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SYNTHESIS OF CARBON-14 LABELLED *CIS*-MALONATO [(4*R*,5*R*)-4,5-BIS(AMINOMETHYL)-2-ISOPROPYL-1,3-DIOXOLANE] PLATINUM(II) (SKI 2053R)

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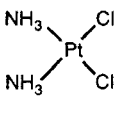
SUMMARY

The synthesis of ^{14}C-labelled *cis*-malonato[(4*R*,5*R*)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane]platinum(II) from [1,4-^{14}C] D-tartaric acid is described. The overall radiochemical yield of the product in a eight-step sequence was 23.8% and radiochemical purity was 98.5%.

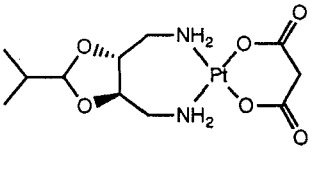
KEY WORDS: *cis*-malonato[(4*R*,5*R*)-4,5-bis(amino[^{14}C]methyl)-2-isopropyl-1,3-dioxolane]platinum(II), SKI 2053R[^{14}C], anticancer agent, radiosynthesis.

INTRODUCTION

Cisplatin[1] is one of the most effective anticancer agents currently available for the treatment of testicular, ovarian, and bladder carcinomas.[2-6] In addition, cisplatin is widely used in combination with other anticancer agents in treating head and neck cancer, lung carcinoma, and stomach carcinoma.[7,8] However, the adverse effects that are observed in patients receiving cisplatin, such as nephrotoxicity, severe nausea and vomiting, and neurotoxicity[9,10] as well as the low activity for some kinds of cancers, such as breast and colon cancers[11] have stimulated the search for new platinum-based anticancer agents that will display reduced toxicity and different spectrum of antitumor activity.[12-16]



Cisplatin



SKI 2053R

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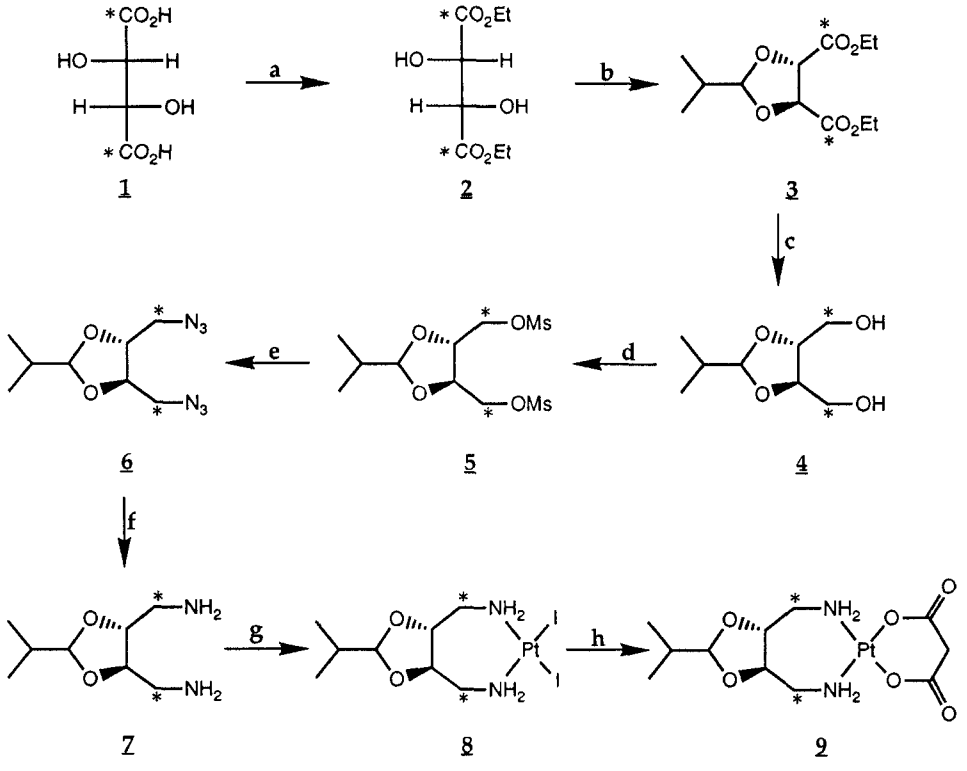
In our efforts to develop a water-soluble new platinum complex that possesses a broader spectrum of antitumor activity, lower toxicity, and lack of cross-resistance to cisplatin, we have recently prepared a series of 2-substituted-1,3-dioxolane-4,5-bis(aminomethane) platinum(II) complexes.[17] Among them, *cis*-malonato[(4*R*,5*R*)-4,5-bis-(aminomethyl)-2-isopropyl-1,3-dioxolane]platinum(II) (SKI 2053R, NSC D644591) showed the excellent antitumor activity against a number of murine tumors including cisplatin-resistant L1210 leukemia and human tumor cell lines,[18-20] reduced renal toxicity in rats and dogs compared to cisplatin,[21,22] and suitable physicochemical properties such as high solubility and stability in aqueous solution. In order to facilitate the pharmacokinetic and metabolic studies of this new platinum complex, we required the carbon-14 labelled compound. In biological systems, platinum complexes are known to undergo aquation in the leaving ligand to generate reactive intermediates, such as aquo, mixed aquo-hydroxo, and hydroxo complexes, which bind preferentially at the N-7 position of the guanine of DNA.[23,24] Considering the mechanism of action, it is desirable to label a carbon in the 2-isopropyl-1,3-dioxolane-4,5-bis(aminomethane) carrier ligand rather than in the malonate leaving ligand. In the carrier ligand, labelling of the carbon of aminomethyl group or the C-4 is preferable to the C-2 because there is a possibility that the 1,3-dioxolane ring moiety may be hydrolyzed chemically or enzymatically in biological fluids. We finally decided to label the carbon of aminomethyl group with ^{14}C rather than the C-4 because of readily available starting material. In this report, we describe the synthesis of *cis*-malonato[(4*R*,5*R*)-4,5-bis(amino[^{14}C]methyl)-2-isopropyl-1,3-dioxolane]platinum(II) from [1,4-^{14}C] D-tartaric acid.

RESULTS AND DISCUSSION

[1,4-^{14}C] D-tartaric acid was reacted with ethanol in the presence of an acid catalyst to obtain diethyl [1,4-^{14}C] D-tartarate **2** in 90% yield. The diester **2** was treated with isobutyraldehyde and anhydrous $CuSO_4$ in the presence of methanesulfonic acid to afford diethyl 2,3-*O*-isobutylidene-[1,4-^{14}C]-D-tartarate **3** in 83% yield after purification. The 1,3-dioxolane diester **3** was then reduced with LAH to produce (4*R*,5*R*)-4,5-bis(hydroxy[^{14}C]methyl)-2-isopropyl-1,3-dioxolane **4** in 88% yield after chromatographic purification. Treatment of dihydroxy compound **4** with methanesulfonyl chloride in pyridine yielded (4*R*,5*R*)-4,5-bis(methanesulfonyloxy[^{14}C]methyl)-2-isopropyl-1,3-dioxolane **5** in 89% yield after recrystallization. Compound **5** was reacted with sodium azide in DMF to give (4*R*,5*R*)-4,5-bis(azido[^{14}C]methyl)-2-isopropyl-1,3-dioxolane **6** in 95% yield after purification. The azide **6** was reduced with hydrogen in the presence of 10% palladium on activated carbon in an alcoholic medium to afford (4*R*,5*R*)-4,5-bis(amino[^{14}C]methyl)-2-isopropyl-1,3-dioxolane **7** in 97% yield. The diamino compound **7** was reacted with an equimolar amount of *in situ* generated potassium tetraiodoplatinate(II) to give *cis*-diiodo[(4*R*,5*R*)-4,5-bis(amino[^{14}C]methyl)-2-isopropyl-1,3-dioxolane]platinum(II) **8** in 76% yield, which was subsequently treated with malonic

Scheme 1[a]



[a](a) EtOH, c-H_2SO_4, reflux, 10 h; (b) isobutyraldehyde, anh. $CuSO_4$, MsOH, toluene, rt, 12 h; (c) LAH, Et_2O, reflux, 5 h; (d) MsCl, pyridine, rt, 10 h; (e) NaN_3, DMF, 100 °C, 8 h; (f) 10% Pd-C, EtOH, H_2 (50 psi), 40 °C, 1 h; (g) K_2PtCl_4, KI, H_2O, 60 °C, 1 h; (h) malonic acid disilver salt, H_2O, 60 °C, 10 h

acid disilver salt in water to give *cis*-malonato[(4*R*,5*R*)-4,5-bis(amino[^{14}C]methyl)-2-isopropyl-1,3-dioxolane]platinum(II) **9** in 58% yield after purification by passing through a celite pad followed by ODS column chromatography. The overall radiochemical yield of **9** from [1,4-^{14}C] D-tartaric acid in a eight-step sequence was 23.8% and radiochemical purity was 98.5%.

EXPERIMENTAL

DL-Tartaric acid [1,4-^{14}C][25,26] was synthesized from potassium [^{14}C] cyanide which

was purchased from Du Pont NEN. Boston, Mass. and optically resolved with (*S*)-(+)-2-phenylglycinol. All other reagents were purchased and used without purification. All other solvents were either distilled or of analytical reagent quality. Infrared spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Unity 300 spectrometer. The chemical shifts are reported in parts per million (ppm) relative to TMS in $CDCl_3$ or DMSO-d_6. ^{1}H noise-decoupled ^{13}C NMR spectra were recorded on a Varian Unity 300 at 75.4 MHz. When $CDCl_3$ was used as solvent, it served as the internal standard at δ 77.0. Analytical HPLC was performed on a Waters Model 510 equipped with UV-detector (Waters Model 484), HPLC radioactivity monitor (Berthold LB-506 C-1), and μ-Bondapak C_{18} ODS column (3.9 X 250 mm) using a mobile phase of MeOH/H_2O (4/6). Preparative HPLC was accomplished on a Waters Model Prep LC 3000 system using same solvent system with Delta Pak C_{18}-100Å reverse-phase bonded silica cartridge.

Diethyl [1,4-^{14}C] D-Tartarate (2). A mixture of [1,4-^{14}C] D-tartaric acid 1 (100 mCi, 357 mg, 2.38 mmol, $[\alpha]^{25}_D$ = -13.77 ° in water) and concentrated sulfuric acid (40 μL) in absolute ethanol (4 mL) was heated at reflux for 10 h. The reaction mixture was cooled to room temperature and to it, aqueous 28% ammonium hydroxide solution (200 μL) was added, and the mixture was stirred for an additional 30 min. The white precipitate was filtered off and the filtrate was evaporated to dryness to give an oil (440 mg, 90%, 90 mCi): TLC radiochemical purity > 98%, R_f = 0.38, silica gel, hexane/EtOAc (1/1); ^{1}H NMR ($CDCl_3$) δ 1.33 (t, *J* = 7.2 Hz, 6 H, 2 CH_3), 3.28 (br s, 2 H, 2 OH), 4.32 (q, *J* = 7.2 Hz, 4 H, 2 CH_2), 4.54 (s, 2 H, 2 CH).

Diethyl 2,3-*O*-Isobutylidene-[1,4-^{14}C]-D-tartarate (3). A mixture of 2 (440 mg, 90 mCi, 2.13 mmol), isobutyraldehyde (970 μL, 10.65 mmol), anhydrous copper(II) sulfate (680 mg, 4.26 mmol) and methanesulfonic acid (1 drop) in anhydrous toluene (7 mL) was stirred at room temperature for 12 h under a nitrogen atmosphere. Anhydrous potassium carbonate (40 mg) was added to the reaction mixture and stirred for an additional 20 min. The reaction mixture was filtered and evaporated to dryness, and the oily residue was purified by flash column chromatography over silica gel with a mixture of ether/hexane (1/4, v/v) as the eluent to give a yellow oil (463 mg, 83%, 74.7 mCi): TLC RCP > 99%, R_f = 0.24, silica gel, ether/hexane (1/4); ^{1}H NMR ($CDCl_3$) δ 1.00 (d, *J* = 6.9 Hz, 3 H, CH_3), 1.01 (d, *J* = 6.9 Hz, 3 H, CH_3), 1.32 (t, *J* = 7.2 Hz, 6 H, 2 CH_3), 1.96 (m, 1 H, C<u>H</u>(CH_3)$_2$), 4.27 (q, *J* = 7.2 Hz, 2 H, CH_2), 4.28 (q, *J* = 7.2 Hz, 2 H, CH_2), 4.65 (d, *J* = 4.2 Hz, 1 H, CH), 4.73 (d, *J* = 4.2 Hz, 1 H, CH), 5.01 (d, *J* = 4.8 Hz, 1 H, CH).

(4*R*,5*R*)-4,5-Bis(hydroxy[^{14}C]methyl)-2-isopropyl-1,3-dioxolane (4). A suspension of lithium aluminum hydride (90 mg, 2.37 mmol) in ether (2.5 mL) was refluxed for 30 min with vigorous stirring. A solution of 3 (463 mg, 74.7 mCi, 1.78 mmol) in ether (1 mL) was added dropwise without heating over 30 min, the heat of reaction causing a gentle refluxing. After additional heating for 5 h, ethyl acetate (0.1 mL) was carefully added, and the reaction mixture was cooled to 0-5 °C. After successive cautious additions of water (0.1 mL), 4N NaOH (0.1 mL) and water (3 mL), the inorganic precipitate which had formed was removed by filtration, and extracted with ethyl

acetate (3 X 5 mL). The combined organic solution was dried over anhydrous magnesium sulfate, evaporated to dryness and purified by flash column chromatography over silica gel with a mixture of ethyl acetate/hexane (2/1, v/v) as the eluent to give a colorless oil (276 mg, 88%, 65.7 mCi): TLC RCP > 98.5%, R_f = 0.21, silica gel, hexane/EtOAc (1/2); IR (neat) 3382 cm^{-1} (OH); ^1H NMR ($CDCl_3$) δ 0.95 (d, *J* = 6.9 Hz, 6 H, 2 CH_3), 1.83 (m, 1 H, C<u>H</u>(CH_3)$_2$), 2.54 (br s, 2 H, 2 OH), 3.68-3.86 (m, 4 H, 2 CH_2), 3.87-4.00 (m, 2 H, 2 CH), 4.84 (d, *J* = 4.5 Hz, 1 H, CH); ^{13}C NMR ($CDCl_3$) δ 16.62, 16.67, 32.12, 62.27, 62.33, 78.11, 78.89, 108.24.

(4*R*,5*R*)-4,5-Bis(methanesulfonyloxy[^{14}C]methyl)-2-isopropyl-1,3-dioxolane (<u>5</u>). To a stirred solution of <u>4</u> (276 mg, 65.7 mCi, 1.57 mmol) in pyridine (1.5 mL) was added methanesulfonyl chloride (444 mg, 3.87 mmol, 300 μL) dropwise at 0 °C and the mixture was stirred for 10 h at room temperature. The reaction mixture was poured into ice-water (2 mL) with stirring. The resulting precipitate was filtered, washed with water and dried under reduced pressure. The crude product was crystallized from absolute ethanol to give <u>5</u> (464 mg, 89%, 58.47 mCi); TLC RCP > 99%, R_f = 0.41, silica gel, hexane/EtOAc (1/1); IR (Nujol) 1360, 1332, 1182 cm^{-1} (O-SO_2).

(4*R*,5*R*)-4,5-Bis(azido[^{14}C]methyl)-2-isopropyl-1,3-dioxolane (<u>6</u>). A mixture of <u>5</u> (464 mg, 58.47 mCi, 1.4 mmol) and sodium azide (364 mg, 5.6 mmol) in anhydrous DMF (2 mL) was heated at 100 °C for 8 h under a nitrogen atmosphere. The reaction mixture was cooled to room temperature, diluted with water (2 mL) and extracted with ether (3 X 3 mL). The ethereal solution was washed with brine (2 mL), dried over anhydrous magnesium sulfate and evaporated to dryness under reduced pressure. The crude product was purified by flash column chromatography over silica gel with a mixture of ether/hexane (1/4, v/v) as the eluent to give a light yellow oil (301 mg, 95%, 55.63 mCi): TLC RCP > 99%, R_f = 0.29, silica gel, ether/hexane (1/4); IR (neat) 2103 cm^{-1} (N_3); ^1H NMR ($CDCl_3$) δ 0.97 (d, *J* = 6.8 Hz, 6 H, 2 CH_3), 1.65-2.05 (m, 1 H, CH), 3.20-3.60 (m, 4 H, 2 CH_2), 3.85-4.15 (m, 2 H, 2 CH), 4.85 (d, *J* = 4.6 Hz, 1 H, CH); ^{13}C NMR ($CDCl_3$) δ 16.51, 16.56, 32.00, 51.81, 51.91, 77.10, 77.90, 108.69.

(4*R*,5*R*)-4,5-Bis(amino[^{14}C]methyl)-2-isopropyl-1,3-dioxolane (<u>7</u>). A solution of <u>6</u> (301 mg, 55.63 mCi, 1.33 mmol) in ethanol (3 mL) was hydrogenated in the presence of 10% palladium on activated carbon (30 mg) at 50 psi at 40 °C for 1 h. The reaction mixture was filtered through a celite pad and evaporated to dryness under reduced pressure to give a colorless oil (225 mg, 97%, 54.1 mCi): IR (neat) 3369, 3301 cm^{-1} (NH_2); ^1H NMR ($CDCl_3$) δ 0.96 (d, *J* = 6.9 Hz, 6 H, 2 CH_3), 1.33 (s, 4 H, 2 NH_2), 1.75-1.90 (m, 1 H, CH), 2.75-2.98 (m, 4 H, 2 CH_2), 3.67-3.77 (m, 2 H, 2 CH), 4.79 (d, *J* = 4.5 Hz, 1 H, CH); ^{13}C NMR ($CDCl_3$) δ 16.65, 16.76, 32.06, 44.01, 44.25, 80.29, 80.91, 107.40.

***cis*-Diiodo[(4*R*,5*R*)-4,5-Bis(amino[^{14}C]methyl)-2-isopropyl-1,3-dioxolane]platinum(II) (<u>8</u>).** To a stirred solution of potassium iodide (1.33 g, 8 mmol) in water (4 mL) was added a filtered solution of potassium tetrachloroplatinate(II) (535 mg, 1.29 mmol) in water (25 mL) that was stirred at room temperature for 30 min in the dark under a nitrogen atmosphere to obtain a black solution of potassium tetraiodoplatinate(II). Water (20 mL) was placed in a flask and stirred at 60 °C under a nitrogen atmosphere,

and into this, the above obtained black solution of potassium tetraiodoplatinate(II) and a solution of 7 (225 mg, 54.1 mCi, 1.29 mmol) in water (30 mL) were simultaneously added dropwise over 40 min at a constant rate. After 1 h, the yellow precipitate was collected by filtration, washed sequentially with water, ethanol and ether, and dried thoroughly *in vacuo* to give 8 as a yellow solid (611 mg, 76%, 41.1 mCi).

***cis*-Malonato[(4*R*,5*R*)-4,5-bis(amino[^{14}C]methyl)-2-isopropyl-1,3-dioxolane]platinum (II) (9).** A suspension of 8 (611 mg, 41.1 mCi, 0.98 mmol) and malonic acid disilver salt (310 mg, 0.98 mmol) in water (80 mL) was stirred at 60 °C for 10 h in the dark. The resulting silver iodide was filtered through a pad of celite and the filtrate was again filtered using a millipore filter (0.22 μm). The filtrate was concentrated under reduced pressure to ~10 mL and the resulting white crystals were filtered to give 221 mg of 9. The mother liquor was purified by preparative HPLC on Delta Pak C_{18}-100Å reverse-phase bonded silica cartridge with a mixture of water/methanol (6/4, v/v) as the mobile phase to give 67 mg of an additional product. The combined crystals were dissolved in water and purified once again by using same preparative HPLC to give 9 as white crystals having a radiochemical purity of 98.5% and a specific activity of 41.86 mCi/mmol (268 mg, 58%, 23.8 mCi). Radiochemical purity was determined by high pressure liquid chromatography: Eluent MeOH/H_2O (4/6, v/v), Flow rate 1 mL/min, Detector UN 200 nm, Temperature 22 °C, Column μ-Bondapak C_{18} (3.9 X 250 mm), Retention time 5.80 min; IR (KBr) 3431, 3205, 3049 cm^{-1} (NH), 1612 cm^{-1} (C=O); ^{1}H NMR (DMSO-d_6) δ 0.87 (d, J = 6.6 Hz, 6 H, 2 CH_3), 1.75 (m, 1 H, C<u>H</u>$(CH_3)_2$), 2.59 (m, 2 H, 2 C<u>H</u>NH_2), 2.98 (m, 1 H, C<u>H</u>NH_2), 3.09 (m, 1 H, C<u>H</u>NH_2), 3.26 (s, 2 H, CH_2), 4.31 (m, 1 H, CH), 4.55 (m, 1 H, CH), 4.80 (d, J = 4.5 Hz, 1 H, CH), 5.31 (br s, 1 H, NH), 5.48 (br s, 3 H, 3 NH).

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dose-free intervals between each course. Severe tubular degeneration and necrosis were observed in the both cisplatin-treated group and SKI 2053R-treated group (2.0 mg/kg/day), but mild tubular degeration was observed in the SKI 2053R-treated group (1.0 mg/kg/day).

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