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Synthesis of Novel *gluco*- and *galacto*-Functionalized Platinum Complexes

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Dedicated to the memory of Professor Peter Köll

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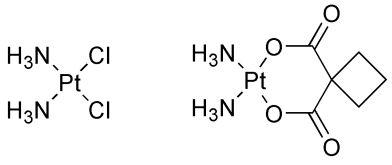
Cisplatin, carboplatin, oxaliplatin and further derivatives are worldwide established cytostatics for the treatment of a vast range of tumours. These drugs showed extraordinary success; however, side effects and primary or developed secondary resistance of tumour cells represent severe problems, which prompt the development of novel functionalized platinum complexes. Selectively protected monohydroxy derivatives of glucose and galactose could be etherified by ω-halo ethers. Further, Finkelstein reaction and malonate synthesis gave precursor glycoconjugates which were easily transformed into their (diammine)platinum complexes. First tests with different tumour cell lines show biological activity of the *gluco*-functionalized platinum complex.

Introduction

With the discovery of the biological activity of platinum complexes in 1965 by B. Rosenberg et al.[1] the interest in such agents increased due to their special anticancer effects.[2] Since 1978, cisplatin (**1**) is used for the treatment of a vast range of tumours, e.g. testicular, vesicle, cervix and head-neck tumours as well as oesophagus and small-cell lung carcinoma.[3] Along the application of **1**, side effects such as renal, neural, nephro- and ototoxicity[4] cannot be avoided. Although nephrotoxicity, an initial limitation, could be controlled by a high hydratisation of the complex,[5] there are still other drawbacks such as reduced efficacy by primary or developed secondary resistances of the tumour cells against **1**.[6] Therefore, a number of approaches were made to modulate and derivatize cisplatin (**1**) (Figure 1).



1 **2**

Figure 1. Cisplatin (**1**) and carboplatin (**2**).

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One of the best-known and successful second-generation platinum drugs is carboplatin (**2**), which contains a cyclobutane-1,1-dicarboxylic acid instead of the two chlorido ligands in **1**.[7] Due to the presence of the bidentate-chelated bis(carboxylato) ligand, **2** differs in the kinetics of its interaction with DNA.[8] Thus, it causes fewer side effects, e.g. less nephro- and ototoxicity,[9] but shows nearly the same efficacy on some tumours such as ovarian and bronchial carcinoma as well as head-neck and cervix tumours. However, myelosuppression connected with **2** remains a limiting factor for its application.[10]

Like most low-molecular-weight drugs, cisplatin and carboplatin show a short blood circulation time, which reduces tumour uptake and intracellular binding.[11] The renal clearance of platinum complexes is 27–45% for **1**[12] and 58–79% for **2** and thus quite high.[13] Therefore, it was envisaged to introduce a natural ligand by forming glyco-functionalized platinum complexes and thus extending the exposure time of the drug in the body.

Due to the toxicity of the deployed platinum complexes the interest in complexes with biologically relevant ligands remains significant.[14,15] Although nowadays carbohydrates are known to play a key role in various biological processes,[16] there were only a few approaches to employ them within platinum-based cancer therapy. Tsubomura et al.[17] reported about glyco-functional platinum complexes formed by using 2,3-diamino-2,3-deoxymannose and -glucose instead of the amino ligands in cisplatin, and the antitumour activity of these as well as corresponding complexes were tested.[18] In 2007 Keppler et al. took the (2,3-diamino-2,3-dideoxyglucose)Pt complex and changed the chloro ligands. The in vitro tests with four different tumour cell lines

of these complexes showed all higher IC_{50} values than carboplatin and oxaliplatin.[19] Amino ligands based on carbohydrates developed by Chen et al.[20] used the glucopyranoside of 1,3-diazidopropan-2-ol, the azido groups of which were reduced to amino groups, and after cleavage of the protecting groups, the platinum complex was formed. In vitro tests showed their activity to be comparable to cisplatin against two human cancer cell lines. Mikata et al.,[21,22] added a number of further complexes of this kind with carbohydrate ligands and also used a 1,2-diaminopropane linker to form a five-membered ring with the platinum atom.

Further approaches connected diolates of carbohydrates (e.g. glycerol,[23] galactitol and mannitol[24]) directly through their hydroxy groups to the platinum atom; however, no biological studies were done. Recently, Tromp et al. reported on the platinum complex of a malonic acid elongated benzyl glycoside of glucuronic acid to be used as prodrug for release of the cytostatic compound by enzymatic reaction with β-glucuronidase.[25] A comprehensive review of all previously available and relevant compounds appeared by Keppler et al. in 2008.[26]

In the following approach we were interested to access platinum complexes of carbohydrates by facile routes by an arbitrarily chosen hydrophobic linker. The objective of reaching a lower toxicity by introducing a natural ligand was thus combined with an enhanced uptake of the cytostatic compound, since tumour cells show a high glycolytic activity.[27]

Results and Discussion

For attaching the carbohydrate derivatives to the platinum atom, an approach was applied in analogy to the synthesis of carboplatin (**2**) by employing malonic acid as the ideal bidentate-chelating ligand. This ligand should be connected to the carbohydrate head group through a spacer, and for first approaches the hydrophobic butyl chain was selected and easily attached. For further studies other alternative and more hydrophilic spacers such as, for example, PEG derivatives will be considered.

For connecting malonic acid through a butyl spacer to the carbohydrate head group, base-stable isopropylidene groups were selected, which for *gluco* and *galacto* structures allowed for facile regioselective attachment in positions 3 and 6, respectively.

As shown in Scheme 1 commercially available 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**3**) and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**4**)[28] were used as starting materials. For attachment of the butyl spacer the Williamson's ether synthesis according to Wang et al.[29] was chosen. Treatment of compounds **3** and **4** with 1-bromo-4-chlorobutane and sodium hydroxide in DMSO at room temperature gave products **5** and **6** in yields of 87 and 64%, respectively. For activation, the 4′-chloro substituent was replaced by iodide in acetone under reflux in a Finkelstein reaction[30] to give the products **7** and **8** after column chromatography in 83 and 85% yield, respectively. Further, reaction with di-*tert*-butyl malonate and potassium *tert*-butoxide in tetrahydrofuran under reflux for 24 h afforded the products **9** and **10** in 67 and 71% yields, respectively. Both, the isopropylidene protecting groups as well as the *tert*-butyl ester could be smoothly removed with trifluoroacetic acid in dichloromethane at room temperature. After neutralisation with 1 M sodium hydroxide, the disodium salts **11** and **12** were isolated in 57 and 42% yields, respectively.

For complexation with platinum, cisplatin (**1**) was converted into the diammine dinitrato complex with silver nitrate in water at room temperature.[31] The precipitated silver chloride was filtered off and the *gluco*-functionalized ligand **11** was added. After stirring at room temperature for 5 h and purification on Biogel P2, the complex **13** could be isolated in 60% yield.

By a similar reaction and workup the *galacto*-functionalized ligand was transformed into the platinum complex **14** in 70% yield.

In first biological tests with different tumour cell lines the IC_{50} values of the novel glucose platinum complex (**13**, glc-pt) in comparison to carboplatin (**2**, c-pt) were determined (Figure 2). Tumour cells were incubated with **2** and **13** at different concentrations for 3, 5, 6 or 7 d, and the survival rates of vital cells were measured. As shown in Figure 2 for the cell line H526 (small-cell lung carcinoma) the two cytostatic compounds differ only little. Graphically determined IC_{50} values after 3 d of incubation are 6 μmol/L for carboplatin (**2**) and 7 μmol/L for the novel complex **13**. Finally, after 5 d of incubation both compounds reached an IC_{50} value of 1.5 μmol/L.

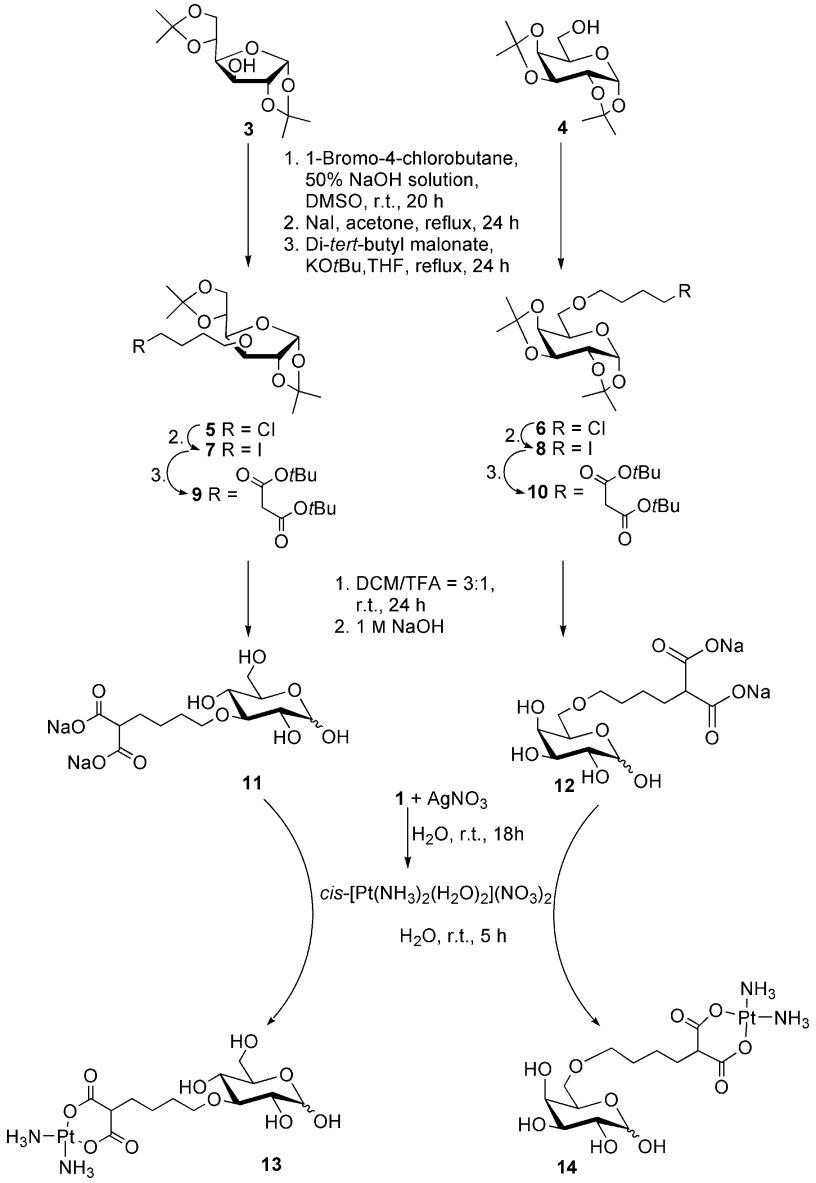
Similar values could be obtained for other small-cell lung carcinoma and non-small-cell lung carcinoma cell lines. Tests with MRC-5 (fibroblast of lung) show that both carboplatin (**2**) and the novel complex **13** are less active against this kind of tumour.

Conclusions

The synthesis of glyco-functionalized platinum complexes through a butyl spacer and malonic acid as chelating ligand can be easily achieved. Selective alkylation of the glucose and galactose derivatives with 1-bromo-4-chlorobutane, Finkelstein reaction and subsequent attachment of the di-*tert*-butyl malonate proceeded in good yields. The simultaneous cleavage of the isopropylidene protecting groups and the *tert*-butyl esters was achieved, and finally the complexation with platinum could be realized in good yields. First biological test for the novel complex **13** showed nearly the same activity on different tumour cell lines as the established cytostatic carboplatin (**2**).

Experimental Section

General Methods: Commercially available starting materials were used without further purification. Solvents were dried according to standard methods. TLC was performed on precoated aluminium



Scheme 1. Synthesis of novel glyco-functionalized platinum complexes.

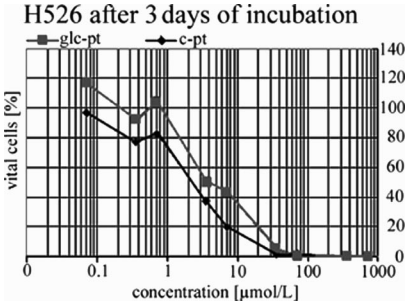


Figure 2. Survival rate of tumour cells (H526) correlated to the concentration of cytostatic compounds after 3 d of incubation.

plates (Silica Gel 60 F_{254}, Merck 5554) charring with 10% H_2SO_4 in ethanol for visualization. For column chromatography Silica Gel 60, 230–400 mesh, 40–63 µm (Merck) was used. ^1H and ^{13}C NMR spectra were recorded with Bruker AMX-400 (400 MHz for ^1H, 100.6 MHz for ^{13}C) and Bruker DRX-500 (500 MHz for ^1H, 125.8 MHz for ^{13}C) instruments at 300 K. Chemical shifts were calibrated to solvent residual peaks.[32] The signals were assigned by H,H-COSY, HSQC and HMBC experiments. Optical rotations were measured by using a Krüss Optronic P8000 (589 nm) instrument at 20 °C. MALDI-TOF-MS was performed with a Bruker Biflex III using dihydroxybenzoic acid as matrix in positive-reflector mode. HR-FAB-MS was performed with a VG 70S mass spectrometer in positive-ion mode using a xenon FAB gun and *m*-nitrobenzyl alcohol as matrix at 5000 resolution. ESI-MS was performed with a Finnigan ThermoQuest MAT 95XL mass spectrometer.

3-*O*-(4′-Chlorobutyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (5): 1-Bromo-4-chlorobutane (2.0 mL, 17 mmol) was slowly added to a solution of **3** (3.04 g, 11.7 mmol) in 50% sodium hydroxide solution (1.6 mL, 20 mmol) and DMSO (20 mL). The mixture was stirred at room temperature for 16 h. Distilled water (10 mL) was added, and the solution was extracted three times with diethyl

ether. The combined organic fractions were washed with saturated sodium chloride solution and dried with Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (petroleum ether ether/ethyl acetate, 2:1) to give **5** as a colourless syrup (3.56 g, 87%). $[\alpha]_D^{20}$ = –54.0 (*c* = 0.10, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.79 (d, $J_{1,2}$ = 3.8 Hz, 1 H, 1-H), 4.45 (d, $J_{1,2}$ = 3.8 Hz, 1 H, 2-H), 4.20 (ddd, $J_{4,5}$ = 8.1, $J_{5,6a}$ = 6.1, $J_{5,6b}$ = 5.6 Hz, 1 H, 5-H), 4.04–3.99 (m, 2 H, 6a-H, 4-H), 3.90 (dd, $J_{5,6b}$ = 5.6, $J_{6a,6b}$ = 8.4 Hz, 1 H 6b-H), 3.78 (d, $J_{3,4}$ = 3.0 Hz, 1 H, 3-H), 3.62–3.56 (m, 1 H, 1′a-H), 3.51–3.45 (m, 3 H, 1′b-H, 4′-H), 1.84–1.76 (m, 2 H, 2′-H), 1.68–1.61 (m, 2 H, 3′-H) 1.42, 1.35, 1.27, 1.24 (4× s, 4×3 H, 4× CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 111.8, 109.0 [2× $C(CH_3)_2$], 105.3 (C-1), 83.0 (C-2), 82.5 (C-3), 81.3 (C-4), 72.4 (C-5), 69.6 (C-1′), 67.4 (C-6), 44.7 (C-4′), 29.3 (C-3′), 27.0 (C-2′), 26.8, 26.7, 26.2, 25.4 (4× CH_3) ppm. MALDI-TOF-MS: *m*/*z* = 372.9 $[M + Na]^+$, 388.8 $[M + K]^+$. HR-FAB-MS: calcd. for $C_{16}H_{28}ClO_6$ 351.1574 $[M + H]^+$; found 351.1569.

6-*O*-(4′-Chlorobutyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (6): 1-Bromo-4-chlorobutane (2.0 mL, 17 mmol) was slowly added to a solution of **4** (3.04 g, 11.7 mmol) in 50% sodium hydroxide solution (1.6 mL, 20 mmol) and DMSO (20 mL). The mixture was stirred at room temperature for 16 h. Distilled water (10 mL) was added, and the solution was extracted three times with diethyl ether. The combined organic fractions were washed with saturated sodium chloride solution and dried with Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (petroleum ether ether/ethyl acetate, 2:1) to give **6** as a colourless syrup (2.63 g, 64%). $[\alpha]_D^{20}$ = –74.9 (*c* = 0.28, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.44 (d, $J_{1,2}$ = 5.1 Hz, 1 H, 1-H), 4.51 (dd, $J_{2,3}$ = 7.9, $J_{3,4}$ = 2.5 Hz, 1 H, 3-H), 4.22 (dd, $J_{1,2}$ = 5.1, $J_{2,3}$ = 7.9 Hz, 1 H, 2-H), 4.15 (dd, $J_{3,4}$ = 2.5, $J_{4,5}$ = 1.8 Hz, 1 H, 4-H), 3.86 (ddd, $J_{4,5}$ = 1.8, $J_{5,6a}$ = 6.9, $J_{5,6b}$ = 5.6 Hz, 1 H, 5-H), 3.54 (dd, $J_{5,6a}$ = 6.9, $J_{6a,6b}$ = 10.2 Hz, 6a-H), 3.51–3.38 (m, 5 H, 6b-H, 1′-H, 4′-H), 1.81–1.73 (m, 2 H, 3′-H), 1.67–1.60 (m, 2 H, 2′-H), 1.45, 1.36, 1.26, 1.24 (4× s, 4×3 H, 4× CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 109.2, 108.5 [2× $C(CH_3)_2$], 96.4 (C-1), 71.2 (C-4), 70.7 (C-2), 70.6 (C-3), 70.4 (C-6), 70.3 (C-1′), 66.8 (C-5), 44.9 (C-4′), 29.7, 29.5 (C-3′, C-2′), 26.9, 26.1, 26.0, 24.9 (4× CH_3) ppm. MALDI-TOF-MS: *m*/*z* = 373.0 $[M + Na]^+$, 389.0 $[M + K]^+$. HR-FAB-MS: calcd. for $C_{16}H_{28}ClO_6$ 351.1574 $[M + H]^+$; found 351.1566.

3-*O*-(4′-Iodobutyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (7): Sodium iodide (1.04 g, 6.93 mmol) was added to a solution of **5** (2.43 g, 6.93 mmol) in acetone (50 mL). The mixture was heated under reflux for 24 h. Filtration, evaporation of the solvent and column chromatography (petroleum ether ether/ethyl acetate, 9:1) gave **7** as a yellow syrup (2.54 g, 83%). $[\alpha]_D^{20}$ = –41.1 (*c* = 0.18, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.77 (d, $J_{1,2}$ = 3.6 Hz, 1 H, 1-H), 4.43 (d, $J_{1,2}$ = 3.6 Hz, 1 H, 2-H), 4.18 (ddd, $J_{4,5}$ = 8.1, $J_{5,6a}$ = 6.1, $J_{5,6b}$ = 5.6 Hz, 1 H, 5-H), 4.03–3.97 (m, 2 H, 6a-H, 4-H), 3.88 (dd, $J_{5,6b}$ = 5.6, $J_{6a/b}$ = 8.7 Hz, 1 H, 6b-H), 3.75 (d, $J_{3,4}$ = 3.1 Hz, 1 H, 3-H), 3.60–3.53 (m, 1 H, 1′a-H), 3.49–3.42 (m, 1 H, 1′b-H), 3.12 (t, $J_{3',4'}$ = 7.1 Hz, 2 H, 4′-H) 1.87–1.75 (m, 2 H, 2′-H), 1.67–1.55 (m, 2 H, 3′-H) 1.40, 1.33, 1.27, 1.22 (4× s, 4×3 H, 4× CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 111.8, 109.0 [2× $C(CH_3)_2$], 105.3 (C-1), 83.1 (C-2), 82.5 (C-3), 82.0 (C-4), 72.4 (C-5), 69.3 (C-1′), 67.4 (C-6), 30.2 (C-2′), 30.1 (C-3′), 26.8, 26.7, 26.2, 25.4 (4× CH_3), 6.4 (C-4′) ppm. MALDI-TOF-MS: *m*/*z* = 464.9 $[M + Na]^+$, 480.8 $[M + K]^+$. HR-FAB-MS: calcd. for $C_{16}H_{28}IO_6$ 443.0931 $[M + H]^+$; found 443.0939.

6-*O*-(4′-Iodobutyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (8): Sodium iodide (1.12 g, 7.49 mmol) was added to a solution of **6** (2.63 g, 7.49 mmol) in acetone (60 mL). The mixture was heated under reflux for 24 h. Filtration, evaporation of the solvent and column chromatography (petroleum ether ether/ethyl acetate, 9:1) gave **8** as a yellow syrup (2.82 g, 85%). $[\alpha]_D^{20}$ = –78.5 (*c* = 0.14, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.44 (d, $J_{1,2}$ = 5.1 Hz, 1 H, 1-H), 4.51 (dd, $J_{2,3}$ = 7.9, $J_{3,4}$ = 2.3 Hz, 1 H, 3-H), 4.22 (dd, $J_{1,2}$ = 5.1, $J_{2,3}$ = 7.9 Hz, 1 H, 2-H), 4.15 (dd, $J_{3,4}$ = 2.3, $J_{4,5}$ = 1.8 Hz, 1 H, 4-H), 3.86 (ddd, $J_{4,5}$ = 1.8, $J_{5,6a}$ = 7.6, $J_{5,6b}$ = 2.3 Hz, 1 H, 5-H), 3.56–3.36 (m, 4 H, 6a/b-H, 1′-H), 3.11 (t, $J_{3',4'}$ = 7.1 Hz, 2 H, 4′-H), 1.80–1.74 (m, 2 H, 2′-H), 1.67–1.56 (m, 2 H, 3′-H), 1.45, 1.35, 1.26, 1.23 (4× s, 4×3 H, 4× CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 109.7, 109.0 [2× $C(CH_3)_2$], 96.8 (C-1), 71.6 (C-4), 71.0 (C-1′), 70.9 (C-2), 70.6 (C-3), 69.9 (C-6), 67.2 (C-5), 30.8, (C-2′), 29.9 (C-3′), 26.4, 25.4, 24.9, 24.8 (4× CH_3), 7.4 (C-4′) ppm. MALDI-TOF-MS: *m*/*z* = 464.8 $[M + Na]^+$, 480.8 $[M + K]^+$. HR-FAB-MS: calcd. for $C_{16}H_{28}IO_6$ 443.0931 $[M + H]^+$; found 443.0951.

3-*O*-(5′,5′-Di-*tert*-butoxycarbonylpentyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (9): Potassium *tert*-butoxide (645 mg, 5.75 mmol) was added under nitrogen to a solution of di-*tert*-butyl malonate (1.6 mL, 7.2 mmol, 1.6 g) in anhydrous tetrahydrofuran (50 mL). After consumption of the potassium *tert*-butoxide, **7** (2.54 g, 5.75 mmol) was added, and the mixture was heated under reflux for 24 h. THF was removed under reduced pressure, and dichloromethane was added. The mixture was washed twice with 5% acetic acid, once with water and dried with Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (petroleum ether ether/ethyl acetate, 9:1) to give **9** as a colourless syrup (2.09 g, 67%). $[\alpha]_D^{20}$ = –60.7 (*c* = 0.14, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.77 (d, $J_{1,2}$ = 3.8 Hz, 1 H, 1-H), 4.43 (d, $J_{1,2}$ = 3.8 Hz, 1 H, 2-H), 4.19 (ddd, $J_{4,5}$ = 6.1, $J_{5,6a}$ = 6.4, $J_{5,6b}$ = 5.6 Hz, 1 H, 5-H), 4.02 (dd, $J_{3,4}$ = 3.1, $J_{4,5}$ = 6.1 Hz, 1 H, 4-H), 3.98 (dd, $J_{5,6a}$ = 6.4, $J_{6a/b}$ = 8.7 Hz, 1 H, 6a-H), 3.88 (dd, $J_{5,6b}$ = 5.6, $J_{6a/b}$ = 8.7 Hz, 1 H, 6b-H), 3.75 (d, $J_{3,4}$ = 3.1 Hz, 1 H, 3-H), 3.54–3.40 (m, 2 H, 1′-H), 3.01 (t, $J_{4',5'}$ = 8.1 Hz, 1 H, 5′-H), 1.75–1.68 (m, 2 H, 2′-H), 1.54–1.46 (m, 2 H, 3′-H), 1.31–1.28 (m, 2 H, 4′-H), 1.40, 1.33, 1.25, 1.22 (4× s, 4×3 H, 4× CH_3), 1.36 (s, 18 H, 6× CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 168.9 (2× C=O), 111.7, 108.9 [2× $C(CH_3)_3$], 105.2 (C-1), 82.5 (C-2), 82.2 (C-3), 81.8 (C-4), 72.5 (C-5), 70.2 (C-1′), 69.0 (C-6), 53.8 (C-5′), 31.9 (C-2′), 29.4 (C-4′), 26.9 [2× C(CH_3)$_3$], 26.8, 26.2, 25.4, 23.8 (4× CH_3) 14.2 (C-3′) ppm. MALDI-TOF-MS: *m*/*z* = 552.9 $[M + Na]^+$, 568.9 $[M + K]^+$. HR-FAB-MS: calcd. for $C_{27}H_{47}O_{10}$ 531.3169 $[M + H]^+$; found 531.3155.

6-*O*-(5′,5′-Di-*tert*-butoxycarbonylpentyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (10): Potassium *tert*-butoxide (820 mg, 7.31 mmol) was added under nitrogen to a solution of di-*tert*-butyl malonate (2.0 mL, 2.0 g, 9.1 mmol) in absolute tetrahydrofuran (70 mL). After potassium *tert*-butoxide was consumed, **8** (3.23 g, 7.31 mmol) was added, and the mixture was heated under reflux for 24 h. THF was removed under reduced pressure, and dichloromethane was added. The mixture was washed twice with 5% acetic acid, once with water and dried with Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (petroleum ether ether/ethyl acetate, 9:1) to give **10** as a colourless syrup (2.75 g, 71%). $[\alpha]_D^{20}$ = –80.0 (*c* = 0.05, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.44 (d, $J_{1,2}$ = 5.1 Hz, 1 H, 1-H), 4.50 (dd, $J_{2,3}$ = 7.9 Hz, 1 H, 3-H), 4.21 (dd, $J_{1,2}$ = 5.1 Hz, 1 H, 2-H), 4.16 (dd, $J_{3,4}$ = 2.3, $J_{4,5}$ = 1.8 Hz, 1 H, 4-H), 3.85 (ddd, $J_{4,5}$ = 1.8, $J_{5,6a}$ = 5.9, $J_{5,6b}$ = 6.6 Hz, 1 H, 5-H), 3.53 (dd, $J_{5,6a}$ 5.9, $J_{6a/b}$ 1 = 0.2 Hz, 1 H, 6a-H), 3.46 (dd, $J_{5,6b}$ = 6.6, $J_{6a/b}$ = 10.2 Hz, 1 H, 6b-H), 3.42–3.32 (m, 2 H, 1′-H), 3.01 (t, $J_{4',5'}$

= 7.6 Hz, 1 H, 5′-H), 1.75–1.68 (m, 2 H, 2′-H), 1.56–1.48 (m, 2 H, 3′-H), 1.44, 1.35, 1.25, 1.23 (4× s, 4×3 H, 4× CH_3), 1.37 (s, 18 H, 6× CH_3), 1.32–1.27 (m, 2 H, 4′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9 (2× C=O), 109.2, 108.5 [2× $C(CH_3)_2$], 96.4 (C-1), 81.2 [2× $C(CH_3)_3$], 71.2 (C-4), 71.0 (C-1′), 70.6 (C-2), 70.4 (C-3), 69.5 (C-6), 66.7 (C-5), 53.0 (C-5′), 29.3 (C-2′), 28.4 (C-3′), 27.9 (6× CH_3), 26.1, 26.0, 25.0, 24.5 (4× CH_3), 23.8 (C-4′) ppm. MALDI-TOF-MS: *m/z* = 552.9 $[M + Na]^+$, 569.0 $[M + K]^+$. HR-FAB-MS: calcd. for $C_{27}H_{47}O_{10}$ 531.3169 $[M + H]^+$; found 531.3173.

3-*O*-(5′,5′-Dicarboxypentyl)-α/β-D-glucopyranose Disodium Salt (11): Compound **9** (1.04 g, 1.89 mmol) was solubilised in dichloromethane (300 mL) and trifluoroacetic acid (100 mL), and the mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure, and water was added. The mixture was extracted twice with diethyl ether and neutralized with 1 M sodium hydroxide solution. The product was purified on Biogel P2 and lyophilized to give **11** (303 mg, 42%). ^{1}H NMR (400 MHz, D_2O): δ = 5.04 (d, $J_{1\alpha,2}$ = 3.1 Hz, 1 H, 1α-H), 4.47 (d, $J_{1\beta,2}$ = 7.6 Hz, 1β-H), 3.69–3.63 (m, 2 H, 1′-H), 3.50–3.38 (m, 2 H, 4-H, 6a-H), 3.33–3.24 (m, 2 H, 3-H, 6b-H), 3.22–3.15 (m, 1 H, 5-H), 3.04–2.97 (m, 1 H, 2-H), 2.91 (t, $J_{4',5'}$ = 7.6 Hz, 1 H, 5′-H), 1.61–1.53 (m, 2 H, 4′-H), 1.52–1.44 (m, 2 H, 2′-H), 1.24–1.14 (m, 2 H, 3′-H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 182.8 (2× C=O), 106.8 (C-1β), 101.2 (C-1α), 85.8 (C-2), 84.1 (C-4), 83.7 (C-3), 75.9 (C-1′), 74.1 (C-6), 72.4 (C-5), 63.4 (C-5′), 32.8 (C-2′), 32.1 (C-4′), 26.8 (C-3′) ppm. ESI-MS: *m/z* = 383.05 $[M + H]^+$, 405.05 $[M + Na]^+$. HR-ESI-MS: calcd. for $C_{13}H_{20}Na_2O_{10}$ 383.0930 $[M + H]^+$; found 383.0913.

3-*O*-(5′,5′-Dicarboxypentyl)-α/β-D-galactopyranose Disodium Salt (12): Compound **10** (1.04 g, 1.89 mmol) was solubilised in dichloromethane (300 mL) and trifluoroacetic acid, and the mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure, and water was added. The mixture was extracted twice with diethyl ether and neutralized with sodium hydroxide solution (1 mol/L). The product was purified on Biogel P2 and lyophilized to give **12** (305 mg, 42%). ^{1}H NMR (400 MHz, D_2O): δ = 5.09 (d, $J_{1\alpha,2}$ = 3.8 Hz, 1 H, 1α-H), 4.42 (d, $J_{1\beta,2}$ = 7.9 Hz, 1 H, 1β-H), 3.74 (dd, $J_{3,4}$ = 3.6, $J_{4,5}$ = 1.8 Hz, 1 H, 4-H), 3.71–3.62 (m, 3 H, 5-H, 6a/b-H), 3.49 (dd, $J_{2,3}$ = 9.9, $J_{3,4}$ = 3.6 Hz, 1 H, 3-H), 3.46–3.38 (m, 2 H, 1′-H), 3.32–3.26 (m, 1 H, 2-H), 2.91 (t, $J_{4',5'}$ = 7.6 Hz, 1 H, 5′-H), 1.60–1.52 (m, 2 H, 3′-H), 1.50–1.41 (m, 2 H, 2′-H), 1.20–1.11 (m, 2 H, 3′-H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 179.7 (2× C=O), 96.4 (C-1β), 92.3 (C-1α), 73.3 (C-4), 72.8 (C-2), 71.9 (C-3), 71.1 (C-1′), 69.6 (C-6), 69.0 (C-5), 58.5 (C-5′), 30.0 (C-2′), 28.5 (C-4′) 24.0 (C-3′) ppm. ESI-MS: *m/z* = 383.07 $[M + H]^+$, 405.05 $[M + Na]^+$. HR-ESI-MS: calcd. for $C_{13}H_{20}Na_2O_{10}$ 383.0930 $[M + H]^+$; found 383.0918.

Glc-3-Pt Complex 13: Cisplatin (**1**; 35.0 mg, 100 μmol) and silver nitrate (35.0 mg, 200 μmol) were dissolved in bidistilled water (2.4 mL) and stirred at room temperature overnight. After filtration of the precipitated silver chloride, **11** (20 mg, 50 μmol) was added, and the mixture was stirred at room temperature for 5 h. The water was removed under reduced pressure, and the product was purified on Biogel P2 and lyophilized to give **13** (17 mg, 60%). ^{1}H NMR (400 MHz, D_2O): δ = 5.13 (d, $J_{1\alpha,2}$ = 2.5 Hz, 1 H, 1α-H), 4.57 (d, $J_{1\beta,2}$ = 7.9 Hz, 1 H, 1β-H), 3.83–3.75 (m, 2 H, 1′-H), 3.74–3.55 (m, 3 H, 4-H, 6a-H, 5′-H), 3.53–3.45 (m, 2 H, 3-H, 6b-H), 3.31–3.24 (m, 1 H, 5-H), 3.24–3.18 (m, 1 H, 2-H), 2.50–2.39 (m, 2 H, 4′-H), 1.68–1.58 (m, 2 H, 2′-H), 1.47–1.36 (m, 2 H, 3′-H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 186.8 (2× C=O), 104.3 (C-1β), 100.9 (C-1α), 86.8 (C-2), 85.4 (C-4), 84.1 (C-3), 72.9 (C-1′), 70.9 (C-6), 69.3 (C-5), 61.4 (C-5′), 34.8 (C-4′), 31.1 (C-2′), 26.1 (C-3) ppm. MALDI-TOF-MS: *m/z* = 588.0 $[M + Na]^+$. HR-ESI-MS: calcd. for $C_{13}H_{26}N_2O_{10}Pt$ 588.1133 $[M + Na]^+$; found 588.1109.

Gal-6-Pt Complex 14: Cisplatin (**1**; 35.0 mg, 100 μmol) and silver nitrate (35.0 mg, 200 μmol) were dissolved in bidistilled water (2.4 mL) and stirred at room temperature overnight. After filtration of the precipitated silver chloride, **12** (20 mg, 50 μmol) was added, and the mixture was stirred at room temperature for 5 h. The water was removed under reduced pressure, and the product was purified on Biogel P2 and lyophilized to give **14** (20 mg, 70%). ^{1}H NMR (400 MHz, D_2O): δ = 5.17 (d, $J_{1\alpha,2}$ = 3.8 Hz, 1 H, 1α-H), 4.49 (d, $J_{1\beta,2}$ = 7.9 Hz, 1 H, 1β-H), 3.83 (dd, $J_{3,4}$ = 3.6, $J_{4,5}$ = 1.3 Hz, 1 H, 4-H), 3.77 (dd, $J_{5,6a}$ = 3.3, $J_{6a,6b}$ = 10.4 Hz, 1 H, 6a-H), 3.74–3.69 (m, 2 H, 5-H, 6b-H), 3.56 (dd, $J_{2,3}$ = 9.9, $J_{3,4}$ = 3.6 Hz, 1 H, 3-H), 3.54–3.48 (m, 3 H, 1′-H, 5′-H), 3.42–3.88 (m, 1 H, 2-H), 2.48–2.39 (m, 2 H, 4′-H), 1.66–1.57 (m, 2 H, 2′-H), 1.44–1.35 (m, 2 H, 3′-H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 188.0 (2× C=O), 99.3 (C-1β), 95.2 (C-1α), 76.2 (C-3), 75.7 (C-4), 74.7 (C-2), 73.9 (C-1′), 72.8 (C-6), 71.5 (C-5), 60.8 (CH), 33.5 (C-4′), 31.1 (C-2′), 26.5 (C-3′) ppm. MALDI-TOF-MS (DHB): *m/z* = 588.6 $[M + Na]^+$, HR-ESI-MS: calcd. for $C_{13}H_{26}N_2O_{10}Pt$ 588.1133 $[M + Na]^+$; found 588.1115.

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