S*)-9a

Prepared from **9** following the procedure described for (*S*)-**5a**, isolated by column chromatography on silica gel (petroleum ether/diethyl ether, 3:2), as an oil, 77% yield, $[\alpha]_D^{25} = +8.1$ (*c* 4.91, $CHCl_3$), 96% ee, determined by GC analysis on a Supelco Beta-DEX 325, 30 m × 0.25 mm, chiral column; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.28 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 2.62 (d, $J = 4.5$ Hz, 1H, OH), 3.87 (dd, $J = 11.1$, 5.4 Hz, 1H, CH_2Cl), 4.00 (dd, $J = 11.1$, 7.8 Hz, 1H, CH_2Cl), 5.09 (dd, $J = 7.8$, 5.4 Hz, 1H, CH), 7.09–7.18 (m, 2H, 2 × CH), 7.32–7.35 (m, 1H, CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 7.8 (CH_3), 14.8 (CH_3), 47.1 (CH_2), 67.2 (CH), 114.1 (CH), 116.9 (CH), 121.4 (C), 122.5 (CH), 125.7 (CH), 129.0 (C), 148.6 (C), 153.0 (C); IR (neat): 3350, 2922, 1453, 1367, 1040, 1003, 746. Anal. Calcd for $C_{12}H_{13}ClO_2$: C, 64.15; H, 5.83; Cl, 15.78. Found: C, 63.85; H, 5.89; Cl, 15.19.

4.17. (*S*)-(+)-2-Chloro-1-(5-ethyl-3-methylbenzofuran-2-yl)ethanol (*S*)-10a

Prepared from **10** following the procedure described for (*S*)-**5a**, isolated by column chromatography on silica gel (petroleum ether/diethyl ether, 3:2), as an oil, 74% yield, $[\alpha]_D^{25} = +9.4$ (*c* 5.30, $CHCl_3$), 97% ee, determined by GC analysis on a Supelco Beta-DEX 325, 30 m × 0.25 mm, chiral column; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (t, $J = 7.6$ Hz, 3H, CH_3), 2.27 (s, 3H, CH_3), 2.60 (d, $J = 5.1$ Hz, 1H, OH), 2.75 (q, $J = 7.6$ Hz, 2H, CH_2), 3.84 (dd, $J = 11.0$, 5.3 Hz, 1H, CH_2Cl), 3.97 (dd, $J = 11.0$, 7.8 Hz, 1H, CH_2Cl), 5.07 (dd, $J = 7.8$, 5.3 Hz, 1H, CH), 7.14 (dd, $J = 8.4$, 1.8 Hz, 1H, CH), 7.30–7.35 (m, 2H, 2 × CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 7.7 (CH_3), 15.1 (CH_3), 28.8 (CH_2), 47.1 (CH_2), 67.1 (CH), 110.8 (CH), 113.8 (C), 118.1 (CH), 125.0 (CH), 129.5 (C), 138.7 (C), 148.9 (C), 152.5 (C); IR (neat): 3528, 2964, 1474, 1455, 1267, 1090, 812. Anal. Calcd for $C_{13}H_{15}ClO_2$: C, 65.41; H, 6.33; Cl, 14.85. Found: C, 65.25; H, 6.31; Cl, 14.86.

4.18. (*R*)-(+)-2-*tert*-Butylamino-1-(7-ethylbenzofuran-2-yl)ethanol (*R*)-1c

To a solution of (*S*)-**7a** (0.18 g, 0.8 mmol) in absolute ethanol (10 mL) was added *tert*-butylamine (0.20 g, 2.8 mmol) and the mixture refluxed for 24 h. The solvent and excess *tert*-butylamine were removed under vacuum and diethyl ether (20 mL) was added. The solution was washed with 10% sodium hydroxide (5 mL), water (5 mL), and dried with anhydrous magnesium sulfate. The solvent was removed and the product isolated by column chromatography on silica gel (petroleum ether/ethyl acetate/diethyl ether/methanol/triethylamine, 6:4:1:0.5:0.2), 0.11 g, 53%, mp 57–58 °C, 96% ee, determined by HPLC analysis on Daicel Chiralcel OD-H, chiral column, *n*-hexane/isopropanol, 95:5, and identified by comparison with (*S*)-**1c** prepared earlier[1]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12 (s, 9H, 3 × CH_3), 1.34 (t, $J = 7.5$ Hz, 3H, CH_3), 2.92 (q, $J = 7.5$ Hz, 2H, CH_2), 3.00 (dd, $J = 12.0$, 6.0 Hz, 1H, NCH_2), 3.06 (dd, $J = 12.0$, 4.5 Hz, 1H, NCH_2), 4.80 (ddd, $J = 6.0$, 4.5 Hz, $J = 0.9$ Hz, 1H, CH), 6.66 (d, $J = 0.9$ Hz, 1H, CH), 7.06–7.17 (m, 2H, 2 × CH), 7.37 (dd, J= 7.5, 1.5 Hz, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (CH_3), 22.8 (CH_2), 29.1 (3 × CH_3), 46.2 (C), 50.3 (CH_2), 66.5 (CH), 103.1 (CH), 118.4 (CH), 122.8 (CH), 123.0 (CH), 127.6 (C), 127.8 (C), 153.4 (C), 158.3 (C).

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