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Synthesis, Absolute Configuration and Circular Dichroism of Some Diarylmethane Derivatives.

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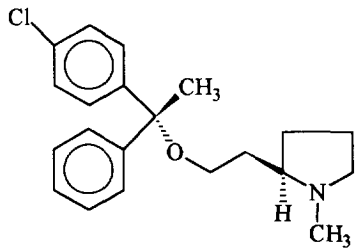
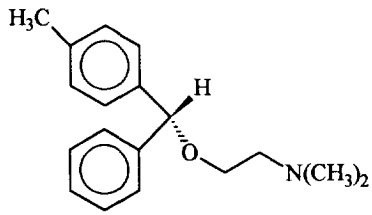
Abstract: Synthesis and assignment of the absolute configuration of different types of compounds bearing the diarylmethane moiety is presented. The absolute configuration was determined using chemical correlation and CD approaches based on the sign of the 0-0 vibronic transition within the α-aromatic (^1L_b) band of the substituted phenyl chromophore.

INTRODUCTION

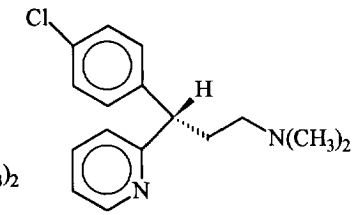
The importance of the diarylmethane moiety for the physiological activity of many organic compounds, e. g. clemastine ((+)-(*R*,*R*)-**1**)[2], neobenodine ((+)-(*R*)-**2**)[3], chlorpheniramine ((+)-(*S*)-**3**)[4], used as drugs with antihistamine, anticholinergic, local-anaesthetic and laxative activities, is well documented[5]. This type of



(+)-(*R*,*R*)-**1**



(+)-(*R*)-**2**



(+)-(*S*)-**3**

compound also possess an oestrogen synthetase inhibitory activity[6]. When one of the aryl group, differs from the other, two optical isomers exist and can display different biostereoselection. For example the antimuscarinic potency of (-)-(*R*)-1-cyclohexyl-1-phenyl-3-(1-pyrrolidinyl)-1-propanol (procyclidine) is about 380 times greater then those of the corresponding (+)-(*S*)-enantiomer[7]. For such compounds Dahlbom concluded "It is evident that the configuration at the benzylic center is of greatest importance"[8]. However, it is very difficult to obtain a compound with 100% enantiomeric purity by means of resolution because the two aryl groups are similar in steric bulkiness[9]. Optically active diarylmethanoles were usually obtained by resolution of their acid phthalates with chiral bases[10]. In the past decade some new methods for their synthesis, such as enantioselec-

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tive addition of chiral titanium reagents to aromatic aldehydes[11], conversion of acyl silanes into chiral alcohols[12] and resolution of racemic carbinols by complexation with brucine[13] were developed. Enantiomerically pure diarylmethylamines were synthesised by adding of aryllithiums to chiral azomethines[14].

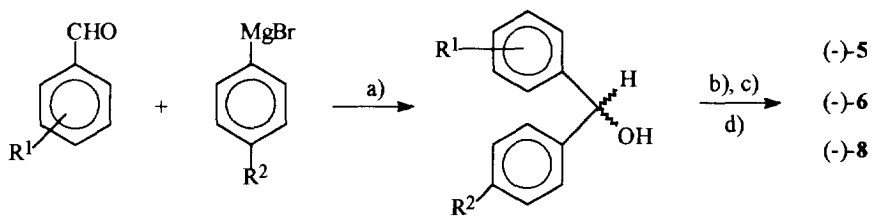
Determination of the absolute configuration of newly synthesised compounds with the diarylmethane moiety could be of a considerable help for the corresponding pharmacological studies. However, the possibilities for the correlation of the absolute configuration for such compounds are difficult, because of the limited number of known standards. Moreover chiroptical techniques can not offer an easy and reliable method to determine the absolute sense of chirality of two different substituted phenyl rings attached to one and the same stereogenic center.

We have recently studied the absolute stereochemistry and chiroptical properties of series chiral 1,2-diarylethanes[15] and α-aryl-2-pyridylmethanes[16]. Now we report the preparation of some optically active diarylmethanes[17] and the determination of their absolute configuration by chemical correlation and circular dichroism based on analysis of the longest wavelength Cotton effect of α-aromatic (^1L_b) band.

RESULTS AND DISCUSSION

1. *Preparation of the model optically active diarylmethane derivatives.* The racemic carbinols **5**, **6** and **8** were synthesised by addition of 4-methylphenyl-, 4-triflouromethylphenyl- and phenylmagnesium bromide to 4-chlorobenzaldehyde and 3-methylbenzaldehyde respectively and were converted to their acid phthalates (Scheme 1). The (±)-**5**-hemiphthalate and (±)-**6**-hemiphthalate were resolved by recrystalization of the cinchonine salts in MeOH/H_2O, while (±)-**8**-hemiphthalate - of quinidine salt from acetone. The optically active hemiphthalates were reduced with $LiAlH_4$ and yielded chiral diarylmethanoles: (-)-**5**; 84.6% ee; (-)-**6**; 85.6% ee; and (-)-**8**; 85.2% ee.

Scheme 1



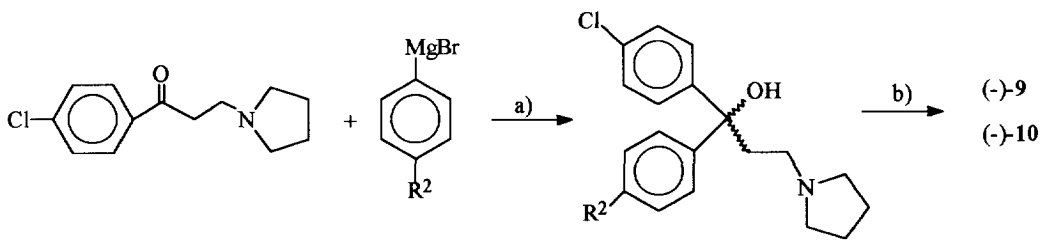
a) Et_2O, 0°C; H_3O^+
b) phthalic anhydride, pyridine; H_3O^+
c) resolution with cinchonidine or quinidine
d) $LiAlH_4$, Et_2O, 22°C

5: R^1 = 4-Cl; R^2 = CH_3
6: R^1 = 4-Cl; R^2 = CF_3
8: R^1 = 3-CH_3; R^2 = H

Racemic 1,1-diaryl-3-(1-pyrrolidinyl)-1-propanols ((±)-**9** and (±)-**10**) were synthesised by a reaction between 4-chloro-3-(1-pyrrolidinyl)propiophenone and phenyl- or 4-methylphenylmagnesium bromide respectively and were resolved with tartaric acid (Scheme 2). Compound (±)-**12** was prepared by reaction between 2-chloroethylpyrrolidine and the sodium salt of 4-chlorobenzhydrol in abs. benzene in 65% yield. (±)-**12** was resolved with O,O'-ditoluoyl-2*R*,3*R*-tartaric acid in i-PrOH (see Experimental). The benzhydrylether (±)-**13** was synthesised by adding of a THF solution of N-methyl-2-chloroacetamide to metallated carbinol (±)-**8** in THF

and subsequent reduction of the amide group with $LiAlH_4$. The homochiral compound (-)-**13** was obtained by resolution of the racemic one with (+)-2*R*,3*R*-tartaric acid in acetone.

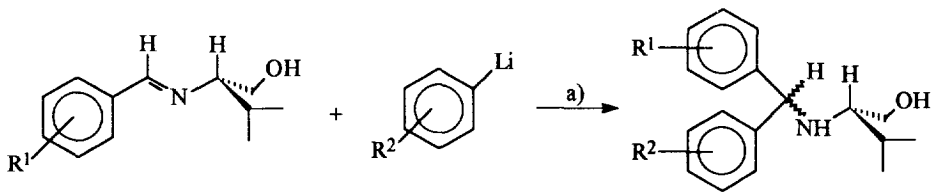
Scheme 2



a) Et_2O, 0°C, H_3O^+; b) resolution with tartaric acid **9**: $R^2 = H$ **10**: $R^2 = CH_3$

Takahashi et al.[14] have synthesised enantiomerically pure (+)-(1*S*,1'*S*)-N-2'-hydroxy-1'-isopropylethyl-1-(4-chlorophenyl)-1-phenylmethylamine ((+)-**14**) and (+)-(1*R*,1'*S*)-N-2'-hydroxy-1'-isopropylethyl-1-(4-methylphenyl)-1-phenylmethylamine ((+)-**16**) and established the absolute configuration by X-ray analysis and on the basis of the proposed reaction mechanism. By reaction of (*E*)-(*S*)-N-2-hydroxy-1-isopropylethyl-arylmethylideneamines[18] (**20-22**) and the corresponding aryllithiums in ether at room temperature the diarylmethylamines **14-19** were obtained (Scheme 3).

Scheme 3.



20: R^1 = 4-Cl
21: R^1 = H
22: R^1 = 2-Cl

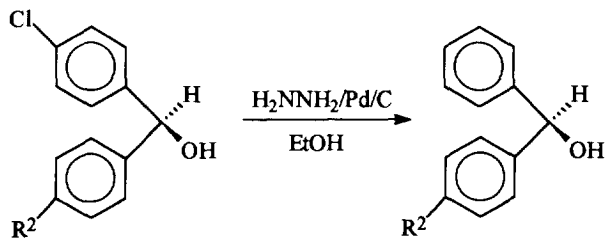
a) Et_2O, 22°C; H_2O

14: R^1 = 4-Cl; R^2 = H
15: R^1 = 4-Cl; R^2 = 4-CH_3
16: R^1 = H; R^2 = 4-CH_3
17: R^1 = 4-Cl; R^2 = 2-CH_3
18: R^1 = 2-Cl; R^2 = 3-CH_3
19: R^1 = 2-Cl; R^2 = H

The chiral compounds (+)-**14** - (+)-**17** were diastereoisomerically pure (no other diastereoisomer was detected in the ^{1}H-NMR spectra). The asymmetric induction in this reaction was directed by the 2-hydroxy-1-isopropylethyl moiety. The proposed mechanism[14] could be explained as follows: the lithium ion of the aryllithium reagent becomes associated with the hydroxide moiety and the lone pair electrons of the nitrogen atom, while the aryl anion of another aryllithium attacks the carbon atom of the C=N bond of the (*E*)-(*S*)-chiral azomethine from the *si-si* face. In the case of 2-chlorosubstituted azomethine **22** (with different steric requirements as **20** and **21**) the substituent shielded the *si-si* face of the C=N bond and the diastereoselectivity decreased (de: 74% for **18**, resp. 80% for **19**).

2. *Absolute configuration of diarylmethane derivatives.* 2.1. *Correlation of the absolute configuration by chemical methods.* In this study the model diarylmethanes **1**, **4**, **7**, **9**, **14** and **16**, with previously established absolute configurations served as standards. Their absolute configuration were determined by X-ray analyses, e.g. **1**[2], **9**[21], **14** and **16**[14]; or by chemical correlation[22] and Horeau's method[23] for benzhydrols **4** and **7**. The limiting number of diarylmethane compounds with known absolute configuration restricts chemical correlations as a method for establishing the configuration of new compounds of this type. We applied this approach to (+)-**5** and (-)-**6**. After dehalogenation using hydrazine hydrate in the presence of Pd/C[24], (+)-**5** and (-)-**6** afforded actively (+)-(*R*)-**4** and (-)-(*R*)-**7**, respectively, both with known configuration[22,23] (Scheme 4). As this reaction proceeds without racemisation the configuration assignment: (*S*) for (+)-**5** and (*S*) for (-)-**6** is correct and was also supported by analysis of the CD spectra of these compounds (see below).

Scheme 4



R^2 = 4-CH_3: (+)-(*S*)-**5** (+)-(*R*)-**4**
R^2 = 4-CF_3: (–)-(*S*)-**6** (–)-(*R*)-**7**

2.2. *Circular dichroic spectra within the α-aromatic (^1L_b) band.* The UV-spectrum of the benzene chromophore possessed three bands at 184, 204 and 254 nm. Only the last one (^1L_b-band) shows well defined vibrational fine structure, clearly observable usually in the CD spectrum. The ring substitution leads to bathochromical shift of ^1L_b fine structure band[25]. Our previous studies showed that CD within α-aromatic band of 1,2-disubstituted-1,2-diphenylethanes is rather complicated. Although associated electronic transition moments are small and no interaction between the two individual phenyl chromophores should take place in this spectral range such CD band is complicated because each phenyl ring gives at least two vibronic series for each of the preferred conformations in solution[15,26]. On the basis of the difference- and sum-CD spectra we showed that the analysis of the such bands may be considerably simplified by taking in consideration only the corresponding 0-0 lines. It is even better if the CD series of both phenyl chromophores could be disentangled by appropriate ring substitutions.

Similar difficulties could be expected in the analysis of α-aromatic band of compounds containing a diarylmethane moiety where no interaction between the two aromatic rings should exist. In this case, however, the required difference in the substitution of both phenyl rings gives some advantages. If the longest wavelength lines of the α-CD band of one of the chromophores are sufficiently bathochromically shifted with respect to the other chromophore and their signs can be read off from the spectrum unequivocally then such CD lines could be useful for the correlation of the absolute configuration. The p- and m-substitution of the phenyl ring(s) should not influence the conformation around the pivot-bond of the phenyl ring. On the other hand, any substituent will introduce an additional electric transition moment in the plane of its benzene ring. According to Petruska's data[27] in isooctane solution 4-chloro- and 4-methyl substitution respectively in the toluene ring leads to a

bathochromic shift of the 0-0 line with *ca.* 1180 cm^{-1} and 780 cm^{-1} respectively. The 0-0 vibrational transitions in the UV spectra of 4-chloro- and 4-methyl substituted ring in the diarylmethane moiety were at *ca.* 276 and 273 nm respectively[14] which is in agreement with Petruska's data. The 1,2-disubstituted-1-chlorophenyl-2-phenyl ethanes show CD lines for 4-chlorophenyl ring at about 276 nm[15b]. The substitution in the benzene ring might cause in some cases a sign inversion of the corresponding Cotton effect. Although we studied the CD-spectra of *ca.* twenty compounds of diarylmethane type we would like to retain from discussing Platt's and Petruska's q-values[27] in detail, because of uncertainty in magnitude and even in their sign of the presented benzyl group. In most cases both individual 0-0 lines for the two aryl chromophores have opposite signs and we can conclude that the q-values of a substituted benzyl group is bigger than that of the methyl-, chloro-, or trifluoromethylsubstituent.

Table 1. CD data and absolute configuration for **1, 4-19**.

Compound	Configuration	Solvent[a)]	CD [nm] ($\Delta\varepsilon$)[b)]
1	*S,S*	E	276 (+ 0.20), 271 (+ 0.18), 268 (- 0.11), 264 (+ 0.06), 261 (- 0.18), 253 (- 0.10), 225 (- 1.54), 214 (+ 4.75).
4	*R*	D	275 (- 0.10), 270 (+ 0.10), 262 (+ 0.15), 256 (+ 0.10), 225 (- 1.33, sh), 223 (- 1.35), 218 (-1.12)
		AC	275 (- 0.09), 269 (+ 0.14), 263 (+ 0.25), 256 (+ 0.18), 225 (- 0.84, sh), 220 (- 1.30).
5	*S*	D	278 (+ 0.04), 274 (- 0.04), 271 (+ 0.05), 267 (- 0.02), 265 (+ 0.02), 261 (- 0.04), 238 (+ 0.28), 216 (+ 2.29), 206 (+ 1.84, sh).
		AC	278 (+ 0.05), 274 (- 0.03), 272 (+ 0.04), 265 (- 0.03), 259 (- 0.04), 228 (- 1.09), 214 (+ 1.45), 206 (+ 1.11).
6	*S*	D	277 (+ 0.05), 269 (- 0.07), 262 (- 0.11), 255 (- 0.09), 229 (+ 0.90), 215 (- 2.08, sh).
		AC	277 (+ 0.03), 270 (- 0.09), 266 (- 0.11), 260 (- 0.15), 227 (+ 0.63), 212 (- 1.60).
7	*R*	D	272 (- 0.08), 267 (- 0.11), 261 (- 0.14), 254 (- 0.08), 225 (+ 1.46), 224 (+ 1.52), 220 (+ 1.14, sh).
		AC	271 (- 0.06), 265 (- 0.09), 225 (+ 1.46).
8	*S*	AC	272 (+ 0.11), 269 (- 0.04), 266 (+ 0.07), 262 (- 0.07) 255 (- 0.06).
9	*S*	D	278 (+ 0.26), 273 (+ 0.17), 267 (+ 0.06), 262 (- 0.15), 256 (- 0.14), 229 (+ 3.18), 212 (- 4.81, sh), 208 (- 5.12).
		AC	277 (+ 0.22), 271 (+ 0.14), 267 (- 0.05), 260 (- 0.23), 254 (- 0.16), 227 (+ 2.96), 210 (- 4.82).
		AC + H^+	277 (+ 0.16), 271 (+ 0.13), 268 (- 0.05), 266 (+ 0.03), 262 (- 0.14), 254 (- 0.09), 229 (+ 1.90, sh), 222 (+ 2.64), 216 (+ 2.66), 201 (+ 2.92).

Table 1. Continued.

Compound	Configuration	Solvent[a]	CD [nm] ($\Delta\varepsilon$)[b]
10	*R*	D	278 (- 0.12), 275 (+ 0.04), 272 (- 0.08), 266 (+ 0.03), 260 (+ 0.03), 229 (- 0.80), 224 (- 0.40, sh), 219 (+ 0.22, sh), 216 (+ 0.25).
		AC	278 (- 0.11), 274 (+ 0.03), 272 (- 0.08), 265 (+ 0.04), 263 (-0.04), 261 (+ 0.03).
11	*S*	AC	275 (+ 0.15), 269 (- 0.02), 267 (+ 0.05), 262 (- 0.12), 255 (- 0.09).
12	*R*	AC	275 (- 0.06), 269 (+ 0.04), 262 (+ 0.10), 255 (- 0.02), 226 (+ 1.15), 212 (- 2.45).
13	*S*	AC	273 (+ 0.11), 269 (- 0.08), 265 (+ 0.04), 262 (- 0.11), 261 (- 0.12), 217 (- 1.06), 209 (- 2.35).
14	1*S*,1'*S*	E (base)	278 (+ 0.11), 275 (+ 0.05), 270 (- 0.16), 263 (- 0.24), 257 (- 0.06), 236 (+ 2.04), 232 (+ 1.78, sh), 218 (- 1.51)
		E (HCl salt)	277 (- 0.14), 232 (- 2.98), 226 (- 2.06), 213 (+ 10.47).
		AC (base)	278 (- 0.17), 275 (+ 0.13), 269 (- 0.06), 267 (+ 0.08), 239 (+ 0.88), 226 (- 0.58), 208 (+ 4.06).
		AC (HCl salt)	276 (- 0.05), 270 (- 0.19), 263 (- 0.21), 257 (- 0.14), 234 (- 3.96), 214 (+ 13.01).
15	1*S*,1'*S*	E (base)	279 (+ 0.54), 275 (- 0.07), 271 (+ 0.69), 267 (- 0.04), 264 (+ 0.05), 235 (+ 2.36).
		E (HCl salt)	277 (- 0.09), 272 (- 0.21), 266 (- 0.18), 258 (- 0.09), 216 (+ 5.72).
		AC (HCl salt)	280 (+ 0.03), 272 (- 0.11), 266 (- 0.10), 235 (- 3.60), 217 (+ 13.89).
16	1*R*,1'*S*	AC (base)	275 (- 0.21), 270 (+ 0.11), 267 (- 0.08), 263 (+ 0.24), 260 (+ 0.04), 256 (+ 0.14), 229 (+ 2.39, sh), 226 (+ 2.61), 208 (- 1.77).
17	1*R*,1'*S*	E (base)	278 (+ 0.18), 272 (+ 0.38), 266 (+ 0.32), 227 (+ 4.97).
		E (HCl salt)	272 (+ 1.38), 267 (+ 1.36), 260 (+ 0.86), 227 (+ 4.97).
		AC (HCl salt)	274 (+ 1.19), 267 (+ 1.18), 246 (+ 0.17), 239 (- 0.72), 220 (+ 2.31, sh), 207 (+ 6.91).
18	1*S*,1'*S*	E (base)	276 (- 0.53), 268 (- 0.44), 261 (- 0.19), 224 (- 14.22).
		E (HCl salt)	276 (- 1.56), 269 (- 1.31), 263 (- 0.64), 227 (- 11.80).
		AC (HCl salt)	276 (- 1.07), 268 (- 0.90), 261 (- 0.52), 227 (- 14.50).
19	1*S*,1'*S*	E (base)	276 (- 0.26), 270 (- 0.43), 263 (- 0.34), 256 (- 0.17), 224 (- 12.64).
		E (HCl salt)	276 (- 0.99), 269 (- 1.27), 263 (- 0.73), 227 (- 11.30), 211 (+ 13.17).
		AC (HCl salt)	275 (- 0.72), 269 (- 0.88), 263 (- 0.58), 227 (- 16.30), 211 (+ 6.93).

[a] AC: acetonitrile; D: dioxane; E: ethanol; [b] CD: a dichrograph Mark III (ISA, Jobin Yvon), connected on line to a PDP-8e. Noise was eliminated by curve-smoothing according to the Golay-Savitzki algorithm[27].

On the basis of these results it is possible to determine the absolute configuration of close analogues in an empirical way by comparison of their CD spectra within the aromatic α-band.

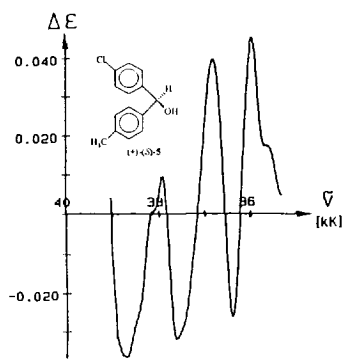
In the Table 1 were presented the circular dichroic data and the absolute configuration of the diarylmethane compounds **1** and **4** to **19**. Figures 1 through 3 show our mode of correlation of the absolute configuration as well as some examples of bisignate CD-spectra within the α-band absorption. The observed 0-0 line positions coincide well with the Δν - values estimate by Petruska's' formula[27] .

*Absolute configuration of diarylmethanols **4**, **6**, **8** and benzhydrylether **13**.* All compounds **4-8** show an α-aromatic band with a pronounced fine structure. The correlation of absolute configuration of (+)-**5** and (-)-**6** with the standard compounds (+)-**4** and (-)-**7** is presented on Figure 1. The 0-0 band of 4-CH_3-C_6H_4-chromophore in (-)-**4** and (+)-**5** has very similar position and negative sign, while the positive sign of 0-0 band of p-chlorosubstituted phenyl ring in (+)-**5** is presented after chemical conversion of **5** as a positive line at 37133 cm^{-1} of unsubstituted benzene ring. The position of 0-0 line of Cl-C_6H_4-ring in (+)-**5** matches very well with this of (-)-**6** and both are positive, while the expected 0-0 band of 4-CF_3-C_6H_4 of (-)-**6** is not detectable. The comparison between homochiral (-)-**6** and (-)-**7** (chemical correlation) reveals clear-cut negative 0-0 band of 4-CF_3-C_6H_4-ring in **7** and confirm the correlation on the base of 0-0 sign of 4-Cl-C_6H_4-, 4-CH_3-C_6H_4- and 4-CF_3-C_6H_4-chromophores. Moreover the observed positions of these lines are in good agreement with the estimated values according Petruska[27]. Therefore, (+)-(*S*)-**5** and (+)-**6** have the same absolute configuration due to the same sign of the Cotton effect for the 4-chlorosubstituted ring at 35945 and 36100 cm^{-1}, respectively. The CD-spectra of the compounds (-)-**8** and (-)-**13** show a positive Cotton effect at 36724 and 36670 cm^{-1}, respectively, which is due to the 0-0 line of the 3-methyl substituted ring, and a negative one at 37133 and 37160 cm^{-1}, respectively, associated with the 0-0-vibronic transition of the unsubstituted phenyl chromophore. The latter one is almost in the same position as the positive 0-0 line for the phenyl chromophore in (+)-(*R*)-**4** (37133 cm^{-1}). On the basis of the CD data presented (Table 1) these two compounds ((-)-**8** and (-)-**13**) were homochiral, although (-)-**13** was not prepared from optically active **8**, and have the same (*S*)-absolute configuration (see Fig. 1).

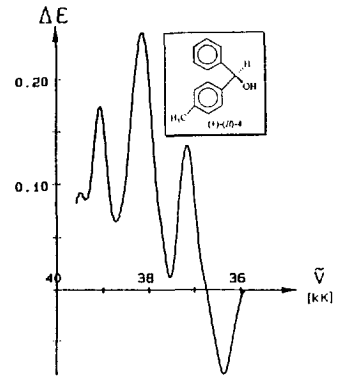
*Absolute configuration of 1,1-diaryl-3-(1-pyrrolidinyl)-1-propanols **9-11** and benzhydrylether **12**.* The 0-0 lines for the 4-chlorosubstituted rings in the CD spectra of (+)-(*S*)-**9** and (-)-(*S,S*)-**1** (see Table 1) are with nearly the same intensity and the same sign at 277 resp. 276 nm and these of the unsubstituted ring are positive at 271 nm for both compounds (Fig. 2). Therefore they should have the same absolute configuration at the benzylic C-atom, namely *S*, which was confirmed by X-ray analysis of both compounds.

The CD spectra of 1,1-diarylpropan-1-ols **9** - **11** are shown in Figure 2. The position of 0-0 lines of 4-chlorosubstituted phenyl chromophore in standard (+)-**9** and (-)-**1**, as well as these in (-)-**10** and (-)-**12** matches very well with the previous data (see Fig. 1). All these transitions are in the longest wavelengths bands and are clearly separated from the opposite in sign 0-0 lines for 4-methylsubstituted- and unsubstituted phenyl ring in (-)-**10**, (+)-**9**, (-)-**1** and (-)-**12**, respectively. The CD correlation of the absolute configuration of (-)-**10** and (-)-**11** from the positive 0-0-band of 4-$CH_3C_6H_4$-chromophore and negative 0-0-lines of 4-Cl-C_6H_4- in **10** and of C_6H_5-ring in **11** was proved by chemical conversion of (-)-**10** into (-)-**11**. On the basis of this empirical comparison we assume (*R*)-absolute configuration for (-)-**10** and (-)-**12**, and (*S*)- for (-)-**11**.

*Absolute configuration of diarylmethylamines **14-19**.* The absolute configuration of (+)-**14** was determined to be (1*S*,1'*S*) by X-ray analysis[14]. Following the described reaction mechanism (see above) and the CD data (Table 1 and Fig. 3) we have determined the absolute configuration of the chiral diarylmethylamines



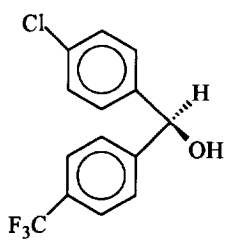
Chem. corr.
CD



4-ClC_6H_4: (+) 35945
4-$CH_3C_6H_4$: (–) 36390

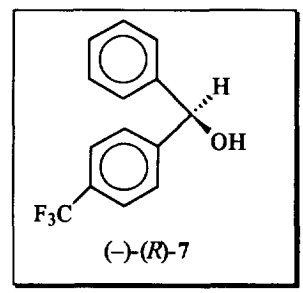
C_6H_5: (+) 37133
4-$CH_3C_6H_4$: (–) 36337

CD



(–)-(*S*)-**6**

Chem. corr.
CD

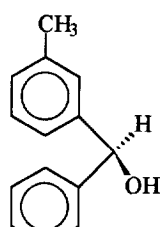


(–)-(*R*)-**7**

4-ClC_6H_4: (+) 36100
4-$CF_3C_6H_4$: not detectable

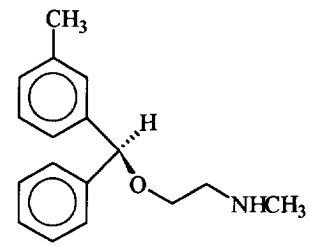
C_6H_5: not detectable
4-$CF_3C_6H_4$: (–) 36887

CD



(–)-(*S*)-**8**

CD

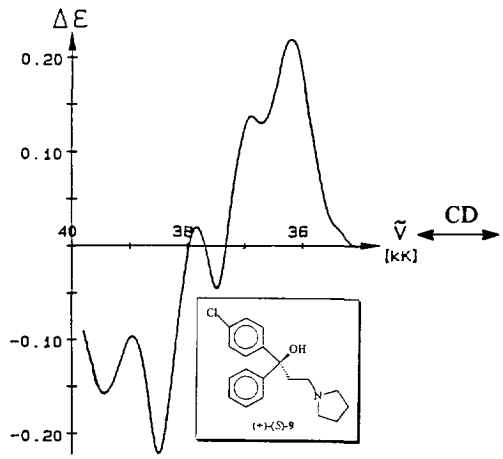


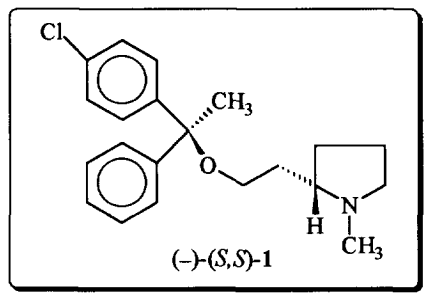
(–)-(*S*)-**13**

C_6H_5: (–) 37133
3-$CH_3C_6H_4$: (+) 36724

C_6H_5: (–) 37160
3-$CH_3C_6H_4$: (+) 36670

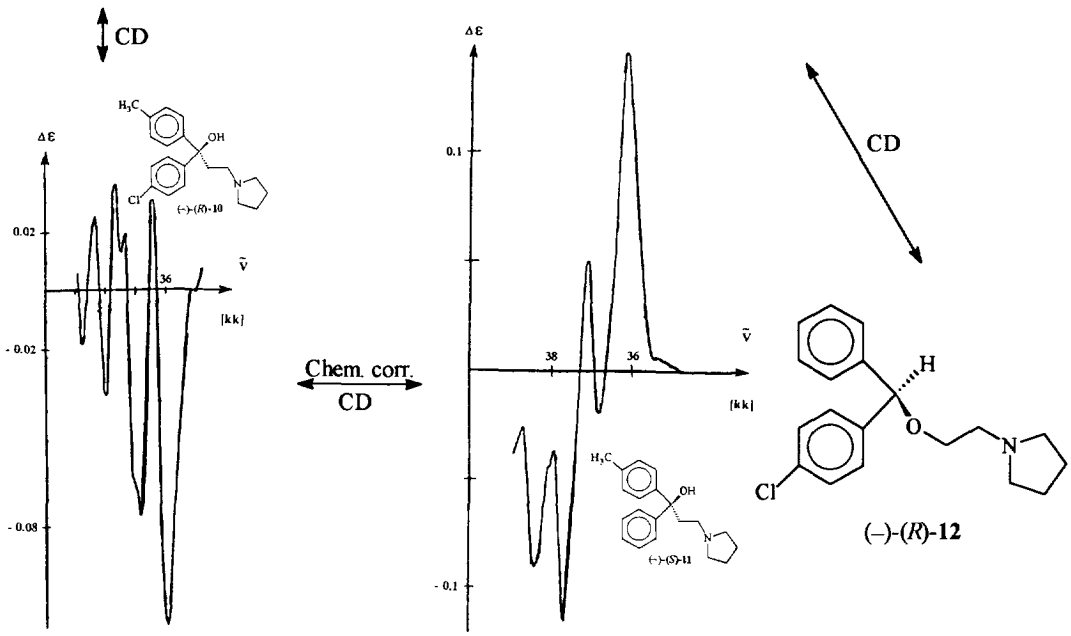
Figure 1. Correlation of the absolute configuration of diarylmethanols **5**, **6**, **8** and benzhydrylether **13**. CD spectra (acetonitrile) of **4** and **5** ($\Delta\varepsilon/\nu$[kk]), sign and exact position of 0-0 Cotton effects (in cm^{-1}).





4-ClC$_6$H$_4$: (+) 36153
C$_6$H$_5$: (–) 37440

4-ClC$_6$H$_4$: (+) 36206
C$_6$H$_5$: (–) 37383



4-ClC$_6$H$_4$: (–) 35945
4-CH$_3$C$_6$H$_4$: (+) 36496

4-CH$_3$C$_6$H$_4$: (+) 36390
C$_6$H$_5$: (–) 37175

4-ClC$_6$H$_4$: (–) 36153
C$_6$H$_5$: (+) 37184

Figure 2. Correlation of the absolute configuration of **9**, **10**, **11** and **12**. CD spectra (acetonitrile) of **9**, **10** and **11** (Δε/ν[kk]), sign and exact position of 0-0 Cotton effects (in cm^{-1}).

15-19. The UV and the CD data of the previously synthesised (+)-(1*S*,1'*S*)-**14** and (+)-(*1R*,1'*S*)-**16** were published[14] but the authors didn't observe the corresponding Cotton effects for the 4-chloro- or 4-methylsubstituted phenyl rings in their CD spectra (measured as HCl-salts in EtOH) at 276 and 272 nm

respectively. They concluded that the absolute configuration of these compounds could not be determined by CD spectroscopy[14]. We have measured the CD spectra of all diarylmethyamines in EtOH and acetonitrile as base and as hydrochlorides and observed the corresponding 0-0 lines from the chlorosubstituted benzene ring at ca. 35800-35900 cm^{-1} and for the methylsubstituted phenyl chromophore at ca. 36300-36400 cm^{-1} (Fig. 3),

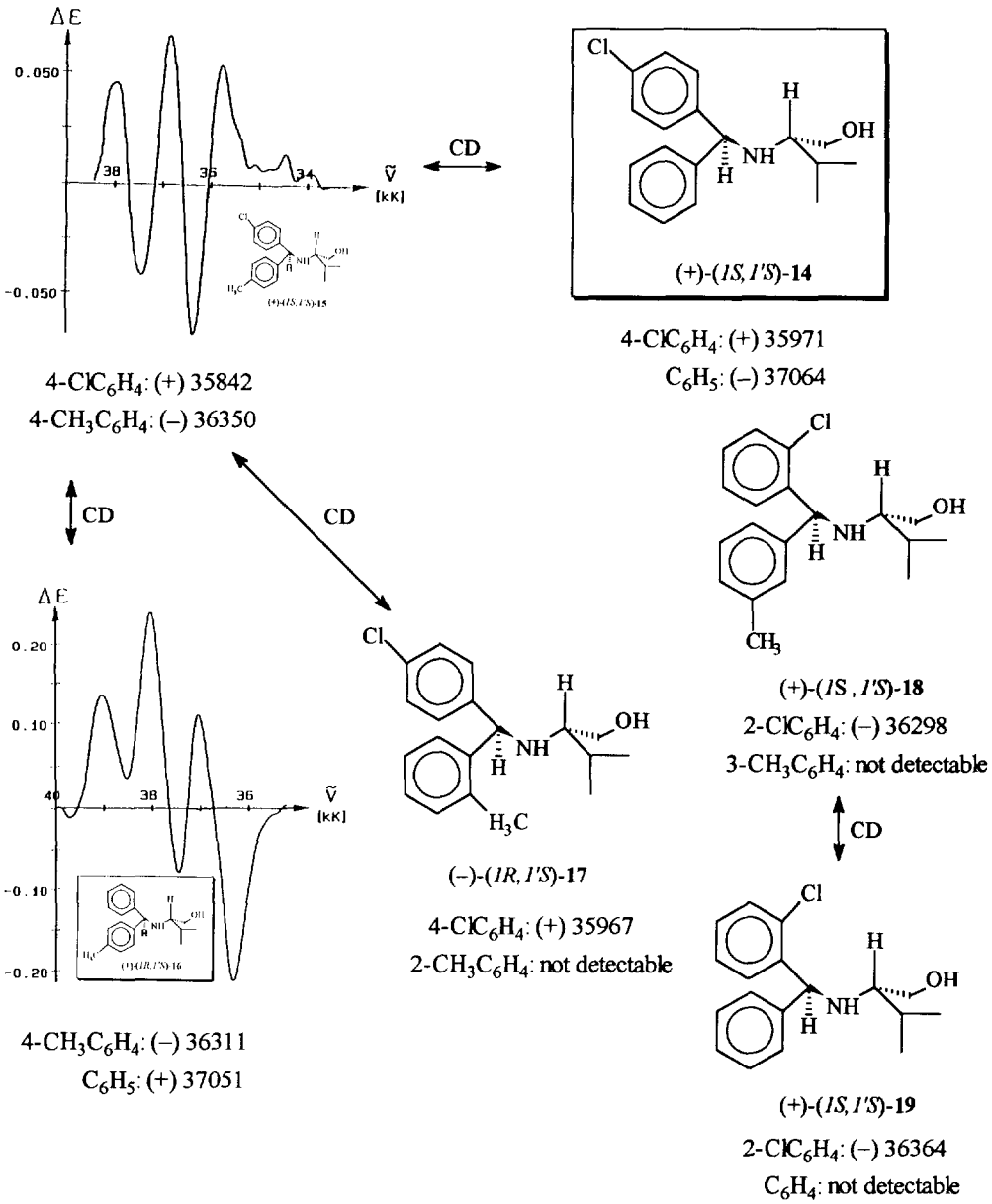


Figure 3. Correlation of the absolute configuration of diarylmethylamines **15**, **16**, **17**, **18** and **19**. CD spectra (acetonitrile) of **15** and **16** ($\Delta\varepsilon/\nu$[kk]), sign and exact position of 0-0 Cotton effects (in cm^{-1}).

which is in agreement with our previous results[15]. There is no doubt that the observed Cotton effects can be used for the correlation of the absolute configuration of these chiral diarylmethane compounds.

The very similar position and same sign of the 0-0 band of p-chlorosubstituted phenyl chromophore in (+)-**14**, (+)-**15** and (-)-**17** evidence their homochirality at the benzylic stereogenic center (Fig. 3 and Table 1). Figure 3 shows the CD spectra of (+)-**15** and (+)-**16**. One can see that the sign of the 0-0 transition for the p-CH_3-C_6H_4 chromophore at *ca.* 36300 cm^{-1} is negative for both compounds. The sign of ^1L_b Cotton effect for p-Cl-C_6H_4 and unsubstituted benzene ring is positive (at 35842 and 37051 cm^{-1}, resp.). From these observations we concluded that the arrangement around the stereogenic center, bearing the diarylmethane moiety, is one and the same for these two compounds and therefore the absolute configuration at this center for **15** is *S* and this of **16** is *R*.

Comparison of the CD spectra of (+)-**19** and (+)-**18** shows that the 0-0 line of the 2-chlorosubstituted ring at *ca.* 36300 cm^{-1} for both compounds is negative (Fig. 3). Therefore these two diarylmethylamines are homochiral. However, the assignment of absolute configuration of **18** and **19** from the negative 0-0 band of 2-Cl-C_6H_4-chromophore could not be straightforward, because of possible conformational difference at the benzylic stereogenic center between 4-Cl-C_6H_4- and 2-Cl-C_6H_4 analogues. Thus, following the proposed reaction mechanism the phenyl- and 3-methylphenyl anion respectively should attack the less hindered side of the C=N double bond (*si-si* face) yielding products with 1*S* configuration. On the basis of these two facts we assumed 1*S* configuration for (+)-**18** and (+)-**19**.

In conclusion, the CD spectra of all diarylmethane compounds studied are with well defined fine structure within the α-aromatic band. The position of the substituent in the benzene ring (p- or m) should not influence the sign of 0-0 transitions, because the spectroscopic moment of the phenyl group is obviously larger than that of the ring substituents (Cl, CH_3, CF_3) and also because the p- and m-substitution should not influence the conformation around the pivot-bond of the phenyl rings. For that reason the empirical correlation of 4-substituted- with 3-substituted phenyl ring seems possible. Finally we would like to emphasise, that for the determination of the absolute configuration of such pharmacological important diarylmethane derivatives, the non destructive and quickly performed CD method can be successfully applied , if a correct model compound of known configuration is available.

EXPERIMENTAL

General: M.p.: Kofler hot-stage apparatus, uncorrected. IR spectra: *Specord 75*; $CHCl_3$ soln.; in cm^{-1}. ^1H NMR: *Bruker WM-250* or *Tesla 60-BS-467* spectrometer; $CDCl_3$ soln.; chemical shifts (δ) in ppm, coupling constants *J* in Hz. MS: *Jeol-LMS-D-300*, for CI-MS: reactant gas: 2-methylpropane. Optical rotations: *Perkin-Elmer 241* instrument. CD spectra: *Dichrograph Mark III (ISA, Jobin Yvon)*, connected on line to PDP-8e. TLC: silica gel alu foils (60 F_{254}, *Merck*). Column chromatography: silica gel 60 (70-230 mesh, *Merck*). Solutions were dried over anh. $MgSO_4$.

1. **Optically active diarylmethanols.** 1.1. **(±)-4-Chlorophenyl-4'-methylphenylmethanol ((±)-5).** To a stirred soln. of 275 mmol 4-toluoylmagnesium bromide in 250 ml of abs. ether at 0°C were added 27.3 g (250 mmol) of 4-chlorobenzaldehyde in 350 ml of abs. ether. The reaction mixture was stirred 4h at 22°C. Then it was poured into HCl/crushed ice, the organic phase was separated and the aq. phase was extracted with ether. The combined org. layers were washed with 5% $NaHSO_3$ soln., brine, 3% Na_2CO_3 soln, brine, dried and evaporated. After recrystallization from hexane 33.5 g (65%) of (±)-**5** were obtained. M.p.: 66-67°C; (lit: 67.5°C[29a] ; 69°C[29b]; 72-74°C[29c]). IR: 3600, 2950, 2870, 1600, 1470. ^1H NMR (60 MHz): 7.35 (m, 8H); 5.76

(s, 1H); 2.31 (s, CH_3); 2.09 (br. s, OH). Anal. calc. for $C_{14}H_{13}ClO$ (232.712): C 72.26, H 5.63, Cl 15.24; found: C 72.10, H 5.61, Cl 15.30.

1.1.1. **(+)-(*S*)-5.** 3.8 g of (±)-**5** as acid phthalate and 2.94g of (-)-cinchonine were dissolved at reflux in 25 ml of MeOH. After cooling to 22°C 3 ml of H_2O were added and the mixture was kept at the same temperature for 12h. The obtained crystals were filtered and recrystallized 5 times from the same solvent: 1.3 g (19%) of the salt. Free acid phthalate has $[\alpha]_D^{22}$ = + 5.59 (c = 0.66, acetone). M.p.: 147-149°C. To a stirred suspension of 0.126 g (3.3 mmol) of $LiAlH_4$ in 10 ml of abs. ether at 22°C were added 0.31 g (0.8 mmol) of (+)-acid phthalate of **5**. The reaction mixture was stirred for 30 min, hydrolysed with H_2O and after column chromatography (CH_2Cl_2) 0.184g (100%) of (+)-(*S*)-**5** were obtained. M.p.: 69-70°C; $[\alpha]_D^{22}$ = + 19.96 (c = 0.27, benzene); 84.6% ee.

1.2. **(±)-4-Chlorophenyl-4'-trifluoromethylphenylmethanol ((±)-6).** Following 1.1 from 10.9 g (77.5 mmol) of 4-chlorobenzaldehyde and 115 mmol of 4-trifluoromethylphenylmagnesium bromide were obtained 21 g (81%) of (±)-**6**. M.p.: 95-96°C. IR: 3590, 2870, 1620, 1590, 1480, 1410, 1325. ^1H NMR (60 MHz): 7.40 (m, 8H); 5.86 (br. s, 1H); 2.46 (br. s, OH). Anal. calc. for $C_{14}H_{10}ClF_3O$ (286.670): C 58.65, H 3.52; found: C 58.83, H 3.60.

1.2.1. **(-)-(*S*)-6.** According to 1.1.1 (±)-**6** was resolved as acid phthalate with (-)-cinchonine in MeOH/H_2O (10:1). M.p. of (-)-(*S*)-**6**: 102.5-104°C; $[\alpha]_D^{22}$ = - 12.67 (c = 0.19, benzene); 89.5% ee.

1.3. **(±)-3-Methylphenyl-phenylmethanol ((±)-8).** From 24 g (200 mmol) of 3-methylbenzaldehyde and 220 mmol of phenyl magnesium bromide following 1.1 were obtained 32 g (80%) of (±)-**8**. M.p.: 50-51°C (lit.: 53°C[29a]; 52-53.5°C[29c]; 53.3°C[30]). IR: 3590, 2990, 2860, 2810, 1600, 1480, 1450. ^1H NMR (60 MHz): 7.45 (m, 9H); 5.72 (s, 1H); 2.40 (br. s, OH); 2.26 (s, CH_3). Anal. calc. for $C_{14}H_{14}O$ (198.251): C 84.82, H 7.11; found: C 84.70, H 7.15.

1.3.1. **(-)-(*S*)-8.** Three recrystallizations of the salt of the acid phthalate of (±)-**8** and (-)-quinidine in acetone gave (-)-(*S*)-3-methylphenyl-phenylmethanol ((-)-**8**). M.p.: 38-41°C; $[\alpha]_D^{22}$ = - 2.28 (c = 2.33, benzene); 85.2% ee (lit.: $[\alpha]_D$ = - 2.5 (c = 0.32, MeOH); 92.1% ee[13]).

1.4. **(+)-(*R*)-4-Methylphenyl-phenylmethanol ((+)-4).** According to the literature procedure[24] from 90 mg (0.4 mmol) of (+)-**5** ($[\alpha]_D^{22}$ = + 19.96) were obtained 62 mg (90%) of (+)-(R)-**4**. M.p.: 61-62 ; $[\alpha]_D^{22}$ = + 8.71 (c = 0.4, benzene); 84.6% ee (lit.: 61-63°C; $[\alpha]_D^{22}$ = - 9.66 (c = 0.1, benzene)[31] $[\alpha]_D^{22}$ = - 10.3 (c = 5.0, benzene) for optically pure (-)-(S)-**4**[22]);. IR: 3600, 2930, 2820, 1600, 1450. ^1H NMR (60 MHz): 7.07 (m, 9H); 5.70 (s, 1H); 2.33 (s, OH); 2.22 (s, CH_3).

1.5. **(-)-(*R*)-4-Trifluoromethylphenyl-phenylmethanol ((-)-7).** 75 mg (0.26 mmol) of (-)-**6** ($[\alpha]_D^{22}$ = - 12.67) were dehalogenated[24] to 57 mg (85%) of (-)-(*R*)-**7**. M.p.: 84-86°C; $[\alpha]_D^{22}$ = - 34.6 (c = 0.19, benzene); 89.5% ee; (lit.: $[\alpha]_D^{22}$ = + 40.4 (c = 5.0, benzene) for optically pure (+)-(S)-**7**[22]). IR: 3600, 2930, 2830, 1600, 1450. ^1H NMR (60 MHz): 7.50 (m, 4H); 7.30 (m, 5H), 5.74 (s, 1H); 2.63 (br. s, OH).

2. **Optically active 1,1-Diaryl-3-(1-pyrrolidinyl)-1-propanols. 2.1. (±)-1-(4-Chlorophenyl)-1-phenyl-3-(1-pyrrolidinyl)-1-propanol (±)-9).** To a stirred soln. of 180 mmol of phenylmagnesium bromide in 250 ml abs. ether at 0°C were added 14.4 g (60 mmol) of 4'-chloro-3-(1-pyrrolidinyl)propiophenone-HCl[32]. The reaction mixture was stirred for 2h at 22°C, then 2h at reflux, and was poured into HCl/crushed ice. The aq. phase was separated, alkalised with conc. NH_3 soln. and extracted with ether. The ethereal soln. was washed with H_2O, dried and evaporated. The crude product was recrystallized from MeOH/H_2O and 9.5 g (50%) of (±)-**9** were obtained. M.p.: 116-117°C (lit.: 118-120°C[33]). IR: 3078, 2960, 2875, 1600, 1480, 1450. ^1H NMR (60 MHz): 7.66 (m, 10H); 2.53 (m, 8H); 1.79 (m, 4H). CI-MS: 316 ($[M+1]^+$).

2.1.1. **(+)-(*S*)-9.** 6.75 g of (±)-**9** and 3.21 g of (-)-(2*S*,3*S*)-tartaric acid were dissolved in 850 ml of acetone at reflux. The soln. was kept for 12h at 0°C, the obtained crystals were filtered and recrystallized 4 times from acetone. The salt was dissolved in H_2O, alkalised with conc. NH_3 and extracted with ether. The ethereal soln. was washed with H_2O, dried and evaporated to gave (+)-(*S*)-**9**. M.p.: 135-137°C; $[\alpha]_D^{22}$ = + 8.28 (c = 0.22, $CHCl_3$).

2.2. **(±)-1-(4-Chlorophenyl)-1-(4-methylphenyl)-3-(1-pyrrolidinyl)-1-propanol ((±)-10).** According to the Exper. 2.1 from 4.73 g (20 mmol) of 4'-chloro-3-(1-pyrrolidinyl)propiophenone and 40 mmol 4-toluoyl-

lithium were obtained 3.6 g (55%) of (±)-**10**. M.p.: 129-131°C. IR: 3080, 2960, 2940, 2880, 2815, 1610, 1580, 1490, 1460. ^{1}H NMR (60 MHz): 7.26 (m, 8H); 2.46 (m, 9H), 2.26 (s, 3H, CH_3); 1.76 (m, 4H). Anal. calc. for $C_{20}H_{24}ClNO$ (329.847): C 72.82, H 7.33, Cl 10.75, N 4.25; found: C 73.11, H 7.30, Cl 10.87, N 4.28.

2.2.1. **(-)-(*R*)-10.** Three recrystallizations of the salt of (±)-**10** and (+)-(2*R*,3*R*)-tartaric acid after alkalisation gave 54% of (-)-(*R*)-**10**. M.p.: 126-127°C; $[\alpha]_D^{22}$ = - 8.37 (c = 0.23, $CHCl_3$).

2.3. **(-)-(*S*)-1-(4-Methylphenyl)-1-phenyl-3-(1-pyrrolidinyl)-1-propanol ((-)-11)**. Following the dehalo-genation procedure[24] 330 mg (1 mmol) of (-)-(*R*)-**10** ($[\alpha]_D^{22}$ = - 8.37) gave 242 mg (82%) of (-)-(*S*)-**11**. M.p.: 135-137°C; ((±)-**11**: 122-124°C). $[\alpha]_D^{22}$ = - 2.22 (c = 0.45, $CHCl_3$). ^{1}H NMR (60 MHz): 7.30 (m, 9H), 2.50 (m, 9H), 2.25 (s, 3H, CH_3), 1.77 (m, 4H). CI-MS: 296 ($[M+1]^+$).

3. **(±)-(2-(1-Pyrrolidinyl)ethyl)-1-(4-chlorophenyl)-1-phenylmethyl ether ((±)-12)**. To a stirred soln. of 22 mmol of NaOEt in 10 ml of abs. EtOH 4.5 g (20.5 mmol) of 4-chlorobenzhydrol were added. The reaction mixture was stirred at 22°C for 30 min, the ethanol was evaporated and 30 ml of abs. benzene were added. To removed the traces of EtOH 15 ml of benzene were distillated and 2.4 g (18 mmol) of 2-chloroethylpyrrolidine were added. The reaction mixture was heated under reflux for 20h and the NaCl formed was filtered. The org. layer was evaporated, the residue dissolved in small amount of water, acidified with 10% hydrochloric acid and extracted with ether. The aq. phase was alkalised with conc. NH_3 soln. and extracted with ether. The combined ethereal extracts were washed with H_2O, dried and evaporated. The crude product was purified by column chromatography (ether/methanol 1:0.5). Yield: 3.7 g (65%) of (±)-**12**, colourless oil. M.p.: of the HCl-salt: 141-142°C (lit.: 144-145°C[34]). IR: 2950, 2860, 2780, 1650, 1600, 1090, 1010. CI-MS: 316 ($[M+1]^+$). Anal. calc. for $C_{19}H_{22}ClNO$ (315.840): C 72.25, H 7.02, N 4.43; found: C 72.03, H 7.10, N 4.45.

3.1. **(-)-(*R*)-12.** 700 mg of (±)-**12** and 850 mg of O,O'-ditoluoyl-(2*R*,3*R*)-tartaric acid were dissolved in 20 ml of i-PrOH. The soln. was kept at 0°C for 48 h, the formed crystals were filtered and recrystallized twice from i-PrOH: 220 mg (14%) salt. M.p.: 139-141°C. Free base ((-)-(*R*)-**12**): $[\alpha]_D^{22}$ = - 5.93 (c = 0.84, EtOH).

4. **(±)-(2-Methylaminoethyl)-1-(3-methylphenyl)-1-phenylmethyl ether ((±)-13)**. To a stirred suspension of 1.94 g (60 mmol) of NaH (50% dispersion in mineral oil) in 15 ml of abs. THF were added 6 g (30 mmol) of (±)-**8** and the mixture was refluxed for 1h. Then was added at 22°C 5.4 g (33 mmol) of N-methyl-2-chloroacetamide in 10 ml of abs, THF and was stirred for 24h. The reaction mixture was hydrolysed with H_2O, extracted with ether, dried and evaporated. The residue was subjected to column chromatography (hexane/ether 3:1) and was isolated 4.0 g (53%) of colourless oil, which was reduced with $LiAlH_4$ to yield (±)-**13** as colourless oil. M.p.: of the HCl-salt: 134-135.5°C. IR: 3600, 3330, 2920, 2865, 2790, 1600, 1490, 1450, 1080, 1070. ^{1}H NMR (250 MHz): 8.90 (br. s, NH); 7.16 (m, 9H); 5.34 (s, 1H); 3.72 (m, 2H); 3.09 (m, 2H); 2.63 (s, CH_3); 2.27 (s, CH_3). CI-MS: 256 ($[M+1]^+$). Anal. calc. for $C_{17}H_{21}NO$ (255.340): C 79.97, H 8.28, N 5.48; found: C 79.90, H 8.30, N 5.51.

4.1. **(-)-(*S*)-13**. 1.7 g of (±)-**13** and 1.0 g of (+)-(2*R*,3*R*)-tartaric acid were dissolved at reflux in 30 ml of acetone. The soln. was kept for 12h at 0°C, the obtained crystals were filtered and recrystallized 5 times from acetone: 22 mg (18%) salt. M.p.: 117-120°C. Free base: $[\alpha]_D^{22}$ = - 3.85 (c = 0.7, $CHCl_3$).

5. **N-2'-hydroxy-1'-isopropylethyl-1,1-Diaryl-methylamines.** 5.1. **Synthesis of the starting azomethines.** 5.1.1. **(+)-(*E*)-(*S*)-N-(2-Hydroxy-1-isopropylethyl)-(4-chlorophenyl)methylideneamine ((+)-20)**. According to the lit.[14] the title compound was synthesised from 4-chlorobenzaldehyde and (S)-valinol[19]. Colourless oil (95%). B.p.: 148-150°C/1 Torr. $[\alpha]_D^{22}$ = + 16.4 (c = 0.52, EtOH). All spectral date were identical with those published in ref.[14]. CI-MS: 226 ($[M+1]^+$).

5.1.2. **(-)-(*E*)-(*S*)-N-(2-Hydroxy-1-isopropylethyl)phenylmethylideneamine ((-)-21)**. Following 5.1.1 the title compound was synthesised in 85% yield. Colourless crystals. M.p.: 71-72°C (pentane). $[\alpha]_D^{22}$ = - 36.08 (c = 0.64, $CHCl_3$). CI-MS: 192 ($[M+1]^+$).

5.1.3. **(-)-(*E*)-(*S*)-N-(2-Hydroxy-1-isopropylethyl)-(2-chlorophenyl)methylideneamine ((-)-22)**. A mixture of 1.74 g (16.9 mmol) of (*S*)-valinol[19] and 1.9 ml (16.9 mmol) of 2-chlorobenzaldehyde in 50 ml of abs. benzene was refluxed for 5h using a Dean-Stark trap. The solvent was evaporated and the crude product was recrystallized from pentane: 2.96 g (79%) of (-)-**22**. M.p.: 88-89°C. $[\alpha]_D^{22}$ = - 20.86 (c = 0.57, $CHCl_3$).

IR: 3600, 2960, 2870, 2850, 1630, 1590, 1460, 1440, 1380, 1265, 1050. ^{1}H NMR (250 MHz): 8.25 (s, 1H-C=N); 7.68 (d, J = 8.5, 2H-Ar); 7.40 (d, J = 8.5 2H-Ar); 2.83 (m, 2H-CH-O); 2.86 (m, 1H); 1.90 (m, 1H); 1.75 (br. s, OH); 1.01 (d, J = 8.5, CH_3); 0.94 (d, J = 8.5, CH_3). EI-MS: 225 ($[M]^+$); 194 ($[M\text{-}CH_2OH]^+$); 182 ($[M\text{-}CH(CH_3)_2]^+$).

5.2. **1,1-Diarylmethylamines**. 5.2.1. **General procedure.** To a soln. of 2 mmol of the azomethines **20** - **22** in 30 ml of abs. ether was added dropwise a ethereal soln. of 5 mmol of the corresponding aryllithium reagent and the reaction mixture was stirred for 5h at 22°C. Then was added a small amount of H_2O, extracted with ether, dried and evaporated. The residue was chromatographied over silica gel (CH_2Cl_2) and yielded pure compounds (**14-19**) as colourless oils. The free bases were converted to their hydrochlorides with HCl/ether.

5.2.2. **(+)-(1*S*,1'*S*)-N-2'-Hydroxy-1'-isopropylethyl-1-(4-chlorophenyl)-1-phenylmethylamine ((+)-14).** From (+)-**20** and phenyllithium followed 5.2.1 (+)-**14** was obtained. Yield: 64%. $[\alpha]_D^{22}$ = + 14.9 (c = 1.57, $CHCl_3$). HCl-salt of (+)-**14**: M.p.: 198-200°C; $[\alpha]_D^{22}$ = + 21.40 (c = 0.68, EtOH); (lit.: 199-200°C; $[\alpha]_D^{22}$ = + 22.0 (c = 0.43, EtOH)[14]). All spectral data were identical with those published in ref[14]. Anal. calc. for $C_{18}H_{22}ClNO$ (303.811): C 71.16, H 7.29, Cl 11.67, N 4.61; found: C 71.31, H 7.31, Cl 11.42, N 4.55.

5.2.3. **(+)-(1*S*,1'*S*)-N-2'-Hydroxy-1'-isopropylethyl-1-(4-chlorophenyl)-1-(4-methylphenyl)methylamine ((+)-15).** Following 5.2.1 from (-)-**20** and 4-methylphenyllithium (+)-15 was obtained in 76% yield. $[\alpha]_D^{22}$ = + 21.12 (c = 0.63, $CHCl_3$). HCl-salt of (+)-**15**: M.p.: 199-200°C; $[\alpha]_D^{22}$ = + 26.77 (c = 0.65, EtOH). IR (film): 3360, 1600, 1460, 1400, 1360. ^{1}H NMR (250 MHz, one diastereoisomer): 7.28 (m, 6H-Ar); 7.12 (d, J = 8.0, 2H-Ar); 4.94 (s, 1H-$CNAr_2$); 3.57 (dd, J = 4.1, 10.8, 1H-CH_2O); 3.40 (dd, J = 6.5, 10.7 1H-CH_2O); 2.41 (m, 1H); 2.30 (s, CH_3); 1.98 (br. s, 2H, OH+NH), 1.90 (m, 1H), 0.91 (t, J = 14.5, 6H, CH_3). EI-MS: 317 ($[M]^+$); 215 ($[Ar_2CH]^+$, 100). Anal. calc. for $C_{19}H_{24}ClNO.HCl$ (354.296): C 64.42, H 7.11, Cl 20.01, N 3.95; found: C 64.61, H 7.15, Cl 19.88, N 4.09.

5.2.4. **(+)-(1*R*,1'*S*)-N-2'-Hydroxy-1'-isopropylethyl-1-(4-methylphenyl)-1-phenylmethylamine ((+)-16).** From starting azomethine (-)-**21** and 4-methylphenyllithium (+)-**16** was received. Yield: 64%; $[\alpha]_D^{22}$ = + 21.96 (c = 0.84, $CHCl_3$). HCl-salt of (+)-**16**: M.p.: 169-170°C: $[\alpha]_D^{22}$ = + 21.11 (c = 0.59, EtOH); (lit.: M.p.: 169°C: $[\alpha]_D^{22}$ = + 22.5 (c = 0.39, EtOH)[14]). All spectral data were identical with those published in ref[14]. Anal. calc. for $C_{19}H_{25}NO.HCl$ (319.843): C 71.57, H 7.90, N 4.39; found: C 71.68, H 7.88, N 4.30.

5.2.5. **(-)-(1*R*,1'*S*)-N-2'-Hydroxy-1'-isopropylethyl-1-(4-chlorophenyl)-1-(2-methylphenyl)methylamine ((-)-17).** The title compound was synthesised from (-)-**20** and 2-methylphenyllithium. Yield: 83%; $[\alpha]_D^{22}$ = - 2.1 (c = 0.9, $CHCl_3$). HCl-salt of (-)-**17**: M.p.: 200-203°C; $[\alpha]_D^{22}$ = - 17.59 (c = 0.62, EtOH). IR (film): 3570, 1600, 1460, 1380. ^{1}H NMR (250 MHz, one diastereoisomer): 7.29 (m, 8H); 5.16 (s, 1H-$CHAr_2$); 3.61 (dd, J = 4.0, 10.9 1H-CH_2O); 3.42 (dd, J = 6.4, 10.9 1H-CH_2O); 2.46 (m, 1H); 2.27 (s, CH_3); 1.96 (m, 3H), therein at 1.98 (s, 2H, OH+NH); 0.92 (d, J = 2.3, CH_3); 0.89 (d, J = 2.3, CH_3). EI-MS: 317 ($[M]^+$); 215 ($[Ar_2CH]^+$, 100). Anal. calc. for $C_{19}H_{24}ClNO.HCl$ (354.296): C 74.42, H 7.11, Cl 20.01, N 3.95; found: C 64.62, H 7.30, Cl 19.78, N 4.21.

5.2.6. **(+)-(1*S*,1'*S*)-N-2'-Hydroxy-1'-isopropylethyl-1-(2-chlorophenyl)-1-(3-methylphenyl)methylamine ((+)-18).** The reaction of azomethine (-)-**22** and 3-methylphenyllithium gave (+)-**18** in 79% yield. HCl-salt of (+)-**18**: m.p.: 184-186°C; $[\alpha]_D^{22}$ = + 44.06 (c = 0.64, EtOH). These crystals were recrystallized from EtOH/ether: **18A**; m.p. 185-187°C; $[\alpha]_D^{22}$ = + 33.48 (c = 1.0, EtOH); (free base: $[\alpha]_D^{22}$ = - 11.52 (c = 2.2, $CHCl_3$); diastereoisomeric mixture 27:73. The mother liqueur was concentrated to *ca.* one third of its volume and additional crystals were collected: **18**; m.p.: 183-185°C; $[\alpha]_D^{22}$ = + 44.48 (c = 0.65, EtOH); (free base: $[\alpha]_D^{22}$ = - 39.81 (c = 2.13, $CHCl_3$); one diastereoisomer. IR: 3360, 1600, 1480, 1400. ^{1}H NMR (250 MHz, one diastereoisomer): 7.57 (dd, J = 1.7, 7.6 1H-Ar); 7.18 (m, 7H); 5.48 (s, 1H-$CHAr_2$); 3.64 (dd, J = 4.0, 10.9, 1H-CH_2O); 3.44 (dd, J = 5.6, 10.9, 1H-CH_2O); 2.39 (m 1H); 2.32 (s, CH_3-Ar); 2.09 (br. s, 2H, NH+OH); 1.90 (m, 1H); 0.92 (d, J = 6.9, CH_3); 0.89 (d, J = 7.0, CH_3). CI-MS: 318 ($[M+1]^+$). Anal. calc. for $C_{19}H_{24}ClNO.HCl$ (354.296): C 64.41, H 7.11, N 3.95; found: C 64.68, H 7.20, N 3.94.1.

5.2.7. **(+)-(1*S*,1'*S*)-N-2'-Hydroxy-1'-isopropylethyl-1-(2-chlorophenyl)-1-phenylmethylamine ((+)-19).** Following the general procedure 5.2.1 from (-)-**22** and phenyllithium (+)-19 was obtained. Yield: 82%. HCl-salt of (+)-**19**: M.p. 178-180°C; $[\alpha]_D^{22}$ = + 49.19 (c = 0.58, EtOH). These crystals were recrystallized

from EtOH/ether: **19**; m.p. 180-181°C; $[\alpha]_D^{22}$ = + 48.68 (c = 0.46, EtOH); (free base: $[\alpha]_D^{22}$ = - 25.87 (c = 3.0, $CHCl_3$); diastereoisomeric mixture 5:95. The mother liqueur was concentrated to *ca.* one third of its volume and additional crystals were collected: **19A**; m.p.: 178-180°C; $[\alpha]_D^{22}$ = + 40.72 (c = 0.53, EtOH); (free base: $[\alpha]_D^{22}$ = - 33.87 (c = 2.25, $CHCl_3$); diastereoisomeric mixture 12:88. IR: 3350, 1600, 1460, 1390. ^1H NMR (250 MHz, diastereoisomeric mixture *ca.* 5:95): 7.67 (dd, *J* = 1.5, 7.6, 0.05H-Ar); 7.58 (dd, *J* = 1.7, 7.7, 0.95H-Ar); 7.28 (m, 8H); 5.51 (s, 1H); 3.64 (dd, *J* = 4.1, 10.9, 1H-CH_2O); 3.43 (dd, *J* = 5.4, 10.9 1H-CH_2O); 2.40 (m, 1H); 2.38 (br. s, 2H, NH+OH); 1.9 (m, 1H); 0.91 (t, *J* = 14.4, 6H, CH_3). CI-MS: 304 ($[M+1]^+$). Anal. calc. for $C_{18}H_{22}ClNO.HCl$ (340.271): C 63.53, H 6.81, N 4.12; found: C 63.63, H 7.01, N 4.35.

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