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Modification of the Cp′ ring in the ferrocifen precursor and its influence on the recognition by the estrogen receptor

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Abstract—A synthetic pathway giving access to diphenyl ethylene organometallic derivatives possessing the ferrocifen precursor skeleton modified in the Cp′ ring is described. It relies on reaction of the (η^5-propionylcyclopentadienyl) (η^6-benzene)iron(II) salt **7** with substituted cyclopentadienyl anions or their heteroanalogs followed by the McMurry coupling reaction with 4,4′-dihydroxybenzophenone. Using this approach pentamethylcyclopentadienyl and 3,4-dimethylphospholyl analogs of ferrocifen precursor (**10** and **11**) have been synthesized. Even with the presence of the bulky and containing phosphorus η^5-ligands these compounds are still recognized by the two subtypes of estrogen receptor(ERα and ERβ).

1. Introduction

Ferrocifen **1** and hydroxyferrocifen **2** are the ferrocenyl analogs of tamoxifen **3**, a drug currently used in the treatment of hormone-dependent breast cancers via its active metabolite, 4-hydroxytamoxifen **4**,[1] which is considered as the archetypal SERM (Selective Estrogen Receptor Modulator) (Chart 1).

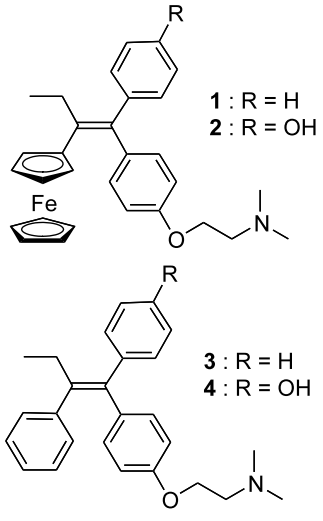

Chart 1.

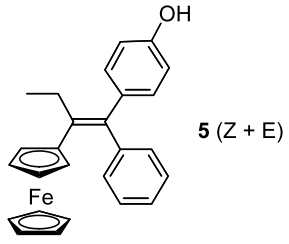

Chart 2.

The replacement of the phenyl ring by the ferrocenyl moiety brought about novel pharmacological properties for **2**. For example it has been shown that **2** displays an in vitro antiproliferative effect on both hormono dependent (MCF7) and independent (MDA-MB231) breast cancer cell lines whereas its phenyl counterpart **4** is active only against hormono dependent cell line.[2] It has also been shown that **5**, a complex deprived of the dimethylamino side chain generally assumed to be responsible for the antiestrogenic effect also displays an antiproliferative activity on MCF7 cells (Chart 2).[3]

So far, the mechanism behind these promising and intriguing properties has not been elucidated. This situation prompted us to start a systematic study on the

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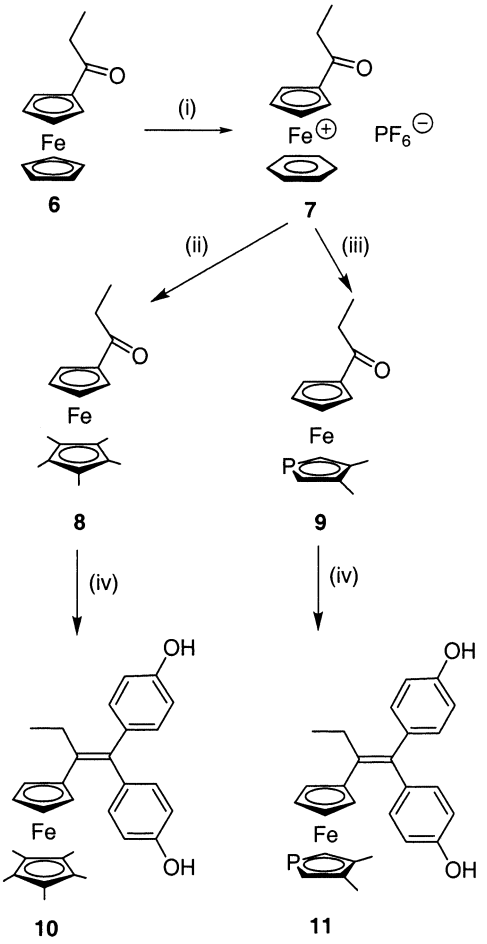
structure–activity relationship of the ferrocifen family. As a first possibility we have considered structural modification of the unsubstituted cyclopentadienyl (Cp′) ligand by introduction of suitable substituent(s) or heteroatoms. In this communication we describe a synthetic way to **10** and **11** compounds of the ferrocifen family with a modified Cp′ ring, namely, 1′,2′,3′,4′,5′-pentamethylferrocenyl and 3′,4′-dimethylphosphaferrocenyl.

2. Results and discussion

Our synthetic strategy is shown in Scheme 1. The key step is the substitution of the η^6-arene ligand in **7** by a substituted η^5-cyclopentadienyl ligand or its heteroanalog. The inspiration for developing this step was found in the work of Roberts and Wells,[4,5] describing reaction of some η^6-arene- η^5-cyclopentadienyl iron(II) cations with phospholyl anions leading to phosphaferrocenes. The yields of this reaction can be moderate since some side processes occur but it is operationally simple and starting materials are readily available.



Scheme 1. *Reagents*: (i) C_6H_6, $AlCl_3$; (ii) C_5Me_5Li; (iii) (3,4-dimethylphospholyl)Li; (iv) TiCl4, Zn, 4,4′-dihydroxybenzophenone.

The starting complex **7** was prepared by the Nesmeyanov reaction[6] of propionylferrocene **6** with benzene and aluminum chloride. It was isolated as the hexafluorophosphate salt in 70% yield and fully characterized.[†] Complex **7** then reacted with pentamethylcyclopentadienyl lithium in DME at 50°C to give a complex reaction mixture, from which **8** was isolated by column chromatography. However, the yield of this compound is rather poor (13%). Apparently, various side reactions take place, especially in the presence of propionyl function prone itself to nucleophilic attack. Similarly, reaction of **7** with 3,4-dimethylphospholyl lithium (generated from 1-phenyl-3,4- dimethyl phosphole and lithium metal)[7] in THF at 50°C yielded **9** in 23% yield. It is worthy noting that it has been suggested that P-nucleophilicity of phospholyl anion directing attack on the iron atom plays an essential role in the reactions studied by Roberts and Wells.[4] Our result reveals that an anion displaying only π-binding properties, such as pentamethyl-cyclopentadienyl anion also can replace the arene ligand in a η^6-arene-η^5-cyclopentadienyl iron(II) complex.

The above results suggest that reaction of η^6-arene-η^5-acylcyclo-pentadienyl iron(II) cations with anionic η^5-ligands could be a general way to ferrocenyl ketones having substituents or heteroatoms in the other ring.

[†] All the synthesized compounds gave correct elemental analyses. **7**. ^{1}H NMR (400 MHz, acetone-d_6, δ): 6.53 (s, 6H, C_6H_6), 5.74 (broad s, 2H, C_5H_4), 5.46 (broad s, 2H, C_5H_4), 3.02 (q, 2H, $J=6.8$ Hz, $C\underline{H}_2CH_3$), 1.14 (t, 3H, $J=6.8$ Hz, $CH_2\underline{H}_3$). ^{13}C NMR (100 MHz, acetone-d_6, δ): 201.1 ($\underline{C}$=O), 90.3 ($\underline{C}_6H_6$), 86.1 (Cp), 79.7 (Cp) 76.9 (Cp), 34.4 ($C\underline{H}_2CH_3$), 7.56 ($CH_2\underline{H}_3$). **8**. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 4.26 (t, 2H $J=1.9$ Hz, C_5H_4), 4.02 (t, 2H $J=1.9$ Hz, C_5H_4), 2.60 (q, 2H, $J=7.3$ Hz, $C\underline{H}_2CH_3$), 1.80 (s, 15H, CH_3 from Cp*) 1.16 (t, 3H, $J=7.3$ Hz, $CH_2C\underline{H}_3$).^{13}C NMR (50 MHz, $CDCl_3$, δ): 203.8 ($\underline{C}$=O), 81.3 (Cp*), 80.2 (Cp), 76.0 (Cp), 71.5 (Cp), 32.8 ($\underline{C}H_2CH_3$), 10.4. (Me from Cp*), 8.0 ($CH_2\underline{C}H_3$). MS (70 eV, m/z): 312 (M^+), 283 ($M-C_2H_5^+$), 255 ($M-COC_2H_5^+$). IR (KBr, cm^{-1}): 1656 (CO). **9**. ^{1}H NMR (400 MHz $CDCl_3$, δ): 4.78 (t, 2H, $J=1.8$ Hz, C_5H_4), 4.42 (t, 2H, $J=1.8$ Hz, C_5H_4), 3.73 (d, 2H, $J_{P-H}=36$ Hz, phospholyl), 2.71 (q, 2H, $J=7.2$ Hz, $C\underline{H}_2CH_3$), 2.10 (s, 6H, $C\underline{H}_3$), 1.16 (t, 3H, $J=7.2$ Hz, $CH_2C\underline{H}_3$).^{13}C NMR (100 MHz, $C\underline{D}Cl_3$, δ): 204.0 ($\underline{C}$=O); 96.35 (d, $^2J_{P-C}=7.1$ Hz, $Me_2\underline{C}_4H_2P$), 81.22 (Cp), 80.98 (d, $^2J_{P-C}=47.5$ Hz, $Me_2\underline{C}_4H_2P$), 75.12 (Cp), 72.30 (Cp), 33.09 ($\underline{C}H_2CH_3$), 15.51 ($\underline{C}H_3$), 8.18 ($CH_2\underline{C}H_3$). ^{31}P NMR (161.9 MHz, $CDCl_3$, δ): 77.5 (d, $^2J_{P-H}=36.2$ Hz). MS (70 eV, m/z): 288 (M^+), 259 ($M-C_2H_5^+$), 231 ($M-COC_2H_5^+$). IR (KBr, cm^{-1}): 1673. **10**. ^{1}H NMR (400 MHz, CD_2Cl_2, δ): 7.02 (d, 2H, $J=8$ Hz, Ph), 6.92 (d, 2H, $J=8$ Hz, Ph), 6.76–6.72 (m, 4H, Ph), 5.0 (very broad s, 2H, O$\underline{H}$), 3.73 (s, 2H, C_5H_4), 3.55 (s, 2H, C_5H_4), 2.16 (broad q, 2H, $J=7.2$ Hz, $C\underline{H}_2CH_3$), 1.52 (s, 15H, CH_3); 0.94 (t, 3H, $J=7.2$ Hz, $CH_2C\underline{H}_3$); ^{13}C NMR (100 MHz CD_2Cl_2, δ): 153.8, 153.6, 137.6, 137.0, 135.9, 130.9, 130.6, 130,2, 114,8, 114.6, 87.8, 73.4, 71.7, 71.3, 26.2, 14.7, 10.3. MS (70 eV, m/z): 494 (M^+). IR (KBr, cm^{-1}): 3414 (OH), 1606 (C=C). **11**. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.06–6.68 (four d, $J=8$ Hz, 8H, Ph), 4.97 (s, 1H, O$\underline{H}$), 4.93 (s, 1H, O$\underline{H}$), 4.00 (broad s, 2H, Cp) 3.96 (broad s, 2H, Cp), 3.33 (d, 2H, $J_{P-H}=36$ Hz, phospholyl), 2.48 (q, 2H, $J=8$ Hz, $C\underline{H}_2CH_3$), 2.12 (s, 6H, $C\underline{H}_3$), 0.95 (t, 3H, $J=8$ Hz, $CH_2C\underline{H}_3$). ^{13}C NMR (100 MHz, acetone-d_6, δ): 154.0, 153.9, 138.1, 137.6, 137.2, 135.8, 131.2, 130.5, 115.3, 95.55 (d, $^2J_{P-C}=10$ Hz,), 89.5, 80.0 (d, $^2J_{P-C}=60$ Hz), 72.8 (Cp), 71.8 (Cp), 28.0 ($\underline{C}H_2CH_3$), 16.0 ($\underline{C}H_3$), 15.4 ($CH_2\underline{C}H_3$). ^{31}P NMR (161.9 MHz, $CDCl_3$, δ): 79.1, $^2J_{P-H}=36.3$ Hz. MS (70 eV, m/z): 470 $(M)^+$. IR (KBr, cm^{-1}): 3430 (OH), 1604 (C=C).

The McMurry coupling reaction of **8** and **9** with 4,4′-dihydroxybenzophenone was carried out according to earlier published procedure[3] and afforded **10** and **11** in 14 and 16% yield, respectively. Both compounds were fully characterized by spectral methods and elemental analyses.[†]

In a preliminary biochemical study the relative binding affinity (RBA) of **10** and **11** have been measured for the alpha and beta forms of the estrogen receptor (ER) using the radiochemical method previously described.[8] Lamb uterus was used as a source of ERα, while ERβ, the second form of the receptor recently identified,[9] was produced in a baculovirus-mediated expression system and purchased from PanVera (USA). The RBA values found for ERα (0.5 for **10** and 1.5 for **11**) are lower than the values found for **5**, the corresponding ferrocenyl derivative (RBA = 5%), while the RBA values found for ERβ are much higher (8.5 and 10%, respectively) and are approximately identical to the value found for **5** (RBA = 10%). These results show that despite the presence of bulkier and containing phosphorus atom η^5-ligands the complexes are still recognized by the two forms of the estrogen receptor. However, the α form seems to be relatively less able to accommodate them.

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