Facile route to ferrocifen, 1-[4-(2-dimethylaminoethoxy)]-1-(phenyl-2-ferrocenyl-but-1-ene), first organometallic analogue of tamoxifen, by the McMurry reaction

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Abstract

As part of the search for tamoxifen substitutes that could be useful in the treatment of breast cancer, the use of organometallic complexes has been investigated. For this purpose a synthesis has been developed for ferrocifen, the prototype of this new series of complexes. Low valent titanium-mediated ($TiCl_4/Zn$) cross-coupling of $4\text{-MeO-}C_6H_4COPh$ with ferrocenyl ethyl ketone affords the corresponding but-1-ene in high yield (66%), from which ferrocifen, **3**, is rapidly prepared in an overall yield of 41%. © 1997 Elsevier Science S.A.

Keywords: Ferrocifen; Ferrocene; Tamoxifen; Anti-tumour

1. Introduction

Tamoxifen (TAM) **1** and its congeners are widely used as a supplementary therapy to control cancers of the breast that test positive for the oestradiol receptor (ER) [1]. This series of molecules has a number of advantages in increasing the survival rate of patients, especially because they are relatively well tolerated over time. However, in the long run patients develop resistance to treatment with TAM, and in fact the development of certain tumours of the breast is eventually stimulated by TAM [2]. Research efforts aimed at finding new and effective anti-estrogens, without the disadvantages of TAM **1** are clearly of great interest today

[3]. With this goal in mind, the company ICI has modified the 7α position of oestradiol [3], while Roussel-Uclaf (RU) has concentrated on the 11β position [4].

In the search for such anti-estrogens we are attempting to follow a new direction, based on organometallic chemistry. We recently suggested that hydroxyferrocifen, **4** (Z), a molecule in which the aromatic β ring of tamoxifen is replaced by a ferrocene moiety, could offer an interesting new approach in this area [5]. The organometallic ferrocene group has in fact been shown to possess aromatic properties, it is stable in biological media, and its first metabolite, the ferricinium ion, is a recognized anti-tumoural agent [6]. A preliminary cytotoxic test for compound **4** has shown a positive activity. It is known that TAM **1** metabolizes into 4-hydroxytamoxifen **2**. Similarly, hydroxyferrocifen **4** may be considered as a metabolite of ferrocifen **3**. This later

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compound might therefore be expected to potentiate the anti-tumour effect of tamoxifen.

(Z)-Tamoxifen (TAM) 1

(Z)-Hydroxytamoxifen (TAM) 2

(Z)-Ferrocifen 3

(Z)-Hydroxyferrocifen 4
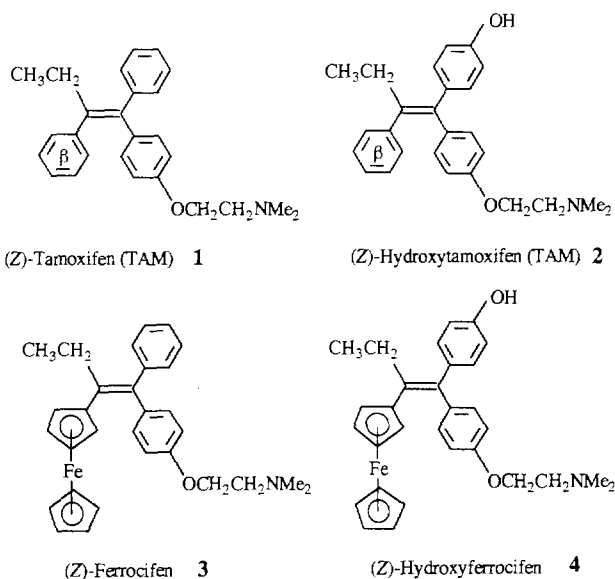
Here we report a rapid and efficient synthetic method for ferrocifen **3**. Two methods have been used. The first method is similar to that of hydroxyferrocifen previously described [5]. It is a long and painstaking route that gave **3** in a very low overall yield, insufficient for the method to be considered of serious potential interest. The second method is more convenient, using a strategy based on McMurry coupling [7]. This strategy was initially developed by Mukaiyama et al. [8] and applied by Coe and Scriven [9] to cross-coupling of benzophenones. One of the two isomers of **3** was identified by X-ray analysis.
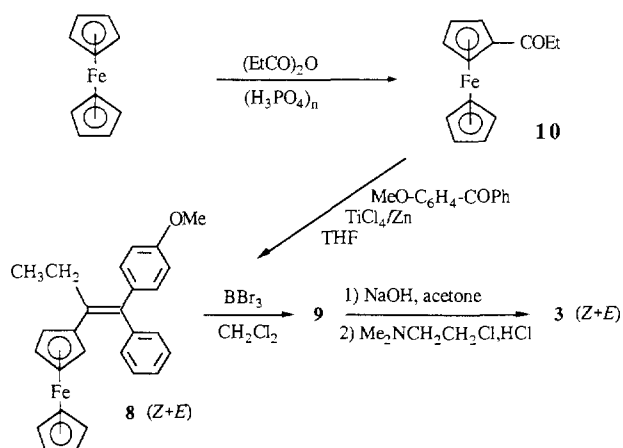
2. Results and discussion

2.1. Synthesis

Following the synthetic method of hydroxyferrocifen **4**, Z- and E-ferrocifen **3** have been prepared for the first time from ferrocenyl acetic acid. The synthetic pathway is shown in Scheme 1.
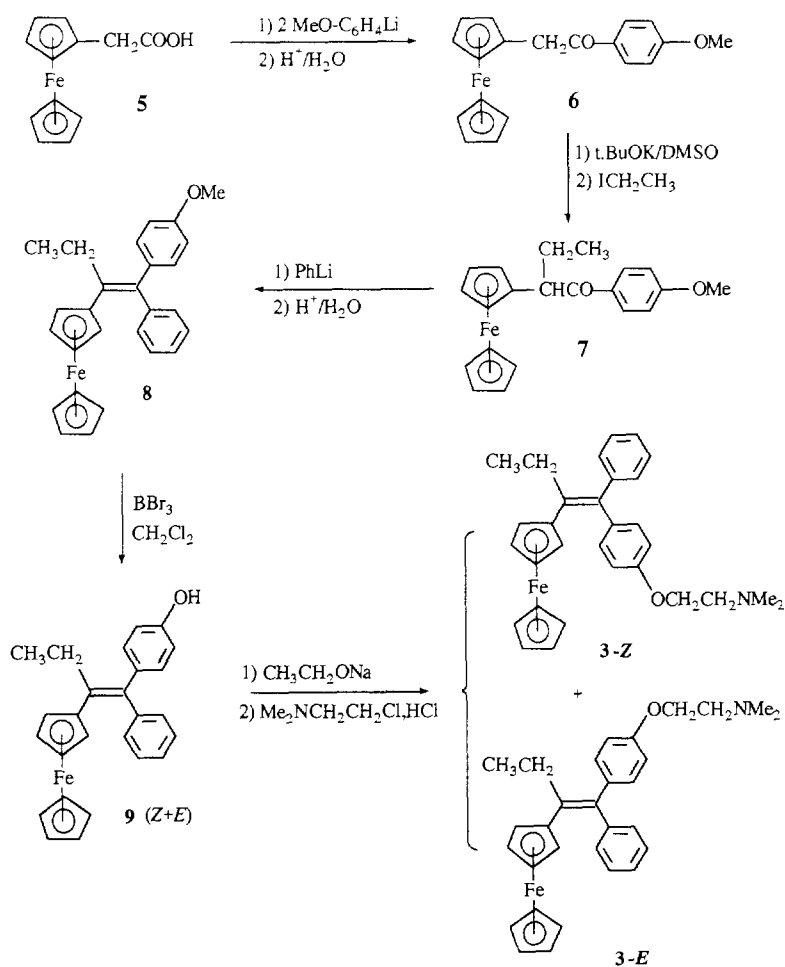
Scheme 1.

Scheme 2.

The first step is to react the organolithium $CH_3OC_6H_4Li$ with ferrocenyl acetic acid **5**, obtained from the corresponding quaternary ammonium salt, to give the ketone **6** (yield 41%). Next an ethyl group is attached at the α position of the ferrocenyl group. This is effected by formation of the anion in the α position of the metallocene, using a strong base, t-BuOK/DMSO, followed by rapid addition of the electrophilic reagent EtI. The immediate hydrolysis of the solution avoids the formation of the disubstituted complex and gives the compound **7** in a yield of 72%. The third step in this synthesis is the formation of the ethylene skeleton by addition of freshly prepared PhLi to the ketone **7** mentioned above. The dehydration of the intermediate alcohol in the ethanol medium by the action of concentrated HCl allows recovery of the 1-butenes (*Z* and *E*) **8** with a yield of 37%. At this step, it is possible to separate the two isomers from one another by fractional crystallization, but it is not worth doing this operation while the final compounds need two more steps and these isomers are the subject of isomerization. The deprotection of the phenol function has been done by using pure BBr_3, leading quantitatively to the *Z* and *E* phenols **9**. Fixation of the amine chain which could give the molecule its anti-estrogen properties can now be carried out. Addition of (dimethylamino)ethyl chloride, hydrochloride, in ethanol solution gives (*Z* and *E*) ferrocifen in a yield of 66%. The *Z* and *E* isomers of ferrocifen **3** are then separated by chromatography on silica gel plates with a toluene/pyridine mixture as eluent, in proportion 6/1 by volume.

Even without taking into account the need to prepare ferrocenyl acetic acid **5**, the synthetic route is quite long, the overall yield of **3** from ferrocenyl acetic acid is only 5.6%. This difficult synthesis prompts us to look for a better synthetic method and we found that the use of the McMurry reaction is very convenient for the preparation of **8**. Scheme 2 shows the synthetic pathway.

First, the ferrocenyl ethyl ketone **10** is prepared, in 80% yield, from ferrocene and propionic anhydride, by an electrophilic substitution catalysed by polyphosphoric acid $(H_3PO_4)_n$ [10]. Next the key step in the synthesis is performed, which is to couple commercially obtained 4-methoxybenzophenone with the ferrocenyl ketone **10** by means of a low-valent titanium complex. The latter is obtained by heating $TiCl_4$ with an excess of Zn under reflux for 2.5 h in an argon atmosphere. It should be noted that to avoid coupling of the ketone **10** to itself, a large (five-fold) excess of 4-methoxybenzophenone must be used. The butene **8** is easily obtained as a mixture (*Z* and *E*) after purification on silica gel plates in a solution of ethyl acetate and pentane (1/20 v/v), in 66% yield.

2.2. X-ray structure of 3-Z

The X-ray structural determination allows the identification of the two isomers without ambiguity. 3-Z

Table 1
Summary of crystallographic data for 3-Z

F_w	479.5
a (Å)	9.427(5)
b (Å)	12.349(3)
c (Å)	21.990(3)
α (°)	99.30(2)
β (°)	96.45(3)
γ (°)	94.52(3)
V (Å^3)	2498(17)
Z	4
Crystal system	Triclinic
Space group	$P\bar{1}$
Linear absorption coefficient μ (cm^{-1})	6.23
Density ρ (g cm^{-3})	1.27
Diffractometer	CAD4 Enraf-Nonius
Radiation	Mo Kα ($\lambda = 0.71069$ Å)
Scan type	$\omega/2\theta$
Scan range (°)	$0.8 + 0.345$ tg θ
θ Limits (°)	1–25
Temperature of measurement	Room temperature
Octants collected	0, 11; -14, 14; -26, 26
No. of data collected	9360
No. of unique data collected	8776
No. of unique data used for refinement	2455 $(F_o)^2 > 3\sigma(F_o)^2$
R_{int}	0.13
$R = \Sigma\|\|F_o\| - \|F_c\|\|/\Sigma\|F_o\|$	0.092
$R_w = \Sigma w(\|F_o\| - \|F_c\|)^2/\Sigma F_o^2$	0.106, $w = 1.0$
Absorption correction	DIFABS (min = 0.90, max = 1.10)
Extinction parameter ($\times 10^{-6}$)	None
Goodness of fit S	3.54
No. of variables	266
$\Delta\rho_{min}$ (e Å^{-3})	-0.88
$\Delta\rho_{max}$ (e Å^{-3})	0.75

Table 2
Interatomic distances (Å) for 3-Z

Fe(1)–C(11)	2.08(2)	Fe(1)–C(12)	2.03(2)
Fe(1)–C(13)	1.99(2)	Fe(1)–C(14)	1.97(2)
Fe(1)–C(15)	2.03(2)	Fe(1)–C(16)	2.02(2)
Fe(1)–C(17)	1.98(2)	Fe(1)–C(18)	2.01(2)
Fe(1)–C(19)	2.02(3)	Fe(1)–C(20)	2.04(2)
O(1)–C(24)	1.39(2)	O(1)–C(27)	1.42(2)
N(1)–C(28)	1.44(3)	N(1)–C(29)	1.38(3)
N(1)–C(30)	1.53(3)	C(1)–C(2)	1.37(2)
C(1)–C(3)	1.55(2)	C(1)–C(11)	1.41(2)
C(2)–C(21)	1.51(2)	C(2)–C(31)	1.51(3)
C(3)–C(4)	1.51(3)	C(11)–C(12)	1.42(2)
C(11)–C(15)	1.43(2)	C(12)–C(13)	1.43(3)
C(13)–C(14)	1.30(3)	C(14)–C(15)	1.35(3)
C(16)–C(17)	1.36(3)	C(16)–C(20)	1.34(3)
C(17)–C(18)	1.37(3)	C(18)–C(19)	1.37(3)
C(19)–C(20)	1.40(3)	C(21)–C(22)	1.33(2)
C(21)–C(26)	1.37(2)	C(22)–C(23)	1.38(2)
C(23)–C(24)	1.41(2)	C(24)–C(25)	1.38(2)
C(25)–C(26)	1.44(2)	C(27)–C(28)	1.57(3)
C(31)–C(32)	1.36(3)	C(31)–C(36)	1.33(3)
C(32)–C(33)	1.37(3)	C(33)–C(34)	1.32(3)
C(34)–C(35)	1.39(3)	C(35)–C(36)	1.42(3)

crystallizes from pentane in the triclinic space group $P\bar{1}$. Crystallographic data and bond lengths are collected in, respectively, Tables 1 and 2. A representation of the molecular structure of 3-Z is shown in Fig. 1. The structure of 3-Z may be compared to that of Z-tamoxifen [11] and to that of E-tamoxifen [12]. The main difference between 3-Z and the tamoxifen is apparent in the double bond length and the angle formed
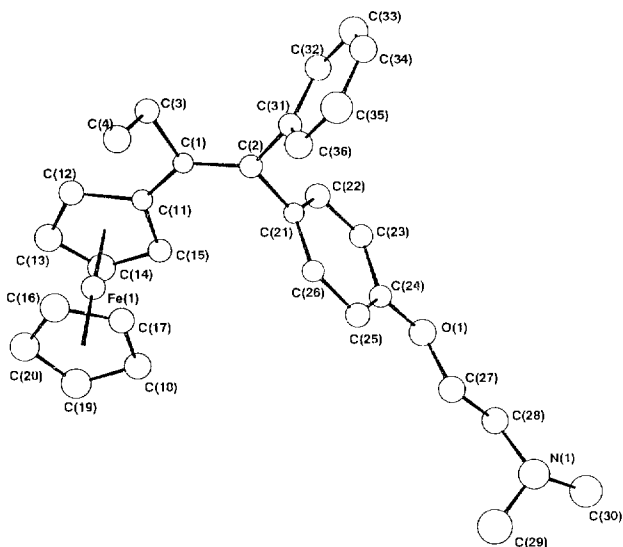

Fig. 1. View of the molecular structure of 1-[4-(2-dimethyl-aminoethoxy)phenyl]-1-(phenyl)-2-ferrocenyl but-1-ene (3-Z) showing the atom numbering. Selected angles (°): C(1)–C(2)–C(21), 122.0(17); C(1)–C(2)–C(31), 125.0(17); C(2)–C(1)–C(11), 129.0(17); C(2)–C(1)–C(3), 115.3(16); C(1)–C(3)–C(4), 114.4(16); C(3)–C(1)–C(11), 115.7(15); C(21)–C(2)–C(31), 113.0(15); C(1)–C(11)–C(15), 129.8(17); C(24)–O(1)–C(27), 117.2(16).

by the double bond and the bond linked to the ferrocenyl group. In the case of 3-Z, the C(1)–C(2) bond length is 1.37(2) Å, clearly longer than that of tamoxifen (1.34 Å for Z-isomer and 1.33 Å for E-isomer). The angles formed by the double bond and each of the four substituents are about 122° to 123°, similar values have been observed for phenyl and substituted phenyl rings for 3-Z, angles C(1)–C(2)–C(21) and C(1)–C(2)–C(31) are respectively 122.0° and 125.0°. The situation on the other end of the alkene is different, the angle C(2)–C(1)–C(11) is now 129.0° and the angle C(2)–C(1)–C(3) is 115.3°. This torsion may be due to the bulky ferrocenyl group which forces the enlargment of the C(2)–C(1)–C(11) angle in order to minimize the steric effect. The planarity of the ethylenic skeleton is almost preserved, the dihedral angle formed by the plane C(11)–C(1)–C(3) and the plane C(21)–C(2)–C(31) is only 1.25°. In the case of tamoxifen, the dihedral angles formed by the aromatic rings and the ethylenic plane are about 50° to 60°. In our case the two aromatic rings of 3-Z are almost perpendicular to the ethylenic plane, respectively 94° for the phenyl ring and 87° for the para substituted ring. It may also be noted that the cyclopentadienyl ring linked to the ethylenic carbon is planar with respect to the ethylenic plane.

The differences between the structures of 3-Z and Z-tamoxifen can be rationalized in terms of a bulkier and better electron donating effect for the ferrocenyl group as compared to a phenyl unit.

2.3. Discussion

Ferrocifen 3 has been prepared by two different methods. In the first, ferrocenyl acetic acid was used as the starting compound. It is a long synthetic pathway which gives only low yield. The second method is based on the McMurry reaction. The intermolecular cross-coupling of ketones is, according to McMurry and others, of contrasted synthetic usefulness. In the present case, this novel synthetic method of 8 is easier and more efficient than the five-step route shown in Scheme 1. We also improved the reaction of the attachment of the dimethylaminoethyl chain by using NaOH in acetone to generate the phenolate instead of sodium ethylate in ethanol, the reaction was faster (1 h instead of 3 h) and gave a better yield. Ferrocifen was obtained from ferrocene in an overall yield 41%.

The structure of 3-Z was determined by X-ray structural determination. The structure of 3-Z is similar to that of Z-tamoxifen with differences in the dihedral angle of aromatic rings and in the length of the double bond.

It is of interest to examine the possibility of using NMR techniques for the identification of isomers. In the case of tamoxifen, it has been observed that the aro-

matic ring located between two other rings is subject to a shielding effect [13]. According to this result, the $-C_6H_4O$ ring of the 3-Z isomer, which is situated between the ferrocenyl moity and the C_6H_5-ring, might appear at upper field with respect to the $-C_6H_4O$ ring of the 3-E isomer. This is indeed the case, the A_2B_2 signals of the $-C_6H_4O$ ring for 3-Z were seen at 6.83 and 6.95 ppm while the corresponding protons of $-C_6H_4O-$ for the isomer 3-E were seen at 6.90 and 7.13 ppm. It is clear that this is due to the shielding effect caused by the phenyl and ferrocenyl groups. This observation is also true for the C_6H_5-ring. Thus, the hypothesis of the shielding effect on the ring located in a sandwich position is once again verified.

The phenomenon of Z, E isomerization is known in the tamoxifen series. The isomerization of pure 3-Z and 3-E to generate an equimolar mixture of 3-Z + 3-E is particularly easy in this series. The ease of the isomerization is closely related to the acidity of the solvent: $CHCl_3 > CH_3CH_2OH \geq CH_3COCH_3 > DMSO$. This can be compared to the high degree of stabilization of carbenium ions by the ferrocenyl group pK_R^+, $CpFe(C_5H_4-CH_2)^+$, -1 [14] as compared to pK_R^+, $C_6H_5CH_2^+$, < -17.3 [15]. This isomerization occurs less rapidly in the tamoxifen series. For this reason, the drug is often administered in the form of a Z, E mixture although it is known that the anti-estrogen activity is produced only by the Z isomer [1].

3. Conclusion

This synthesis of ferrocifen represents the first synthesis of the prototype of a potential new family of organometallic anti-estrogens. The biological study of ferrocifen is currently underway, both on MCF7 type cancer cells and in animals (nude mice) that have received breast cancer implants. Only after this study is complete will it be possible to assess the validity of the idea that led to this synthesis.

4. Experimental section

All reactions were carried out under an atmosphere of argon. Ethyl ether was distilled over sodium/benzophenone, dichloromethane was distilled from P_2O_5 and DMSO was distilled under vacuum over molecular sieves. TLC separations were performed in air by using silicagel plates. ^1H NMR spectra were recorded on a Bruker AM-200 spectrometer. Ferrocenylacetic acid 5 was prepared following the literature methods [16].

4.1. [(Ferrocenyl)methyl](4-methoxyphenyl)ketone 6

10.01 g (42.80 mmol) of iodoanisole was dissolved in dry ether (30 ml). This solution was cooled to 0 °C and then 26.75 ml of a 1.6 M solution of n-BuLi in hexane (42.80 mmol) was added dropwise via a dropping funnel. After complete addition, the stirring was maintained for 20 min more by keeping the temperature at 0 °C. A solution of ferrocenyl acetic acid 5 (2.6 g, 10.7 mmol) in 50 ml of dry ether was added slowly to the first solution. After 2 h of stirring, the solution was hydrolyzed with 60 ml of HCl 1/10. The product was extracted with ether and the organic phase was washed with 2×40 ml of saturated Na_2CO_3 solution and with 40 ml of water. After drying over magnesium sulfate the solution was filtrated and concentrated with a rotavapor. White crystals of unreacted iodoanisole were precipitated from the solution. The solid was removed from the solution by filtration and pentane was added into the solution. [(Ferrocenyl)methyl](4-methoxyphenyl)ketone 6 was precipitated as maroon crystals (1.45 g, m.p. 124 °C, 40.6%). ^1H NMR (200 MHz, $CDCl_3$): δ 8.01 and 6.95 (d, d, 2H, $J = 8.8$ Hz, C_6H_4), 4.16 (m, 2H, C_5H_4), 4.12 (s, 7H, Cp and C_5H_4), 3.93 (s, 2H, CH_2), 3.88 (s, 3H, OMe).

4.2. [(1-Ferrocenyl)propyl](4-methoxyphenyl)ketone 7

0.42 g (3.81 mmol) of t-BuOK was added in one portion to a solution of 6 (1.27 g, 3.81 mmol) in 10 ml of dry DMSO. The solution turned from orange to deep red. After 5 min, 1.01 g (6.47 mmol) of ethyliodide was added in one portion. The solution turned to orange and 2 min later the solution was poured into 100 ml of iced water. The product was extracted with 3×40 ml of ether. The organic phase was washed with 2×40 ml of water, dried over $MgSO_4$ and filtrated. After solvent removal, the crude product was purified by chromatography on silica gel plate and elution with ether/pentane (2/7) to yield 5 (0.99 g, 71.7% yield, m.p. 54 °C). Anal. Found: C, 69.64; H, 6.18. $C_{21}H_{22}O_2Fe$ Calc.: C, 69.65; H, 6.08%. ^1H NMR (200 MHz, $CDCl_3$): δ 8.10 and 7.02 (d, d, 2H, $J = 8.8$ Hz, C_6H_4), 4.24 and 4.06 (m, m, 2H, H-3′ and H-5′ of C_5H_4), 3.98 (s, 5H, Cp), 3.96 (s, 3H, OMe), 2.10 and 1.79 (m, m, 1H, 1H, CH_2), 0.89 (t, 3H, $J = 7.4$ Hz, Me).

4.3. Ferrocenyl ethyl ketone 10

4.00 g (21.50 mmol) of ferrocene was dissolved in 11 ml of propionic anhydride (86 mmol). To this solution was added 0.9 ml of polyphosphoric acid. The mixture was heated to 100 °C for 15 min. The solution was then hydrolyzed with 100 ml of iced water and neutralized with Na_2CO_3 solution. The product was extracted with 3×60 ml ether and the organic phase was washed with 3×100 ml of water. After drying over magnesium sulfate the solution was filtrated and concentrated with a rotavapor. The crude product was purified by chromatography on silica gel plate and elution with ether/pentane (1/3) to yield 10 as a dark

red solid (4.16 g, 80% yield). ^{1}H NMR (200 MHz, CDCl$_3$): δ 4.80 and 4.49 (m, m, 2H, 2H, C$_5$H$_4$), 4.20 (s, 5H, C$_5$H$_5$), 2.74 (q, 2H, $J = 7.4$ Hz, -CH_2-CH$_3$), 1.21 (t, 3H, $J = 7.3$ Hz, -CH$_2$-CH_3).

4.4. 1-(4-Methoxyphenyl)-1-(phenyl)-2-ferrocenyl-but-1-ene 8

From 7: A 2 M solution of PhLi was prepared from 1.40 g (0.20 mol) of lithium and 15.70 g (0.10 mol) of PhBr in 20 ml of ether. 4.30 ml (8.60 mmol) of this solution was introduced into a Schlenk tube containing 5 ml of dry ether. After cooling to 0 °C, a solution of 1.56 g (4.3 mmol) of **7** in ether (15 ml) was added dropwise. The stirring was maintained for 1 h and then the temperature was allowed to rise to room temperature. The solution was evaporated and 10 ml of ethanol was added followed by 1 ml of conc. HCl. The mixture was stirred for 5 min and poured into 150 ml of iced water. The product was extracted with 3 × 50 ml of ether. The organic phase was washed with 60 ml of water, dried over MgSO$_4$ and filtrated. After solvent removal, the crude product was chromatographed on silica gel plate and elution with ether/pentane (2/7) to yield a yellow solid of **8** (0.670 g, 37%). The two isomers Z and E of **8** were separated by fractional crystallization in ether/pentane. First isomer: m.p. 95 °C. Anal. Found: C, 76.74; H, 6.16. C$_{27}$H$_{26}$O$_2$Fe Calc.: C, 76.80; H, 6.16%. ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.24 (m, 5H, C$_6$H$_5$), 7.01 (d, 2H, $J = 8.6$ Hz, C$_6$H$_4$), 6.77 (d, 2H, $J = 8.6$ Hz, C$_6$H$_4$), 4.17 (s, broad, 5H of C$_5$H$_5$ and 2H of C$_5$H$_4$), 3.99 (s, broad, 2H, C$_5$H$_4$), 3.78 (s, 3H, OMe), 2.51 (q, 2H, $J = 7.4$ Hz, -CH_2-CH$_3$), 1.01 (t, 3H, $J = 7.3$ Hz, -CH$_2$-CH_3). Second isomer: m.p. 178 °C. Anal. Found: C, 76.74; H, 6.28. C$_{27}$H$_{26}$O$_2$Fe Calc.: C, 76.80; H, 6.16%. ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.19 (m, 5H, C$_6$H$_5$), 7.13 (d, 2H, $J = 8.5$ Hz, C$_6$H$_4$), 6.86 (d, 2H, $J = 8.5$ Hz, C$_6$H$_4$), 4.13 (s, 5H, C$_5$H$_5$), 4.09 (s, broad, 2H, C$_5$H$_4$), 3.90 (s, broad, 2H, 2H, C$_5$H$_4$), 3.81 (s, 3H, OMe), 2.57 (q, 2H, $J = 7.4$ Hz, -CH_2-CH$_3$), 1.04 (t, 3H, $J = 7.3$ Hz, -CH$_2$-CH_3).

By McMurry reaction: 2.25 ml (20.50 mmol) of TiCl$_4$ was added dropwise to a suspension of 2.68 g (41 mmol) of zinc powder in 15 ml of THF at -10 °C. The blue mixture obtained was heated at reflux for 2.5 h and then allowed to cool to 18 °C. A second solution was prepared by dissolving 4.39 g (21 mmol) of 4-methoxy-benzophenone and 1.00 g (4,10 mmol) of ferrocenyl ethyl ketone **10** in 10 ml of THF. This latter solution was added dropwise to the first solution and then the resulting mixture was heated for 15 h. After cooling to room temperature, the mixture was hydrolyzed with 50 ml of a 10% K$_2$CO$_3$ solution. After ether extraction

and solvent removal, the crude product was chromatographed on silica gel plates with ethyl acetate/pentane 1/20 as eluent to give 1.14 g of **8** (66% yield).

4.5. 1-(4-Hydroxyphenyl)-1-(phenyl)-2-ferrocenyl-but-1-ene 9

0.487 g (1.15 mmol) of (Z + E)-**8** was dissolved in 10 ml of dry CH$_2$Cl$_2$. The solution was cooled to -78 °C and then 0.11 ml (1.15 mmol) of pure BBr$_3$ was added in one portion. The cooling bath was removed and the solution was stirred for 30 min. The solution was poured into 50 ml of iced water. After being stirred for 10 min, NaCl was added to saturate the solution. The product was extracted with 3 × 60 ml of CH$_2$Cl$_2$. The organic phase was washed with 40 ml of Na$_2$S$_2$O$_3$ solution followed by 40 ml of water, dried over MgSO$_4$ and filtrated. After solvent removal, 0.470 g of crude **9** was obtained. The compound was purified by crystallization to give a mixture of Z and E isomers. ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.27 (m, 10H, C$_6$H$_5$), 7.01 and 6.77 (d, d, 2H, C$_6$H$_4$), 7.04 and 6.73 (d, d, 2H, C$_6$H$_4$), 4.72 (s, 1H, OH), 4.68 (s, 1H, OH), 4.20 (m, 18H, C$_5$H$_5$ and C$_5$H$_4$), 2.45 (q, q, 2H, 2H, 2 -CH_2-CH$_3$), 0.99 (t, t, 3H, 3H, 2 CH$_2$-CH_3).

4.6. 1-[4-(2-Dimethylaminoethoxy)phenyl]-1-(phenyl)-2-ferrocenyl-but-1-ene 3-Z and 3-E

Method A: A solution of sodium ethanolate was prepared by treating 0.034 g (1.47 mmol) sodium with 10 ml ethanol. To this solution was added 0.210 g (1.47 mmol) 2-chloroethyl-dimethylamine hydrochloride. Another solution of sodium ethanolate was prepared with the same scale. To this second solution was added 0.300 g (0.73 mmol) of **9** and the solution was heated to 80 °C. The solution of chloroethyl-dimethylamine was then dropwise added. After 3 h of heating, the solution was left to cool to room temperature and then hydrolyzed with 100 ml of water before the product was extracted with ether (2 × 60 ml). The organic phase was washed with water, dried over magnesium sulfate, filtered and the solvent evaporated. The crude product was chromatographed on silica gel plates with (C$_2$H$_5$)$_3$N/ethyl acetate 1/9 as eluent to give first a mixture of two isomers of **3** (0.232 g, 66%). A second chromatography was performed with pyridine/toluene 2/12 as eluent in order to separate the two isomers. After five migrations, **3**-Z and **3**-E were finally separated. Characteristics of **3**-Z: m.p. 51–53 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.29 (m, 5H, C$_6$H$_5$), 6.95 and 6.83 (d, d, 2H, 2H, $J = 8.8$ Hz, C$_6$H$_4$), 4.12 (s, 5H, C$_5$H$_5$), 4.09 (m, 2H of substituted C$_5$H$_4$), 3.99 (t, 2H, $J = 5.7$ Hz, OCH$_2$), 3.82 (m, 2H of substituted C$_5$H$_4$),

2.58 (t, 2H, $J = 5.7$ Hz, CH$_2$N), 2.49 (partially obscured by signals from DMSO, 2H, –CH_2–CH$_3$), 2.19 (s, 6H, N(CH$_3$)$_2$), 0.99 (t, 3H, $J = 7.4$ Hz, CH$_2$–CH_3). Characteristics of **3-E**: m.p. 84–86 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.10 (m, 5H, C$_6$H$_5$), 7.13 and 6.90 (d, d, 2H, 2H, $J = 8.7$ Hz, C$_6$H$_4$), 4.13 (s, 5H, C$_5$H$_5$), 4.08 (m, 2H of substituted C$_5$H$_4$), 4.02 (t, 2H, $J = 5.8$ Hz, OCH$_2$), 3.77 (m, 2H of substituted C$_5$H$_4$), 2.61 (t, 2H, $J = 5.8$ Hz, CH$_2$N), 2.50 (partially obscured by signals from DMSO, 2H, –CH_2–CH$_3$), 2.21 (s, 6H, N(CH$_3$)$_2$), 1.01 (t, 3H, $J = 7.4$ Hz, CH$_2$–CH_3).

Method B: 0.76 g (1.86 mmol) of **9** was dissolved in 15 ml of acetone. To this solution was added 0.745 g (18.6 mmol) of powdered NaOH and the mixture was heated at reflux for 10 min. 1.34 g (9.3 mmol) of 2-chloroethyl-dimethylamine hydrochloride was then added. After 1 h of heating, the solution was left to cool to room temperature and then hydrolyzed with 100 ml of water before the product was extracted with ether (2 × 60 ml). The organic phase was washed with water, dried over magnesium sulfate, filtered and the solvent evaporated. The crude product was chromatographed on silica gel plates with ethyl acetate/pentane 15/1 as eluent to give **3-Z** and **3-E** with 78% overall yield.

4.7. X-ray crystal structure determination for 3-Z

Suitable crystals of **3-Z** were crystallized from pentane in the triclinic space group $P\bar{1}$. Accurate cell dimensions and orientation matrices were obtained by least-squares refinement of 25 accurately centred reflections. No significant variations were observed in the two check reflections during data collection. The data were corrected for Lorentz and polarization effects; an empirical absorption (DIFABS) was applied [17]. Computations were performed by using the PC version of CRYSTALS [18]. Scattering factors and corrections for anomalous absorption were taken from Ref. [19].

5. Supplementary material available

Table S2 of fractional coordinates (1 page), Table S3 of interatomic distances (1 page), Table S4 of bond angles (1 page), and a listing of structure factors for **3-Z** (11 pages). Ordering information is given on any current masthead page.

References

[1] V.C. Jordan, C.S. Murphy, Endocr. Rev. 11 (1991) 578; J.C. Dore, J. Gilbert, E. Bignon, A. Crastes de Paulet, T. Ojasoo, M. Pons, J.P. Raynaud, J.F. Miquel, J. Med. Chem. 35 (1992) 573; P.R. Kym, G.M. Anstead, K.G. Pinney, S.R. Wilson, J.A. Katzenellenbogen, J. Med. Chem. 36 (1993) 3910; S.G. Nayfield, J.E. Karp, L.G. Ford, F.A. Dorr, B.S. Kramer, J. Nat. Cancer Inst. 23 (1991) 1450; S. Ray, A. Tandon, I. Dwivedy, S.R. Wilson, J.P. O'Neil, J.A. Katzenellenbogen, J. Med. Chem. 37 (1994) 696.
[2] S.Y. Jiang, C.J. Parker, V.C. Jordan, Breast Cancer Res. Treat. 26 (1993) 139.
[3] M.G. Parker, Breast Cancer Res. Treat. 26 (1993) 131.
[4] P. Van de Velde, F. Nique, F. Bouchoux, J. Brémaud, M-C. Hameau, D. Lucas, C. Moratille, S. Viet, D. Philibert, G. Teutsch, J. Steroid Biochem. 48 (1994) 187.
[5] S. Top, J. Tang, A. Vessières, D. Carrez, C. Provot, G. Jaouen, J. Chem. Soc., Chem. Commun. (1996) 955.
[6] P. Köpf-Maier, H. Köpf, Chem. Rev. 87 (1987) 1137; A. Houlton, R.M.G. Roberts, J. Silver, J. Organomet. Chem. 418 (1991) 107; E.W. Neuse, F. Kanzawa, Appl. Organomet. Chem. 4 (1990) 19.
[7] J.E. McMurry, J. Am. Chem. Soc. 96 (1974) 1708; Acc. Chem. Res. 16 (1983) 405.
[8] T. Mukaiyama, T. Sato, J. Hanna, Chem. Lett. (1973) 1041.
[9] P.L. Coe, C.E. Scriven, J. Chem. Soc., Perkin Trans I. (1986) 475.
[10] P.J. Graham, R.V. Lindsey, G.W. Parshall, M.L. Peterson, G.M. Whitman, J. Am. Chem. Soc. 79 (1957) 3416.
[11] G. Precigoux, C. Courseille, S. Geoffre, M. Hospital, Acta Crystallogr. B35 (1979) 3070.
[12] B.T. Kilbourn, P.G. Owston, J. Chem. Soc. B (1970) 1.
[13] D.J. Collins, J.J. Hobbs, C.W. Emmens, J. Med. Chem. 14 (1971) 952; G.R. Bedford, D.N. Richardson, Nature 212 (1966) 733.
[14] C.A. Bunton, N. Carrasco, W.E. Watts, J. Chem. Soc., Perkin Trans. 2 (1979) 1267.
[15] N.C. Deno, P.T. Groves, J.J. Jaruzelski, N.N. Lugasch, J. Am. Chem. Soc. 82 (1960) 4719.
[16] D. Lednicer, J.K. Lindsay, C.R. Hauser, J. Org. Chem. 23 (1958) 653.
[17] N. Walker, D. Stuart, Acta Crystallogr. A39 (1983) 159.
[18] D.J. Watkins, J.R. Carruthers, P.W. Bettridge, CRYSTALS User Guide, Chemical Crystallography Laboratory, University of Oxford, UK, 1988.
[19] D.T. Cromer, International Tables for X-ray Crystallography, vol. IV, Kynoch Press, Birmingham, UK, 1974.