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SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 4519–4527

Synthesis and structural characterisation of novel platinum-based drug candidates with extended functionality by incorporation of bis(diphenylphosphino)ferrocene units as metal chelators

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Received 1 September 2005; revised 26 January 2006; accepted 16 February 2006

Available online 13 March 2006

Abstract—Among the metal-based anticancer drugs, cisplatin (*cis*-diaminedichloroplatinum(II)) is the most widely used species in therapy. Despite its clinical success, cisplatin still suffers in generating resistance, as well as being highly toxic due to poor selectivity between healthy and sick cells. By molecular design it ought to be possible to generate new *cis*-platinum compounds with increased selectivity and improved cellular behaviour. In this paper, we report a synthetic pathway for construction of derivatives of 1,1′-bis(diphenylphosphino)-ferrocene, together with their corresponding *cis*-platinum compounds with the aim testing them for their interaction capacity with respect to various DNA models. We also report a synthetic route for a nucleoside-based *cis*-platinum compound containing a bidentate ferrocenylphosphine derivative connected through a succinamic-based linker to the 5-position of the heterocyclic moiety of uridine. Our preliminary kinetic investigation of 5-{*N*-[1-[1′,2-bis(diphenylphosphino)ferrocenyl]ethyl]-*N*′-[prop-2-yn-3-yl]succinamide} uridinedichloroplatinum(II) showed that this compound reacted faster with the phosphorothioate containing oligonucleotides d(T_6p(S)T_6), with an observed first-order rate constant $k_{obs}=(1.4\pm0.1)\times10^{-4}\ s^{-1}$, compared with the G-N7 target in d(T_7GGT_7), for which the observed first-order rate constant is $k_{obs}=(7.2\pm0.5)\times10^{-4}\ s^{-1}$.

1. Introduction

In the 1960s, Rosenburg discovered that cell division could be inhibited by the platinum complex *cis*-[$PtCl_2(NH_3)_2$], also known as 'cisplatin'.[1,2] Cisplatin was introduced to the clinic around 1980 and the drug has been successfully used against many forms of cancer, particularly for the treatment of testicular and ovarian cancers.[3,4] The mechanism of action of cisplatin has not been fully elucidated, and is still a matter of intense research.[5–7] So far, it has been suggested that cisplatin acts on nuclear DNA preferentially by formation of GG and AG adducts along the DNA sequence.[4] It has been shown that formation of such adducts results in disruption of the DNA double helical structure[8,9] with consequences for the cellular machinery involved in both DNA repair and the induction of apoptosis[5–7] Nevertheless, there is growing evidence that nuclear DNA is not the only intracellular target and cellular components such as *t*RNA and structural elements along the *m*RNA sequence also could function as targets sites for cisplatin.[10]

Despite its clinical success, cisplatin has several side effects comprising toxicity and resistance[11] as a result of its non-selective interaction with healthy as well as cancer cells. As a result, there is an urgent need for novel compounds with an improved reactivity spectrum, preferentially with properties able to reduce the general toxicity but with retained target localisation. So far, only a few alternatives to cisplatin are available, namely oxaliplatin, carboplatin and nedaplatin.[5,7,12,13]

The long-term goal of this project is to develop a straightforward synthetic pathway for the production of ferrocenyl-based platinum compounds to be used as tentative replacement drugs for cisplatin in the clinic. Earlier studies have shown that this class of compound exhibits promising both antineoplastic and antimicrobial activity.[14,15] In this article, the synthetic pathway for some new chiral derivatives of 1,1′-bis-(diphenylphosphino)ferrocene and

Keywords: Cisplatin; Pt(dppf); Anticancer; Kinetics; Nucleoside analogue; Linker.
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0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.057

their corresponding *cis*-platinum complexes is described. We also describe a synthetic route for the production of a uridine analogue containing a bidentate ferrocenylphosphine derivative connected through a linker arm to the 5-position of the heterocyclic moiety of the uridine molecule. The preliminary kinetic data reveals a reactivity of these compounds towards short DNA oligonucleotides of a magnitude similar to that of cisplatin.

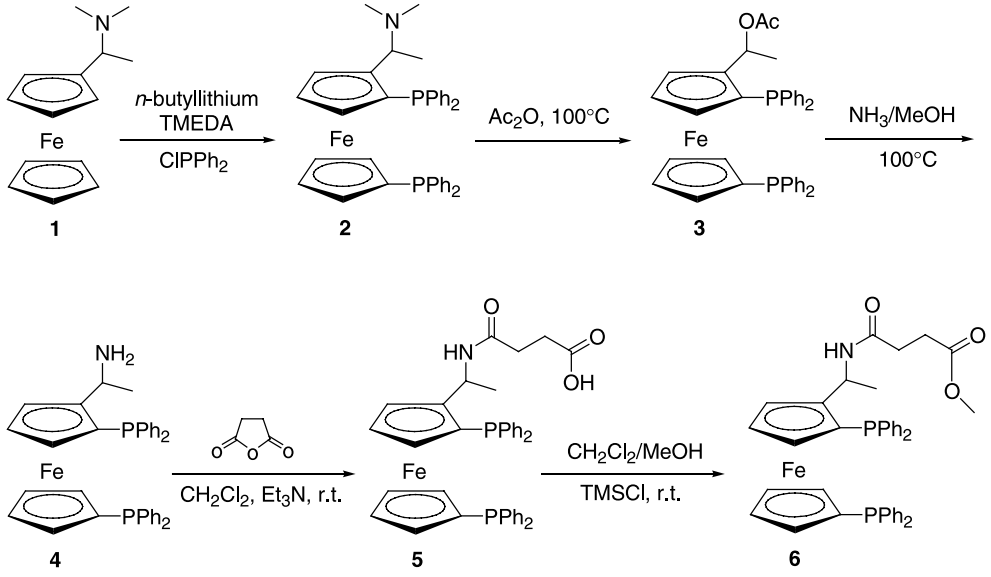
2. Results and discussion

2.1. Synthesis of ferrocenylphosphine derivatives

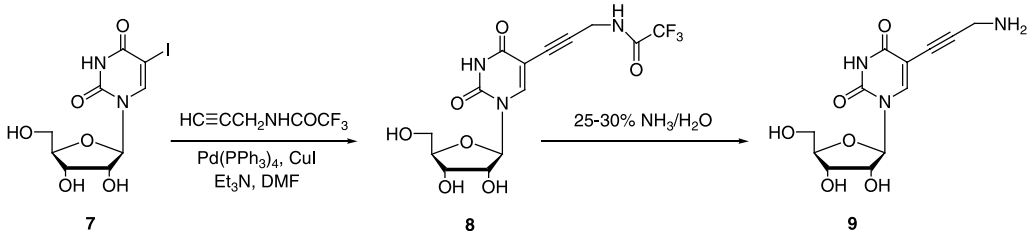
The ferrocenylphosphine derivatives were prepared from the commercially-available racemic mixture of (+/−)-*N*,*N*-dimethyl-1-ferrocenylethylamine **1**. Compound **4** was prepared according to the literature,[16] but its synthesis is briefly described as the purification steps were modified to simplify procedures for large scale production.

In the first step, the cyclopentadienyl rings of compound **1** were lithiated using *n*-butyllithium and *N*,*N*,*N*′*N*′-tetramethylethylenediamine (TMEDA). The organolithium reagent alone is not reactive enough, but the enhanced reactivity of using a mixture consisting of *n*-butyllithium and TMEDA allows for lithiation on both cyclopentadienyl rings of ferrocene.[17] The dilithiation of ferrocene is performed by stepwise addition of butyllithium in hexane to the reaction mixture, followed by the addition of *n*-butyllithium-TMEDA. The following diphenylphosphination to produce compound **2** was performed by an in situ reaction with chlorodiphenylphosphine with a yield of 56% (Scheme 1). Besides the central element of chirality, also a planar element of chirality exists due to the 1,2-unsymmetrically substituted ferrocene of compound **2**. Previous studies have demonstrated that because of the highly diastereoselective *ortho*-lithiation in this particular reaction sequence and substrate all compounds synthesised from **1** are assumed to be racemic mixtures consisting of (*R*)(*S*) and (*S*)(*R*) enantiomers in equal amounts.[16,18] and their corresponding diastereomers (*R*)(*R*) and (*S*)(*S*) are produced in a minor amount of 4%. All compounds produced will be tested in in vitro assay systems as mixture of isomers and only separated if they exhibit any interesting biological activity.

Purification, producing pure **2**, was achieved by silica gel column chromatography using toluene–diethyl ether–Et_3N (89/10/1) as the eluent. Transformation of the dimethylamino substituent on the ferrocene molecule to an amino group (Scheme 1) was accomplished via the formation of an acetoxy group by treatment of pure acetic anhydride at 100 °C.[16] Orange crystals precipitated directly in the reaction vessel, which were isolated in 90% yield. The desired amino-containing ferrocenyl compound **4** was created by reacting **3** with a saturated solution of ammonia in methanol in a sealed tube at 100 °C.[16] The two-step transformation of **2** to **4** both involve nucleophilic substitution reactions, which are both known to proceed with retention of configuration on the stereogenic carbon center.[16] Molecule **5** was produced by treatment of **4** with succinic anhydride in the presence of triethylamine (Scheme 1). Purification of **5** by silica gel column chromatography using CH_2Cl_2/MeOH as eluent produced dark red crystals in 81% yield. The carboxylic acid group in compound **5** was methylated by using chlorotrimethylsilane (TMSCl) as reagent in a solvent mixture consisting of MeOH–CH_2Cl_2 (2/1). The resulting compound **6** was purified by silica gel column chromatography using a gradient of heptane–EtOAc–EtOH (69/30/1) to EtOAc–EtOH (99/1) as eluents producing dark red crystals after removal of the solvents in vacuo in 74% yield. Uridine derivative **9** was synthesised to enable connection of the ferrocenyl complex **5** to the C-5 position of the heterocyclic moiety of uridine (Scheme 3). The synthesis of **9** was performed according to the literature in a two-step strategy (Scheme 2).[19] In the first step a Sonogashira reaction[20] between 5-iodouridine **7** and *N*-trifluoroacetyl propargyl amine[19] in the presence of $Pd(PPh_3)_4$, CuI and Et_3N in dry *N*,*N*-dimethylformamide (DMF) was utilised. The resulting



Scheme 1. Synthesis of target molecules **5** and **6**.



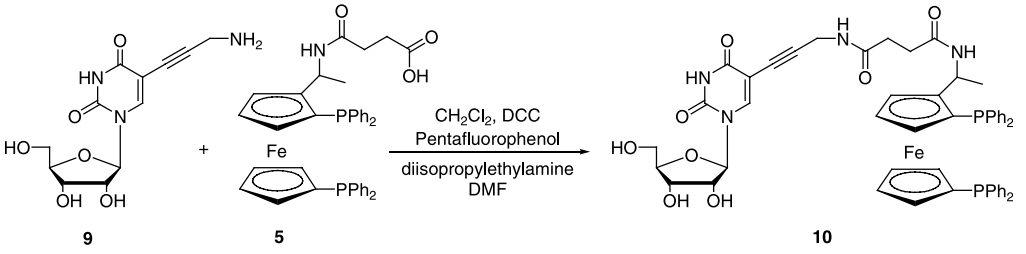
Scheme 2. Synthesis of the nucleoside derivative **9**.

nucleoside derivative **8** was purified by silica gel column chromatography using CH_2Cl_2–MeOH (9/1) as eluent resulting in orange crystals in 80% yield. In the second step, the trifluoroacetyl group was removed by treatment of **8** with 25–30% NH_3/H_2O at 4 °C producing **9** in a yield of 77%.

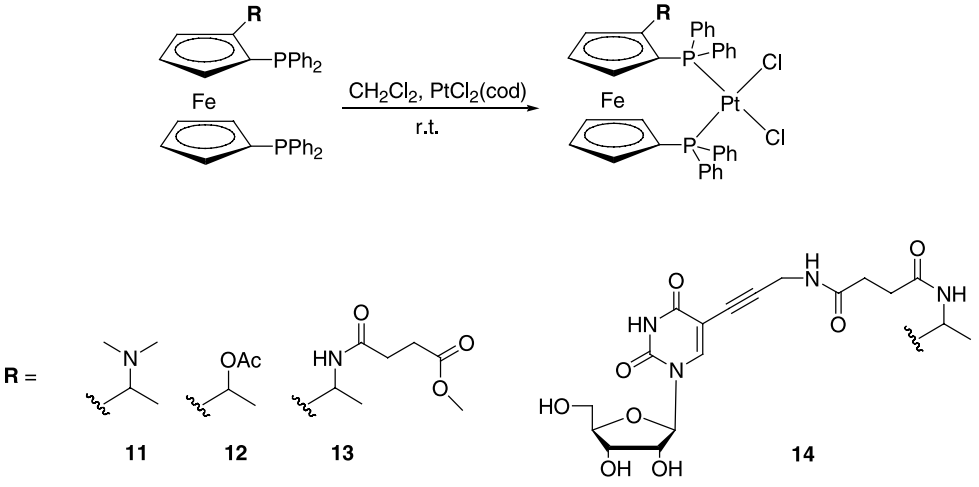
As discussed above, reacting succinic anhydride with the free amino group of the ferrocenyl complex **4**, a carbon chain linker with an internal amide bond and a free carboxylic acid group was created (Scheme 1). The ferrocenyl complex **5** was attached to the C-5 position of the heterocyclic moiety of uridine by reacting with uridine derivative **9** (Scheme 3). The coupling reaction between **9** and **5** was accomplished by using pentafluorophenol, *N*,*N*-dicyclohexylcarbodiimide (DCC) and diisopropylethylamine using CH_2Cl_2 and DMF as solvent producing **10** in 78% yield. The nucleoside-based ferrocenyl complex **10** was purified by silica gel chromatography using CH_2Cl_2–MeOH (93/7) as the eluent. Recently, it has been shown that the introduction of chemical modifications at the C-5 position are tolerated by both the *taq* polymerase[21] and the RNA polymerase thus making such nucleoside modifications interesting for future applications within the RNA chemistry field.[22] Some of the here reported complexes have already been tested with respect to their interaction with L-cystein and L-methionine.[23]

2.2. Synthesis of *cis*-platinum compounds 11, 12, 13 and 14

The prepared ferrocenyl ligands **2**, **3**, **6** and **10** were transformed to their corresponding *cis*-platinum complexes. These reactions were initiated by dissolving compounds **2**, **3**, **6**, or **10** in CH_2Cl_2, followed by addition of (1,5-cyclooctadiene)platinum(II)chloride, [$PtCl_2$(cod)] (Scheme 4). The reaction mixture was stirred for 1–2 h followed by reduction of the reaction volume of about 15–20%, whereupon crystals could be obtained by addition of ether. Before reacting ligand **10** with [$PtCl_2$(cod)], 1% methanol, calculated on the total reaction volume, was added to the reaction mixture in order to properly dissolve the ligand.



Scheme 3. Synthesis of the nucleoside containing ferrocenyl complex **10**.



Scheme 4. Reaction illustrating production of the platinum complexes **11**, **12**, **13** and **14**.

Comparison of the ^{31}P NMR spectra for the ferrocenyl complexes and their corresponding platinum complexes indicates that the bidentate ligands are bound to platinum as typical ^{195}Pt satellites could be observed on each ^{31}P signal and their coupling constants are of expected size. The *cis*-platinum complexes have also been verified by CV experiments, see below (Section 2.3).

2.3. Cyclic voltammetry

Cyclic voltammetry (CV) is a very powerful technique for characterising redox active compounds.[24] The ferrocene molecule is known to be redox active and it has been suggested that its biological activity (antineoplastic activity) could be connected with its redox processes in vivo[25] and following CV was chosen as one of the techniques to characterise compounds **11**, **12**, **13** and **14**. To compare the electrochemical behaviour of the platinated compounds, CV was also run on ferrocene (see Supplementary material data), 1,1′-bis(diphenylphosphino)ferrocene (dppf) and [$PtCl_2$(dppf)] and their corresponding CV voltammograms A and B, respectively, are shown in Figure 1. Since the CV voltammograms for the substituted complexes **11**, **12** and **13** were more or less identical to each other, only voltammogram of compound **13** is illustrated (Fig. 1C). The nucleoside containing compound **14** showed a somewhat different electrochemical behaviour shown in Figure 1D.

The CV of dppf contains two sets of redox reactions, those of the ferrocene moiety (1–2 in Fig. 1A) and those of the phosphino groups (3–4 in Fig. 1A). The $i_{p,c}/i_{p,a}$ ratio of the ferrocene redox reaction is highly sweep rate dependent (a ratio of 0.28 and of 0.18 at 100 and 50 mV/s, respectively) due to a fast chemical electron transfer from the ferrocene to the phosphino groups. The complex redox behaviour of dppf has been reported by Pilloni et al.[26]

The CV of platinated dppf, [$PtCl_2$(dppf)], contains only one set of redox waves (Fig. 1B) with a considerably higher formal potential ($E^{0'}$) in comparison with that of uncoordinated dppf ($E^{0'}=390$ mV vs dppf). The coordination of $PtCl_2$ to dppf results in blocking of the intramolecular ferrocene reduction, resulting in a reversible redox action ($\Delta E_p=60$ mV) with a $i_{p,c}/i_{p,a}$ ratio closer to unity than for dppf.

Modification of the cyclopentdienyl ring resulted in an increased $i_{p,c}/i_{p,a}$ ratio. Zanello et al.[27] have previously shown that modifications of the cyclopentadienyl ring of non-platinated dppf can, depending on the electron donating ability of the substituent, result in a partial stabilisation of the dppf monocation, observed as an increase in the $i_{p,c}/i_{p,a}$ ratio. The three substituted compounds **11**, **12** and **13** showed no significant difference in electrochemical behaviour (CV voltammogram for compound **13** is illustrated in Fig. 1C).

The nucleoside containing complex **14** showed different redox behaviour, that is, the peak current of the reduction wave of the ferrocene moiety is larger for the corresponding oxidation (Fig. 1D). The narrow shape of the reduction peak indicates that the oxidised species could be absorbed. The reduction peak current was proportional to the sweep rate ($R^2=0.999$) whereas the oxidation peak current was proportional to the square root of the sweep rate ($R^2=0.997$). This result suggests that the oxidised species might be adsorbed on the platinum electrode whereas the reduced specie is dissolved.[24]

2.4. DNA platination rates

To estimate the reactivity of this series of compounds towards DNA targets, a preliminary study of the reactivity of compound **14** was performed. Two types of oligomers were used as targets, one containing the GG sequence, which is preferred by cisplatin in vivo, d(T_7GGT_7), and the other containing the slightly more reactive phosphorothioate group d($T_6p(S)T_6$).[28,29] The kinetics for platination of the

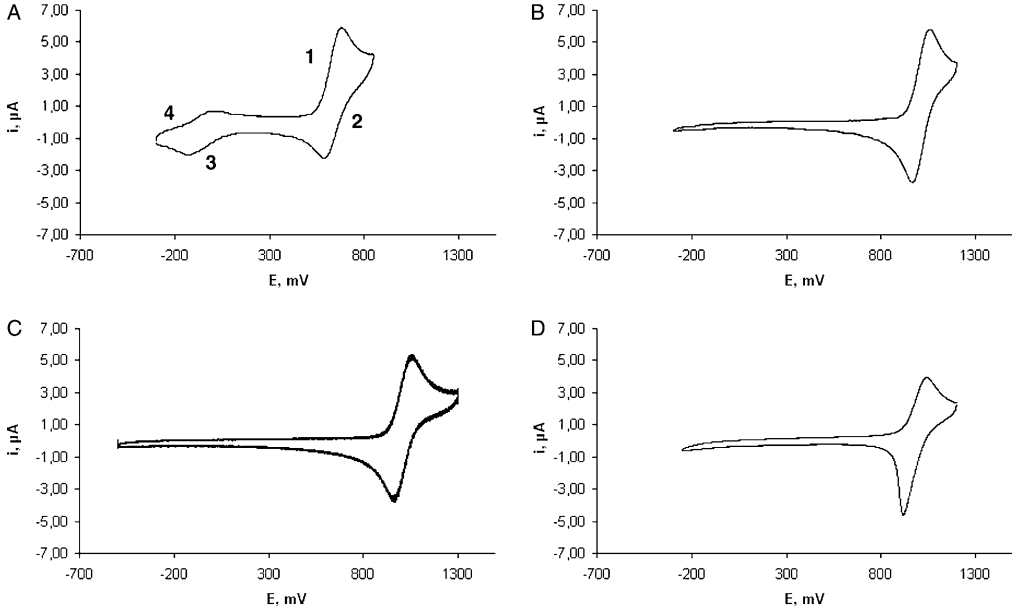


Figure 1. CV voltammograms of dppf (A), [$PtCl_2$(dppf)] (B), compound **10** (C) and nucleoside containing compound **14** (D).

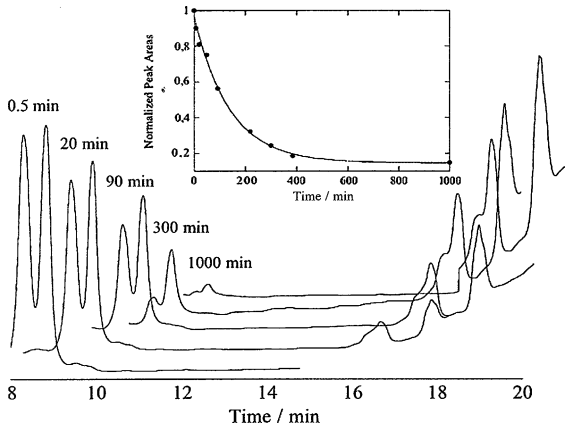


Figure 2. Selected HPLC chromatograms at different reaction times illustrating the platination of $d(T_6p(S)T_6)$. The two diastereomers of the unplatinated oligonucleotides are eluting at $t_r \approx 8$ and $t_r \approx 9$ min, and the product peaks start to elute at $t_r \approx 16$ min. The inserted graph displays the fit of a single exponential function to normalised, integrated peak areas versus time for the unplatinated oligonucleotide. Reaction conditions: $[Pt(II)] = 1.0 \times 10^{-5}$ M, $[d(T_6p(S)T_6)] = 2.0 \times 10^{-6}$ M, $[Na^+] = 10.0$ mM.

oligonucleotides was evaluated by the observed decrease in HPLC peak areas of the unplatinated reactant. The time course for the decline of the integrated area of the DNA-fragments were all found to follow first-order kinetics. Figure 2 shows typical HPLC chromatograms, illustrating the decrease of $d(T_6p(S)T_6)$ during the reaction with compound **14**, the inset shows a fit of a single exponential function to the normalised integrated peak areas. The platination rate was found to be twice as high for the phosphorothioate containing oligonucleotide compared to the G-N7 target in $d(T_7GGT_7)$. The obtained observed first-order rate constants were determined to $k_{obs} = (1.4 \pm 0.1) \times 10^{-4}\ s^{-1}$ and $(7.2 \pm 0.5) \times 10^{-5}\ s^{-1}$ for $d(T_6p(S)T_6)$ and $d(T_7GGT_7)$ respectively, all in agreement with the more pronuced nucleophilicity exhibited by the phosphorothiophate compared with G-N7. Thus, these reactions have half-lives of 1.4 and 2.7 h for the reactions with G-N7 and p(S), respectively, that is, indicating a slightly higher reactivity of **14** compared with cisplatin.[30,31]

3. Conclusions

We here report a successful synthetic pathway for the construction of several unique dppf-based platinum compounds with chemical modifications introduced in the ferrocenyl moiety. So far, the majority of chemical modifications have been focused on changing the properties of the phosphine groups. The limiting factor for many of the produced *cis*-platinum compounds is their poor aqueous solubility, lack of selectivity and high toxicity. By modulating the chemical properties we hope to construct new unique *cis*-platinum complexes with retained or improved in vivo activity. One such compound identified in this study is the nucleoside containing complex **14**, which show improved water solubility and thus allows for facile kinetics studies with DNA models systems. Its reactivity is similar to cisplatin with a reaction half-life in the hour range.

4. Experimental

4.1. General

Analytical thin-layer chromatography (TLC) was performed by using silica gel 60 F_{254} plates purchased from Merck and 5-iodouridine **7** was purchased from Aldrich. Column chromatography was carried out using Matrex silica gel 60A/35–70. The compounds were visualised on the TLC plates by three different methods: (1) using UV-light; (2) using a solution of *p*-methoxybenzaldehyde (10 mL), concentrated sulfuric acid (50 mL) and ethanol (95%, 950 mL) and (3) using a ninhydrin solution. Melting points were taken on a Sanyo Gallenkamp melting point apparatus (MPD.350.BM3.5) and are uncorrected. IR spectra were recorded on a Shimadzu 8300 FTIR instrument and $KBr_{(s)}$ was used as matrix. NMR spectra were recorded on a Bruker ARX300 or a DRX400 spectrometer and all chemical shifts (δ) are relative to the residual peak of the deuterated solvent and given in parts per million, apart from compound **9**, where ^{13}C NMR shifts are given relative to 3-(trimethylsilyl)-propanesulfonic acid sodium salt (D_2O) as external reference. Chemical shifts in ^{31}P NMR spectra are reported in parts per million relative to external 85% H_3PO_4 at 0.00 ppm. To enable determination of the various peaks, phosphorus decoupled ^{13}C NMR was run on compounds **3**, **5**, **6** and **10**. For the platinated compounds NMR experiments such as COSY, HMQC and HMBC were carried out. All solvents used in the synthetic procedures were distilled prior to use.

4.2. Synthesis

4.2.1. *N*,*N*-Dimethyl-1-[1′,2-bis(diphenylphosphino) ferrocenyl]ethylamine (2). *n*-BuLi (1.6 M in hexane, 5.84 mL, 9.3 mmol) was slowly added to a solution of racemic (+/−)-*N*,*N*-dimethyl-1-ferrocenylethylamine **1** (1.99 g, 7.74 mmol) dissolved in dry diethyl ether (12 mL) over a period of 20 min. The reaction flask was equipped with a septum, whereupon slowly filled with argon followed by setting the temperature of the reaction mixture to 25 °C. The reaction mixture was stirred for 1 h at room temperature, whereupon a mixture of *N*,*N*, *N*′,*N*′-tetramethylethylenediamine (1.4 mL, 9.3 mmol) and *n*-BuLi (1.6 M in hexane, 6.32 mL, 10.1 mmol) was added over a period of 15 min. The reaction mixture was kept at room temperature for 5 h followed by cooling to −15 °C. Chlorodiphenylphosphine (4.19 mL, 23.3 mmol) was slowly added and the reaction mixture was allowed to reach room temperature followed by gentle stirring overnight. Saturated $NaHCO_3$ (aq) was added with stirring, the two phases were separated, and the aqueous phase was extracted with toluene (3×60 mL). The combined organic phases were dried over Na_2SO_4, filtered and the product was isolated by evaporation under reduced pressure. The crude product was purified by silica gel column chromatography using toluene–ether–Et_3N (89/10/1) as eluent. The resulting product was isolated as red crystals in 56% yield (2.72 g). ^1H NMR spectrum was in agreement with the literature.[16] ^{31}P NMR ($CDCl_3$, ppm): δ −16.93 (s), −23.01 (s); mp 151.3–152.0 °C.

4.2.2. 1-[1′,2-Bis(diphenylphosphino)ferrocenyl]ethylacetate (3). *N*,*N*-Dimethyl-1-[1′,2-bis(diphenylphosphino)-ferrocenyl]ethylamine **2** (0.577 g, 0.922 mmol) and acetic anhydride (3 mL) were mixed together in a glass tube, degassed and heated to 100 °C for 2 h. The reaction mixture was slowly cooled to room temperature followed by further cooling to −20 °C, whereupon orange crystals started to precipitate. The product was isolated by filtration and dried under reduced pressure overnight resulting in 90% yield (532 mg) of **3**. ^{1}H NMR spectrum was in agreement with the literature,[16] ^{13}C NMR (100.61 MHz, CD_2Cl_2, ppm): δ 18.6, 20.3, 68.6 (d, J_{P-C}=9.1 Hz), 71.6 (d, J_{P-C}=2.7 Hz), 72.1 (d, J_{P-C}=2.1 Hz), 73.7 (d, J_{P-C}=9.9 Hz), 73.8 (d, J_{P-C}=2.6 Hz), 74.0 (d, J_{P-C}=10.4 Hz), 74.5 (d, J_{P-C}=4.6 Hz), 75.6 (d, J_{P-C}=18.9 Hz), 77.7 (d, J_{P-C}=14.5 Hz), 77.8 (d, J_{P-C}=16.4 Hz), 93.1 (d, J_{P-C}=24.5 Hz), 128.4, 128.5 (d, J_{P-C}=6.0 Hz), 128.69 (d, J_{P-C}=7.0 Hz), 128.72 (d, J_{P-C}=7.0 Hz), 128.73 (d, J_{P-C}=6.0 Hz), 129.0, 129.2, 129.9, 133.0 (d, J_{P-C}=19.1 Hz), 133.7 (d, J_{P-C}=19.1 Hz), 134.1 (d, J_{P-C}=20.1 Hz), 135.6 (d, J_{P-C}=21.1 Hz), 137.1 (d, J_{P-C}=9.1 Hz), 139.1 (d, J_{P-C}=10.1 Hz), 139.8 (d, J_{P-C}=10.1 Hz), 140.2 (d, J_{P-C}=10.1 Hz), 169.9; ^{31}P NMR ($CDCl_3$, ppm): δ −17.39 (s), −24.99 (s); mp 159.4–160.4 °C.

4.2.3. 1-[1′,2-Bis(diphenylphosphino)ferrocenyl]ethylamine (4). A mixture of 1-[1′,2-bis(diphenylphosphino)-ferrocenyl]ethylacetate **3** (423 mg, 0.660 mmol) and saturated ammonia–methanol (5 mL) was heated to 100 °C in a sealed glass tube. The mixture was stirred for 7 h followed by cooling to room temperature, whereupon 20 mL of toluene was added carefully. The reaction mixture was washed with 1 M NaOH (2×15 mL), and the organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography using toluene–EtOH–Et_3N (98/1/1) as eluent, and **4** was isolated in a 87% yield (342 mg). ^{1}H NMR spectrum was in agreement with the literature,[16] ^{31}P NMR ($CDCl_3$, ppm): δ −18.48 (s), −25.89 (s).

4.2.4. *N*-[1-[1′,2-Bis(diphenylphosphino)ferrocenyl]-ethyl]succinamic acid (5). 1-[1′,2-Bis(diphenylphosphino) ferrocenyl]ethylamine **4** (559 mg, 0.936 mmol) was dissolved in dry CH_2Cl_2 (12 mL) followed by the addition of succinic anhydride (936 mg, 9.36 mmol) and Et_3N (0.390 mL, 2.80 mmol), whereupon the mixture was stirred under argon overnight. Prior to washing with 1 M HCl (2×20 mL) and water (3×20 mL), CH_2Cl_2 (10 mL) was added to the reaction mixture. The combined organic phases were dried over Na_2SO_4, filtered, and the solvent was removed by evaporation under reduced pressure. The resulting crude product was purified by silica gel column chromatography using CH_2Cl_2–MeOH (96/4) as eluent giving **5** as dark red crystals in an 81% yield (530 mg); IR (KBr, cm^{-1}): 3365, 3052, 1729, 1620, 1430; ^{1}H NMR ($CDCl_3$, ppm): δ 1.36 (d, 3H, J=6.6 Hz, CHCH_3), 1.41–1.47, 1.80–2.00, 2.15–2.40 (m, 4H, COCH_2CH_2-CO), 3.50–3.70, 4.05–4.55 (m, 7H, C_5H_4FeC_5H_3), 5.19 (m, 1H, CHCH$_3$), 5.65 (br s, NHCO), 7.10–7.80 (m, 20H, PC_6H_5); ^{13}C NMR (100.61 MHz, D_6-DMSO, ppm): δ 20.2, 28.9, 29.2, 42.0 (d, J_{P-C}=9.1 Hz), 70.6 (d, J_{P-C}=1.8 Hz), 70.9 (d, J_{P-C}=3.6 Hz), 71.9 (d, J_{P-C}=4.7 Hz), 72.7 (d, J_{P-C}=9.5 Hz), 72.9, 74.0 (d, J_{P-C}=4.9 Hz), 74.7 (d, J_{P-C}=20.4 Hz), 75.4 (d, J_{P-C}=11.4 Hz), 76.0 (d, J_{P-C}=8.8 Hz), 96.3 (d, J_{P-C}=26.2 Hz), 127.5, 127.8 (d, J_{P-C}=5.0 Hz), 128.1 (d, J_{P-C}=7.0 Hz), 128.2 (d, J_{P-C}=7.0 Hz), 128.3 (d, J_{P-C}=6.0 Hz), 128.4, 128.7, 129.2, 131.8 (d, J_{P-C}=18.1 Hz), 132.6 (d, J_{P-C}=19.1 Hz), 133.2 (d, J_{P-C}=20.1 Hz), 134.8 (d, J_{P-C}=22.1 Hz), 136.8 (d, J_{P-C}=9.1 Hz), 137.9 (d, J_{P-C}=10.1 Hz), 139.0 (d, J_{P-C}=11.1 Hz), 139.7 (d, J_{P-C}=11.1 Hz), 168.3, 173.7; ^{31}P NMR ($CDCl_3$, ppm): δ −17.28 (s), −25.15 (s); mp 175.0–175.5 °C; HRMS (FAB$^+$) *m*/*z* calculated for $C_{40}H_{37}FeNO_3P_2$: 697.1598. Found: 697.1590.

4.2.5. *N*-[1-[1′,2-Bis(diphenylphosphino)ferrocenyl]-ethyl]succinamic acid methylester (6). Chlorotrimethylsilane (0.450 mL, 3.52 mmol) was slowly added to a solution of *N*-[1-[1′,2-bis(diphenylphosphino)ferrocenyl]ethyl]succinamic acid **5** (460 mg, 0.659 mmol) in dry MeOH (6 mL) and CH_2Cl_2 (3 mL). The reaction mixture was stirred overnight under argon followed by removal of the solvents by evaporation under reduced pressure. The crude product was purified by silica gel column chromatography using two different solvent systems starting with heptane–EtOAc–EtOH (69/30/1) and, in later fractions, EtOAc–EtOH (99/1) to give **6** in 74% yield (348 mg); IR (KBr, cm^{-1}): 3374, 3062, 1724, 1663, 1173; ^{1}H NMR ($CDCl_3$, ppm): δ 1.33 (d, 3H, J=6.7 Hz, CHCH_3), 1.55–2.60 (m, 4H, COCH_2CH_2CO), 3.64 (s, 3H, OCH_3), 3.50–3.60, 4.10–4.60 (m, 7H, C_5H_4FeC_5H_3), 5.15 (m, 1H, CHCH$_3$), 5.75 (br d, 1H, J=6.4 Hz, NHCO), 7.10–7.70 (m, 20H, PC_6H_5); ^{13}C NMR (100.61 MHz, CD_2Cl_2, ppm): δ 21.1, 29.5, 30.5, 44.7 (d, J_{P-C}=7.0 Hz), 52.0, 71.8 (d, J_{P-C}=2.3 Hz), 72.2 (d, J_{P-C}=2.9 Hz), 73.4 (d, J_{P-C}=4.6 Hz), 73.77 (d, J_{P-C}=8.7 Hz), 73.81 (d, J_{P-C}=4.4 Hz), 74.7 (d, J_{P-C}=4.1 Hz), 75.8 (d, J_{P-C}=20.7 Hz), 76.0 (d, J_{P-C}=10.7 Hz), 77.5 (d, J_{P-C}=8.6 Hz), 96.1 (d, J_{P-C}=24.3 Hz), 128.66 (d, J_{P-C}=6.0 Hz), 128.69 (d, J_{P-C}=6.0 Hz), 128.73 (d, J_{P-C}=7.0 Hz), 128.8 (d, J_{P-C}=7.0 Hz), 128.9, 129.2, 129.9, 132.9 (d, J_{P-C}=19.1 Hz), 133.5 (d, J_{P-C}=19.1 Hz), 134.2 (d, J_{P-C}=20.1 Hz), 135.5 (d, J_{P-C}=21.1 Hz), 137.0 (d, J_{P-C}=8.0 Hz), 139.0 (d, J_{P-C}=10.1 Hz), 140.0 (d, J_{P-C}=11.1 Hz), 140.4 (d, J_{P-C}=10.1 Hz), 169.2, 173.6; ^{31}P NMR ($CDCl_3$, ppm): δ −17.06 (s), −24.67 (s); mp 186–187 °C; HRMS (FAB$^+$) *m*/*z* calculated for $C_{41}H_{39}FeNO_3P_2$: 711.1755. Found: 711.1757.

4.2.6. 5-(3″-Trifluoroacetamidopropynyl)uridine (8). 5-Iodouridine **7** (373 mg, 1.01 mmol) was dissolved in dry DMF (5 mL) followed by the addition of CuI (38 mg, 0.20 mmol), Et_3N (0.280 mL, 2.0 mmol), *N*-propargyl trifluoroacetamide[32] (453 mg, 3.00 mmol), and $Pd(PPh_3)_4$ (116 mg, 0.10 mmol). The reaction mixture was stirred overnight under argon atmosphere at room temperature, whereupon the solvent was removed by evaporation under reduced pressure. The crude product was purified by using silica gel column chromatography using CH_2Cl_2–MeOH (9/1) as eluent resulting in **8** as orange crystals in 80% yield (318 mg). ^{1}H NMR spectrum was in agreement with the literature. ^{1}H NMR (D_4-MeOH, ppm): δ 3.73 (dd, 1H, J=12.2, 2.7 Hz), 3.86 (dd, 1H, J=12.2, 2.5 Hz), 4.01 (m, 1H), 4.15 (m, 2H), 4.26 (s, 2H), 5.87 (d, 1H, J=3.8 Hz), 8.39 (s, 1H).

4.2.7. 5-(3″-Aminopropyin-1-yl)uridine (9). 5-(3″-Trifluoroacetamidopropynyl)uridine **8**[19] (305 mg, 0.776 mmol) was stirred in ammonium hydroxide solution (10 mL, 25–30% NH_3 in H_2O) for 15 h at 4 °C followed by the removal of the solvent by evaporation under reduced pressure. The crude product was purified by silica gel column chromatography using CH_2Cl_2–MeOH–Et_3N (69/30/1) as eluent resulting in a white solid product in 77% yield (178 mg); IR (KBr, cm^{-1}): 3384, 3071, 1691, 1663, 1610, 1278, 1107, 1083; ^1H NMR (D_2O, ppm): δ 3.70 (dd, 1H, J=4.0, 12.9 Hz, uridine 5′-H), 3.77 (s, 2H, CH_2NH$_2$), 3.82 (dd, 1H, J=2.7, 12.9 Hz, uridine 5′-H), 4.02 (m, 1H), 4.09 (m, 1H), 4.19 (m, 1H), 5.77 (d, 1H, J=3.7 Hz, uridine 1′-H), 8.07 (s, 1H, uridine 6-H); ^{13}C NMR (100.61 MHz, D_2O, ppm): δ 32.8, 63.2, 71.7, 76.7, 80.2, 86.6, 90.0, 92.7, 101.2, 147.4, 156.6, 171.7; mp 185 °C; HRMS (FAB$^+$) m/z calculated for $C_{12}H_{15}N_3NaO_6$: 320.0859 [M+Na]$^+$. Found: 320.0859 [M+Na]$^+$.

4.2.8. 5-{*N*-[1-[1′,2-Bis(diphenylphosphino)ferrocenyl]-ethyl]-*N*′-[prop-2-yn-3-yl]succinamide}uridine (10). *N*,*N*′-Dicyclohexylcarbodiimid (76 mg, 0.37 mmol, 1 equiv) was added to a solution of **5** (20 mL, 253 mg, 0.363 mmol) and 2,3,4,5,6-pentafluorophenol (86 mg, 0.47 mmol) in dry CH_2Cl_2 (20 mL). The reaction mixture was stirred overnight, whereupon the solvent was removed by evaporation under reduced pressure. After removal of the solvent, dry DMF (20 mL) was added together with compound **9** (140 mg, 0.472 mmol) and diisopropylethylamine (125 μL). The reaction mixture was stirred for additional 16 h followed by removal of the solvent by evaporation under reduced pressure. The crude product was purified by silica gel column chromatography using CH_2Cl_2–MeOH (93/7) as eluent producing orange crystals of compound **10** in 78% yield (276 mg); IR (KBr, cm^{-1}): 3403, 3062, 1691, 1648, 1534, 1430, 1278, 1093; ^1H NMR (D_3-MeOD, ppm): δ 1.15–1.32 and 1.73–2.18 (m, 4H, COCH_2CH_2CO), 1.38 (d, 3H, J=6.7 Hz, CHCH_3), 3.50–3.68 (m, 2H, ferrocene), 3.70–3.95 (m, 2H, uridine 5′-H), 4.02 (m, 1H, uridine 4′-H), 4.06 (m, 2H, CH_2NHCO), 4.10–4.20 (m, 5H), 4.45–4.55 (m, 2H, ferrocene), 5.17 (m, 1H, CH$_3$C*H*NH), 5.88 (m, 1H, uridine 1′-H), 7.04–7.45 (m, 20H, PPh), 8.40 (s, 1H, uridine 6-H); ^1H NMR (D_6-DMSO, ppm): δ 1.15–1.28 and 1.65–2.10 (m, 4H, COCH_2CH_2CO), 1.30 (d, 3H, J=6.7 Hz, CHCH_3), 3.40–3.55 (m, 2H, ferrocene), 3.55–3.75 (m, 2H, uridine 5′-H), 3.86 (m, 1H), 3.95–4.25 (m, 7H), 4.40–4.53 (m, 2H, ferrocene), 4.90–5.05 (m, 1H, C*H*CH$_3$), 5.09 (d, 1H, J=5.0 Hz, O*H*), 5.23 (t, 1H, J=4.5 Hz, O*H*), 5.42 (d, 1H, J=5.3 Hz, O*H*), 5.75 (d, 1H, J=4.5 Hz, uridine 1′-H), 6.90–7.50 (m, 21H, PPh and CHN*H*CO), 8.15 (t, 1H, J=5.3 Hz, CH$_2$N*H*CO), 8.24 (s, 1H, uridine 6-H), 11.64 (br s, 1H, uridine 3-H); ^{13}C NMR (100.61 MHz, D_3-MeOD, ppm): δ 20.3, 30.5, 31.3, 31.8, 44.7 (d, J_{P-C}=9.1 Hz), 62.1, 71.2 (d, J_{P-C}=3.6 Hz), 72.4, 72.5 (d, J_{P-C}=4.8 Hz), 74.1 (d, J_{P-C}=4.8 Hz), 74.6, 74.7 (d, J_{P-C}=10.5 Hz), 75.2, 75.4 (d, J_{P-C}=4.8 Hz), 76.2, 76.3 (d, J_{P-C}=18.1 Hz), 77.7 (d, J_{P-C}=10.9 Hz), 78.4 (d, J_{P-C}=8.1 Hz), 86.6, 90.2, 91.1, 96.7 (d, J_{P-C}=25.2 Hz), 100.2, 129.3, 129.4 (d, J_{P-C}=6.0 Hz), 129.7, 130.0, 130.6, 133.7 (d, J_{P-C}=19.1 Hz), 134.4 (d, J_{P-C}=20.1 Hz), 134.8 (d, J_{P-C}=20.1 Hz), 136.5 (d, J_{P-C}=21.1 Hz), 138.4 (d, J_{P-C}=8.0 Hz), 140.0 (d, J_{P-C}=11.1 Hz), 140.8 (d, J_{P-C}=10.1 Hz), 141.4 (d, J_{P-C}=10.1 Hz), 145.7, 151.6, 164.6, 171.9, 174.3; ^{31}P NMR (D_3-MeOD, ppm): δ −17.02 (s), −24.40 (s); ^{31}P NMR (D_6-DMSO, ppm): δ −18.02 (s), −24.10 (s); HRMS (FAB$^+$) m/z calculated for $C_{52}H_{51}FeN_4O_8P_2$: 977.2532 [M+H]. Found: 977.2517 [M+H]; mp 157–158 °C.

4.2.9. [PtCl$_2$(P-P)] {P-P=*N*,*N*-dimethyl-1-[1′,2-bis(diphenylphosphino)ferrocenyl]ethylamine} (11). [PtCl$_2$(cod)] (252 mg, 0.674 mmol) was added to a solution of *N*,*N*-dimethyl-1-[1′,2-bis(diphenylphosphino)ferrocenyl]-ethylamine **2** (425 mg, 0.679 mmol) in dry CH_2Cl_2 (20 mL). The reaction mixture was stirred under argon for 2 h, whereupon the reaction mixture was concentrated to a volume of about 13 mL. After concentration, dry diethyl ether (80 mL) was added with stirring resulting in precipitation of yellow crystals. The crystals were collected, washed with ether and dried under reduced pressure overnight at room temperature to give **11** in a 95% yield (571 mg). ^1H NMR spectrum was in agreement with the literature;[33] ^{31}P NMR (CD_2Cl_2, ppm): δ 16.08 (d, J_{PP}=9.4 Hz, ^{195}Pt satellites J_{PtP}=3851 Hz), 9.28 (d, J_{PP}=9.4 Hz, ^{195}Pt satellites J_{PtP}=3736 Hz).

4.2.10. [PtCl$_2$(P-P)] {P-P=1-[1′,2-bis(diphenylphosphino)ferrocenyl]ethylacetate} (12). 1-[1′,2-Bis(diphenylphosphino)ferrocenyl]ethylacetate **3** (583 mg, 0.910 mmol) was dissolved in dry CH_2Cl_2 (20 mL) followed by the addition of [PtCl$_2$(cod)] (337 mg, 0.901 mmol). The reaction mixture was stirred for 2 h under argon, whereupon concentrated to about 10 mL. The concentrated solution was kept at room temperature with stirring and dry Et_2O (80 mL) was carefully added resulting in precipitation of a slightly orange product. The product was isolated by filtration, washed with ether and dried under reduced pressure producing a crystalline product of **12** in 97% yield (792 mg); IR (KBr, cm^{-1}): 3071, 1729, 1430, 1221; ^1H NMR (CD_2Cl_2, ppm): δ 1.47 (d, 3H, J=6.2 Hz, CHCH_3), 1.67 (s, 3H, COCH_3), 3.54, 3.91, 4.25–4.4, 4.75 (m, 7H, $C_5H_4FeC_5H_3$), 7.07 (q, 1H, J=6.3 Hz, C*H*CH$_3$), 7.14–8.30 (m, 20H, PC$_6H_5$); ^{13}C NMR (100.62 MHz, CD_2Cl_2); δ 18.5, 21.8, 69.0 (d, J_{P-C}=2.0 Hz), 72.1 (d, J_{P-C}=7.2 Hz), 72.8 (d, J_{P-C}=6.8 Hz), 74.0 (d, J_{P-C}=7.5 Hz), 74.2 (dd, J_{P-C}=64.5 Hz, $J_{P'-C}$=2.7 Hz), 74.6 (d, J_{P-C}=10.0 Hz), 74.8 (d, J_{P-C}=7.0 Hz), 77.6 (dd, J_{P-C}=65.8 Hz, $J_{P'-C}$=3.9 Hz), 78.9 (d, J_{P-C}=5.4 Hz), 79.9 (d, J_{P-C}=8.3 Hz), 93.0 (d, J_{P-C}=13.0 Hz), 127.1 (d, J_{P-C}=11.6 Hz), 128.5 (d, J_{P-C}=11.6 Hz), 128.6 (d, J_{P-C}=11.6 Hz), 128.8 (d, J_{P-C}=10.9 Hz), 130.9 (d, J_{P-C}=2.9 Hz), 131.0 (d, J_{P-C}=67.9 Hz), 131.3 (d, J_{P-C}=61.9 Hz), 131.65 (d, J_{P-C}=2.9 Hz), 131.7 (d, J_{P-C}=69.0 Hz), 131.9 (d, J_{P-C}=2.9 Hz), 132.3 (d, J_{P-C}=71.8 Hz), 132.5 (d, J_{P-C}=2.4 Hz), 135.79 (d, J_{P-C}=11.2 Hz), 135.84 (d, J_{P-C}=10.0 Hz), 136.0 (d, J_{P-C}=10.2 Hz), 137.0 (d, J_{P-C}=12.3 Hz), 170.1; ^{31}P NMR (CD_2Cl_2, ppm): δ 14.42 (d, J_{PP}=9.80 Hz, ^{195}Pt satellites J_{PtP}=3817 Hz), 9.63 (d, J_{PP}=9.80 Hz, ^{195}Pt satellites J_{PtP}=3717 Hz); HRMS (FAB$^+$) m/z calculated for $C_{38}H_{34}Cl_2FeO_2P_2Pt$: 905.0408. Found: 905.0410.

4.2.11. [PtCl$_2$(P-P)] {P-P=*N*-[1-[1′,2-bis(diphenylphosphino)ferrocenyl]ethyl]succinamic acid methylester} (13). [PtCl$_2$(cod)] (151 mg, 0.404 mmol) was added to a solution of *N*-[1-[1′,2-bis(diphenylphosphino)ferrocenyl]-ethyl]succinamic acid methylester **6** (289 mg, 0.406 mmol)

in dry CH_2Cl_2 (20 mL) and the reaction mixture was stirred for 2 h under argon. The crude reaction mixture was reduced to a total volume of ca. 5 mL under reduced pressure, and orange crystals started to precipitate after addition of dry Et_2O (50 mL). The produced crystals were washed with ether, collected by filtration and dried under reduced pressure to give **13** in 92% yield (367 mg); IR (KBr, cm^{-1}): 3488, 3336, 3052, 1724, 1667, 1530, 1430; ^1H NMR (CD_2Cl_2, ppm): δ 1.88 (d, 3H, $J=6.9$ Hz, $CHCH_3$), 1.92–2.50 (m, 4H, $COCH_2CH_2CO$), 3.64 (s, 3H, OCH_3), 3.45–3.60, 4.15–5.05 (m, 7H, $C_5H_4FeC_5H_3$), 6.77 (m, 1H, $CHCH_3$), 6.93 (br s, 1H, NHCO), 6.97–8.40 (m, 20H, PC_6H_5); ^{13}C NMR (100.61 MHz, CD_2Cl_2, ppm): δ 17.7, 29.4, 31.1, 46.5 (d, $J_{P-C}=3.0$ Hz), 52.0, 69.8 (d, $J_{P-C}=67.3$ Hz), 71.5 (d, $J_{P-C}=7.2$ Hz), 72.6 (d, $J_{P-C}=7.1$ Hz), 73.4 (d, $J_{P-C}=7.2$ Hz), 74.3 (d, $J_{P-C}=9.2$ Hz), 76.4 (d, $J_{P-C}=8.1$ Hz), 76.5 (d, $J_{P-C}=67.6$ Hz), 77.7 (d, $J_{P-C}=4.3$ Hz), 79.9 (d, $J_{P-C}=9.8$ Hz), 98.0 (d, $J_{P-C}=14.1$ Hz), 127.5 (d, $J_{P-C}=12.1$ Hz), 128.4 (d, $J_{P-C}=12.1$ Hz), 128.5 (d, $J_{P-C}=11.1$ Hz), 129.4 (d, $J_{P-C}=11.1$ Hz), 129.7 (d, $J_{P-C}=59.4$ Hz), 130.8 (d, $J_{P-C}=3.0$ Hz), 131.3 (d, $J_{P-C}=3.0$ Hz), 131.8 (d, $J_{P-C}=67.4$ Hz), 132.5 (d, $J_{P-C}=3.0$ Hz), 132.6 (d, $J_{P-C}=2.0$ Hz), 132.7 (d, $J_{P-C}=70.4$ Hz), 133.6 (d, $J_{P-C}=67.4$ Hz), 134.2 (d, $J_{P-C}=10.1$ Hz), 134.4 (d, $J_{P-C}=11.1$ Hz), 135.9 (d, $J_{P-C}=10.1$ Hz), 136.7 (d, $J_{P-C}=12.1$ Hz), 171.3, 173.6; ^{31}P NMR (CD_2Cl_2, ppm): δ 16.20 (s, ^{195}Pt satellites $J_{PtP}=3801$ Hz), 10.63 (s, ^{195}Pt satellites $J_{PtP}=3748$ Hz); mp 271.5–272.5 °C; HRMS (FAB^+) *m/z* calculated for $C_{41}H_{39}Cl_2FeNO_3P_2Pt$: 976.0779. Found: 976.0774.

4.2.12. [$PtCl_2$(P-P)] (P-P=10) (14). [$PtCl_2$(cod)] (30 mg) was added to a solution of **10** (78 mg, 0.080 mmol) in a mixture of dry CH_2Cl_2–MeOH (99/1) (5 mL). The reaction mixture was stirred for 2 h under argon, whereupon the reaction volume was reduced to about 2 mL. After addition of dry Et_2O (10 mL), yellow crystals started to precipitate, which were filtrated and carefully washed with Et_2O and dried under reduced pressure at room temperature to give **14** in 93% yield (92 mg); IR (KBr, cm^{-1}): 3393, 3052, 1691, 1530, 1430, 1278, 1093; ^1H NMR (D_6-DMSO, ppm): δ 0.97 (d, 3H, $J=6.4$ Hz, $CHCH_3$), 1.75–2.23 (m, 4H, $COCH_2$-CH_2CO), 3.52–3.70 (m, 2H, uridine 5′-H), 3.86 (m, 1H, uridine 4′-H), 3.93 (m, 1H, ferrocene), 3.97 (m, 1H, uridine 3′-H), 4.05 (m, 3H, CH_2NH and uridine 2′-H), 4.09–4.15 and 4.27–4.70 (m, 6H, ferrocene), 5.03–5.13 (m, 2H, $CHCH_3$ and OH), 5.20 (t, 1H, $J=4.8$ Hz, OH), 5.40 (d, 1H, $J=5.4$ Hz, OH), 5.75 (m, 1H, uridine 1′-H), 7.22 (d, 1H, $J=7.1$ Hz, CHNHCO), 7.27–8.12 (m, 20H, PPh), 8.17 (s, 1H, uridine 6-H), 8.28 (t, 1H, $J=5.4$ Hz, CH_2NH), 11.65 (s, 1H, uridine 3-H); ^{13}C NMR (100.61 MHz, D_6-DMSO, ppm): δ 19.9, 27.3, 28.4, 30.1, 42.9, 60.4, 69.4, 71.2 (d, $J_{P-C}=7.2$ Hz), 71.6 (dd, $J_{P-C}=65.4$ Hz, $J_{P'-C}=2.0$ Hz), 72.5 (d, $J_{P-C}=7.5$ Hz), 73.2 (d, $J_{P-C}=11.3$ Hz), 73.6, 73.8 (d, $J_{P-C}=7.5$ Hz), 73.98 (d, $J_{P-C}=6.3$ Hz), 74.01, 75.9 (dd, $J_{P-C}=70.4$ Hz, $J_{P'-C}=3.8$ Hz), 77.1 (d, $J_{P-C}=7.5$ Hz), 78.6 (d, $J_{P-C}=7.5$ Hz), 84.8, 88.0, 89.6, 95.0 (d, $J_{P-C}=12.6$ Hz), 98.1, 126.9 (d, $J_{P-C}=11.3$ Hz), 127.9 (d, $J_{P-C}=11.3$ Hz), 128.0 (d, $J_{P-C}=10.1$ Hz), 128.6 (d, $J_{P-C}=66.7$ Hz), 130.2 (d, $J_{P-C}=66.7$ Hz), 130.5 (d, $J_{P-C}=3.0$ Hz), 130.7 (d, $J_{P-C}=3.0$ Hz), 131.3 (d, $J_{P-C}=3.6$ Hz), 131.4 (d, $J_{P-C}=3.1$ Hz), 131.9 (d, $J_{P-C}=62.9$ Hz), 133.9 (d, $J_{P-C}=10.1$ Hz), 135.09 (d, $J_{P-C}=12.5$ Hz), 135.11 (d, $J_{P-C}=9.1$ Hz), 135.7 (d, $J_{P-C}=11.1$ Hz), 143.7, 149.6, 161.4, 169.3, 171.0; ^{31}P NMR (D_6-DMSO, ppm): δ 16.04 (d, $J_{PP}=9.5$ Hz, ^{195}Pt satellites $J_{PtP}=3894$ Hz), 12.95 (d, $J_{PP}=9.5$ Hz, ^{195}Pt satellites $J_{PtP}=3800$ Hz); HRMS (FAB^+) *m/z* calculated for $C_{52}H_{50}ClFeN_4O_8P_2Pt$: 1206.1790 [M−Cl]. Found: 1206.1799 [M−Cl].

4.3. Cyclic voltammetry

Cyclic voltammetry measurements were carried out at room temperature using a Gamry FAS2 Femtostat (Gamry Instruments, Warminster, USA) using a 2 mm Pt disk working electrode, an Ag/AgCl (3 M LiCl in ethanol) reference electrode (Radiometer) and a Pt-wire counter electrode. Prior to experiments, the Pt-working electrode was mechanically polished with a 0.1 μm alumina suspension and electrochemically cleaned in 0.5 M sulphuric acid. Experiments performed in N_2 saturated dichloromethane using 0.1 M tetrabutylammonium perchlorate as supporting electrolyte and a sample concentration of 500 μM.

4.4. Kinetic investigation by HPLC measurement

4.4.1. Chemicals. The oligonucleotides $d(T_6p(S)T_6)$ and $d(T_7GGT_7)$ were bought from Scandinavian Gene Synthesis AB. They were received in aqueous solutions and were kept frozen at −80 °C. Concentrations of the oligomers were determined by absorption measurements at 260 nm using calculated extinction coefficients. Spectra were recorded using a Nanodrop 3.0.0. spectrophotometer at ambient conditions. The kinetic measurements were performed in aqueous solution with 10 mM $NaClO_4$ (Merck p.a.), pH 6.2. The non-ionic surfactant Triton X-100 (Sigma) was added to the solution in 0.05% v/v, in order to avoid precipitation of the Pt(II)-complexes. Aqueous solutions were prepared using Millipore water, (18 MΩ, ELGA PURELAB Ultragenetic) and stored at room temperature, the pH was determined by use of a Methrom 744 pH meter.

4.4.2. HPLC measurements. The HPLC analysis was carried out on a LaChrome (Merck Hitachi) chromatograph system with a D-7000 interface and a D-7400 UV/vis detector set at 260 nm and at 30 °C. Separation of platinated from unreacted oligonucleotides was obtained by using reversed phase technique, a C18 YMC Hydrosphere column (250⇔4.6 mm I.D., 5 μm particle diameter), equipped with guard, was employed. 0.10 M ammonium acetate buffer (Merck) pH 6.0 was used as the mobile phase with different acetonitrile (LAB-Scan, HPLC grade) gradients, 10–25% for 15 min, 0.8 mL/min flow for separation of $d(T_6p(S)T_6)$. The chromatograms were evaluated by use of an on-line HPLC System Manager Software working under Microsoft Windows NT Workstation version 4.0.

4.4.3. Kinetic measurements. Stock solutions of compound **14** were made in DMSO (Aldrich), kept at −20 °C. The platination reactions were initiated by addition of appropriate amount of oligonucleotides to the thermostated aqueous solution containing the platinum compound (the final DMSO concentration was less than 0.25% v/v). The reactions were performed at 25 °C, the concentrations of the reactants were; [oligonucleotide]$=2.0\times10^{-6}$ M and [Pt(II)]$=1.0\times10^{-5}$ M. Aliquots were withdrawn at different time intervals and directly quenched by eight-fold

dilutions. The samples were stored in liquid nitrogen at −196 °C and injected on HLPC directly after thawing. The time-dependent decrease of the integrated peak areas of the nonreacted oligonucleotides was used to follow the kinetics. The observed first-order rate constant, k_{obs}, was determined by a fit of single exponential function to the experimental data points. The measurements were performed three times and averaged.

Acknowledgements

We are grateful to FLÄK (Forskarskolan i Läkemedelsvetenskap), Lund University, Crafoordska Stiftelsen, Schybergs Stiftelse, The Swedish Cancer Society (contract no. 040607) and The Swedish Research Council (contract no. 40446101 and 40447601) for their financial support. We are also grateful to Dr. Ola Wendt, Roger Johansson and Dr. Karl-Erik Bergquist for their kind help with the ^{13}C NMR experiments.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2006.02.057.

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