# Synthesis of Platinacyclobutanes Bearing Biological Components for Targeted, Cisplatin Prodrugs

Bridget L. Stocker[†] and John O. Hoberg*[,‡]

*School of Chemical and Physical Sciences, Victoria University, Wellington, New Zealand, and Department of Chemistry, University of Wyoming, Laramie, Wyoming 82071*

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A new series of platinacyclobutanes with attached biomolecules have been prepared. Biological components include thymidine, cholesterol, glucose, and proline, all of which have been coupled to cyclopropylmethanol and then reacted with platinum(II), in the form of Zeise's dimer, to give the respective platinacycle.

## Introduction

The development of cisplatin (Figure 1) marked a watershed in the treatment of cancer, and the subsequent platinum drugs represent a unique and important class of antitumor agents.[1] Since Rosenberg's discovery of the antitumor properties of cisplatin,[2] a myriad of second- and third-generation analogues have been reported.[3,4] However, the development of a Pt(IV)-based drug has been overshadowed by Pt(II)-based substrates, and only in the past decade has the desire to develop an orally active drug spurred interest in Pt(IV) drugs. Complexes such as JM216[5] show a lack of cross-resistance with cisplatin and are orally active, but this and related complexes are thought to be reduced to their Pt(II) counterparts by extracellular and intracellular agents prior to reaction with DNA.[6,7] Pt(IV) complexes of the general type **1** are also well-known,[8] though their use in cancer treatment has not been documented to our knowledge. Thus, our goal has been to synthesize novel Pt(IV) complexes similar to **1** that will undergo reduction after uptake into the nucleus of cancerous cells. The incorporation of R groups that are both cancer-targeting and water-soluble will facilitate this objective. To date, platinacycles attached to complex biomolecules have not been reported.

Our strategy for a Pt(IV) cisplatin analogue involved the formation of platinacycles[8] from the reaction of Zeise's dimer ($[Pt(C_2H_4)Cl_2]_2$) with cyclopropanes bearing biomolecules (R) to achieve increased water-solubility and cancer targeting, Scheme 1. Formation of platinacyclobutanes is proposed to involve initial coordination of a nucleophilic cyclopropane to an electrophilic Pt(II) center to form an edge transition state

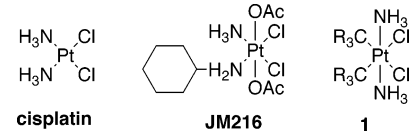
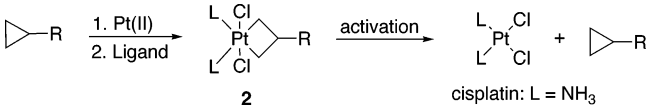



**Figure 1.**

**Scheme 1**




complex. Subsequent oxidative addition with loss of ethylene and dimerization gives a precipitated tetramer that upon addition of ligands gives the monomeric species **2**. Typically, nitrogen donor liginds such as aromatic amines are used since ligands such as $PR_3$, DMSO, and CO generally result in reductive elimination of the cyclopropane. We postulated that the use of a platinacycle such as **2** would provide for an inactive form of cisplatin that upon delivery to the site of the tumor could be reduced[9] to cisplatin, or a hydrated derivative[10] and a cyclopropane byproduct. Therefore, our studies began with the formation of platinacyclobutanes bearing four types of biomolecules: amino acids, cholesterol, nucleosides, and carbohydrates. Such molecules represent known, or model substrates for, cancer-targeting agents, and by incorporating them in the synthesis of platinacyclobutanes, significant advances in the field of platinacycle chemistry can also be made. To date, previously reported platinacyclobutanes have generally used very unadorned cyclopropanes,[8] such as phenylcyclopropanes, cyclopropylmethanol, and norbonyl derivatives; therefore successful formation of such complex platinacycles would represent a significant advancement in this field. For these studies, the usual aromatic nitrogen ligands were used for characterization purposes, with future work to involve more cisplatin-related ligands.

* To whom correspondence should be addressed. E-mail: hoberg@uwyo.edu. Phone: 307 766-2795.
[†] Victoria University.
[‡] University of Wyoming.

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(9) A number of methods including external radiation and cellular agents are being invesitagated and will be reported in due course.
(10) After passive diffusion across the cellular membrane, the lower chloride concentration of the cytoplasm allows the chloride ligands of cisplatin to exchange with water. The aqua ligands may also be displaced by hydroxide ions depending on the hydrogen ion concentration. See ref 1.

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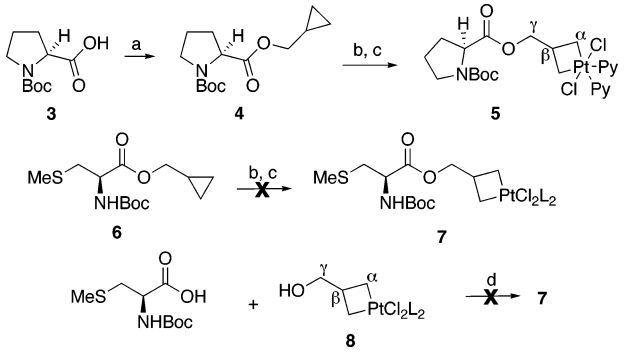
**Scheme 2**[a]




[a] (a) Cyclopropylmethanol, DIC, DMAP, $CH_2Cl_2$, 88%; (b) [Pt($C_2H_4$)$Cl_2$]$_2$, $Et_2O$, 98%; (c) pyridine; (d) DCC, DMAP; or HBTU, collidine; or EDCI, DMAP.

## Results and Discussion

**Amino Acids.** Small peptides, such as the disulfide cyclic pentamer CNGRC,[11] have shown remarkable cancer-targeting abilities. Consequently, an amino acid connected to a cyclopropane was chosen as a model substrate. Although cyclopropanes bearing α-cyclopropylidene electron-withdrawing substituents are typically resistant to platinum insertion,[12] the insertion of platinum into cyclopropanes bearing methylene mesylates or benzoates has been reported.[13] Therefore, substrates such as **4**, Scheme 2, would appear to be viable candidates for platinum insertion. Synthesis of such a substrate was achieved via coupling of protected proline **3** and cyclopropylmethanol to give **4**. Gratifyingly, insertion of platinum occurred smoothly to give the expected precipitated complex that was initially ligated with dipyridyl. Unfortunately, the dipyridyl-ligated platinacycle was prone to reductive elimination, giving cyclopropane **4**, and therefore neat deuterated pyridine was used to give the stable complex **5**. As in the case of **4**, the NMR spectra of complex **5** appeared as a mixture of rotamers, but the indicative resonance at −12 ppm with a Pt−C coupling of 356 Hz was observed for the α-carbons. With a view to synthesizing the CNGRC cyclic pentamer, the analogous reaction using cyclopropane **6** was attempted, which is readily formed from *N*-Boc-*S*-methyl cysteine[14] and cyclopropylmethanol. Numerous attempts were made at inserting platinum into **6** but with no success. Stirring a solution **6** in THF or $Et_2O$ with Zeise's dimer, either at room temperature or at reflux, resulted in the reisolation of **6**, while use of refluxing toluene gave a brown, intractable oil. Presumably this was due to the preferential complexation of platinum to the amino/sulfur moieties. The synthetic pathway was then altered and attempts were made to couple known platinacyclobutane **8** (L = dipyridal)[15] with methyl cysteine to give our target platinacycle **7**. The use the coupling reagent DCC or HBTU in $CH_2Cl_2$ gave the corresponding amino acid anhydride, while use of refluxing dioxane as the solvent resulted in the elimination of platinum to give cyclopropyl ester **6**. A change in coupling reagent to EDCI proved somewhat more promising, as NMR indicated the desired platinacycle **7** had been produced. Unfortunately though, this product could not be adequately purified.

Characterization of platinacyclobutanes is easily achieved via $^{13}$C NMR in which the two ring carbons and γ-carbon have diagnostic chemical shifts and Pt−C coupling. For example, the α-carbon of **8**, which has also been characterized by X-ray crystallography, resonates at −11.3 ppm and has a Pt−C coupling of 350 Hz, Table 1.[15] Both these values are typical of monosubstituted platinacyclobutanes. Additionally, the *β*-carbon has a typical chemical shift in the low 40's and decreasing Pt−C coupling (∼100 Hz), while the *γ*-carbon's Pt−C coupling is approximately 50 Hz. As shown in Table 1, the equivalent carbons of complex **5** are consistent with these values, as are the remaining complexes reported herein.

**Table 1. $^{13}$C NMR Chemical Shifts (ppm) and Pt−C Coupling Constant (Hz) Data**

| complex | $C^{\alpha}$ ($^1J_{Pt-C}$) | $C^{\beta}$ ($^2J_{Pt-C}$) | $C^{\gamma}$ ($^3J_{Pt-C}$) |
|---|---|---|---|
| **8** | −11.3 (350.1) | 45.6 (99.1) | 67.1 (49.0) |
| **5** | −12.5 (356.0) | 42.7 (103.7) | 69.3 (52.7) |
| **11** | −12.3 (351.4) | 42.4 (99.0) | 71.4 (66.2) |
| **14** | −9.3 (356.0) | 43.2 (100.0) | 47.8 (63.8) |
| **17** | −11.4 (342.2)<br>−12.1 (342.0) | 42.0 (98.0) | 76.2 (46.3) |
| **18** | −11.0 (337.5)<br>−11.1 (338.6) | 42.7 (96.0) | 76.4 (43.4) |

**Cholesterol.** Though highly water-insoluble, cholesterol has been used as a carrier of carborane[16] and in liposomal compositions for targeting lung metastatic cancer.[17] This prompted us to construct a platinacyclobutane cholesterol derivative via linkage through the lone hydroxyl moiety, Scheme 3. Cyclopropanation of known allyl ether **9**[18] was readily accomplished in good yield using the Simmons−Smith reaction. It should be noted that attempts at cyclopropanating adduct **9** using Furukawa conditions[19,20] ($Et_2Zn$, $CH_2I_2$) resulted in a 2:1 mixture of the desired cyclopropane and unreacted starting material. Novel platinacyclobutane **11** was then prepared by reacting cyclopropane **10** with Zeise's dimer, followed by dipyridyl as a ligand, to give the amorphous yellow-orange platinacyclobutane **11** in a respectable 84% yield. Characterization by NMR indicated formation of the platinacycle with characteristic peaks at −12.3 and 42.4 ppm for the ring carbons, Table 1.

**Nucleosides.** The mammalian deoxyribonucleoside kinases, deoxycytidine kinases, thymidine kinase 1 and 2, and deoxyguanosine kinase, phosphorylate deoxyribonucleosides and thereby provide an alternative to the de novo synthesis of DNA building blocks. More importantly these enzymes are essential for the activation of several chemotherapeutically important nucleoside analogues.[21] In view of this, platinacycle-bound nucleosides may be promising candidates for the selective targeting of tumor cells because of their potential metabolic fate. For example, the key step for the intracellular entrapment would be the phosphorylation by cytosolic thymidine kinase (TK1) to the corresponding 5′-monophosphate. This would occur primarily in proliferating tumor cells since the expression of TK1 is tightly regulated during the cell cycle and the active enzyme is found only in S-phase cells. TK1 is therefore widely distributed and expressed in all proliferating neoplastic cells, but it is virtually absent in all nonproliferating normal tissue. The synthesis of a platinacycle−nucleoside complex began with

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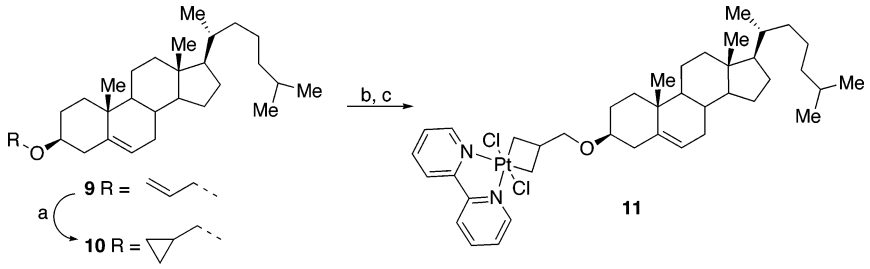
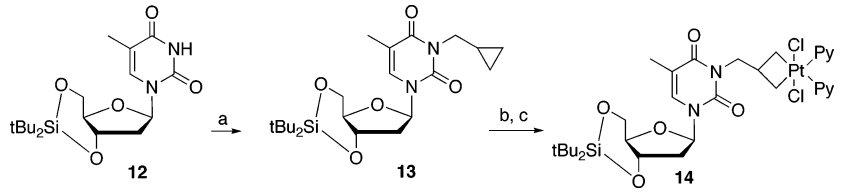
**Scheme 3** [a]



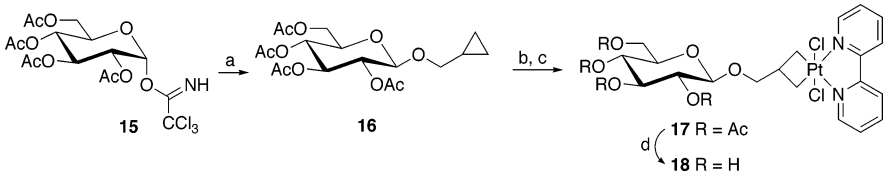

[a] (a) $CH_2I_2$, Zn/CuCl, 87%; (b) $[Pt(C_2H_4)Cl_2]_2$, THF; (c) 2,2′-dipyridyl, 84% two steps.

**Scheme 4** [a]




[a] (a) Cyclopropylmethanol, DEAD, $PPh_3$, THF, 83%; (b) $[Pt(C_2H_4)Cl_2]_2$, $Et_2O$, 93%; (c) pyridine.

**Scheme 5** [a]




[a] (a) Cyclopropylmethanol, TMSOTf, $CH_2Cl_2$, 98%; (b) $[Pt(C_2H_4)Cl_2]_2$, $Et_2O$; (c) 2,2′-dipyridyl; (d) NaOMe, MeOH, 73% over 3 steps.

formation of **12**, which is readily available by the quantitative bis-silylation of thymidine using literature procedures, Scheme 4.[22] Standard Mitsunobu reaction with cyclopropylmethanol gave **13** in good yield, and insertion of platinum occurred readily. However, the choice of the nitrogen ligand was found to be critical, as use of dipyridyl or ethylenediamine gave complexes that were highly insoluble in all NMR solvents used. Conversely, dilution of the initial platinum complex in $d_5$-pyridine gave **14** that was readily characterizable in $d_5$-pyridine. Again, the presence of **14** was confirmed by the multiple resonances in the $^{13}C$ NMR containing Pt−C coupling, Table 1. Desilylation of **14** has been problematic due to characterization being hindered by poor solubility. Only modest solubility in water could be achieved by ligation of the initial platinum complex with ethylenediamine, desilylation with $Bu_4NF$, and extraction with $D_2O$. Loss of the silyl group and an intact platinacycle appeared to have been achieved; however quality spectra were unattainable. It is apparent that the use of a highly water-soluble platinum ligand, such as 2, 3-diaminopropionic acid, will be required for good aqueous solubility in this complex. Nevertheless, the general strategy for the formation of type **14** platinacycles appears to be reliable.

**Carbohydrates.** Anticancer drugs bound to macromolecular carriers such as *N*-(2-hydroxypropyl)methacrylamide (HPMA) copolymers containing monosaccharides have been shown to be efficient carriers for anticancer drugs. Examples include an HPMA−doxorubicin (DOX) conjugate containing fucosylamine moieties that enhance survival time of mice bearing L1210 tumors,[23] efficient liver targeting using galactosamine incorporated HPMA−DOX conjugates,[24] and effective human colon cancer targeting using an HPMA−DOX incorporated with a lactose/galactosamine conjugate system.[25] Given the effectiveness of carbohydrates as targeting agents for cancer cell wall receptors, a simple example of such a carrier has been included in our studies. This proof of concept was accomplished by initially glycosylating glucose imidate **15**[26,27] with cyclopropylmethanol to give **16** in 98% yield and an 8.5:1 ratio of $\beta$:$\alpha$ anomers, Scheme 5. Subsequent insertion of platinum was very facile; however ligation of the initially precipitated complex gave an unstable platinacyclobutane when treated with pyridine. Treatment with dipyridyl produced **17**, which although still prone to decomposition in solution, was conducive to NMR characterization.

As with the above platinacyclobutanes, **17** displayed a characteristic Pt−C coupling of 342 Hz to the methylene carbons of the platinacycle, Table 1. Noticeable are the chemical shift differences of these two methylene carbons, a result of the *exo*-anomeric effect.[28] In addition, this effect can also be seen in **16** for the two methylene cyclopropane carbons, which also have a chemical shift difference of 0.7 ppm. As explained previously in other pyranosides, the preferred conformation of the aglycon about the anomeric center and hence the NMR chemical shifts for both methylenes are effected by $n_O \rightarrow \sigma^*_{C-O}$ stabilizing orbital interactions[29] and interactions with the C-2 OAc and pyranose-ring oxygen.[30] Cyclohexylmethyl glucopyranosides

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have also been reported that show this effect.[31] Further confirmation was obtained from the Pt−C couplings of the $\beta$-($J$ = 98 Hz) and $\gamma$-carbons ($J$ = 46 Hz). Finally, Zemplen deprotection of **17** occurred efficiently to give the water-soluble pyranoside **18**, which was easily characterized in $D_2O$. Not surprising, the chemical shift difference of the two methylene carbons in **18** decreased considerably upon deprotection.

In conclusion, insertion of platinum into a variety of cyclopropanes bearing biomolecules has been achieved. These Pt(IV) complexes are the first of their kind and represent a new branch of platinacycle chemistry. Although successful formation of a platinacycle incorporating an amino acid appears to be dependent on the type of amino acid, coupling of additional amino acids remains viable once a purification method is determined. Of noticeable ease is the use of carbohydrates, which appear to contain adequate hydroxyl groups to provide for water-solubility. Future work will include further investigations into the use of peptides and nucleosides, as well as the incorporation of other targeting agents such as folic acid.[32] Testing of the complexes for bioavailability, activation, and activity is currently underway. Nonetheless, we can report that cholesterol complex **11** has been tested in a leukemia cell line and gave no indication of activity. Hence it appears that this concept has potential as a cisplatin prodrug.

## Experimental Section

**General Procedures.** All reagents were of commercial quality, and solvents were dried using standard procedures. Standard syringe techniques were used, and all reactions were carried out under argon unless otherwise noted. Reaction progress was monitored using precoated TLC plates with silica UV254 and visualized by either UV radiation (254 nm) or ceric ammonium molybdate dip. Flash chromatography was performed using silica gel 60 (220−240 mesh) with the solvent systems as indicated. $^1$H and $^{13}$C NMR spectra were recorded on either a Bruker Avance 400 or a Varian Inova 300 and referenced to solvent peaks ($^1$H, residual $CHCl_3$; $^{13}$C, $CDCl_3$). Accurate masses were recorded on a Mariner time-of-flight spectrometer.

***N*-Boc-L-proline Cyclopropylmethyl Ester, 4.** To a solution of Boc proline **3** (567 mg, 2.63 mmol) in $CH_2Cl_2$ (10 mL) were added cyclopropylmethanol (230 $\mu$L, 2.90 mmol), DIC (454 mg, 2.90 mmol), and DMAP (36 mg, 0.29 mmol), and the reaction was stirred at room temperature for 18 h. The solution was poured into water (25 mL) and extracted with $CH_2Cl_2$ (3 × 25 mL). The combined extracts were washed with water (2 × 25 mL) and brine (2 × 20 mL) and then dried over $MgSO_4$. Flash chromatography (cyclohexane/EtOAc, 4:1) gave **4** (623 mg, 88%) as a viscous, colorless oil. $^1$H NMR (mixture of rotamers): $\delta$ 4.3 (m, 1H), 3.95 (m, 2H), 3.50 (m, 2H), 2.23 (m, 1H), 1.90 (m, 3H), 1.48 (s, 3H), 1.41 (s, 6H), 1.11 (m, 1H), 0.58 (m, 2H), 0.28 (m, 2H). $^{13}$C NMR: $\delta$ 173.4, 173.1, 154.4, 153.9, 79.8, 79.6, 69.6, 69.5, 59.2, 58.9, 46.5, 46.3, 31.0, 30.0, 28.4, 28.3, 26.9, 24.3, 23.6, 9.8, 9.7, 3.3, 3.2, 3.1, 3.0. IR (neat): 2975, 2881, 1745, 1700, 1396, 1366, 1162, 972 cm$^{-1}$. HRMS: calcd for $C_{14}H_{24}NO_4$ 270.1705 (M + H), found 270.1700.

***N*-Boc-L-proline Platinacyclobutylmethyl Ester, 5.** To a solution of **4** (143 mg, 0.531 mmol) in $Et_2O$ (7 mL) was added Zeise's dimer (156 mg, 0.265 mmol), and the mixture was heated at reflux for 24 h. The solvent was reduced to ca. 2 mL, and pentane (5 mL) was added. The solid was filtered, washed with additional pentane, and dried to give 278 mg of a yellow solid (98%). Dilution in $d_5$-pyridine gave complex **5**. NMR was reported as a mixture of rotamers. $^1$H NMR (Py): $\delta$ 4.41 (m, 3H), 3.63 (m, 2H), 3.48 (m, 1H), 2.95 (dd, $J_{H,H}$ = 4.5, 9.0 Hz, $J_{Pt,H}$ = 84.6 Hz, 1H), 2.89 (m, $J_{Pt,H}$ = 91.2 Hz, 1H), 2.77 (t, $J_{H,H}$ = 6.6 Hz, $J_{Pt,H}$ = 80.0 Hz, 1H), 2.71 (m, $J_{Pt,H}$ = 82.6 Hz, 1H), 2.15−1.50 (m, 4H). $^{13}$C NMR ($CDCl_3$): $\delta$ 173.4, 173.2. 154.3, 153.8, 79.2, 79.1, 69.3 ($J_{Pt,C}$ = 52.7 Hz), 59.3, 46.6, 42.7 ($J_{Pt,C}$ = 103.7 Hz), 30.8, 30.0, 28.2, 24.3, 23.5, −12.5 ($J_{Pt,C}$ = 356.0 Hz). IR (neat): 2930, 1740, 1695, 1398, 1160, 977 cm$^{-1}$. HRMS: calcd for $C_{24}H_{33}Cl_2N_3O_4Pt$ 692.1496, found 692.1522.

***N*-Boc-L-cysteine-*S*-methyl Cyclopropylmethyl Ester, 6.** To a solution of Boc methyl cysteine (420 mg, 1.85 mmol) in $CH_2Cl_2$ (10 mL) were added cyclopropylmethanol (165 $\mu$L, 1.87 mmol), DCC (419 mg, 1.87 mmol), and DMAP (23 mg, 0.17 mmol), and the reaction was stirred at room temperature overnight. The solution was diluted with $CH_2Cl_2$ and filtered, and the filtrate was washed with water (3 × 25 mL), 5% acetic acid solution (3 × 25 mL), and again water (3 × 25 mL) and then dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude material purified by flash chromatography (hexanes/EtOAc, 3:1) to give ester **6** (432 mg, 83%) as a viscous, clear oil that crystalized upon standing, mp 40−43 °C. $^1$H NMR: $\delta$ 5.37 (brd, $J$ = 5.6 Hz, 1H), 4.58 (m, 1H), 4.03 (d, $J$ = 7.5 Hz, 2H), 3.01 (brd, $J$ = 5.1 Hz, 2H), 2.18 (s, 3H), 1.18 (m, 1H), 1.49 (s, 9H), 0.62 (m, 2H), 0.33 (m, 2H). $^{13}$C NMR: $\delta$ 128.9, 128.1, 125.2, 107.1, 70.4, 61.6, 53.0, 49.1, 36.7, 36.6, 33.7, 28.2, 25.5, 24.8, 16.2, 14.1, 9.6, 3.3. IR (neat): 3372, 2975, 2928, 1731, 1684, 1518, 1366, 1300, 1240, 1167, 1034, 988 cm$^{-1}$.

**Cholesterol Cyclopropylmethyl Ether, 10.** A 25 mL flask with sidearm and condenser containing CuCl (208 mg, 2.10 mmol) and Zn (128 mg, 2.10 mmol) was charged with freshly distilled diethyl ether (7 mL) and the suspension stirred at room temperature for 30 min. Allylcholesterol **9** (240 mg, 0.56 mmol) in a solution of diethyl ether (6 mL) was cannulated into the reaction flask, followed by diiodomethane (170 $\mu$L, 2.10 mmol), and the resulting solution was heated under reflux. The reaction was monitiored by GC, and additional increments of 2.10 mmol, 2.10 mmol, then 1.05 mmol of CuCl, Zn, and diiodomethane were added over a period of 24 h, following prior cooling of the solution to room temperature. Upon completion of the reaction, the cooled mixture was filtered and washed three times with diethyl ether. The ether layer was washed twice with saturated $NH_4Cl$ and once with water, then dried over $NaSO_4$. The solvent was removed under reduced pressure and the crude product purified by flash chromatography (hexanes/EtOAc, 3:1) to give cyclopropane **10** (216 mg, 87%) as a white, crystalline solid, mp 85−86 °C. $^1$H NMR: $\delta$ 5.34 (d, $J$ = 5.1 Hz, 1H), 3.29 (d, $J$ = 6.9 Hz, 2H), 3.16 (m, 1H), 2.36 (m, 1H), 2.23 (m, 1H), 2.08−1.76 (m, 5H), 1.68−0.97 (m, 22 H), 1.00 (s, 3H), 0.91 (d, $J$ = 7.1 Hz, 3H), 0.88 (d, $J$ = 6.6 Hz, 3H), 0.86 (d, $J$ = 6.6 Hz, 3H), 0.68 (s, 3H), 0.55 (m, 2H), 0.19 (m, 2H). $^{13}$C NMR: $\delta$ 141.4, 121.6, 79.0, 73.2, 57.0, 56.4, 50.4, 42.5, 40.0, 39.7, 39.4, 37.5, 37.1, 36.4, 36.0, 32.2, 28.5, 28.3, 24.5, 24.1, 23.1, 22.8, 21.3, 19.6, 18.9, 12.1, 11.3, 3.3. IR (neat): 3095, 2948, 2863, 1572, 1374, 1363, 1140, 1094, 1023, 797 cm$^{-1}$.

**Cholesterol Platinacyclobutylmethyl Ether, 11.** To a solution of cyclopropane **10** (200 mg, 0.45 mmol) in THF (7 mL) was added Zeise's dimer (107 mg, 0.18 mmol), and the mixture was stirred for 36 h at room temperature in the dark. The solvent was then removed under reduced pressure and the residue suspended in $CH_2Cl_2$ (2.5 mL). Dipyridyl (87.5 mg, 0.56 mmol) was added and the resulting precipitate stirred for 5 min. The solvent was removed under reduced pressure and the precipitate washed twice with pentane to yield platinacyclobutane **11** (132 mg, 84%) as a yellow-orange solid. $^1$H NMR ($CDCl_3$): $\delta$ 5.33 (d, $J$ = 5.1 Hz, 1H), 3.35 (d, $J$ = 7.5 Hz, 2H), 3.16 (m, 1H), 3.12 (m, 4H), 2.57 (m, 1H), 2.54 (dd, $J_{H,H}$ = 5.1, $J_{H,H}$ = 7.0 Hz, $J_{Pt,H}$ = 84.6 Hz, 2H), 2.15 (dd, $J_{H,H}$ = 5.1, $J_{H,H}$ = 7.0 Hz, $J_{Pt,H}$ = 81.6 Hz, 2H), 2.34 (m, 1H),

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2.28 (m, 1H), 2.08−1.76 (m, 5H), 1.68−0.97 (m, 21 H), 1.00 (s, 3H), 0.91 (d, $J$ = 6.6 Hz, 3H), 0.89 (d, $J$ = 7.2 Hz, 3H), 0.89 (d, $J$ = 7.2 Hz, 3H), 0.67 (s, 3H). $^{13}$C NMR ($CDCl_3$): $\delta$ 139.2, 119.5, 77.0, 71.4 ($J_{Pt,C}$ = 66.2 Hz), 54.9, 54.3, 48.3, 42.4 ($J_{Pt,C}$ = 99.0 Hz), 40.5, 38.0, 37.7, 35.5, 35.0, 34.4, 34.0, 30.2, 30.1, 26.9, 26.5, 26.2, 22.5, 22.1, 21.0, 20.7, 19.3, 17.5, 16.9, 10.0, −12.3 ($J_{Pt,C}$ = 351.4 Hz). IR (neat): 2930, 2830, 2869, 1665, 1592, 1094, 1042, 1015 cm$^{-1}$.

**3-Cyclopropylmethyl-3′,5′-*O*-(di-*tert*-butylsilanediyl)thymidine, 13.** To a solution of cyclopropylmethanol (0.353 mL, 4.33 mmol), **12** (1.48 g, 4.33 mmol), and $PPh_3$ (1.14 g, 4.33 mmol) in THF (40 mL) at room temperature was added a solution of DEAD (0.682 mL, 4.33 mmol) in THF (10 mL) dropwise. The mixture was stirred overnight, quenched with water, and extracted twice with $Et_2O$. The combined ether extractions were washed once with brine, dried over $MgSO_4$, and then concentrated. Flash chromatography (hexanes/EtOAc, 10:1) gave **13** (1.41 g, 83%) as a sticky, white foam. $^1$H NMR: $\delta$ 7.02 (s, 1H), 6.26 (dd, $J$ = 6.3, 4.5 Hz, 1H), 4.44 (dd, $J$ = 9.3, 5.1 Hz, 1H), 4.19 (q, $J$ = 9.0 Hz, 1H), 4.10 (t, $J$ = 10.2 Hz, 1H), 3.81 (dd, $J$ = 7.2, 2.1 Hz, 2H), 3.68 (m, 2H), 2.36 (m, 1H), 1.95 (s, 3H), 1.24 (m, 3H), 1.07 (s, 9H), 1.01 (s, 9H), 0.42 (m, 2H). $^{13}$C NMR: $\delta$ 163.3, 151.0, 132.9, 110.7, 76.6, 74.9, 67.3, 45.7, 38.5, 27.4, 27.1, 22.6, 20.0, 13.5, 9.7, 3.8. IR (neat): 2935, 2860, 1669, 1640, 1464, 1272, 1111, 826, 748 cm$^{-1}$. HRMS: calcd for $C_{22}H_{37}N_2O_5Si$ 437.2450 (M + H), found 437.2466.

**3′,5′-*O*-(Di-*tert*-butylsilanediyl)-3-platinacyclobutylmethyl Thymidine, 14.** A solution of **13** (130.0 mg, 0.298 mmol) and Zeise's dimer (87.6 mg, 0.149 mmol) in $Et_2O$ (6 mL) was refluxed for 6 h, then cooled and concentrated to 2 mL. The mixture was washed with pentane twice and dried to give 198.5 mg (95%) of a yellow solid. The solid and pyridine were cooled to 0 °C and then mixed to give **14**. $^1$H NMR ($d_5$-Py): $\delta$ 7.61 (s, 1H), 6.65 (t, $J$ = 6.5 Hz, 1H), 4.63 (m, 1H), 4.48 (m, 2H), 4.41 (m, 1H), 4.20 (t, $J$ = 11.7 Hz, 1H), 4.0 (m, 1H), 3.69 (m, 1H) 3.12 (m, $J_{Pt,H}$ = 80.9 Hz, 2H), 2.96 (m, $J_{Pt,H}$ = 82.6 Hz, 2H), 2.71 (m, 1H), 2.50 (m, 1H), 1.90 (s, 3H), 1.09 (s, 18H). $^{13}$C NMR ($d_5$-Py): $\delta$ 164.2, 164.0 152.2, 151.9, 135.9, 135.1, 110.9, 85.4, 78.8, 76.1, 68.1, 47.8 ($J_{Pt,C}$ = 63.8 Hz), 46.3, 43.2 ($J_{Pt,C}$ = 100.0 Hz), 28.0 (C*Me*$_3$), 27.9 (C*Me*$_3$), 23.1 (*C*Me$_3$), 20.7 (*C*Me$_3$), 10.9, −9.3 ($J_{Pt,C}$ = 356.0 Hz). IR (neat): 2930, 2858, 1670, 1637, 1272, 1110 cm$^{-1}$. HRMS: calcd for $C_{32}H_{46}Cl_2N_4O_5Pt$ 859.2262, found 859.2218.

**Cyclopropylmethyl 2,3,4,6-Tetra-*O*-acetyl-$\beta$-D-glucopyranoside, 16.** Trichloroacetimidate **15** (905.0 mg, 1.837 mmol), $CH_2Cl_2$ (20 mL), 200 mg of freshly dried 4 Å molecular sieves, and cyclopropylmethanol (223 $\mu$L, 2.76 mmol) were cooled to −78 °C, and TMSOTf (67 $\mu$L, 0.37 mmol) was added. The reaction was stirred at −78 °C for 1 h, then an additional hour at 0 °C before being quenched with triethylamine (100 $\mu$L). The solution was filtered through a small pad of Celite, washing with additional $CH_2Cl_2$ (10 mL), and the filtrate was concentrated under reduced pressure. The resulting pale yellow oil was purified by flash chromatography (hexanes/EtOAc, 2:1) to give 573 mg of the $\beta$-anomer and 150 mg of a 1:1 mixture of α- and $\beta$-anomers (98% combined yield), in which the $\beta$-anomer crystallized upon standing. $^1$H NMR ($CDCl_3$): $\delta$ 5.20 (t, $J$ = 9.3 Hz, 1H), 5.07 (t, $J$ = 9.6 Hz, 1H), 4.98 (dd, $J$ = 8.1, 9.6 Hz, 1H), 4.59 (d, $J$ = 6.9 Hz, 1H), 4.24 (dd, $J$ = 4.8, 12.6 Hz, 1H), 4.12 (dd, $J$ = 2.7, 12.3 Hz, 1H), 3.66 (m, 2H), 3.39 (dd, $J$ = 6.9, 10.5 Hz, 1H), 2.07 (s, 3H), 2.04 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.01 (m, 1H), 0.52 (m, 2H), 0.19 (m, 2H) ppm. $^{13}$C NMR: $\delta$ 171.0, 170.6, 169.7, 169.7, 100.3, 74.4, 73.1, 72.0, 71.6, 68.7, 62.2, 21.0, 20.9, 20.9, 20.8, 10.4, 3.5, 2.3 ppm. IR (neat): 3436, 3301, 2920, 1744, 1367, 1217, 1037 cm$^{-1}$. HRMS: calcd for $C_{18}H_{26}O_{10}$ 402.1526, found 402.1531.

**Platinacyclobutylmethyl 2,3,4,6-Tetra-*O*-acetyl-$\beta$-D-glucopyranoside, 17.** A solution of cyclopropane **16** (92.0 mg, 0.229 mmol), $Et_2O$ (5 mL), and Zeise's dimer (67.0 mg, 0.114 mmol) was refluxed for 4 h, then cooled and concentrated under reduced pressure. The residue was washed with pentane, dried, and suspended in $CDCl_3$ (2.5 mL). 2,2′-Dipyridal (36 mg, 0.229 mmol) was added to yield platinacyclobutane **17** as a yellow solution. $^1$H NMR ($CDCl_3$): $\delta$ 8.63 (d, $J$ = 5.1 Hz, 2H), 8.19 (d, $J$ = 6.2 Hz, 2H), 8.01 (m, 2H), 7.63 (t, $J$ = 7.3 Hz, 2H), 5.23 (t, $J$ = 9.5 Hz, 1H), 5.10 (t, $J$ = 9.5 Hz, 1H), 5.04 (dd, $J$ = 8.0, 8.3 Hz, 1H), 4.58 (d, $J$ = 8.0 Hz, 1H), 4.29 (dd, $J$ = 4.5, 4.8 Hz, 1H), 3.86 (dd, $J$ = 7.0, 7.0 Hz, 1H), 3.72 (m, 1H), 3.58 (t, $J$ = 8.3 Hz, 1H), 3.36 (m, 1H), 2.63 (m, $J_{Pt,H}$ = 84.1 Hz, 2H), 2.30 (m, $J_{Pt,H}$ = 80.8 Hz, 2H), 2.11 (s, 3H), 2.09 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H). $^{13}$C NMR ($CDCl_3$): $\delta$ 170.9, 170.4, 169.5, 169.4, 153.7 147.9, 139.3, 137.2, 127.0, 123.3, 101.1, 76.2 ($J_{Pt,C}$ = 46.3 Hz), 73.0, 71.7, 71.5, 68.5, 62.1, 42.0 ($J_{Pt,C}$ = 98.0 Hz), 20.9, 20.8, 20.7, 20.6, −11.4 ($J_{Pt,C}$ = 342.2 Hz), −12.1 ($J_{Pt,C}$ = 342.0 Hz). IR (neat): 2917, 2850, 1724, 1270, 1023 cm$^{-1}$.

**Platinacyclobutylmethyl $\beta$-D-glucopyranoside, 18.** A solution of cyclopropane **16** (105 mg, 0.262 mmol), $Et_2O$ (5 mL), and Zeise's dimer (75.0 mg, 0.128 mmol) was refluxed for 4 h, then cooled and concentrated under reduced pressure. The residue was washed with pentane, dried, and suspended in MeOH (3 mL). 2,2′-Dipyridal (60 mg, 0.384 mmol) was added, the mixture was stirred 15 min, and 3 drops of 15% NaOMe were added. After stirring 7 h, the solution was concentrated and purified by flash chromatography ($MeOH/CH_2Cl_2$, 1:4) to give 125 mg (73%) of platinacyclobutane **18** as a yellow solid. $^1$H NMR ($CD_3CD_2OD$): $\delta$ 8.65 (s, 2H), 8.55 (d, $J$ = 6.9 Hz, 2H), 8.22 (m, 2H), 7.79 (t, $J$ = 7.3 Hz, 2H), 4.40 (d, $J$ = 7.8 Hz, 1H), 3.86 (m, 2H), 3.72 (m, 1H), 3.52 (m, 1H), 3.49−3.26 (m, 5H), 2.61 (m, $J_{Pt,H}$ = 81.1 Hz, 2H), 2.33 (m, $J_{Pt,H}$ = 77.5 Hz, 2H). $^{13}$C NMR ($CD_3CD_2OD$): $\delta$ 154.6 148.4, 140.9, 128.2, 124.7, 103.7, 77.0 (2C), 76.4 ($J_{Pt,C}$ = 43.4 Hz), 74.2, 70.6, 61.7, 42.7 ($J_{Pt,C}$ = 96.0 Hz), −11.0 ($J_{Pt,C}$ = 337.5 Hz), −11.1 ($J_{Pt,C}$ = 338.6 Hz). IR (neat): 3366, 2922, 1445, 1070, 1028, 831 cm$^{-1}$. HRMS: calcd for $C_{20}H_{26}Cl_2N_2O_6Pt$ 655.0816, found 655.0880.

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**Supporting Information Available:** NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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