Synthesis of the Anti-tumor Agent CI-973 {[SP-4-3-(R)]-[1,1-Cyclobutanedicarboxylato(2)](2-methyl-1,4-[4-^{14}C]butanediamine-N,N')platinum}

I. Victor Ekhato*, James D. Hoeschele, Che C. Huang, Bela Nanavaty, and Helen T. Lee

Radiochemistry, Dept. of Chemical Development
and
Department of Chemistry
Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company
Ann Arbor, Michigan 48105.

SUMMARY

Starting from the chiral compound 1, (R)-(+)-2-methyl-1,4-[^{14}C]butanediamine 7 was synthesized in a sequence of reactions in which ^{14}C-label was introduce using label potassium cyanide. Compound 7 was reacted with potassium tetraiodoplatinate and silver 1,1-cyclobutanedicarboxylate to make the title compound {[SP-4-3-(R)]-[1,1-cyclobutanedicarboxylato(2)](2-methyl-1,4-butanediamine-N,N')platinum} 11.

Key Words: {[SP-4-3-(R)]-[1,1-cyclobutanedicarboxylato(2)](2-methyl-1,4- butane-N,N')platinum}, (R)-(+)-2-methyl-1,4-butanediamine, antitumor drug, silver 1,1-cyclobutanedicarboxylate, square-planar diaminoplatinum (ll) chelate complex.

Introduction

{[SP-4-3-(R)]-[1,1-Cyclobutanedicarboxylato(2)](2-methyl-1,4-butanediamine-N,N')platinum} (CI-973) (11) is a potential third generation platinum antitumor drug, currently in phase II clinical trials in the United States (1). We required labeled version for drug metabolism, distribution and disposition studies, and it was prepared by incorporating labeled (R)-(+)-2-methyl-1,4-butanediamine ((R)-2-methylputrescine, 7) into the square-planar diaminoplatinum(II) chelate complex. Preparation of the chiral diamine 7 was accomplished in a sequence starting from commercial (R)-(-)-3-bromo-2-methyl-1-propanol (1). Towards the end of the sequence, radiolabel was introduced as the ^{14}C nitrile and hydrogenated to the labeled primary

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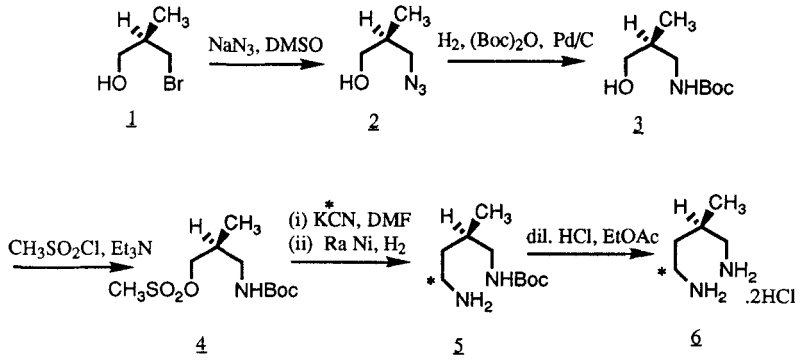
amine. By sequentially treating potassium tetraiodoplatinate with the free butanediamine and silver 1,1-cyclobutanedicarboxylate, the chelate complex, {[SP-4-3-(R)]-[1,1-cyclobutanedicarboxylato(2-)](2-methyl-1,4-[4-^{14}C]butanediamine-N,N')platinum (CI-973) (11) was made.

Results and Discussion

In a previous study, Santaniello et al (2) achieved the chiral synthesis of 2-methyl-1,4-butanediamine (7) by a modification of published procedure. Both (R,S)- and (R)-2-methyl-1,4-butanediamine were prepared via Curtius rearrangement from commercially available (R,S)- and (R)-methyladipic acid. (S)-(-)-2-Methyl-1,4-butanediamine on the other hand, was prepared from a dichloride, which was itself made from (S)-citronellic acid. By this approach, however, our desired target ligand (R)-(+)-2-methyl-1,4-[4-^{14}C]butanediamine could not be made.

SCHEME 1

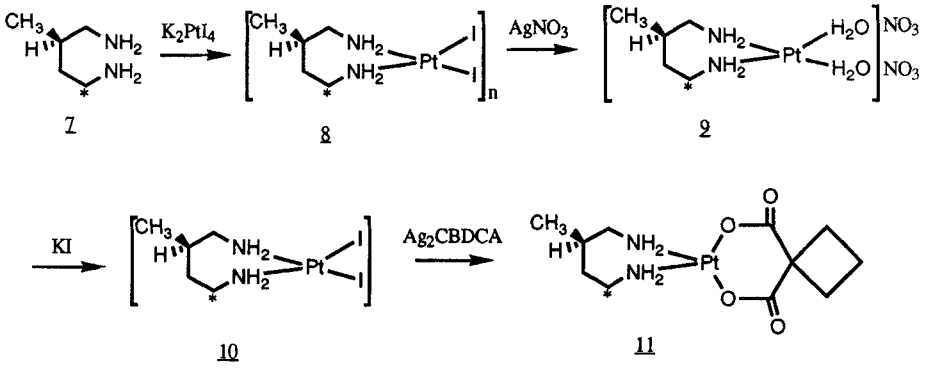


The present approach (**Scheme 1**) involved a sequence of transformations from chiral 3-bromo-2-methyl-1-propanol (1) to the N'-[(1,1-dimethylethoxy)carbonyl]-amino alcohol 3. These reactions were not expected to compromise chirality in starting compound. Furthermore, the subsequent facile conversion of N'-[(1,1dimethylethoxy)carbonyl]-amino alcohol to the N-boc-α,ω–alkanediamine (3), N'-[(1,1-dimethylethoxy)carbonyl]-(R)-2-methyl-1,4-butanediamine (5), was expected to furnish stable crystalline hydrochloride by mild acid deprotection condition. Compound 1, underwent smooth conversion to (S)-3-azido-2-methyl-1-propanol (2), and by catalytic reduction 2 was transformed to (S)-3-amino-2-methyl-1-propanol.

The amino alcohol was treated with di-tert-butyl dicarbonate to give N′–[(1,1dimethylethoxy)carbonyl]-amino alcohol 3 . In an alternative preparation, compound 3 was obtained by direct catalytic reduction of compound 2 in the presence of a molar equivalent of di-tert-butyl dicarbonate. Construction of the primary amine moiety $-^{14}CH_2NH_2$ required the derivatization of compound 3 as the mesylate, which upon displacement reaction with $K^{14}CN$ followed by catalytic hydrogenation yielded (R)-(+)-N′-[(1,1-dimethylethoxy)carbonyl]-2-methyl-1,4-[4-^{14}C]butanediamine (5). Purification at this step was followed by dilute hydrochloric acid cleavage of N′-[(1,1-dimethylethoxy)carbonyl] (boc) group (4) in ethyl acetate to provide crystalline hydrochloride salt 6. In order to validate the spectroscopic and analytical data obtained for compound 6 the unlabeled (R)-(+)-2-methyl-1,4-butanediamine was prepared from (R)-(+)-2-methyladipic acid according to reported method (5). Proton NMR data of the compound 6 were identical with those of the unlabeled compound prepared from (R)-(+)-2-methyladipic acid by this method (5).

In preparing the square-planar diaminoplatinum(II) chelate complex 11, from the diamine ligand 7, a refinement of the procedure due to Nowatari et al (6) was required. The modified protocol allowed a microscale preparation with an improved yield of 40% with good radiochemical purity . We found that the simultaneous addition of molar equivalent solutions of the free diamine 7 and K_2PtI_4 (generated *in situ*) into a reaction vessel maintained at 60°C was critical to the yield of the final product 11 obtained. Compound 8, the insoluble product from this step (**Scheme 2**), was treated with 10% excess of $AgNO_3$ and digested at 60°C for 1hr to give a monomeric diaqua species 9 and an insoluble polymeric aqua species.

SCHEME 2



The desired soluble compound 9 was isolated, excess Ag^+ removed by treatment with HCl, and upon reaction with KI compound 10 was formed. The reaction between compound 10 and silver salt of 1,1-dicarboxylatocyclobutane (Ag_2CBDCA) provided the target compound (CI-973, 11). Initial purification of crude CI-973 was by column chromatography employing a mixed-bed ion-exchange resin (in OH^- and H^+ forms). Approximately 3% radiochemical impurity detectable only by tlc proved difficult to eliminate by either ion-exchange, reverse or normal phase silica gel chromatography. Column chromatography on deactivated neutral alumina furnished higher purity grade compound.

In conclusion, a convenient chiral synthesis of ^{14}C labelled (R)-(+)-methyl-1,4-butanediamine 7 was developed, and in turn it allowed us to prepare {[SP-4-3-(R)]-[1,1-cyclobutanedicarboxylato(2)](2-methyl-1,4-[4-^{14}C]butanediamine-N,N')platinum (11) by a modified literature procedure.

Experimental

General Methods.

All reactions were carried out under inert atmosphere. ^1H-NMR spectra were recorded on a Varian (EM 390) 90 MHz spectrometer, a Gemini 200 MHz or a Varian XL 300 MHz spectrometer. Radiochemical purity of every labeled compound was determined by tlc radiochromatogram with Bioscan 200 imaging scanner. Radiochemical counting was performed on a Packard 574 liquid scintillation counter using Beckman Readi-Solv MP cocktail. HPLC analyses of final products were performed on a Waters Associates 600E system with on-line Applied BioSystems 1000S diode array detector and either a β-RAM radioactivity detector or Radiomatic series A-200 radioactivity flow detector. Column chromatography was carried out on a Merck Kieselgel 60 (230μ).

(S)-3-{N'-[(1,1-Dimethylethoxy)carbonyl] amino}-2-methylpropyl methanesulfonate (4).

(R)-(-)-Bromo-2-methyl-1-propanol (10.0g, 65.78 mmol) in anhydrous DMSO (120mL) and NaN_3 (5.6g, 86.14 mmol) was stirred at 70°C under N_2 overnight. It was cooled to room temperature and poured onto ice-water mixture. The combined ethereal extract (3X500mL) was washed with water (2X200mL), dried, and concentrated

to give a liquid (6.8g). Total crude was hydrogenated over 10% Pd/C in methanol in the presence of di-*tert*-butyl dicarbonate (15.8g, 72.39 mmol) overnight. Solvent was stripped, and residue was taken up in ether (400 mL) and washed with saturated $NaHCO_3$ (100 mL), water, and then brine. The ether solution was dried and evaporated to give a liquid (16.20 g). To the entire product (16.20 g) in methylene chloride (162 mL) cooled in an ice-water bath was added dry triethylamine (8.69g 11.9mL, 85.78 mmol) in one portion. Methanesulfonyl chloride (6.6 mL, 85.27 mmol) was added, stirred for 10 min, and the ice-water bath was removed. After additional stirring for 1h it was diluted with ether (600 mL), washed with water (200 mL) and saturated $NaHCO_3$ (100 mL), and brine (300 mL). Solvent was removed using a rotary evaporator to give a liquid. The oil was purified by column chromatography on silica gel eluted with ether-pet. ether (60:40) to give, after earlier fractions of impurity, the mesylate 4 (11.58 g). Proton nmr (200MHz) (δ, $CDCl_3$), 4.8, br s 1H; 4.1, m, 2H; 3.1, br, 2H; 3.0, s, 3H; 2.1, m, 1H; 1.4, s, 9H; 1.0, d, 3H.

(R)-(+)-2-Methyl-1,4-[4-^{14}C]butanediamine [(R)-2-Methylputrescine] hydrocloride (6)

To (S)-3-{N'–[(1,1-dimethylethoxy)carbonyl] amino}-2-methylpropyl methanesulfonate (4) (1.9 g, 7.1mmol) in anhydrous DMSO (25 mL) was added $K^{14}CN$ (454.5 mg, Sp.Act 58 mCi/mmol) and the mixture was heated at 80°C overnight. After it was cooled to room temperature, chloroform (120 mL) was added, washed with deionized water (4X30 mL) and dried. Solvent was removed *in vacuo*, and the liquid was dried for 3 h under high vaccum. It was dissolved in methanol (saturated with ammonia) (120 mL) and hydrogenated at 65 psi pressure in the presence of Ra-Ni (1.40 g) overnight. The reaction mixture was filtered (Caution!) through a bed of Celite, and the solvent was evaporated under reduced pressure. The oily product was re-dissolved in ethyl acetate (50 mL), and 6N HCl (10 mL) was added and stirred for 30 min at room temperature. Solvent was removed at reduced pressure, and the residue was redissolved in isopropanol. It was azeotroped twice with toluene and crystallized from methanol-ether to give (R)-(+)-2-methyl-1,4-[4-^{14}C]butanediamine hydrochloride (742 mg), specific activity 55.5mCi/mmol, optical rotation $[\alpha]_D$ +5.0 (10mg/mL H_2O). HPLC T_R 3.19min, CP 98.2%, RCP 100% on Alltech Econosil CN, 10μ, 4.6mm ID X 250mm, acetonitrile:water (1:1), flow rate 1mL/min. TLC silica gel 60 F-254, (EtOH:NH_4OH;

8:2), Rf 0.18, 98.21%, RCP 100%. NMR (D_2O) δ 4.9, br s, (H_2O); 3.0, m, 3H, 2.75, m, (1H), 1.85, dm, 2H, 1.6, m, 1H, and 1.10, d, 3H.

[[SP-4-3-(R)]-[1,1-Cyclobutanedicarboxylato(2)](2-methyl-1,4-butanediamine-N,N′) platinum], CI-973 (11).

To a solution of K_2PtCl_4 (1.76 g 4.24 mmol) in 10.0 mL of deionized water in ice-bath was added in one portion KI (4.22 g, 25.42 mmol) in 6.0 mL of water. While stirring under nitrogen atmosphere, the free diamine was prepared by dissolving (R)-(+)-2-methyl-1,4[4^{14}C]butanediamine.2HCl (6) , (742 mg, 4.24 mmol) in 1.0N NaOH solution (8.48 mL) and subsequently made up to 18.0 mL with deionized water.

After stirring for 45 min during which K_2PtI_4 was generated *in situ*, the solution and the free diamine were simultaneously added in roughly equivalent proportions to a reaction vessel maintained at 60°C in the dark. The reaction was aged at 60°C for 1h and stirring was continued at room temperature overnight. The solid product was harvested by centrifugation, resuspended in deionized water (30.0 mL) and treated with $AgNO_3$ (1.59g, 9.35 mmol) in 5.0mL of water. After stirring for 45 min, the yellow precipitate formed was separated and discarded. The solution was washed with 1N HCl (2.0 mL), spun three times, and the residual solid was similarly discarded. To the solution was then added KI (1.4g, 8.4 mmol) in 5.0mL of water, and the solid product was isolated by centrifugation after reaction for 1h with stirring at room temperature.

The solid was resuspended in deionized water (40.0 mL) and Ag_2CBDA (1.08g) was added and stirred at 60°C to digest. After 1h the reaction temperature was lowered and stirred at room temperature overnight. The reaction mixture was applied to a pre-equilibrated column of neutral alumina and eluted with EtOH:BuOH:H_2O (60:30:10) to give the product which crystallized from methanol to afford 11 (744 mg). Specific activity (55mCi/mmol), Optical rotation $[\alpha]_D$ +29.0 (10.0mg/ml H_2O). TLC silica gel 60 F-254, (acetone:water 75:25), Rf 0.73, 97.2%. HPLC T_r 10.11min, RCP 100%, on Alltech Econosil CN, 10μ, 4.6mm ID X 250mm, 1% KH_2PO_4 : MeOH, (80:20), flow rate 1.0 ml/min, uv 215 nm. NMR (D_2O) δ 4.75, br s (D_2O); 2.6 to 2.85, m, 7H ; 2.33, m, 2H ; 1.85, m, 3H; 1.65, m, 1H ; and 0.9 , d, 3H .

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