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Synthesis of ^{195}Au and ^{14}C-labeled antineoplastic gold(I) phosphine complexes

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Abstract

Bis[1,2-bis(diphenylphosphino)ethane]gold(I) 2-hydroxypropanoate (SK & F 104524) has been synthesized in carbon-14 (**2b**) and gold-195 (**2c**) labeled forms. The radiolabeled products were formed via reaction of labeled [μ-1,2-bis(diphenylphosphino)ethanebis(gold(I) chloride)] with excess ^{14}C-labeled or unlabeled bis(diphenylphosphino)ethane (dppe). Carbon-14 labeled [μ-1,2-bis(diphenylphosphino)-ethane]bis[(1-thio-β-D-glucopyranosato-*S*)gold(I)] (**1**, SK&F 102912) was prepared via the same intermediate. The key intermediate in these syntheses, [μ-1,2-bis(diphenylphosphino)ethanebis(gold(I) chloride)] (**4a,4b**), was prepared in carbon-14 labeled form using [^{14}C]dppe, and in gold-195 labeled form from chloro[^{195}Au]auric acid. [$^{14}C_2$]Dppe was prepared in good yield by the double addition of diphenyl phosphide anion to the inexpensive and readily available [$^{14}C_2$]acetylene. Hence, these syntheses provide means of obtaining radiolabeled phosphine complexes that are commercially unavailable.

Introduction

There is emerging evidence that many gold(I) phosphine complexes are potent cytotoxic agents. The antiarthritic agent auranofin (2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranosato-*S*-triethylphosphinegold(I)) has been shown to have antitumor activity against P388 leukemia [1]. A large number of other gold(I) phosphine coordination complexes were studied for their activity against various tumor models [2], and a number of these showed potent in vitro and in vivo activity. More recently, interest has focused on complexes of bis(diphenylphosphino)alkanes, many of which are active against a spectrum of transplantable tumor models [3]. Detailed

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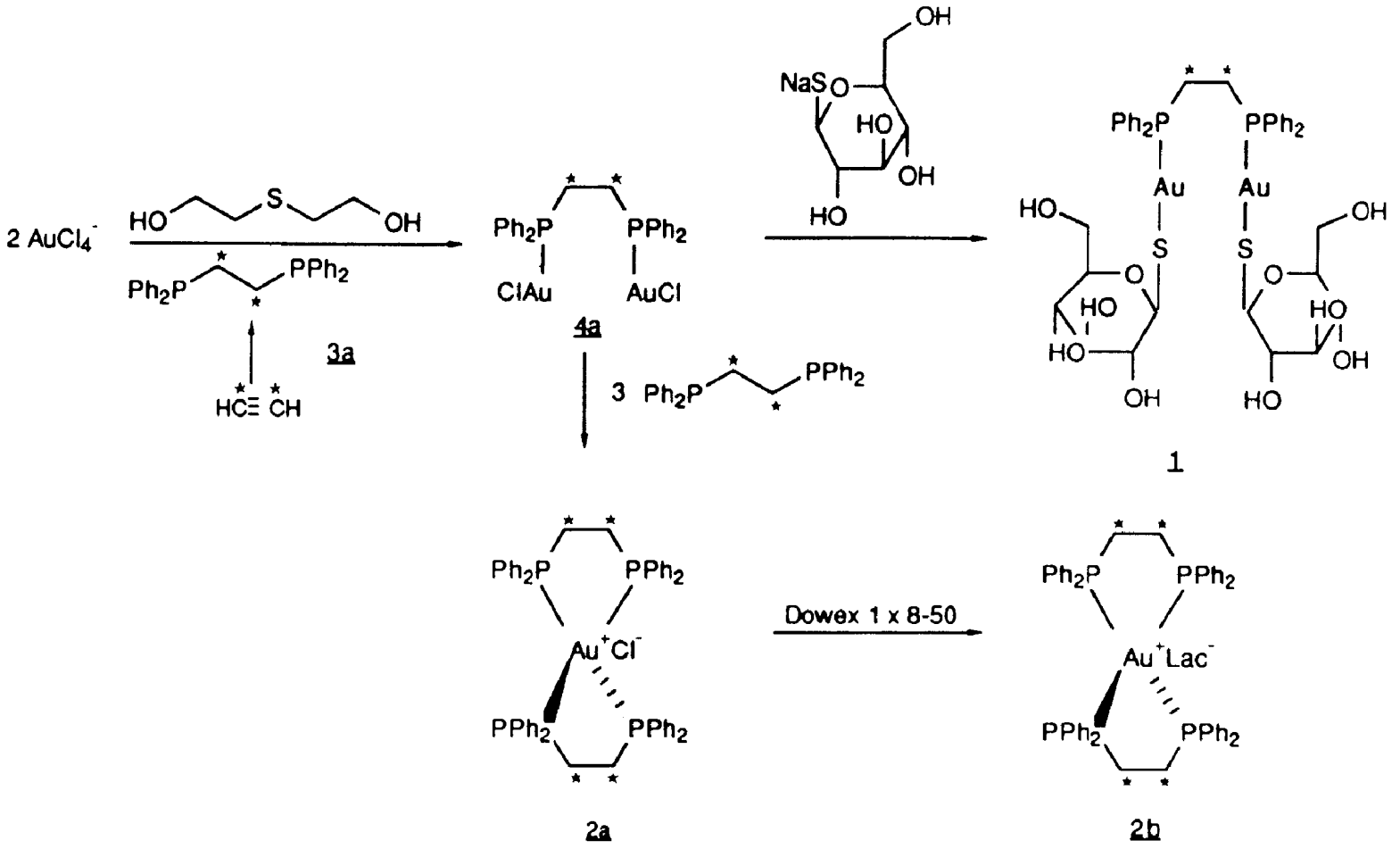


Scheme 1. ★ denotes ^{14}C. Lac denotes d,l-$CH_3CH(OH)CO_2^-$.

studies have been reported on [μ-1,2-bis(diphenylphosphino)ethane]bis[1-thio-β-D-glucopyranosato-*S*)gold(I)] (**1**, SK&F 102912) [4], and bis[1,2-bis(diphenylphosphino)ethane]gold(I) chloride (**2a**, SK&F 101772) [5]. The latter compound is an example of a structurally unique class of tetrahedral, 4-coordinate gold(I) complexes only recently discovered [6].

It was of particular interest to obtain two of these compounds in radiolabeled form for use in studies of cellular binding, metabolism, pharmacokinetics and biodistribution. Specific targets for synthesis have included compound **1** labeled with carbon-14, and the lactate **2b** in forms labeled with carbon-14 and with the gamma-emitting isotope gold-195 ($t_{1/2}$ 183 d).

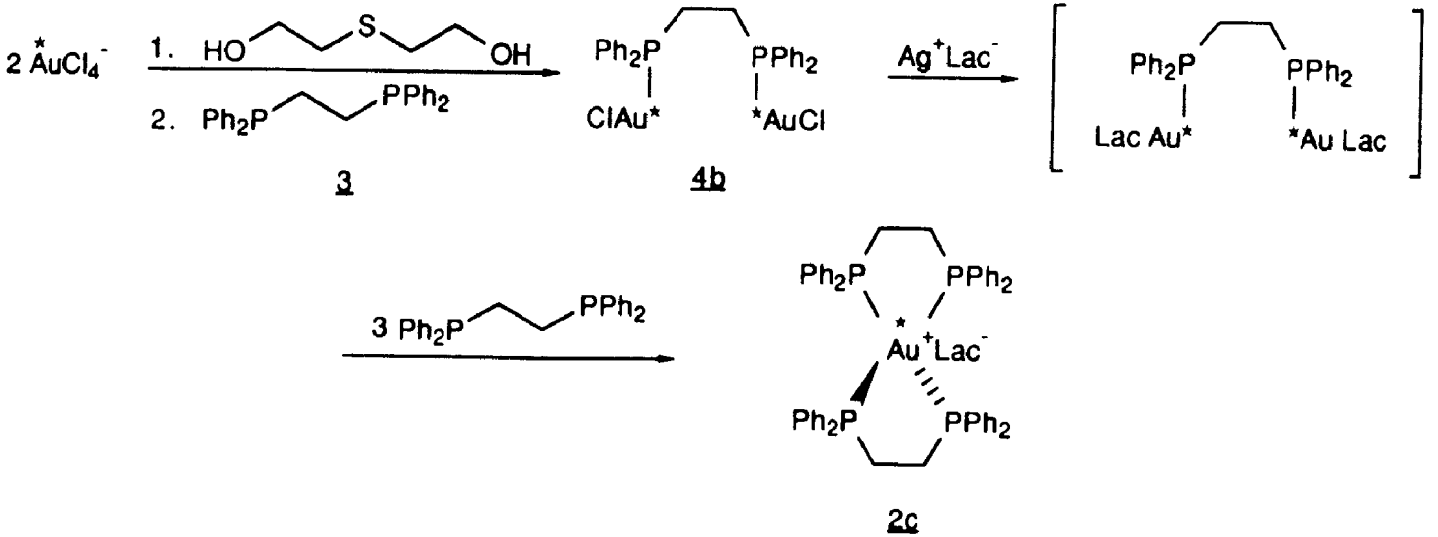
Results and discussion

[μ-1,2-Bis(diphenylphosphino)ethanebis(gold(I) chloride)] (**4**) is a common intermediate in the preparation of carbon-14 labeled phosphine complex **1** and gold-195 labeled phosphine complex **2** (Schemes 1 and 2). Both labeled forms of complex **4** were prepared by reduction of aqueous $[AuCl_4]^-$ with thiodiethanol, followed by addition of 0.5 equivalent 1,2-bis(diphenylphosphino)ethane (dppe, **3**) [3]. The ^{195}Au labeled complex was prepared in 53% radiochemical yield beginning with chloro[^{195}Au]auric acid (1.36 Ci/mmol). The desired carbon-14 labeled compound was prepared in 79% radiochemical yield via radiolabeled dppe.

Although dppe is a widely used ligand, its synthesis in radiolabeled form has not been reported. Development of an efficient synthesis ethane labeled material was based on the observation by Aguiar and Archibald [7] that dppe was formed in undefined yield upon bubbling acetylene into a THF solution of lithium diphenylphosphide. Experiments were carried out in our (SK&F) laboratories to develop a procedure for dppe synthesis using [$^{14}C_2$]acetylene, which is prepared readily from barium [^{14}C]carbonate [8]. It was found in unlabeled trial reactions that the maximum achievable yield of dppe based on acetylene was about 50%. This results presumably from the conversion of an equivalent amount of acetylene to dilithium acetylide in the absence of an added proton source. When an appropriate proton source was added (for example, aniline: pK ~ 23) yields of dppe as high as 90% could be obtained in tracer runs using [$^{14}C_2$]acetylene of low specific activity. A 53% yield of [^{14}C]dppe was obtained using this new procedure with [$^{14}C_2$]acetylene at 45 mCi/mmole (Scheme 1). The lower yield in this case, as compared to tracer runs, resulted in part from losses during workup and handling caused by the extremely facile oxidation of the radiolabeled dppe in air and undegassed solvents.

Complex **4a** was stirred in degassed 1/1 methanol/methylene chloride with 3.12 equivalents of [$^{14}C_2$]dppe (**3a**) at room temperature, giving bis[1,2-bis(diphenylphosphino)[$^{14}C_2$]ethane]gold(I) chloride (**2a**) in 81% radiochemical yield (from **3a** and **4a**) and 97% radiochemical purity after recrystallization from degassed acetone (Scheme 1). Gold chloride complex **2a** was converted to gold lactate complex **2b** by ion exchange chromatography. The 270 MHz ^{1}H NMR spectrum of the labeled product matched that of unlabeled standard. The final specific activity obtained was 49.2 mCi/mmol.

During method development for the preparation of lactate **2b** it was found that the chloride complex **2a** contained a late eluting impurity by HPLC, accounting for about 8% of the total radioactivity, when 3.0 equivalents of [$^{14}C_2$]dppe (**3a**) relative



Scheme 2. ★ denotes ^{195}Au. Lac denotes d,l-$CH_3CH(OH)CO_2^-$.

to gold chloride **4a** were used. This compound contains both gold and phosphine ligand(s), and is of relatively high molecular weight based on its mobility using gel chromatography. The material is converted to chloride complex **2a** upon reaction with additional dppe. Based on this evidence, the impurity is believed to be a linear oligomeric complex containing an oxidized dppe ligand. This ligand may arise as either an impurity in the dppe starting material, or as an oxidation product resulting from incomplete reduction of the Au^{III} acid by thiodiethanol [3]. Reaction with added dppe expels the oxidized ligand, allowing ring closure to the stable tetrahedral complex **2a**. Since it was not possible to entirely remove oxidized contaminants from the [$^{14}C_2$]dppe because of its propensity for oxidation, subsequent syntheses utilized a slight excess of [$^{14}C_2$]dppe. Little or no late eluting byproduct was observed under these conditions.

The synthesis of the gold-195 labeled gold-dppe complex (**2c**, SK & F [^{195}Au]104524) is shown in Scheme 2. Bis-gold chloride complex **4b** (1.22 Ci/mmol) was suspended in 1/1 methanol/methylene chloride and treated with 2 equivalents of silver lactate dissolved in 1/1 methanol/water. This procedure resulted in exchange of lactate for chloride. Reaction of the lactate complex with 3.15 equivalents of dppe gave 7.0 mCi (20% overall radiochemical yield from chloro[^{195}Au]auric acid) of the final product **2c** with a radiochemical purity (by HPLC) of 96.4%. Purity was improved to 97.6% by HPLC purification. This procedure necessitated subsequent re-conversion to the lactate salt by ion exchange since the HPLC mobile phase contained trifluoroacetic acid. The labeled product **2c** was diluted with unlabeled material to a specific activity of 284 mCi/mmol. Gold labeled phosphine complex **2c** was obtained from chloro[^{195}Au]auric acid in 14% overall radiochemical yield.

The syntheses of carbon-14 (**2b**) and gold-195 (**2c**) labeled lactates differ in the order of dppe addition and conversion to their corresponding lactate salts. At the time of the gold-195 synthesis, initial conversion of chloride **4b** to its lactate followed by addition of dppe appeared to be the most efficient route to complex **2c**. Subsequent development of this reaction sequence indicated that initial reaction with dppe followed by ion exchange using DOWEX resin as the final step was the more efficient route. This reaction sequence was employed in the synthesis of carbon-14 labeled **2b**.

The preparation of bis(gold-thioglucose) complex **1** (SK&F [$^{14}C_2$]102912) was carried out as shown in Scheme 1 by modification of the published procedure [3]. Recrystallization of **1** from ethanol significantly reduces the amount of a late eluting impurity and increases the radiochemical purity to a minimum of 90%. Product structure and purity was confirmed by elemental analysis for gold content and by both proton and carbon-13 NMR. Complex **1** was obtained in 59% radiochemical yield from **4a**.

Experimental

No-carrier-added chloro[^{195}Au]auric acid was obtained from Dupont-NEN Research Products (Boston, MA). Barium [^{14}C]carbonate was purchased from Amersham (Arlington Heights, IL). Additional quantities of 1,2-bis(diphenylphosphino)[$^{14}C_2$]ethane (**3a**, 31.5 mCi/mmol) and 1,2-bis(diphenylphosphino)[$^{14}C_2$]-ethanebis(gold(I) chloride) (**4a**, 13.64 and 15.3 mCi/mmol) were synthesized by the

ICI Physics and Radioisotope Services Group (Billingham, England) following the procedures developed in this (SK&F) laboratory. Diphenylphosphine, n-butyllithium, dppe, thiodiethanol, and chloroauric acid trihydrate were purchased from Aldrich Chemicals (Milwaukee, WI). 1-Thio-β-D-glucosesodium salt was purchased from Sigma Chemical Company. Unlabeled lactate **2b** was prepared by Johnson–Matthey Inc. (West Chester, PA). Clin Elut™ tubes were purchased from Analytichem International (Harbor City, CA). All solvents were of HPLC grade, and were degassed prior to use.

HPLC radioactivity was monitored with either a Ramona Radioactivity Detector using Tru-Count (IN-US, Fairfield, NJ) scintillation cocktail, or a Radiomatic Flo-One Radioactivity Detector using Tru-Count or Biofluor cocktail (DuPont NEN Products, Boston, MA). Gamma counting for gold-195 was performed on a Beckman Instruments Model LB 5500 Gamma Counter. TLC radioactivity was monitored with a Berthold LB2832 Linear Analyzer.

Analyses by GC were performed on a Varian 3700 instrument equipped with a flame ionization detector, on Supelco 3% SP 2250 on 100/120 Supelcoport 2 mm I.D. × 1 meter column, helium flow 30 psi, range 10–12 milliamps/mV, at a column temperature of 280 °C.

Proton NMR spectra (270 MHz) and proton decoupled ^{13}C NMR spectra (67.8 mHz) were taken on a Varian Instruments Model JNM GX 270 FT NMR spectrometer.

Gold content analysis of **1** was performed on an Instruments S.A. Model ICP 2500 (Inductively Coupled Plasma).

[$^{14}C_2$]Acetylene was prepared from $Ba^{14}CO_3$ by the method of J.D. Cox and R.J. Warne [8].

*1,2-Bis(diphenylphosphino)[$^{14}C_2$]ethane (**3a**).* A 50 ml 2-neck round bottom flask fitted with septum stopcock adaptor was attached to a vacuum manifold, evacuated and filled with helium. Dry THF (10 ml) was injected through the septum, followed by 696 μl of diphenylphosphine (2.7 mmol). The solution was cooled to 0–5 °C, and 14.8 ml of n-butyllithium (2.7 *M* in hexane, 4.0 mmol) was injected slowly. The resulting orange solution was cooled to −78 °C, and 1.0 ml of a solution of aniline in THF (372 mg/ml, 4.0 mmol) was injected. The mixture was frozen in liquid nitrogen, evacuated, and 1.5 mmol (64.5 mCi) of [$^{14}C_2$]acetylene was introduced. The flask was isolated from the manifold, then warmed to −78 °C with stirring. The reaction mixture was stirred at −78 °C for 3 h, allowed to warm to room temperature, and stirred for an additional 30 h. A small amount of the solvent was vacuum transferred into the cold trap during this step and contained no significant radioactivity, indicating complete reaction of the [$^{14}C_2$]acetylene. The excess phosphide anion was quenched by addition of 0.3 ml of methanol to the reaction mixture, and most of the solvent was removed under vacuum. The residue was taken up in ethyl acetate, and the solution then washed twice each with water, 1 *N* HCl, saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride. After drying by passage through a ClinElut™ tube, the solvent was evaporated *in vacuo*. The resulting crude product (34.3 mCi, 798 mg) was purified by flash chromatography on 50 g of silica gel eluted with 95/5 hexane/ethyl acetate. The product was crystallized by cooling and partial evaporation of the column eluent to provide 315 mg (53%) of white crystalline **3a** having a specific activity of 43.5 mCi/mmol. The radiochemical purity by TLC (silica gel, 80/20 hexane/acetone

and 95/5 cyclohexane/ethyl acetate) was > 97%. The material was diluted with unlabeled carrier and recrystallized from degassed ethanol/n-propanol to give white needles; m.p. 140–141.5 °C (authentic unlabeled standard m.p. 139.5–140.5 °C); IR (KBr) matched authentic unlabeled standard; specific activity 11.0 mCi/mmol.

*[μ-1,2-Bis(diphenylphosphino)[$^{14}C_2$]ethane-bis(gold(I)chloride)] (**4a**).* A 1.569 g (3.98 mmol) portion of chloroauric acid trihydrate was dissolved in a mixture of 13 ml of water and 20 ml of methanol under an argon atmosphere. The solution was cooled to 0 °C, and a solution of 1.459 g (11.96 mmol) of 2,2′-thiodiethanol in 6.6 ml of methanol was added dropwise over 5 min. The yellow color of Au^{III} was extinguished by the end of the addition. A solution of 756 mg (1.90 mmol, 10.96 mCi/mmol) of 1,2-bis(diphenylphosphino)[$^{14}C_2$]ethane (**3a**) in 24 ml of 1/1 (v/v) chloroform/methanol was then added dropwise. The resulting suspension was stirred for 2 h and then filtered. The solid was triturated twice each with methanol and ethanol, and dried in vacuo giving 1.302 g (79.2%) of gold chloride **4a**. Radiochemical purity by TLC (silica gel, $CHCl_3$ or CH_2Cl_2) was 95.5–97%; m.p. 285–289 °C (dec.). The IR spectrum (KBr) matched an authentic unlabeled sample; specific activity was 11.00 mCi/mmol; ^{1}H NMR ($CDCl_3$): δ 2.63(s, 4H, CH_2P), 7.26–7.67(m, 20H, arom.)

*[μ-1,2-Bis(diphenylphosphino)[$^{14}C_2$]ethane]-bis[(1-thio-β-D-glucopyranosato-S)-gold(I)] (**1**).* A 1.07 g portion of **4a**, (1.24 mmol, 13.64 mCi, 11.0 mCi/mmol) dissolved in 110 ml of methylene chloride and 45 ml of ethanol was added dropwise to a solution containing 0.54 g of 1-thio-β-D-glucose sodium salt (2.48 mmol) in 20 ml of water and 70 ml of ethanol. The reaction mixture was stirred rapidly for 18 h at room temperature. The crude reaction mixture was extracted three times with 100 ml of methylene chloride, and the combined organic extracts were dried over 5 g of anhydrous magnesium sulfate. The suspension was filtered and the filtrate was evaporated *in vacuo*, producing a glassy solid. The solid was dissolved in 2 ml of methanol, and the solution was cooled to 0 °C. Diethyl ether (10 ml) was added to the solution, resulting in the immediate formation of a white precipitate. The precipitate was collected by filtration and washed with several volumes of cold diethyl ether. The solid was dried *in vacuo* at 0.1 mm Hg to provide 1.02 g (69.6%) of crude **1**. The crude product was recrystallized from ethanol and dried *in vacuo* to give 0.864 g of **1** (8.05 mCi, 59% from **4a**) at a radiochemical purity exceeding 90%. The specific activity, corrected for residual ethanol (determined by 270 MHz proton NMR), was found to be 11.04 mCi/mmol. Ethanol content (determined by ^{1}H NMR): 5.7%; Gold content: Found 32.65%; Calculated 33.31%; ^{13}C NMR (CD_3OD): δ 134.66, 134.58, 133.19 and 130.66 (arom.); 86.89, 82.20, 81.77, 78.95, 72.27 and 63.45 (glucosyl carbons); 25.16, 24.90, 24.61 (merged doublets, PCH_2CH_2P).

*Bis[1,2-bis(diphenylphosphino)[$^{14}C_2$]ethane]-gold(I)chloride] (**2a**).* A 0.471 g portion of complex **4a**, (0.546 mmol, 8.37 mCi, 15.3 mCi/mmol), dissolved in 22 ml of degassed methylene chloride and 22 ml of degassed methanol, was stirred with 0.679 g of [$^{14}C_2$]dppe (**3a**, 1.705 mmol, 53.7 mCi, 31.5 mCi/mmol) for 2 h at room temperature. The reaction mixture was concentrated in vacuo giving 1.22 g (60.0 mCi) of chloride **2a** as a glassy solid, with a radiochemical purity of 95.1% by HPLC (Whatman ODS-3, 5 μm, 60/40 ethanol w/0.1% trifluoroacetic acid/water, 1.0 ml/min, UV at 230 nm).

The crude product was purified by recrystallization from 2.0 ml of degassed

acetone in an inert-atmosphere flask. This procedure gave 1.09 g (94.8%) of chloride complex **2a** (50 mCi, 81% radiochemical yield from **3a** and **4a**) as a white crystalline solid. An additional 0.12 g was collected from the filtrate. The radiochemical purity of the first crop was determined to be 97% by HPLC (same conditions as above). This crop was used directly in the next step. ^{1}H NMR (CD_3OD): δ 2.52 (m, 8H, CH_2P), 7.18–7.39 (m, 40H, arom.).

*Bis[1,2-bis(diphenylphosphino)[$^{14}C_2$]ethane-gold(I)], 2-hydroxypyropanoate (**2b**).* Compound **2a** was converted to the lactate salt by passing the compound through a Dowex 1 × 8–50 lactate modified ion exchange column (made by exchanging lactate for chloride) using 1/1 ethanol/water as eluent at a resin/**2a** molar ratio of 50.1. The eluate was collected under argon at −80 °C and lyophilized to give 1.09 g (49.0 mCi, 79% radiochemical yield from **3a** and **4a**) of lactate **2b** with a radiochemical purity of 98.4%. The final specific activity of **2b** was 49.2 mCi/mmol. ^{1}H NMR ($CDCl_3$) δ 1.40 (d, *J* 6.3 Hz, 3H, $CH_3CH(OH)$), 2.35 (m, 8H, CH_2P), 4.07 (q, *J* 6.8 Hz, 1H, $CH_3CH(OH)$), 7.15–7.38 (m, 40H, arom.).

*[μ-1,2-Bis(diphenylphosphino)ethanebis[^{195}Au]gold(I) chloride)] (**4b**).* Chloro-[^{195}Au]auric acid (34 mCi, 4000 Ci/mmol) in 1.34 ml of 4 *M* HCl was diluted to a specific activity of 1.36 Ci/mmol by adding 11.6 mg (0.029 mmol) of unlabeled chloroauric acid. To this solution was added 10.82 mg of 2,2′-thiodiethanol (0.086 mmol) in 2 ml of degassed isopropanol under argon over 3 h at ambient temperature. A solution of unlabeled 1,2-bis(diphenylphosphino)ethane (5.90 mg, 0.015 mmol) in 2 ml of degassed acetone was added, and stirring was continued for 16 h under argon.The reaction mixture was partitioned between 5% aqueous sodium bicarbonate and chloroform. The separated organic layer was evaporated to dryness under a stream of argon to give 13 mg of chlorine **4b** as an off-white powder. The crude product was purified by performing two successive precipitations from 5 ml of chloroform/methanol giving 12.7 mg of **4b** (18 mCi by ^{195}Au external standard method, 53% radiochemical yield) with a radiochemical purity of 94% by TLC (silica gel, 98/2 CH_2Cl_2/methanol).

*Bis[1,2-bis(diphenylphosphino)ethane][^{195}Au]gold(I) 2-hydroxypropanoate (**2c**).* Bis(gold chloride) complex **4b** (12.7 mg, 14.7 μmol, 1.22 Ci/mmol) was dissolved in 1.0 ml of degassed methanol and 0.5 ml of degassed methylene chloride. To this solution was added a solution of silver lactate (5.82 mg, 0.030 mmol, Fluka) in 0.5 ml of degassed methanol and 0.5 ml of water. The mixture was shielded from light and stirred for 3 h at room temperature. The solution was filtered through Celite, and the filtrate was collected. Dppe (18.0 mg, 46.6 μmol), was added to the filtrate and the solution was stirred for 60 min. The solution was filtered through Celite and concentrated under a stream of argon. The product was partitioned between 1.0 ml of water and 1.0 ml of methylene chloride, the layers were separated, and the aqueous layer was extracted twice with 1 ml of methylene chloride. The combined organic extracts were concentrated under a stream of argon to give 12.1 mg (11 μmol) of crude Au-195 labeled complex **2c** (16 mCi by ^{195}Au external standard method).

Precipitation from methylene chloride/toluene gave 5.29 mg (44% radiochemical yield) of lactate **2c** (7.0 mCi) at 96.4% radiochemical purity by HPLC (Lichrosorb Diol 5 μm, 0.1% TFA in methanol, 1.0 ml/min., UV at 230 nm, Radiomatic Flow Detector). Final purification was achieved by semi-preparative HPLC (IBM phenyl column, 25 cm × 5 mm I.D., 90/10 methanol with 0.1% trifluoroacetic acid/water,

1.0 ml/min, UV at 230 nm). After lyophilization, this material was dissolved in 1.0 ml of ethanol and was re-converted to the lactate salt by passing it through a Dowex 1 × 8-50 lactate ion exchange column using 1/1 ethanol/water as eluent at a resin/**2c** molar ratio of 1600/1. Those fractions exhibiting radiochemical purity greater than 96.4% (average 97.6%) after lactate ion exchange were combined, diluted with 15.09 mg unlabeled lactate **2c** (Lotnumber JM481–93), lyophilized, and redissolved in absolute ethanol to a final volume of 3 ml. The yield of [^{195}Au]**2c** was 4.8 mCi (14% overall radiochemical yield, from chloro[^{195}Au]auric acid) at a specific activity of 284 mCi/mmol and 97.7% radiochemical purity by HPLC (PLRP-S 5 μm, 90/10 0.02 *M* Bu_4NClO_4 in acetonitrile/water, 1.0 ml/min, UV at 230 nm, Ramona radioactivity detector).

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