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Synthesis and hydrolysis studies of novel glyco-functionalized platinum complexes

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ABSTRACT

Cisplatin and some of its derivatives are among the most active cytostatics for cancer treatment. Unfortunately, application of platinum complexes always indicates side effects, and frequently primary or developed resistance of tumour cells appear. Therefore, development of novel analogues especially with natural ligands is expedited. Glyco-functionalized ligands were obtained via ether synthesis with ω-halo ethers, Finkelstein reaction, with further treatment with malonate and final deprotection followed by preparation of the disodium salts. Subsequent complexation led to novel platinum derivatives, the stabilities of which in aqueous solution media were studied.

1. Introduction

The biological activity of platinum complexes was found by chance in 1965 by B. Rosenberg.[1] Nowadays cisplatin (diammine dichloro platinum(II), **1**) and some of its derivatives are used for treatment of a large variety of cancers such as testicular, vesicle, cervix and head–neck-tumours as well as oesophagus and small-cell lung carcinoma.[2] Due to side effects such as renal, neural, nephro- and ototoxicity[3] which always accompany the application of cisplatin (**1**), approaches to develop new active derivatives represent contemporary research. Change of chloro ligands which are substituted in cells to give the active compounds induces altered stabilities of the complexes. Different stabilities in turn lead to other side effects[4] shown for example by carboplatin (**2**), in which the chloro ligands are substituted by a 2,2-cyclobutane dicarboxylato group[5] or nedaplatin (**4**), which shows less nephro- and neurotoxicity compared to cisplatin.[6] Derivatization of the ammine ligands like those shown in oxaliplatin (**3**) leads to a different structure of Pt–DNA-adducts which are responsible for the cytotoxic activity.[7] Change of the structure of Pt–DNA-adducts induces altered and enhanced activity, and thus treatment of cisplatin resistant tumours can be accomplished (Fig. 1).[8]

Due to the side effects and the primary or developed resistance of some tumours a number of novel platinum compounds were introduced over the last decades. Some of these approaches also incorporate natural ligands, for example, carbohydrates.[9] For example, 2,3-diaminosugars were used by Berger et al. to serve as ammine ligands for platinum. These complexes all showed higher IC_{50} values compared to cisplatin and carboplatin in preliminary biological tests.[10] 1,2- or 1,3-Diaminopropanol glycosidically linked to saccharides was also used for complexation to platinum to give five- or six-membered rings by Mikata et al., and their activity was shown to be comparable to cisplatin against two different cell lines.[11] A glucuronic acid containing platinum complexes was developed by Tromp et al. to function as a prodrug releasing the active compound via enzymatic cleavage of the glycolytic bond with β-glucuronidase.[12]

2. Results and discussion

In order to reach lower toxicity combined with enhanced uptake carbohydrates were connected to platinum using an arbitrarily chosen hydrophobic spacer and malonic acid as chelating moiety in this approach.

2.1. Synthesis of monosaccharide platinum complexes

Following the facile approach via Williamson's ether synthesis (GP 1),[13] Finkelstein reaction (GP 2)[14] and reaction with di-*tert*-butyl malonate (GP 3)[15] previously shown to be advantageous for synthesis of *gluco*- and *galacto*-derivatives and to achieve glyco-functionalized platinum complexes,[16] a series of other saccharides were prepared as precursors for novel complexes. Therefore, selectively protected alkylidene (isopropylidene or Ley's group) protected D-fructose, D-arabinose, D-ribose and D-mannose derivatives were chosen. Williamson's ether synthesis employing 50% aqueous sodium hydroxide and 1-bromo-4-chlorobutane could

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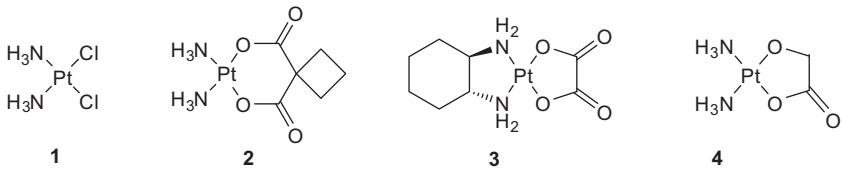


Figure 1. Platinum complexes for cancer treatment.

be achieved in yields from 37% to 87% depending on the used protected saccharide. For Finkelstein reaction yields between 53% and 98% were obtained, and after reaction with di-*tert*-butyl malonate/potassium *tert*-butoxide as base the products could be isolated in yields between 23% and 95% (Scheme 1, Table 1).

Simultaneous deprotection of all blocking groups in compounds obtained by GP 3 was performed using trifluoroacetic acid in dichloromethane to give the disodium salts of the unprotected saccharides following treatment with 1 M sodium hydroxide solution (GP 4) in yields between 19% and 94%. The novel glyco-functionalized ligands were readily complexed to platinum. Starting with cisplatin and substitution of the chloro ligands with aqua ligands by using silver nitrate gave the reagent which was used for transfer into the glyco-functionalized compounds (GP 5)[15] in yields between 28% and 80% (Scheme 2, Table 2). Complexation could be verified via ^{1}H NMR spectroscopy apparent by a downfield shift of the spacer protons. Especially the CH_2-groups at the 4th position of the spacer (CH_2-4′) are shifted downfield from about 1.8 ppm in the free ligands to 2.5 ppm in the complexes.

2.2. Preparation of a di-*O*-methyl glucofuranose platinum complex

Due to the results of first biological tests for **45**[16] which showed nearly the same activity for this novel complex compared to carboplatin more hydrophobic glyco-functionalized platinum complexes were synthesized. To obtain this partial methylated complex which perhaps can cross the cell membrane more facilely 3-(4′-chlorobutyl)-diacetone glucose (**5**) was selectively deprotected with 0.4% sulfuric acid (yield 70%)[17] and the free 5,6-positions methylated in 31% yield. Following the general procedures 2–5 the more hydrophobic glucose platinum complex **71** was synthesized in yields between 37% (complexation) and 68% (Finkelstein reaction) (Scheme 3).

2.3. Synthesis of lactoside platinum complex

In addition to the synthesis for monosaccharide platinum complexes a lactoside ligand **76** was obtained. Starting with methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2′,3′,6′-tri-*O*-benzyl)-β-D-galctopyranosyl)-β-D-glucopyranoside (**72**) Williamson's ether synthesis with 1-bromo-4-chlorobutane leads to compound **73** in 25% yield. Following Finkelstein reaction (80%) the transformation with di-*tert*-butyl malonate gave **74** in 45% yield. Removal of the benzyl groups by hydrogenolysis (palladium on charcoal) followed by acidic cleavage of *tert*-butyl esters was obtained in 93% yield. Complexation of disodium salt **76** with platinum was achieved in 47% yield to give methyllactoside platinum complex **77** (Scheme 4).

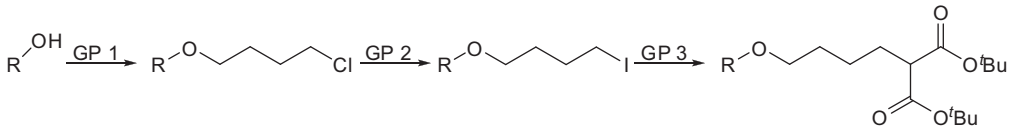
2.4. Synthesis of 2,6- and 4,6-substituted glucopyranoside bis platinum complexes

Attaching two platinum-binding malonato groups to one saccharide via a butyl spacer could be achieved facilely employing two different gluco-derivatives protected with Ley's group. Therefore, methyl α-D-glucopyranoside (**78**) was converted into a mixture of 3,4- (**79**) and 2,3-protected derivatives (**80**)[18] (99% yield). Following the synthesis of 6-*O*-silyl ethers[19], isomeres **81** and **82** were easily separated by column chromatography (84% yield). Cleavage of 6-*O*-silyl ether gave the two protected gluco-derivatives (yields: 98% for **79** and 87% for **80**) which were reacted with 1-bromo-4-chlorobutane following GP 1, however, reducing the amount of sodium hydroxide solution. Additional to dialkylated products **83** (43% yield) and **85** (48% yield) a mixture of monoalkylated products **35** and **84** (28% yield using 3.3 equiv sodium hydroxide) as well as **41** and **86** (50% yield) were obtained. Using 4.8 equiv sodium hydroxide for ether synthesis with **83** only 6-OH unprotected derivative **35** (47% yield) was obtained as side product. A small amount of **41** (37%) could be separated by column chromatography. The mixture of **35** and **84** as well as the mixture of **41** and **86** was reacted with TBDPSCl to give **32** (67%) and **38** (41%), which also were converted to platinum-complexing ligands like those shown in Table 1.

Finkelstein reaction on both side chains with yields of 77% (to give **87**) and 94% (to give **88**) followed by reaction with di-*tert*-butyl malonate in yields of 24% (to give **89**) and 60% (to give **90**) were performed. After deprotection of the sugar moiety, cleavage of di-*tert*-butyl ester gave tetra sodium salts **91** and **92**, respectively, and complexation to platinum could be achieved to give bis-platinum complexes **93** (yield 54%) and **94** (yield 70%) (Scheme 5).

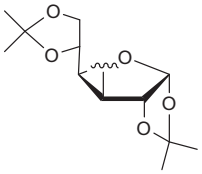
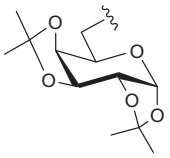
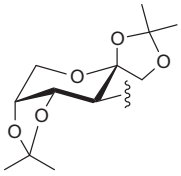
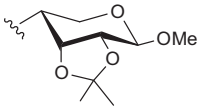
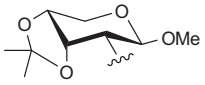
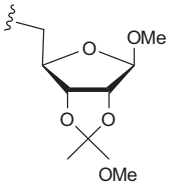
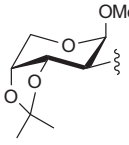
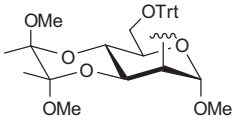
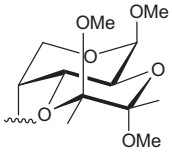
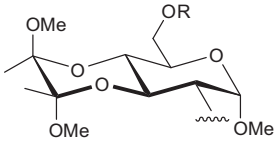
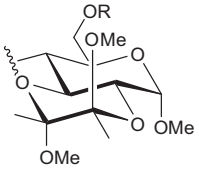
2.5. Hydrolysis studies

All presently applied platinum complexes in medicine represent prodrugs which are activated in cells by substitution of the non-amino ligands. Therefore, it was of interest to study the stability of the novel complexes. Previously, for the substitution of 2,2-cyclobutane dicarboxylato group in carboplatin (0.02 M) a rate constant was determined to be $k_{obs} = 1.2 \times 10^{-6}\ s^{-1}$ in a chloride (0.14 M) and hydrogen phosphate (0.1 M) solution by ^{1}H NMR analysis. The concentration of carboplatin (**2**) at equilibrium was measured to be 12 mM (64.1% did not react).[20]



Scheme 1. Construction of monosaccharide-tethered malonates. Reagents and conditions: GP 1: 50% NaOH-solution, 1-bromo-4-chlorobutane, DMSO; GP 2: NaI, acetone; GP 3: di-*tert*-butyl malonate, KO^{t}Bu, THF.

Table 1
Construction of monosaccharide-tethered malonates

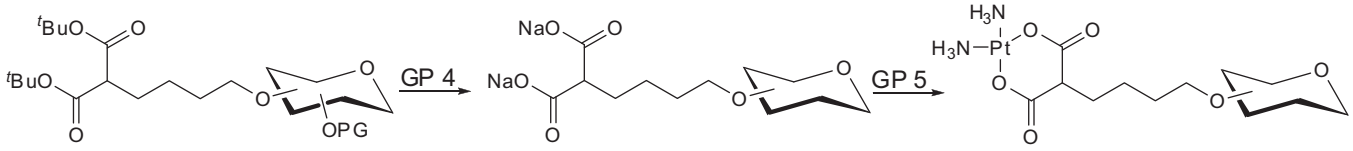
R		Reaction GP 1 No. (yield)	Reaction GP 2 No. (yield)	Reaction GP 3 No. (yield)
		**5** (87%[16])	**6** (83%[16])	**7** (67%[16])
		**8** (64%[16])	**9** (85%[16])	**10** (71%[16])
		**11** (59%)	**12** (84%)	**13** (60%)
		**14** (37%)	**15** (98%)	**16** (83%)
		**17** (43%)	**18** (84%)	**19** (95%)
		**20** (59%)	**21** (74%)	**22** (50%)
		**23** (66%)	**24** (90%)	**25** (55%)
		**26** (48%)	**27** (88%)	**28** (29%)
		**29** (50%)	**30** (99%)	**31** (34%)
	R = TBDPS R = H	**32** (67%)[a] **35** (47%)[b]	**33** (74%) **36** (91%)	**34** (23%) **37** (80%/80%[c])
	R = TBDPS R = H	**38** (41%)[a] **41** (37%)[b]	**39** (53%) **42** (78%)	**40** (26%) **43** (66%/74%[c])

Reagents and conditions: GP 1: 50% NaOH-solution, 1-bromo-4-chlorobutane, DMSO; GP 2: NaI, acetone; GP 3: di-*tert*-butyl malonate, KO^{t}Bu, THF.

[a] Obtained by silylation with TBDPSCl of mixtures of **34** and **84** as well as **40** and **86**.

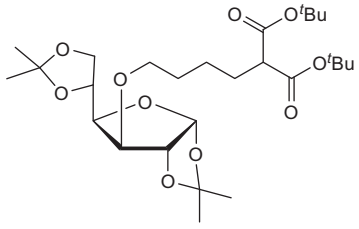
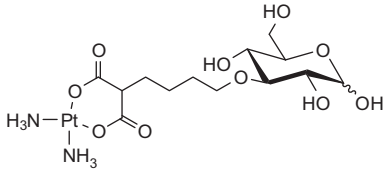
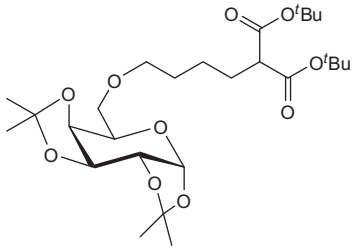
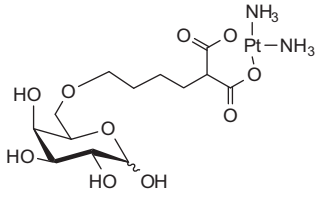
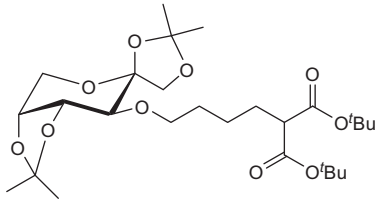
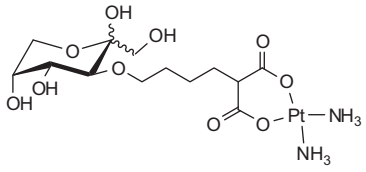
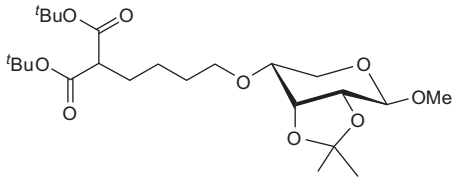
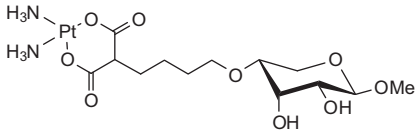
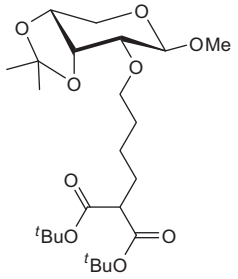
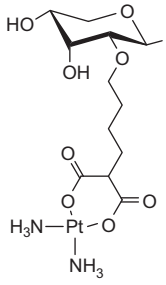
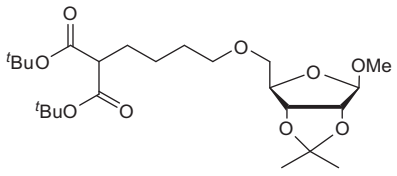
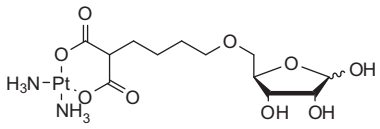
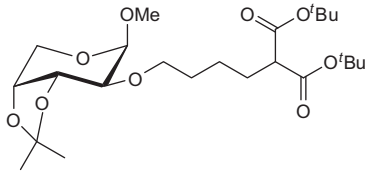
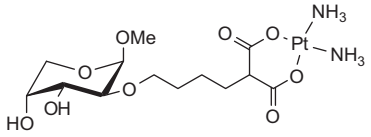
[b] Obtained as side product by synthesis of **83** and **85** following GP 1.

[c] Obtained by cleavage of the TBDPS-groups from **34** and **40**.



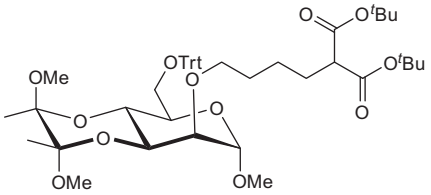
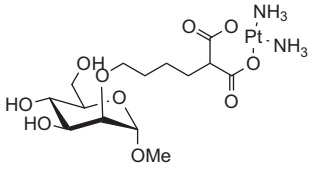
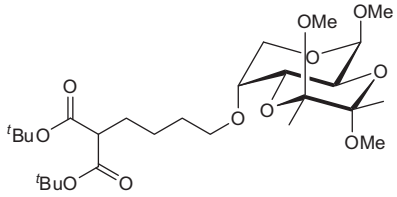
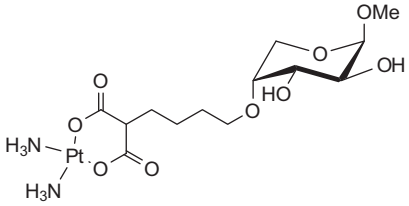
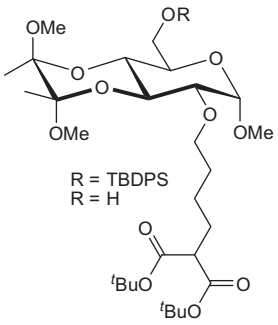
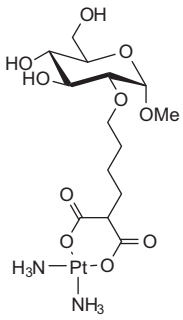
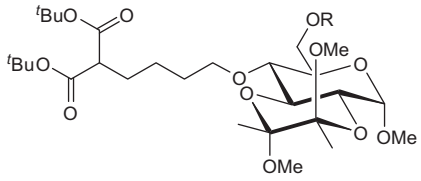
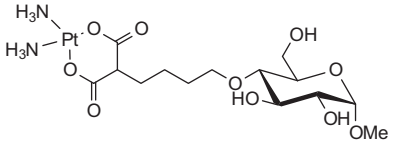
Scheme 2. Formation of monosaccharide-functionalized platinum complexes. Reagents and conditions: GP 4: CH_2Cl_2/TFA 3:1; GP 5: cisplatin, $AgNO_3$, H_2O.

Table 2
Formation of monosaccharide-functionalized platinum complexes

Protected sugar derivative	Reaction GP 4 No. (yield)	Reaction GP 5 No. (yield)	Platinum complex
	**44** (66%[16])	**45** (60%[16])	
	**46** (58%[16])	**47** (70%[16])	
	**48** (67%)	**49** (77%)	
	**50** (54%)	**51** (55%)	
	**52** (63%)	**53** (61%)	
	**54** (19%)	**55** (28%)	
	**56** (80%)	**57** (28%)	

(*continued on next page*)

Table 2 (*continued*)

Protected sugar derivative	Reaction GP 4 No. (yield)	Reaction GP 5 No. (yield)	Platinum complex
	**58** (54%)	**59** (62%)	
	**60** (44%)	**61** (42%)	
	**62** (94%)	**63** (59%)	
	**64** (83%)	**65** (80%)	

Reagents and conditions: GP 4: CH_2Cl_2/TFA 3:1; GP 5: cisplatin, $AgNO_3$, H_2O.

As a follow-up to this study, the stabilities of some of the novel glyco-functionalized complexes were examined by ^1H NMR spectroscopy. Selection for comparison to **2** was based on considerations for structural diversity as well as access to the required amount of material available. Thus, 3-substuituted glucopyranose derivative **45**, 6-substituted galacto isomer **47**, 5-substituted ribofuranose **55**, and 2-substituted mannopyranoside **59** were preliminary measured. Studies of glucofuranose, the lactose and the bis-glucopyranose complexes **71**, **77**, **93**, and **94** will be done in due course.

A favourable and facile analysis could be based on the large downfield shift of the protons of butyl spacer's CH_2 groups when the ligand is complexed to platinum. As depicted in Figure 2, especially the CH_2-4′ protons were shifted widely from 1.8 ppm with free ligand to 2.5 ppm in the complex (Scheme 6, Fig. 2). The decrease of the signal at 2.5 ppm is proportional to the decrease of the concentration of complex in solution (phosphate buffered solution, pH 7.08 in D_2O). For examinations the different complexes (**2**, **45**, **47**, **55** and **59**) were first dissolved in D_2O and lyophilized, and then a 9 mmol/L of complex in buffered solution (D_2O) was prepared. NMR-spectra were taken after several days over a period of about one month.

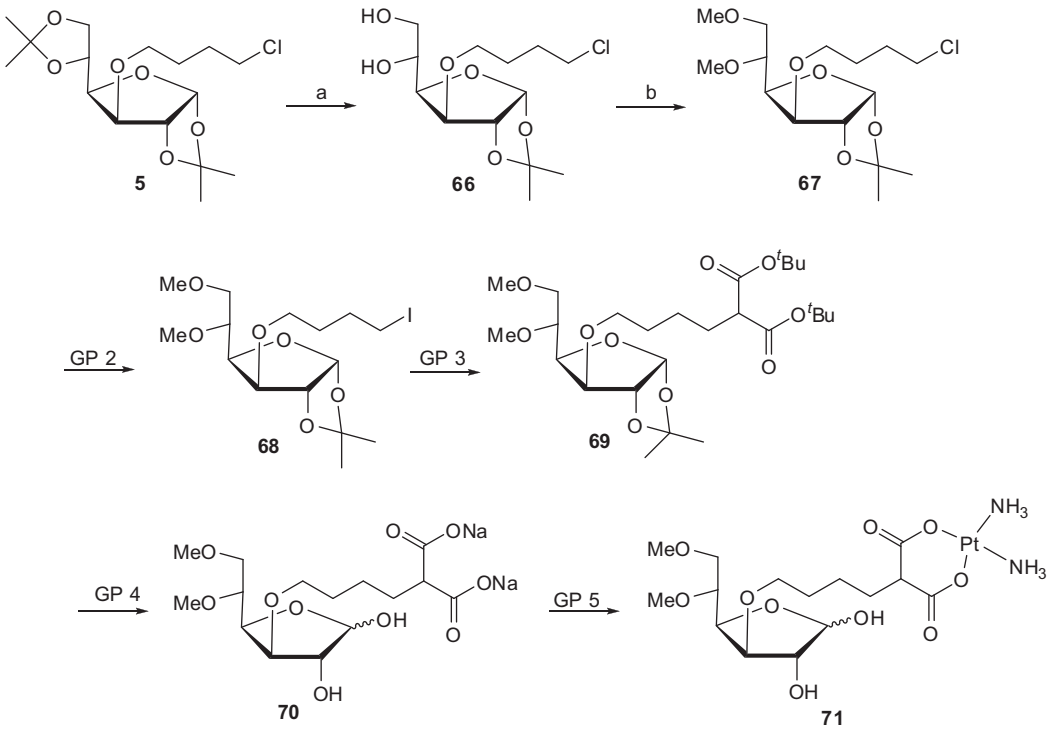
For analysis the decrease of the signal at 2.5 ppm was converted into concentration of the complex at the time the NMR spectra were taken. These values were plotted against the time (Fig. 3), and with assumption of a pseudo-first order reaction with a steady state at equilibrium the constant k_{obs} for different complexes was determined (Table 3).

As shown in Table 3 all determined rate constants of the substitution of the glyco-functionalized ligands are in the same range and comparable to k_{obs} for carboplatin measured by Frey et al.[20] Only k_{obs} for **55** showed that the ribofuranose ligand was substituted more slowly. Comparing the concentration of complex at equilibrium determined in this study with the concentration determined by Frey et al. shows that less complex is left using a 9 M solution instead of a 20 M solution of complex.

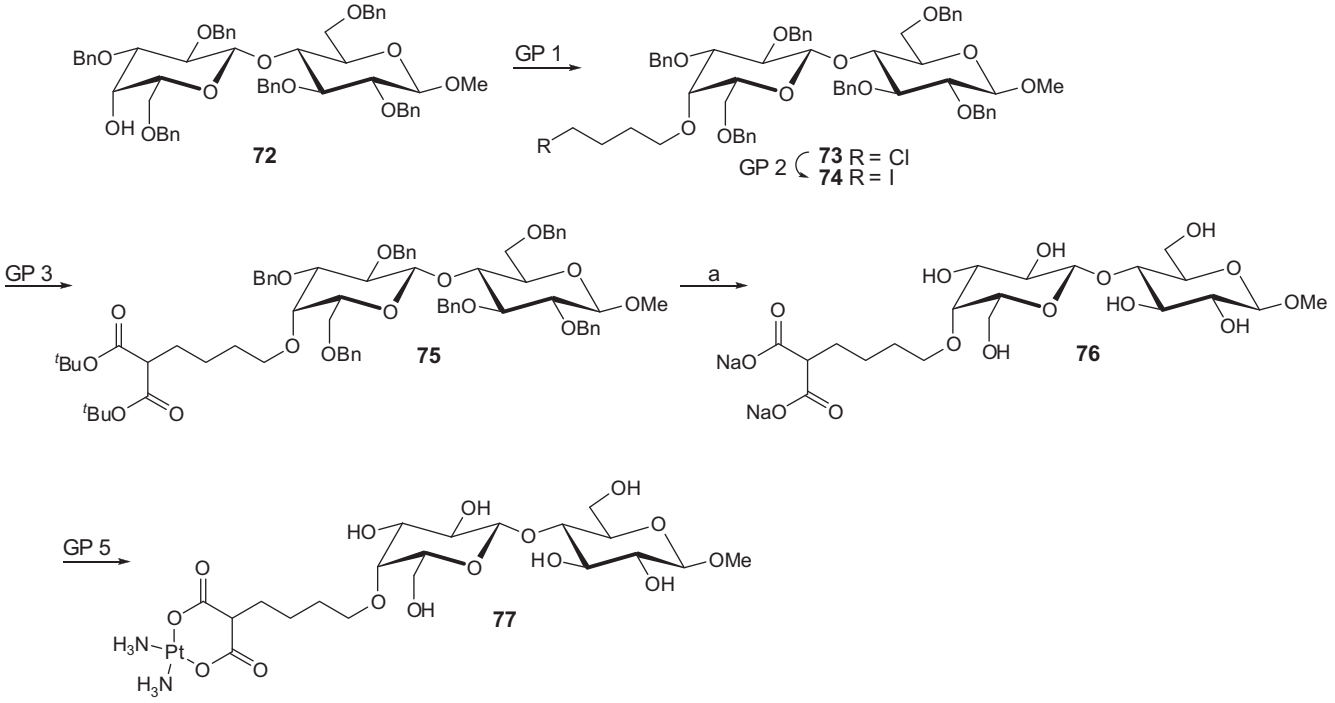
2.6. Conclusion

In this work carbohydrates were chosen as natural ligands for complexation with platinum. Following a facile route thirteen novel complexes could be generated. The method chosen consists of four steps:

1. Selective protection of the different carbohydrates,
2. Williamson's ether synthesis, Finkelstein reaction and substitution with malonate to connect carbohydrates with an ideal bidentate-chelating moiety,
3. Deprotection of carbohydrates and
4. Complexation of different ligands to platinum.



Scheme 3. Synthesis of dimethoxy glucofuranose platinum complex. Reagents and conditions: (a) 0.4% H_2SO_4, MeOH/H_2O 1:1; (b) MeI, 50% NaOH-solution, DMSO; GP 2: NaI, acetone; GP 3: di-*tert*-butyl malonate, KO^{t}Bu, THF; GP 4: CH_2Cl_2:TFA 3:1; GP 5: cisplatin, $AgNO_3$, H_2O.

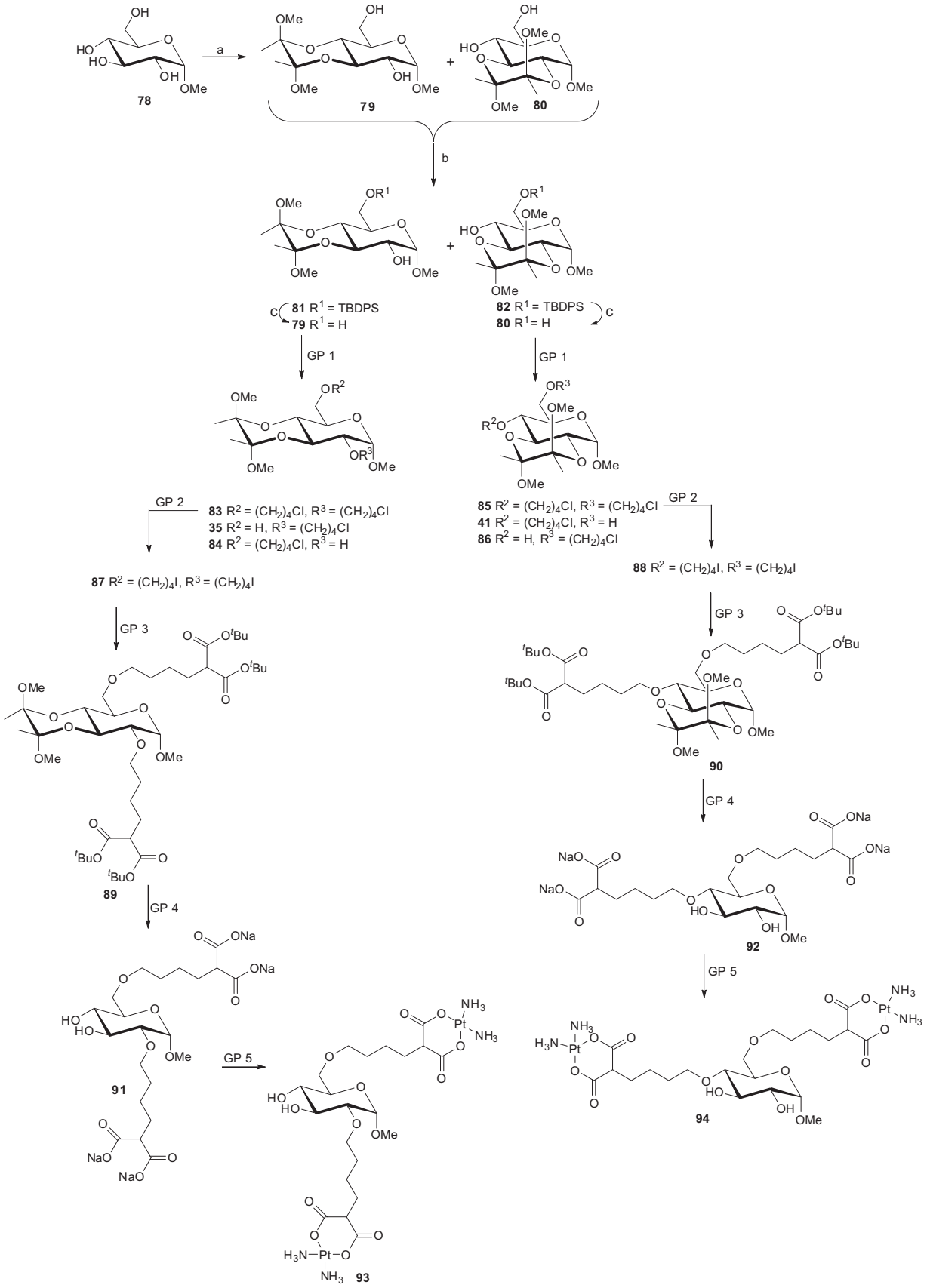


Scheme 4. Formation of lactoside platinum complex. Reagents and conditions: GP 1: 50% NaOH-solution, 1-bromo-4-chlorobutane, DMSO; GP 2: NaI, acetone; GP 3: di-*tert*-butyl malonate, KO^{t}Bu, THF; (a) H_2, C–Pd; GP 5: cisplatin, $AgNO_3$, H_2O.

All syntheses could be achieved in moderate to very good yields.

The stability of selected glyco-funtionalized platinum complexes (**45**, **47**, **55** and **59**) was measured in a PBS-buffer system. Employing NMR-spectroscopy the downfield shifts of the signals of the spacer protons were used to determine the decrease of the concentration of the glyco-functionalized complexes. It could be shown, that the *gluco*-ligand **45** was substituted the fastest with a rate constant of $k_{obs'} = 1.91 \times 10^{-6}$ 1/s.

Further, biological tests employing different tumour cell lines such as small-cell lung carcinoma (H526) and fibroblast of lung



Scheme 5. Construction of disubstituted glucopyranoside platinum complexes. Reagents and conditions: (a) butandione, CSA, trimethyl orthoformate, MeOH; (b) TBDPSCl, imidazole, THF; (c) TBAF, THF; GP 1: 50% NaOH-solution, 1-bromo-4-chlorobutane, DMSO; GP 2: NaI, acetone; GP 3: di-*tert*-butyl malonate, KO^{t}Bu, THF; GP 4: CH_2Cl_2/TFA 3:1; GP 5: cisplatin, $AgNO_3$, H_2O.

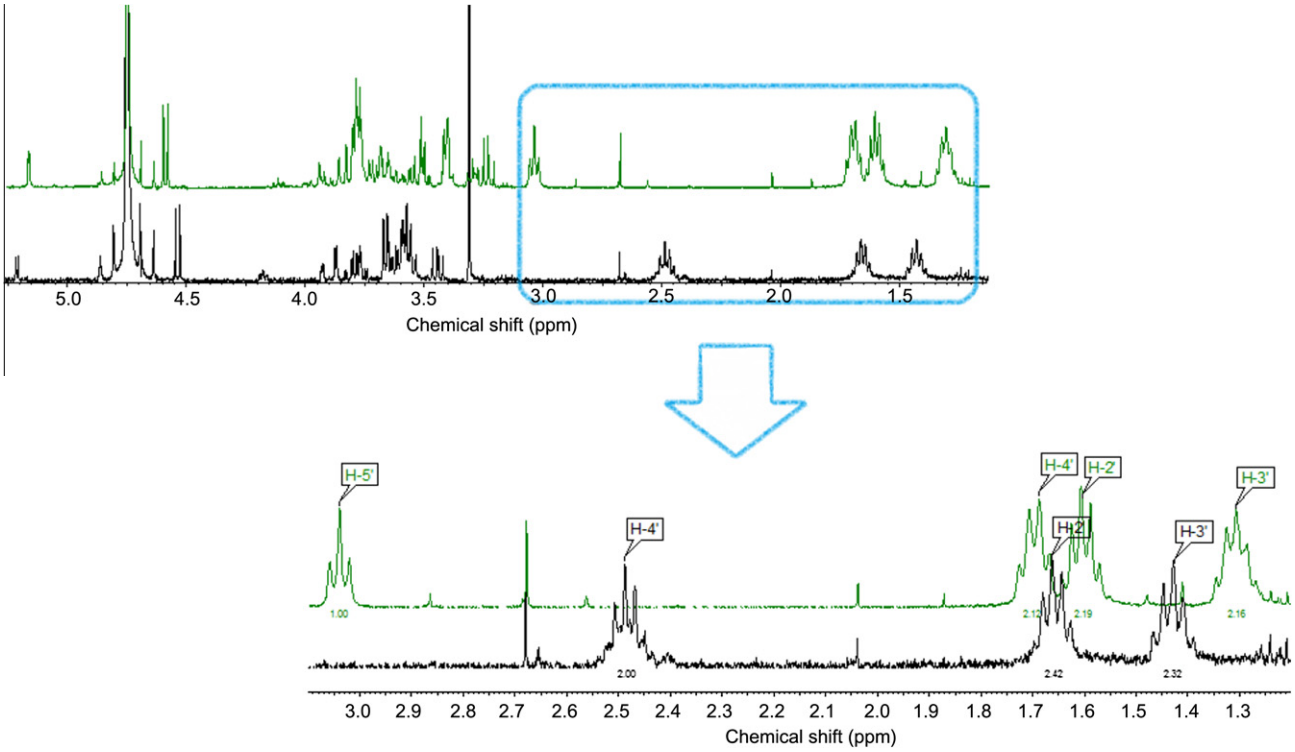
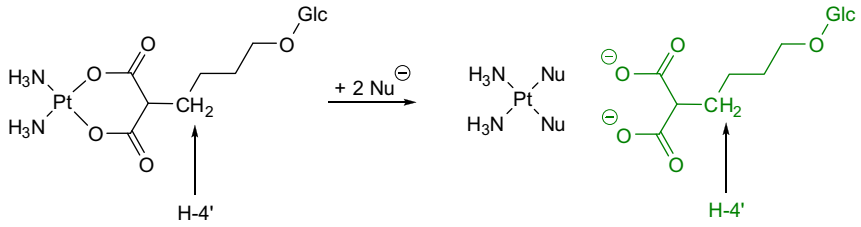


Figure 2. NMR survey of hydrolysis.



Scheme 6. Hydrolysis of saccharide-tethered platinum complexes.

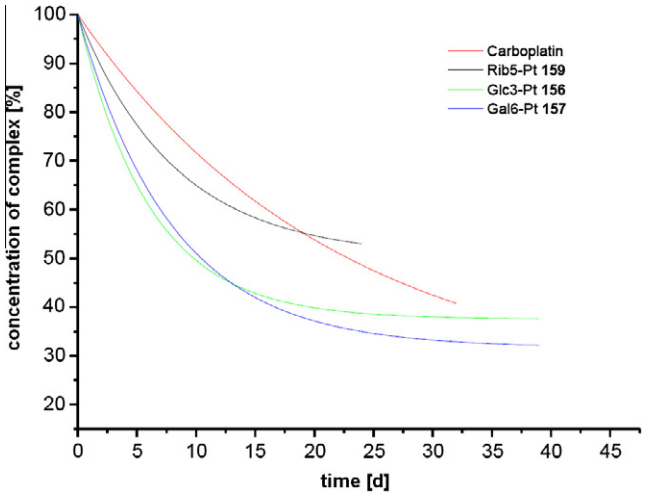


Figure 3. Plots for hydrolysis of saccharide-tethered platinum complexes.

Table 3
Hydrolysis constants of saccharide-tethered platinum complexes

Complex	k_{obs} (1/s)	$c_{equilibrium}$ (%)
Carboplatin (**2**)	1.41×10^{-6}	50
Glc3Pt **45**	1.91×10^{-6}	35
Gal6Pt **47**	1.46×10^{-6}	30
Rib5Pt **55**	5.30×10^{-7}	22
Man2Pt **59**[a]	1.40×10^{-6}	22

[a] Data not shown in Figure 3; only one series of measurements.

(MRC-5) to obtain the IC_{50} values of the novel glycol-platinum complexes in comparison to carboplatin (**2**) are under way and will be reported elsewhere.

3. Experimental

3.1. General methods

Commercially available starting materials were used without further purification. Solvents were dried according to standard methods. TLC was performed on precoated aluminium plates (Silica Gel 60 F_{254}, Merck 5554), and charring was with 10% H_2SO_4 in ethanol for visualization. For column chromatography Silica Gel 60,

230–400 mesh, 40–63 μm (Merck) was used. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AMX-400 (400 MHz for ^{1}H, 100.6 MHz for ^{13}C) and on Bruker DRX-500 (500 MHz for ^{1}H, 125.8 MHz for ^{13}C) at 300 K. Chemical shifts were calibrated to solvent residual peaks.[21] The signals were assigned by H,H-COSY, HSQC and HMBC experiments. Optical rotations were measured using a Krüss Optronic P8000 (589 nm) at 20 °C. MALDI-TOF-MS was performed on a Bruker Biflex III with dihydroxybenzoic acid as matrix in positive reflector mode. HRFAB-MS was performed on a VG 70S mass spectrometer in positive ion mode with a xenon FAB-gun and *m*-nitrobenzyl alcohol as matrix at 5000 resolution.

3.2. General procedures

3.2.1. GP 1

The selectively protected saccharide (1 equiv) was dissolved in DMSO and for each hydroxyl group 1.3 equiv 50% sodium hydroxide solution and 1.5 equiv 1-bromo-4-chlorobutane were added. The mixture was stirred at room temperature for 20 h. Distilled water 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 to give the product.

3.2.2. GP 2

Sodium iodide (1 equiv) was added to a solution of compound received from GP 1 (1 equiv) in acetone. The mixture was heated under reflux for 24 h. Filtration, evaporation of the solvent and column chromatography gave the product.

3.2.3. GP 3

Potassium *tert*-butoxide (1 equiv) was added under nitrogen to a solution of di-*tert*-butyl malonate (1.3 equiv) in anhydrous tetrahydrofuran. After consumption of potassium *tert*-butoxide at reflux, compound received from GP 2 was added (1 equiv) and the mixture was heated under reflux for 20–30 h. Tetrahydrofuran 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 with column chromatography to give the product.

3.2.4. GP 4

Compound received from GP 3 was solubilised in dichloromethane and trifluoroacetic acid (ratio 3:1), and the mixture was stirred at room temperature for several hours. 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.

3.2.5. GP 5

Cisplatin (1 equiv) and silver nitrate (2 equiv) were dissolved in bidistilled water and stirred at room temperature overnight. After filtration of the precipitated silver chloride, compound received from GP 4 (0.5 equiv) was added, and the mixture was stirred at room temperature for several hours. The water was removed under reduced pressure, and the product was purified on Biogel P2.

3.3. Syntheses

All novel prepared compounds are listed here with their rational names. If only the name is given the corresponding detailed experimental and analytical description with all physical and spectroscopic data are found in the Supplementary data.

3.3.1. 3-*O*-(4′-Chlorobutyl)-1,2:4,5-di-*O*-isopropylidene-α-D-fructopyranose (11)

3.3.2. 3-*O*-(4′-Iodobutyl)-1,2:4,5-di-*O*-isopropylidene-α-D-fructopyranose (12)

3.3.3. 3-*O*-(5′,5′-Di-*tert*-butoxycarbonylpentyl)-1,2:4,5-di-*O*-isopropylidene-α-D-fructopyranose (13)

3.3.4. Methyl 4-*O*-(4′-chlorobutyl)-2,3-*O*-isopropylidene-β-D-ribopyranoside (14)

3.3.5. Methyl 4-*O*-(4′-iodobutyl)-2,3-*O*-isopropylidene-β-D-ribopyranoside (15)

3.3.6. Methyl 4-*O*-(5′,5′-di-*tert*-butoxycarbonylpentyl)-2,3-*O*-isopropylidene-β-D-ribopyranoside (16)

3.3.7. Methyl 2-*O*-(4′-chlorobutyl)-3,4-*O*-isopropylidene-β-D-ribopyranoside (17)

3.3.8. Methyl 2-*O*-(5′,5′-di-*tert*-butoxycarbonylpentyl)-3,4-*O*-isopropylidene-β-D-ribopyranoside (19)

3.3.8.1. Methyl 2-O-(4′-iodobutyl)-3,4-O-isopropylidene-β-D-ribopyranoside (18)

3.3.8.2. Methyl 2-O-(5′,5′-di-tert-butoxycarbonylpentyl)-3,4-O-isopropylidene-β-D-ribopyranoside (19)

3.3.9. Methyl 5-*O*-(4′-chlorobutyl)-2,3-*O*-isopropylidene-β-D-ribofuranoside (20)

3.3.10. Methyl-5-*O*-(4′-iodobutyl)-2,3-*O*-isopropylidene-β-D-ribofuranoside (21)

3.3.11. Methyl 5-*O*-(5′,5′-di-*tert*-butoxycarbonylpentyl)-2,3-*O*-isopropylidene-β-D-ribofuranoside (22)

3.3.12. Methyl 2-*O*-(4′-chlorobutyl)-3,4-*O*-isopropylidene-β-D-arabinopyranoside (23)

3.3.13. Methyl 2-*O*-(4′-iodobutyl)-3,4-*O*-isopropylidene-β-D-arabinopyranoside (24)

3.3.14. Methyl 2-*O*-(5′,5′-di-*tert*-butoxycarbonylpentyl)-3,4-*O*-isopropylidene-β-D-arabinopyranoside (25)

3.3.15. (2′*S*,3′*S*)-Methyl 2-*O*-(4″-chlorobutyl)-3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyle)-6-*O*-trityl-α-D-mannopyranoside (26)

3.3.16. (2′*S*,3′*S*)-Methyl-2-*O*-(4″-iodobutyl)-3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyle)-6-*O*-trityl-α-D-mannopyranoside (27)

3.3.17. (2′*S*,3′*S*)-Methyl-2-*O*-(5″,5″-di-*tert*-butoxycarbonylpentyl)-3,4-*O*-(2′,3′-dimthox-ybutane-2′,3′-diyle)-6-*O*-trityl-α-D-mannopyranoside (28)

3.3.18. (2′*S*,3′*S*)-Methyl-4-*O*-(4″-chlorobutyl)-2,3-*O*-(2′,3′-dimethoxybutane-2′,3′-diyle)-β-D-arabinopyranoside (29)

3.3.19. (2′*S*,3′*S*)-Methyl-4-*O*-(4″-iodobutyl)-2,3-*O*-(2′,3′-dimethoxybutane-2′,3′-diyle)-β-D-arabinopyranoside (30)

3.3.20. Methyl-4-*O*-(5″,5″-di-*tert*-butoxycarbonylpentyl)-2,3-*O*-(2′,3′-dimethoxybutane-2′,3′-diyle)-β-D-arabinopyranoside (31)

3.3.21. (2′*S*,3′*S*)-Methyl-6-*O*-*tert*-butyldiphenylsilyl-2-*O*-(4″-chlorobutyl)-3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-α-D-glucopyranoside (32)

3.3.22. (2′*S*,3′*S*)-Methyl-6-*O*-*tert*-butyldiphenylsilyl-2-*O*-(4″-iodobutyl)-3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-α-D-glucopyranoside (33)

3.3.23. (2′*S*,3′*S*)-Methyl-6-*O*-*tert*-butyldiphenylsilyl-2-*O*-(5″,5″-di-*tert*-butoxycarbonyl-pentyl)-3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyle)-α-D-glucopyranoside (34)

3.3.24. (2′*S*,3′*S*)-Methyl-2-*O*-(4″-iodobutyl)-3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyle)-α-D-glucopyranoside (36)

3.3.25. (2′*S*,3′*S*)-Methyl-2-*O*-(5″,5″-di-*tert*-butoxycarbonylpentyl)-3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyle)-α-D-glucopyranoside (37)

3.3.26. (2′*R*,3′*R*)-Methyl-6-*O*-*tert*-butyldiphenylsilyl-4-*O*-(4″-chlorobutyl)-2,3-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-α-D-glucopyranoside (38)

3.3.27. (2′*R*,3′*R*)-Methyl-6-*O*-*tert*-butyldiphenylsilyl-4-*O*-(4″-iodobutyl)-2,3-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-α-D-glucopyranoside (39)

3.3.28. (2′*R*,3′*R*)-Methyl-6-*O*-*tert*-butyldiphenylsilyl-4-*O*-(5″,5″-di-*tert*-butoxycarbonyl-pentyl)-2,3-*O*-(2′,3′-dimethoxybutane-2′,3′-diyle)-α-D-glucopyranoside (40)

3.3.29. (2′*S*,3′*S*)-Methyl-2-*O*-(4″-iodobutyl)-3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyle)-α-D-glucopyranoside (42)

3.3.30. (2′*R*,3′*R*)-Methyl-4-*O*-(5″,5″-di-*tert*-butoxycarbonyl-pentyl)-2,3-*O*-(2′,3′-dimethox-ybutane-2′,3′-diyle)-α-D-glucopyranoside (43)

3.3.31. 3-*O*-(5′,5′-Disodium carboxypentyl)-D-fructose (48)

3.3.32. D-Fructose platinum complex (49)

Using GP 5 compound **48** (100 mg, 262 μmol) was reacted with cisplatin (175 mg, 583 μmmol) and silver nitrate (175 mg, 1.03 mmol) in water (6 mL) to give **49**; (110 mg, 77%); ^{1}H NMR (D_2O, 400 MHz): δ 3.04 (t, 1H, $J_{4',5'}$ 7.4 Hz, CCH-5′), 1.74–1.64 (m, 2H, CH_2-4′), 1.61–1.47 (m, 2H, CH_2-2′), 1.33–1.19 (m, 2H, CH_2-3′); ^{13}C NMR (D_2O, 100.6 MHz): δ 29.6 (C-2′), 28.8 (C-4′), 24.1 (C-3′); both pyranose forms and both furanose forms could be observed in the NMR thus assignment of signals was not possible and except for significant groups of the spacer HR-ESI-MS: *m/z* $[M+Na]^+$ found 588.1130, calcd 588.1133.

3.3.33. Methyl-4-*O*-(5′, 5′-disodium carboxypentyl)-β-D-ribopyranoside (50)

3.3.34. Methyl-β-D-ribopyranoside platinum complex I (51)

Following GP 5 compound **50** (50.0 mg, 136 μmol) was reacted with cisplatin (91.5 mg, 304 μmol) and silver nitrate (102 mg, 602 μmol) in water (12 mL) to give **51**; (41.3 mg, 55%); $[\alpha]_{546}^{20}$ −67.3 (*c* 0.2, H_2O); ^{1}H NMR (D_2O, 400 MHz): δ 4.67 (d, 1H, $J_{1,2}$ 5.4 Hz, H-1), 4.18 (dd, 1H, $J_{2,3}$ 3.5 Hz, $J_{3,4}$ 1.9 Hz, H-3), 3.85 (dd, 1H, $J_{4,5a}$ 3.8 Hz, $J_{5a,5b}$ 11.7 Hz, H-5a), 3.80 (dd, 1H, $J_{4,5b}$ 6.9 Hz, $J_{5a,5b}$ 11.7 Hz, H-5b), 3.75–3.59 (m, 4H, H-4, CH_2-1′, CCH-5′), 3.56 (dd, 1H, $J_{1,2}$ 5.4 Hz, $J_{2,3}$ 3.5 Hz, H-2), 3.49 (s, 3H, OMe), 2.58–2.41 (m, 2H, CH_2-4′), 1.76–1.66 (m, 2H, CH_2-2′), 1.54–1.45 (m, 2H, CH_2-3′); ^{13}C NMR (D_2O, 100.6 MHz): δ 167.2 (2 × C=O), 101.5 (C-1), 75.2 (C-4), 70.2 (C-2) 69.2 (C-1′), 66.7 (C-3), 65.3 (C-5′), 60.5 (C-5), 56.3 (OMe), 30.6 (C-2′), 28.4 (C-4′), 23.5 (C-3′). MALDI-TOF-MS: *m/z* = 550.1 $[M+H]^+$.

3.3.35. Methyl-2-*O*-(5′, 5′-disodium carboxypentyl)-β-D-ribopyranoside (52)

3.3.36. Methyl-β-D-ribopyranoside platinum complex II (53)

Compound **52** (18 mg, 50 μmol) was reacted with cisplatin (35 mg, 0.10 mmol) and silver nitrate (35 mg, 0.20 mmol) in water (2.4 mL) following GP 5 to give **53**; (17 mg, 61%); $[\alpha]_{546}^{20}$ −43.2 (*c* 0.1, H_2O); ^{1}H NMR (D_2O, 400 MHz): δ 4.68 (d, 1H, $J_{1,2}$ 5.9 Hz, H-1), 4.16 (dd, 1H, $J_{2,3}$ 3.2 Hz, $J_{3,4}$ 3.3 Hz, H-3), 3.89–3.83 (m, 2H, H-4, H-5a), 3.80–3.69 (m, 3H, CH_2-1′, H-5b), 3.75–3.59 (m, 2H, H-2, CCH-5′), 3.55 (s, 3H, OMe), 2.59–2.45 (m, 2H, CH_2-4′), 1.79–1.68 (m, 2H, CH_2-2′), 1.55–1.45 (m, 2H, CH_2-3′); ^{13}C NMR (D_2O, 100.6 MHz): δ 169.2 (2 × C=O), 100.5 (C-1), 76.2 (C-2), 69.1 (C-1′), 68.3 (C-4), 66.6 (C-3), 64.3 (C-5′), 60.2 (C-5), 56.3 (OMe), 30.6 (C-2′), 28.7 (C-4′), 23.6 (C-3′). MALDI-TOF: *m/z* 550.4 $[M+H]^+$.

3.3.37. 5-*O*-(5′, 5′-Disodium carboxylpentyl)-α/β-D-ribofuranose (54)

3.3.38. α/β-D-Ribofuranose platinum complex (55)

Using GP 5 compound **54** (100 mg, 273 μmol) was reacted with cisplatin (174 mg, 569 μmol) and silver nitrate (206 mg, 1.14 mmol) in water (7 mL) to give **55**; (42.7 mg, 28%); ^{1}H NMR (D_2O, 400 MHz): δ 5.29 (d, 1H, $J_{1,2}$ 3.9 Hz, H-1α), 4.13 (ddd, 1H, $J_{3,4}$ 8.0 Hz, $J_{4,5a}$ 3.0 Hz, $J_{4,5b}$ 5.1 Hz, H-4α), 4.05–3.96 (m, 2H, H-2α, H-3α), 3.63 (dd, 1H, $J_{4,5a}$ 3.0 Hz, $J_{5a,5b}$ 11.3 Hz, H-5αa), 3.60–3.50 (m, 4H, H-5αb, CH_2-1′, CCH-5′), 2.50–2.44 (m, 2H, CH_2-4′), 1.67–1.58 (m, 2H, CH_2-2′), 1.44–1.35 (m, 2H, CH_2-3′); ^{1}H NMR (D_2O, 400 MHz): δ 5.16 (d, 1H, $^3J_{1,2}$ 1.7 Hz, H-1β), 4.10 (dd, 1H, $^3J_{1,2}$ 1.7 Hz, $^3J_{2,3}$ 4.7 Hz, H-2β), 3.98 (ddd, 1H, $J_{3,4}$ 6.8 Hz, $J_{4,5a}$ 3.0, $J_{4,5b}$ 3.7 Hz, H-4β) 3.91 (dd, 1H, $J_{2,3}$ 4.7 Hz, $J_{3,4}$ 6.8 Hz, H-3β), 3.68 (dd, 1H, $J_{4,5a}$ 3.0 Hz, $J_{5a,5b}$ 11.3 Hz, H-5βa), 3.58–3.48 (m, 4H, H-5βb, CH_2-1′, CCH-5′), 2.50–2.44 (m, 2H, CH_2-4′), 1.67–1.58 (m, 2H, CH_2-2′), 1.44–1.35 (m, 2H, CH_2-3′); ^{13}C NMR (D_2O, 100.6 MHz): δ 162.3 (2 × C=O), 96.2 (C-1α), 81.5 (C-4α), 71.2 (C-5α), 70.8 (C-2α), 70.7 (C-3α), 70.0 (C-1′), 65.8 (C-5′), 30.6 (C-4′), 28.1 (C-2′), 23.5 (C-3′); ^{13}C NMR (D_2O, 100.6 MHz): δ 164.1 (2 × C=O), 101.1 (C-1β), 80.7 (C-4β), 75.0 (C-2β), 71.7 (C-5β), 71.1 (C-1′), 70.7 (C-3β), 65.8 (C-5′), 30.6 (C-4′), 28.1 (C-2′), 23.5 (C-3′). MALDI-TOF: *m/z* 535.9 $[M+H]^+$, 558.9 $[M+Na]^+$.

3.3.39. Methyl 2-*O*-(5′,5′-disodium carboxypentyl)-β-D-arabinopyranoside (56)

3.3.40. Methyl β-D-arabinopyranoside platinum complex I (57)

Following GP 5 compound **56** (100 mg, 50 μmol) was reacted with cisplatin (35 mg, 0.10 mmol) and silver nitrate (35 mg, 0.20 mmol) in water (2.4 mL) to give **57**; (7.5 mg, 28%), $[\alpha]_{546}^{20}$ −35.6 (*c* 0.1, H_2O); ^{1}H NMR (D_2O, 400 MHz): δ 4.99 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 3.96 (ddd, 1H, $J_{3,4}$ 2.5 Hz, $J_{4,5a}$ 3.4 Hz, $J_{4,5b}$ 6.3 Hz, H-4), 3.86–3.78 (m, 2H, H-3, H-5a), 3.71–3.49 (m, 5H, H-2, H-5b, CH_2-1′, CH-5′), 3.37 (s, 3H, OMe), 2.57–2.41 (m, 2H, CH_2-4′), 1.71–1.62 (m, 2H, CH_2-2′), 1.49–1.40 (m, 2H, CH_2-3′); ^{13}C NMR (D_2O, 100.6 MHz): δ 97.6 (C-1), 76.4 (C-2), 70.6 (C-1′), 68.8 (C-4), 68.0 (C-3), 65.5 (C-5), 57.8 (C-5′), 55.1 (OMe), 30.7 (C-4′), 28.7 (C-2′), 23.7 (C-3′); the carbonyl-C was not detected. MALDI-TOF: *m/z* 550.1 $[M+H]^+$.

3.3.41. Methyl 2-*O*-(5′, 5′-disodium carboxypentyl)-α-D-mannopyranoside (58)

3.3.42. Methyl α-D-mannopyranoside platinum complex (59)

Compound **58** (40 mg, 0.10 mmol) was reacted with cisplatin (70 mg, 0.20 mmol) and silver nitrate (70 mg, 0.40 mmol) in water (5 mL) following GP 5 to give **59**; (36 mg, 62%); $[\alpha]_{546}^{20}$ +35.3 (*c* 0.2, H_2O); ^{1}H NMR (D_2O, 400 MHz): δ 4.79 (d, 1H, $J_{1,2}$ 1.0 Hz, H-1), 3.90 (dd, 1H, $J_{5,6a}$ 1.6 Hz, $J_{6a,6b}$ 12.8 Hz, H-6a), 3.80 (dd, 1H, $J_{2,3}$ 3.5 Hz, $J_{3,4}$ 9.1 Hz, H-3), 3.76 (dd, 1H, $J_{5,6b}$ 5.8 Hz, $J_{6a,6b}$ 12.8 Hz, H-6b), 3.73–3.67 (m, 3H, H-2, CH_2-1′), 3.66–3.57 (m, 3H, H-4, H-5, CH-5′), 3.42 (s, 3H, OMe), 2.59–2.48 (m, 2H, CH_2-4′), 1.78–1.66 (m, 2H, CH_2-2′), 1.53–1.43 (m, 2H, CH_2-3′); ^{13}C NMR (D_2O, 100.6 MHz): δ 98.4 (C-1), 78.1 (C-2), 72.6 (C-5), 71.5 (C-1′), 70.4 (C-3), 67.0 (C-4), 60.8 (C-6), 57.9 (C-5′), 54.7 (OCH_3), 30.4 (C-4′), 28.6 (C-2′), 23.5 (C-3′). Carbonyl-C was not detected. MALDI-TOF: *m/z* 580.4 $[M+H]^+$.

3.3.43. Methyl 4-*O*-(5′, 5′-disodium carboxypentyl)-β-D-arabinopyranoside (60)

3.3.44. Methyl β-D-arabinopyranoside platinum complex II (61)

Using GP 5 compound **60** (19 mg, 50 μmol) was reacted with cisplatin (35 mg, 0.10 mmol) and silver nitrate (35 mg, 0.20 mmol) in water (2.4 mL) to give **61**; (11 mg, 42%); $[\alpha]_{546}^{20}$ −89.2 (*c* 0.1, H_2O); ^{1}H

NMR (D_2O, 400 MHz): δ 4.80 (d, 1H, $J_{1,2}$ 3.4 Hz, H-1), 3.87–3.79 (m, 3H, H-2, H-5a/b), 3.37–3.66 (m, 3H, CH_2-1′a, H-3, H-4), 3.62–3.56 (m, 2H, CH_2-1′b, CH-5′), 3.38 (s, 3H, OMe), 2.56–2.47 (m, 2H, CH_2-4′), 1.75–1.65 (m, 2H, CH_2-2′), 1.52–1.42 (m, 2H, CH_2-3′); ^{13}C NMR (D_2O, 100.6 MHz): δ 200.1 (2 × C=O), 99.8 (C-1), 77.1 (C-3), 70.1 (C-1′), 68.8, 68.6 (C-2, C-4), 59.6 (C-5), 57.9 (C-5′), 55.3 (OMe), 30.7 (C-4′), 28.5 (C-2′), 23.6 (C-3′). MALDI-TOF: *m/z* 550.2 $[M+H]^+$.

3.3.45. Methyl 2-*O*-(5′, 5′-disodium carboxypentyl)-α-D-glucopyranoside (62)

3.3.46. Methyl α-D-glucopyranoside platinum complex I (63)

Compound **62** (20 mg, 50 μmol) was reacted with cisplatin (35 mg, 0.10 mmol) and silver nitrate (35 mg, 0.20 mmol) in water (2.4 mL) to give **63** following GP 5. $[\alpha]_{546}^{20}$ −12.2 (*c* 0.1, H_2O); ^{1}H NMR (D_2O, 400 MHz): δ; 4.96 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 3.82 (dd, 1H, $J_{5,6a}$ 2.2 Hz, $J_{6a,6b}$ 12.3 Hz, H-6a), 3.71 (dd, 1H, $J_{5,6b}$ 5.5 Hz, $J_{6a,6b}$ 12.3 Hz, H-6b), 3.70–3.59 (m, 5H, H-3, H-5, CH_2-1′a/b, CH-5′), 3.42–3.35 (m, 4H, H-4, OMe), 3.30 (dd, 1H, $J_{1,2}$ 3.6 Hz, $J_{2,3}$ 9.8 Hz, H-2), 2.58–2.50 (m, 2H, CH_2-4′), 1.75–1.65 (m, 2H, CH_2-2′), 1.52–1.42 (m, 2H, CH_2-3′); ^{13}C NMR (D_2O, 100.6 MHz): δ 194.0 (2 × C=O), 97.8 (C-1), 79.8 (C-2), 73.4 (C-3), 71.9 (C-5), 72.4 (C-1′), 69.4 (C-4), 60.8 (C-6), 59.2 (C-5′), 55.0 (OMe), 30.9 (C-4′), 29.7 (C-2′), 26.0 (C-3′). MALDI-TOF: *m/z* 579.9 $[M+H]^+$, 602.5 $[M+Na]^+$.

3.3.47. Methyl 4-*O*-(5′, 5′-disodium carboxypentyl)-α-D-glucopyranoside (64)

3.3.48. Methyl α-D-glucopyranoside platinum complex II (65)

Compound **64** (20 mg, 50 μmol) was reacted with cisplatin (35 mg, 0.10 mmol) and silver nitrate (35 mg, 0.20 mmol) in water (2.4 mL) to give **65** following GP 5. $[\alpha]_{546}^{20}$ +83.2 (*c* 1.2, H_2O); ^{1}H NMR (D_2O, 400 MHz): δ 4.87 (d, 1H, $J_{1,2}$ 3.7 Hz, H-1), 3.94–3.83 (m, 2H, H-6a, CH_2-1′a), 3.85–3.75 (m, 2H, H-6b, H-3), 3.73–3.63 (m, 3H, H-5, CH_2-1′b, CH-5′), 3.63 (dd, 1H, $J_{1,2}$ 3.7 Hz, $J_{2,3}$ 9.4 Hz, H-2), 3.50 (s, 3H, OMe), 3.34 (dd, 1H, $J_{3,4}$ 9.3 Hz, $J_{4,5}$ 9.3 Hz, H-4), 2.50–2.43 (m, 2H, CH_2-4′), 1.76–1.65 (m, 2H, CH_2-2′), 1.54–1.44 (m, 2H, CH_2-3′); ^{13}C NMR (D_2O, 100.6 MHz): δ 199.2 (2 × C=O), 99.8 (C-1), 77.6 (C-4), 73.4 (C-3), 73.9 (C-1′), 71.9 (C-2), 71.4 (C-5), 60.6 (C-6), 58.2 (C-5′), 54.9 (OMe), 30.9 (C-4′), 29.8 (C-2′), 25.7 (C-3′); MALDI-TOF: *m/z* 580.3 $[M+H]^+$.

3.3.49. 3-*O*-(4′-Chlorobutyl)-1,2-*O*-isopropylidene-β-D-glucofuranose (66)

3.3.50. 3-*O*-(4′-Chlorobutyl)-1,2-*O*-isopropylidene-5, 6-di-*O*-methyl-β-D-glucofuranose (67)

3.3.51. 3-*O*-(4′-Iodobutyl)-1,2-*O*-isopropylidene-5,6-di-O-methyl-β-D-glucofuranose (68)

3.3.52. 3-*O*-(5′,5′-Di-*tert*-butoxycarbonylpentyl)-1,2-*O*-isopropylidene-5,6-di-*O*-methyl-β-D-glucofuranose (69)

3.3.53. 5,6-Di-*O*-methyl-4-*O*-(5′,5′-disodium carboxypentyl)-α/β-D-glucopyranose (70)

3.3.54. 5,6-Di-*O*-methyl-α/β-D-glucofuranose platinum complex (71)

Using GP 5 compound **70** (37 mg, 0.10 mmol) was reacted with cisplatin (70 mg, 0.20 mmol) and silver nitrate (70 mg, 0.40 mmol) in water (4.8 mL) to give **71**; (22 mg, 37 μmol); ^{1}H NMR (D_2O, 400 MHz): δ 5.50 (d, 1H, $J_{1\alpha,2\alpha}$ 4.1 Hz, H-1α), 5.36 (s, 1H, H-1β), 4.24–4.20 (m, 1H, H-2α/β), 3.92–3.81 (m, 2H, H-3β, H-6βa), 3.82–3.70 (m, 5H, H-4α, H-5β, H-6βb, CH_2-1′α/βa), 3.68–3.50 (m, 9H, H-3α, H-4β, H-5α, H-6αa/b, CH_2-1′α/βb, CH-5′α/β), 3.46, 3.40 (2 × s, 4 × 3H, 2 × OMe α/β), 2.49–2.41 (m, 2H, CH_2-4′α/β), 1.77–1.70 (m, 4H, CH_2-2′α/β), 1.46–1.35 (m, 4H, CH_2-3′α/β); ^{13}C NMR (D_2O, 100.6 MHz): δ 172.7 (4 × C=O), 102.5 (C-1β), 96.9 (C-1α), 83.5 (C-4α), 82.4 (C-2β), 78.5 (C-4β), 77.4 (C-3α), 77.3 (C-5α), 77.2 (C-5β), 76.1 (C-3β), 73.3 (C-2α), 70.4 (C-6α), 70.5 (C-1′α/β), 70.1 (C-6β), 57.7 (CH-5′α/β), 57.4, 57,2 (4 × OMe α/β), 30.9 (C-4′α/β), 28.5 (C-2′α/β), 26.1 (C-3′α/β). MALDI-TOF: *m/z* 383.1 $[M+H]^+$.

3.3.55. Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2′,3′,6′-tri-*O*-benzyl-4′-*O*-(4″-chlorobutyl)-β-D-galactopyranosyl)-β-D-glucopyranoside (73)

3.3.56. Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2′,3′,6′-tri-*O*-benzyl-4′-*O*-(4″-iodobutyl)-β-D-galactopyranosyl)-β-D-glucopyranoside (74)

3.3.57. Methyl-2,3,6-tri-*O*-benzyl-4-*O*-(2′,3′,6′-tri-*O*-benzyl-4′-*O*-(5″,5″-di-*tert*-butoxy-carbonylpentyl)-β-D-galactopyranosyl)-β-D-glucopyranoside (75)

3.3.58. Methyl 3-*O*-(4′-*O*-(5″,5″-disodium carboxypentyl)-β-D-galactopyranosyl)-β-D-glucopyranoside (76)

3.3.59. Methyl β-D-lactoside platinum complex (77)

Following GP 5 compound **76** (28 mg, 50 μmol) was reacted with cisplatin (35 mg, 0.10 mmol) and silver nitrate (35 mg, 0.20 mmol) in water (2.4 mL) to give 77; (17 mg, 70%); $[\alpha]_{546}^{20}$ −10.0 (*c* 0.4, H_2O); ^{1}H NMR (H_2O, 400 MHz): δ 4.32 (d, 1H, $J_{1,2}$ 7.6 Hz, H-1), 4.16 (d, 1H, $J_{1',2'}$ 7.8 Hz, H-1′), 3.92–3.85 (m, 2H, H-6′a, CH_2-1″a), 3.81 (dd, 1H, $J_{5',6'b}$ 2.3 Hz, $J_{6'a,6'b}$ 12.1 Hz, H-6′b), 3.78–3.62 (m, 3H, H-4, H-6a, CH_2-1″b), 3.65 (dd, 1H, $J_{5,6b}$ 4.6 Hz, $J_{6a,6b}$ 11.5 Hz, H-6b), 3.55–3. 52 (m, 2H, H-4′, H-5), 3.50 (dd, 1H, $J_{1,2}$ 7.6 Hz, $J_{2,3}$ 9.7 Hz, H-2), 3.49–3.46 (m, 4H, H-3′, OMe), 3.44–3.34 (m, 3H, H-3, H-5′, CH-5″), 3.18 (dd, 1H, $J_{1',2'}$ 7.8 Hz, $J_{2',3'}$ 8.2 Hz, H-2′), 2.52–2.45 (m, 2H, CH_2-4″), 1.83–1.74 (m, 2H, CH_2-2″), 1.46–1.40 (m, 2H, CH_2-3″); ^{13}C NMR (H_2O, 100.6 MHz): δ 180.3 (2 × C=O), 104.3 (C-1′), 105.2 (C-1), 80.7 (C-4′), 77.1 (C-5), 76.5 (C-5′), 76.5 (C-3′), 74.9 (C-3), 74.8 (C-2′), 72.6 (C-2), 70.4 (C-4), 64.2 (C-1″), 62.5 (C-6), 61.9 (C-6′), 56.4 (OMe), 54.1 (C-5″), 30.8 (C-4″), 29.3 (C-2″), 25.3 (C-3″).

3.3.60. (2′*S*,3′*S*)-Methyl 3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyle)-α-D-glucopyranoside (79)

Compound **81**[19] (3.61 g, 6.60 mmol) was reacted with 1 M tetrabutyl ammonium fluoride solution in anhydrous THF (13 mL) at room temperature for 20 h. The solvent was removed to give **79** after column chromatography (CH_2Cl_2/MeOH 9:1); (1.99 g, 98%); mp 157.0 °C; $[\alpha]_{546}^{20}$ +258.5° (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.80 (d, 1H, $J_{1,2}$ 3.8 Hz, H-1), 3.93 (dd, 1H, $J_{2,3}$ 10.2 Hz, $J_{3,4}$ 9.2 Hz, H-3), 3.82 (dd, 1H, $J_{5,6a}$ 8.9 Hz, $J_{6a,6b}$ 13.2 Hz, H-6a), 3.79–3.64 (m, 4H, H-2, H-4, H-5, H-6b), 3.43 (s, 3H, OMe at C-1), 3.31, 3.26 (2 × s, 2 × 3H, 2 × OMe), 1.34, 1.30 (2 × s, 2 × 3H, 2 × CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 100.3, 99.9 (2 × *C*(OMe)CH_3), 99.6 (C-1), 70.2 (C-3), 70.0, 69.7 (C-2, C-4), 66.0 (C-5), 61.3 (C-6), 55.3 (OMe at C-1), 48.0, 47.9 (2 × OMe), 17.7, 17.6 (2 × CH_3). ESI-HRMS(+): *m/z* found 331.1365, calcd $[M+Na]^+$ 331.1363.

3.3.61. (2′*R*,3′*R*)-Methyl 2,3-*O*-(2′, 3′-dimethoxybutane-2′,3′-diyle)-α-D-glucopyranoside (80)

3.3.62. (2′*S*,3′*S*)-Methyl 6-*O*-*tert*-butyldiphenylsilyl-3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyle)-α-D-glucopyranoside (81) and (2′*R*,3′*R*)-Methyl 6-*O*-*tert*-butyldiphenylsilyl-2,3-*O*-(2′,3′-dimethoxybutane-2′,3′-diyle)-α-D-glucopyranoside (82)

A mixture of compounds **79** and **80**[22] (6.867 g, 22.28 mmol) was reacted with imidazole (2.725 g; 40.02 mmol) and *tert*-butyldiphenyl chlorosilane (5.6 mL, 22 mmol) at room temperature for 48 h. After filtration and evaporation of the solvent, **81** and **82** were ob-

tained after column chromatography (petroleum ether/ethyl acetate 2:1); (**81**: 4.334 g, 37%); (**82**: 5.532, 47%); **81**: mp 63.7 °C; $[\alpha]_{546}^{20}$ +140 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72–7.70 (m, 4H, *o-Ph*), 7.43–7.34 (m, 6H, *p,m-Ph*), 4.80 (d, 1H, $J_{1,2}$ 4.0 Hz, H-1), 3.93 (dd, 1H, $J_{2,3}$ 10.2 Hz, $J_{3,4}$ 9.2 Hz; H-3), 3.92–3.86 (m, 2H, H-6a/b), 3.80–3.68 (m, 3H, H-2, H-4, H-5), 3.40 (s, 3H, OMe at C-1), 3.31, 3.19 (2 × s, 2 × 3H, 2 × OMe), 1.34, 1.28 (2 × s, 2 × 3H, 2 × CH_3), 1.04 (s, 9H, ^{t}Bu); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 135.9, 135.6 (4 × *o-Ph*), 133.0 (2 × q. *Ph*), 129.8, 127.7 (6 × *p,m-Ph*), 99.9, 99.5 (2 × *C*(OMe)CH_3), 97.9 (C-1), 71.3 (C-2), 70.0 (C-4), 69.3 (C-3), 68.2 (C-5), 64.7 (C-6), 54.9 (OMe at C-1), 48.0, 47.8 (2 × OMe), 26.8 (C(*C*H_3)$_3$), 19.2 (*C*(CH_3)$_3$), 17.8, 17.7 (2 × CH_3). MALDI-TOF: *m/z* 568.1 $[M+Na]^+$, 584.0 $[M+K]^+$. Compound **82**: mp 65.0 °C; $[\alpha]_{546}^{20}$ −41.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72–7.68 (m, 4H, *o-Ph*), 7.45–7.37 (m, 6H, *p,m-Ph*), 4.72 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 4.05 (dd, 1H, $J_{2,3}$ 10.2 Hz, $^3J_{3,4}$ 9.3 Hz, H-3), 3.91–3.85 (m, 2H, H-6a/b), 3.79 (dd, 1H, $J_{3,4}$ 9.3 Hz, $^3J_{4,5}$ 1.8 Hz, H-4), 3.75–3.68 (m, 2H, H-2, H-5), 3.38 (s, 3H, OMe at C-1), 3.31, 3.27 (2 × s, 2 × 3H, 2 × OMe), 1.36, 1.33 (2 × s, 2 × 3H, 2 × CH_3), 1.06 (s, 9H, ^{t}Bu); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 135.6 (4 × *o-Ph*), 133.0 (2 × q-*Ph*), 129.8, 127.7 (6 × *p,m-Ph*), 99.9, 99.5 (2 × *C*(OCH_3)CH_3), 97.9 (C-1), 71.3 (C-2), 70.0 (C-4), 69.3 (C-3), 68.2 (C-5), 64.7 (C-6), 54.9 (OMe at C-1), 48.0, 47.8 (2 × OMe), 26.8 (C(*C*H_3)$_3$), 19.2 (*C*(CH_3)$_3$), 17.8, 17.7 (2 × CH_3); MALDI-TOF: *m/z* 568.1 $[M+Na]^+$, 584.1 $[M+K]^+$.

3.3.63. (2′*S*,3′*S*)-Methyl 2,6-di-*O*-(4″-chlorobutyl)-3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyle)-α-D-glucopyranoside (83)

Following GP 1 compound **79** (1.440 g, 4.669 mmol) was reacted with 50% sodium hydroxide solution (410 μL; 15.5 mmol) and 1-bromo-4-chlorobutane (1.6 mL; 14 mmol) in DMSO (12 mL) to give **83** after purification (petroleum ether/ethyl acetate 2:1); (987 mg, 43%). Additionally **35** and **84** were obtained (518 mg, 28%); **79**: $[\alpha]_{546}^{20}$ +156 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.81 (d, 1H, $J_{1,2}$ 3.8 Hz, H-1), 4.06 (dd, 1H, $J_{2,3}$ 10.2 Hz, $J_{3,4}$ 9.2 Hz, H-3), 3.82 (dd, 1H, $J_{5,6a}$ 2.9 Hz, $J_{6a,6b}$ 13.2 Hz, H-6a), 3.72–3.44 (m, 12H, H-2, H-4, H-5, H-6b, 2 × CH_2-1″, 2 × CH_2-4″), 3.39 (s, 3H, OMe at C-1), 3.29, 3.26 (2 × s, 2 × 3H, 2 × OMe), 1.90–1.81 (m, 4H, 2 × CH_2-3″), 1.76–1.70 (m, 4H, 2 × CH_2-2″), 1.31, 1.30 (2 × s, 2 × 3H, 2 × CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 99.6, 99.5 (2 × *C*(OMe)CH_3), 98.6 (C-1), 77.4 (C-2), 70.9, 70.8 (2 × C-1″), 69.5 (C-4), 68.8 (C-6), 68.7 (C-3), 66.3 (C-5), 55.0 (OMe at C-1), 48.0, 47.9 (2 × OMe), 44.9, 44.8 (2 × C-4″), 29.5, 29.4 (2 × C-3″), 27.2, 27.1 (2 × C-2″), 17.8, 17.7 (2 × CH_3). MALDI-TOF: *m/z* 511.2 $[M+Na]^+$, 527.2 $[M+K]^+$. Compound **35**: mp 106.3 °C, $[\alpha]_{546}^{20}$ +197 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.79 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 4.08 (dd, 1H, $J_{2,3}$ 9.8 Hz, $^3J_{3,4}$ 9.8 Hz, H-3), 3.82 (dd, 1H, $J_{5,6a}$ 2.9 Hz, $J_{6a,6b}$ 11.7 Hz, H-6a), 3.79–3.66 (m, 5H, H-4, H-5, H-6b, CH_2-1″a/b), 3.58 (t, 2H, $J_{3'',4''}$ 6.7 Hz, CH_2-4″), 3.44 (dd, 1H, $^3J_{1,2}$ 3.5 Hz, $^3J_{2,3}$ 9.8 Hz, H-2), 3.40 (s, 3H, OMe at C-1), 3.29, 3.27 (2 × s, 2 × 3H, 2 × OMe), 1.93–1.83 (m, 2H, CH_2-3″), 1.78–1.68 (m, 2H, CH_2-2″), 1.31, 1.30 (2 × s, 2 × 3H, 2 × CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 99.6, 99.5 (2 × *C*(OMe)CH_3), 98.6 (C-1), 77.5 (C-2), 71.0 (C-1″), 69.3 (C-5), 69.1 (C-3), 66.5 (C-4), 61.3 (C-6), 55.1 (OMe at C-1), 48.0, 47.9 (2 × OMe), 44.8 (C-4″), 29.4 (C-3″), 27.2 (2 × C-2″), 17.8, 17.6 (2 × CH_3). MALDI-TOF: *m/z* 421.1 $[M+Na]^+$, 437.1 $[M+K]^+$.

3.3.64. (2′*R*,3′*R*)-Methyl 4, 6-di-*O*-(4″-chlorobutyl)-2, 3-*O*-(2′,3′-dimethoxybutane-2′,3′-diyle)-α-D-glucopyranoside (85)

3.3.65. (2′*S*,3′*S*)-Methyl-2,6-di-*O*-(4″-iodobutyl)-3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyle)-α-D-glucopyranoside (87)

Compound **83** (473 mg, 966 μmol) was reacted with sodium iodide (290 mg, 1.93 mmol) in acetone (10 mL) to give **87** as syrup following GP 2 after column chromatography (petroleum ether/ethyl acetate 9:1); (469 mg, 77%); $[\alpha]_{546}^{20}$ +124° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.81 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 4.06 (dd, 1H, $J_{2,3}$ 10.1 Hz, $J_{3,4}$ 9.8 Hz, H-3), 3.82 (dd, 1H, $J_{5,6a}$ 8.9 Hz, $J_{6a,6b}$ 13.2 Hz, H-6a), 3.72–3.43 (m, 12H, H-2, H-4, H-5, H-6b, 2 × CH_2-1″, 2 × CH_2-4″), 3.30 (s, 3H, OMe at C-1), 3.29, 3.25 (2 × s, 2 × 3H, 2 × OMe), 1.96–1.80 (m, 4H, 2 × CH_2-3″), 1.76–1.65 (m, 4H, 2 × CH_2-2″), 1.31, 1.29 (2 × s, 2 × 3H, 2 × CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 99.6, 99.5 (2 × *C*(OMe)CH_3), 98.5 (C-1), 77.3 (C-2), 70.9, 70.8 (2 × C-1″), 69.5 (C-4), 68.7 (C-6), 68.6 (C-3), 66.2 (C-5), 55.0 (OMe at C-1), 48.0, 47.9 (2 × OMe), 29.5, 29.4 (2 × C-3″), 27.2, 27.1 (2 × C-2″), 17.8, 17.7 (2 × CH_3), 6.7 (2 × C-4″). MALDI-TOF: *m/z* 695.1 $[M+Na]^+$, 711.2 $[M+Na]^+$.

3.3.66. (2′*R*,3′*R*)-Methyl 4,6-di-*O*-(4″-iodobutyl)-2,3-*O*-(2′,3′-dimethoxybutane-2′,3′-diyle)-α-D-glucopyranoside (88)

3.3.67. (2′*S*,3′*S*)-Methyl 2,6-di-*O*-(5″,5″di-*tert*-butoxycarbonylpentyl)-3, 4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyle)-α-D-glucopyranoside (89)

Following GP 3 compound **87** (871 mg, 1.39 mmol) was reacted with a solution of di-*tert*-butyl malonate (730 μL, 700 mg, 3.25 mmol) and potassium *tert*-butoxide (292 mg, 2.60 mmol) in THF (25 mL) to give **89** as syrup after purification (petroleum ether/ethyl acetate 9:1); (703 mg, 60%); $[\alpha]_{546}^{20}$ +95.8 (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.72 (d, 1H, $J_{1,2}$ 3.4 Hz, H-1), 4.06 (dd, 1H, $J_{2,3}$ 10.8 Hz, $J_{3,4}$ 9.6 Hz, H-3), 3.89 (m, 1H, H -1″a), 3.73 (dd, 1H, $J_{1,2}$ 3.4 Hz, $J_{2,3}$ 10.8 Hz, H-2), 3.65–3.57 (m, 3H, H-5, H-6a/b), 3.57–3.39 (m, 4H, H -1″b/c/d, H-4), 3.38 (s, 3H, OMe at C-1), 3.29 3.24 (2 × s, 2 × 3H, 2 × OMe), 3.14–3.06 (m, 2H, 2 × CH-5″), 1.85–1.77 (m, 4H, 2 × CH_2-4″), 1.66–1.52 (m, 4H, 2 × CH_2-2″), 1.45, 1.44 (2 × s, 2 × 18H, 4 × ^{t}Bu), 141–1.34 (m, 4H, 2 × CH_2-3″), 1.33, 1.29 (2 × s, 2 × 3H, 2 × CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 168.9 (4 × C═O), 99.2 (2 × C(OMe)CH_3), 97.8 (C-1), 75.1 (C-4), 72.4 (C-1″a/b), 71.4 (C-1″c/d), 70.7 (C-5), 70.3 (C-3), 69.3 (C-6), 68.3 (C-2), 54.9 (OMe an C-1), 53.9, 53.8 (2 × C-5″), 47.9, 47.7 (2 × OMe), 30.1, 29.4 (2 × C-2″), 28.5, 28.4 (2 × C-4″), 27.9 (4 × ^{t}Bu), 24.0, 23.9 (2 × C-3″), 17.9, 17.7 (2 × CH_3). MALDI-TOF: *m/z* 871.5 $[M+Na]^+$.

3.3.68. (2′*R*,3′*R*) Methyl 4, 6-di-*O*-(5″,5″di-*tert*-butoxycarbonylpentyl)-2, 3-*O*-(2′,3′-dimethoxybutane-2′,3′-diyle)-α-D-glucopyranoside (90)

3.3.69. Methyl 2,6-di-*O*-(5′,5′-disodium carboxypentyl)-α-D-glucopyranoside (91)

Following GP 4 compound **89** (594 mg, 670 μmol) was reacted with trifluoroacetic acid (4 mL) in CH_2Cl_2 (12 mL) to give **91** as solid; (341 mg, 85%); mp 217.1 °C; $[\alpha]_{546}^{20}$ +21.7 (*c* 0.1, H_2O); ^{1}H NMR (D_2O, 400 MHz): δ 4.88 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 3.68–3.59 (m, 4H, H-6a/b, CH_2-1′a/b), 3.57–3.48 (m, 4H, H-3, H-5, CH_2-1′c/d), 3.36–3.30 (m, 4H, H-4, OMe), 3.29 (dd, 1H, $J_{1,2}$ 3.6 Hz, $J_{2,3}$ 9.4 Hz, H-2), 3.10 (t, 2H, $J_{4',5'}$ 7.7 Hz, CH-5′), 1.74–1.66 (m, 4H, CH_2-4′), 1.60–1.53 (m, 4H, CH_2-2′), 1.34–1.24 (m, 4H, CH_2-3′); ^{13}C NMR (D_2O, 100.6 MHz): δ 180.3 (4 × C═O), 97.1 (C-1), 78.1 (C-2), 73.1 (C-1′c/d), 72.5 (C-3), 71.6 (C-1′a/b), 70.3 (C-4), 69.5 (C-5), 68.4 (C-6), 58.6 (2 × C-5′), 55.3 (OMe), 30.3, 30.1 (C-4′), 29.4, 28.7 (C-2′), 24.3 (2 × C-3′).

3.3.70. Methyl 4, 6-di-*O*-(5′,5′-disodium carboxypentyl)-α-D-glucopyranoside (92)

3.3.71. Methyl α-D-glucopyranoside bisplatinum complex I (93)

Using GP 5 compound **91** (21 mg, 35 μmol) was reacted with cisplatin (35 mg, 0.10 mmol) and silver nitrate (35 mg, 0.20 mmol)

in water (2.4 mL) to give **93** as solid; (18.3 mg, 54%); mp 177.2 °C; $[\alpha]_{546}^{20}$ +17.2 (*c* 0.1, H_2O); ^{1}H NMR (D_2O, 400 MHz): δ 4.81 (d, 1H, $J_{1,2}$ 3.7 Hz, H-1), 3.78–3.56 (m, 8H, H-3, H-5, H-6a/b, CH_2-1′a/b, 2 × CH-5′), 3.58–3.47 (m, 3H, H-2, CH_2-1′c/d), 3.45 (s, 3H, OMe), 3.28 (dd, 1H, $J_{3,4}$ 9.4 Hz, $J_{4,5}$ 9.6 Hz, H-4), 2.53–2.42 (m, 4H, 2 × CH_2-4′), 1.75–1.64 (m, 2H, 2 × CH_2-2′), 1.56–1.44 (m, 2H, 2 × CH_2-3′), ^{13}C NMR (D_2O, 100.6 MHz): δ 199.8 (4 × C=O), 100.0 (C-1), 78.0 (C-4), 74.1 (C-1′c/d), 72.6 (C-3), 72.7 (C-1′a/b), 71.9 (C-2), 69.7 (C-5), 69.3 (C-6), 58.9 (2 × C-5′), 55.1 (OMe), 30.6, 30.5 (2 × C-4′), 29.5, 28.8 (2 × C-2′), 24.7 (2 × C-3′).

3.3.72. Methyl α-D-glucopyranoside bisplatinum complex II (94)

Using GP 5 compound **92** (15 mg, 25 μmol) was reacted with cisplatin (35 mg, 0.10 mmol) and silver nitrate (35 mg, 0.20 mmol) in water (2.4 mL) to give **93** as solid; (17 mg, 70%); mp 175.6 °C; $[\alpha]_{546}^{20}$ +64.9 (*c* 0.1, H_2O); ^{1}H NMR (D_2O, 400 MHz): δ 4.98 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 3.72–3.58 (m, 6H, H-6a/b, CH_2-1′a/b, 2 × CH-5′), 3.62–3.51 (m, 4H, H-3, H-5, CH_2-1′c/d), 3.39–3.32 (m, 4H, H-4, OMe), 3.39 (dd, 1H, $J_{1,2}$ 3.6 Hz, $J_{2,3}$ 9.5 Hz, H-2), 2.53–2.42 (m, 4H, 2 × CH_2-4′), 1.75–1.64 (m, 4H, 2 × CH_2-2′), 1.56–1.44 (m, 4H, 2 × CH_2-3′); ^{13}C NMR (D_2O, 100.6 MHz): δ 200.3 (4 × C=O), 99.1 (C-1), 78.8 (C-2), 73.4 (C-1′c/d), 72.7 (C-3), 71.9 (C-1′a/b), 70.8 (C-4), 69.6 (C-5), 68.4 (C-6), 59.6 (2 × C-5′), 55.0 (OMe), 30.5, 30.2 (2 × C-4′), 29.5, 28.7 (2 × C-2′), 24.7 (2 × C-3′) ppm.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2011.08.024.

References

1. van Camp, L.; Krigas, T.; Rosenberg, B. *Nature* **1965**, *205*, 698–699.
2. Prestayko, A. W.; D'Aoust, J. C.; Issell, B. F.; Crooke, S. T. *Cancer Treat. Rev.* **1979**, *6*, 17–39.
3. Cooley, M. E.; Davis, L.; Abraham, J. *Cancer Nurs.* **1994**, *17*, 283–293.
4. Ranford, J. D.; Sadler, P. J.; Balmanno, K.; Newell, R. *Magn. Reson. Chem.* **1991**, *29*, 125–129.
5. Kwon, Y.-E.; Whang, K.-J.; Park, Y.-J.; Kim, K. H. *Bioorg. Med. Chem.* **2003**, *11*, 1669–1676.
6. Alberto, M. E.; Lucas, M. F.; Pavelka, M.; Russo, N. *J. Phys. Chem.* **2009**, *113*, 14473–14479.
7. Connors, T. A.; Jones, M.; Ross, W. C. J.; Braddock, P. D.; Khokhar, A. R.; Tobe, M. L. *Chem. Biol. Interact.* **1972**, *5*, 415–424.
8. Rixe, O.; Ortuzar, W.; Alvarez, M.; Parker, R.; Reed, E.; Paull, K.; Fojo, T. *Biochem. Pharmacol.* **1996**, *52*, 1855–1865.
9. Hartinger, C. G.; Nazarov, A. A.; Ashraf, S. M.; Dyson, P. J.; Keppler, B. K. *Curr. Med. Chem.* **2008**, *15*, 2574–2591.
10. Berger, I.; Nazarov, A. A.; Hartinger, C. G.; Groessl, M.; Valiahdi, S.-M.; Jakupec, M. A.; Keppler, B. K. *ChemMedChem* **2007**, *2*, 505–514.
11. (a) Mikata, Y.; Shinohara, Y.; Yoneda, K.; Nakamura, Y.; Esaki, K.; Tanahashi, M.; Brudziñska, I.; Yokoyama, M.; Mogami, K.; Tanase, T.; Kitayama, T.; Takashiba, K.; Nabeshima, K.; Takagi, R.; Takatani, M.; Okamoto, T.; Kinoshita, I.; Doe, M.; Hamazawa, A.; Morita, M.; Nishida, F.; Sakakibara, T.; Orvig, C.; Yano, S. *J. Org. Chem.* **2001**, *66*, 3783–3789; (b) Mikata, Y.; Shinohara, Y.; Yoneda, K.; Nakamura, Y.; Brudziñska, I.; Tanase, T.; Kitayama, T.; Takagi, R.; Okamoto, T.; Kinoshita, I.; Doe, M.; Orvig, C.; Yano, S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 3045–3047.
12. Tromp, R. A.; van Boom, S. S. G. E.; Timmers, C. M.; van Zutphen, S.; van der Marel, G. A.; Overkleeft, H. S.; van Boom, J. H.; Reedijk, J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4273–4276.
13. Wang, H.; Sun, L.; Galzebnik, S.; Zhao, K. *Tetrahedron Lett.* **1995**, *36*, 2953–2956.
14. Finkelstein, H. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 1528–1532.
15. Aronov, O.; Horowitz, A. T.; Gabizon, A.; Gibson, D. *Bioconjugate Chem.* **2003**, *14*, 563–574.
16. Möker, J.; Thiem, J. *Eur. J. Org. Chem.* **2009**, 4842–4847.
17. Schmidt, O. T. *Methods Carbohydr. Chem.* **1963**, *2*, 318–325.
18. Nepogodiev, S. A.; Dedola, S.; Marmuse, L.; De Oliveira, M. T.; Field, R. A. *Carbohydr. Res.* **2007**, 529–540.
19. (a) Grice, P.; Ley, S. V.; Pietruszka, J.; Priepke, H. W. M.; Warriner, S. L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 351–363; (b) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975–2977.
20. Frey, U.; Ranford, J. D.; Sadler, P. J. *Inorg. Chem.* **1993**, *32*, 1333–1340.
21. Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512–7515.
22. Hense, A.; Ley, S. V.; Osborn, H. M. I.; Owen, D. R.; Poisson, R. F.; Warriner, S. L.; Wesson, K. E. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2023–2031.