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Synthesis and Antiproliferative Effects of [3]Ferrocenophane Transposition Products and Pinacols Obtained from McMurry Cross-Coupling Reaction

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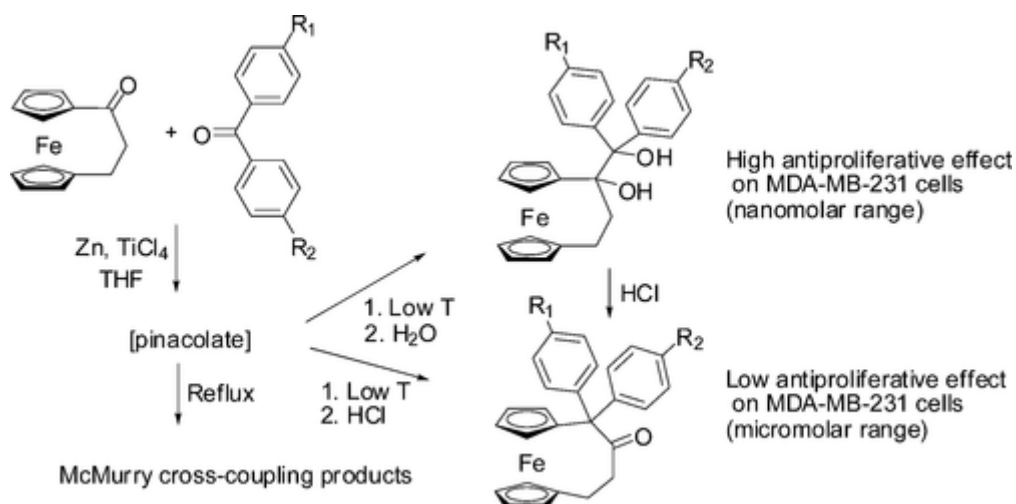
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Abstract

We here report the synthesis and antiproliferative activities of two new series of ferrocenophanes obtained from McMurry cross-coupling reactions of [3]ferrocenophan-1-one with benzophenone, 4-hydroxybenzophenone, 4,4'-dihydroxybenzophenone, and 4,4'-diacetylaminobenzophenone. In addition to the main formation of olefins at reflux, tetrahedral transposition products, resulting from a pinacolic rearrangement, were also isolated in about 10% yields. Lowering the temperature of the reaction to 0 °C allowed the isolation of pinacols, which could be transformed into transposition compounds in good yields. Three ferrocenophane compounds have been characterized by X-ray crystallography: 1-(*p*-hydroxyphenyl)-1-phenyl-2-oxo[4]ferrocenophane (**7b**), 1,1-diphenyl-2-oxo[4]ferrocenophane (**7c**), and 1-hydroxy-1-[1-hydroxy-1-[3]ferrocenophanyl][3]ferrocenophane (**12**) crystallize in monoclinic $P2_1/n$, triclinic $P\bar{1}$, and monoclinic $P2_1/c$ space groups, respectively. The antiproliferative effects on hormone-independent breast cancer cells (MDA-MB-231) of the transposition compounds are generally lower than those of their corresponding butene analogues (IC_{50} values in micromolar versus nanomolar range). In contrast and quite surprisingly, the pinacol complexes are significantly cytotoxic (IC_{50} in the nanomolar range), among the most cytotoxic ferrocene compounds prepared so far. This antiproliferative activity may be linked to their oxidative cleavage.



Introduction

Within the recent research activity in bioinorganic chemistry, the topic of medicinal organometallic chemistry is now a particularly fertile field. (1-6) This domain can be defined as the synthesis and evaluation of organometallic compounds for diagnostic and therapeutic applications, as well as investigation into their mode of action. (7)

We have recently shown that, in certain favorable cases, the biological properties of organic polyphenols can be substantially modified by substitution of a ferrocenyl entity in place of an aryl group on the molecular skeleton. The organic diphenol **1**, ferrocenyl diphenol **2a**, resveratrol **3**, hydroxytamoxifen **4**, and ferrocifen **5** (Chart 1) are all known to interact with the estrogen receptors (ER) present in MCF-7 cells. This leads, at low concentration, to an estrogenic (proliferative) effect for **1**, **2a**, and **3** and to an antiestrogenic (antiproliferative) effect for **4** and **5** due to specific interactions of the hormone-receptor complex with DNA. Interestingly, the ferrocenyl derivatives **2a** and **5** produce a powerful antiproliferative effect on MDA-MB-231 cells, which lack the ER (IC_{50} around $0.5\ \mu\text{M}$). Indeed, on this cell line **3** and **4** show only a weak antiproliferative effect (IC_{50} values of 20 and $30\ \mu\text{M}$, respectively), rendering them not viable at the therapeutic level. (10, 11) We have therefore worked to adjust these levels via organometallic modification, and following a suitable formulation of **2a**, encouraging in vivo results have been obtained on implanted tumors in rat (9L gliosarcoma). (12)

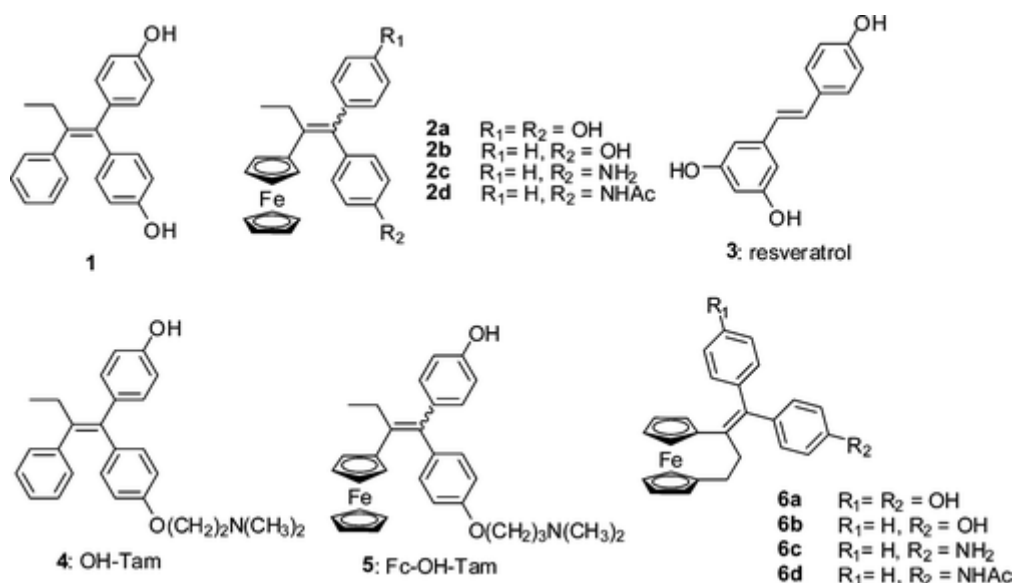


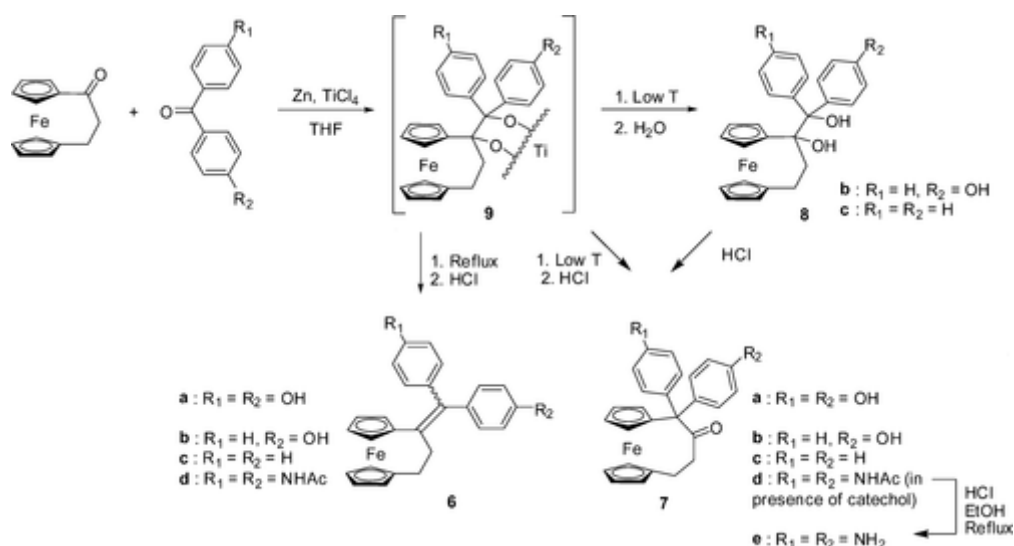
Chart 1. Tamoxifen and Related Molecules

It seems likely that the presence of the redox-active ferrocene group favors the generation of quinone methides in cancer cells, possibly leading to cell death via interaction with nucleophiles such as glutathione and proteins. (13, 14) In addition to electrochemical experiments, this hypothesis has been supported by the observation that the [ferrocene-conjugated spacer-*p*-phenol] motif seems to be crucial for strong antiproliferative effects, and a change in the position of either the hydroxyl group or the ferrocene results in weakening of the antiproliferative effect. (15, 16) This behavior, first observed with MDA-MB-231 cells, pertains to other types of cancer cells as well (prostate, colon, glioma, and melanoma, inter alia). Importantly, healthy cells are not affected at these concentrations (1 μM). (17-20)

These promising results were further elaborated through discovery of new structures with even greater efficacy in vitro and by a successful transition in vivo. We have already obtained some success in vitro by changing the substituent (e.g., OH for NH_2) in series **2** (21, 22) and in formulating **2a** for in vivo administration. (18, 23, 24) Furthermore, a cyclic series (Chart 1), (25-28) for which diphenol **6a** is the archetypal example, is about 2–4 times more active than **2a** in the NCI 60 cell line panel, particularly against melanoma, leukemia, CNS cancer, and renal cancer. (28)

In performing the reductive cross-coupling (29, 30) to obtain series **6** molecules, we have observed that another series of molecules, **7** (Scheme 1), resulting from a pinacolic rearrangement to a transposition product is also accessible and that the yield of this secondary

product is influenced by the reaction conditions. Although the transposition geometry, with a tetrahedral carbon core, does not apparently lend itself to the ferrocene-mediated formation of quinone methides, thought to be the key to the antiproliferative effects of **2** and **6**, the antiproliferative activities of **7a–d** are nonetheless in the low micromolar range. We therefore became interested in the competitive synthesis of **6** and **7**, as well as the examination of the importance of pinacols of type **8** (Scheme 1) in their generation. The antiproliferative effects on MDA-MB-231 cancer cells are reported for **7**, **8**, and some related molecules; to our knowledge, this is the first communication concerning the anticancer activity of organometallic pinacols.



Scheme 1. General Trends in the Reactivity of the Pinacolate **9 Formed by [3]Ferrocenophan-1-one and Benzophenones in the Presence of Low-Valent Titanium**

Results and Discussion

Synthesis

The McMurry cross-coupling reaction between [3]-ferrocenophan-1-one (**31**) and a disubstituted benzophenone (Scheme 1) yielded the olefin **6** and/or the transposition product **7**, depending on the reaction conditions (Table 1).

Table 1. Yields of 6 and 7 According to Varying Reaction Conditions

temp	yield (%)	
	series 6	series 7
reflux (THF)	55 (a)	10 (a)
	62 (b)	11 (b)
	93 (c)	0 (c)
	44 (d)	10 (d)
0 °C	23 (a)	12 (a)
	0 (b)	80 (b)
	0 (c)	71 (c)
	0 (d)	0 (d)
−25 °C	19 (a)	33 (a)
reflux + catechol	0 (a)	13 (a)
	19 (b)	0 (b)
	0 (c)	12 (c)
	0 (d)	33 (d)

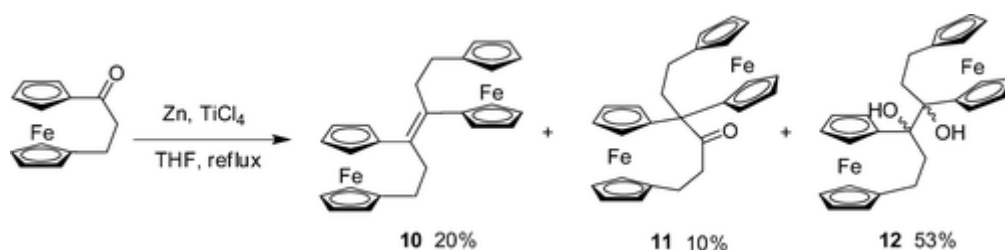
It is commonly accepted that the pinacolate **9** is a reactive intermediate in the McMurry reaction. (29, 30, 32) Depending on the nature of the reactants and the reaction conditions, the pinacolate can evolve toward the classic cross-coupling product **6** or toward other products, principally the transposition product **7**. (33, 34) For example, at THF reflux, we quantitatively obtained the olefin **6c**, while at 0 °C, only the transposition product **7c** was found after acid workup. This result is similar for the reaction with 4-hydroxybenzophenone, although a small quantity of the transposition product **7b** was also isolated at reflux. This suggests that the pinocolates **9b,c** are quite stable at 0 °C. With 4,4'-dihydroxybenzophenone, the results were not quite as straightforward: at both reflux and 0 °C we obtained a mixture of the olefin **6a** and the transposition product **7a**, although the ratio of **7a** to **6a** was improved at lower temperatures. This indicates that the pinacolate **9a** is less stable than that of **9c**, and the low yields of **6a** and **7a** suggest that the pinacolate likely evolves toward other unidentified products. (35) Lowering the temperature to −25 °C further stabilized **9a** and increased the yield of **7a** to 33%. In the case of the diacetamidobenzophenone, we primarily obtained the olefin **6d** under reflux conditions, but at 0 °C no reaction was observed. This is not surprising,

as it is known that McMurry coupling with aminobenzophenones proceeds relatively slowly. (36)

It was recently found that the addition of catechol to the reaction medium favors the production of the transposition compound, (37, 38) by chelating the titanium ion and thus stabilizing the pinacolate. Indeed, in the presence of catechol, the reaction of 4,4'-diacetamidobenzophenone at reflux permitted the isolation of **7d** in 33% yield and further deprotection of **7d** by HCl gave access to the diamino compound **7e**. For the other benzophenones, the addition of catechol blocked olefin formation but did not consistently increase the yield of the transposition product.

As seen in Table 1, the fate of the pinacolate is very sensitive to the reaction temperature, and at 0 °C, evolution toward the olefin or transposition product is slow enough that hydrolysis at this temperature allowed us to isolate the pinacols **8b,c** in good yields (80% and 82%, respectively). (35, 39) Compound **8b** exists as two diastereomers, **8b1** and **8b2**, which are separable by HPLC. Treatment of the isolated pinacols **8b,c** with acid generates the transposition products **7b,c** in yields of 98% and 79%, respectively.

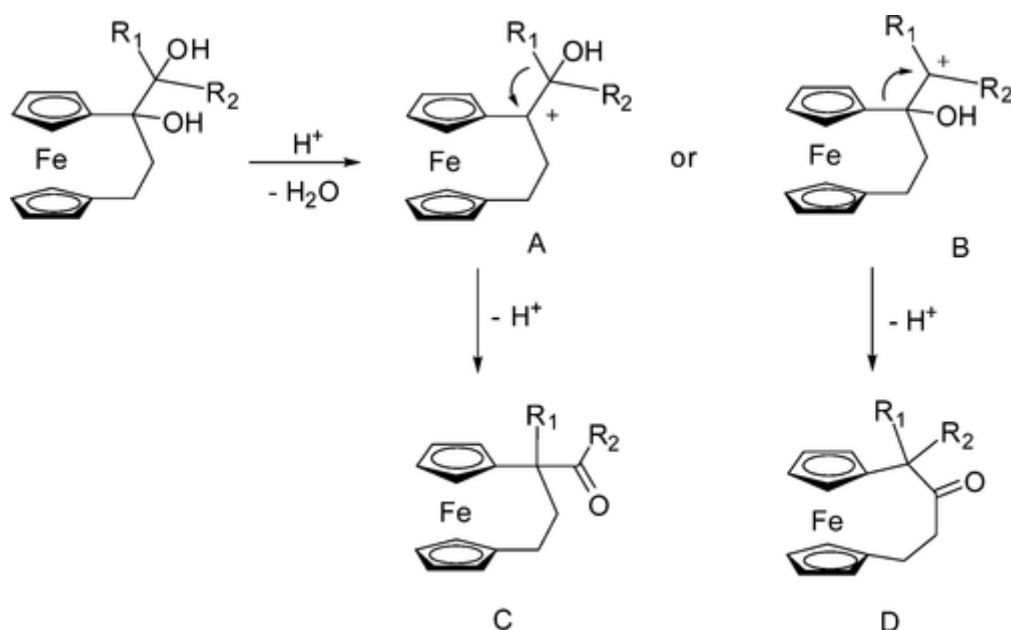
It is interesting to note that the reaction of [3]ferrocenophan-1-one in the absence of a benzophenone led to the pinacol **12** in 53% yield. Only a small amount of the corresponding olefin **10** or transposition product **11** (Scheme 2) was obtained after H₂O hydrolysis, suggesting that the pinacolate of [3]ferrocenophan-1-one is stable even under reflux conditions.



Scheme 2. Homocoupling of [3]Ferrocenophan-1-one

In order to study the influence of the aromatic rings on the generation of such compounds, we examined the reaction between [3]ferrocenophan-1-one and 4-hydroxybenzaldehyde at 0 °C



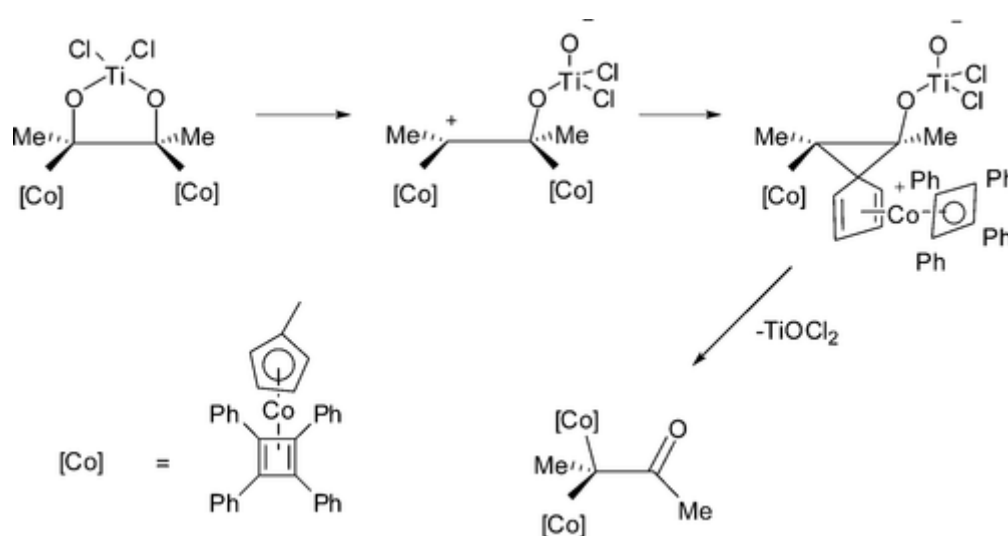


Scheme 4. Pinacol Rearrangement

The identity of the final product strongly depends on where the initial carbocation is formed. It is known that the ferrocenyl substituent stabilizes carbocations better than does a phenyl ring, according to the following reported pK_R^+ values (going from least to most stable): <-17.3 for PhCH_2^+ , (41) -13.3 for Ph_2CH^+ , (42) -5.7 for $(4\text{-MeO-C}_6\text{H}_4)_2\text{CH}^+$, (42) -1.28 for FcCH_2^+ , (43) and $+0.35$ for FcCH^+Ph . (44) Therefore, a priori, one might anticipate that cation **A** should be more stable than cation **B** in Scheme 4. However, the reactions with the benzophenones exclusively give molecules of type **D**: that is, those proceeding via cation **B**. Although stabilization of the cation located β to the ferrocenyl unit has been observed in cyclic systems, this occurs via a through-space interaction when the cation is on the bridging carbon. (45, 46) This is not the case here; instead, the β -carbon is positioned far from the ferrocenyl moiety. However, the rigidity of the bridge may impair a through-space stabilization of cation **A** with the iron atom, which is an important contribution to the stability of the cation $[\text{FcCH}_2]^+$. Thus, the destabilization of cation **A** relative to cation **B** could be attributable to the lack of a stabilizing contribution of the iron atom to the α position. Indeed, the destabilization of the cation in the [3]ferrocenophane series compared to the ferrocene series is reflected by its pK_R^+ value of -3.2 for an α cation of [3]ferrocenophane, (47) which is thus less stable than FcCH_2^+ but still more stable than the Ph_2CH^+ cation.

However, the rearrangement process is not controlled solely by the identity of the initially generated cation. The different abilities of the competing fragments to undergo migration can also be a dominant factor. McGlinchey et al. have isolated a pinacolic rearrangement product from a McMurry homocoupling of (η^5 -acetylcyclopentadienyl)cobalt(η^4 -tetraphenylcyclobutadiene) (Scheme 5). (40)

The preferential migration of the cobalt sandwich moiety rather than a methyl group is rationalized in terms of the enhanced migratory aptitude of the organometallic moiety in such a way that the positive charge can be delocalized onto the metal center in the transition state. The ferrocenyl moiety should likewise possess this migration capacity. In agreement with these observations, quantum mechanical semiempirical PM3 calculations show that, in the case of the diphenol compound **7a**, the variation of the enthalpy activation energy (ΔH°) necessary for the transformation of cation **A** to pinacolone **C** is 95.9 kcal mol⁻¹, while that for the transformation of cation **B** to pinacolone **D** is 26.3 kcal mol⁻¹. Therefore, the transformation of **B** to **D** is the more favorable process.



Scheme 5. Proposed Rearrangement Mechanism for a Cobalt Sandwich Complex

The migration of the ferrocenyl group instead of the aryl group may also be favored due to an additional contribution of strain release by cycle expansion. This would explain the exclusive formation of the **D** type compound. In the case of 4-OH-benzaldehyde, the contribution to the stability of the cation comes only from one aromatic ring, and thus the role of these effects on the stability of cations **A** and **B** should be similar. However, compound **13**, the ring expansion product, is the major product in this reaction.

X-ray Structures

Suitable crystals of **7b,c** and **12** were obtained from dichloromethane/hexane or ether. ORTEP diagrams are shown in Figure 1, crystallographic data are given in Table S1 in the Supporting Information, and selected bond distances and bond angles are collected in Table 2.

Table 2. Selected Bond Distances (Å) and Bond Angles (deg) for 7b,c and 12

	7b	7c		12
Fe1–C _{Cp}	2.030(8)–2.095(4)	2.056(19)–2.081(16)	Fe1–C _{Cp}	2.0162(16)–2.047(17)
C _{Cp} –C _{Cp}	1.383(18)–1.442(7)	1.419(4)–1.448(2)	Fe2–C _{Cp}	2.0088(15)–2.058(17)
C1–C11	1.549(6)	1.556(2)	C _{Cp} –C _{Cp} (Fe1)	1.414(3)–1.434(2)
C11–C12	1.562(5)	1.568(2)	C _{Cp} –C _{Cp} (Fe2)	1.416(2)–1.434(2)
C11–C21	1.549(5)	1.554(2)	C11–C26	1.576(2)
C12–C13	1.518(7)	1.530(2)	C11–O1	1.4291(19)
O1–C12	1.231(5)	1.222(2)	C26–O2	1.4371(19)
C6–C14	1.508(7)	1.520(3)	C1–C11	1.515(2)
O2–C24	1.371(5)		C11–C12	1.543(2)
C13–C14	1.531(6)	1.544(3)	C12–C13	1.532(2)
			C13–C6	1.496(2)
C1–C11–C12	102.0(3)	107.53(13)	C1–C11–C12	111.53(13)
C12–C11–C15	111.8(3)	107.52(13)	C1–C11–C26	113.25(13)
C12–C11–C21	112.7(3)	110.72(13)	C1–C11–O1	105.98(12)
C11–C12–C13	120.0(4)	118.40(14)	C12–C11–C26	109.77(12)
O1–C12–C13	120.3(4)	119.34(16)		
O1–C12–C11	119.7(4)	122.23(15)		

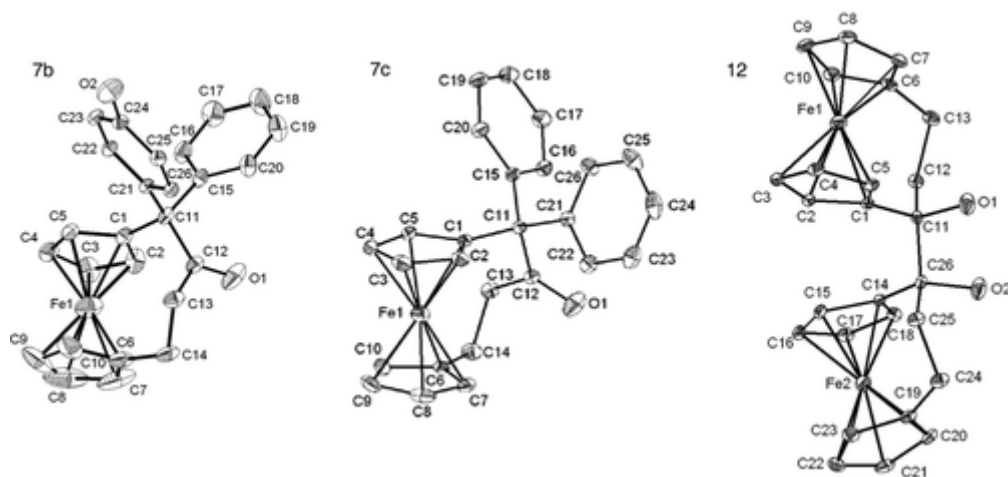


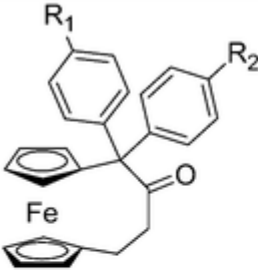
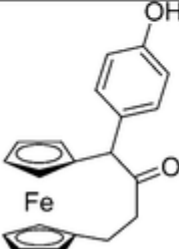
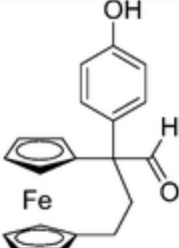
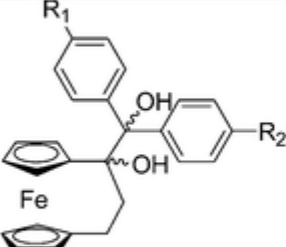
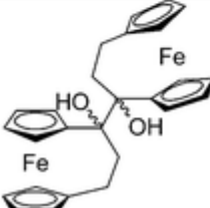
Figure 1. ORTEP diagrams of 7b,c and 12.

In the [4]ferrocenophanes **7b,c**, the dihedral angle between the η^5 -C₅H₄ ring planes is close to parallel: 6(1) and 7(1)° in the two independent molecules of **7b** and 2.7(2)° in **7c**. In **12**, the bis[3]ferrocenophane system, these angles have widened somewhat to 8.6(1) and 10.2(1)° as a consequence of the shorter chain connecting the cyclopentadienyl rings. Interestingly, in **7b** and **12**, the Cp rings are very nearly eclipsed, whereas in **7c** they are almost perfectly staggered. Most of the bond distances and bond angles of **7b,c** are similar. Compound **7b** is a racemate, and only the *S* enantiomer is shown. The pinacol **12** also crystallizes as a racemic mixture, and the molecule shown in Figure 1 is the *S,S* enantiomer; the dihedral angle between the two hydroxy groups is 46.7°.

Antiproliferative Activities

The antiproliferative effects of all the new compounds against hormone-independent MDA-MB-231 breast cancer cells were evaluated (Table 3).

Table 3. IC₅₀ Values (μM) of Compounds on Breast Cancer Cells (MDA-MB-231)

		R ₁	R ₂	IC ₅₀
	7a	OH	OH	12.5 ± 0.3
	7b	H	OH	1.45 ± 0.49
	7c	H	H	20.1 ± 5.4
	7e	NH ₂	NH ₂	15.4 ± 0.2
	7d	NHAc	NHAc	9.38 ± 1.82
	13			No effect at 10 ⁻⁵ M
	14			2.83 ± 0.65
	8c	H	H	0.17 ± 0.01
	8b1	H	OH	0.06 ± 0.01
	8b2	H	OH	0.14 ± 0.01
	12			3.48 ± 0.83

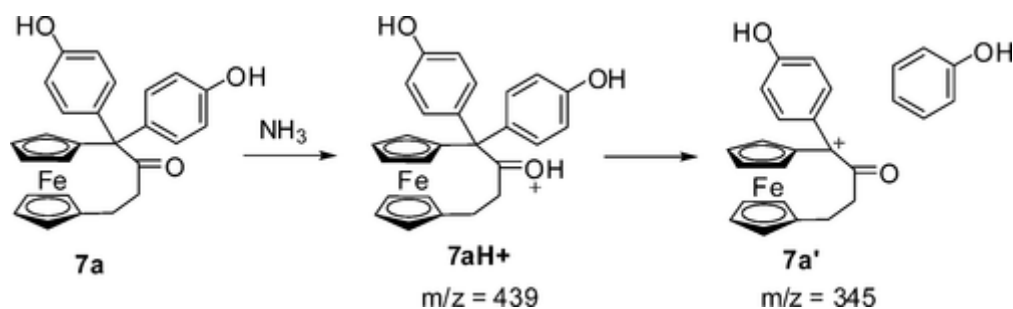
In general, the transposition compounds are not very active, with IC₅₀ values between 9.38 and 20.1 μM. Compound **7b**, with one hydroxy group, is the exception, with an IC₅₀ value of

1.45 μM . Compound **13**, which possesses only one hydroxyphenyl group, is completely inactive. However, compound **14**, which also possesses one hydroxyphenyl group has activity comparable to that of **7b**, evidently due to the presence of an aldehyde group.

Most remarkably, the pinacols **8** are all very active, and the isomer **8b1** has the best activity with an IC_{50} value of 0.06 μM . This is one of the most antiproliferative compounds prepared to date in our laboratory. In this series, it is clear that the phenol group does not play an important role, as **8c**, which lacks this function, is one of the most active compounds with an IC_{50} value of 0.17 μM . Finally, the pinacol **12** has only moderate activity, which may be a consequence of the low accessibility to the OH group that is sterically blocked by bulky neighboring groups.

Reactivity Studies

We next turned our attention to possible chemical transformations that could be involved in the toxicity of these molecules. An interesting observation was made from the mass spectrum of **7a** (Supporting Information). In chemical ionization mode, using NH_3 as a vector gas, the following ions were detected: m/z 456 $[\text{M} + \text{NH}_4]^+$, 439 $[\text{M} + \text{H}]^+$, and 345 $[\text{M} - \text{C}_6\text{H}_5\text{OH}]^+$. The last peak corresponds to the loss of a $\text{C}_6\text{H}_5\text{OH}$ group to generate the cation **7a'** (Scheme 6). The same process was observed when NH_3 was replaced by ND_3 . The mass spectrum of the diamine **7e** shows this fragmentation pattern as well.



Scheme 6. Mass Fragmentation of 7a

We have also examined the fragmentation observed in mass spectrometry by a theoretical approach. The potential energy curves for the displacement of one phenol group of 7aH^+ and

7bH⁺ (protonated ketones) and for the displacement of one aniline group of **7eH⁺** were calculated using semiempirical PM3 methods. The calculations were carried out by starting to protonate the oxygen atom, and then the phenyl bond to be broken was gradually lengthened from 1.517 to 5.517 Å (in 81 steps). Figure 2 shows the calculated curve of energy versus bond distance for **7aH⁺**.

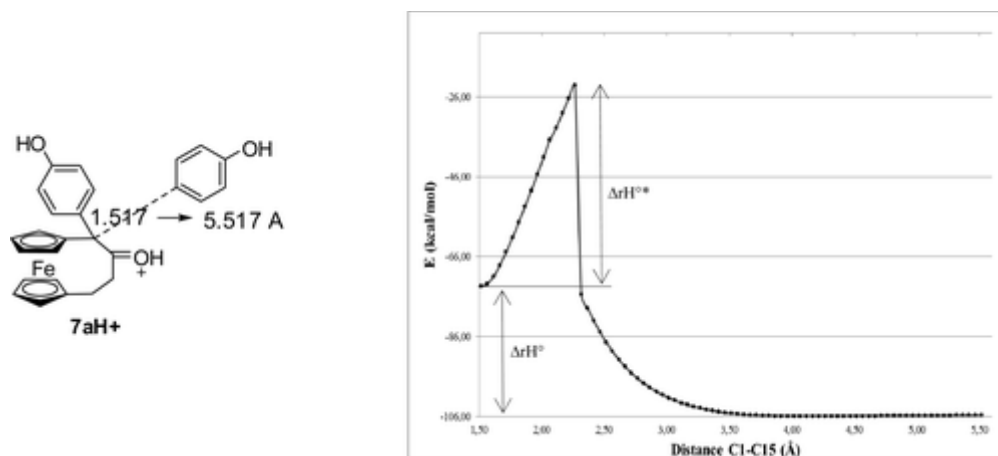


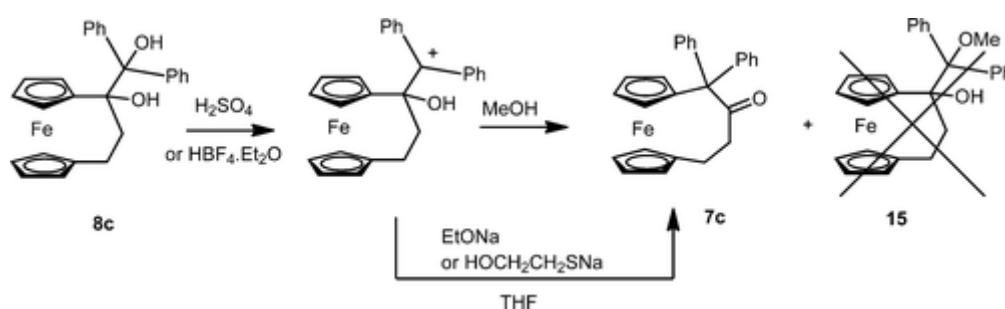
Figure 2. Calculated energy versus bond distance curve for **7aH⁺.**

Enthalpies of activation ($\Delta H^{\circ*}$) of 50.3, 50.8, and 80.5 kcal mol⁻¹ and variations of the enthalpy of the reaction (ΔrH°) of -32.3, -32.5, and -108.3 kcal mol⁻¹ were obtained for **7a,b,e**, respectively. While these exothermic reactions indicate that the formation of the cations **7a',b',e'** are thermodynamically favorable, the high activation energies needed to lose the aryl ring seem to preclude this transformation under biological conditions, although the involvement of enzymes in such a process cannot be entirely discounted. It should also be mentioned that the activation energies for **7a,b** are the same, while their biological activities are very different, suggesting that their activity cannot be explained solely in terms of chemical transformations.

In the case of pinacols **8b,c** their activities cannot be obviously linked with quinone methide formation, as the presence of a phenol group is not a major factor in their activity. These pinacols easily evolve to transposition products in acidic medium. As transposition products have considerably lower activity than the pinacols themselves, it is clear that the transposition compounds are not their active metabolites. One might postulate that the activity of pinacols is linked to the reaction of the cation intermediate generated with any nucleophile present in

the medium. We have investigated this reaction by using methanol as a nucleophile and have shown that this type of reaction is instantaneous. (48)

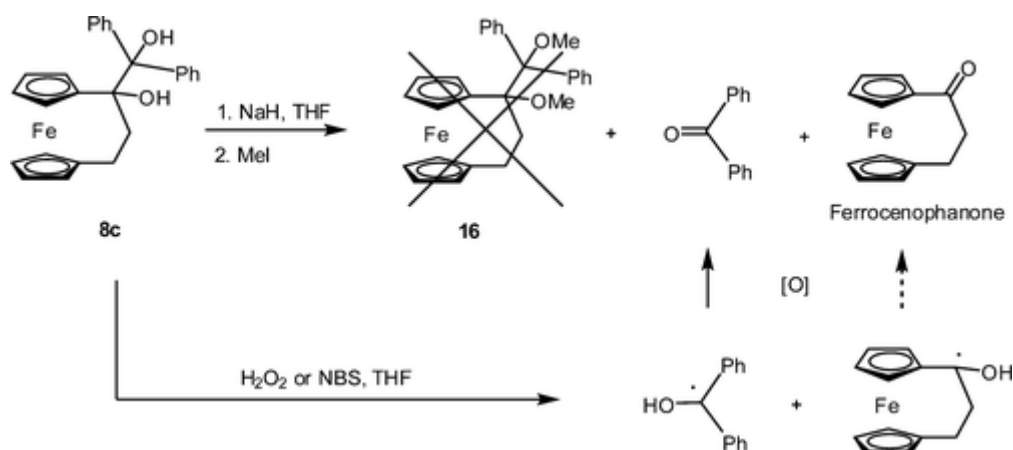
When concentrated H_2SO_4 was added to the solution of **8c** in methanol (Scheme 7), only the formation of **7c** was observed with no trace of the methoxy compound **15**, indicating that the pinacolic rearrangement is faster than the reaction of methanol and suggesting that migration and loss of water are synchronous processes. When $\text{HBF}_4 \cdot \text{Et}_2\text{O}$ was added to a yellow solution of **8c** in anhydrous dichloromethane and cooled to -70°C , the solution immediately became blue, characteristic of cation generation. Likewise, addition of EtONa or $\text{HOCH}_2\text{CH}_2\text{SNa}$ to the cation solution produced only transposition compound **7c**. It is clear that the pinacolic rearrangement is a fast process and rules out a link between the reactivity of pinacol and its cation intermediate.



Scheme 7. Reactivity of 8c

Having ruled out a carbocation species as the active intermediate, we turned our attention to the pinacolate and its interaction with electrophiles. The pinacolate was prepared by addition of sodium hydride to a THF solution of **8c** (Scheme 8). Addition of iodomethane to the pinacolate suspension led to the formation of ferrocenophanone and benzophenone with no trace of **16**, thus revealing an oxidation process. The oxidation of pinacol is a well-known reaction and has been extensively studied. It has been found that several metals, (49) O_2 , (50, 51) H_2O_2 , (52) and *N*-iodosuccinimide (53) can oxidize pinacol to radicals which undergo cleavage to ketones. We found that addition of H_2O_2 or *N*-bromosuccinimide to a THF solution of **8c** led to the formation of benzophenone with complete disappearance of starting material. Ferrocenophanone was only detected in small amounts (5%) in the case of NBS addition. The very low yield of ferrocenophanone may be attributed to its sensitivity toward oxidizing reagents, and the antiproliferative activity of pinacols may also be linked to these

oxidative cleavage properties. The involvement of redox systems in cells which are not present in normal cells has been exemplified with hydroxyferrocifen and related species (18, 54) and with aminoferrocenyl-based prodrugs. (58) This is in agreement with the observed antiproliferative effects. Moreover, in this case, quinone methides have been isolated. (14)



Scheme 8. Reaction of Iodomethane on Pinacolate and Oxidation of 8c

Conclusions

We have described the synthesis and antiproliferative activities of two new series of ferrocenophanes obtained from the McMurry cross-coupling reaction between [3]ferrocenophan-1-one and benzophenone derivatives and have also studied the conditions of their production. The first series concerns transposition compounds **7a–d**, resulting from a pinacolic rearrangement occurring within the reaction. The second series comprises the intermediate pinacols that could be isolated from the reaction. The antiproliferative effects of transposition compounds are moderate, while the monophenol **7b** is at least 10 times more active than diphenyl (**7c**), diphenol (**7a**), and dianiline (**7e**). Surprisingly, the pinacol series is very active; compounds **8b,c** are almost as active as **6a–d** and are far more active than **7a–e**. We suggest that this excellent activity is probably linked to the oxidation of pinacols. This work will be continued in order to gain insight into the mechanism of action of pinacols.

Experimental Section

General Remarks

All reactions were carried out under an argon atmosphere using standard Schlenk techniques. Anhydrous THF was obtained by distillation from sodium/benzophenone. The preparative HPLC separations were performed on a Shimadzu apparatus with a Nucleodur C18 column (length of 25 cm, diameter of 3.2 cm, and particle size of 10 μm) using acetonitrile as the eluent. The analytical HPLC controls were performed on a Shimadzu apparatus with a Nucleodur C18 column (length of 15 cm, diameter of 0.46 cm, and particle size of 5 μm) using acetonitrile or methanol/water as the eluent. Infrared spectra were obtained on an IRFT BOMEM Michelson-100 spectrometer equipped with a DTGS detector as a KBr plate. ^1H and ^{13}C NMR spectra were recorded on a 300 MHz Bruker spectrometer. Mass spectrometry was performed with a Nermag R 10-10C spectrometer. HRMS measurements were performed on a Thermo Fischer LTQ-Orbitrap XL apparatus equipped with an electrospray source by the Institut Parisien de Chimie Moléculaire (UMR 7201), Université Pierre et Marie Curie, Paris, France. Elemental analyses were performed by the microanalysis services of the ICSN (Gif sur Yvette, France). Due to the presence of water or crystallization solvents, compounds **7a,d,e**, **8b**, and **12** did not provide satisfactory elemental analyses. For these compounds ^1H NMR spectra are given in the Supporting Information as proof of their purity. Melting points were measured with a Kofler device. Determination of the cytotoxicity of the complexes was performed at the IMAGIF (ICSN, Gif sur Yvette, France).

General Synthesis for **7a–c**, **13**, and **14**

Zinc powder was suspended in anhydrous THF at room temperature, and titanium tetrachloride was slowly added via a syringe while stirring. The reaction mixture was refluxed for 2 h and then cooled to 0 or $-25\text{ }^{\circ}\text{C}$ (see below), after which a THF solution containing [3]ferrocenophan-1-one and the appropriate benzophenone were added. After the reaction was complete (see below), the reaction mixture was poured into water and extracted with dichloromethane. The organic layer was washed with water, dried over magnesium sulfate, and filtered, and the solvent was evaporated. The oil was purified by HPLC. Recrystallizations were performed from convenient solvent systems.

1,1-Bis(*p*-hydroxyphenyl)-2-oxo[4]ferrocenophane (7a): zinc powder (2.86 g, 43.7 mmol), titanium tetrachloride (3.43 mL, 31.2 mmol), [3]ferrocenophan-1-one (1.5 g,

6.25 mmol), *p,p*-dihydroxybenzophenone (1.34 g, 6.25 mmol), time 2 days, $T = -25$ °C. Recrystallization from acetonitrile/water gave **7a** as yellow crystals (0.90 g, 33% yield). Mp: 230 °C dec. ^1H NMR (300 MHz, acetone- d_6): δ 2.72–2.81 (m, 2H, CH₂), 3.07–3.16 (m, 2H, CH₂), 4.08 (t, $J = 1.7$ Hz, 2H, C₅H₄), 4.21 (t, $J = 1.7$ Hz, 2H, C₅H₄), 4.29 (s, 4H, C₅H₄), 6.74 (d, $J = 8.8$ Hz, 4H, C₆H₄), 7.04 (d, $J = 8.8$ Hz, 4H, C₆H₄), 8.24 (s, 2H, OH). ^{13}C NMR (75.4 MHz, acetone- d_6): δ 28.0 (CH₂), 44.6 (CH₂), 69.0 (2CH, C₅H₄), 69.2 (2CH, C₅H₄), 70.3 (C), 72.7 (2CH, C₅H₄), 74.2 (2CH, C₅H₄), 88.6 (C_{ip}), 93.9 (C_{ip}), 115.9 (2 × 2CH, C₆H₄), 132.1 (2 × 2CH, C₆H₄), 137.2 (2C, C₆H₄), 157.2 (2C, C₆H₄), 205.5 (CO). IR (KBr, ν , cm⁻¹): 3380 (OH), 3010, 2914, 2856 (CH₂), 1681 (CO). MS (CI, NH₃): m/z 439 [M + H]⁺, 456 [M + NH₄]⁺. HRMS (ESI, C₂₆H₂₂FeNaO₃ [M + Na]⁺): calcd 461.081 18, found 461.081 76. Anal. Calcd for C₂₆H₂₂FeO₃·H₂O: C, 68.43; H, 5.30. Found: C, 67.93; H, 5.16.

1-(*p*-Hydroxyphenyl)-1-phenyl-2-oxo[4]ferrocenophane (7b): zinc powder (0.95 g, 14.6 mmol), titanium tetrachloride (1.14 mL, 10.4 mmol), [3]ferrocenophan-1-one (0.5 g, 2.08 mmol), *p*-hydroxybenzophenone (0.41 g, 2.08 mmol), time 2 h, $T = 0$ °C. Concentrated HCl (10.2 mL, 125.0 mmol) was added, and the mixture was stirred for 1 h at 0 °C. Recrystallization from diethyl ether gave **7b** as orange crystals (0.70 g, 80% yield). ^1H NMR (300 MHz, CDCl₃): δ 2.78–2.85 (m, 2H, CH₂), 3.11–3.16 (m, 2H, CH₂), 4.05 (s, 2H, C₅H₄), 4.20 (s, 2H, C₅H₄), 4.27 (s, 2H, C₅H₄), 4.31 (s, 2H, C₅H₄), 4.82 (s, 1H, OH), 6.70 (d, $J = 8.7$, 2H, C₆H₄), 7.08 (d, $J = 8.7$, 2H, C₆H₄), 7.13–7.26 (m, 5H, C₆H₅). ^{13}C NMR (75.4 MHz, CDCl₃): δ 26.9 (CH₂), 43.9 (CH₂), 67.7 (2CH, C₅H₄), 67.8 and 67.9 (2CH, C₅H₄), 69.9 (C), 71.3 and 71.4 (2CH, C₅H₄), 72.7 (2CH, C₅H₄), 86.2 (C_{ip}), 92.7 (C_{ip}), 114.8 (2CH, C₆H₄), 126.4 (CH, C₆H₅), 127.9 (2CH, C₆H₄), 129.3 (2CH, C₆H₅), 130.6 (2CH, C₆H₅), 136.2 (C, C₆H₄), 144.2 (C, C₆H₄), 154.1 (C, C₆H₄), 204.9 (CO). IR (KBr, ν , cm⁻¹): 3311.2 (OH), 3021, 2969, 2917, 2859 (CH₂), 1678 (CO). MS (EI, 70 eV): m/z 422 [M]⁺, 394 [M – CO]⁺. HRMS (ESI, C₂₆H₂₂FeNaO₂ [M + Na]⁺): calcd 445.086 26, found 445.086 14. Anal. Calcd for C₂₆H₂₂FeO₂: C, 73.94; H, 5.47. Found: C, 73.36; H, 5.47.

1,1-Diphenyl-2-oxo[4]ferrocenophane (7c): zinc powder (0.95 g, 14.6 mmol), titanium tetrachloride (1.14 mL, 10.4 mmol), [3]ferrocenophan-1-one (0.5 g, 2.08 mmol),

benzophenone (0.38 g, 2.1 mmol), time 2 h, $T = 0\text{ }^{\circ}\text{C}$. The solvent was then evaporated, the oily reaction mixture was dissolved in CH_2Cl_2 and cooled to $0\text{ }^{\circ}\text{C}$, and concentrated HCl (38.5 mL, 468.6 mmol) was added portion by portion and then the mixture was stirred for 1 day at room temperature. Recrystallization from hexane/dichloromethane gave **7c** as orange crystals (0.6 g, 71% yield). Mp: $177\text{ }^{\circ}\text{C}$. ^1H NMR (300 MHz, CDCl_3): δ 2.81–2.85 (m, 2H, CH_2), 3.13–3.17 (m, 2H, CH_2), 4.04 (t, $J = 1.7$, 2H, C_5H_4), 4.20 (t, $J = 1.7$, 2H, C_5H_4), 4.27 (t, $J = 1.7$, 2H, C_5H_4), 4.33 (t, $J = 1.7$, 2H, C_5H_4), 7.12–7.20 (m, 2H, C_6H_5), 7.22 (s, 5H, C_6H_5), 7.23 (s, 3H, C_6H_5). ^{13}C NMR (75.4 MHz, CDCl_3): δ 26.9 (CH_2), 44.0 (CH_2), 67.7 (2CH, C_5H_4), 67.9 (2CH, C_5H_4), 70.5 (C), 71.3 (2CH, C_5H_4), 72.7 (2CH, C_5H_4), 83.3 (C_{ip}), 92.9 (C_{ip}), 126.5 ($2 \times 1\text{CH}$, C_6H_5), 127.9 ($2 \times 2\text{CH}$, C_6H_5), 129.4 ($2 \times 2\text{CH}$, C_6H_5), 144.2 ($2 \times 1\text{C}$, C_6H_5), 204.2 (CO). IR (KBr, ν , cm^{-1}): 2926 (CH_2), 1698 (CO). MS (EI, 70 eV): m/z 406 $[\text{M}]^+$, 378 $[\text{M} - \text{CO}]^+$, 301, 228, 165. Anal. Calcd for $\text{C}_{26}\text{H}_{22}\text{FeO}$: C, 76.85; H, 5.45. Found: C, 76.81; H, 5.38.

1-(*p*-Hydroxyphenyl)-2-oxo[4]ferrocenophane (13) and 1-(*p*-Hydroxyphenyl)-1-formyl[3]ferrocenophane (14): zinc powder (0.95 g, 14.6 mmol), titanium tetrachloride (1.14 mL, 10.4 mmol), [3]ferrocenophan-1-one (0.5 g, 2.08 mmol), *p*-hydroxybenzaldehyde (0.76 g, 6.20 mmol), $T = 0\text{ }^{\circ}\text{C}$, time one night. Concentrated HCl (10.3 mL, 125.0 mmol) was added, and the mixture was stirred for 4 h at $0\text{ }^{\circ}\text{C}$. The crude product was subjected to column chromatography with diethyl ether/petroleum ether as eluent. Two fractions were collected. Recrystallization of the first fraction from dichloromethane/pentane gave **13** as orange crystals (0.19 g, 27% yield, mp $212\text{ }^{\circ}\text{C}$). ^1H NMR (300 MHz, acetone- d_6): δ 2.49–2.71 (m, 2H, CH_2), 2.88–3.06 (m, 2H, CH_2), 3.90–4.06 (m, 6H, C_5H_4), 4.08–4.10 (m, 1H, C_5H_4), 4.14–4.16 (m, 1H, C_5H_4), 4.99 (s, 1H, CH), 6.55 (d, $J = 8.4\text{ Hz}$, 2H, C_6H_4), 6.95 (d, $J = 8.4\text{ Hz}$, 2H, C_6H_4), 8.02 (s, 1H, OH). ^{13}C NMR (75.4 MHz, acetone- d_6): δ 25.7 (CH_2), 42.8 (CH_2), 53.5 (CH), 68.5 (CH, C_5H_4), 69.0 (2CH, C_5H_4), 69.2 (CH, C_5H_4), 69.3 (CH, C_5H_4), 69.6 (CH, C_5H_4), 69.9 (CH, C_5H_4), 70.3 (CH, C_5H_4), 81.9 (C_{ip}), 87.7 (C_{ip}), 115.3 (2CH, C_6H_4), 130.4 (2CH, C_6H_4), 132.3 (C, C_6H_4), 157.0 (C, C_6H_4), 207.7 (CO). MS (CI, NH_3): m/z 347 $[\text{M} + \text{H}]^+$, 364 $[\text{M} + \text{NH}_4]^+$. Anal. Calcd for $\text{C}_{20}\text{H}_{18}\text{FeO}_2$: C, 69.38; H, 5.24. Found: C, 69.61; H, 5.23. Recrystallization of the second fraction from

dichloromethane/pentane gave **14** as orange crystals (0.04 g, 7%, mp 166.5 °C). ¹H NMR (300 MHz, acetone-*d*₆): δ 2.14–2.27 (m, 1H, CH₂), 2.34–2.56 (m, 2H, CH₂), 2.83–3.01 (m, 1H, CH₂), 3.90–3.92 (m, 1H, C₅H₄), 3.98–4.00 (m, 1H, C₅H₄), 4.02–4.04 (m, 1H, C₅H₄), 4.08–4.11 (m, 2H, C₅H₄), 4.15–4.17 (m, 1H, C₅H₄), 4.18–4.21 (m, 1H, C₅H₄), 4.52–4.55 (m, 1H, C₅H₄), 6.81 (d, *J* = 8.7 Hz, 2H, C₆H₄), 7.21 (d, *J* = 8.7 Hz, 2H, C₆H₄), 8.49 (s, 1H, OH), 9.54 (s, 1H, CHO). ¹³C NMR (75.4 MHz, acetone-*d*₆): δ 22.2 (CH₂), 41.2 (CH₂), 54.6 (C), 68.9 (CH, C₅H₄), 69.1 (2CH, C₅H₄), 69.2 (CH, C₅H₄), 69.3 (CH, C₅H₄), 69.7 (CH, C₅H₄), 70.0 (CH, C₅H₄), 71.6 (CH, C₅H₄), 87.6 (C_{ip}), 89.0 (C_{ip}), 116.2 (2CH, C₆H₄), 130.8 (C, C₆H₄), 130.9 (2CH, C₆H₄), 157.5 (C, C₆H₄), 198.7 (CO). MS (CI, NH₃): *m/z* 347 [M + H]⁺, 364 [M + NH₄]⁺, 318 [M – CHO]⁺. HRMS (ESI, C₂₀H₁₈FeO₂: [M]⁺): calcd 346.065 07, found 346.065 15. Anal. Calcd for C₂₀H₁₈FeO₂·0.5H₂O: C, 68.61; H, 5.39. Found: C, 68.11; H, 5.31.

1,1-Bis(*p*-acetamidophenyl-2-oxo[4]ferrocenophane (7d): Zinc powder (0.93 g, 14.2 mmol) was suspended in THF at room temperature, and titanium tetrachloride (1.1 mL, 10.1 mmol) was slowly added via a syringe with stirring. The reaction mixture was heated at reflux for 2 h and then cooled to room temperature. *o*-Dihydroxybenzene (catechol; 1.12 g, 10.1 mmol) was added, and the reaction mixture was stirred for 20 min at room temperature. The reaction mixture was heated to reflux, after which a THF solution containing [3]ferrocenophan-1-one (0.49 g, 2.03 mmol) and *p,p*-diacetylaminobenzophenone (0.3 g, 1.01 mmol) (**55**) were added. The mixture was refluxed for 3 days. The reaction mixture was poured into water, acidified with HCl, and extracted with dichloromethane. The organic layer was washed with water, dried over magnesium sulfate, and filtered, and the solvent was evaporated. The obtained oil was purified by HPLC. Recrystallization was performed in hexane/dichloromethane. Compound **7d** was obtained as yellow crystals (0.17 g, 33% yield). Mp: 286 °C dec. ¹H NMR (300 MHz, DMSO-*d*₆): δ 1.99 (s, 6H, CH₃), 2.67–2.71 (m, 2H, CH₂), 3.08–3.12 (m, 2H, CH₂), 4.05 (s, 2H, C₅H₄), 4.18–4.20 (m, 4H, C₅H₄), 4.32 (s, 2H, C₅H₄), 7.05 (d, *J* = 8.7, 4H, C₆H₄), 7.40 (d, *J* = 8.7, 4H, C₆H₄), 9.88 (s, 2H, NH). ¹³C NMR (75.4 MHz, DMSO-*d*₆): δ 23.8 (2CH₃), 26.3 (CH₂), 42.9 (CH₂), 67.2 (2CH, C₅H₄), 67.4 (2CH, C₅H₄), 69.0 (C), 70.6 (2CH, C₅H₄), 71.8 (2CH, C₅H₄),

86.2 (C_{ip}), 92.7 (C_{ip}), 118.2 (2 × 2CH, C₆H₄), 129.0 (2 × 2CH, C₆H₄), 137.1 (2C, C₆H₄), 139.1 (2C C₆H₄), 168.1 (2CONH), 203.7 (CO). IR (KBr, ν, cm⁻¹): 3289, 3247 (NH), 3111, 3058 (CH₃, CH₂), 1698 (CO), 1663 (CO). MS (EI, 70 eV): *m/z* 520 [M]⁺, 492 [M – CO]⁺, 400, 357, 179. HRMS (ESI, C₃₀H₂₈FeN₂NaO₃ [M + Na]⁺): calcd 543.134 30, found 543.133 04. Anal. Calcd for C₃₀H₂₈FeN₂O₃: C, 69.23; H, 5.42; N, 5.38. Found: C, 68.74; H, 5.65; N, 5.62.

1,1-Bis(*p*-aminophenyl)-2-oxo[4]ferrocenophane (7e): 1,1-Bis(*p*-acetamidophenyl)-2-oxo[4]ferrocenophane (**7d**; 0.23 g, 0.44 mmol) was dissolved in ethanol, and concentrated hydrochloric acid (8.7 mL, 106 mmol) was added. The solution was refluxed for 3 days. After it was cooled to room temperature, the solution was poured into a saturated NaHCO₃ solution portion by portion. Water was added, the solution was extracted with dichloromethane, the solvent was removed under reduced pressure, and the product was purified by column flash chromatography (diethyl ether/petroleum ether 2/1). Recrystallization from dichloromethane/hexane gave **7e** as orange-yellow crystals (0.06 g, 32%). Mp: 216 °C dec. ¹H NMR (300 MHz, CDCl₃): δ 2.75–2.79 (m, 2H, CH₂), 3.07–3.11 (m, 2H, CH₂), 3.58 (broad s, 4H, NH₂), 4.02 (s, 2H, C₅H₄), 4.16 (s, 2H, C₅H₄), 4.21 (s, 2H, C₅H₄), 4.27 (s, 2H, C₅H₄), 6.55 (d, *J* = 7.5, 4H, C₆H₄), 6.95 (d, *J* = 7.5, 4H, C₆H₄). ¹³C NMR (75.4 MHz, CDCl₃): δ 26.8 (CH₂), 43.5 (CH₂), 67.6 (2CH, C₅H₄), 67.7 (2CH, C₅H₄), 68.9 (C), 71.3 (2CH, C₅H₄), 72.9 (2CH, C₅H₄), 86.7 (C_{ip}), 92.2 (C_{ip}), 114.5 (2 × 2CH C₆H₄), 130.3 (2 × 2CH, C₆H₄), 134.4 (2C, C₆H₄), 144.6 (2C, C₆H₄), 205.5 (CO). IR (KBr, ν, cm⁻¹): 3351, 3218 (NH₂), 3089, 3080, 3026, 2923 (CH₂), 1687 (CO). MS (CI, NH₃): *m/z* 437 [M + H]⁺, 344, 223. Anal. Calcd for C₂₆H₂₄FeN₂O: C, 71.55; H, 5.55; N, 6.42. Found: C, 68.98; H, 5.58; N, 6.19 (the NMR spectrum shows the presence of dichloromethane and hexane).

General Synthesis for 8b,c

Zinc powder was suspended in THF at room temperature, and titanium tetrachloride was slowly added via a syringe with stirring. The reaction mixture was heated at reflux for 2 h and then cooled to 0 °C, after which time a THF solution containing

[3]ferrocenophan-1-one and the appropriate amount of benzophenone were added. The mixture was stirred at 0 °C for 2 h. The reaction mixture was poured into water and extracted with dichloromethane. The organic layer was washed with water, dried over magnesium sulfate, and filtered, and the solvent was evaporated. The crude product was purified by flash chromatography and/or HPLC to give the pinacol.

1-Hydroxy-1-(hydroxydiphenylmethyl)[3]ferrocenophane (8c): zinc powder (0.95 g, 14.6 mmol), titanium tetrachloride (1.14 mL, 10.4 mmol), [3]ferrocenophan-1-one (0.5 g, 2.08 mmol), and benzophenone (0.38 g, 2.08 mmol). The crude product was purified by column flash chromatography with petroleum ether as eluent followed by HPLC (acetonitrile/water 85/15). Pinacol **8c** was obtained as orange-yellow crystals (0.72 g, 82%). ¹H NMR (300 MHz, CDCl₃): δ 1.95–2.30 (m, 4H, CH₂), 2.52 (s broad, 1H, OH), 2.86 (s broad, 1H, OH), 3.65 (s, 1H, C₅H₄), 3.87 (s, 1H, C₅H₄), 3.89 (s, 1H, C₅H₄), 3.95 (s, 3H, C₅H₄), 4.08 (s, 1H, C₅H₄), 4.18 (s, 1H, C₅H₄), 7.11–7.23 (m, 6H, C₆H₅), 7.49–7.56 (m, 4H, C₆H₅). ¹³C NMR (75.4 MHz, CDCl₃): δ 19.4 (CH₂), 42.9 (CH₂), 67.5 (CH, C₅H₄), 67.7 (CH, C₅H₄), 67.9 (CH, C₅H₄), 68.3 (CH, C₅H₄), 69.0 (CH, C₅H₄), 69.2 (CH, C₅H₄), 69.4 (CH, C₅H₄), 71.8 (CH, C₅H₄), 77.3 (C), 82.4 (C), 86.7 (C_{ip}), 88.7 (C_{ip}), 127.1 (2CH, C₆H₅), 127.3 (2CH, C₆H₅), 127.6 (2CH, C₆H₅), 128.5 (2CH, C₆H₅), 128.7 (2CH, C₆H₅), 144.3 (2C). IR (KBr, ν, cm⁻¹): 3572, 3557 (OH), 2957, 2923, 2888 (CH₂). MS (EI, 70 eV): *m/z* 424 [M]⁺, 241 [C₁₃H₁₃FeO]⁺, 213, 199. MS (CI, NH₃): *m/z* 425 [M + H]⁺, 407 [M + H – H₂O]⁺, 241 [C₁₃H₁₃FeO]⁺, 199. HRMS (ESI, C₂₆H₂₄FeO₂: [M]⁺): calcd 424.112 02, found 424.111 71. Anal. Calcd for C₂₆H₂₄FeO₂·0.5H₂O: C, 72.07; H, 5.82. Found: C, 72.06; H, 5.83.

1-Hydroxy-1-(hydroxy-*p*-hydroxyphenylphenylmethyl)[3]ferrocenophane (8b): zinc powder (0.95 g, 14.6 mmol), titanium tetrachloride (1.14 mL, 10.4 mmol), [3]ferrocenophan-1-one (0.5 g, 2.08 mmol) and 4-hydroxybenzophenone (0.41 g, 2.1 mmol). The oil was purified by column flash chromatography (diethyl ether/petroleum ether 1/2) followed by HPLC (acetonitrile/water 80/20). Two diastereoisomers were obtained. Recrystallizations of the two diastereoisomers were performed from ether/hexane (0.44 g, 48% and 0.30 g, 32%). Data for diastereomer 1 are as follows. ¹H NMR (300 MHz, acetone-*d*₆): δ 2.05–2.30 (m, 2H, CH₂), 2.45 (s broad,

2H, CH₂), 3.45 (s, 1H, OH), 3.89 (s, 1H, C₅H₄), 3.94 (s, 2H, C₅H₄), 3.99 (s, 1H, C₅H₄), 4.03 (s, 1H, C₅H₄), 4.14 (s, 1H, C₅H₄), 4.19 (s, 1H, C₅H₄), 4.37 (s, 1H, C₅H₄), 4.38 (s, 1H, OH), 6.60 (d, *J* = 8.7, 2H, C₆H₄), 7.18–7.29 (m, 3H, C₆H₅), 7.46 (d, *J* = 8.7, 2H, C₆H₄), 7.78 (d, *J* = 7.2, 2H, C₆H₅). 8.09 (s, 1H, OH). ¹³C NMR (75.4 MHz, acetone-*d*₆): δ 20.8 (CH₂), 44.8 (CH₂), 68.4 (CH, C₅H₄), 68.7 (CH, C₅H₄), 68.9 (CH, C₅H₄), 69.8 (2CH, C₅H₄), 70.3 (CH, C₅H₄), 70.9 (CH, C₅H₄), 73.0 (CH, C₅H₄), 78.3 (C), 83.3 (C_{ip}), 88.4 (C), 91.7 (C_{ip}), 115.0 (2CH, C₆H₄), 127.8 (CH, C₆H₅), 128.5 (2CH_{arom}), 130.5 (2CH_{arom}), 131.5 (2CH_{arom}), 138.4 (C), 148.1 (C), 157.3 (C). IR (KBr, ν, cm⁻¹): 3538, 3501, 3328 (OH), 2948, 2920, 2851 (CH₂). HRMS (ESI, C₂₆H₂₄FeNaO₃ [M + Na]⁺): calcd 463.096 84, found 463.095 77. Anal. Calcd for C₂₆H₂₄FeO₃: C, 70.92; H, 5.49. Found: C, 70.92; H, 5.51. Data for diastereomer 2 are as follows. ¹H NMR (300 MHz, acetone-*d*₆): δ 2.05–2.35 (m, 2H, CH₂), 2.33 (s broad, 2H, CH₂), 3.44 (s, 1H, OH), 3.71 (s broad, 2H, C₅H₄), 3.75 (s, 1H, C₅H₄), 3.82 (s, 1H, C₅H₄), 3.86 (s, 1H, C₅H₄), 4.02 (s, 2H, C₅H₄), 4.17 (s, 1H, C₅H₄), 4.41 (s, 1H, OH), 6.57 (d, *J* = 8.8, 2H, C₆H₄), 6.87–7.00 (m, 3H, C₆H₅), 7.36–7.51 (m, 4H, C₆H₄ + C₆H₅), 8.03 (s, 1H, OH). ¹³C NMR (75.4 MHz, acetone-*d*₆): δ 20.7 (CH₂), 44.7 (CH₂), 68.3 (CH, C₅H₄), 68.7 (CH, C₅H₄), 68.9 (CH, C₅H₄), 69.8 (2CH, C₅H₄), 70.3 (CH, C₅H₄), 70.9 (CH, C₅H₄), 73.0 (CH, C₅H₄), 78.2 (C), 83.3 (C_{ip}), 88.5 (C), 91.6 (C_{ip}), 115.4 (2CH, C₆H₄), 127.5 (CH, C₆H₅), 128.1 (2CH_{arom}), 130.2 (2CH_{arom}), 131.7 (2CH_{arom}), 138.4 (C), 147.9 (C), 157.5 (C). IR (KBr, ν, cm⁻¹): 3539, 3457, 3365, (OH), 2976, 2945, 2904 (CH₂). HRMS (ESI, C₂₆H₂₄FeO₃, [M]⁺⁺): calcd 440.106 94, found 440.106 49. Anal. Calcd for C₂₆H₂₄FeO₃: C, 70.92; H, 5.49. Found: C, 70.34; H, 5.24.

Synthesis of 7c from 8c

To a solution of **8c** (50 mg, 0.12 mmol) in CH₂Cl₂ was added concentrated HCl (2.3 mL, 28.8 mmol) portion by portion at 0 °C, and the mixture was stirred for 1 day at room temperature. The reaction mixture was poured into water and extracted with dichloromethane. The organic layer was washed with water, dried over magnesium sulfate, and filtered, and the solvent was evaporated. The crude product was purified by column flash chromatography (petroleum ether) to give **7c** (38 mg, 79%).

Synthesis of 7b from 8b: To a solution of **8b** (50 mg, 0.11 mmol) in THF was added concentrated H₂SO₄ (0.07 mL, 1.32 mmol) portion by portion at 0 °C. Then, the mixture was stirred for 1 h at room temperature. The reaction mixture was poured into water and extracted with dichloromethane. The organic layer was washed with water, dried over magnesium sulfate, and filtered, and the solvent was evaporated. The crude product was purified by column flash chromatography (diethyl ether/petroleum ether), giving **7b** (47 mg, 98%).

1-Hydroxy-1-[1-hydroxy-1[3]ferrocenophanyl][3]ferrocenophane (12): Zinc powder (0.49 g, 7.5 mmol) was suspended in THF at room temperature, and titanium tetrachloride (0.55 mL, 5.0 mmol) was added slowly via a syringe with stirring. The reaction mixture was refluxed for 2 h, after which a THF solution containing [3]ferrocenophan-1-one (0.3 g and 1.25 mmol) was added, and the mixture was refluxed for 2 h. The reaction mixture was poured into water and extracted with dichloromethane. The organic layer was washed with water, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography and recrystallized from dichloromethane/hexane. Pinacol **12** was obtained (0.16 g, 53%). ¹H NMR (300 MHz, DMSO-*d*₆): δ 1.82–2.03 (m, 4H, CH₂), 2.11–2.35 (m, 4H, CH₂), 3.83–3.90 (m, 6H, C₅H₄), 3.90–3.93 (m, 2H, C₅H₄), 3.94–3.97 (m, 2H, C₅H₄), 4.07–4.11 (m, 4H, C₅H₄), 4.18–4.21 (m, 4H, OH + C₅H₄). ¹³C NMR (75.4 MHz, DMSO-*d*₆): δ 19.2 (2CH₂), 41.8 (2CH₂), 66.6 (2CH, C₅H₄), 67.2 (2CH, C₅H₄), 67.3 (2CH, C₅H₄), 67.4 (2CH, C₅H₄), 67.5 (2CH, C₅H₄), 68.4 (2CH, C₅H₄), 68.5 (2CH, C₅H₄), 71.4 (2CH, C₅H₄), 73.9 (2C), 86.6 (2C_{ip}), 89.2 (2C_{ip}). MS (EI, 70 eV): *m/z* 482 [M]⁺, 242, 199. HRMS (ESI, C₂₆H₂₆Fe₂O₂: [M]⁺): calcd 482.062 62, found 482.061 61. Anal. Calcd for C₂₆H₂₆Fe₂O₂·0.5H₂O: C, 63.57; H, 5.54. Found: C, 63.53; H, 5.46.

Reaction of Pinacol 8c with Methanol: Compound **8c** (30 mg) was dissolved in methanol (2 mL), and 10 drops of concentrated H₂SO₄ were added. After it was stirred for 1 h, the mixture was poured into water and extracted with diethyl ether. The NMR spectrum of the crude product obtained showed mainly the presence of **7c**.

Reaction of Pinacol 8c with EtONa or HOCH₂CH₂SNa: Compound **8c** (42 mg, 0.1 mmol) was dissolved in 2 mL of anhydrous CH₂Cl₂. The solution was cooled to -70 °C, and when HBF₄·Et₂O (0.1 mL, 0.7 mmol) was added, the solution turned blue. After 5 min, EtONa (50 mg, 0.7 mmol) was added, and after it was stirred for 15 min, the mixture was poured into water and extracted with diethyl ether. CCM of the crude product showed only the presence of **7c**. The analogous reaction with HOCH₂CH₂SNa, prepared from 2-mercaptoethanol and NaH, gave the same result.

Reaction of Pinacol 8c with Iodomethane: **8c** (42 mg, 0.1 mmol) was dissolved in 2 mL of anhydrous THF to which NaH (15 mg, 0.6 mmol) was added. After the mixture was stirred for 30 min, iodomethane (141 mg, 1 mmol) was added and the stirring was maintained for 1 h. The mixture was then poured into water and extracted with diethyl ether. HPLC of the crude product obtained showed only the presence of ferrocenophanone and benzophenone in a 50/50 ratio.

Reaction of Pinacol 8c with Hydrogen Peroxide: Compound **8c** (21 mg, 0.05 mmol) was dissolved in 1 mL of anhydrous THF. A 0.2 mL portion of hydrogen peroxide (30 wt % solution in water) was added. The reaction was monitored by TLC and HPLC. **8c** progressively disappeared, with formation of benzophenone and two other compounds. After 1 h of stirring, **8c** completely disappeared.

Reaction of Pinacol 8c with *N*-Bromosuccinimide: Compound **8c** (21 mg, 0.05 mmol) was dissolved in 1 mL of anhydrous THF. *N*-Bromosuccinimide (9 mg, 0.05 mmol) was added. The reaction was monitored by TLC. After 5 min of stirring **8c** almost disappeared with formation of ferrocenophanone and benzophenone. HPLC showed the presence of ferrocenophanone and benzophenone in a 5/95 ratio.

X-ray Crystal Structure Determinations for 7b,c and 12

Crystal data were collected at 200 K with a Kappa-CCD Enraf-Nonius diffractometer with Mo K α radiation. The structures were solved by direct methods and refined by full-matrix least-squares techniques on *F* using the CRYSTALS programs. (56, 57) All non-hydrogen atoms were refined with anisotropic displacement parameters. All

hydrogen atoms were located with geometrical restraints in riding mode. Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC 886312–886314. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax, +44-1223-336033; e-mail, deposit@ccdc.cam.ac.uk; web, <http://www.ccdc.cam.ac.uk>).

Cell Culture and Cell Proliferation Assay

The breast adenocarcinoma cell line MDA-MB-231 was obtained from ATCC. Cells were grown in RPMI medium supplemented with 10% fetal calf serum, in the presence of penicillin, streptomycin, and fungizone in a 75 cm² flask under 5% CO₂. Cells were plated in 96-well tissue culture plates in 200 µL of medium and treated 24 h later with 2 µL stock solutions of compounds dissolved in DMSO using a Biomek 3000 instrument (Beckman-Coulter). Controls received the same volume of DMSO (1% final volume). After 72 h of exposure, MTS reagent (Promega) was added and incubated for 3 h at 37 °C: the absorbance was monitored at 490 nm and results expressed as the inhibition of cell proliferation calculated as the ratio $(1 - (\text{OD}_{490} \text{ treated} / \text{OD}_{490} \text{ control})) \times 100$ in triplicate experiments. For IC₅₀ determination (50% inhibition of cell proliferation), cells were incubated for 72 h following the same protocol with compound concentrations ranging from 5 nM to 100 µM in separate duplicate experiments.

Theoretical Calculations

Theoretical calculations were performed with Spartan'4 software (Wavefunction Inc., 18401 Von Karman Ave., Suite 370, Irvine, CA 92612). A geometry optimization was performed on each molecule to find the absolute energetic minimum using the semiempirical PM3 Hamiltonian.

Supporting Information

A table, figures, and CIF files giving crystallographic data and NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Notes

The authors declare no competing financial interest.

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REFERENCES

- (1) Gianferrara, T.; Bratsos, I.; Alessio, E. *Dalton Trans.* **2009**, 7588–7598.
- (2) Hartinger, C. G.; Dyson, P. J. *Chem. Soc. Rev.* **2009**, 38, 391–401.
- (3) Dyson, P. J. *Chimia* **2007**, 61, 698–703.
- (4) Dougan, S. J.; Sadler, P. J. *Chimia* **2007**, 61, 704–715.
- (5) Hillard, E. A.; Jaouen, G. *Organometallics* **2011**, 30, 20–27.
- (6) Meggers, E. *Curr. Opin. Chem. Biol.* **2007**, 11, 287–292.
- (7) *Medicinal Organometallic Chemistry*; Jaouen, G., Metzler-Nolte, N., Eds.; Springer: Berlin, 2010; Topics in Organometallic Chemistry 32.
- (8) Vessièrès, A.; Top, S.; Pigeon, P.; Hillard, E. A.; Boubeker, L.; Spéra, D.; Jaouen, G. *J. Med. Chem.* **2005**, 48, 3937–3940.
- (9) Nguyen, A.; Vessièrès, A.; Hillard, E. A.; Top, S.; Pigeon, P.; Jaouen, G. *Chimia* **2007**, 61, 716–724.
- (10) Minutolo, F.; Sala, G.; Bagnacani, A.; Bertini, S.; Carboni, I.; Placanica, G.; Protà, G.; Rapposelli, S.; Sacchi, N.; Macchia, M.; Ghidoni, R. *J. Med. Chem.* **2005**, 48, 6783–6786.
- (11) Yao, D.; Zhang, F.; Yu, L.; Yang, Y.; Breemen, R. B. v.; Bolton, J. L. *Chem. Res. Toxicol.* **2001**, 14, 1643–1653.
- (12) Allard, E.; Jarnet, D.; Vessièrès, A.; Vinchon-Petit, S.; Jaouen, G.; Benoît, J.-P.; Passirani, C. *Pharm. Res.* **2010**, 27, 56–64.
- (13) Hillard, E. A.; Vessièrès, A.; Thouin, L.; Jaouen, G.; Amatore, C. *Angew. Chem., Int. Ed.* **2006**, 45, 285–290.

- (14) Hamels, D.; Dansette, P.; Hillard, E. A.; Top, S.; Vessières, A.; Herson, P.; Jaouen, G.; Mansuy, D. *Angew. Chem., Int. Ed.* **2009**, *48*, 9124–9126.
- (15) Hillard, E. A.; Pigeon, P.; Vessières, A.; Amatore, C.; Jaouen, G. *Dalton Trans.* **2007**, 5073–5081.
- (16) Tan, Y. L. K.; Pigeon, P.; Hillard, E. A.; Top, S.; Plamont, M.-A.; Vessières, A.; McGlinchey, M. J.; Müller-Bunz, H.; Jaouen, G. *Dalton Trans.* **2009**, 10871–10881.
- (17) Vessières, A.; Corbet, C.; Heldt, J. M.; Lories, N.; Jouy, N.; Laïos, I.; Leclercq, G.; Jaouen, G.; Toillon, R.-A. *J. Inorg. Biochem.* **2010**, *104*, 503–511.
- (18) Allard, E.; Passirani, C.; Garcion, E.; Pigeon, P.; Vessières, A.; Jaouen, G.; Benoit, J. P. *J. Controlled Release* **2008**, *130*, 146–153.
- (19) Michard, Q.; Jaouen, G.; Vessières, A.; Bernard, B. A. *J. Inorg. Biochem.* **2008**, *102*, 1980–1985.
- (20) Nguyen, A.; Marsaud, V.; Bouclier, C.; Top, S.; Vessières, A.; Pigeon, P.; Gref, R.; Legrand, P.; Jaouen, G.; Renoir, J.-M. *Int. J. Pharm.* **2008**, *347*, 128–135.
- (21) Pigeon, P.; Top, S.; Zekri, O.; Hillard, E. A.; Vessières, A.; Plamont, M. A.; Buriez, O.; Labbé, E.; Huché, M.; Boutamine, S.; Amatore, C.; Jaouen, G. *J. Organomet. Chem.* **2009**, *694*, 895–901.
- (22) Zekri, O.; Hillard, E. A.; Top, S.; Vessières, A.; Pigeon, P.; Plamont, M. A.; Huché, M.; Boutamine, S.; McGlinchey, M. J.; Müller-Bunz, H.; Jaouen, G. *Dalton Trans.* **2009**, 4318–4326.
- (23) Huynh, N. T.; Morille, M.; Béjaud, J.; Legras, P.; Vessières, A.; Jaouen, G.; Benoît, J. P.; Passirani, C. *Pharm. Res.* **2011**, *28*, 3189–3198.
- (24) Allard, E.; Huynh, N. T.; Vessières, A.; Pigeon, P.; Jaouen, G.; Benoit, J.-P.; Passirani, C. *Int. J. Pharm.* **2009**, *379*, 317–323.
- (25) Plazuk, D.; Vessières, A.; Hillard, E. A.; Buriez, O.; Labbé, E.; Pigeon, P.; Plamont, M. A.; Amatore, C.; Zakrzewski, J.; Jaouen, G., *J. Med. Chem.* **2009**, *52*, 4964–4967.
- (26) Görmén, M.; Pigeon, P.; Hillard, E. A.; Plamont, M. A.; Plazuk, D.; Top, S.; Vessières, A.; Jaouen, G. *Tetrahedron Lett.* **2010**, *51*, 118–120.
- (27) Görmén, M.; Pigeon, P.; Top, S.; Vessières, A.; Plamont, M.-A.; Hillard, E.; Jaouen, G. *MedChemComm* **2010**, *1*, 149–151.
- (28) Görmén, M.; Pigeon, P.; Top, S.; Hillard, E. A.; Huché, M.; Hartinger, C. G.; de Montigny, F.; Plamont, M.-A.; Vessières, A.; Jaouen, G. *ChemMedChem* **2010**, *5*, 2039–2050.
- (29) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513–1524.

- (30) McMurry, J. E. *Acc. Chem. Res.* **1983**, *16*, 405.
- (31) Turbitt, T. D.; Watts, W. E. *J. Organomet. Chem.* **1972**, *46*, 109–117.
- (32) Fürstner, A.; Bogdanovic, B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2442–2469.
- (33) Bogdanovic, B.; Bolte, A. *J. Organomet. Chem.* **1995**, *502*, 109–121.
- (34) Goldberg, S. I.; Bailey, W. D.; McGregor, M. L. *J. Org. Chem.* **1971**, *36*, 761–769.
- (35) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S. *J. Org. Chem.* **1976**, *41*, 260.
- (36) Duan, X.-F.; Zeng, J.; Lü, J.-W.; Zhang, Z.-B. *J. Org. Chem.* **2006**, *71*, 9873–9876.
- (37) Balu, N.; Nayak, S. K.; Banerji, A. *J. Am. Chem. Soc.* **1996**, *118*, 5932–5937.
- (38) Seo, J. W.; Kim, H. J.; Se Lee, B.; Katzenellenbogen, J. A.; Chi, D. Y. *J. Org. Chem.* **2008**, *73*, 715–718.
- (39) Mukaiyama, T.; Sato, T.; Hanna, J. *Chem. Lett.* **1973**, 1041–1044.
- (40) Ortin, Y.; Grealis, J.; Scully, C.; Müller-Bunz, H.; Manning, A. R.; McGlinchey, M. J. *J. Organomet. Chem.* **2004**, *689*, 4683–4690.
- (41) Deno, N. C.; Groves, P. T.; Jaruzelski, J. J.; Lugasch, M. N. *J. Am. Chem. Soc.* **1960**, *82*, 4719–4723.
- (42) Deno, N. C.; Jaruzelski, J. J.; Schriesheim, A. *J. Am. Chem. Soc.* **1955**, *77*, 3044–3051.
- (43) Hill, E. A.; Wiesner, R. *J. Am. Chem. Soc.* **1969**, *91*, 509–510.
- (44) Ceccon, A.; Gobbo, A.; Venzo, A. *J. Organomet. Chem.* **1978**, *162*, 311–321.
- (45) Ortaggi, G.; Riccio, P.; Tritto, I. *J. Org. Chem.* **1979**, *44*, 2920–2923.
- (46) Hisatome, M.; Yamakawa, K. *Tetrahedron Lett.* **1971**, 3533–3536.
- (47) Cerichelli, G.; Floris, B.; Ortaggi, G. *J. Organomet. Chem.* **1974**, *78*, 241.
- (48) Top, S.; Jaouen, G. *J. Organomet. Chem.* **1980**, *197*, 199–215.
- (49) Hanson, S. K.; Baker, R. T.; Gordon, J. C.; Scott, B. L.; Sutton, A. D.; Thorn, D. L. *J. Am. Chem. Soc.* **2009**, *131*, 428–429.
- (50) Takezawa, E.; Sakaguchi, S.; Ishii, Y. *Org. Lett.* **1999**, *1*, 713–715.
- (51) Vries, G. D.; Schors, A. *Tetrahedron Lett.* **1968**, *9*, 5689–5690.
- (52) Vettorello, C.; Ricci, M. *J. Org. Chem.* **1986**, *51*, 1599–1602.

- (53) Beebe, T. R.; Hii, P.; Reinking, P. *J. Org. Chem.* **1981**, *46*, 1927–1929.
- (54) Messina, P.; Labbé, E.; Buriez, O.; Hillard, E. A.; Vessièrès, A.; Hamels, D.; Top, S.; Jaouen, G.; Frappart, Y.; Mansuy, D.; Amatore, C. *Chem. Eur. J.* **2012**, *18*, 6581–6587.
- (55) Kirkwood, S.; Philips, P. H. *J. Am. Chem. Soc.* **1947**, *69*, 934–936.
- (56) Watkin, D. J.; Prout, C. K.; Pearce, L. J. *CAMERON*; Chemical Crystallography Laboratory, Oxford, U.K., 1996.
- (57) Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.
- (58) Hagen, H.; Marzenell, P.; Jentzsch, E.; Wenz, F.; Veldwijk, M. R.; Mokhir, A. *J. Med. Chem.* **2012**, *55*, 924–934.