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Labeling of organic biomolecules with ethynylferrocene

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The Sonogashira coupling reaction of ethynylferrocene with adenine, uracil, tyrosine and steroid derivatives was studied; with the exception of tyrosine it was proved to be a good route for the attachment of ferrocene to these representative biomolecules. In addition the transformation of alkynyl uracil to furanopyrimidone derivatives was investigated and the formation of the furanopyrimidone ring was confirmed by an X-ray crystallographic analysis carried out on product **16**.

Introduction

Nowadays, the detection of biomolecules in the nanogram and subnanogram region is routinely performed with methods based mainly on enzyme and luminescent labels,[1] which are replacing the traditional radioactive labels. During the last decade electrochemical biosensors have attracted high and continuously increasing interest as another alternative for the analytical determination of biomolecules.[2] In this regard ferrocene and its derivatives are attractive electrochemical probes, because they are stable with convenient synthetic chemistry and they possess reversible and tunable redox properties.[3,4] Especially, ferrocene labeled oligonucleotides have emerged as important versatile tools for the development of bioelectronic gene-sensing systems.[5]

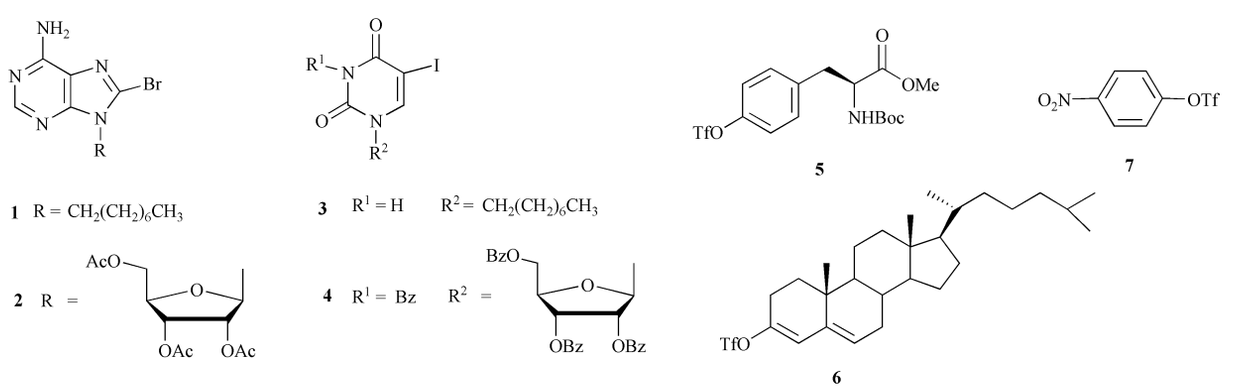
The reaction of choice for the formation of the covalent bond between the label and the biomolecule is often the Sonogashira coupling reaction[6,7] of terminal label-substituted alkynes with suitably derivatised biomolecules. The use of Sonogashira coupling allows low polarity covalent bonds to be formed without the participation of polar functional groups necessary in a nucleophilic substitution or electrophilic addition type of reaction. For ferrocene labeling the most appropriate alkyne seems to be ethynylferrocene since it lacks any other functionalities, it is straight and positions the label remote from essential functional groups on the biomolecule. Furthermore, using ethynylferrocene the label is connected with a carbon–carbon bond without the intervention of enzyme-sensitive ester or amide groups, which are the most common connecting links for ferrocene labeling.[3,4] Despite these good prospects, Sonogashira coupling reactions of ethynylferrocene have been used to a rather limited extent.[8] To the best of our knowledge, in regard to biomolecule labeling only its reaction with iododeoxyuridine has been reported,[5e] in which besides the expected alkyne derivative a cyclization product was also obtained.

In connection with our previous studies on ferrocene chemistry,[9] in this paper we examine the Sonogashira coupling reactions of ethynylferrocene with some representative organic biomolecules.

Results and discussion

As representative biomolecules for the purposes of our study we have chosen uracil, adenine, amino acid and steroid derivatives. Compounds **1**–**6** (Scheme 1) were readily prepared and their Sonogashira coupling with ethynylferrocene **8** was studied. Also, for reasons of comparison, the reaction with the activated triflate **7** was examined. For the substituted uracils and adenines we have used C-5 pyrimidine and C-8 purine substituted derivatives. The C-5 pyrimidine and C-8 purine positions are usually the position of choice for labeling of nucleic bases since they are not involved in the Watson–Crick base pairing; furthermore C-5 substituted pyrimidines and C-8 substituted purines are compatible with polymerase enzymes.[5c,5h,5i]

The Sonogashira approach for the reaction between a terminal alkyne and an aryl or vinyl halide includes a catalytic amount of Pd^{o} or Pd^{II} complexes, copper iodide and an excess of amine.[6c] Different conditions have been employed for this reaction depending on the reactivity of the halide and the alkyne. Although $Pd^{o}L_2$ has been postulated as a common intermediate with both Pd^{o} and Pd^{II} catalysts, considerable differences have been observed in their reactivity and selectivity



Scheme 1

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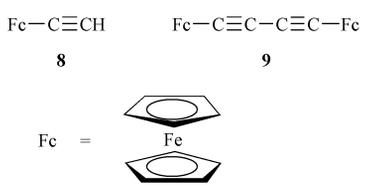
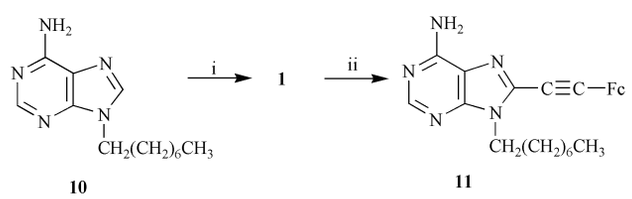
over several substrates. For our coupling experiments we have used both Pd° and Pd^{II} catalysts employing two methods: method A) $Pd(PPh_3)_4$–CuI–NEt_3; method B) $Pd(PPh_3)_2Cl_2$–CuI–$NHPr^i_2$. A potential problem in palladium coupling of alkynes with an organic electrophile is the formation of the homocoupled alkyne in preference to the cross-coupled product. Thus despite the inert atmosphere applied, the formation of alkyne dimers is usually observed in this kind of reaction.[7c,7d] In our case compound **9** (Scheme 2), the dimerization product of ethynylferrocene, was also detected in all reactions studied. After testing several reaction temperatures and reaction times we have found as the optimum conditions to minimize its formation the use of lower temperature (room temperature) and longer reaction times (24 h). Furthermore ethynylferrocene was used in a moderate excess (1.5 equiv.) and it was added gradually during the course of the reaction.



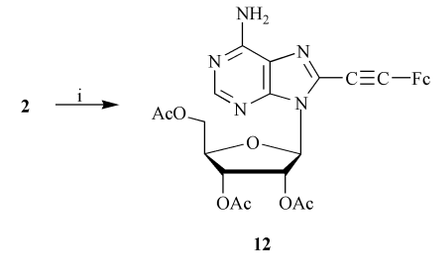
Scheme 2

The reaction of ethynylferrocene **8** with bromoadenine derivative **1**, prepared from 9-octyladenine, proceeded without complications with both $PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$ catalysts to give the expected alkyne derivative **11**. Pd^{II} catalyst under conditions B was proved to be more suitable, affording **11** (Scheme 3) in higher yield (82%) than Pd° (50%). Analogous behaviour was shown by the nucleoside **2**, which gave under conditions B the alkyne derivative **12** in 80% yield (Scheme 4).



Scheme 3 i) Br_2, CH_3CO_2Na, 50 °C, 48 h; ii) Fc–C≡CH, $Pd(PPh_3)_4$, CuI, NEt_3, DMF or Fc–C≡CH, $Pd(PPh_3)_2Cl_2$, CuI, $NHPr^i_2$, DMF, rt, 24 h.

The reaction of ethynylferrocene **8** with the uracil derivative **3**, prepared by alkylation of iodouracil, was more complicated (Scheme 5). Thus with Pd° it gave the expected alkyne derivative **14** as the main product (80% yield) and in low yields compounds **15**, **16** and **17** (10%, 3% and 5% respectively). The



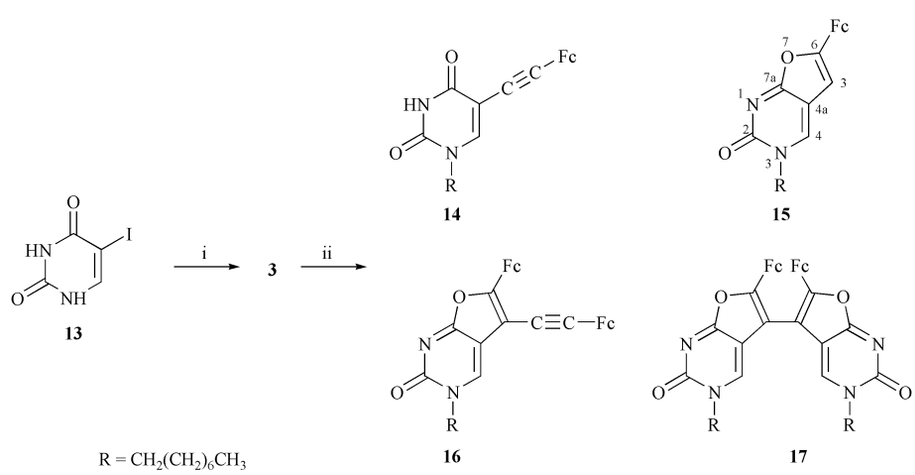
Scheme 4 i) Fc–C≡CH, $Pd(PPh_3)_2Cl_2$, CuI, $NHPr^i_2$, DMF, rt, 24 h.

reaction with Pd^{II} catalyst afforded **14** in lower yield (58%) and a significant amount of compound **16**.

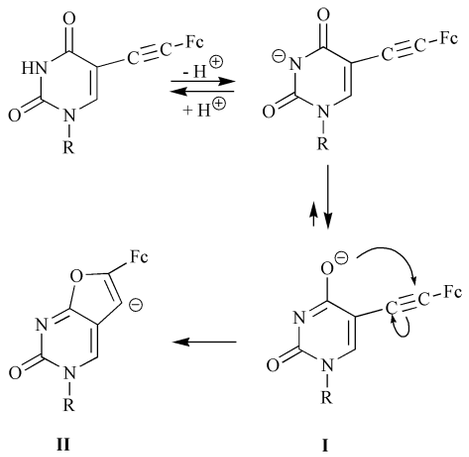
The furanopyrimidone derivative **15** is a rather expected byproduct since Sonogashira coupling with 5-iodouracil substrates is known to give often as byproducts substantial amounts of furano[2,3-*d*]pyrimidin-2-ones formed by cyclization of the initial alkyne derivatives.[5e,7a,7c,7f] Concerning the mechanism of the cyclization Yu and coworkers[5e] proposed a base initiated cyclization in contrast to the results of Robins and Barr who suggested a metal catalysed cyclization.[7a] In order to clarify the conditions for the transformation of **14** to **15** we also carried out some blank experiments. Thus triethylamine and CuI were sequentially added to a solution of **14** in DMF. After each addition the solution was allowed to stay at room temperature for 24 h and then was heated to 50 °C for 6 h. As monitored by TLC, substantial formation of **15** and total consumption of **14** were observed only after heating with both triethylamine and CuI, although traces of **15** were observed even in the test sample at room temperature without any catalyst.

Compounds **16**, **17** are unexpected products since formation of analogous derivatives has not been reported in Sonogashira coupling of uracil substrates. At first, compound **15** was considered to be a possible precursor of both. Thus coupling of **15** with ethynylferrocene could give **16**, whereas homocoupling could lead to **17**. However blank experiments performed with both **14** and **15** showed that **16** and **17** are formed only from **14**. Thus to a solution of ethynylferrocene and **14** or **15** in DMF were added sequentially triethylamine and CuI and the reactions were monitored by TLC. After each addition the reaction mixture was allowed to stay at room temperature for 24 h and then was heated to 50 °C for 6 h. Only in the reaction starting from **14** and after the addition of CuI **16** and **17** were formed, whereas after heating **14** was totally consumed.

Probably a common precursor of all of **15**, **16**, **17** is the anion **II** formed in basic conditions by cyclization of the oxy anion of uracil **I** (Scheme 6). Thus **II** gives **15** by back proton transfer, whereas coupling with ethynylferrocene or homocoupling gives **16** and **17** respectively with mechanisms analogous to that



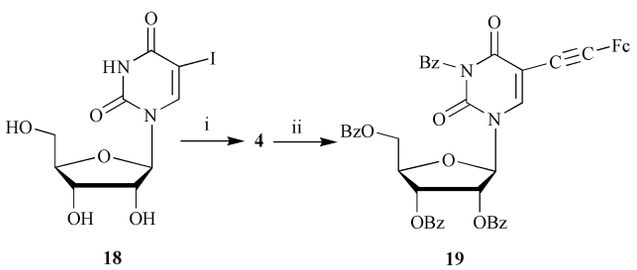
Scheme 5 i) $(CH_3)_3SiSi(CH_3)_3$, $(NH_4)_2SO_4$, reflux, 15 h and then $CH_3(CH_2)_6CH_2Br$, DMF, 80 °C, 24 h; ii) Fc–C≡CH, $Pd(PPh_3)_4$, CuI, NEt_3, DMF or Fc–C≡CH, $Pd(PPh_3)_2Cl_2$, CuI, $NHPr^i_2$, DMF, rt, 24 h.



Scheme 6

postulated for the homocoupling of alkynes.[6e] The driving force for the cyclization step and the subsequent transformations is probably the high electrophilic character of the ferrocene moiety-adjacent carbon atom of the triple bond.

In contrast to **3**, the fully protected nucleoside **4**, prepared from iodouridine, in which cyclization is not possible, reacted with ethynylferrocene under conditions A to give the expected alkyne derivative **19** in satisfactory yield (76%) without the formation of analogous byproducts (Scheme 7).



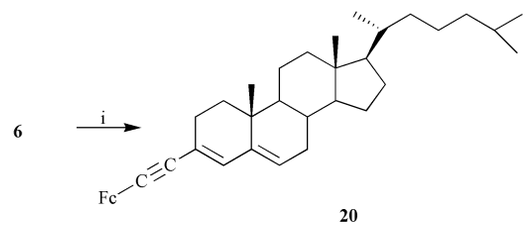
Scheme 7 i) BzCl, pyridine, 0 °C, 24 h; ii) Fc–C≡CH, $Pd(PPh_3)_4$, CuI, NEt_3, DMF, rt, 24 h.

As another target molecule the protected tyrosine triflate **5** was examined for labeling with ethynylferrocene. The attachment of the ferrocene moiety to amino acids is of high interest not only for the purposes of labeling but also for the understanding of electron transfer processes in peptide assemblies.[4a,4b,4c] On the other hand, due to their facile preparation from carbonyl compounds and phenols trifluoromethanesulfonates (triflates) have been widely used in the last ten years instead of halides in cross-coupling reactions with organometallics, exhibiting the same reactivity with bromides.[10] However, reaction of **5** with alkyne **8** using method A or B failed to give any coupled product. Recently, tyrosine triflates have been reported to be coupled with alkynes under palladium catalysis at 70 °C.[7e] So, in a series of experiments the reaction was repeated with increases in the reaction temperature (up to 70 °C) and the amount of catalyst (up to 1 equiv.) without success. The alkyne dimer **9** was isolated in all cases as the only identifiable product. Probably the stability of alkyne **8** cannot stand the higher temperature demands of the reaction. The failure of the reaction of **5** with **8** under the applied conditions can be explained on the basis of the relative reactivity scales in Sonogashira couplings. The relative reactivity of halides is I > Br ~ OTf > Cl whereas with respect to an sp^2 centre the reactivity is vinylic > heteroaromatic > aromatic. In accordance with these reactivity scales ethynylferrocene reacted under mild conditions with heteroaromatic bromides as the adenine derivatives **1** and **2** and failed to react with aromatic triflates.

The steroid derivative **6** was also examined as another interesting biomolecule for labeling. Its triflate, easily prepared from the corresponding ketone as a vinylic triflate, is expected to be more reactive than **5**. Indeed compound **6** reacted with the ethynylferrocene **6** employing both methods A and B and gave the coupling product **20** in 87% and 65% yields respectively (Scheme 8).

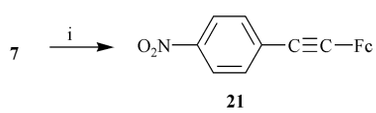
Table 1 sp^2 Carbon chemical shifts of **15**, **16**, **17**

	Chemical shifts, δ					
Compound	C-2	C-4	C-4a	C-5	C-6	C-7a
15	155.2	137.5	108.5	94.7	157.6	171.7
16	155.3	137.9	108.8	96.3	159.5	170.4
17	155.1	138.9	106.8	100.0	154.3	171.1



Scheme 8 i) Fc–C≡CH, $Pd(PPh_3)_4$, CuI, NEt_3, DMF or Fc–C≡CH, $Pd(PPh_3)_2Cl_2$, CuI, $NHPr^i_2$, DMF, rt, 24 h.

In order to extend the scope of Sonogashira coupling of ethynylferrocene with triflates we examined the reaction of 4-nitrophenol triflate **7**, an activated aromatic triflate. Electron withdrawing substituents on the aromatic ring are expected to enhance the coupling reaction since they increase the reactivity towards oxidative addition to Pd° which is considered to be the first stage of the reaction and resembles aromatic nucleophilic substitution. As expected, nitrophenol triflate **7** reacted readily with ethynylferrocene employing method A to give **21** in 90% yield (Scheme 9).



Scheme 9 i) Fc–C≡CH, $Pd(PPh_3)_4$, CuI, NEt_3, DMF, rt, 24 h.

The spectral and analytical data of all new compounds are in accordance with the proposed structures. The differentiation of the two isomeric uracil derivatives **14** and **15** was mainly based on their ^{1}H NMR spectra. The ^{1}H NMR spectrum of **14** exhibits a chemical shift at δ 8.97 corresponding to the NH proton, whereas in the spectrum of **15** this peak is missing and there is a peak at δ 6.25 consistent with a vinyl proton. For compound **16** both MS and NMR data suggest the coupling of one uracil with two ferrocene moieties. In the ^{1}H NMR spectrum NH and vinyl hydrogen chemical shifts are missing, whereas there is a peak at δ 7.79 very close to the value 7.73 observed in **15** for 4-H. The main evidence for the assignment of structure **17** comes from its MS spectrum where the molecular ion peak at *m/z* 862 suggests that **17** is an oxidative dimer of **14** or **15**. In the ^{1}H NMR and ^{13}C NMR spectra there is only a set of peaks for the ferrocene and uracil moieties indicating a symmetric dimer, whereas the absence of NH and vinyl hydrogen chemical shifts in the ^{1}H NMR spectrum is consistent with a furanopyrimidone structure dimerized from the 5-position. The broadenings of some chemical shifts in both ^{1}H NMR and ^{13}C NMR of **17** are attributed to dynamic effects due to the hindered rotation around the C5–C5′ bond. The existence of the common furanopyrimidine ring in compounds **15**, **16** and **17** is further supported by the close similarity observed in their sp^2 carbon chemical shifts as depicted in Table 1.

Finally the structure of compound **16** was unambiguously confirmed by the results of a crystallographic X-ray analysis.

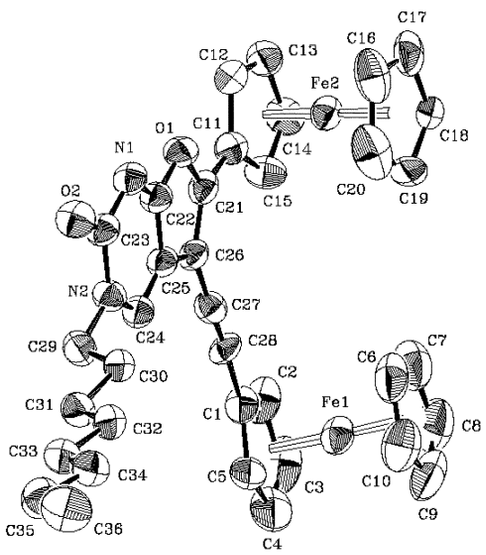


Fig. 1 The molecular structure of compound **16**. The Cp ring defined by C16–C20 is disordered over two orientations; only one is shown in the ORTEP diagram above. Average selected bond distances (Å): Fe(1)–Cp(1) = 2.038(6) Å, Fe(1)–Cp(2) = 2.031(6) Å, Fe(2)–Cp(3) = 2.037(6) Å, Fe(2)–Cp(4) = 2.053(6) Å (Cp(1), Cp(2), Cp(3) and Cp(4) are defined by the atoms C(1)–C(5), C(6)–C(10), C(11)–C(15) and C(16)–C(20) respectively).

An ORTEP diagram showing the atomic labeling is given in Fig. 1.

In conclusion, we have shown that, with the exception of the aromatic triflate **5** the Sonogashira coupling reaction of ethynylferrocene with organic biomolecules bearing aromatic or vinylic halogens or triflates provides an efficient entry for their labeling with the sensitive electrochemical probe of ferrocene without the intervention of ester or amide groups. The reactions proceed smoothly at room temperature providing a significant practical advantage to those that require elevated temperatures. Furthermore the transformation of alkynyl uracil was investigated and the formation of the furanopyrimidone ring was unambiguously proved.

Experimental

Mps are uncorrected and were determined on a Kofler hot-stage microscope. IR spectra were recorded on a Perkin-Elmer 297 spectrometer. ^{1}H NMR spectra were recorded at 300 MHz on a Bruker 300 AM spectrometer and ^{13}C NMR spectra at 75.5 MHz on the same spectrometer and are quoted relative to tetramethylsilane as internal reference, in deuteriochloroform solutions, unless otherwise stated. *J* Values are given in Hz. Mass spectra were performed on a VG-250 spectrometer with ionisation energy maintained at 70 eV. Microanalyses were performed on a Perkin-Elmer 2400-II element analyser. Column chromatography was carried out on Merck Kieselgel (particle size 0.063–0.200 mm) and solvents were distilled before use. Pyridine, NEt_3 and $NHPr^i_2$ were dried with KOH, distilled and stored over molecular sieves 4 Å. DMF was dried with CaH_2, distilled under reduced pressure and stored over molecular sieves 4 Å. Ethynylferrocene was obtained from ferrocenecarboxaldehyde according to a previously described method.[11] The known compounds **2**,[12a] **5**,[12b] **6**,[12c] **7**,[12d] **10**[12e] were also prepared according to the literature procedures.

8-Bromo-9-octyladenine 1

Bromine (2.08 g, 13 mmol) was added to a solution of 9-octyladenine **10** (1 g, 4.05 mmol) and CH_3CO_2Na (1.56 g, 19.02 mmol) in glacial acetic acid (12 cm^3) and the reaction mixture was heated at 50 °C for 48 h. After that ethyl acetate (30 cm^3) was added, the precipitated salts were filtered off and the filtrate was extracted with a 10% $NaHSO_3$ solution (3 × 20 cm^3) and a saturated $NaHCO_3$ solution (2 × 20 cm^3). After the organic layer was dried and evaporated under reduced pressure the residue was purified by column chromatography on silica using ethyl acetate as eluent to give the bromo derivative **1** (1.02 g, 77%) as a beige solid R_f 0.74 (ethyl acetate). Mp 140–142 °C (Found: C, 48.0; N, 21.0; H, 6.1. Calc. for $C_{13}H_{20}BrN_5$: C, 47.9; N, 21.5; H, 6.2%); ν_{max}(Nujol)/cm^{-1} 3270, 3100 (NH_2), 1650 (C=N); δ_H 0.87 (3 H, t, *J* 6.4, CH_3), 1.26 (10 H, m, CH_2CH_2-(CH_2)$_5$$CH_3$), 1.84 (2 H, m, $CH_2CH_2(CH_2)_5CH_3$), 4.20 (2 H, t, *J* 7.3, $CH_2CH_2(CH_2)_5CH_3$), 6.32 (2 H, br s, NH_2), 8.31 (1 H, s, 2-H); δ_C 14.2 (CH_3), 22.5, 26.5, 29.0, 29.4 and 31.7 (CH_2-(CH_2)$_6$$CH_3$), 44.5 ($CH_2(CH_2)_6CH_3$), 119.9 (C-5), 127.2 (C-8), 151.2 (C-4), 152.8 (C-2), 154.3 (C-6); *m*/*z* 325 (M$^+$, 16%), 246.

5-Iodo-1-octyluracil 3

A mixture of 5-iodouracil (0.5 g, 2.1 mmol), 1,1,1,3,3,3-hexamethyldisilazane (1.3 cm^3, 6.3 mmol) and $(NH_4)_2SO_4$ (0.008 g, 0.06 mmol) was heated at reflux for 15 h under an argon atmosphere. The solution was then concentrated by rotary evaporator and to the residue were added DMF (3 cm^3) and bromooctane (0.6 g, 3.1 mmol). The resulting solution was heated at 80 °C for 24 h. Ice–water (30 cm^3) was then added and the mixture was stirred for 30 min and then extracted with dichloromethane (2 × 40 cm^3). After the organic phase was dried and evaporated the residue was purified by column chromatography on silica with hexane–ethyl acetate (3 : 1) as eluent to give **3** (0.36 g, 50%) as a pale yellow solid R_f 0.33 (hexane–ethyl acetate 3 : 1). Mp 151–154 °C (Found: C, 41.3; N, 8.2; H, 5.3. Calc. for $C_{12}H_{19}IN_2O_2$: C, 41.2; N, 8.0; H, 5.5%); ν_{max}(Nujol)/cm^{-1} 3120 (NH), 1660 (C=O); δ_H 0.81 (3 H, t, *J* 6.4, CH_3), 1.22 (10 H, m, CH_2CH_2(CH_2)$_5$$CH_3$), 1.62 (2 H, m, $CH_2CH_2(CH_2)_5CH_3$), 3.69 (2 H, t, *J* 6.4, $CH_2CH_2(CH_2)_5CH_3$), 7.61 (1 H, s, 6-H), 10.16 (1 H, s, NH); δ_C 13.9 (CH_3), 22.4, 26.2, 28.9, 30.0 and 31.5 (CH_2(CH_2)$_6$$CH_3$), 49.1 ($CH_2(CH_2)_6CH_3$), 67.4 (C-5), 149.0 (C-6), 150.1 (C-2) and 160.9 (C-4)); *m*/*z* 350 (M$^+$, 18%), 223 (100, M − I).

3-Benzoyl-2′,3′,5′-tri-*O*-benzoyl-5-iodouridine 4

Benzoyl chloride (0.2 cm^3, 1.7 mmol) was added to a solution of 5-iodouridine **18** (0.1 g, 0.29 mmol) in pyridine (1 cm^3) under cooling and the reaction solution was allowed to remain in the refrigerator for 24 h. Then it was decanted into ice–water (5 cm^3) and extracted with chloroform (2 × 10 cm^3). The organic phase was dried, evaporated and chromatographed on silica with hexane–ethyl acetate (3 : 1) to afford **4** (0.2 g, 88%) as a white solid R_f 0.22 (hexane–ethyl acetate 3 : 1). Mp 180–182 °C (Found: C, 56.5; N, 3.4; H, 3.4. Calc. for $C_{37}H_{27}IN_2O_{10}$: C, 56.5; N, 3.6; H, 3.5%); ν_{max}(Nujol)/cm^{-1} 1700 (C=O, ester), 1655 (C=O, amide); δ_H 4.72–4.85 (3 H, m, 4′-H and 5′-H), 5.77 (1 H, apparent t, ΣJ 12.2, 2′-H), 5.92 (1 H, dd, $J_{2',3'}$ 5.8, $J_{3',4'}$ 3.2, 3′-H), 6.38 (1 H, d, *J* 6.4, 1′-H), 7.30–7.66 (12 H, m, Ph-H), 7.89 (4 H, t, Ph-H), 7.98 (1 H, s, 6-H), 8.03 (2 H, d, *J* = 7, Ph-H), 8.15 (2 H, d, *J* = 7, Ph-H); δ_C 63.8 (C-5′), 69.4 (C-5), 71.5 (C-3′), 74.0 (C-2′), 81.1 (C-4′), 87.7 (C-1′), 128.2, 128.5, 128.55, 128.6, 128.65, 129.0, 129.05, 129.1, 129.7, 129.8, 129.9, 130.6, 130.9, 133.8, 133.9 and 135.1 (C-Ph), 143.6 (C-6), 149.1 (C-2), 158.4 (C-4), 165.3, 165.5, 166.1 and 167.1 (C=O).

General procedure for the coupling reactions

Method A. To a stirred suspension of the halide or triflate (0.2 mmol), $Pd(PPh_3)_4$ (0.022 g, 0.02 mmol) and CuI (0.008 g, 0.04 mmol) in DMF (2 cm^3) deoxygenated with Ar were added sequentially ethynylferrocene **8** (0.042 g, 0.2 mmol) and triethylamine (0.4 cm^3) and the reaction mixture was stirred at rt for 12 h under Ar. TLC showed full consumption of the alkyne. Then a second portion of **8** (0.021 g, 0.1 mmol) was added and the stirring was continued for another 12 h. The solvent was

removed under reduced pressure and the residue separated by column chromatography on silica.

Method B. To a stirred suspension of the halide or triflate (0.2 mmol), $Pd(PPh_3)_2Cl_2$ (0.010 g, 0.013 mmol) and CuI (0.008 g, 0.04 mmol) in DMF (2 cm^3) were added sequentially ethynylferrocene **8** (0.042 g, 0.2 mmol) and diisopropylamine (1 cm^3) and the reaction mixture was stirred at rt for 12 h under Ar. TLC showed full consumption of the alkyne. Then a second portion of **8** (0.021 g, 0.1 mmol) was added and the stirring was continued for another 12 h. The solvent was removed under reduced pressure and the residue separated by column chromatography on silica.

8-(2-Ferrocenylethynyl)-9-octyladenine 11

From the reaction of the alkyne **8** with the substrate **1** the title compound was obtained (45 mg, 50% using method A or 75 mg, 82% using method B) by column chromatography (eluent: 2% NEt_3 in hexane–ethyl acetate, 1 : 1) as a red-orange solid R_f 0.3 (hexane–ethyl acetate 1 : 1). Mp 168–170 °C (Found: C, 65.8; N, 15.15; H, 6.1. Calc. for $C_{25}H_{29}FeN_5$: C, 65.9; N, 15.4; H, 6.4%); ν_{max}(Nujol)/cm^{-1} 3310, 3100 (NH_2), 2200 (C≡C), 1640 (C=N); δ_H 0.85 (3 H, t, *J* 6.7, CH_3), 1.26–1.38 (10 H, m, $CH_2CH_2(CH_2)_5CH_3$), 1.94 (2 H, m, $CH_2CH_2(CH_2)_5CH_3$), 4.28 (7 H, m, $CH_2CH_2(CH_2)_5CH_3$ and Fc-H), 4.37 (2 H, t, *J* 1.9, Fc-H), 4.62 (2 H, t, *J* 1.9, Fc-H), 5.86 (2 H, br s, NH_2), 8.39 (1 H, s, 2-H); δ_C 14.0 (CH_3), 22.6, 26.7, 29.1, 29.7 and 31.7 ($CH_2(CH_2)_6CH_3$), 43.8 ($CH_2(CH_2)_6CH_3$), 61.9, 69.9, 70.3 and 72.0 (C-Fc), 74.9 (C-8α), 96.2 (C-8β), 119.7 (C-5), 135.8 (C-8), 149.9 (C-4), 153.2 (C-2), 154.6 (C-6); *m*/*z* 455 (M^+, 65%).

8-(2-Ferrocenylethynyl)-2′,3′,5′-tri-*O*-acetyladenosine 12

From the reaction of the alkyne **8** with the substrate **2** the title compound was obtained (96 mg, 80%, using method B) by column chromatography (eluent hexane–ethyl acetate 5 : 1 and then ethyl acetate) as an orange solid R_f 0.48 (ethyl acetate). Mp 106–108 °C (Found: C, 55.4; N, 11.3; H, 4.8; Calc. for $C_{28}H_{27}FeN_5O_7$: C, 55.9; N, 11.65; H, 4.5%); ν_{max}(Nujol)/cm^{-1} 3320, 3160 (NH_2), 2200 (C≡C), 1720–1660 (C=O, C=N); δ_H 2.05 (3 H, s, CH_3), 2.12 (3 H, s, CH_3), 2.16 (3 H, s, CH_3), 4.31–4.43 (9 H, m, Fc-H, 4′-H and 5′-Ha), 4.56 (1 H, dd, $J_{5'\text{-}Ha,5'\text{-}Hb}$ 11.0, $J_{4',5'\text{-}Hb}$ 2.9, 5′-Hb), 4.67 (2 H, m, Fc-H), 5.83 (2 H, br s, NH_2), 5.95 (1 H, apparent t, Σ*J* 11.5, 3′-H), 6.28–6.34 (2 H, m, 1′-H and 2′-H), 8.37 (1 H, s, 2-H); δ_C 20.5, 20.55 and 20.7 (CH_3), 62.9 and 63.1 (C-5′ and C-Fc), 70.1, 70.4, 72.2, 72.3 and 72.4 (C-3′, C-2′ and C-Fc), 74.0 (C-8α), 80.0 (C-4′), 87.4 (C-1′), 97.4 (C-8β), 128.8 (C-5), 130.9 (C-8), 149.4 (C-4), 150.8 (C-2), 153.3 (C-1), 169.3, 169.4 and 170.6 (C=O, ester); *m*/*z* 601 (M^+, 13%).

Reaction of ethynylferrocene 8 with 5-iodo-1-octyluracil 3

After using method A or B the reaction mixture was separated on a silica column with hexane–ethyl acetate (2 : 1) as eluent to give in order of elution: **14** (69 mg, 80%), **16** (4 mg, 3%), **15** (9 mg, 10%) and **17** (5 mg, 5%) using method A; **14** (50 mg, 58%) and **16** (19 mg, 15%) using method B.

5-(2-Ferrocenylethynyl)-1-octyluracil 14

This compound was obtained as a yellow solid R_f 0.63 (hexane–ethyl acetate 1 : 1). Mp 125–127 °C (Found: C, 66.45; N, 6.2; H, 6.4. Calc. for $C_{24}H_{28}FeN_2O_2$: C, 66.7; N, 6.5; H, 6.5%); ν_{max}(Nujol)/cm^{-1} 3150 (NH), 2210 (C≡C), 1670 (C=O); δ_H 0.89 (3 H, t, *J* 6.4, CH_3), 1.29 (10 H, m, $CH_2CH_2(CH_2)_5CH_3$), 1.68 (2 H, m, $CH_2CH_2(CH_2)_5CH_3$), 3.76 (2 H, t, *J* 6.4, $CH_2CH_2(CH_2)_5CH_3$), 4.24 (7 H, m, Fc-H), 4.49 (2 H, apparent s, Fc-H), 7.45 (1 H, s, 6-H), 8.97 (1 H, s, NH); δ_C 14.1 (CH_3), 22.6, 26.3, 29.0, 29.05, 29.1 and 31.7 ($CH_2(CH_2)_6CH_3$), 49.2 ($CH_2(CH_2)_6CH_3$), 64.2, 68.9, 70,0 and 71.0 (C-Fc), 75.9 (C-5α), 93.2 (C-5β), 100.7 (C-5), 145.8 (C-6), 149.7 (C-2), 161.6 (C-4); *m*/*z* 432 (M^+, 11%).

6-Ferrocenyl-3-octylfuro[2,3-*d*]pyrimidin-2(3*H*)-one 15

This compound was obtained as an orange solid R_f 0.21 (hexane–ethyl acetate 1 : 1). Mp 225 °C (under dec.) (Found: C, 66.5; N, 6.8; H, 6.25. Calc. for $C_{24}H_{28}FeN_2O_2$: C, 66.7; N, 6.5; H, 6.5%); ν_{max}(Nujol)/cm^{-1} 1690–1660 (C=O and C=N); δ_H 0.88 (3 H, t, *J* 7.1, CH_3), 1.29 (10 H, m, $CH_2CH_2(CH_2)_5CH_3$), 1.82 (2 H, m, $CH_2CH_2(CH_2)_5CH_3$), 3.97 (2 H, t, *J* 7.2, $CH_2CH_2(CH_2)_5CH_3$), 4.15 (5 H, s, Fc-H), 4.41 (2 H, apparent s, Fc-H), 4.72 (2 H, apparent s, Fc-H), 6.25 (1 H, s, 5-H), 7.73 (1 H, s, 4-H); δ_C 14.0 (CH_3), 22.6, 26.6, 29.1, 29.15, 29.2 and 31.7 ($CH_2(CH_2)_6CH_3$), 52.3 ($CH_2(CH_2)_6CH_3$), 66.5, 69.9, 70.0 and 72.6 (C-Fc), 94.7 (C-5), 108.5 (C-4a), 137.5 (C-4), 155.2 and 157.6 (C-2 and C-6), 171.7 (C-7α); *m*/*z* 432 (M^+, 85%).

6-Ferrocenyl-5-(2-ferrocenylethynyl)-3-octylfuro[2,3-*d*]-pyrimidin-2(3*H*)-one 16

This compound was obtained as a red solid R_f 0.45 (hexane–ethyl acetate 1 : 1). Mp 180–182 °C (Found: C, 67.3; N, 4.6; H, 5.95. Calc. for $C_{36}H_{36}Fe_2N_2O_2$: C, 67.5; N, 4.4; H, 5.7%); ν_{max}(Nujol)/cm^{-1} 1660 (C=O); δ_H 0.88 (3 H, t, *J* 6.6, CH_3), 1.29 (10 H, m, $CH_2CH_2(CH_2)_5CH_3$), 1.56 (2 H, m, $CH_2CH_2(CH_2)_5CH_3$), 4.02 (2 H, t, *J* 7.3, $CH_2CH_2(CH_2)_5CH_3$), 4.22 (5 H, s, Fc-H), 4.31 (5 H, s, Fc-H), 4.34 (2 H, t, *J* 1.8, Fc-H), 4.51 (2 H, t, *J* 1.8, Fc-H), 4.58 (2 H, t, *J* 1.8, Fc-H), 5.14 (2 H, t, *J* 1.8, Fc-H), 7.79 (1 H, s, 4-H); δ_C 14.0 (CH_3), 22.6, 26.6, 29.0, 29.1, 29.2 and 31.7 ($CH_2(CH_2)_6CH_3$), 52.4 ($CH_2(CH_2)_6CH_3$), 64.6, 67.4, 69.3, 70.0, 70.1, 70.5, 71.4, 71.9 (C-Fc), 75.1 (C-5α), 93.25 (C-5β), 96.3 (C-5), 108.8 (C-4a), 137.9 (C-4), 155.3 (C-2), 159.5 (C-6), 170.4 (C-7α); *m*/*z* 640 (M^+, 16%).

6-Ferrocenyl-5-(6-ferrocenyl-3-octyl-2-oxo-2,3-dihydrofuro[2,3-*d*]pyrimidin-5-yl)-3-octylfuro[2,3-*d*]pyrimidin-2(3*H*)-one 17

This compound was obtained as a red solid R_f 0.09 (hexane–ethyl acetate 1 : 1). Mp 250 °C (under dec.) (Found: C, 66.6; N, 6.7; H, 6.05. Calc. for $C_{48}H_{54}Fe_2N_4O_4$: C, 66.8; N, 6.5; H, 6.3%); ν_{max}(Nujol)/cm^{-1} 1650 (C=O); δ_H 0.87 (6 H, t, *J* 7.1, CH_3), 1.23 (20 H, m, $CH_2CH_2(CH_2)_5CH_3$), 1.63 (4 H, m, $CH_2CH_2(CH_2)_5CH_3$), 3.71 (2 H, br, $CH_2CH_2(CH_2)_5CH_3$), 3.96 (2 H, br, $CH_2CH_2(CH_2)_5CH_3$), 4.23 (10 H, s, Fc-H), 4.42 (6 H, m, Fc-H), 4.84 (2 H, apparent s, Fc-H), 7.24 (2 H, s, 4-H); δ_C 14.0 (CH_3), 22.5, 26.4, 28.9, 29.15, 29.1 and 31.7 ($CH_2(CH_2)_6CH_3$), 52.2 ($CH_2(CH_2)_6CH_3$), 67.6, 68.2, 70.1, 71.7 (C-Fc), 100.0 (C-5), 106.8 (C-4a), 138.9 (C-4), 154.3 and 155.1 (C-2 and C-6), 171.1 (C-7α); *m*/*z* 862 (M^+, 7%).

3-Benzoyl-2′,3′,5′-tri-*O*-benzoyl-5-(ferrocenylethynyl)uridine 19

From the reaction of the alkyne **8** with the substrate **4** the title compound was obtained (130 mg, 76%, using method A) by column chromatography (eluent hexane–ethyl acetate 3 : 1) as an orange solid R_f 0.63 (hexane–ethyl acetate 3 : 1). Mp 92–94 °C (Found: C, 67.45; N, 3.1; H, 4.3. Calc. for $C_{49}H_{36}FeN_2O_{10}$: C, 67.75; N, 3.2; H, 4.2%); ν_{max}(Nujol)/cm^{-1} 2200 (C≡C), 1700 (C=O, ester), 1660 (C=O, amide); δ_H 4.19 (7 H, m, Fc-H), 4.34 (1 H, apparent s, Fc-H), 4.38 (1 H, apparent s, Fc-H), 4.75–4.79 (3 H, m, 4′-H and 5′-H), 5.77 (1 H, apparent t, Σ*J* 11.6, 2′-H), 5.92 (1 H, dd, $J_{2',3'}$ 5.5, $J_{3',4'}$ 3.7, 3′-H), 6.37 (1 H, d, *J* 6.1, 1′-H), 7.25–7.62 (12 H, m, Ph-H), 7.83 (1 H, s, 6-H), 7.87 (2 H, d, *J* = 7.9, Ph-H), 7.91 (2 H, d, *J* = 7.9, Ph-H), 7.97 (2 H, d, *J* = 7.9, Ph-H), 8.05 (2 H, d, *J* = 8.5, Ph-H); δ_C 63.8 (C-5′and C-Fc), 68.9, 70.1 and 71.4 (C-Fc), 71.6 (C-3′), 74.0 (C-2′), 75.1 (C-5α), 81.0 (C-4′), 88.2 (C-1′), 94.5 (C-5β), 102.6 (C-5), 126.2, 128.2, 128.3, 128.5, 128.6, 128.8, 128.9, 129.1, 129.6, 129.8, 129.9, 130.6, 131.1, 133.6, 133.8 and 135.2 (C–Ph), 140.1 (C-6), 148.4 (C-2), 159.9 (C-4), 165.2, 165.5, 166.1 and 167.5 (C=O).

3-(2-Ferrocenylethynyl)cholesta-3,5-diene 20

From the reaction of the alkyne **8** with the substrate **6** the title compound was obtained (100 mg, 87%, using method A, or

75 mg, 65%, using method B) by column chromatography (eluent hexane–ethyl acetate 5 : 1) as an orange solid R_f 0.83 (hexane–ethyl acetate 5 : 1). Mp 134–136 °C (Found: C, 81.4; H, 9.3. Calc. for $C_{39}H_{52}Fe$: C, 81.2; H, 9.1%); ν_{max}(Nujol)/cm^{-1} 2190 (C≡C); δ_H 0.64 (3 H, s, CH_3), 0.79–2.35 (38 H, m), 4.12 (2 H, t, *J* 1.8, Fc-H), 4.14 (5 H, s, Fc-H), 4.34 (2 H, t, *J* 1.8, Fc-H), 5.45 (1 H, m, 6-H), 6.24 (1 H, s, 4-H); δ_C 12.0, 18.7, 19.1, 21.0, 22.6, 22.8, 23.8, 24.2, 27.2, 28.0, 28.2, 31.8, 32.1, 33.7, 34.6, 35.8, 36.2, 39.5, 39.8, 48.2, 56.2 and 56.9 (sp^3 C), 66.0, 68.6, 69.9 and 71.2 (C-Fc), 87.7 and 87.9 (C-3α and C-3β), 117.7, 125.7, 134.5 and 141.6 (C-3, C-4, C-5 and C-6); *m*/*z* 576 (M^+, 38%).

4-(2-Ferrocenylethynyl)-1-nitrobenzene 21

From the reaction of the alkyne **8** with the substrate **7** the title compound was obtained (60 mg, 90%, using method A) by column chromatography (eluent hexane–ethyl acetate 10 : 1) as a dark red solid R_f 0.73 (hexane–ethyl acetate 10 : 1). Mp 144–145 °C (Found: C, 65.4; N, 4.2; H, 4.1. Calc. for $C_{18}H_{13}FeNO_2$: C, 65.3; N, 4.2, H, 4.0%); ν_{max}(Nujol)/cm^{-1} 2165 (C≡C); δ_H 4.26 (5 H, s, Fc-H), 4.32 (2 H, t, *J* 1.8, Fc-H), 4.55 (2 H, t, *J* 1.8, Fc-H), 7.60 (2 H, d, *J* 8.5, 3-H), 8.19 (2 H, *J* 8.5, 2-H); δ_C 63.7, 69.5, 70.1 and 71.8 (C-Fc), 84.4 and 95.2 (C-4α and C-4β), 123.6, 131.1, 131.8 and 146.4 (C–Ar); *m*/*z* 331 (M^+, 100%).

Crystal structure determination of compound 16 †

A yellow/orange crystal of compound **16** (0.03 × 0.20 × 0.60 mm) was mounted in air. Diffraction measurements were made on a $P2_1$ Nicolet diffractometer upgraded by Crystal Logic using graphite monochromated Cu radiation. Unit cell dimensions were determined and refined by using the angular settings of 25 automatically centered reflections in the range 22 < 2θ < 54°. Intensity data were recorded using a θ–2θ scan to 2θmax = 121°, with scan speed 1.5° min^{-1} and scan range 2.6° plus $\alpha_1\alpha_2$ separation. Three standard reflections monitored every 97 reflections showed less than 3% variation and no decay. Lorentz, polarization and ψ-scan absorption corrections were applied using Crystal Logic software. The structure was solved by direct methods using SHELXS-86[13a] and refined by full-matrix least-squares techniques on F^2 with SHELXL-93.[13b] All non-hydrogen atoms were refined anisotropically. The Cp ring defined by the atoms C(16)–C(20) was found disordered and refined anisotropically in two orientations with occupation factors 0.53 and 0.47 respectively. Thus, no hydrogen atoms for that Cp ring were included in the refinement. The rest of the hydrogen atoms were located by difference maps and were refined isotropically.

Crystal data

$C_{36}H_{36}Fe_2N_2O_2$, M = 640.37, monoclinic, a = 16.192(5), b = 10.689(4), c = 17.644(6) Å, β = 91.95(2)°, V = 3052(2) Å^3, T = 298 K, space group $P2_1/c$, Z = 4, μ(Cu-Kα) = 7.892 mm^{-1}, 4701 reflections measured, 4538 unique (Rint = 0.0391), 4238 reflections used in all calculations. The final $wR(F^2)$ was 0.2006 (all data), the final R = 0.0600 for 2594 reflections with $I > 2\sigma(I)$.

† CCDC reference number 200800. See http://www.rsc.org/suppdata/ob/b3/b300191a/ for crystallographic files in .cif or other electronic format.

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