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Configurational assignment of *vic*-amino alcohols from their circular dichroism spectra with dirhodium tetraacetate as an auxiliary chromophore

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Abstract

The in situ formed complexes of dirhodium(II) tetraacetate with optically active derivatives of the 1,2-amino alcohols ephedrine and adrenaline show circular dichroism spectra suitable for determination of their absolute configuration. According to the M- or P-helicity of the N–C–C–O moiety the investigated compounds generate negative or positive Cotton effects at around 300 and 440 nm, respectively. The third prominent CE of an opposite sign to the first two occurs at ca. 380 nm. It is demonstrated that the in situ method allows fast and easy configurational assignment based on the helicity rule that connects the signs of the Cotton effects at around 300 and 440 nm with the sign of the N–C–C–O torsional angle.

1. Introduction

Amino alcohols represent an important class of compounds due to their significant biological activity and application in synthesis. In general, an amino alcohol unit is present in many anticancer drugs, antibiotics and other bioactive natural products. Among these products are daunorubicin and doxorubicin, currently considered to be the most potent and clinically useful agents in cancer chemotherapy, or a variety of antibiotics, e.g. a newly synthesised bisanthracycline antibiotic WP631 or naloxone, the monoamine opioid antagonist.[1,2] Topically applied β-adrenoceptor antagonists containing an amino alcohol moiety, e.g. timolol, betaxolol, levobunolol, metipranolol and carteolol have become the drugs of choice in the management of ocular hypertension and glaucoma.[3] Amino alcohols are also known to be very useful substances in the total synthesis of a variety of natural products,[4,5] being widely used in asymmetric synthesis, as building elements for heterocycles and employed as reagents or catalytic agents in organic chemistry.[6–8]

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Development of methods for the unequivocal determination of the absolute configuration of bioactive substances remains very important because enantiomers may differ substantially in their pharmacological effects and potency at particular receptors. Circular dichroism spectroscopy (CD) appears to be a very convenient, sensitive and fast technique for stereochemical assignments provided the structures studied are non-racemic and absorbed in an accessible frequency range. Very recently two new strategies for the CD exciton coupling method (ECCD) have been reported for assigning the absolute configuration of amino alcohols.[9,10] In the first strategy, the achiral chromophoric tweezer binds to an acyclic chiral α-amino alcohol derivatised with glycine through nitrogen/zinc coordination to form a macrocyclic host–guest complex. The CD of this complex reflects the absolute configuration of the α-amino alcohol.[9] In the second strategy, the *p*-dimethylaminobenzoate chromophore is used for chromophoric derivatisation of both amino and hydroxy groups present in the fumonisin molecule.[10] Moreover, an application of the on-line HPLC–exciton CD analysis using (*S*)-2-*tert*-butyl-2-methyl-1,3-benzodioxole-4-carboxylic acid [(*S*)-TBMBC-OH] which allows the simultaneous determination of the enantiomeric composition and the absolute configuration of acyclic vicinal amino alcohols has been described very recently.[11]

The aim of this paper is to report on a convenient method for determining the absolute configuration of optically active amino alcohols by preparing cottonogenic derivatives. The method consists of the in situ generation of chiral complexes of amino alcohols with dirhodium tetraacetate acting as an auxiliary chromophore. The stereochemical assignment based on the CD spectra of a variety of amino alcohols in the presence of the Rh_2-dimer is described.

2. Results and discussion

It is known that the binuclear dirhodium tetraacetate [$Rh_2(O_2CCH_3)_4$] (Fig. 1) can exchange in situ one or more of its acetate units with different types of ligands, such as α- and β-hydroxy as well as α-amino acids, *vic*-diamines, carboxylic acids etc.[12,13] In these cases the introduced ligands act as bidentate ligands to form chiral complexes of a bridging or a chelating structure. Due to the great ability of dirhodium tetraacetate to bind a wide variety of ligands in the axial positions,[14] unidentate ligation along the Rh–Rh bond involving the d_{z^2}-orbitals of the metal atoms is also possible.[15] After an exchange or axial coordination of chiral ligands, the achiral chromophore becomes chiral because it is now incorporated in a chiral environment. Therefore, the chiroptical properties manifest themselves and these properties become a sensitive function of the electronic character of the ground and excited states of the system. In all cases, e.g irrespective of the complexation mode, the CD arising within the *d–d* absorption bands of the metal cluster depends upon the chirality of the compound acting as ligand(s).

As can be seen in Fig. 1, the investigated compounds may be categorised as ephedrine (compounds **1**–**17**) or adrenaline (compounds **18**–**20**) types, depending on the presence of the amino group at a secondary or a primary carbon atom.

CD data of the in situ formed rhodium complexes of amino alcohols **1**–**20** are summarised in Table 1. In general, in the presence of dirhodium tetraacetate up to five Cotton effects (A–E) can be observed for a chiral *vic*-amino alcohol in the 650–300 nm range. In this region the circular dichroism spectrum of each compound with a Rh-core has three prominent bands. Two bands with the same sign appear near 310 nm (E) and 440 nm (C) and a third one (D), of opposite sign to the first two, occurs at 380 nm. The band C, however, is only rarely detectable as a distinct minimum or maximum. Most probably, this CE is too small to circumvent the contributions of the very strong neighbouring D band and therefore, in most cases, it can only be observed as a positive or a negative minimum (Table 1).

Two additional CD bands occur in the spectra of amino alcohols with a Rh-core at around 485 nm (band

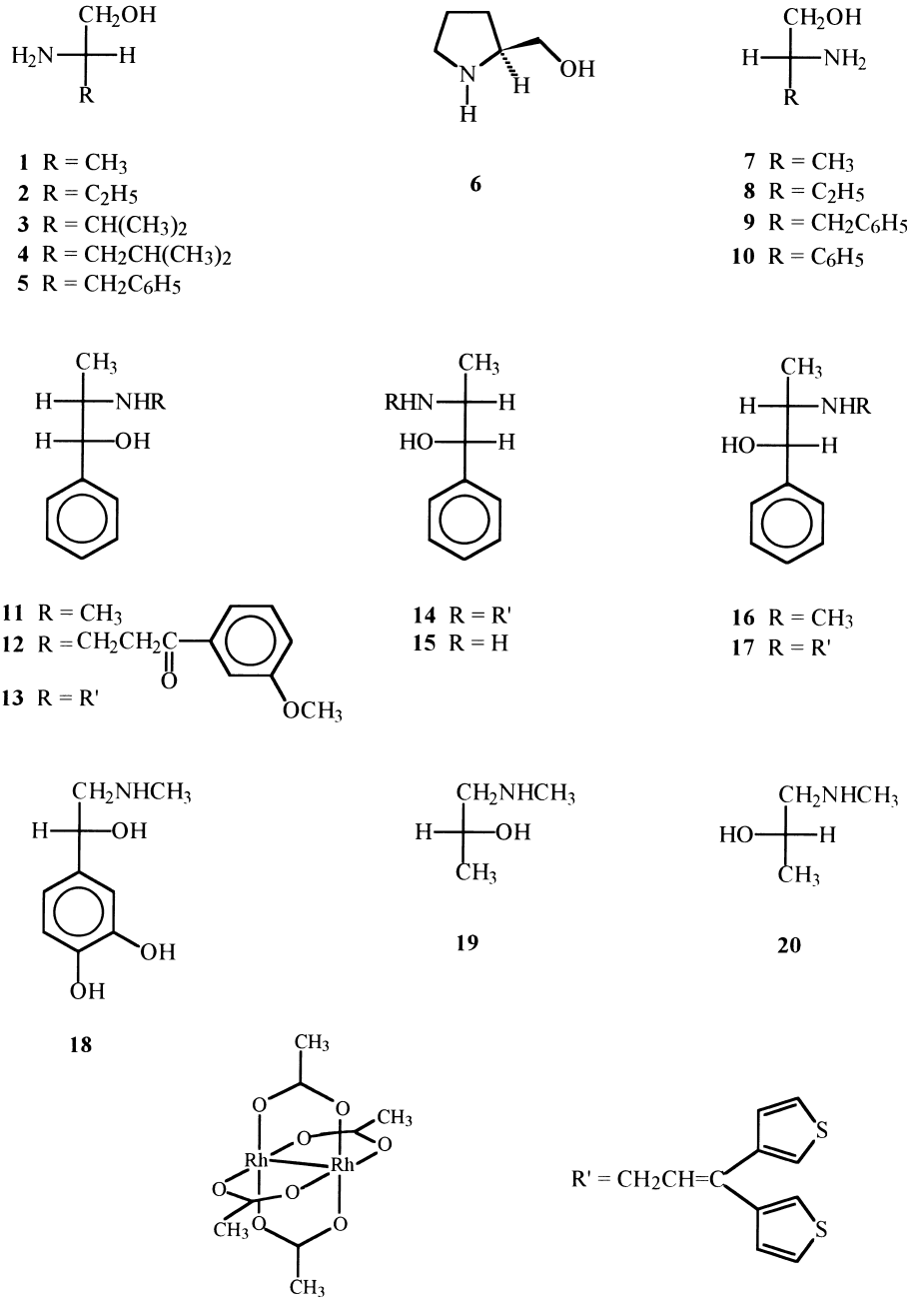

Figure 1. Compounds **1**–**20** and dirhodium(II) tetraacetate

B) and 590 nm (band A). The electronic structure of the A, B and C bands is unequivocally established. According to the literature data,[14,16] CD bands near 600 and 440 nm are assigned as electronically allowed components of the transitions π*(Rh–Rh)→σ*(Rh–O) and π(Rh–Rh, Rh–O)→σ*(Rh–O), respectively, whereas the band at 500 nm is assigned to be the magnetically allowed δ(Rh–Rh)→σ*(Rh–O) transition. Therefore, the 500 nm band is only seen in the CD spectrum and does not correspond directly to any of the transitions in the electronic spectrum. In the case of Rh-complexes of amino alcohols **1**–**20**,

Table 1
CD data of in situ formed Rh-complexes of compounds **1**–**20** measured in ethanol. Values are given as $\Delta\varepsilon'$(nm)*

Comp.	Band E	Band D	Band C	Band B	Band A
1	+1.66 (309)	–2.03 (378)	a (445)	–0.16 (472)	+0.05 (588)
2	+1.54 (312)	–2.47 (381)	a (447)	–0.17 (473)	+0.07 (594)
3	+1.11 (317)	–2.54 (382)	a (452)	–0.23 (479)	+0.14 (590)
4	+1.46 (312)	–2.11 (380)	a (441)	–0.12 (478)	+0.06 (605)
5	+1.39 (312)	–1.94 (381)	a (448)	–0.19 (479)	+0.08 (591)
6	+0.59 (321)	–1.12 (374)	a (429)	–0.42 (450)	–0.13 (597)
7	–1.57 (311)	+2.47 (379)	b (447)	+0.10 (474)	–0.18 (594)
8	–1.20 (311)	+1.41 (379)	b (448)	+0.10 (474)	–0.03 (594)
9	–1.37 (317)	+2.39 (382)	b (450)	+0.34 (465)	–0.04 (595)
10	–0.94 (313)	+2.07 (382)	b (455)	+0.10 (484)	–0.09 (587)
11	–0.28 (315)	+0.24 (372)	–0.20 (423)	+0.12 (489)	–0.02 (612)
12	–0.30 (334)	+0.25 (382)	–0.12 (437)	+0.03 (500)	–0.02 (563)
13	–0.24 (325)	+0.09 (366)	–0.33 (433)	a (525)	–0.06 (636)
14	+0.14 (290)	b (344)	+0.11 (432)	b (520)	+0.01 (632)
15	+0.03 (309)	–0.11 (380)	+0.07 (454)		
16	+0.29 (314)	–0.72 (374)	+0.08 (436)	–0.05 (487)	+0.01 (646)
17	+0.13 (316)	–0.30 (371)	b (431)	–0.09 (475)	
18	–0.85 (328)	a (374)	–0.51 (424)	+0.03 (491)	
19	–0.62 (308)	+2.01 (371)	–0.06 (432)	+0.06 (477)	–0.05 (599)
20	+0.90 (300)	–1.94 (367)	+0.16 (426)	–0.05 (487)	+0.05 (591)

a - negative minimum; b - positive minimum; * for explanation of term $\Delta\varepsilon'$ see text.

there are two well-developed bands in the visible spectra, which correspond to the $\pi^*\rightarrow\sigma^*$ and $\pi\rightarrow\sigma^*$ electronic transitions. The intense absorption bands in the near UV region between 220 and 250 nm arise from a $\sigma(Rh_2)\rightarrow\sigma^*(Rh_2)$ transition.[14] The origin of the transitions between 300 and 380 nm has not been unequivocally determined until now.

The same shape of the CD spectra is observed for amino alcohols of both ephedrine and adrenaline types, as demonstrated in Fig. 2. This fact suggests the same mode of complexation to the metal core of all compounds studied.

As can be seen in Fig. 2, the CD spectra of Rh-complexes of enantiomeric amino alcohols are of mirror image type (compounds **1**, **7** and **19**, **20**). Small differences in the magnitude of particular CEs can originate from the fact that the real concentration of the chiral complex formed in situ in the solution is not known. Therefore, the CD data are presented as artificial $\Delta\varepsilon'$ values. These $\Delta\varepsilon'$ values are calculated in the usual way as $\Delta\varepsilon'=\Delta A/c\times d$, were c is the molar concentration of the amino alcohol, assuming 100% complexation. For the purpose of determination of the absolute configuration, however, only the signs and relative magnitudes of the CEs are important, not the absolute values.

Bands C, D and E appear to be the most useful for correlation between the stereostructure of an amino alcohol and its CD. These CD bands are relatively strong in comparison with the other bands and appear in the spectra of all compounds studied, as can be seen in Table 1. On the grounds of the data presented in Table 1, investigated compounds **1**–**17** may be divided into two groups differing in sign of the 310 nm (E), 380 nm (D), and 440 nm (C) bands. In the first containing L-amino alcohols, the CEs around 310 and 440 nm are positive with a strong negative CE at ca. 380 nm. In the second group, represented by amino alcohols of the D series, the opposite relation of sign pattern is observed, e.g. both CD bands at ca. 310

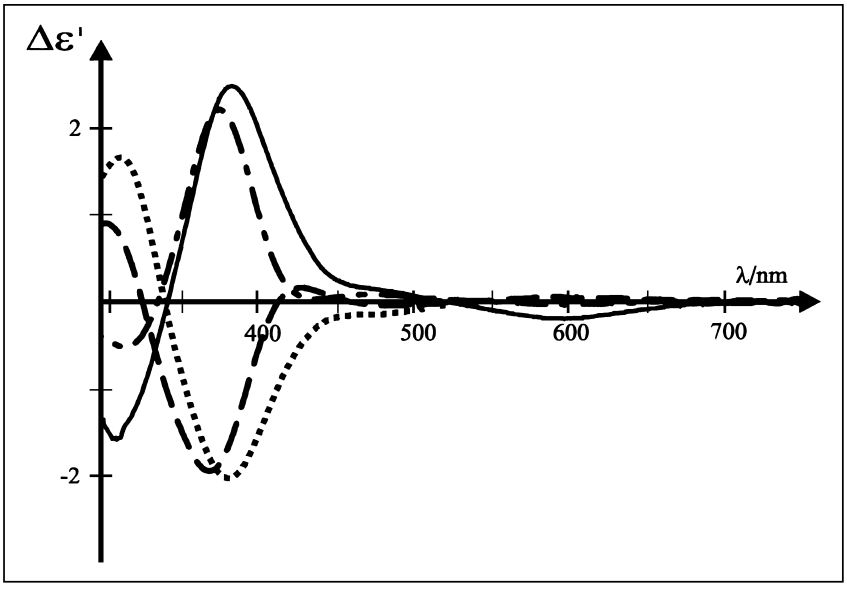

Figure 2. CD spectra of in situ formed Rh-complexes of compounds **1** (···), **7** (—), **19** (– · –) and **20** (– – –) recorded in ethanol

and 440 nm are negative and the one near 380 nm is positive. However, compounds **18**–**20**, belonging to the adrenaline type, do not follow this regularity. In compounds **18**–**20** the signs of particular CEs are opposite relative to the signs of ephedrine type compounds **1**–**17** with the same L- or D-configuration. Therefore, a common rule for the correlation between CD and the absolute configuration that would obey all compounds in question has to be found.

For the interpretation of the CD spectra one can assume a bridging ligation (β-form) of a 1,2-amino alcohol molecule to the Rh-core, analogous to the case of amino alcohols with dimolybdenum tetraacetate.[17] This seems to be very straightforward, since α-dimolybdenum complexes with e.g. chelating diphosphines and diamines show no measurable CD.[18] The bridged type of bidentate ligation leading to the dirhodium core with a one- to four-bridged cage is also favoured for Rh-complexes with various bidentate ligands, such as acetamidates, trifluoroacetamidates or phosphino-phenoxides.[19,20]

An additional indication of the bidentate mode of complexation of compounds **1**–**20** to the Rh-cluster is provided by the visible isotropic absorption (vis) data. In general, the electronic absorption spectra of dirhodium tetracarboxylates consists of two weak bands in the visible region, band I at ca. 600 nm and band II near 450 nm. Two stronger bands occur in the UV range, namely band III near 250 nm (shoulder) and band IV at around 220 nm. Band I is strongly influenced by changes in the axial ligands and is shifted to lower wavelengths depending on the nature of ligands, whereas band II remains constant. On the contrary, band II is more sensitive to changes in the identity of the equatorial binding ligands.[21,22] For compounds **1**–**20** band I appears in the range 590–600 nm whereas band II generally occurs as a shoulder of band III in the 380–420 nm range, showing a blue shift of around 30–50 nm, in comparison with the standard complex. These data are in line with the previous statement that amino alcohols **1**–**20** exchange acetate ligand(s) acting as the bidentate bridging ligands. The only exception in respect to the position of band II presents compound **18** (Fig. 3). In its vis spectrum, band II is well separated and occurs at 438 nm. This fact may suggest an axial ligation to the Rh-cluster. However, according to the literature data[22] the axial coordination through the amino group should shift the long-wavelength band from ca. 600 nm to approximately 550 nm. On the other hand, it is known that dirhodium(II) tetraacetate represents an alcohol acceptor which is not strong enough to produce CEs by ligating through the hydroxy group.[23]

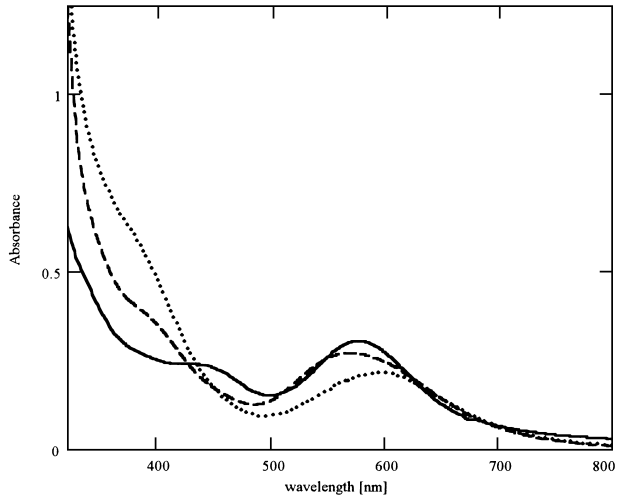

Figure 3. UV–vis spectra of in situ formed complexes of compounds **9** (···), **11**(– – –) and **18** (—) recorded in ethanol

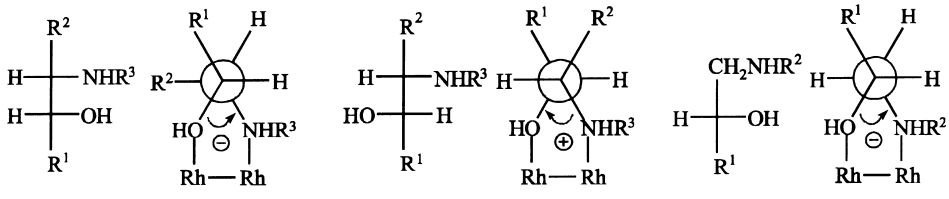

Figure 4. Preferred antiperiplanar conformation of an aliphatic 1,2-amino alcohol from ephedrine type—(1*R*,2*S*)-*erythro* (left) and (1*S*,2*S*)-*threo* (middle)—as well as from adrenaline type (right) when complexed to Rh-dimer

Therefore, the bidentate bridging mode of binding to the Rh-core seems to be most probable in the case of compound **18** also. The characteristic shapes of the UV–vis spectra of the representative in situ formed Rh-complexes, in the 300–800 nm range, are shown in Fig. 3.

An amino alcohol can best be accommodated on the metal core in a conformation with a torsional angle (Rh–O)–C–C–(N–Rh) of approximately ±60°. The conformation of an acyclic amino alcohol in the Rh-complex, for steric reasons, should be fixed in such a way that each O–C–C–R and N–C–C–R moiety adopts an antiperiplanar conformation (Fig. 4). This means that the bulky R-groups point away from the rest of the complex. This seems very reasonable since only in such a conformation does the bigger group R avoid a steric interaction with the still-present acetate ligands in the complex. Thus, *erythro* amino propanol drugs with 1*S*,2*R* configurations such as **14** and **15**, in general, follow P-helicity whereas those with 1*R*,2*S* configurations such as **11**–**13** obey M-helicity. This is in accord with the dimensions of phenyl and methyl groups. Therefore, a preferred conformation in the Rh-complex is the one with a phenyl group in an antiperiplanar arrangement relative to the nitrogen atom, as shown in Fig. 4. In the *threo* series, the compounds with 1*S*,2*S* configurations represented by D-ψ-epedrine **16** and D-tinophedrine **17** follow P-helicity. In this case, both O–C–C–CH_3 and N–C–C–C_6H_5 units adopt an antiperiplanar arrangement leading to a positive torsional angle, as presented in the middle of Fig. 4. A preferred steric arrangement for adrenaline type compounds **18**–**19** with resulting negative torsional angle is demonstrated in Fig. 4.

The conformational preferences of the resulting Rh_2-containing rings impose a twist about the Rh–Rh bond so that it is no longer in an eclipsed state. Thus, the achiral chromophore is incorporated into a chiral ring (‘chiral second sphere’) which implies that the CD is mainly governed by a ‘helicity rule’: the sign of the torsional angle determines the signs of the CEs, and also, to a great extent, their magnitudes. Therefore, the diagnostic CEs can be correlated with the torsional angle of an amino alcohol unit. Thus,

the amino alcohols showing a positive sign of the C and E bands and a negative sign of the D band follow P-helicity, which correlates the positive CEs with the positive torsional angle. On the other hand, an opposite pattern of the signs sequence in the same spectral range, e.g negative–positive–negative for the C, D and E bands, respectively, occurs with a negative torsional angle. Therefore, the amino alcohols exhibiting such characteristics obey M-helicity.

All investigated compounds **1**–**20**, regardless of their ephedrine or adrenaline types, follow the helicity rule without exception. Thus, compounds **1**–**6**, **14**–**17**, and **20** generate prominent E and C bands of a positive sign that can be compared with the N–C–C–O positive torsional angle, according to their P-helicity. On the contrary, for compounds **7**–**13** and **18**–**19** one can make use of the M-helicity, which can be compared with the negative torsional angle of the N–C–C–O unit. Accordingly, the negative sign of E and D bands have been found in the CD spectra of these compounds.

3. Conclusion

The present study demonstrates that the absolute configuration of *vic*-amino alcohols can successfully be determined on the basis of their CD spectra measured with $[Rh_2(O_2CCF_3)_4]$ in ethanol. The great advantage of the in situ method is that it is not necessary to synthesise, isolate and purify any derivatives, as required in the above mentioned exciton coupled method.[9,10]

The Rh-complex reduces the conformational freedom of the ligands and forces flexible molecules into only one single conformation. This leads to better interpretable CD spectra and often also to larger CEs. In addition, it is noteworthy that this restriction of the conformational freedom makes an absolute configuration assignment possible on the basis of the chiroptical data alone.

It is shown that three of the CEs, namely C, D and E, can be used for the determination of the torsional angle sign of the complexing amino alcohol. This in turn is induced by the absolute configuration of the amino alcohol moiety. Therefore, the absolute configurational assignment of the *vic*-amino alcohols becomes possible with help of the in situ CD method using dirhodium(II) tetraacetate as an auxiliary chromophore.

4. Experimental

UV–vis spectra were measured on a Cary 100 spectrophotometer in ethanol. CD spectra were recorded between 230 and 700 nm at room temperature with a Jasco 715 spectropolarimeter using ethanol solutions in cells of 1 or 2 cm path length (spectral band with 2 nm, sensitivity 10×10^{-6} or 20×10^{-6} ΔA-unit/nm). Depending on the S/N ratio the λ-scan speed was 0.2 or 0.5 nm/s.

For CD measurements, the solid chiral amino alcohol (1–5 mg) was dissolved in a solution of the stock rhodium(II) acetate (6–7 mg) in ethanol so that the molar ratio of the stock complex to ligand was about 1:0.5 to 1:0.7. Some of the $\Delta\varepsilon'$-values were very small, but nevertheless the signal-to-noise ratio in each case was better than at least 10:1. At room temperature, ethanol solutions of the chiral complexes were stable for a very long time. The CD spectra of amino alcohols with Rh(II)-core taken from the solutions kept for several days differ only in the magnitude of CEs, which rose slightly during the first 24 hours.

Source of compounds: compounds **1**–**11**, **15**, **16** and **18**–**20** were commercially available from Fluka and were used without further purification. Dirhodium tetraacetate and ethanol (Uvasol) were commercially available from Aldrich and Merck, respectively, and were used without further purification.

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