Tetrahedron: *Asymmetry* 20 (2009) 1138–1143

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Asymmetric synthesis of β-dialkylamino alcohols by transfer hydrogenation of α-dialkylamino ketones

Tomasz Kosmalski, Andrzej Wojtczak, Marek Zaidlewicz *

Faculty of Chemistry, Nicolaus Copernicus University, 7 Gagarin St., Torun, Poland

ARTICLE INFO

Article history:
Received 13 February 2009
Accepted 18 March 2009
Available online 22 April 2009

ABSTRACT

Transfer hydrogenation of representative aryl and heteroaryl dialkylaminomethyl ketones with formic acid–triethylamine, catalyzed by RuCl[(*R*,*R*)-TsDPEN](η-*p*-cymene), produces the corresponding β-dialkylamino alcohols, 97–99% ee, in 50–73% yields. Asymmetric synthesis of (*R*)-macromerine, 98% ee, the cactus *Coryphantha macromeris* alkaloid, is also described.

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1. Introduction

Chiral β-amino alcohols are widely used as auxiliaries and ligands,[1–4] components of oxazaborolidines,[5,6] and are also important physiologically active compounds.[7,8] Various syntheses of pure enantiomers, by aminohydroxylation of olefins,[9] catalytic hydrogenation of α-functionalized ketones,[10] their reduction with hydrides,[11–13] borane/oxazaborolidines,[5,6] and by other approaches,[14–18] have been developed. Resolution of racemic β-amino alcohols, enzymatic reductions, and catalytic enantioselective hydrogenation of α-amino ketones have been applied on an industrial scale.[19] An attractive alternative to the aforementioned reductive methods is the asymmetric transfer hydrogenation of α-functionalized ketones, due to its simplicity and avoiding the use of dihydrogen under pressure, and employing phosphine-free catalysts.[1,2,10,20–23]

In our earlier asymmetric syntheses of β-amino alcohols, the reduction of α-halo ketones with chlorodiisopinocampheylborane or by transfer hydrogenation with formic acid–triethylamine, catalyzed by RhCl[(*R*,*R*)-TsDPEN](C_5Me_5) was used.[24,25] The product β-halohydrins were transformed into the corresponding β-amino alcohols by treatment with amines or via the intermediate epoxides. However, these reactions are not always highly regioselective, and mixtures of isomeric β-amino alcohols are often produced.[11,20,26,27] Consequently, transfer hydrogenation of α-amino ketones, leading directly to β-amino alcohols, is highly desirable. Very recently, it was employed for the highly enantioselective reduction of α-imidazole-substituted acetophenone.[1,28]

In this study we focused on the transfer hydrogenation of representative dialkylaminomethyl ketones with formic acid–triethylamine 5:2, catalyzed by RuCl[(*R*,*R*)-TsDPEN](η-*p*-cymene). The product amino alcohols are useful synthetic intermediates, for example, β-dimethylamino alcohols can be readily transformed into the corresponding epoxides,[14] and β-alkyl(benzyl)amino alcohols are intermediates in the industrial synthesis of β-alkylamino alcohols.[19] Certain β-dialkylamino alcohols are physiologically active.[29–32]

2. Results and discussion

Aryl and heteroaryl dialkylaminomethyl ketones **1**–**8**, **10**, and **11** were prepared from the corresponding methyl ketones by bromination followed by treatment of the product α-bromo ketones with secondary amines. 2-Benzofuryl and 2-furyl amino ketones **6**–**8** are not stable for prolonged periods, and should be freshly prepared. The reduction reactions were carried out with formic acid–triethylamine 5:2 in the presence of RuCl[(*R*,*R*)-TsDPEN](η-*p*-cymene) catalyst in ethyl acetate at room temperature. The substrate/catalyst ratio was 400. The product β-amino alcohols were isolated by column chromatography, crystallization or distillation. The results are presented in Table 1.

The pyrrolidino- and piperidino-substituted ketones **3** and **4** react faster when compared to other amino ketones as shown in Table 1. On the other hand, the presence of the sterically demanding dibenzylamino group prevents the reduction of **10**. Yields of the product β-amino alcohols (50–73%) indicate that the catalyst is not deactivated by the amino ketones or the reaction products. Aryl and heteroaryl aminomethyl ketones **1**–**8** are reduced with high enantioselectivity (>95% ee), however, the simplest alkyl diethylaminomethyl ketone **9** is reduced with much lower enantioselectivity producing **9a**, 60% ee. The same configurations of the product amino alcohols **1a**–**5a** indicate similar orientations of the corresponding amino ketones approaching the catalyst. The (*S*)-configurations of **6a**–**8a** reflect the nomenclature priority of benzofuryl and furyl groups over the aminomethyl moiety, opposite to the aryl groups of **1a**–**5a**. The configuration assignments for **1a**–**4a** are based on comparison of the signs of the specific rotation with the literature data. The assignments for naphthyl and

* Corresponding author. Fax: +48 56 6542477.
E-mail address: zaidlevi@chem.uni.torun.pl (M. Zaidlewicz).

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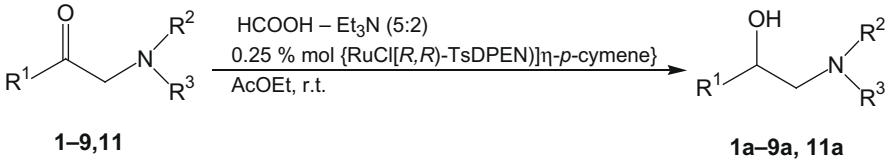
doi:10.1016/j.tetasy.2009.03.014

Table 1
Asymmetric transfer hydrogenation of amino ketones **1**–**11**, catalyzed with RuCl[(*R*,*R*)-TsDPEN)]η-*p*-cymene in ethyl acetate at room temperature



1–9,11 **1a–9a, 11a**

No.	Amino ketone			Time, days	Amino alcohol			
	R^1	R^2	R^3			Yield[a] (%)	ee (%)	Conf.
1	Ph	Me	Me	5	**1a**	58	97[b]	(*R*)[d]
2	Ph	Et	Et	6	**2a**	73	98[b]	(*R*)[d]
3	Ph	$(CH_2)_4$		3	**3a**	57	99[b]	(*R*)[d]
4	Ph	$(CH_2)_5$		3	**4a**	63	99[b]	(*R*)[d]
5	2-Naphthyl	Me	Me	6	**5a**	60	98[c]	(*R*)[e]
6	2-Benzofuryl	Me	Me	5	**6a**	69	98[c]	(*S*)[e]
7	2-Benzofuryl	$(CH_2)_2O(CH_2)_2$		7	**7a**	62	97[c]	(*S*)[e]
8	2-Furyl	Me	Me	5	**8a**	61	98[c]	(*S*)[f]
9	Me	Et	Et	7	**9a**	50	60[b]	(*R*)[d]
10	Ph	Bn	Bn	7	n.r.			
11	3,4-$(MeO)_2C_6H_3$	Me	Me	7	**11a**	55	98[c]	(*R*)[d]

[a] Isolated.
[b] Determined by GC on a chiral column, Supelco Beta-DEX 325, 30 m × 0.25 mm. Racemates were also analyzed.
[c] Determined by HPLC on a chiral column, Daicel Chiralcel OD-H, 250 × 4.6 mm, 5 μm. Racemates were also analyzed.
[d] Assigned by comparison of the sign of rotation with the literature data (see Section 4).
[e] Assigned by X-ray analysis.
[f] Assignment is based on the close structural similarity to **6a** and **7a**, and the same sign of rotation.

benzofuryl amino alcohols **5a**–**7a** follow from X-ray analyses of their crystals (Figs. 1–3). The (*S*)-configuration of 2-furyl amino alcohol **8a** is based on the same sign of rotation and close structural similarity to **6a** and **7a**.

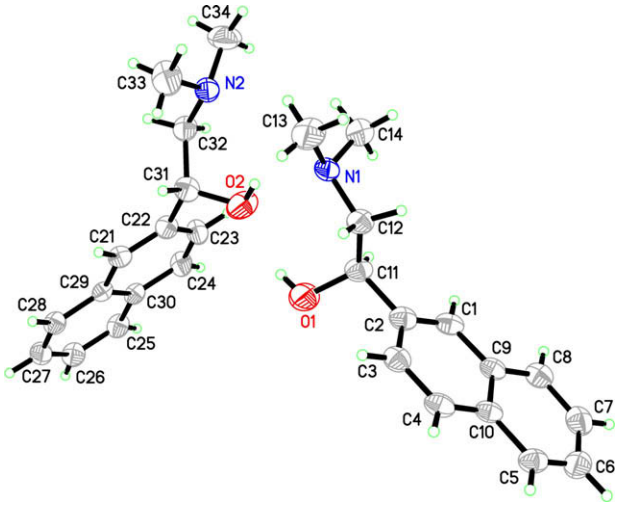


Figure 1. The X-ray structure of **5a**.

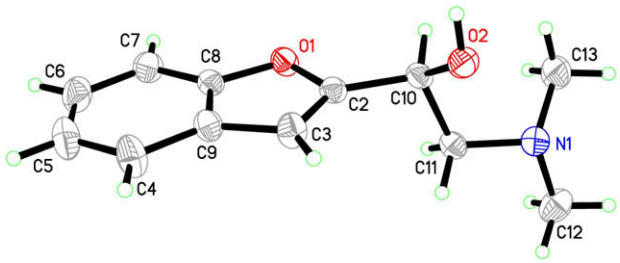


Figure 2. The X-ray structure of **6a**.

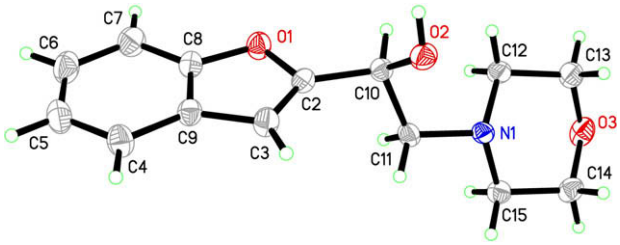
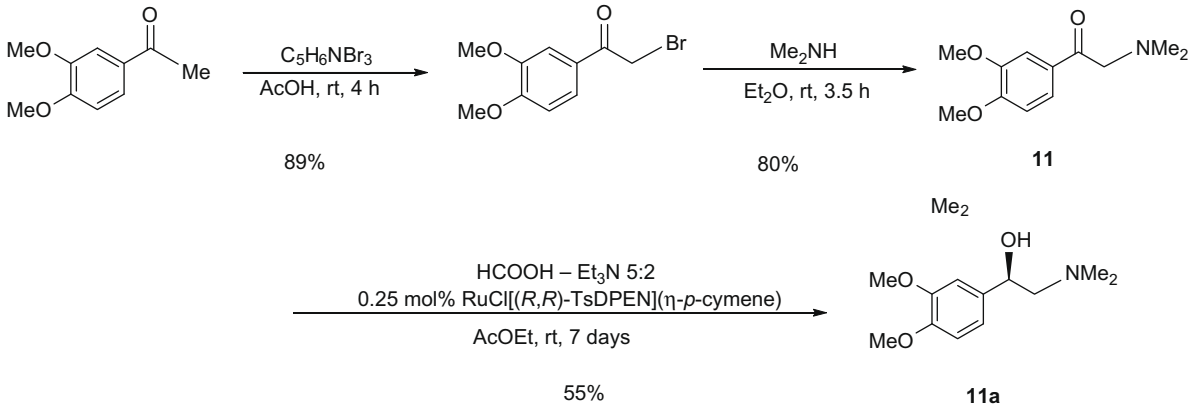


Figure 3. The X-ray structure of **7a**.

High enantioselectivity of the reduction of dialkylaminomethyl ketones described above, prompted us to apply the method to the synthesis of (*R*)-(−)-macromerine **11a**, which occurs in cactus *Coryphantha macromeris*, exhibits a hallucinogenic activity,[33] and is structurally related to (*R*)-(−)-adrenaline. The synthesis started from 3,4-dimethoxyacetophenone, which was brominated with pyridinium perbromide, followed by treatment with dimethylamine, and transfer hydrogenation of 1-(3,4-dimethoxyphenyl)-2-(dimethylamino)ethanone **11** producing **11a**, 98% ee, in an overall 39% yield (Scheme 1).

3. Conclusion

Asymmetric transfer hydrogenation of dialkylaminomethyl aryl and heteroaryl ketones with high enantioselectivity has been achieved using formic acid–triethylamine and RuCl[(*R*,*R*)-TsDPEN](η-*p*-cymene) catalyst. The method provides direct access to the corresponding β-amino alcohols, avoiding the formation of regioisomeric amino alcohols observed in the reaction of β-halohydrins with secondary amines. It was applied to the synthesis of (*R*)-(−)-macromerine, 98% ee, the cactus *C. macromeris* alkaloid.



Scheme 1.

4. Experimental

4.1. General

Experiments with air and moisture sensitive materials were carried under an argon atmosphere. Glassware was oven dried for several hours, assembled hot, and cooled in a steam of argon. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 multinuclear instrument and on a Bruker AMX 300 MHz instrument. MS spectra were recorded on an AMD 604 spectrometer. Optical rotations were measured on an Optical Activity PolAAr 3000 automatic polarimeter. GC analyses were performed on a Perkin–Elmer Auto System XL chromatograph, and HPLC analyses on a Shimadzu LC-10AT chromatograph. X-ray analyses were performed on an Oxford Sapphire CCD diffractometer, using Mo Kα radiation $\lambda = 0.71073$ Å, by $\omega - 2\theta$ method. Melting points were determined in open glass capillaries and are uncorrected. Elemental analyses were performed by the Microanalysis Laboratory, Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw.

4.2. Materials

Silica Gel 60, Merck 230–400 mesh was used for preparative column chromatography. Macherey-Nagel Polygram Sil G/UV254 0.2 mm plates were used for analytical TLC. Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl. RuCl[(*R*,*R*)-TsDPEN](η-*p*-cymene) was prepared from $[RuCl_2(\eta\text{-}p\text{-cymene})]_2$ and (1*R*,2*R*)-*N*-*p*-tolylsulfonyl-1,2-diphenylethylenediamine (TsDPEN) according to the literature.[34]

4.3. 2-(Dimethylamino)-1-phenylethanone 1

Prepared from 1-phenyl-2-bromoethanone and dimethylamine in benzene/diethyl ether, 12 h, room temperature, 60% yield, bp 76–78 °C/0.5 mmHg. Lit.[35] 130–132 °C/20 mmHg. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38 (s, 6H, CH_3), 3.76 (s, 2H, CH_2), 7.45 (tm, $J = 7.2$ Hz, 2H, CH), 7.56 (tt, $J = 7.2$, 1.5 Hz, 1H, CH), 7.99 (ddd, $J = 7.2$, 2.1, 1.5 Hz, 2H, CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.83 (2 NCH_3), 65.61 (CH_2N), 128.09 (2CH), 128.53 (2CH), 133.16 (CH), 135.99 (C), 196.84 (CO).

4.4. 2-(Diethylamino)-1-phenylethanone 2

Prepared from 1-phenyl-2-bromoethanone and diethylamine in benzene/diethyl ether, 45 °C, 30 h, 67% yield, bp 88–90 °C/0.5 mmHg. Lit.[35] bp 85 °C/0.2 mmHg. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (t, $J = 7.2$ Hz, 6H, CH_3), 2.71 (q, $J = 7.2$ Hz, 4H, CH_2), 3.92 (s, 2H, CH_2N), 7.58–7.42 (m, 3H, CH), 8.00 (dm, $J = 7.5$ Hz, 2H, CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.75 (2CH_3), 47.69 (2NCH_2), 59.61 (NCH_2), 128.06 (CH), 128.33 (CH), 132.90 (CH), 136.18 (C), 198.13 (CO).

4.5. 1-Phenyl-2-(pyrrolidin-1-yl)ethanone 3

Prepared from 1-phenyl-2-bromoethanone and pyrrolidine in benzene/diethyl ether, 45 °C, 6 h, 41% yield, bp 100–102 °C/0.5 mmHg. Lit.[36] bp 88–89/0.1 mmHg ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84 (m, 4H, CH_2), 2.68 (m, 4H, CH_2), 3.99 (s, 2H, CH_2N), 7.45 (tm, $J = 7.5$ Hz, 2H, CH), 7.55 (tt, $J = 7.5$, 1.5 Hz, 1H, CH), 7.99 (dm, $J = 7.2$ Hz, 2H, CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.66 (2CH_2), 54.34 (2CH_2N), 62.34 (CH_2N), 127.96 (2CH), 128.51 (2CH), 133.06 (CH), 136.00 (C), 196.75 (CO).

4.6. 1-Phenyl-2-(piperidin-1-yl)ethanone 4

Prepared from 1-phenyl-2-bromoethanone and piperidine in benzene/diethyl ether, 45 °C, 9 h, 79% yield, bp 110–112 °C/0.3 mmHg. Lit.[35] bp 134–136 °C/1 mmHg. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (quintet, $J = 5.4$ Hz, 2H, CH_2), 1.64 (quintet, $J = 5.4$ Hz, 4H, CH_2), 2.53 (t, $J = 5.4$ Hz, 4H, CH_2), 3.77 (s, 2H, CH_2N), 7.44 (tdd, $J = 7.5$, 2.1, 1.5 Hz, 2H, CH), 7.56 (tt, $J = 7.5$, 1.5 Hz, 1H, CH), 8.02 (ddd, $J = 7.2$, 2.1, 1.5 Hz, 2H, CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.96 (CH_2), 25.77 (2CH_2), 54.83 (2CH_2N), 65.32 (CH_2N), 128.14 (2CH), 128.44 (2CH), 133.05 (CH), 136.23 (C), 196.85 (CO).

4.7. 2-(Dimethylamino)-1-(2-naphthyl)ethanone 5

Prepared from 1-(2-naphthyl)-2-bromomethanone and dimethylamine in diethyl ether, −10 °C, 30 min, room temperature, 4 h, 86% yield, hydrochloride mp 215–217 °C. Lit.[37] mp 216–217 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 6H, CH_3), 3.91 (s, 2H, CH_2N), 7.54 (td, $J = 7.5$, 1.5 Hz, 1H, CH), 7.60 (td, $J = 7.5$, 1.5 Hz, 1H, CH), 7.82–7.92 (m, 2H, CH), 7.96 (dm, $J = 8.7$ Hz, 1H, CH), 8.04 (dd, $J = 8.7$, 1.8 Hz, 1H, CH), 8.54 (d, $J = 1.5$ Hz, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.73 (2CH_3), 65.53 (CH_2N), 123.76 (CH), 126.62 (CH), 127.64 (CH), 128.25 (CH), 128.35 (CH), 129.48 (CH), 129.62 (CH), 132.34 (C), 133.22 (C), 135.52 (C), 196.66 (CO).

4.8. 1-(2-Benzofuryl)-2-(dimethylamino)ethanone 6

Prepared from 1-(2-benzofuranyl)-2-bromoethanone and dimethylamine in diethyl ether, −10 °C, 15 min, 10 °C, 20 min,

80% yield, 100–105 °C/0.05 mmHg. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 6H, CH_3), 3.75 (s, 2H, CH_2), 7.31 (ddd, J = 7.8, 7.2, 1.2 Hz, 1H, CH), 7.47 (ddd, J = 7.2, 1.2, 7.0 Hz, 1H, CH), 7.57 (ddd, J = 7.4, 1.8, 0.9 Hz, 1H, CH), 7.66 (d, J = 0.9 Hz, 1H, CH), 7.70 (ddd, J = 7.4, 1.2, 0.9 Hz, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.88 ($2CH_3$), 65.50 (CH_2), 112.40 (CH), 113.44 (CH), 123.33 (CH), 123.90 (CH), 126.90 (C), 128.31 (CH), 151.67 (C), 155.44 (C), 188.18 (CO). HRMS (ESI) $[M+H]^+$, found 204.1011, $C_{12}H_{13}NO_2$, requires 204.1019.

4.9. 1-(2-Benzofuryl)-2-(morpholin-4-yl)ethanone 7

Prepared from 1-(2-benzofuryl)-2-bromoethanone and morpholine in diethyl ether, room temperature, 4 h, 59% yield, mp 101–103 °C (from diethyl ether). Lit.[38] mp 101.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.65 (dd, J = 3.6, 1.8 Hz, 4H, CH_2), 3.80 (dd, J = 4.8, 1.8 Hz, 4H, CH_2), 3.81 (s, 2H, CH_2N), 7.32 (ddd, J = 7.8, 6.9, 1.5 Hz, 1H, CH), 7.49 (ddd, J = 7.8, 7.4, 1.5 Hz, 1H, CH), 7.58 (ddd, J = 7.8, 1.8, 1.2 Hz, 1H, CH), 7.69 (d, J = 0.9 Hz, 1H, CH), 7.72 (ddd, J = 7.8, 1.8, 0.9 Hz, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.84 ($2CH_2N$), 64.55 (CH_2N), 66.75 ($2CH_2O$), 112.39 (CH), 113.54 (CH), 123.35 (CH), 123.96 (CH), 126.82 (C), 128.43 (CH), 151.59 (C), 155.44 (C), 187.41 (CO).

4.10. 1-(2-Furyl)-2-(dimethylamino)ethanone 8

Prepared from 1-(2-furyl)-2-bromoethanone and dimethylamine in diethyl ether, 0 °C, 10 min, room temperature, 30 min, 46% yield, bp 58–59 °C/0.20 mmHg. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 6H, CH_3), 3.62 (s, 2H, CH_2), 6.52 (dd, J = 1.8, 3.6 Hz, 1H, CH), 7.30 (dd, J = 0.9, 3.6 Hz, 1H, CH), 7.57 (dd, J = 0.9, 1.8 Hz, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.69 (CH_3), 64.72 (CH_2), 112.00 (HC_{Ar}), 117.49 (HC_{Ar}), 146.21 (HC_{Ar}), 151.70 (C), 185.97 (CO). MS (EI, 70 eV) *m/z*: 153 (M^+, 2), 112 (16), 95 (30), 58 (100). HRMS (EI): $[M^+]$, found 153.0783, $C_8H_{11}NO_2$ requires 153.0790.

4.11. 1-*N*,*N*-Diethylamino-2-propanone 9

Prepared from chloroacetone and diethylamine in diethyl ether, reflux 24 h, 65% yield, bp 155–157 °C/760 mmHg. Lit.[39] bp 154–158 °C/760 mmHg. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.01 (t, J = 7.2 Hz, 6H, CH_3), 2.15 (t, J = 0.4 Hz, 3H, CH_3), 2.53 (q, J = 7.2 Hz, 4H, CH_2), 3.80 (s, 2H, CH_2N). ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.88 ($2CH_3$), 27.36 (CH_3), 48.04 ($2NCH_2$), 63.89 (CH_2N), 209.13 (CO).

4.12. 2-(Dibenzylamino)-1-phenylethanone 10

Prepared from 1-phenyl-2-bromoethanone and dibenzylamine in benzene, reflux 24 h, 41% yield, mp 78–79 °C (from *n*-hexane). Lit.[40] mp 79–81 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 (s, 4H CH_2), 3.85 (s, 2H, CH_2), 7.22–7.56 (m, 13H, CH), 7.83 (d, J = 7.2 Hz, 2H, CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 58.319 (CH_2N), 59.23 ($2CH_2$), 127.16 (CH), 128.26 (CH), 128.30 (CH), 128.70 (CH), 129.12 (CH), 133.01 (CH), 136.10 (C), 138.79 (C), 198.93 (CO).

4.13. 1-(3,4-Dimethoxyphenyl)-2-(dimethylamino)ethanone 11

Prepared from 1-(3,4-dimethoxyphenyl)-2-bromoethanone and dimethylamine in diethyl ether, 3.5 h, room temperature, 55% yield, hydrochloride hydrate, mp 98–100 °C. Lit.[33] mp 100 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.37 (s, 6H, CH_3), 3.72 (s, 2H, CH_2), 3.924 (d, J = 0.2 Hz, 3H, OCH_3), 3.930 (d, J = 0.2 Hz, 3H, OCH_3), 6.86 (d, J = 8.2 Hz, 1H), 7.55 (d, J = 2.2 Hz, 1H), 7.66 (dd, J = 8.2, 2.2 Hz, 1H, CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ 45.72 (NCH_3), 55.97 (OCH_3), 56.03 (OCH_3), 65.30 (CH_2), 110.09 (CH), 110.53 (CH), 122.80 (CH), 129.38 (C), 149.10 (C), 153.44 (C), 195.40 (CO).

4.14. (*R*)-(−)-2-(Dimethylamino)-1-(phenyl)ethanol 1a: typical procedure

To a solution of **1** (1.63 g, 10 mmol) in ethyl acetate (5 mL), RuCl[(*R*,*R*)-TsDPEN](η-*p*-cymene) (20 mg, 0.02 mmol), triethylamine (0.1 mL), and an azeotrope mixture of formic acid–triethylamine 5:2 (2.5 mL) were added under argon at room temperature. The brown-red mixture was stirred for 5 days. The solvent was removed under reduced pressure, 2 M sodium hydroxide (10 mL) was added, and the mixture was extracted with diethyl ether (2 × 40 mL). The extract was washed with water (10 mL), saturated brine (5 mL), and dried with anhydrous magnesium sulfate. The product was isolated by distillation 0.95 g, 58% yield, bp 66–68 °C/1 mmHg. An analytical sample was purified by preparative gas chromatography, $[\alpha]_D^{28} = -72.3$ (*c* 1.536, MeOH). Lit.[41] (*S*)-isomer, $[\alpha]_D^{21} = +74.8$ (*c* 0.95, MeOH). GC analysis on a chiral column Supelco Beta-DEX 325, 30 m, 0.25 mm, isotherm 105 °C, 97% ee, t_R 44.5 *R*, 45.9 *S*. The racemate was also analyzed. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 6H, CH_3), 2.37 (dd, J = 12.2, 3.8 Hz, 1H, CH_2N), 2.49 (dd, J = 12.2, 10.2 Hz, 1H, CH_2N), 3.95 (br s, 1H, OH), 4.69 (dd, J = 10.2, 3.8 Hz, 1H, OCH), 7.20–7.40 (m, 5H, CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.21 (CH_3), 67.54 (NCH_2), 69.48 (OCH), 125.75 (2CH), 127.27 (CH), 128.16 (2CH), 142.28 (C).

4.15. (*R*)-(−)-2-(Diethylamino)-1-(phenyl)ethanol 2a

Yield 73%, bp 76–78 °C/1 mmHg, $[\alpha]_D^{25} = -79.0$ (*c* 1.28, MeOH), Lit.[41] (*S*)-isomer, $[\alpha]_D^{25} = +81.0$ (*c* 1.03 MeOH) >99% ee. GC analysis on a chiral column Supelco Beta-DEX 325, 30 m, 0.25 mm, isotherm 110 °C, 98% ee. t_R 79.5 *S*, 81.1 *R*. Racemate was also analyzed. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (t, J = 7.2 Hz, 6H, CH_3), 2.44 (dd, J = 12.6, 10.5 Hz, 1H, CH_2N), 2.59 (dq, J = 13.2, 7.2 Hz, 2H, $2CH_2$), 2.63 (dd, J = 12.6, 3.6 Hz, 1H, CH_2N), 2.73 (dq, J = 13.2, 7.2 Hz, 2H, $2CH_2$), 4.31 (br s, 1H, OH), 4.63 (dd, J = 10.5, 3.6 Hz, 1H, OCH), 7.24–7.39 (m, 5H, CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.93 ($2CH_3$), 46.79 ($2CH_2$), 61.76 (CH_2N), 69.14 (OCH), 125.71 (2CH), 127.20 (CH), 128.17 (2CH), 142.62 (C).

4.16. (*R*)-(−)-1-Phenyl-2-(pyrrolidin-1-yl)ethanol 3a

Yield 57%, mp 72–73 °C (from *n*-hexane). $[\alpha]_D^{27} = -41.0$ (*c* 1.80, EtOH). Lit.[41] (*S*)-isomer, mp 75 °C, $[\alpha]_D^{27} = +43.8$ (*c* 0.96, MeOH), 99% ee. Lit.[14] (*R*)-isomer, mp 69.5–70.5 °C, $[\alpha]_D^{20} = -40.3$ (*c* 1.88, EtOH), 95% ee. GC analysis on a chiral column Supelco Beta-DEX 325, 30 m, 0.25 mm, isotherm 130 °C, 97% ee, t_R 67.3 *R*, 69.2 *S*. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.81 (m, 4H, $2CH_2$), 2.48 (dd, J = 12.3, 3.3 Hz, 1H, CH_2), 2.50–2.60 (m, 2H, CH_2), 2.77 (m, 2H, CH_2), 2.79 (dd, J = 12.3, 10.5 Hz, 1H, CH_2), 4.07 (br s, 1H, OH), 4.71 (dd, J = 10.5, 3.3 Hz, 1H, OCH), 7.25–7.45 (m, 5H, CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.63 ($2CH_2$), 53.79 ($2CH_2$), 64.06 (CH_2), 70.64 (OCH), 125.83 (2CH), 127.37 (CH), 128.25 (2CH), 142.42 (C).

4.17. (*R*)-(−)-1-Phenyl-2-(piperidin-1-yl)ethanol 4a

Yield 63%, mp 83–84 °C (from *n*-hexane), $[\alpha]_D^{29} = -80.5$ (*c* 1.05, $CHCl_3$). Lit.[41] mp 84–84.5 °C. Lit.[42] (*S*)-isomer, $[\alpha]_D^{25} = +81.4$ (*c* 1.0, $CHCl_3$). GC analysis on a chiral column Supelco Beta-DEX 325, 30 m, 0.25 mm, isotherm 140 °C, 99% ee, t_R 63.0 *R*, 64.7 *S*, 99% ee. Racemate was also analyzed. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.50 (quintet, J = 5.6 Hz, 2H, CH_2), 1.60–1.75 (m, 4H, $2CH_2$), 2.39 (dd, J = 12.6, 10.2 Hz), 1H, CH_2N), 2.30–2.50 (m, 2H, CH_2), 2.50 (dd, J = 12.6, 4.0 Hz, 1H, CHN), 2.60–2.80 (m, 2H, CH_2), 3.95 (br s, 1H, OH), 4.72 (dd, J = 10.2, 4.0 Hz, 1H, OCH), 7.20–7.40 (m, 5H, CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.26 (CH_2), 26.11 ($2CH_2$), 54.45 (CH_2N), 66.90 (CH_2N), 68.65 (OCH), 125.83 (2CH), 127.32 (CH), 128.26 (2CH), 142.49 (C).

4.18. (*R*)-(−)-2-(Dimethylamino)-1-(2-naphthyl)ethanol 5a

Yield 60%, mp 64–66 °C (from ethyl acetate), $[\alpha]_D^{23} = -56.0$ (*c* 1.11, MeOH). Lit.[35] mp 53 °C, racemate. HPLC analysis on a chiral OD-H column, *n*-hexane/isopropanol, 98:2 + 0.5% Et_2NH, 0.4 mL/min, 25 °C, 98.0% ee, t_R 15.5 *R*, 17.4 *S*. Racemate was also analyzed. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.41 (s, 6H, CH_3), 2.47 (dd, *J* = 12.2, 3.8 Hz, 1H, CH_2N), 2.60 (dd, *J* = 12.2, 10.2 Hz, 1H, CH_2N), 4.42 (br s, 1H, OH), 4.89 (dd, *J* = 10.2, 3.8 Hz, 1H, OCH), 7.44–7.52 (m, 3H, CH), 7.82–7.88 (m, 4H, CH). ^{13}C NMR (50 MHz, $CDCl_3$) δ 45.25 ($2CH_3$), 67.32 (CH_2N), 69.53 (OCH), 123.97 (CH), 124.58 (CH), 125.64 (CH), 125.98 (CH), 127.63 (CH), 127.88 (CH), 128.00 (CH), 132.96 (C), 133.32 (C), 139.63 (C). X-ray crystal structure: $C_{14}H_{17}NO$, M_r = 215.29, colorless needle 0.56 × 0.24 × 0.14 mm, monoclinic, space group $P2_1$ (no. 4), *a* = 5.9378(5), *b* = 24.112(2), *c* = 8.6327(6) Å, β = 94.255(6)°, *V* = 1232.57(16) Å^3, *Z* = 4, ρ_{calcd} = 1.160 Mg/m^3, μ(Mo Kα) = 0.073 mm^{-1}, *T* = 291(2) K, Θ range 2.37–33.54°. Numerical absorption correction,[43] maximum and minimum transmission 0.9899 and 0.9603. Reflections: 12313 collected, 7006 unique, R_{int} = 0.0466. The structure was solved by direct methods and refined with the full-matrix least-squares method F^2 with the use of SHELX-97 program package.[44] Refinement: 7006 reflections, 296 parameters, H atoms located on a Fourier difference map and constrained, *R* = 0.0584, *wR2* = 0.1410. Absolute structure determined with the Flack method:[45] Flack parameter *x* = 0.2(18). Structural data have been deposited with Cambridge Crystallographic Data Centre, the CCDC number 719590.

4.19. (*S*)-(−)-1-(2-Benzofuryl)-2-(dimethylamino)ethanol 6a

Isolated by column chromatography, aluminum oxide, diethyl ether/ethyl acetate (gradient), 69% yield, mp 87–88 °C, $[\alpha]_D^{20} = -46.5$ (*c* 3.20, MeOH). HPLC analysis on a chiral OD-H column, *n*-hexane/isopropanol, 97:3 + 0.5% Et_2NH, 0.6 mL/min, 15 °C, 98% ee, t_R 31.1 *S*, 33.1 *R*. Racemate was also analyzed. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 6H, CH_3), 2.59 (dd, *J* = 12.3, 3.9 Hz, 1H, CH_2N), 2.87 (dd, *J* = 12.3, 7.2 Hz, 1H, CH_2N), 4.11 (br s, 1H, OH), 4.85 (ddd, *J* = 10.2, 3.3, 0.6 Hz, 1H, OCH), 6.69 (t, *J* = 0.7 Hz, 1H, CH), 7.21 (td, *J* = 7.5, 1.2 Hz, 1H, CH), 7.26 (td, *J* = 7.2, 1.5 Hz, 1H, CH), 7.46 (dm, *J* = 7.5 Hz, 1H, CH), 7.54 (ddd, *J* = 7.2, 1.5, 0.6 Hz, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.36 (CH_3), 63.26 (CH_2), 64.14 (CH_2), 103.34 (CH), 111.18 (CH), 120.93 (CH), 122.66 (CH), 123.99 (CH), 128.11 (C), 154.83 (C), 157.62 (C).

X-ray crystal structure: $C_{12}H_{15}NO_2$, M_r = 205.25, colorless needle 0.70 × 0.22 × 0.15 mm, monoclinic, space group $P2_1$ (no. 4), *a* = 8.2366(8), *b* = 5.7561(8), *c* = 12.3929(11) Å, β = 105.617(8)°, *V* = 565.86(11) Å^3, *Z* = 2, ρ_{calcd} = 1.205 Mg/m^3, μ(Mo Kα) = 0.082 mm^{-1}, *T* = 289(2) K, Θ range 3.41–31.33°. Numerical absorption correction,[43] maximum and minimum transmission 0.9879 and 0.9445. Reflections: 5600 collected, 2513 unique, R_{int} = 0.0385. The structure was solved by direct methods and refined with the full-matrix least-squares method F^2 with the use of SHELX-97 program package.[44] Refinement: 2513 reflections, 139 parameters, H atoms located on a Fourier difference map and constrained, *R* = 0.0403, *wR2* = 0.0992. Absolute structure: Flack parameter *x* = −1.5(10). Absolute structure is consistent with that determined for **5a** and **7a**. Structural data have been deposited with Cambridge Crystallographic Data Centre, the CCDC number 719591. MS (EI, 70 eV), *m/z* 205 (M^+, 1), 187 (M^+−18, 10), 144 (11), 131 (14), 91 (15), 58 (100). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.99; H, 7.48; N, 6.63.

4.20. (*S*)-(−)-1-(2-Benzofuryl)-2-(morpholin-4-yl)ethanol 7a

Isolated by column chromatography, silica gel, ethyl acetate, 62% yield, mp 100–101 °C. $[\alpha]_D^{20} = -32.0$ (*c* 0.85, EtOH). Lit.[38] mp 82 °C, racemate. HPLC analysis on a chiral OD-H column *n*-hexane/isopropanol, 90:10 + 0.5% Et_2NH, 0.6 mL/min, 25 °C, 98% ee, t_R 22.8 (*S*), 24.3 (*R*). Racemate was also analyzed. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.52 (m, 2H, $2CH_2$), 2.72 (m, 2H, $2CH_2$), 2.75 (dd, *J* = 12.6, 3.6 Hz, 2H, $2CH_2$), 2.90 (dd, *J* = 12.6, 9.6 Hz, 1H, CH_2), 3.76 (m, 4H, $2OCH_2$), 4.92 (ddd, *J* = 9.6, 3.6, 0.6 Hz, 1H, CH), 6.70 (t, *J* = 0.9 Hz, 1H, CH), 7.22 (td, *J* = 7.5, 1.2 Hz, 1H, CH), 7.27 (td, *J* = 7.2, 1.5 Hz, 1H, CH), 7.46 (dm, *J* = 7.8 Hz, 1H, CH), 7.54 (ddd, *J* = 7.5, 1.5, 0.9 Hz, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.52 ($2CH_2$), 62.41 (NCH_2), 63.43 (OCH), 66.98 ($2OCH_2$), 103.46 (HC), 111.19 (HC), 120.97 (HC), 122.75 (HC), 124.11 (HC), 128.05 (C), 154.85 (C), 157.32 (C). X-ray crystal structure: $C_{14}H_{17}NO_3$, M_r = 247.29, colorless plate 0.57 × 0.31 × 0.14 mm, orthorhombic, space group $P2_12_12_1$ (no. 19), *a* = 5.8543(6), *b* = 9.9940(6), *c* = 21.919(2) Å, *V* = 1282.44(18) Å^3, 4 = 2, ρ_{calcd} = 1.281 Mg/m^3, μ(Mo Kα) = 0.090 mm^{-1}, *T* = 291(2) K, Θ range 2.76–31.25°. Numerical absorption correction,[43] maximum and minimum transmission 0.9876 and 0.9506. Reflections: 12719 collected, 3930 unique, R_{int} = 0.0507. The structure was solved by direct methods and refined with the full-matrix least-squares method F^2 with the use of SHELX-97 program package.[44] Refinement: 2513 reflections, 139 parameters, H atoms located on a Fourier difference map and constrained, *R* = 0.0463, *wR2* = 0.0975. Absolute structure determined with the Flack method:[45] Flack parameter *x* = −0.2(11). Structural data have been deposited with Cambridge Crystallographic Data Centre, the CCDC number 719592. MS (EI, 70 eV) *m/z*: 229 (M^+−18, 2), 144 (5), 131 (3), 100 (100), 91 (7), 56 (15). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.08; H, 6.73; N, 5.67.

4.21. (*S*)-(−)-1-(2-Furyl)-2-(dimethylamino)ethanol 8a

Yield 59%, bp 69–71 °C/0.80 mmHg, mp 36.0–37.5 °C, $[\alpha]_D^{22} = -42.5$ (*c* 2.01, MeOH). HPLC analysis on a chiral OD-H column, *n*-hexane/isopropanol, 90:10 + 0.5% Et_2NH, 0.6 mL/min, 25 °C, 98% ee, t_R 7.84 (*S*), 8.89 (*R*). Racemate was also analyzed. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 (s, 6H, CH_3), 2.44 (dd, *J* = 12.3, 3.6 Hz, 1H, NCH_2), 2.82 (dd, *J* = 12.3, 10.5 Hz, 1H, NCH_2), 3.80 (br s, OH), 4.72 (dd, *J* = 10.5, 3.6 Hz, 1H, OCH), 6.29 (ddd, *J* = 3.0, 1.8, 0.9 Hz, 1H, CH), 6.33 (dd, *J* = 3.0, 1.8 Hz, 1H, CH), 7.38 (dd, *J* = 1.8, 0.9 Hz, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.28 ($2CH_3$), 63.29 (NCH_2), 63.58 (OCH), 106.69 (HC), 110.10 (HC), 142.08 (HC), 154.64 (C). MS (EI, 70 eV) *m/z* 155 (M^+, 1), 137 (M^+−18, 8), 94 (8), 81 (6), 58 (100). Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.97; H, 8.57; N, 9.11.

4.22. (*R*)-1-*N*,*N*-Diethylaminopropan-2-ol 9a

Yield 54%, bp 120–135 °C/760 mmHg. $[\alpha]_D^{20} = -25.1$ (*c* 4.05, EtOH), 55% ee. Lit.[12] (*R*)-isomer, $[\alpha]_D^{22} = -10.95$ (*c* 4.07, EtOH), 24% ee. GC analysis on a chiral column Supelco Beta-DEX 325, 30 m, 0.25 mm, isotherm 50 °C, 60% ee, t_R 31.5 *S*, 33.9 *R*. Racemate was also analyzed. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (t, 6H, CH_3), 1.11 (d, *J* = 6.3 Hz, 3H, CH_3), 2.19 (dd, *J* = 12.6, 10.5 Hz, 1H, NCH_2), 2.38 (dd, *J* = 12.6, 3.3 Hz, 1H, NCH_2), 2.46 (dq, *J* = 12.6, 7.2 Hz, 2H, $2CH_2$), 2.60 (dq, *J* = 12.6, 7.2 Hz, 2H, $2CH_2$), 3.71 (ddq, *J* = 10.5, 6.3, 3.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.98 (CH_3), 19.86 (CH_3), 46.95 (CH_2), 61.05 (CH_2), 62.75 (CH).

4.23. (*R*)-(−)-1-(3,4-Dimethoxyphenyl)-2-(dimethylamino) ethanol 11a

Yield 55%, mp 63.0–63.5 °C (from diethyl ether/*n*-hexane, 1:1). $[\alpha]_D^{24} = -43.75$ (*c* 2, EtOH). Lit.[33] mp 66–67.5 °C, $[\alpha]_D^{25} = -42.6$ (*c* 2, EtOH). HPLC analysis on a chiral OD-H column *n*-hexane/isopropanol, 90:10 + 0.5% Et_2NH, 0.6 mL/min, 15 °C, 98% ee, t_R 18.39 *R*,

28.70 *S*. ^{1}H NMR (300 MHz, C_6D_6) δ 1,98 (s, 6H, CH_3), 2.17 (dd, J = 12.0, 3.3 Hz, 1H, NCH_2), 2.39 (dd, J = 12.3, 10.5 Hz, 1H, NCH_2), 3.43 (s, 3H, CH_3), 3.47 (s, 3H, CH_3), 3.95 (s, 1H, OH), 4.71 (dd, J = 10.5, 3.3 Hz, 1H, OCH), 6.69 (d, J = 8.1 Hz, 1H, CH), 6.97 (dd, J = 8.1, 2.1 Hz, 1H, CH), 7.13 (d, J = 2.1 Hz, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.28 ($2NCH_3$), 55.82 (OCH_3), 55.90 (OCH_3), 67.55 (NCH_2), 69.27 (OCH), 109.01 (CH), 110.98 (CH), 118.86 (CH), 134.86 (C), 148.34 (C), 149.02 (C).

Acknowledgment

Financial support from the Ministry of Science and Higher Education, Warsaw, Grant PBZ-KBN 126/T09/2004, is acknowledged.

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