Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 3, pp. 469–476, 1997

Printed in Great Britain
PII: S0957-4166(96)00528-9
0957-4166/97 $17.00 + 0.00

Stereoselective synthesis of thienyl and furyl analogues of ephedrine[1]

Franz Effenberger * and Joachim Eichhorn †

Institut für Organische Chemie der Universität Stuttgart, Pfaffenwaldring 55, D-70569 Stuttgart, Germany

Abstract: The stereoselective syntheses of thienyl and furyl analogues of ephedrine starting from (*R*)- and (*S*)-cyanohydrins, respectively, are described. Addition of methyl Grignard to the O-trimethylsilyl protected optically active cyanohydrins (*R*)- and (*S*)-**3** and hydrogenation of the resulting imino intermediates gives the *erythro*-2-amino alcohols **4** with high diastereoselectivity. Their reductive methylation leads to the enantiomerically pure thiophene analogues (1*S*,2*S*)- and (1*R*,2*R*)-**6a**, (1*R*,2*S*)- and (1*S*,2*R*)-**6b** as well as to the furan analogues (1*S*,2*S*)-**6c** and (1*R*,2*S*)-**6d** of ephedrine. The biological activity of the new compounds is under investigation. © 1997 Elsevier Science Ltd. All rights reserved.

2-Amino-1-phenylpropanols are of great pharmacological importance as α- and β-sympathomimetics and are widely used vasodilators and bronchodilators.[2] In numerous examples it was demonstrated that the substitution of a phenyl ring in pharmaceuticals by e.g. a thienyl group results in products with comparable or resembling biological activity.[3] Therefore, an investigation of heteroaryl analogues of 2-amino-1-phenylpropanols and the change of biological activity caused by substitution of the phenyl by a heteroaryl moiety in these compounds should be of interest.

As early as 1927, S. Kanao[4] has prepared various branched and unbranched 2-amino-1-furyl alcohols which show mydriatic activity. C. Seelkopf has published the synthesis of a series of racemic 1-heteroaryl (3-pyridyl-, 2-furyl-, 2- and 3-thienyl-, 3-indolyl- and 2-pyrrolyl)-2-amino alcohols of the ephedrine type.[5] In case of 2-methylamino-1-(2-thienyl)propanol the *erythro*- and *threo*-isomer could be separated due to their solubility and insolubility, respectively, in ether.[6] The hypotensive activity of the racemic *erythro*-compound in this case amounts to one third of L (−) ephedrine whereas the racemic *threo*-form is biologically inactive.[6] Only one of the two enantiomers of the *erythro*-compound was obtained in pure form using (−)-di-*p*-toluoyltartaric acid for resolution of the enantiomers.[6] More recent investigations[7] of the biological activity of 2-alkylamino-1-(2-thienyl) alcohols demonstrate greater hypertensive effect for the *threo*-isomer but longer lasting activity for the *erythro*-form; moreover the *threo*-derivative has greater psychostimulating activity than the *erythro*-compound which is a better analgesic.

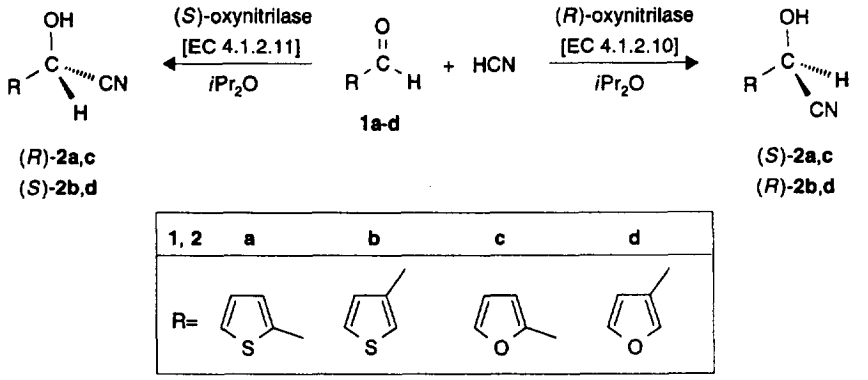
Besides the 2-thienyl analogue of ephedrine also 2-methylamino-1-(3-thienyl)propanol has been synthesized.[6b] The *erythro*- and *threo*-compounds were separated in this case via different solubility of their picrates. Whereas the *threo*-isomer was resolved in both enantiomers, the resolution of the *erythro*-isomer failed.[6b] Nothing is mentioned on the biological activity of these compounds.

Since thienyl and furyl analogues of L (−) ephedrine have not yet been prepared and described in enantiomerically pure form and furthermore their biological activity is controversial,[6,7] we were interested in the stereoselective preparation of the pure enantiomers of these compounds.

In the present publication we report on the enantioselective synthesis of heterocyclic analogues of ephedrine starting from the corresponding (*R*)- and (*S*)-cyanohydrins, respectively.[8] The reaction sequence involves addition of a Grignard reagent to the nitrile group of the O-silylated cyanohydrins, subsequent hydrogenation with $NaBH_4$ to the 2-amino-1-heteroaryl alcohols,[1,9,10] and reductive N-methylation of the amino alcohols[1,11] to the corresponding ephedrine analogues.

* Corresponding author. Email: ioc@po.uni-stuttgart.de

† Part of dissertation, Universität Stuttgart, 1995.



Scheme 1.

Table 1. (*R*)- and (*S*)-Cyanohydrins (*R*)- and (*S*)-**2** by enzyme catalyzed addition of HCN to the aldehydes **1** in diisopropyl ether at room temperature

Aldehydes **1**	Oxynitrilase	[U/mmol **1**]	React.-time [h]	Cyanohydrins (*R*)- and (*S*)-**2**	Conversion [%][a]	*ee* [%]
1a	(*R*)	25	5	(*S*)-**2a**[b]	71	99
1a	(*S*)	79	8	(*R*)-**2a**[b]	64	91
1b	(*R*)	50	6	(*R*)-**2b**	95	99
1b	(*S*)	47	27	(*S*)-**2b**	95	98
1c	(*R*)	35	4	(*S*)-**2c**[b]	96	99
1c	(*S*)	101	9	(*R*)-**2c**[b]	80	80
1d	(*R*)	34	4	(*R*)-**2d**	96	99
1d	(*S*)	91	33	(*S*)-**2d**	88	87

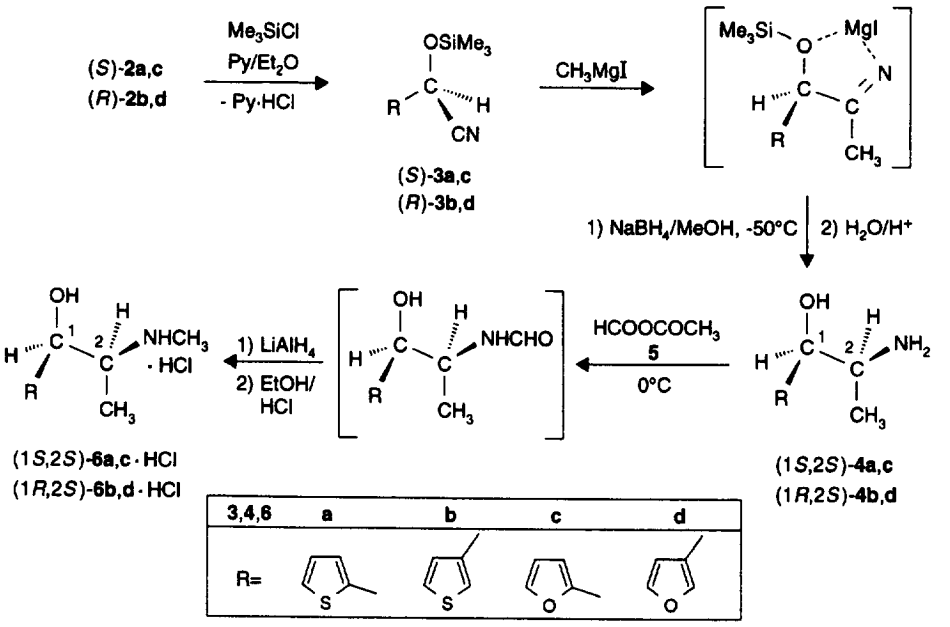
[a] Preparative scale with the exception of (*R*)-**2c**, (*S*)-**2d**; conversion determined by ^{1}H NMR spectroscopy.

[b] Change of configuration due to change of substituent priority.

Preparation of (*R*)- and (*S*)-thiophene- and furanaldehyde cyanohydrins (*R*)- and (*S*)-2

(*R*)- and (*S*)-Thiophene- and furancarbaldehyde cyanohydrins (*R*)- and (*S*)-**2** are easily accessible with high enantiomeric excesses by (*R*)-oxynitrilase [EC 4.1.2.10] and (*S*)-oxynitrilase [EC 4.1.2.11] catalyzed addition of HCN to aldehydes **1** (Scheme 1, Table 1).[8] Under the reaction conditions applied earlier[12] the enantiomeric excesses obtained, particularly with the (*S*)-oxynitrilase, could be markedly improved compared to the values published.[8a,d–f] The change of configuration at C-1 of the 2-thiophene- and 2-furanaldehyde cyanohydrins **2a** and **2c** is due to the change of priority of the substituents.

Table 1 shows that (*S*)- and (*R*)-**2a** are obtained in the case of thiophene-2-aldehyde cyanohydrins with high enantiomeric excesses of 99% and 91% but with only 71% and 64% conversion, respectively. On the contrary, for the thiophene-3-aldehyde cyanohydrins (*R*)- and (*S*)-**2b** the aldehyde/cyanohydrin equilibrium is almost completely on the product side and thus both (*R*)- and (*S*)-**2b** are obtained with 95% conversion and 98–99% *ee* (Table 1). The furanaldehydes **1c** and **d** are excellent substrates for (*R*)-oxynitrilase. The corresponding cyanohydrins (*S*)-**2c** and (*R*)-**2d** are obtained with 96% conversion and 99% *ee*. With (*S*)-oxynitrilase as catalyst, however, the conversion and the enantiomeric excesses of the resulting cyanohydrins (*R*)-**2c** and (*S*)-**2d** are lower. The reaction of the 3-substituted aldehydes



Scheme 2.

1b and **1d**, respectively, with (*S*)-oxynitrilase is markedly slower, therefore the reaction times had to be increased (Table 1).

Preparation of *erythro*-2-methylamino-1-thienyl and 1-furylpropanols 6

Based on published procedures,[1,10,11] the synthetic route to ephedrine-type 1-heteroaryl-2-methylamino alcohols (1*S*,2*S*)-**6a,c** and (1*R*,2*S*)-**6b,d**, starting from cyanohydrins (*R*)- and (*S*)-**2**, respectively, involves silylation to O-protected cyanohydrins (*R*)- and (*S*)-**3**, addition of a methyl Grignard to the nitrile group followed by hydrogenation of the imino intermediate to the 2-amino alcohols (1*S*,2*S*)-**4a,c** and (1*R*,2*S*)-**4b,d** and subsequent reductive methylation of the optically pure 2-amino alcohols **4** via the N-formylamino compounds (Scheme 2, Tables 2 and 3).

Scheme 3 shows the reaction sequence to the enantiomerically pure 2-N-methylamino-1-(2-thienyl)propanol (1*R*,2*R*)-**6a** and 2-N-methylamino-1-(3-thienyl)propanol (1*S*,2*R*)-**6b** starting from the silylated cyanohydrins (*R*)-**3a** and (*S*)-**3b**.

Analogous to literature procedures[1,10b] the cyanohydrins **2a–d** were treated with trimethylchlorosilane in 1.5 fold excess based on **2** in presence of pyridine to give the silylated cyanohydrins (*S*)-, (*R*)-**3a**, (*R*)-, (*S*)-**3b** as well as (*S*)-**3c** and (*R*)-**3d** in 76–85% yield without loss of stereochemical integrity as colorless liquids after distillation (Table 2).

The preparation of the 2-amino-1-heteroarylpropanols (1*S*,2*S*)-**4a,c**, (1*R*,2*R*)-**4a**, (1*R*,2*S*)-**4b,d** and (1*S*,2*R*)-**4b** was performed analogous to known methods[10] (Schemes 2 and 3, Table 2). The diastereomeric excesses of the crude amino alcohols **4** were determined by ^{1}H NMR spectroscopy via the integrals of the respective proton at C-1; the *de*-values of 86–95% were confirmed by gas chromatography (Table 2). The enantiomeric excesses at C-1 determined in case of the thiophene derivatives (1*S*,2*S*)-**4a** and (1*R*,2*R*)-**4a** as well as (1*R*,2*S*)-**4b** and (1*S*,2*R*)-**4b** are comparable with those of the starting cyanohydrins (*R*)- and (*S*)-**2a** and **b**. The Grignard addition and hydrogenation therefore proceed, as reported in previous publications,[8a,10b] without racemization.

The amino alcohols **4** had to be purified either as hydrochlorides by recrystallization or by

Table 2. Synthesis of *erythro*-2-amino alcohols **4** from the respective cyanohydrins (*R*)- and (*S*)-**2** via the trimethylsilyl ethers **3**, addition of methyl Grignard and subsequent hydrogenation with $NaBH_4$

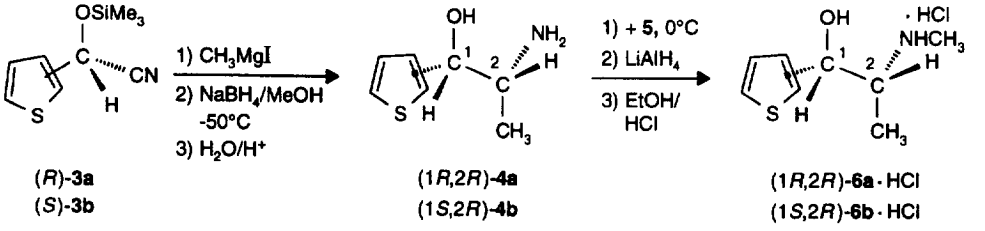
Cyanohydrins **2**		Silylated Cyanohydrins **3**			*erythro*-2-Amino Alcohols **4**				
			Yield	$[\alpha]_D^{20}$		Yield	*de*	*ee*	$[\alpha]_D^{20}$
	(*ee*%)		[%]	(*c*, CH_2Cl_2)		[%][a]	[%][b]	[%][c]	(*c*, solvent)
(*S*)-**2a**	96	(*S*)-**3a**	76	+34.9 (1.59)	(1*S*,2*S*)-**4a**	67	94	95.5	+6.1 (2.04, EtOH)
(*S*)-**2c**	98	(*S*)-**3c**	85	+12.5 (1.0)	(1*S*,2*S*)-**4c**	22	95[d]	-	+4.4 (0.68, CH_2Cl_2)
(*R*)-**2b**	99	(*R*)-**3b**	85	+19.6 (1.9)	(1*R*,2*S*)-**4b**	71	86	>99	-14.2 (2.16, EtOH)
(*R*)-**2d**	99	(*R*)-**3d**	80	+29.8 (1.98)	(1*R*,2*S*)-**4d**	35	89	-	+5.4 (0.83, CH_2Cl_2)
(*R*)-**2a**	86	(*R*)-**3a**	76	-26.0 (1.63)	(1*R*,2*R*)-**4a**	50	90	82	-4.3 (1.73, EtOH)
(*S*)-**2b**	99	(*S*)-**3b**	76	n.d.	(1*S*,2*R*)-**4b**	64	87	99	+11.0 (1.0, EtOH)

[a] After chromatography on silica gel. [b] Determined from crude products by ^1H NMR spectroscopy. [c] Determined after pivaloylation on chiral valine-bornylamide phases by gas chromatography. [d] Determined after pivaloylation by capillary gas chromatography.

Table 3. Synthesis of N-methylated *erythro*-2-amino-1-heteroarylpropanol hydrochlorides **6**·HCl by N-formylation with **5** and subsequent hydrogenation with $LiAlH_4$

Educts		*erythro*-2-Methylamino-1-heteroarylpropanol Hydrochlorides **6**·HCl				
4	(*de*%)		Yield [%][a]	Yield [%][b]	$[\alpha]_{578}^{20}$ (*c*, EtOH)	mp [°C]
(1*S*,2*S*)-**4a**	84	(1*S*,2*S*)-**6a**	83	31	-22.2 (0.50)	176-177
(1*S*,2*S*)-**4c**	88	(1*S*,2*S*)-**6c**	61	39	-36.8 (0.53)	135-136[c]
(1*R*,2*S*)-**4b**	86	(1*R*,2*S*)-**6b**	89	77	-49.3 (0.68)	184-185
(1*R*,2*S*)-**4d**	88	(1*R*,2*S*)-**6d**	83	26	-21.0 (0.50)	183
(1*R*,2*R*)-**4a**	90	(1*R*,2*R*)-**6a**	80	53	+23.6 (0.55)[d]	179-180[d]
(1*S*,2*R*)-**4b**	87	(1*S*,2*R*)-**6b**	100	65	+47.0 (0.50)	186

[a]Crude products. [b]As hydrochlorides after recrystallization from ethanol/diethyl ether; yield based on *de*-value of educt **4**. [c]Ref.[13]. [d]Ref.[6a].



(*R*)-**3a** (*S*)-**3b** (1*R*,2*R*)-**4a** (1*S*,2*R*)-**4b** (1*R*,2*R*)-**6a**·HCl (1*S*,2*R*)-**6b**·HCl

Scheme 3.

chromatography on silica gel with THF/NH_3 sat. ethanol (12:1), since in all cases a secondary amine was formed as a by-product in various amounts. This by-product was isolated during the preparation of (1*R*,2*S*)-**4b**, and was identified and characterized as bis[2-(1-(3-thienyl)propanol)]amine. Depending on the activity of the applied $NaBH_4$ the transimination reaction leading to the secondary bis[2-(1-heteroarylpropanol)]amine as by-product could be suppressed by addition of the hydrogenation agent in up to fourfold excess. In this way the *erythro*-compounds (1*S*,2*S*)-**4a** and (1*R*,2*R*)-**4a** as well as (1*R*,2*S*)-**4b** and (1*S*,2*R*)-**4b** were isolated in optically pure form in 50–71% yield (Table 2). The

corresponding furan derivatives (1*S*,2*S*)-**4c** and (1*R*,2*S*)-**4d** partly decomposed during chromatography and thus enantiomerically pure (1*S*,2*S*)-**4c** and (1*R*,2*S*)-**4d** were obtained only in 22% and 35% yield, respectively (Table 2).

For introduction of the N-methyl group in the 2-amino alcohols **4** we have used the reductive methylation described in the preceding publication.[1] The purified compounds (1*S*,2*S*)-**4a**,**c**, (1*R*,2*S*)-**4b**,**d**, (1*R*,2*R*)-**4a** and (1*S*,2*R*)-**4b** were reacted at 0°C with acetic formic anhydride (**5**) to give N-formyl intermediates,[1,11] which were hydrogenated after removal of the volatile components directly with $LiAlH_4$[1,11] to the 2-methylamino alcohols **6a–d** (Schemes 2 and 3). The diastereomeric excesses of compounds **6a–d**, however, could not be determined at this stage. For purification the viscous yellow oils were converted into the hydrochlorides and recrystallized from ethanol/diethyl ether (Table 3). ^1H NMR investigations show that in all cases the *de*-values of the recrystallized products **6a–d** are 100% of the *erythro*-configuration. The configuration was confirmed by comparison of the specific rotation of (1*R*,2*R*)-2-methylamino-1-(2-thienyl)propanol hydrochloride (1*R*,2*R*)-**6a**·HCl (Table 3) with published data of (+)-hydrochloride of the *erythro*-isomer.[6a]

The low yields in case of the furan derivatives (1*S*,2*S*)-**6c**·HCl and (1*R*,2*S*)-**6d**·HCl are caused by difficult crystallization and moreover by a limited stability of these compounds already reported for 2-amino-1-(2-furyl)propanol **4c**,[4] but not for the corresponding N-methylated compound.[13]

The synthetic route described in this paper offers an easy approach to optically active heterocyclic analogues of ephedrine starting from (*R*)- and (*S*)-cyanohydrins.

Experimental

Materials and methods

Avicel cellulose was purchased from Merck. (*R*)-Oxynitrilase was prepared according to Ref.[14] and (*S*)-oxynitrilase according to Ref.[15] All solvents were purified and dried as described in the literature. Melting points were determined on a Büchi SMP-20 and are uncorrected. ^1H NMR spectra were recorded on a Bruker ACF 250 with TMS as internal standard. Optical rotations were performed in a Perkin–Elmer polarimeter 241 LC. Preparative column chromatography was performed with glass columns of different size packed with silica gel S, grain size 0.032–0.063 mm (Riedel-de Haen). GC for determination of enantiomeric and diastereomeric excess: a) Carlo Erba HRGC 5300 Mega Series with FID, Carlo Erba Mega Series integrator, 0.4–0.5 bar or 0.36 bar hydrogen, column 20 m, phase OV 1701 or PS086 with 10% permethylated β-cyclodextrin or Amid-Dex (valeroyl-L-valine-(*R*)-bornylamide, β-cyclodextrin); b) Carlo Erba Fractovap 4160 with FID, Spectra Physics minigrator, 0.5 bar hydrogen, column 50 m, phase OV 1701 with 10% permethylated β-cyclodextrin.

Enzyme catalyzed preparation of (R)- and (S)-cyanohydrins 2

Performed according to Ref.[12] with up to 30 mmol of aldehyde **1** using (*R*)- and (*S*)-oxynitrilase as catalysts (Table 1).

Determination of the enantiomeric excess of cyanohydrins 2

Performed according to Ref.[12].

Preparation of O-silylated cyanohydrins (R)- and (S)-3; general procedure[10b]

At 0°C trimethylchlorosilane (ca. 1.5 fold excess based on **2**) was added dropwise within 30 min to a solution of **2** (19–55 mmol) in abs. diethyl ether and pyridine (ca. 1.5 fold excess based on **2**) under argon atmosphere. The reaction mixture was stirred for 5–6 h [(*S*)-**2c**, (*R*)-**2d**] or 15–18 h [(*R*)-, (*S*)-**2a**,**2b**]. Precipitated pyridinium hydrochloride was filtered off, washed with abs. diethyl ether, and the combined filtrates were concentrated. The residue was fractionally distilled *in vacuo* [bp (°C/0.01 Torr): (*S*)-**3a**: 60–62; (*R*)-**3a**: 60–63; (*R*)-**3b**: 58–60; (*S*)-**3b**: 57–60; (*S*)-**3c**: 60; (*R*)-**3d**: 61].

Preparation of erythro-2-amino alcohols 4; general procedure[10b]

Compounds **3** (4–13 mmol) were dropped via syringe at 0°C within 30 min to a solution of the Grignard reagent[10b] in diethyl ether under argon atmosphere, and the reaction mixture stirred for 5–6 h at room temperature. After addition of 25 vol% abs. tetrahydrofuran (THF) the reaction mixture was cooled to −50°C and solid $NaBH_4$ (1–4 fold excess based on **3**) was added followed by methanol (7–20 ml). The reaction mixture was warmed up to 5°C within 16 h, hydrolyzed with water and HCl (10%), and the organic phase was extracted three times with 15 ml HCl (10%) each. The combined aqueous phases were extracted with diethyl ether, set to pH 10 with conc. NaOH solution and extracted five times with 25 ml ethyl acetate each. The combined extracts were dried ($MgSO_4$), concentrated, and the diastereomeric excess was determined from the residue by ^1H NMR spectroscopy. The products **4** either were converted into the hydrochlorides and recrystallized from ethanol/diethyl ether or chromatographed on silica gel with THF/NH_3 sat. ethanol (12:1).

Determination of the diastereomeric and enantiomeric excess of 4

50 µl Pivaloyl chloride were added to a solution of ca. 5 mg crude **4** in 200 µl pyridine. After standing at room temperature for 24 h, the reaction mixture was filtered through a silica gel column (3×0.5 cm) with 3 ml dichloromethane. The diastereomeric excesses were determined directly from the filtrate by capillary gas chromatography on OV 1701 or PS086 phases with 10% permethylated β-cyclodextrin. The enantiomeric excesses of **4a,b** were determined on a chiral amide phase.

^1H NMR data of compounds 4 (250 MHz, $CDCl_3$, δ) and 6·HCl (250 MHz, DMSO-d_6, δ)

4a	1.04 (d, *J*=6.5 Hz, 3 H, CH_3), 2.30 (bs, 2 H, NH,OH), 3.19 (dq, J_1=6.5, J_2=4.9 Hz, 1 H, CHN), 4.74 (d, *J*=4.8 Hz, 1 H, C*H*OH), 6.95-7.01 (m, 2 H, Ar-H), 7.25 (dd, J_1=5.0, J_2=1.4 Hz, 1 H, Ar-H)
4b	0.99 (d, *J*=6.6 Hz, 3 H, CH_3), 2.30 (bs, 2 H, NH,OH), 3.17 (dq, J_1=6.5, J_2=4.7 Hz, 1 H, CHN), 4.63 (d, *J*=4.7 Hz, 1 H, C*H*OH), 7.03 (dd, J_1=5.0, J_2=1.2 Hz, 1 H, Ar-H), 7.19 (dd, J_1=2.9, J_2=0.8 Hz, 1 H, Ar-H), 7.30 (dd, J_1=5.0, J_2=3.0 Hz, 1 H, Ar-H)
4c	1.04 (d, *J*=6.6 Hz, 3 H, CH_3), 2.10 (bs, 2 H, NH,OH), 3.23 (dq, J_1=6.5, J_2=5.2 Hz, 1 H, CHN), 4.50 (d, *J*=5.1 Hz, 1 H, C*H*OH), 6.27 (d, *J*=3.2 Hz, 1 H, Ar-H), 6.34 (dd, J_1=3.2, J_2=1.8 Hz, 1 H, Ar-H), 7.37 (dd, J_1=1.8, J_2=0.7 Hz, 1 H, Ar-H)
4d	1.02 (d, *J*=6.6 Hz, 3 H, CH_3), 2.00 (bs, 2 H, NH,OH), 3.12 (dq, J_1=6.5, J_2=4.7 Hz, 1 H, CHN), 4.48 (d, *J*=4.7 Hz, 1 H, C*H*OH), 6.37 (t, *J*=1.2 Hz, 1 H, Ar-H), 7.40 (d, *J*=1.3 Hz, 2 H, Ar-H)
6a·HCl	1.05 (d, *J*=6.7 Hz, 3 H, CH_3), 2.60 (t, *J*=5.4 Hz, 3 H, NCH_3), 3.38-3.48 (m, 1 H, CHN), 5.38 (bs, 1 H, C*H*OH), 6.58 (d, *J*=4.8 Hz, 1 H, OH), 7.01-7.06 (m, 2 H, Ar-H), 7.46 (dd, J_1=4.7, J_2=1.5 Hz, 1 H, Ar-H), 8.98 (bs, 2 H, $NH_2^+Cl^-$)
6b·HCl	0.99 (d, *J*=6.7 Hz, 3 H, CH_3), 2.59 (t, *J*=5.4 Hz, 3 H, NCH_3), 3.35-3.46 (m, 1 H, CHN), 5.19 (d, *J*=1.8 Hz, 1 H, C*H*OH), 6.15 (bs, 1 H, OH), 7.10 (dd, J_1=5.0, J_2=1.1 Hz, 1 H, Ar-H), 7.39 (m_c, 1 H, Ar-H), 7.54 (dd, J_1=4.9, J_2=3.0 Hz, 1 H, Ar-H), 9.00 (bs, 2 H, $NH_2^+Cl^-$)
6c·HCl	1.09 (d, *J*=6.7 Hz, 3 H, CH_3), 2.57 (t, *J*=5.4 Hz, 3 H, NCH_3), 3.30-3.55 (m, 1 H, CHN), 5.12 (d, *J*=2.3 Hz, 1 H, C*H*OH), 6.33 (bs, 1 H, OH), 6.38 (d, *J*=3.2 Hz, 1 H, Ar-H), 6.45 (dd, J_1= 3.2, J_2=1.8 Hz, 1 H, Ar-H), 7.65 (dd, J_1=1.6, J_2=0.7 Hz, 1 H, Ar-H), 9.05 (bs, 2 H, $NH_2^+Cl^-$)
6d·HCl	1.05 (d, *J*=6.7 Hz, 3 H, CH_3), 2.58 (t, *J*=5.4 Hz, 3 H, NCH_3), 3.29-3.35 (m, 1 H, CHN), 5.06 (d, *J*=1.6 Hz, 1 H, C*H*OH), 6.00 (bs, 1 H, OH), 6.48 (m_c, 1 H, Ar-H), 7.57 (s, 1 H, Ar-H), 7.65 (t, *J*=1.6 Hz, 1 H, Ar-H), 8.97 (bs, 2 H, $NH_2^+Cl^-$)

Preparation of erythro-2-methylamino-1-heteroarylpropanols **6**; *general procedure*[1,11]

At 0°C acetic formic anhydride **5** (ca. 2 fold excess based on **4**) was added to a solution of **4** (2.3–7.3 mmol) in abs. diethyl ether/THF (2:1 or 4:1), and the reaction mixture stirred for 1 h. After removal of volatile compounds and acetic acid *in high vacuo*, the residue was taken up in abs. diethyl ether/THF and added dropwise within 1–1.5 h to an ice-cold suspension of $LiAlH_4$ (ca. 1.5–3 fold excess based on **4**) in abs. diethyl ether under argon atmosphere. The reaction mixture was allowed to warm to room temperature, stirred for further 15–20 h and hydrolyzed with NaOH solution (ice cooling). The aqueous phase was extracted five times with 20 ml diethyl ether each. The combined extracts were dried ($MgSO_4$) and concentrated. The residue was dissolved in abs. diethyl ether and HCl sat. ethanol was added. After removal of the volatile compounds the residue was taken up in a small volume of ethanol and abs. diethyl ether was added dropwise until the start of crystallization. The crystals were filtered off, washed with a small volume of abs. diethyl ether and dried *in vacuo* to give diastereomerically pure products **6**·HCl.

Elemental analytical data of compounds ***4a–c*** *and* ***6***·*HCl*

	Molecular Formula (Molecular Weight)	Calculated/Found C	H	N	S	Cl
(1*S*,2*S*)-**4a**	$C_7H_{11}NOS$	53.47	7.05	8.91	20.39	-
	(157.2)	53.24	7.04	8.71	20.13	
(1*R*,2*S*)-**4b**·HCl	$C_7H_{12}ClNOS$	43.42	6.24	7.23	16.55	18.30
	(193.7)	43.57	6.40	7.18	16.38	18.45
(1*S*,2*S*)-**4c**	$C_7H_{11}NO_2$	59.56	7.85	9.92	-	-
	(141.2)	59.34	7.80	9.57		
(1*S*,2*S*)-**6a**·HCl	$C_8H_{14}ClNOS$	46.26	6.79	6.74	15.43	17.07
	(207.7)	46.31	6.91	6.69	15.15	17.26
(1*R*,2*S*)-**6b**·HCl	$C_8H_{14}ClNOS$	46.26	6.79	6.74	15.43	17.07
	(207.7)	46.18	6.88	6.60	15.21	17.17
(1*S*,2*S*)-**6c**·HCl	$C_8H_{14}ClNO_2$	50.14	7.36	7.31	-	18.50
	(191.7)	50.14	7.46	7.14		18.67
(1*R*,2*S*)-**6d**·HCl	$C_8H_{14}ClNO_2$	50.14	7.36	7.31	-	18.50
	(191.7)	50.04	7.46	7.14		18.70

Acknowledgements

This work was generously supported by the Bundesministerium für Bildung und Forschung (Zentrales Schwerpunktprogramm Bioverfahrenstechnik, Stuttgart). We thank Stephan Krinke for his experimental contributions.

References

1. Enzyme Catalyzed Reactions, Part 27. Part 26: Effenberger, F.; Gutterer, B.; Jäger, J. *Tetrahedron: Asymmetry* **1997**, *8*, 459–467.
2. a) Engel, J. *Chem.-Ztg.* **1982**, *106*, 169–183. b) Kleemann, A.; Engel, J. *Pharmazeutische Wirkstoffe, Synthesen, Patente, Anwendungen*; 2nd ed.; Thieme Verlag, Stuttgart, **1982**, and supplementary volume **1987**.
3. Engel, J. *Chem.-Ztg.* **1979**, *103*, 161–172.
4. Kanao, S. *J. Pharm. Soc. Japan* **1927**, *550*, 1019–1035; *Chem. Abstr.* **1928**, *22*, 1588.
5. Seelkopf, C. *Rev. Fac. Farm., Univ. Los Andes (Venezuela)*, **1974**, *15*, 157–185; *Chem. Abstr.* **1975**, *83*, 78998q.

6. a) Barker, J. M.; Byron, D. J.; Huddleston, P. R. *J. Chem. Soc. (C)* **1969**, 2183–2185. b) Barker, J. M.; Huddleston, P. R. *J. Chem. Soc., Perkin Trans 1* **1973**, 1200–1203.
7. Mavrova, A.; Zhelyazkov, L. *Farmatsiya (Sofia)* **1986**, *36*, 1–5; *Chem. Abstr.* **1988**, *108*, 130714v.
8. a) Effenberger, F. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1555–1564. b) Ziegler, T.; Hörsch, B.; Effenberger, F. *Synthesis* **1990**, 575–578. c) Effenberger, F.; Ziegler, T.; Förster, S. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 458–460. d) Niedermeyer, U.; Kula, M.-R. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 386–387. e) Niedermeyer, U.; Kragl, U.; Kula, M.-R.; Wandrey, C.; Makryaleas, K.; Drauz, K.-H. (Kernforschungsanlage Jülich GmbH; Degussa AG), Eur. Pat. Appl. EP 326,063 A2, 1989; *Chem. Abstr.* **1990**, *112*, 234012p. f) Niedermeyer, U. *Dissertation*, Universität Düsseldorf, 1989.
9. a) Kruse, C. G. In *Chirality in Industry*; Collins, A. N.; Sheldrake, G. N.; Crosby, J., Eds.; Wiley, New York, **1992**, pp. 279–299. b) Jackson, W. R.; Jacobs, H. A.; Jayatilake, G. S.; Matthews, B. R.; Watson, K. G. *Aust. J. Chem.* **1990**, *43*, 2045–2062.
10. a) Brussee, J.; Dofferhoff, F.; Kruse, C. G.; van der Gen, A. *Tetrahedron* **1990**, *46*, 1653–1658. b) Effenberger, F.; Gutterer, B.; Ziegler, T. *Liebigs Ann. Chem.* **1991**, 269–273.
11. Wessely, F.; Swoboda, W. *Monatsh. Chem.* **1951**, *82*, 621–627.
12. Effenberger, F.; Eichhorn, J.; Roos, J. *Tetrahedron: Asymmetry* **1995**, *6*, 271–282.
13. Hildebrandt, G.; Klavehn, W. (Knoll A.-G.), Ger. 585,667; Appl. 6.10.1933; *Chem. Abstr.* **1934**, *28*, 1355.[8,9].
14. a) Hochuli, E. *Helv. Chim. Acta* **1983**, *66*, 489–493. b) Kaul, R.; Mattiasson, B. *Biotechnol. Appl. Biochem.* **1987**, *9*, 294–302. c) Lauble, H.; Müller, K.; Schindelin, H.; Förster, S.; Effenberger, F. *Proteins: Struct., Funct., Genet.* **1994**, *19*, 343–347.
15. a) Bové, C.; Conn, E. E. *J. Biol. Chem.* **1961**, *236*, 207–210. b) Seely, M. K.; Criddle, R. S.; Conn, E. E. *J. Biol. Chem.* **1966**, *241*, 4457–4462. c) Smitskamp-Wilms, E.; Brussee, J.; van der Gen, A.; van Scharrenburg, G. J. M.; Sloothaak, J. B. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 209–215.

(Received in UK 27 November 1996)