

# Tumor Inhibiting Properties of Stereoisomeric [1,2-Bis(3-hydroxyphenyl)ethylenediamine]dichloroplatinum(II)-Complexes, Part I: Synthesis

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The synthesis of the stereoisomeric 1,2-bis(3-hydroxyphenyl)ethylenediamines (1-4) from meso-1,2-bis(2-hydroxyphenyl)ethylenediamine and 3-methoxybenzaldehyde by a diaza-Cope-rearrangement and subsequent ether cleavage with BBr<sub>3</sub> and their conversion into the [1,2-bis(3-hydroxyphenyl)ethylenediamine]dichloroplatinum(II)-complexes with K<sub>2</sub>PtCl<sub>4</sub> (1-PtCl<sub>2</sub> - 4-PtCl<sub>2</sub>) is described.

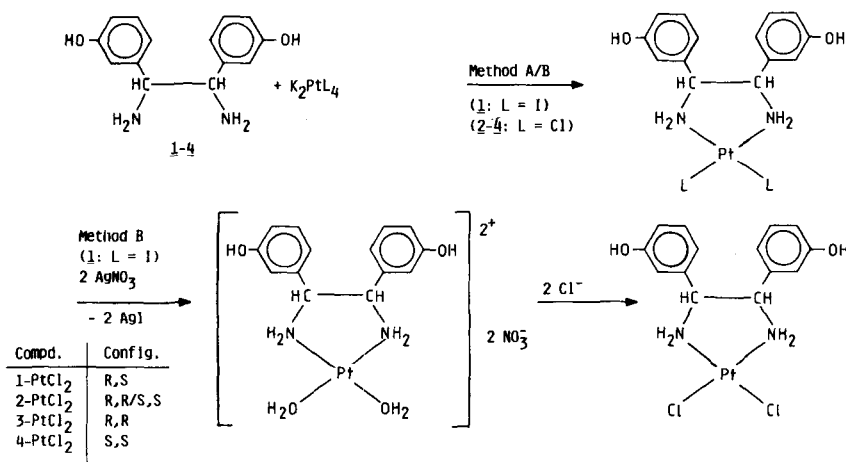
Tumor-hemmende Eigenschaften der stereoisomeren [1,2-Bis(3-hydroxyphenyl)ethylenediamin]dichloroplatin(II)-Komplexe, Teil 1: Synthese

Die Synthese der stereoisomeren 1,2-Bis(3-hydroxyphenyl)ethylenediamine (1-4) aus meso-1,2-Bis(2-hydroxyphenyl)-ethylenediamin und 3-Methoxybenzaldehyd durch Diaza-Cope-Umlagerung und anschließende Etherspaltung mit BBr<sub>3</sub> und ihre Reaktion mit K<sub>2</sub>PtCl<sub>4</sub> zu den [1,2-Bis(3-hydroxyphenyl)ethylenediamin]dichloroplatin(II)-Komplexen (1-PtCl<sub>2</sub> - 4-PtCl<sub>2</sub>) wird beschrieben.

In recent publications<sup>1-3)</sup> we have shown that dichloro(1,2-diphenylethylenediamine)platinum(II)-complexes with fluorine and hydroxy substituents in 4-positions of both benzene rings possess marked antitumor activities. By variation of the position and number of the substituent (F or OH,

resp.) or by combination of both substituents in one drug molecule a further increase of the tumor inhibiting properties was achieved<sup>4)</sup>.

In this connection the stereoisomeric [1,2-bis(3-hydroxyphenyl)ethylenediamine]dichloroplatinum(II)-complexes



**Table 1.** [1,2-Bis(3-hydroxyphenyl)ethylenediamine]dichloroplatinum(II)-Complexes - Analytical Data

compd.	config.	yield %	formula	C%		H%		N%		Cl%	
				calcd.	found	calcd.	found	calcd.	found	calcd.	found
1-PtCl <sub>2</sub>	R,S	53	C <sub>14</sub> H <sub>16</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub> Pt	32.95	33.0	3.16	3.20	5.5	5.4	13.9	14.4
2-PtCl <sub>2</sub>	R,R/S,S	68			32.9		3.12		5.4		14.1
3-PtCl <sub>2</sub>	R,R	63			32.3		2.84		5.7		13.7
4-PtCl <sub>2</sub>	S,S	71			32.8		3.27		5.6		14.1

**Table 2.** <sup>1</sup>H-NMR-Data of [1,2-Bis(3-hydroxyphenyl)ethylenediamine]dichloroplatinum(II)-Complexes and of their Ligandes (δ (ppm), TMS<sub>int</sub>)

compd. (config.)	arom. H	CH (benzylic)	NH	OH	OCH <sub>3</sub>
1-PtCl <sub>2</sub> <sup>a)</sup> (R,S)	7.40 (s, 2 H) 6.98 (t, J=8 Hz, 2 H) 6.71 (m, 4 H)	4.38 (br, 2 H)	6.10 (br, 2 H) 5.49 (br, 2 H)	9.7 (s, 2 H)	
2-PtCl <sub>2</sub> <sup>a)</sup> (R,R/S,S)	7.39 (d, J=8 Hz, 2 H) 7.12 (s, 2 H) 7.07 (d, J=8 Hz, 2 H) 6.65 (m, 2 H)	5.23 (br, 2 H)	6.48 (br, 2 H) 5.83 (br, 2 H)	9.5 (s, 2 H)	
1 <sup>c)</sup> (R,S)	6.50-7.25 (m, 8 H)	3.75 (s, 2 H)			
2 <sup>c)</sup> (R,R/S,S)	6.20-7.07 (m, 8 H)	4.00 (s, 2 H)			
1a <sup>b)</sup> (R,S)	6.30-7.38 (m, 8 H)	4.02 (s, 2 H)	1.42 (s, 4 H)		3.85 (s, 6 H)
2a <sup>b)</sup> (R,R/S,S)	6.75-7.34 (m, 8 H)	4.09 (s, 2 H)	1.51 (s, 4 H)		3.73 (s, 6 H)

<sup>a)</sup> 250 MHz, DMF-D<sub>7</sub>. <sup>b)</sup> 90 MHz, CDCl<sub>3</sub>. <sup>c)</sup> 90 MHz, CD<sub>3</sub>OD/NaOD

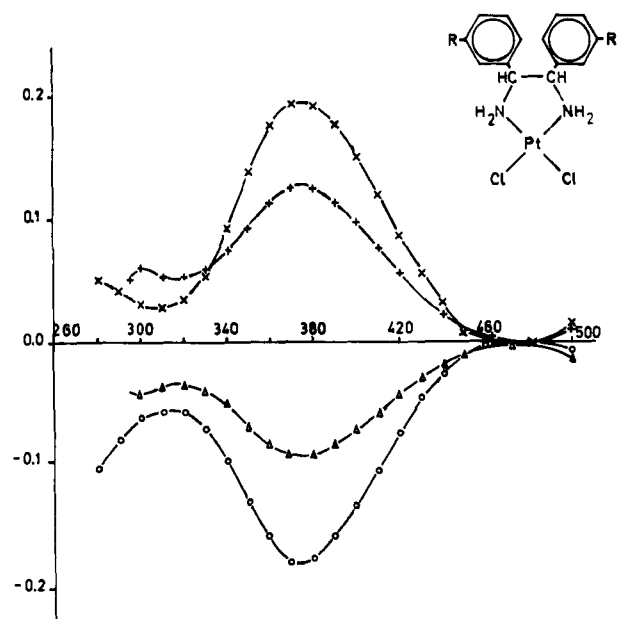
proved to be of special interest. In part I we describe the synthesis and in part II the biological properties of this type of platinum complex.

With the exception of 1-PtCl<sub>2</sub> (R,S-configured ligand) the stereoisomeric [1,2-bis(3-hydroxyphenyl)ethylenediamine]dichloroplatinum(II)-complexes were synthesized by reaction of the respective 1,2-bis(3-hydroxyphenyl)ethylenediamine with K<sub>2</sub>PtCl<sub>4</sub> (Scheme I, Method A, L = Cl). Owing to the steric facts, the formation of the R,S-configured complex proceeds very slowly and requires reaction times of several days. Therefore 1-PtCl<sub>2</sub> was synthesized via the easier accessible diaminediiodoplatinum(II)-complex (1-PtI<sub>2</sub>). The exchange of iodine by chlorine was performed in a two step reaction: a) Transformation of 1-PtI<sub>2</sub> into 1-Pt(OH<sub>2</sub>)<sub>2</sub><sup>2+</sup> with AgNO<sub>3</sub>. b) Displacement of the Pt-bound H<sub>2</sub>O-molecules by Cl<sup>-</sup> by addition of NaCl (Scheme I, Method A/B, L = I).

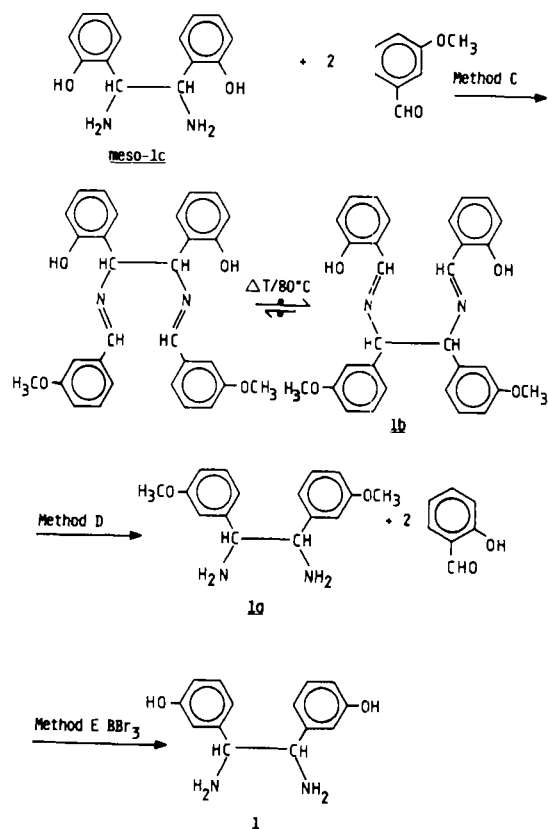
The analytical data are listed in tables 1 and 2.

1-PtCl<sub>2</sub> to 4-PtCl<sub>2</sub> show IR-spectra typical for diaminedichloroplatinum(II)-complexes: 1. The N-H stretching vibration shifts considerably to lower wave numbers upon formation of the Pt-N bond (free ligand; ν N-H = 3400-3300 cm<sup>-1</sup>; Pt-bond ligand; ν N-H = 3300-3100 cm<sup>-1</sup>). - 2. Two absorption bands appear in the far IR region, one between 650 and 450 cm<sup>-1</sup> indicating a Pt-N stretching vibration and another between 345 and 320 cm<sup>-1</sup> indicating a Pt-Cl stretching vibration.

The <sup>1</sup>H-NMR-spectra are also characteristic for (1,2-diphenylethylenediamine)dichloroplatinum(II)-complexes. By the formation of the platinum complexes all absorption



**Figure 1:** CD-spectra of the enantiomeric dichloro(1,2-diphenylethylenediamine)platinum(II) and of the enantiomeric [1,2-bis(3-hydroxyphenyl)ethylenediamine]dichloroplatinum(II)-complexes: x:R = H (R,R), (+); +:R = OH (R,R), (+); O:R = H (S,S), (-); Δ:R = OH (S,S), (-).



bands of the 1,2-diphenylethylenediamines, particularly those of the amine and benzylic protons are shifted to lower field. Since the complexation blocks rotation around the C-N axis, both N-bound protons become diastereotopic owing to the neighbourhood of the asymmetric C-atoms. This leads to the appearance of separate signals for the axially and for the equatorially orientated N-H atoms. Due to a coupling between NH<sub>2</sub>, CH (benzylic) and <sup>195</sup>Pt the N-H and C-H signals are broadened.

The absolute configuration of 3-PtCl<sub>2</sub> and 4-PtCl<sub>2</sub> was determined by comparison of their CD spectra with those of (+) and (-) dichloro(1,2-diphenylethylenediamine)-platinum(II), whose absolute configuration is known ((+)  $\Delta$  R,R; (-)  $\Delta$  S,S)<sup>5</sup>. Also in the case of the enantiomeric [1,2-

bis(3-hydroxyphenyl)ethylenediamine]dichloroplatinum(II)-complexes the (+) rotating compound 3-PtCl<sub>2</sub> is R,R- and the (-) rotating compound 4-PtCl<sub>2</sub> S,S-configured (see Figure 1).

The diastereomeric 1,2-bis(3-hydroxyphenyl)ethylenediamines 1 and 2 were synthesized by the [3,3]sigmatropic diaza-Cope rearrangement reaction according to the method of Vögtle and Goldschmitt<sup>6</sup> (Scheme II and III). At a temp. below 120 °C N,N'-disalicylidene-meso-1,2-bis(3-methoxyphenyl)ethylenediamine (1b) is formed quantitatively from 3-methoxybenzaldehyde and meso-1,2-bis(2-hydroxyphenyl)ethylenediamine (1c) in a stereospecific reaction (Scheme II, Method C). Meso-1,2-bis(2-hydroxyphenyl)ethylenediamine (meso-1c), originally described by Japp and Hooker<sup>7</sup>, was synthesized from benzil, salicylic aldehyde and ammonia using an improved method published by Vögtle and Goldschmitt<sup>6</sup>.

By hydrolysis of 1b with 3 N H<sub>2</sub>SO<sub>4</sub> the meso-1,2-bis(3-methoxyphenyl)ethylenediamine (1a) is generated (Scheme II, Method D). The demethylation of the methoxy compound 1a to 1 was readily effected with BBr<sub>3</sub> (Scheme II, Method E).

The d,l-configured 1,2-bis(3-hydroxyphenyl)ethylenediamine (2a) was achieved by the meso d,l-stereoisomerisation of N,N'-bis(3-methoxybenzylidene)-meso-1,2-bis(3-methoxyphenyl)ethylenediamine which takes place during the diaza-Cope rearrangement at high temp. (> 120 °C; Scheme III, Method F).

The meso, d,l-mixture was first submitted to hydrolysis and the diastereomeric ligands were then separated by crystallisation of the bases in ether (Scheme III, Method G). The two enantiomers 3a and 4a were obtained by separation of (±)-1,2-bis(3-methoxyphenyl)ethylenediamine with tartaric acid. The free hydroxy derivatives (d,l-1 to 3) were synthesized by method E.

The biological properties of 1-PtCl<sub>2</sub> to 4-PtCl<sub>2</sub> are described in the subsequent publication.

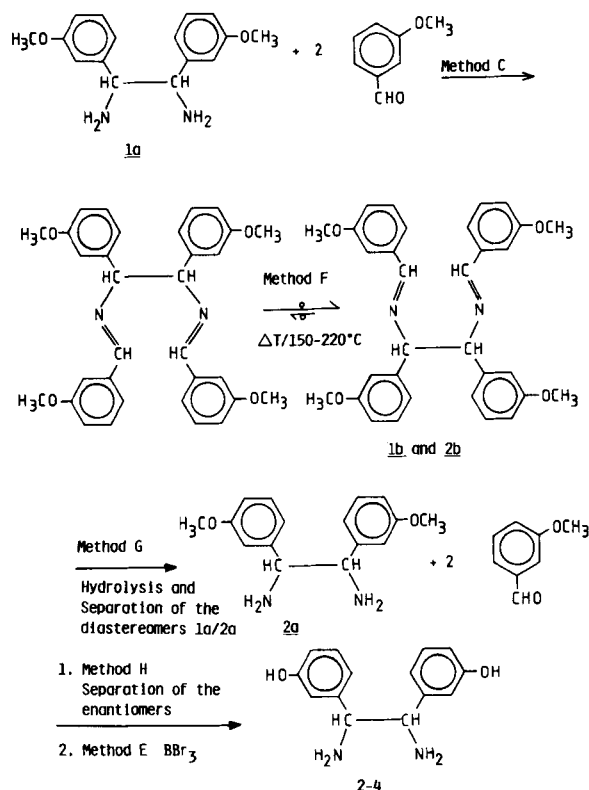
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Table 3. 1,2-Bis(3-methoxyphenyl)ethylenediamines and 1,2-Bis(3-hydroxyphenyl)ethylenediamines - Analytical Data

compd.	config.	yield %	mp. °C	formula	C%		H%		N%	
					calcd.	found	calcd.	found	calcd.	found
1-a	R,S	75	115-117	C <sub>16</sub> H <sub>20</sub> N <sub>2</sub> O <sub>2</sub>	70.6	71.0	7.40	7.32	10.3	10.3
2-a <sup>a)</sup>	R,R/S,S	38	oil <sup>a)</sup>	C <sub>16</sub> H <sub>20</sub> N <sub>2</sub> O <sub>2</sub> · 2 HCl	55.6	55.5	6.42	6.44	8.1	8.1
3-a <sup>b,c)</sup>	R,R	46	oil	C <sub>16</sub> H <sub>20</sub> N <sub>2</sub> O <sub>2</sub>						
4-a <sup>b,d)</sup>	S,S	63	oil	C <sub>16</sub> H <sub>20</sub> N <sub>2</sub> O <sub>2</sub>						
1	R,S	55	225-226	C <sub>14</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub> · 0.75 H <sub>2</sub> O	65.2	65.3	6.92	6.51	10.9	10.6
2	R,R/S,S	43	214-216	C <sub>14</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub> · 2 HBr · H <sub>2</sub> O	39.7	40.1	4.75	4.50	6.6	6.6
3 <sup>e)</sup>	R,R	78	214-215	C <sub>14</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub> · 2 HCl	53.0	52.8	5.72	5.89	8.8	8.7
4 <sup>f)</sup>	S,S	63	214-215	C <sub>14</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub> · 2 HBr	41.4	41.5	4.47	4.39	6.9	6.9

<sup>a)</sup> Dihydrochloride: mp = 248-250 °C. <sup>b)</sup> Not analyzed for C, H, N. <sup>c)</sup> [α]<sub>546</sub><sup>25</sup> = + 130.9° (c = 1, methanol). <sup>d)</sup> [α]<sub>546</sub><sup>25</sup> = - 132.0° (c = 1, methanol).

<sup>e)</sup> [α]<sub>346</sub><sup>20</sup> = - 22.6° (dihydrobromide, c = 1, methanol). <sup>f)</sup> [α]<sub>346</sub><sup>20</sup> = + 22.4° (dihydrobromide, c = 1, methanol).



## Experimental Part

**General Procedures.** Melting points, (uncorrected): Büchi 510 melting point apparatus or Petri melting point apparatus if higher than  $220^\circ\text{C}$ . - IR data: Perking Elmer Model 580 A. -  $^1\text{H}$ -NMR spectra: Varian EM 390 A 80 MHz spectrometer.  $^1\text{H}$ -NMR spectra of the platinum complexes: Bruker PFR-NMR spectrometer WM 250 at 250 MHz. - Elemental analyses: microlaboratory of the University of Regensburg.

### Syntheses

Methods A-H are representative for the syntheses of the compounds reported in Tables I and III.

#### Method A

[*d,l*-1,2-Bis(3-hydroxyphenyl)ethylenediamine]dichloroplatinum(II) (2-PtCl<sub>2</sub>)

An aqueous solution of *d,l*-1,2-bis(3-hydroxyphenyl)ethylenediamine dihydrochloride ( $2 \cdot 2 \text{ HCl}$ , 634 mg = 2 mmol in 20 ml H<sub>2</sub>O) was slowly added to an aqueous K<sub>2</sub>PtCl<sub>4</sub> solution (830 mg = 2 mmol in 20 ml H<sub>2</sub>O). The mixture was stirred in the dark, while the forming HCl was repeatedly neutralized with 0.5 N NaOH (pH 5.5 – 6.5). After 6 to 10 h 2-PtCl<sub>2</sub> was collected as a yellow powder by suction filtration using a no. 3 fritted glass filter and washed with 0.5 N HCl and H<sub>2</sub>O. For purification the complex was dissolved in DMF and precipitated with H<sub>2</sub>O. Yield 68 %.

#### Method B

[*meso*-1,2-Bis(3-hydroxyphenyl)ethylenediamine]dichloroplatinum(II) (1-PtCl<sub>2</sub>)

1 mmol K<sub>2</sub>PtCl<sub>4</sub> and 4 mmol KI were stirred in 10 mL H<sub>2</sub>O for about 20 min in the dark. Then the ligand 1 (244 mg = 1 mmol) was added and the mixture was stirred for about 7 h while the pH was repeatedly adjusted to

5.5 – 6.5 with 0.5 N NaOH. After isolation, the diiodoplatinum(II)-complex was suspended in H<sub>2</sub>O, 2 mmol AgNO<sub>3</sub> were added per mmol complex and the mixture was stirred overnight. The precipitated AgI was filtered off using a no. 4 fritted glass filter and the Ag<sup>+</sup>-free solution stirred with an excess of NaCl overnight. 1-PtCl<sub>2</sub> (yellow powder) was isolated and purified as described in Method A. Yield 53%.

#### Method C

*N,N'*-Disalicylidene-*meso*-1,2-bis(3-methoxyphenyl)ethylenediamine (1b)

*meso*-1,2-Bis(2-hydroxyphenyl)ethylenediamine (1c, 24.4 g = 100 mmol) and 3-methoxybenzaldehyde (27.2 g = 200 mmol) were refluxed in 200 mL MeCN for 3 h. The solution was concentrated and the yellow precipitate was collected in an Buchner funnel, washed with small amounts of ice-cold MeCN and acetone and dried over P<sub>2</sub>O<sub>5</sub>. Yield 88%, yellow powder, mp. 205–206.5 °C.

#### Method D

*meso*-1,2-Bis(3-methoxyphenyl)ethylenediamine (1a)

1b (40.8 g = 85 mmol) was hydrolyzed with 500 mL 3 N H<sub>2</sub>SO<sub>4</sub> and the forming salicylic aldehyde was removed by steam distillation. The hot solution was filtered and alkalized with 20% NaOH under ice cooling. The diamine was extracted with CH<sub>2</sub>Cl<sub>2</sub>, the org. layer was washed with H<sub>2</sub>O, dried over MgSO<sub>4</sub>, and evaporated. The crude product was recrystallized in acetonitrile. Yield 75%, colorless crystals, mp. 115–117 °C.

#### Method E

*meso*-1,2-Bis(3-hydroxyphenyl)ethylenediamine (1)

A solution of 1a (4.08 g = 15 mmol) in 150 mL dry CH<sub>2</sub>Cl<sub>2</sub> was cooled to  $-60^\circ\text{C}$ . BBr<sub>3</sub> (15.0 g = 60 mmol) was added in a N<sub>2</sub> atmosphere. The reaction mixture was stirred for 30 min at  $-60^\circ\text{C}$  and overnight at room temp. Then 50 mL MeOH were added slowly under cooling and the solvents were removed under reduced pressure. The residue was dissolved in 50 mL H<sub>2</sub>O, filtered and the product was precipitated with NaOH at pH 9–11 under cooling. The precipitate was sucked off, washed with great amounts of H<sub>2</sub>O, and dried over P<sub>2</sub>O<sub>5</sub>. Yield 55 %, colorless powder, mp. 225 °C.

#### Method F and G

*d,l*-1,2-Bis(3-methoxyphenyl)ethylenediamine (2a)

Stereoisomerisation was performed by heating 1b (50.8 g = 100 mmol) to 210–220 °C for about 10 min. Thereafter, 300 mL 3N H<sub>2</sub>SO<sub>4</sub> were added to the mixture of 1c and 2c. The mixture was heated, and the forming 3-methoxybenzaldehyde was removed by steam distillation. The hot solution was filtered and made alkaline with 20 % NaOH under icecooling. The precipitated diastereomeric bases 1a and 2a were extracted with CH<sub>2</sub>Cl<sub>2</sub>, the org. layer was separated, washed with H<sub>2</sub>O and dried over MgSO<sub>4</sub>. After removal of the solvent the residue was treated with ether. 2a which is soluble in ether, was readily separated from the insoluble, 1a. After evaporation of the solvent 2a remained as oil.

#### Method H

(+)- and (-)-1,2-Bis(3-methoxyphenyl)ethylenediamine (3a and 4a)

2a (10.0 g = 36.8 mmol), dissolved in 40 ml 75 % EtOH, was given to the solution of L-(+)-tartaric acid (5.25 g = 36.8 mmol in 35 ml 75 % EtOH) and boiled under reflux for 10 min. The solution was allowed to cool slowly and 4a-tartrate crystallized at room temp. It was recrystallized from 75 % EtOH several times, then treated with 5 % NaOH and CHCl<sub>3</sub>.

The org. layer was separated and dried and, after removal of the solvent, **4a** remained as colorless oil (Yield 62 %;  $[\alpha] = -132.0^\circ$ ,  $c = 1$ , MeOH). From the above filtrate **3a** was isolated and purified in the same manner by crystallization of the D-(-)-tartrate (Yield 46 %;  $[\alpha] = +131^\circ$ ,  $c = 1$ , MeOH).

#### CD Spectra

The spectra were obtained with a JASCO J-40 A spectropolarimeter (time constant 16 s; scan speed 5 nm/min) and recorded in Me<sub>2</sub>SO at room temp. in 5-cm quartz cells. The concentrations were  $2 \times 10^{-3}$  M 3-PtCl<sub>2</sub> (R,R), 4-PtCl<sub>2</sub> (S,S) and (S,S)-dichloro(1,2-diphenylethylenediamine)platinum(II) and  $4 \times 10^{-3}$  M (R,R)-dichloro(1,2-diphenylethylenediamine)platinum(II).

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