Synthesis of diaminodideoxyalditol analogs of cisplatin as antitumor agents

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Acyclic vicinal polyol complexes related to cisplatin were synthesized from D-mannitol by stereocontrolled manipulation of the hydroxy groups. Controlled cleavage of a 3,4-diazido hexitol gave the corresponding D-threitol and D-xylitol analogs, which were converted to their diamino platinum complexes. The antitumor activity of these compounds is reported.

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Des dérivés acycliques de diamino polyols vicinaux ont été synthétisés à partir du D-mannitol en utilisant des méthodes de transformations stéréocontrôlées. Le clivage sélectif du dérivé 3,4-diazido hexitol a donné les analogues correspondants du D-threitol et du D-xylitol. Les diamines ont été transformées en complexe de platine et l'activité antitumorale des complexes est rapportée.

Two decades after its discovery (1), *cis*-diammine dichloroplatinum(II) (cisplatin) and its structural variants (for recent reviews, see ref. 2) remain as one of the most widely used group of oncolytic drugs against a variety of cancers (3) (Fig. 1). To date, well over 1000 analogs of cisplatin have been synthesized and examined for antitumor activity, particularly against cancer of the testes, ovaries, bladder, head, and neck. Concurrently, the molecular mechanism of action of cisplatin has been the subject of intensive studies (4). The drug has been shown to bind covalently to chromosomal DNA in the cell nucleus, thus inhibiting replication (5). The site of most stable binding is at the N-7 position of guanine in the DNA, which results in the weakening of hydrogen bonding of the base pairs and the inevitable unwinding of the double helix (6).

In spite of its dramatic success in the treatment of certain types of cancer (7), cisplatin has a number of drawbacks that present difficulties in its continued use. Toxicity of several types (8), narrow range of activity, cross-resistance, and lack of solubility are among the more serious limitations. A number of derivatives in which the dichloro ligands have been changed to other anionic groups (e.g., 1,1-cyclobutanedicarboxylato (carboplatin)) (9) have shown reduced toxicity, presumably due to better pharmacokinetic properties. Several other second and third generation platinum complexes are known (2, 3).

We wish to report on the synthesis and antitumor properties of a series of stereochemically defined, novel platinum complexes derived from a diaminotetritol, -pentitol, and -hexitol, having the generalized structure shown in Fig. 1. After our work was completed a report of cisplatin analogs of 2,3-diamino-2,3-dideoxy-1,4-di-*O*-methyl-D- and -L-threitol was published by Haines *et al.* (10). Other examples of chiral or racemic diaminoalcohol complexes of platinum are found in the patent literature (11).

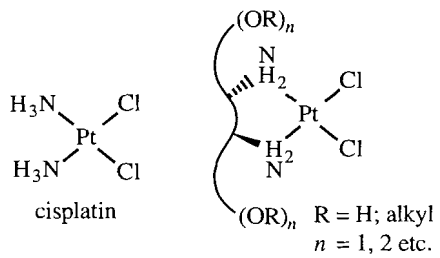

FIG. 1

The design of our alditol-derived platinum analogs took into consideration the distinctly superior activity of cisplatin compared to the *trans* isomer (1). Our synthetic plan took advantage of the C_2 symmetrical properties of D-mannitol and the possibility of preparing *trans*-oriented vicinal diaminodideoxy derivatives therefrom. As shown in Scheme 1, a double nucleophilic displacement of the crystalline dimesylate derivative **2**, employing tetra-*n*-butyl ammonium azide in toluene (12), gave the pivotal diazido derivative **3** as a syrup. The yield of **3** was lower when DMF or DMSO was used in the presence of sodium azide. Hydrolysis of the acetal functions led to the corresponding tetrol **4**, which was methylated in the usual way to give **5**. Hydrogenation of **4** and **5** individually, followed by treatment of the corresponding diamino derivatives with dipotassium tetrachloroplatinate, gave the crystalline complexes **6** and **7**, respectively. The double inversion of configuration in the displacement of **2** with azide ion was anticipated in the absence of neighboring group participation. The structure of **6** was unequivocally confirmed by single crystal X-ray analysis (see below).

With the availability of the diazidohexitol **4**, we could now address the problem of a single and double cleavage of the terminal vicinal glycol units in order to obtain four- and five-carbon diamino cisplatin polyols, respectively. The diazidohexitol **4**, when treated with 1 equivalent of sodium metaperiodate at 0°C, followed by reduction of the corresponding lactol, gave the diazidodideoxy-D-xylitol derivative **8** in good overall yield. Hydrogenation of **8** followed by formation of the platinum(II) complex gave **9** as bright yellow crystals.

Oxidation of **4** with 2 equivalents of sodium metaperiodate at 0°C, followed by reduction with sodium borohydride, gave the crystalline diazidodideoxy-D-threitol derivative **10**. Hydrogenation and treatment of the resulting diamino compound with dipotassium dichloroplatinate afforded the crystalline platinum(II) complex **11**. A number of other di-*O*-alkyl and mono-*O*-alkyl Pt(II) derivatives in this series were also prepared, and were obtained in crystal-

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line form. All the complexes described were water soluble at concentrations ranging from 4 to 10 mg/mL at 25°C. The interaction of several of the diaminopolyol platinum(II) complexes reported here with guanosine, 5′-GMP, and 3′-GMP has been studied by FT-IR and ^{1}H NMR spectroscopy (13).

X-ray crystallographic analysis of compound **6**

Compound **6** crystallized as yellow plates belonging to space group $C222_1$ (polymorph I). A small amount of another polymorph, II (space group $P2_12_12_1$), appeared as yellow needles upon recrystallization from water. The crystal data and refined coordinates are listed in Tables 1 and 2, respectively.

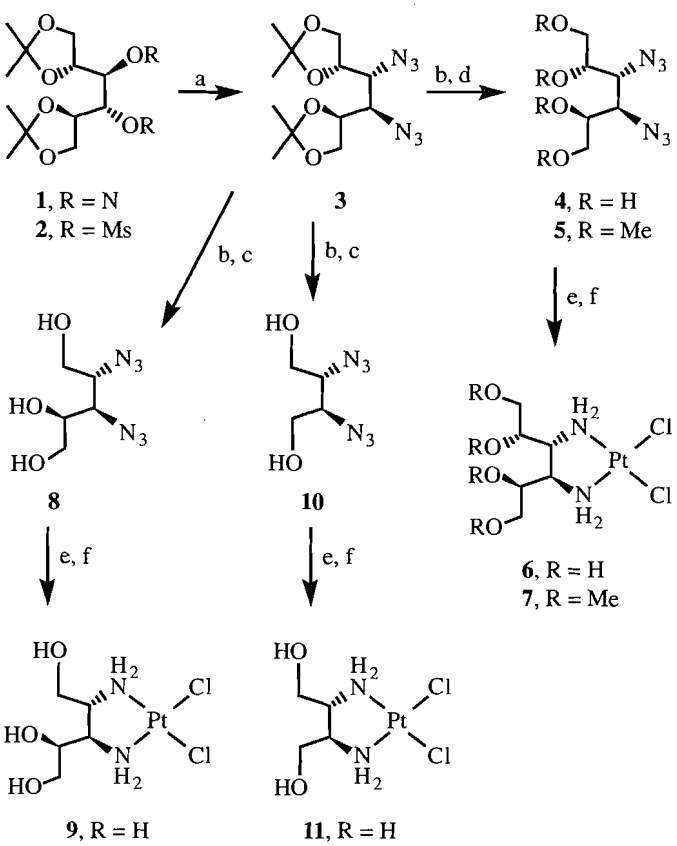
Both crystalline modifications contain the monomeric square-planar *cis*-$PtCl_2$(L–L) complex. Molecule *c* (polymorph II) is shown in Fig. 2. The Pt atom and the middle of the C(3c)—C(4c) bond lie on an approximate twofold axis bisecting the N—Pt—N and Cl—Pt—Cl angles. Coordination is very similar in the two independent types of molecules (*a* and *b*) in polymorph I (drawings in supplementary material), but in these cases the twofold axis is imposed by crystallographic symmetry. Individual distances and angles are provided as supplementary material.[2] The mean Pt—Cl and Pt—N distances (2.32 and 2.03 Å, respectively) compare well with those found in $PtCl_2N_2$ systems with related ligands. The "bite" of the diamine reduces the N—Pt—N angle to 83.8° with a concomitant increase of the Cl—Pt—Cl angle to 94.5°, as found in other diamines forming five-membered chelate rings (14). The puckered chelate ring has the δ conformation (N—C—C—N = 45–56°). The $PtCl_2N_2$ unit is planar with 1σ for molecules *a* and *c*. In molecule *b*, the atom-to-plane distance reaches 0.20(4) Å, the $PtCl_2$ plane being twisted by 9.2° about the twofold axis with respect to the PtN_2 plane. The three independent molecules adopt different conformations of their -CH(OH)-CH_2OH "arms". This likely results from molecular packing, which is largely controlled by hydrogen bonding between water, coordinated chloride, and ligand -OH and -NH_2 groups.

Antitumor activity

The hydroxy analogs **6**, **9**, and **11** showed significant in vitro activity against sensitive strains of L1210 leukemia and P388 with ID_{50} values ranging between 2 and 4.45 μg/mL (cisplatin showed 0.25 μmL) (15). In vivo tests (subcutaneous and intravenous) against PU-239 showed levels of activity approaching that of cisplatin. In vivo test results with M5076 sarcona were inferior to cisplatin.

The *O*-methyl analog **7**, as well as *O*-methyl analogs of **9** and **11** (16), also showed significant in vitro and in vivo antitumor activity against several tumor lines. In vitro tests against sensitive *and* resistant strains of L1210 leukemia showed ID_{50} values of 6–15 μg/mL). The same trend was observed in vivo with values of ID_{50} 13–30 μM for the *O*-methyl analogs with good resistant/sensitive ratios compared to cisplatin (0.8 sens. and 9.9 resist. μM). In vitro activity was demonstrated by **7** and related *O*-methyl analogs of **9** and **11** (15) against P388 (sensitive and resistant with values ranging from 15 to 28 μg/mL (compare cisplatin with 0.25–485 μg/mL). The ratio activity of the *O*-methyl analogs resistant and sensitive strains is an interesting observation that indicates a potential for better cross-resistance.

Although more detailed biological studies are still required, the promising antitumor activity exhibited by these stereochemically well-defined, novel platinum(II) complexes derived from diaminodideoxy alditols should open newer avenues to explore in this important area of cancer chemotherapy.



(a) NaN_3, Bu_4NCl, toluene, reflux; (b) AcOH, H_2O, 60°C, 1 h; (c) 1 equiv. $NaIO_4$, 0°C, 1.5 h and then $NaBH_4$; for **10**, 2 equiv. $NaIO_4$; (d) MeI, NaH, DMF; (e) Pd/C, H_2, MeOH; (f) K_2PtCl_4, H_2O

SCHEME 1

Experimental

Melting points (mp) were determined on a Fisher–Johns apparatus and they are uncorrected. Optical rotations were measured at 25°C using a Perkin–Elmer model 241 automatic polarimeter. Chromatography was done on silica gel (Merck) according to Still et al. (17). Combustion analyses were done at Guelph Laboratories, Ltd., Guelph, Ontario.

[2]Detailed crystallographic results (hydrogen coordinates, temperature factors, distances and angles, torsion angles, least-squares plane calculations, hydrogen-bond geometry, structure factors, and ORTEP drawings) (18 pages) may be purchased from: The Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, Canada K1A OS2.

Tables of hydrogen coordinates, distances and angles, and hydrogen-bond geometry, as well as ORTEP drawings, have also been deposited with the Cambridge Crystallographic Data Centre and can be obtained on request from The Director, Cambridge Crystallographic Data Centre, University Chemical Laboratory, 12 Union Road, Cambridge, CB2 1EZ, U.K.

TABLE 1. Crystal data and conditions for data collection

	Polymorph I	Polymorph II
Formula	$C_6H_{16}Cl_2PtN_2O_4 \cdot H_2O$	$C_6H_{16}Cl_2PtN_2O_4 \cdot H_2O$
Formula weight	464.22	464.22
Crystal system	Orthorhombic	Orthorhombic
Space group	$C222_1$	$P2_12_12_1$
a, Å	7.283(3)	6.720(9)
b, Å	25.949(7)	11.549(9)
c, Å	12.691(6)	15.371(9)
V, Å^3	2398.4	1192.9
D_{calc}, g cm^{-3}	2.571	2.585
Z	8	4
Radiation, λ (Å)	MoKα, 0.71069	MoKα, 0.71069
μ, cm^{-1}	122.9	123.5
Crystal size, mm	0.018 × 0.185 × 0.192	0.025 × 0.025 × 0.60
Transmission range	0.19–0.65	0.67–0.77
Scan type	ω/2θ	ω/2θ
Scan range Δω, deg	1.00 + 0.35 tan θ	1.00 + 0.35 tan θ
Scan speed, deg(ω) min^{-1}	1.0	1.0
2θ max, deg	50.0	50.0
No. unique reflections measured	1223 ($h + k = 2n$)	927
No. observed reflections	699	734
Rejection criterion, $I/\sigma(I) <$	3.0	3.0
T, K	298	298
R^a	0.039	0.023
$R_w{}^a$	0.044	0.028
Goodness-of-fit ratio, S	1.60	1.12

$^aR = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, $R_w = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{1/2}$.

*1,2:5,6-Di-*O*-isopropylidene-3,4-di-*O*-methanesulfonyl-*D*-mannitol (**2**)*

A solution of 1,2:5,6-di-*O*-isopropylidene-D-mannitol (25 g, 95 mmol) in dry methylene chloride (430 mL) and triethylamine (32 g, 0.3 mmol) was treated with methanesulfonyl chloride (26.6 g, 0.233 mmol) dropwise at 0°C under nitrogen atmosphere. After allowing the mixture to warm up to room temperature, it was washed abundantly with cold distilled water, and the organic phase was dried (sodium sulfate) and evaporated under vacuum. The resulting crude solid was recrystallized from a mixture of hot methanol and water to afford 34 g (85%) of long white needles, mp 142–143°C; $[\alpha]_D$ −5.3 (*c* 1, $CHCl_3$). Anal. calcd. for $C_{14}H_{26}O_{10}S_2$: C 40.19, H 6.22; found: C 40.11, H 6.02.

*3,4-Diazido-3,4-dideoxy-1,2:5,6-di-*O*-isopropylidene-*D*-iditol (**3**)*

To a solution of **2** (12 g, 28.7 mmol) in dry toluene (300 mL) was added sodium azide (50 g, 25 equiv.) and tetrabutylammonium chloride (25 g, 3 equiv.). The mixture was heated at reflux temperature under mechanical stirring for 16 h, poured into ice-water (500 mL), and extracted with ethyl acetate. The organic extract was washed with brine, dried over sodium sulfate, filtered, and evaporated. Chromatography of the residue on silica gel (40:2 toluene–acetone) afforded a pale yellow syrup (5.12 g, 57%), which when sublimed at 110°C (0.3 Torr; 1 Torr = 133.3 Pa) gave a low-melting crystalline product; $[\alpha]_D$ +130 (*c* 1, $CHCl_3$). Anal. calcd. for $C_{12}H_{20}N_6O_4$: C 46.15, H 6.41, N 26.92; found: C 45.92, H 6.22, N 26.86.

*3,4-Diazido-3,4-dideoxy-*D*-iditol (**4**)*

A solution **3** (1.32 g, 4.2 mmol) in a mixture of acetic acid (25 mL) and water (13 mL) was heated at 80°C for 75 min. Evaporation gave a dark-brown syrup that was dissolved in methanol and treated with activated charcoal. The pale yellow filtrate was evaporated to dryness to give a chromatographically homogeneous syrup (895 mg, 91%). A portion was crystallized from a mixture of ethyl acetate and hexanes, mp 87–88°C; $[\alpha]_D$ −124 (*c* 1, H_2O). Anal. calcd. for $C_6H_{12}N_6O_4$: C 31.03, H 5.20, N 36.19; found: C 31.21, H 5.13, N 35.94.

*3,4-Diazido-3,4-dideoxy-1,2:5,6-tetra-*O*-methyl-*D*-iditol (**5**)*

A solution of **4** (500 mg, 2.15 mmol) in dry *N*,*N*-dimethylformamide (7.5 mL) was transferred to a round-bottom flask containing sodium hydride (1.037 g, 20 equiv.) in dry *N*,*N*-dimethylformamide (5 mL) at 0°C under nitrogen atmosphere. Upon ceasing of the effervescence, methyl iodide (3.05 g, 10 equiv.) was added dropwise. The reaction mixture was then stirred at 0°C for 1 h, and neutralized with methanol followed by 1 N sulfuric acid. The mixture was evaporated, dissolved in chloroform (50 mL), and washed with distilled water and saturated sodium thiosulfate solution. The organic extract was dried (sodium sulfate) and evaporated under vacuum, and the resulting syrup chromatographed on silica gel (35:65 ethyl acetate – hexanes) to afford the pure product as a colorless syrup (554 mg, 89%); $[\alpha]_D$ 188 (*c* 1, $CHCl_3$).

*3,4-Diamino-3,4-dideoxy-*D*-iditol*

To a solution of **4** (406 mg, 1.75 mmol) in methanol (30 mL) and distilled water (5 mL) was added 10% palladium-on-charcoal (150 mg) suspended in water (5 mL). The mixture was hydrogenated under atmospheric pressure at room temperature for 12 h; the catalyst was then removed by filtration through Celite, washed with distilled water (~5 mL), and the filtrate was evaporated to dryness from absolute ethanol several times. A white solid was obtained (302 mg, 85%); recrystallization form hot ethanol – water afforded colorless needles, mp 160–161°C; $[\alpha]_D$ −104 (*c* 1, H_2O). Anal. calcd. for $C_6H_{16}N_2O_4$: C 40.00, H 8.89, N 15.56; found: C 39.87, H 8.66, N 15.01.

*(SP-4-2)-Dichloro(3,4-diamino-3,4-dideoxy-*D*-iditol-*N*,*N*′) platinum (**6**)*

The preceding diaminopolyol (487 mg, 2.7 mmol) in 2 mL of water was added to a solution containing K_2PtCl_4 (1.124 g, 2.7 mmol) in distilled water (12 mL). The mixture was stirred manually until it became homogeneous, and the solution was left standing in the dark. After 2 h bright yellow plates were obtained

TABLE 2. Atomic coordinates ($\times 10^3$, Pt $\times 10^5$, Cl $\times 10^4$) and equivalent isotropic temperature factors ($\times 10^3$)

	x	y	z	U_{eq}
Polymorph I				
Pt(1a)	0	−694(8)	25000	21
Pt(1b)	50000	205(6)	25000	21
Cl(1a)	647(21)	531(4)	3796(7)	32
Cl(1b)	4406(24)	−591(4)	1214(8)	41
O(1a)	249(3)	−210(1)	487(2)	33
O(1b)	110(3)	203(1)	113(2)	24
O(2a)	−90(3)	−161(1)	423(2)	33
O(2b)	502(4)	203(1)	144(1)	24
O(10a)	−364(4)	−217(1)	321(2)	62
N(3a)	59(6)	−65(1)	352(3)	34
N(3b)	424(6)	61(1)	152(3)	25
C(1a)	240(5)	−162(1)	434(2)	29
C(1b)	202(4)	165(1)	178(3)	31
C(2a)	71(5)	−159(1)	364(2)	12
C(2b)	391(5)	157(1)	140(3)	28
C(3a)	81(5)	−115(1)	291(2)	17
C(3b)	499(8)	111(1)	191(2)	19
Polymorph II				
Pt(1c)	20251(7)	23153(4)	225(5)	20
Cl(1c)	2038(6)	4324(3)	103(3)	33
Cl(2c)	2013(6)	2255(3)	−1490(2)	30
O(1c)	491(2)	90(1)	353(1)	41
O(2c)	1(2)	95(1)	264(1)	42
O(5c)	427(2)	−131(1)	91(1)	31
O(6c)	142(2)	−311(1)	78(1)	33
O(10c)	675(2)	−65(1)	233(1)	45
N(3c)	203(2)	217(1)	133(1)	30
N(4c)	207(2)	55(1)	6(1)	25
C(1c)	327(3)	150(1)	320(1)	33
C(2c)	212(3)	77(1)	256(1)	31
C(3c)	259(2)	100(1)	161(1)	25
C(4c)	160(2)	15(1)	98(1)	26
C(5c)	227(3)	−113(1)	113(1)	26
C(6c)	98(3)	−190(1)	59(1)	29

and the crystallization was allowed to continue until the original red color of the solution became yellow or orange-yellow. The crystals were filtered, washed with cold water (2–3 mL), and dried in the absence of light, to afford bright yellow crystals (565 mg), mp 226–229°C (gradual darkening at 190°C); $[\alpha]_D$ 6.3 (*c* 0.4, H_2O). Concentration of the mother liquors in vacuo (50°C) yielded a second crop of **6** (91 mg). Anal. calcd. for $C_6H_{16}N_2O_4PtCl_2 \cdot H_2O$: C 15.52, H 3.90, N 6.03, Cl 15.27; found: C 15.41, H 3.58, N 6.11, Cl 15.03.

The procedure described above yielded yellow plates belonging to space group $C222_1$. By recrystallization from water, the same crystalline phase was obtained as the major component, but the sample also contained a small amount of yellow needles, which were identified as a second crystalline modification of the same compound with space group $P2_12_12_1$. X-ray work was carried out on both polymorphs (see below).

*2,3-Diazido-2,3-dideoxy-D-threitol (**10**)*

To a solution of **4** (500 mg, 2.15 mmol) in distilled water (10 mL) was added solid sodium metaperiodate (925 mg, 4.32 mmol) portionwise at 0°C, in the absence of light. The mixture was stirred for 2 h, and sodium borohydride (0.9 g) was added. After 2 h at 0°C, the solution was acidified with 1 N sulfuric acid, decolorized with sodium thiosulfate, and evaporated under vacuum. The residue was dissolved in water (25 mL) and extracted with ethyl acetate (5 × 40 mL); the combined organic extracts were decolorized

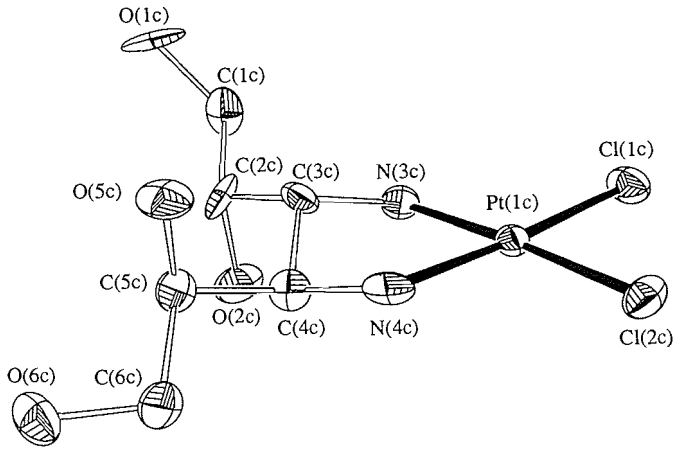


FIG. 2. ORTEP drawing of molecule *c* in polymorph II. Ellipsoids correspond to 50% probability. Hydrogens are omitted for simplicity. Drawings for the two independent molecules (*a* and *b*) of polymorph I are provided in the supplementary material.

with sodium thiosulfate, dried, and evaporated under vacuum to afford a colorless oil (390 mg, 95%). Thin-layer chromatography of the oil showed the presence of diol and triol in equal proportions. The product was recycled through the oxidative cleavage and the reduction as described above, and the reaction mixture was processed to afford the diol **10** in the form of white crystals. Recrystallization from chloroform–hexanes yielded 303 mg (82%) of product, mp 78–79°C; $[\alpha]_D$ +41.4 (*c* 0.5, MeOH). Anal. calcd. for $C_4H_8N_6O_2$: C 27.91, H 4.65, N 48.84; found: C 27.62, H 4.44, N 48.53.

2,3-Diamino-2,3-dideoxy-D-threitol

To a solution of the diazide **10** (487 mg, 2.83 mmol) in methanol – distilled water (1:1, 20 mL) was added palladium-on-charcoal (300 mg) suspended in methanol (5 mL). The mixture was hydrogenated under atmospheric pressure at room temperature for 12 h. The catalyst was then removed by filtration over Celite, and the filtrate was evaporated under vacuum. The residue was co-evaporated with ethanol to dryness to afford a colorless syrup (333 mg, 98% yield); $[\alpha]_D$ −151 (*c* 1, H_2O).

*(SP-4-2)-Dichloro(2,3-diamino-2,3-dideoxy-D-threitol-N,N′) platinum (**11**)*

The previous diamino derivative was dissolved in distilled water (0.7 mL) and added to a solution containing K_2PtCl_4 (1 equiv.) in distilled water (4.4 mL for 1 mmol). The mixture was stirred manually until it became homogeneous, and the solution was left standing in darkness. After 2 h, bright yellow crystals were formed. When the original red color of the solution became yellow or orange-yellow, the crystals were filtered, washed with cold water (1–2 mL), and dried under air suction in the absence of light for several hours, to afford bright yellow crystals (yield 60%), mp > 300°C; $[\alpha]_D$ −94 (*c* 0.083, H_2O). Anal. calcd. for $C_4H_{12}N_2O_2PtCl_2$: C 12.47; H 3.12, N 7.27, Cl 18.18; found: C 12.60, H 3.13, N 7.22, Cl 18.60.

*2,3-Diazido-2,3-dideoxy-D-xylitol (**8**)*

To a solution of **4** (1 g, 4.3 mmol) in distilled water (25 mL) was added sodium metaperiodate (920 mg) in distilled water (10 mL), portionwise at 0°C, and in the absence of light. The mixture was stirred 90 min at 0°C, then it was treated with sodium borohydride (1.75 g) in distilled water (20 mL). After 1 h, the reaction was acidified with 1 N sulfuric acid, decolorized with a few millilitres of saturated sodium thiosulfate, and evaporated under vacuum. The residue was dissolved in water (25 mL) and extracted with ethyl acetate (5 × 100 mL). The combined organic extract was decolorized with sodium thiosulfate, dried, and evaporated under vacuum

and the residue was chromatographed on silica gel (85:15 ethyl acetate – hexanes) to afford the triol **8** (577 mg; 66% yield); $[\alpha]_D$ −239 (*c* 1.35, CH_3OH).

2,3-Diamino-2,3 dideoxy-D-xylitol

To a solution of **8** (577 mg, 28 mmol) in methanol (25 mL) was added palladium-on-charcoal (300 mg) suspended in methanol–water (1:1, 5 mL). The mixture was hydrogenated at room temperature under atmospheric pressure for 12 h. The catalyst was removed by filtration through Celite, the filtrate was evaporated under vacuum, and the residue was coevaporated with ethanol to dryness to afford a colorless syrup (421 mg, yield 98%); $[\alpha]_D$ −200 (*c* 1, H_2O).

(SP-4-3)-Dichloro(2,3-diamino-2,3-dideoxy-D-xylitol-N,N′*) platinum (9)*

The above diamino derivative was dissolved in distilled water (1 mL), and added to a solution containing K_2PtCl_4 (1 equiv.) in distilled water (5 mL). The mixture was stirred manually until homogeneous, and was left standing in the dark. After 2 h, bright yellow plates were formed. When the original red color of the solution became yellow or orange-yellow, the crystals were filtered, washed with cold water, and dried, in the absence of light for several hours, to afford bright yellow crystals (yield 57%); mp 255°C (dec.); $[\alpha]_D$ −52 (*c* 0.27, H_2O). Anal. calcd. for $C_5H_{14}N_2O_3PtCl_2$: C 14.46, H 3.37, N 6.75, Cl 16.87; found: C 14.40, H 3.38, N 6.80, Cl 17.32.

(SP-4-2)-Dichloro(3,4-diamino-3,4-dideoxy-1,2,4,6-tetra-O-*methyl-D-iditol*-N,N′*) platinum (7)*

A solution of **5** (0.5 g) was hydrogenated as described above and the resulting diamino derivative was treated with K_2PtCl_4 as described for **6**. The title compound **7** was obtained as a crystalline product in 52% yield, mp 286–287°C (dec.); $[\alpha]_D$ −25.2 (*c* 0.33, H_2O). Anal. calcd. for $C_{10}H_{22}N_6O_4PtCl_2$: C 23.91, H 4.81, N 5.57, Cl 14.11; found: C 23.98, H 4.72, N 5.56, Cl 14.48.

X-ray data collection and structure determination

Crystal data are provided in Table 1. Starting cell parameters and space group were determined from precession and cone-axis photographs. For both polymorphs, the space group was uniquely defined from the systematic absences: *hkl*, $h + k \neq 2n$ and 00*l*, $l \neq 2n$ for $C222_1$ (polymorph I); *h*00, $h \neq 2n$; 0*k*0, $k \neq 2n$; 00*l*, $l \neq 2n$ for $P2_12_12_1$ (polymorph II).

The intensity data were collected on an Enraf–Nonius CAD-4 diffractometer with graphite-monochromatized MoKα radiation, following the procedure described elsewhere (18). The data were corrected for the effects of Lorentz, polarization, and absorption (Gaussian integration, grid 10 × 10 × 10).

For polymorph I, the Patterson synthesis provided relative positions for the Pt atoms, but there were eight nonequivalent ways of positioning this pattern with respect to the origin in the $C222_1$ unit cell and each of these starting models showed pseudosymmetry. The ΔF map phased on any of these models showed, around each Pt atom, eight peaks corresponding to two superimposed square-planar units in which the Cl and N corners could not be differentiated. A small number of starting points could be rejected because they generated abnormally short intermolecular contacts. The remaining models were systematically tested. By structure factor and ΔF map calculations, resolution could generally progress up to a certain point, where inconsistencies developed in the positions of the ligand free "arms". The correct model turned out to contain two nonequivalent sets of Pt atoms occupying twofold axes (independent *4b* equipoints). The known absolute configuration was imposed. Isotropic refinement of the non-hydrogen atoms using full-matrix least squares converged to $R = 0.096$. The hydrogens on C and N atoms were fixed at idealized positions (N—H = 0.87, C—H = 0.95 Å, $B_{iso} = 6.0$ Å^2). Their parameters were not refined, but the coordinates were recalculated after each cycle of refinement. The hydrogens of the hydroxyl groups and water molecule were not detected. Anisotropic refinement of the non-hydrogen atoms converged to $R = 0.039$ and $R_w = 0.044$. The goodness-of-fit ratio was 1.60. The final ΔF map showed maximum residuals of ±1.3 e Å^{-3} within 1 Å from Pt atoms. The general background was lower than ±0.5 e Å^{-3}.

For polymorph II, the Pt atoms occupying a general equipoint were located from the Patterson map. The remaining non-hydrogen atoms were then found from a ΔF map. The structure was refined by full-matrix least squares. Isotropic refinement converged to $R = 0.052$. Hydrogens were handled as above. Anisotropic refinement of the non-hydrogen atoms converged to $R = 0.023$ and $R_w = 0.028$. The goodness-of-fit ratio was 1.12. The final ΔF map showed a general background below ±0.3 e Å^{-3}, except for a few peaks of ±|0.3–0.6| e Å^{-3} near Pt or Cl.

The scattering curves used were those of Cromer and Waber (19), except for hydrogen (20). The anomalous dispersion terms of Pt and Cl were taken from Cromer (21). The programs used are listed elsewhere (22).

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