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Organometallic cluster analogues of tamoxifen: Synthesis and biochemical assay

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Abstract

Simple organometallic cluster analogues of tamoxifen containing triosmium or dicobalt carbonyl fragments have been prepared. Attempts at elaboration of these towards the tamoxifen skeleton were hampered by sensitivity of the cluster–ligand linkage towards the McMurry coupling conditions. Preliminary biological tests on various substrates indicate that the transition metal carbonyl fragment increases lipophilicity dramatically and reduces affinity for the estrogen receptor.

Keywords: Osmium; Cobalt; Cluster; Tamoxifen

1. Introduction

Tamoxifen is widely used for the treatment of hormone-dependent breast cancer [1]. However, it is known to be completely effective for a long period only in about one in three such cases. There is thus still considerable effort put into the development of modified tamoxifen, either to increase its efficacy directly, or to use it as a vehicle for introducing other cytotoxic agents. In addition to organic modifications, inorganic and organometallic modifications have been explored as well. These include platinum complexes [2], carborane complexes [3], organorhenium [4], titanocene [5], ferrocene [6], and ruthenocene [7]. Among these, the most well-studied and potentially most successful metal-containing analogues of tamoxifen are those containing the ferrocene moiety, or ferrocifens. For example, hydroxyferrocifen was found to have a stronger anti-proliferative effect than hydroxytamoxifen, and this has been attributed to the cytotoxic activity of the ferrocenium ion, which results from the oxidation of the ferrocene moiety in vivo [6e].

Hydroxyferrocifen was originally synthesized via a series of Grignard and dehydration reactions [6a], but since then this has been superseded by a more efficient McMurry coupling route (Scheme 1) [6e]. The same McMurry coupling route has been adopted for the incorporation of $CpRe(CO)_3$ into the tamoxifen skeleton, illustrating the usefulness of the McMurry protocol [4a]. Since tamoxifen is capable of tolerating a considerable degree of structural variation while still retaining its affinity for the estrogen receptor, we were interested in investigating the effect of incorporating a metal carbonyl cluster. It was hoped that the multiple low-valent metal centres in such derivatives may be oxidized to yield a multiply-charged cluster which would represent a potent cytotoxic species contained within a small volume, enabling tumour suppression to be more effective.

No organometallic cluster-containing derivative of tamoxifen has ever been reported. We were thus interested in exploring the possibilities for synthesizing such a class of

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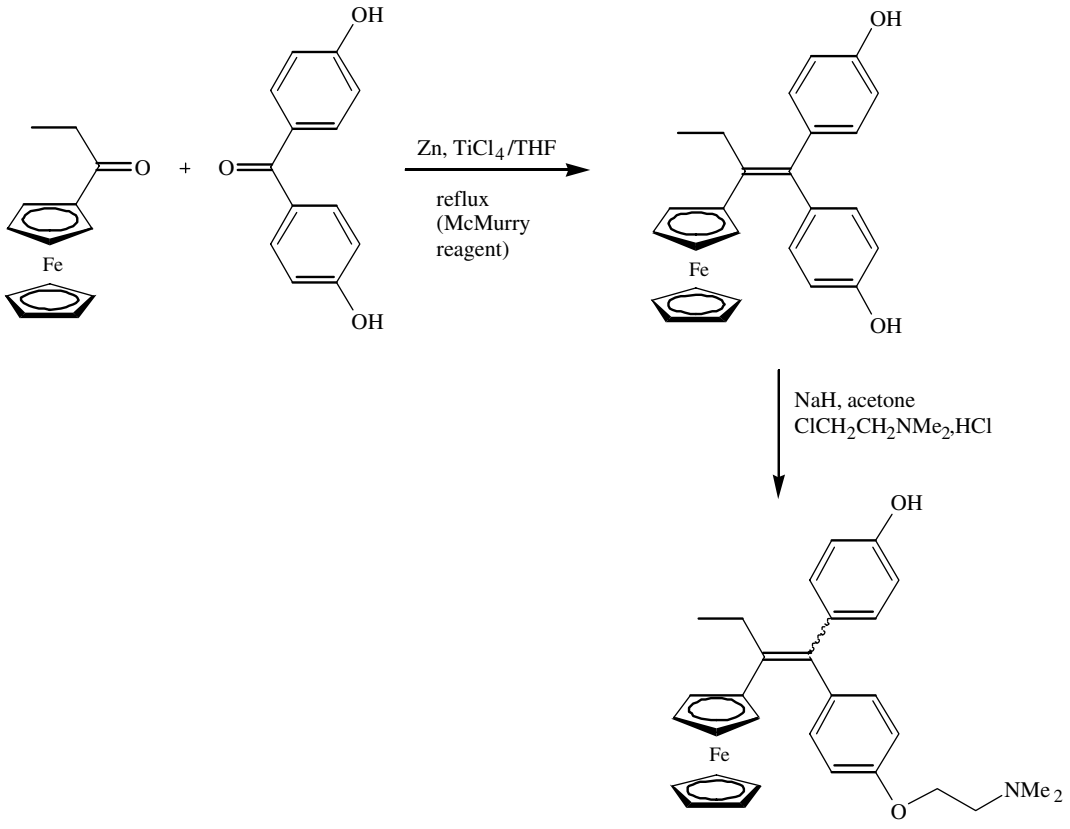


Scheme 1.

modified tamoxifens. Our plan was to explore the synthetic routes towards a tamoxifen-like derivative containing a triosmium carbonyl cluster, as these clusters are generally quite stable. In this paper, we wish to report our attempts at this goal.

2. Results and discussion

2.1. Studies on the incorporation of clusters into tamoxifen

Our initial explorations involved tamoxifen-like derivatives containing a carboxylate-cluster linkage as these linkages are expected to be stable, and hence would also be amenable to further transformations of the cluster; we were thus interested in derivatives such as that given in Fig. 1. For the synthesis of triosmium-carboxylate clusters, the parent triosmium carbonyl cluster $Os_3(CO)_{12}$, **1a**, is of limited utility as it is rather inert; often an activated derivative such as $Os_3(CO)_{10}(NCMe)$, **2a**, $Os_3(CO)_{10}(NCMe)_2$, **2b**, or $Os_3(CO)_{10}(\mu\text{-H})(\mu\text{-OH})$, **3**, is employed instead. Triosmium-carboxylate clusters can be conveniently prepared by the reaction of **3** with the appropriate carboxylic acid in the presence of $HBF_4 \cdot OEt_2$ as an acid catalyst [8]. We have thus prepared a series of such triosmium-carboxylate clusters, **5**, starting from the appropriate carboxylic acids, **4** (Scheme 2 and Table 1). Clusters **5a**–**f** were simple but close analogues to the target; the alkenic functionality in

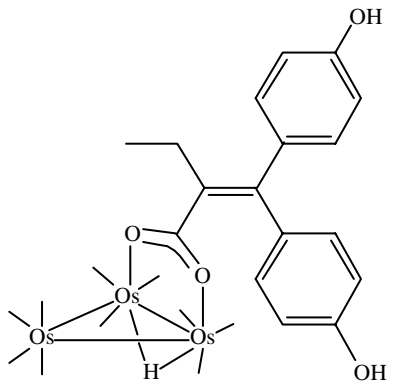
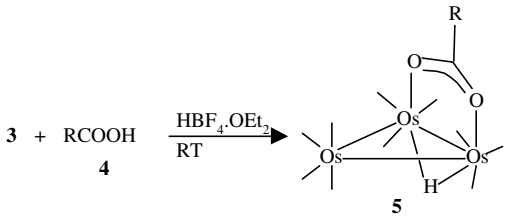


Fig. 1. Targetted triosmium cluster derivative of tamoxifen.

tamoxifen was retained, and they were synthesized for tests on their potential biochemical activity.

These reactions leading to the carboxylate clusters can be quite fast when acid is present; thus, for example, ^1H NMR spectroscopic monitoring of the reaction of **3** and crotonic acid, **4c**, showed the instantaneous formation of E-$Os_3(CO)_{10}(\mu\text{-H})\{\mu\text{-}O_2C{=}C(H)C(H)CH_3\}$, **5e**. In the absence of HBF_4, no reaction occurred even after 6 h. This is in contrast to **2b**, which reacted gradually with carboxylic acids [9]. However, the ease of reaction was found to depend on the size and functional groups present on the carboxylic acids. While the reactions of smaller carboxylic



		Yield(%)
a	$CH{=}CH_2$	41
b	$CEt{=}CH_2$	86
c	*E*-CH=CHMe	82
d	*E*-CH=CHPh	77
e	*E*-CH=CH-*p*-C_6H_4OH	0.4
f	*E*-CMe=CHPh	80
g	COEt	66
h	COPh	72
i	CH_2CH_2COMe	97
j	*E*-CH=CHCOPh	89
k	*p*-C_6H_4COMe	1.2

Scheme 2.

acids (e.g., **4c** and **4g**) were completed in 10 min, larger carboxylic acids (e.g., **4i** and **4j**) required more than 5 h to reach completion. On the other hand, while **4d** and **4i** gave good yields of **5d** (77%) and **5i** (97%), respectively, the closely related acids **4e** and **4k** gave very poor yields of **5e** (0.4%) and **5k** (1.2%), respectively. These point to subtle electronic effects; slightly better yields of clusters **5e** and **5k** were obtained when the corresponding carboxylic acids were reacted with **2b** (14% and 5.3%, respectively).

The structure of **5h** has also been confirmed by a single crystal X-ray crystallographic study. There are two crystallographically independent molecules in the asymmetric unit; the ORTEP diagram for one of the molecules, together with selected bond parameters, is shown in Fig. 2. The molecular structure shows that the benzoyl formate ligand occupies two axial positions on adjacent osmium atoms. The Os(1A)–Os(2A) [2.9297(5) Å] edge is longer than the Os(1A)–Os(3A) [2.8562(4) Å] and Os(2A)–Os(3A) [2.8708(5) Å] edges, which is a common feature of hydride–bridged Os–Os edges [10]. The Os(1A)–C(12A) [1.867(6) Å] and Os(2A)–C(22A) [1.864(6) Å] bonds are shorter than the Os(3A)–C(32A) [1.964(7) Å] bond. This reflects the σ-donating and weak π-accepting properties of the carboxylate ligand, which together results in more electron density being donated from Os(1A) and Os(2A) to the *trans* carbonyls, CO(12A) and CO(22A), respectively.

Since the McMurry reaction involved Lewis acidic conditions, cluster **5c** was first tested under the normal McMurry conditions (reflux with the McMurry reagent); **5c** was detected as the only hydride-containing cluster, indicating that the carboxylate linkage would be stable in the McMurry reaction. Cluster **5h** was also reacted with HCl in $PhCH_3$, CH_2Cl_2, THF, CH_3CN, and DMSO, since HCl was a likely side-product from hydrolysis of the McMurry reagent; it remained stable in all the solvents tested except CH_3CN, in which it was converted to the known $Os_3(CO)_{10}(\mu\text{-H})(\mu\text{-Cl})$, **6**. The formation of **6** in CH_3CN could be due to labilization of the carboxylate ligand by CH_3CN itself; for example, nucleophilic substitution in clusters of the type $Os_3(CO)_{10}(\mu\text{-H})(\mu\text{-OR})$ by EPh_3 (E = P, As, Sb) occur at a bridged Os, suggesting that it is the electrophilic site [11]. A similar process involving initial attack by CH_3CN could have occurred.

Unfortunately, the attempted McMurry coupling of **5g** and **5h** with 4,4′-dihydroxybenzophenone both yielded cluster **6** instead of the McMurry coupled product. The identity of **6** from this reaction has also been confirmed by a single crystal X-ray crystallographic study (see Supporting Information), which yielded a different polymorph from that reported earlier [12]. Since we have shown that the carboxylate linkage itself was stable towards the McMurry reagent, the substitution of $RCOO^-$ by Cl^- was presumably related to the presence of the α-keto group, which could have labilized the carboxylate linkage through chelation to the McMurray reagent (Fig. 3). Attempts to circumvent this by moving the keto group further away and yet retaining the proximity of the cluster moiety to the two phenolic rings (the sites of estrogen receptor recognition) [13], viz., **5i** and **5j**, were also unsuccessful, leading again to the formation of **6**. The McMurry reagent has been reported to be capable of forming alkenic macrocycles with ring sizes from 4 to 23 [14], and this may be operative here. Hopes that the inflexible phenyl separating the keto and carboxylate groups in **5k** may resolve the problem were unfortunately pre-empted by its low yield.

As it appeared that the problem was with the oxophilicity of titanium, we thought that perhaps the chelation effect may be diminished if the carboxylate linkage was replaced by a thiolate; the softer sulfur was also expected to bind more strongly with the low-valent osmium. Two thiolate clusters were prepared using the same procedure as for the carboxylate clusters, viz., $Os_3(CO)_{10}(\mu\text{-H})\{\mu\text{-SC(=O)Ph}\}$, **5l**, and $Os_3(CO)_{10}(\mu\text{-H})(\mu\text{-SCH}_2CH_2OH)$, **5m**, and tested in their reactions with the McMurry reagent. Cluster **5l** has previously been synthesized from the reaction of thiobenzoic acid with $Os_3(CO)_{10}(MeCN)_2$ [15]. Although **5m** was inert to the McMurry reagent, as judged by ^1H NMR monitoring, the reaction of **5l** and 4,4′-dihydroxybenzophenone with the McMurry reagent led to the known cluster $Os_3(CO)_9(\mu\text{-H})_2(\mu_3\text{-S})$, **7**, instead. Thus it appeared that there was nucleophilic attack by Cl^- on the carbonyl group of **5n** leading to displacement of the cluster moiety; this was supported by the observation that **7** was formed when **5l** was treated with aq. HCl (Scheme 3).

An attempt to circumvent the nucleophilicity of the chloride ion by adding $AgBF_4$ to remove it from the McMurry reagent prior to the addition of **5g** and 4,4′-dihydroxybenzophenone led to an intractable brown mixture.

Table 1
Spectroscopic data for cluster compounds **5**

Compound	ν(CO)/cm^{-1}	^{1}H NMR/δ	Elemental analysis: Calc. (Found)/%
5a	2114w, 2075vs, 2064s, 2028vs, 2017vs, 2011w, 1988w	5.97 (dd, 1H, CH=CH_2, $^3J_{trans}$ = 17.32 Hz, $^2J_{gem}$ = 2.47 Hz), 5.87 (dd, 1H$_a$, CH=CH$_2$, $^3J_{cis}$ = 9.90 Hz), 5.15 (dd, 1H, CH=CH_2), −10.42 (s, 1H, OsHOs)	For $C_{13}H_4O_{12}Os_3$: C,16.92; H, 0.44. Found: C, 17.06; H, 0.30
5b	2113w, 2074vs, 2064s, 2028vs, 2017vs, 2012w, 1983w	5.76 (s, 1H, C=CH_2), 5.25 (s, 1H, C=CH_2), 2.05 (q, 2H$_b$, CH_2CH$_3$, ^3J = 7.43 Hz), 0.92 (t, 3H, CH$_2$CH_3), −10.42 (s, 1H, OsHOs)	For $C_{15}H_8O_{12}Os_3$: C, 18.95; H, 0.85. Found: C,18.90; H, 0.64
5c	2113w, 2075vs, 2064s, 2027vs, 2017vs, 2010w, 1984w	6.56 (dq, 1H, C=CHCH$_3$, $^3J_{cis}$ = 6.60 Hz, $^3J_{trans}$ = 15.26 Hz), 5.62 (dq, 1H, CH=CHCH$_3$, ^4J = 1.65 Hz), 1.80 (dd, 3H, CH=CHCH_3), −10.43 (s, 1H, OsHOs)	For $C_{14}H_6O_{12}Os_3$: C, 17.95; H, 0.65. Found: C, 18.31; H, 0.95
5d	2113w, 2075vs, 2063s, 2027vs, 2017vs, 2010w, 1985w	7.44–7.40 (m, 2H, *o*-C$_6H_5$), 7.35–7.33 (m, 3H, *m*,*p*-C$_6H_5$), 7.24 (d, 1H$_b$, CH=CH, $^3J_{trans}$ = 16.50 Hz), 6.23 (d, 1H, CH=CH), −10.35 (s, 1H, OsHOs)	For $C_{19}H_8O_{12}Os_3 \cdot 1/4C_6H_{14}$: C, 24.13; H, 1.14. Found: C, 24.35; H, 1.06
5e	2113w, 2075vs, 2063s, 2027vs, 2017vs, 2010w, 1985w	7.32 (d, 2H, C$_6H_4$, $^3J_{cd}$ = 9.08 Hz), 7.18 (d, 1H, CH=CH, $^3J_{trans}$ = 15.67 Hz), 6.79 (d, 2H, C$_6H_4$), 6.09 (d, 1H, CH=CH), 4.96 (s, 1H, OH), −10.35 (s, 1H, OsHOs)	For $C_{19}H_8O_{13}Os_3 \cdot 1/4C_6H_{14}$: C, 23.75; H, 1.12. Found: C, 23.46; H, 0.85
5f	2113w, 2075vs, 2064s, 2027vs, 2017vs, 2013w, 1982w	7.37–7.24 (m, 6H, C$_6H_5$ and C=CH), 1.85 (d, 3H, CH_3C=C, $^4J_{trans}$ = 1.85 Hz), −10.27 (s, 1H, OsHOs)[a]	For $C_{20}H_{10}O_{12}Os_3$: C, 23.71; H, 1.00. Found: C, 23.65; H, 0.83
5g	2113w, 2074vs, 2063s, 2025vs, 2017vs, 2010w, 1986w	2.59 (q, 2H, CH_2CH$_3$, ^3J = 7.43 Hz), 0.99 (t, 3H, CH$_2$CH_3), −10.45 (s, 1H, OsHOs)	For $C_{14}H_6O_{13}Os_3$: C, 17.65; H, 0.64. Found: C, 17.93; H, 0.83
5h	2114w, 2075vs, 2063s, 2027vs, 2017vs, 2010w, 1984w	7.69–7.61 (m, 3H, C$_6H_5$), 7.52–7.46 (m, 2H, C$_6H_5$), −10.25 (s, 1H, OsHOs)	For $C_{18}H_6O_{13}Os_3$: C, 21.60; H, 0.60. Found: C, 21.62; H, 0.55
5i	2113w, 2074vs, 2064s, 2027vs, 2017vs, 2012w, 1986w	2.52 (t, 2H, CH_2CH$_2$, ^3J = 5.78 Hz), 2.45 (t, 2H, CH$_2$CH_2), 2.13 (s, 3H, COCH_3), −10.45 (s, 1H, OsHOs)	For $C_{15}H_8O_{13}Os_3$: C, 18.64; H, 0.84. Found: C, 18.86; H, 1.05
5j	2113w, 2075vs, 2062s, 2028vs, 2017vs, 2010w, 1987w	7.90 (d, 2H, *o*-C$_6H_5$, $^3J_{cd}$ = 8.25 Hz), 7.61 (t, 1H, *p*-C$_6H_5$, $^3J_{de}$ = 7.42 Hz), 7.50 (td, 2H, *m*-C$_6H_5$), 7.41 (d, 1H, CH=CH, $^3J_{trans}$ = 15.67 Hz), 6.60 (d, 1H, CH=CH), −10.38 (s, 1H, OsHOs)	For $C_{20}H_8O_{13}Os_3$: C, 23.39; H, 0.79. Found: C, 23.49; H, 0.80
5k	2114w, 2075vs, 2064s, 2027vs, 2017vs, 2011w, 1986w	7.88 (d, 2H, C$_6H_4$, ^3J = 8.25 Hz), 7.78 (d, 2H, C$_6H_4$), 2.59 (s, 3H, COCH_3), −10.25 (s, 1H, OsHOs)	For $C_{19}H_8O_{13}Os_3$: C, 22.48; H, 0.79. Found: C, 22.80; H, 0.52
5m	2110w, 2069vs, 2059s, 2025vs, 2021sh, 2001w, 1990w, 1984w	3.84 (td, 2H, CH_2OH), 2.61 (t, 2H, SCH_2, ^3J = 5.79 Hz), 1.74 (t, 1H, OH, ^3J = 4.95 Hz), −17.36 (s, 1H)	For $C_{12}H_6O_{11}Os_3S$: C, 15.52; H, 0.65; S, 3.45. Found: C, 15.51; H, 0.79; S, 3.01

[a] In CD_2Cl_2.

Several unsuccessful attempts at incorporating a functionality such as a carboxylic acid, phenol, trichloromethyl, nitrile or phosphine, which can be subsequently functionalized with an organometallic cluster, onto the tamoxifen skeleton were also made. A partially successful strategy was found with the incorporation of an alkyne functionality following a similar procedure to that reported for the synthesis of a *nido*-carborane analogue of tamoxifen [16]. Deprotection of **8** or **10** with BBr_3 were not successful but treatment of **10** with $Co_2(CO)_8$, **1b**, afforded **11** as an oil (Scheme 4). The incorporation of a terminal alkyne functionality is useful as it can react readily with a number of organometallic clusters. Reactions of various terminal alkynes with $Os_3(CO)_{10}(\mu\text{-}H)_2$ or **1a** [17], as well as with $Ru_3(CO)_{12}$ to give alkylidyne clusters [18], are known. The reaction of **1b** with alkynes is a well-known reaction for the protection of the latter in organic syntheses. Furthermore, $Co_2(CO)_6$ complexes of terminal alkynes have been found to be cytotoxic against melanoma and lung carcinoma cell lines [19]. Thus, the incorporation of $Co_2(CO)_6$ into the tamoxifen skeleton can be expected to impart cytotoxic effect against breast cancer cells as well.

The McMurry coupling of disubstituted alkynes has also been demonstrated previously [20], and we have employed this in the syntheses outlined in Scheme 5 to afford **12**. It has been shown that **2a** can be used to introduce a triosmium moiety onto disubstituted alkynes [21], unfortunately, **12** failed to react. On the other hand, **12** reacted smoothly with **1b** to give **13**, which was crystallized from pentane/ether as a deep purple solid. While **13** is purple in the solid form, its solutions in pentane, ether, chloroform, DMSO, and methanol are green. This is unexpected, as most analogous alkyne–$Co_2(CO)_6$ complexes, including **11**, are dark red in solution. The solution IR spectrum of **13** displayed three bands as expected of an alkyne–$Co_2(CO)_6$. It is stable in the solid form when kept under

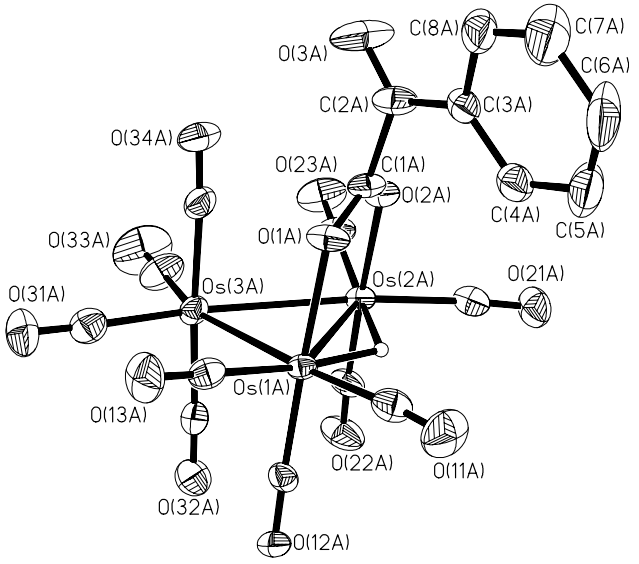


Fig. 2. ORTEP diagram and selected bond lengths (Å) and angles (°) for molecule A of **5h** (50% probability thermal ellipsoids.) Os(1A)–Os(2A) = 2.9297(5); Os(2A)–Os(3A) = 2.8708(5); Os(1A)–Os(3A) = 2.8562(4); Os(1A)–O(1A) = 2.146(4); Os(2A)–O(2A) = 2.148(4); O(1A)–C(1A) = 1.253(7); O(2A)–C(1A) = 1.254(7); O(3A)–C(2A) = 1.198(8); C(1A)–C(2A) = 1.536(8); C(2A)–C(3A) = 1.466(9); O(1A)–Os(1A)–Os(3A) = 91.87(12); O(1A)–Os(1A)–Os(2A) = 80.55(11); Os(3A)–Os(1A)–Os(2A) =59.477(11); O(2A)–Os(2A)–Os(3A) = 95.36(12); O(2A)–Os(2A)–Os(1A) = 80.87(11); Os(3A)–Os(2A)–Os(1A) = 58.987(8); Os(1A)–Os(3A)–Os(2A) = 61.536(13); O(1A)–C(1A)–O(2A) = 126.8(5).

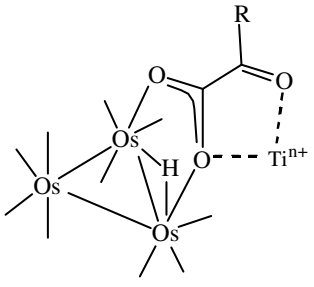


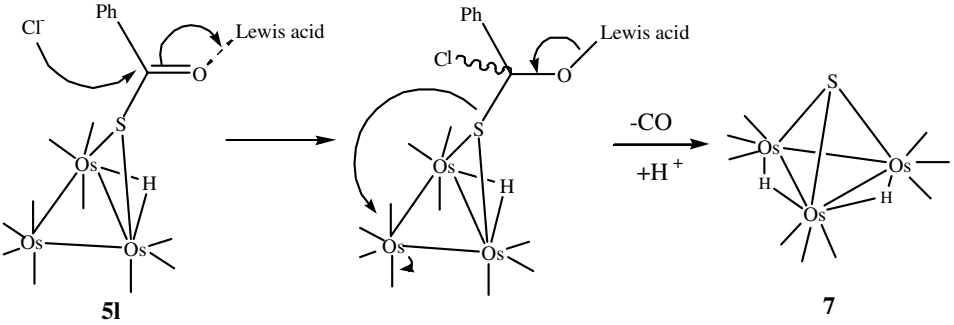
Fig. 3. Possible chelation leading to loss of carboxylate group.

Ar, but decomposes slowly in solution to form a yellow solution. This solution showed no carbonyl stretching bands and reversed phase HPLC indicated that **12** was present; the ^{1}H NMR spectrum displayed broad peaks, suggesting the presence of paramagnetic species. These observations suggest that Co has been oxidized, resulting in the release of **12** and loss of CO.

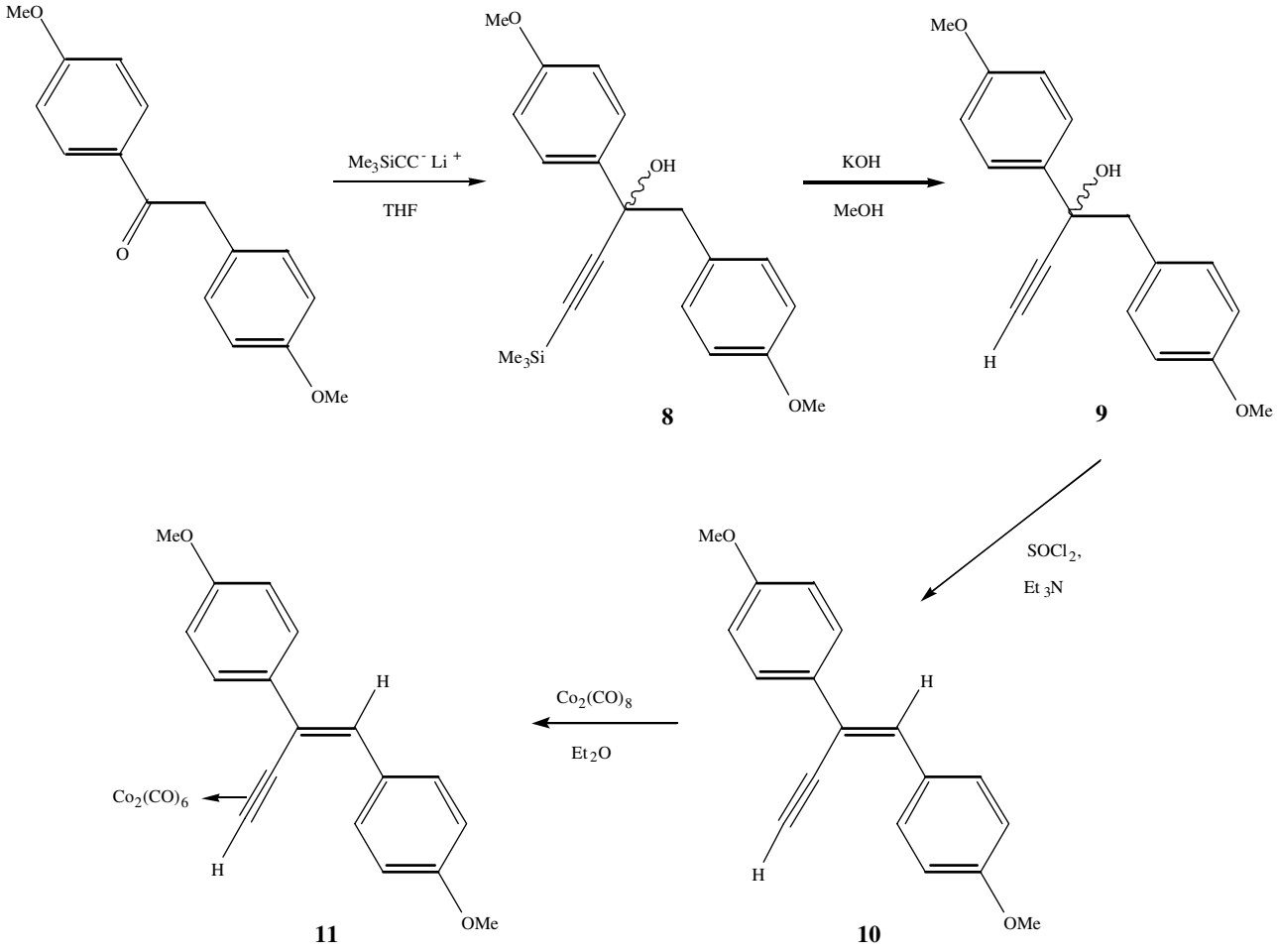
The structure of **13** has been determined by a single crystal X-ray crystallographic study. The ORTEP diagram showing the molecular structure, together with selected bond parameters, is shown in Fig. 4. Co(1) is symmetrically bound to the alkyne (1.950(6) and 1.950(5) Å for Co(1)–C(1) and Co(1)–C(2), respectively) but the Co(2) is asymmetrically bound; the Co(2)–C(2) bond is significantly longer than the Co(2)—C(1) bond (1.988(5) and 1.959(5) Å, respectively.) The olefinic bond length (C(3)–C(4) = 1.352(8) Å) is close to that for the Co_2-coordinated C≡C bond length (C(1)–C(2) = 1.321(8) Å), indicating that some multiple bond character is retained despite binding to $Co_2(CO)_6$. As has been observed for ferrocifen [6e], the two C_6H_4OH rings are almost perpendicular to the ethene plane, and the C(421)–C(4)–C(3), C(411)–C(4)–C(3), and C(2)–C(3)–C(4) bond angles (122.5(5), 125.3(5) and 128.3(5)°, respectively) are larger than 120°. These have been attributed to the steric bulk of ferrocene, and in **13** may similarly be attributed to the steric bulk of the $Co_2(CO)_6$ moiety.

2.2. Determination of lipophilicity and relative binding affinity for estrogen receptor

One of the criteria for a biomimetic is that it has to be hydrophilic enough to be transported in the bloodstream to the target tissue, and yet sufficiently hydrophobic to penetrate the cell membrane. This criterion can be assessed by the determination of the octanol–water partition coefficient, log($P_{o/w}$), using the method of Pomper et al. [22]; a higher value indicates greater hydrophobicity. The ideal range for a biomimetic is recognized to be 3.3–5.5; the reference compound, estradiol, has a value of 3.4. The relative binding affinity (RBA), is a measure of how strongly the estrogen receptor recognizes and binds the tamoxifen mimetic. The biomimetic should have an RBA as large as possible so that it can compete more effectively with estradiol for the receptor binding site and exert its cytotoxic effect. Table 2 shows the log($P_{o/w}$) and RBA values determined for some of the tamoxifen mimetics reported here.



Scheme 3.



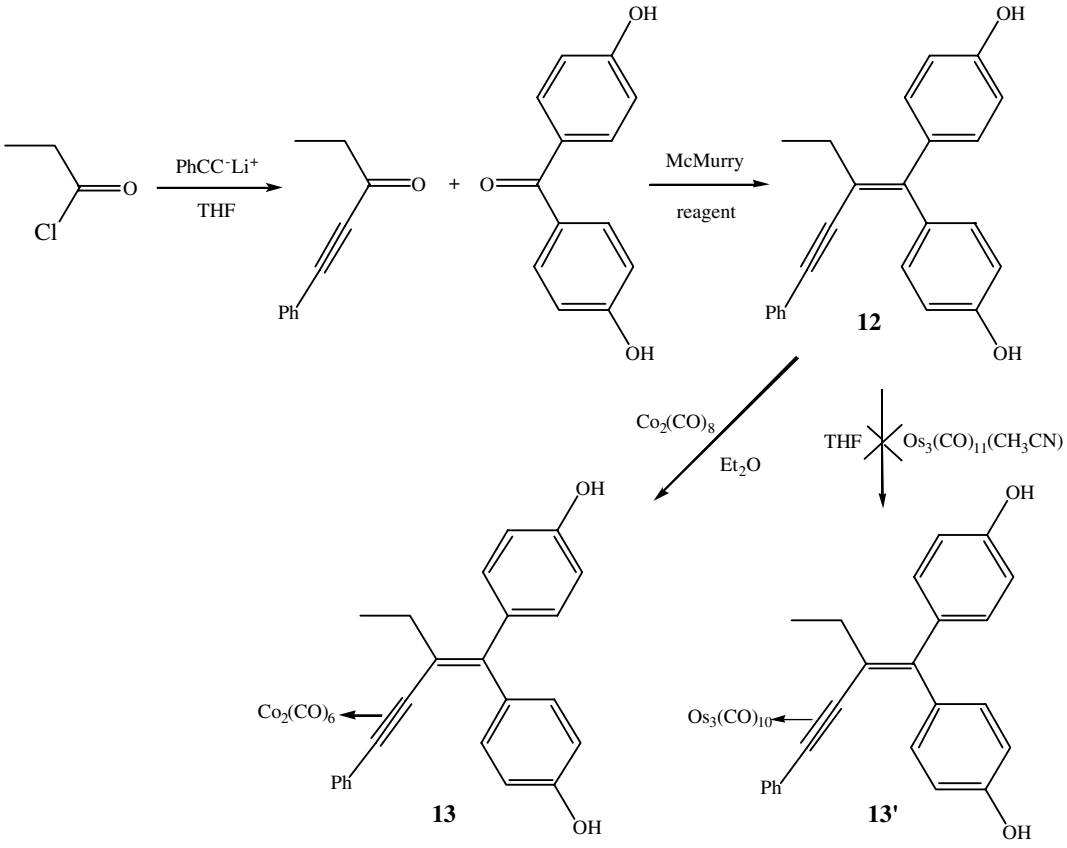
Scheme 4.

The table showed, not unexpectedly, that the simplest triosmium clusters were very hydrophobic. The addition of hydrocarbon groups to the basic structure (**5a**) increased the $\log(P_{o/w})$ very quickly, while addition of polar groups decreased the $\log(P_{o/w})$ by a relatively smaller value. A comparison with the values for 1,1-*p*-dihydroxyphenyl-2-phenyl-but-1-ene and 1,1-*p*-dihydroxyphenyl-2-ferrocenyl-but-1-ene ($\log(P_{o/w}) = 4.4$ and 5.0, respectively) [6f] shows that while inserting a C≡C function or replacing the phenyl ring with a ferrocene group in the former increased the lipophilicity slightly, introduction of the $Co_2(CO)_6$ unit increased it considerably (+1.5 units w.r.t. **12**). This suggests that the carbonyl units were very efficient in increasing the lipophilicity of the biomimetic.

Among triosmium cluster compounds, molecules **5d** and **5e** are closest to diethylstilbestrol. Therefore, these two compounds should have better affinity toward the receptor of 17β-estradiol than the others. Unfortunately, **5d** and **5e** were not recognized by the receptor (RBA = 0). This result is more surprising for **5e** as this complex has a phenol that is known to be crucial for the binding to the estrogen receptor [23]. On the other hand, **12**, a pure organic compound exhibited a good affinity for the receptor (RBA = 6.7%) while **13**, its corresponding $Co_2(CO)_6$ complex, showed a moderate RBA value (RBA = 3.3%). Thus the addition of the $Co_2(CO)_6$ moiety decreased receptor recognition, which may be attributed to the steric bulk of the cobalt cluster. Such a diminution in RBA value has also been observed for estradiol on coupling with alkyne–$Co_2(CO)_6$ [24]. In comparison with hydroxyferrocifen which has an RBA of 14.6, it is more poorly recognized by the estrogen receptor [25]. This could be due to a combination of both the bulkier and the greater lipophilicity of $Co_2(CO)_6$ relative to ferrocifens which may increase the level of non-specific binding.

3. Concluding remarks

We have synthesized a number of simple triosmium cluster derivatives that may mimic tamoxifen. Attempts at elaboration into the tamoxifen skeleton shows that the various cluster–ligand linkages used here proved unsuitable for the McMurry coupling. On the other hand, derivatisation of the tamoxifen skeleton with an alkyne functionality prior to introduction of a dicobalt fragment was successful. Further development of this latter strategy should prove useful. The lipophilicity and RBA tests conducted on the compounds synthesized suggest that transition metal car-



Scheme 5.

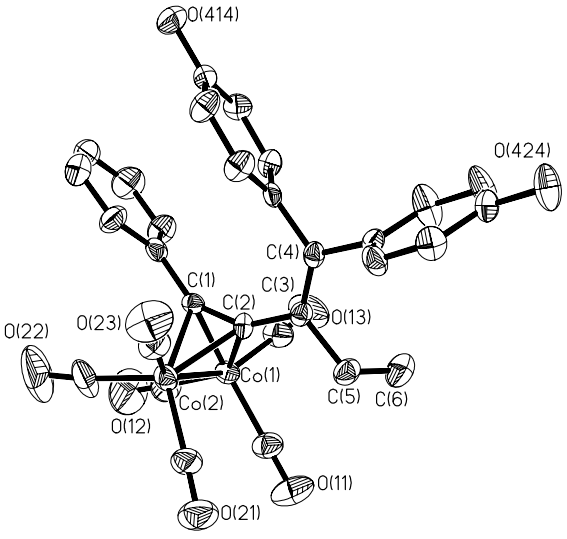


Fig. 4. ORTEP diagram and selected bond lengths (Å) and angles (°) for **13** (50% probability thermal ellipsoids.) Co(1)–Co(2) = 2.4510(11); Co(1)–C(1) = 1.950(5); Co(1)–C(2) = 1.950(6); Co(2)–C(1) = 1.959(5); Co(2)–C(2) = 1.988(5); Co(1)–C(11) = 1.822(7); Co(1)–C(12) = 1.813(7); Co(1)–C(13) = 1.788(7); Co(2)–C(21) = 1.813(7); Co(2)–C(22) = 1.822(7); Co(2)–C(23) = 1.796(7); C(1)–C(2) = 1.321(8); C(2)–C(3) = 1.475(8); C(3)–C(4) = 1.352(8); C(2)–C(3)–C(5) = 115.8(5); C(421)–C(4)–C(411) = 112.2(5).

bonyl groups increase the lipophilicity dramatically and also reduce RBA via steric hindrance. This would mean that potential molecular targets should incorporate more hydrophilic groups, and possibly placing the organometallic fragment further from the tamoxifen skeleton.

Table 2
$\log P_{o/w}$ and relative binding affinity values (RBA) for the estrogen receptor of selected compounds

Compound	**5a**	**5b**	**5c**	**5d**	**5e**	**5f**	**5j**	**12**	**13**
$\log(P_{o/w})$	6.2	7.1	6.6	7.7	7.0	8.3	7.0	5.0	6.5
RBA[a]				0.0	0.0			6.7	3.3

[a] As % for ERα in DMSO, 4 °C, 3 h.

4. Experimental

All manipulations were carried out using standard Schlenk techniques under an argon or nitrogen atmosphere [24]. Solvents that were used for reactions were distilled over the appropriate drying agents under nitrogen before use. Reaction mixtures were separated by flash column chromatography or TLC using silica gel (impregnated with fluorescent indicator; 254 nm) pre-coated on glass plates (0.25 mm layer thickness). The clusters **2a**, **2b** and **3** were prepared according to reported procedures [25]. All other reactants and reagents were purchased and used as supplied without further purification. 1D and 2D NMR spectra were recorded on Bruker ACF-300 and Bruker AMX-500 FT-NMR spectrometers, respectively. All spectra were recorded as $CDCl_3$ solutions at 300 K unless otherwise stated. Mass spectrometric determinations were performed on a VG Micromass 7035

mass spectrometer coupled with a Hewlett–Packard 5890A GC system or Nermag R 10–10C. Microanalyses were carried out by the elemental analysis laboratory at the Department of Chemistry, National University of Singapore. Lipophilicity constants were determined on a System Gold HPLC System (Beckman Coulter, Inc) equipped with a Photo Diode Array detector (277 nm) and a 32 Karat Workstation (version 3.0).

4.1. General procedure for the syntheses of 5

To a solution of **3** and the carboxylic acid (excess) in dichloromethane (0.5 mL) was added a drop of $HBF_4 \cdot Et_2O$, resulting in a white precipitate that may disappear on prolonged stirring. The mixture was allowed to stir at ambient temperature for 30 min before purification by thin-layer chromatography.

4.2. Alternative syntheses of 5e and 5k

To **2b** (200 mg, 0.214 mmol) in THF (20 mL) was added 4-hydroxycinnamic acid (40.3 mg, 0.245 mmol), after which the Carius tube was sealed and evacuated with three cycles of freeze–pump–thaw. The mixture was then heated at 60 °C for 3 h. After the solvent was removed in vacuo, the residue was re-dissolved in 0.5 mL of dichloromethane and separated by TLC. Yield of **5e** = 30.7 mg (14.1%).

A similar procedure was followed for the synthesis of **5k** from **2b** (200 mg, 0.214 mmol) and 4-acetoxybenzoic acid (50.3 mg, 0.307 mmol). Yield = 11.5 mg (5.3%).

4.3. General procedure for McMurry reactions of 5

To a suspension of Mg/Zn powder in THF (10 ml) was injected $TiCl_4$ dropwise at 0 °C, after which the mixture was refluxed for 2 h to a black suspension. An equimolar solution of **5** and 4,4′-dihydroxybenzophenone in THF (20 ml) was then injected into the freshly generated McMurry reagent at 0 °C. After refluxing the mixture for 5 h, the reaction was quenched with saturated aqueous sodium carbonate (100 mL). The aqueous fraction was extracted with ethyl acetate (3 × 50 mL). The combined yellowish ethereal fraction was washed with saturated aqueous brine (3 × 30 mL) and dried with sodium sulfate for 30 min. After the solvent was removed in vacuo, the residue was either re-dissolved in $CDCl_3$ and analyzed by ^{1}H NMR (**5c**, **5k**), or separated by TLC (**5g**, **5h**, **5i**, **5j**, **5l**). For **5g**–**5j**, cluster **6** was isolated as the main product in their respective yields: **5g** (11.6 mg, 56.1%), **5h** (9.8 mg, 47.1%), **5i** (44.0 mg, 67.9%), and **5j** (35.0 mg, 52.6%). For **5l**, cluster **7** was isolated as the main product (24.1 mg, 69.6%).

4.4. Synthesis of 8

To (trimethylsilyl)acetylene (0.588 g, 6.00 mmol) in THF (10 mL) was injected *n*-butyllithium (4.2 mL, 1.6 M, 6.72 mmol) dropwise at −78 °C, after which the solution was allowed to stir at the same temperature for 15 min. A solution of 2-(4-methoxyphenyl)-4′-methoxyacetophenone (1.026 g, 3.92 mmol) in THF (50 mL) was then injected dropwise into the freshly generated (trimethylsilyl)acetylide lithium reagent maintained at −78 °C, after which the mixture was allowed to warm up to ambient temperature with stirring. After 14 h, the reaction was quenched with saturated aqueous ammonium chloride (5 mL). The aqueous fraction was extracted with diethylether (3 × 20 mL). The combined ethereal fraction was washed with saturated aqueous brine (3 × 20 mL) and dried with magnesium sulfate for 30 min. After the solvent was removed in vacuo, the colourless oil was purified by flash column chromatography to yield a white solid.

Yield: 1.040 g (73.2%). R_f: 0.49 (ether/pentane; 1/5 v/v). ^{1}H NMR: δ 7.49 (d, 2H, C_6H_4, $^3J = 8.92$ Hz), 7.08 (d, 2H, C_6H_4, $^3J = 8.69$ Hz), 6.87 (d, 2H, C_6H_4), 6.79 (d, 2H, C_6H_4), 3.82 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.06 (d, 2H, CH_2, $^4J = 2.27$ Hz), 2.37 (s, 1H, O*H*), 0.19 (s, 9H, $Si(CH_3)_3$). ^{13}C NMR: δ 159.3, 158.8, 136.2, 132.2, 128.1, 127.1, 113.5, 113.3, 107.8, 91.9 (aromatic); 73.5 (*C*OH); 55.5, 55.4 (*Me*O); 51.1 (*C*H$_2$); 0.0 (*Me*$_3$Si). EI-MS (*m*/*z*, rel. abundance): 354.1 (<1, M^+), 336.1 (60.0, $M^+ - H_2O$). HR-EI: Calc. for $C_{21}H_{26}O_3Si$: 354.1651. Found: 354.1642.

4.5. Synthesis of 9

To **8** (2.35 g, 6.64 mmol) in methanol (25 mL) was added potassium hydroxide powder (0.451 g, 8.03 mmol) at ambient temperature, after which the mixture was allowed to stir for 3 h. After methanol was removed in vacuo, the colourless oil was partitioned between a mixture of diethylether (20 mL) and water (20 mL). The aqueous fraction was extracted with diethylether (3 × 20 mL). The combined ethereal fraction was washed with saturated aqueous brine (3 × 20 mL) and dried with magnesium sulfate for 30 min. After the solvent was removed in vacuo, the white residue was purified by flash column chromatography to yield a white solid. Yield: 1.596 g (85.2%). R_f: 0.27 (ether/pentane; 1/4 v/v). ^{1}H NMR: δ 7.50 (d, 2H, C_6H_4, $^3J = 8.96$ Hz), 7.08 (d, 2H, C_6H_4, $^3J = 8.75$ Hz), 6.87 (d, 2H, C_6H_4), 6.80 (d, 2H, C_6H_4), 3.82 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.11 (s, 2H, CH_2), 2.67 (s, 1H$_h$, C≡C−*H*), 2.41 (s, 1H, O*H*). ^{13}C NMR: δ 159.2, 158.7, 135.8, 131.9, 127.6, 126.8, 113.4, 113.3; 86.1 (C−*C*≡); 75.1 (C≡*C*H); 72.8 (*C*−C≡); 55.3, 55.1 (*Me*O); 50.6 (*C*H$_2$). EI-MS (*m*/*z*, rel. abundance, ion): 282.1 (19, M^+), 264.1 (59, $M^+ - H_2O$), 249.1 (47, $M^+ - H_2O$ – Me). HR-EI: Calc. for $C_{18}H_{18}O_3$: 282.1256. Found: 282.1255.

4.6. Synthesis of 10

To **9** (0.658 g, 2.33 mmol) in triethylamine (6 mL) and diethylether (2 mL) was injected dropwise thionyl chloride (0.424 g, 3.56 mmol) [11] at 0 °C. A yellowish-brown solid precipitated gradually and the suspension darkened over time. After stirring at ambient temperature for 2 h, the

reaction was quenched with water (20 mL). The aqueous fraction was extracted with diethylether (3 × 10 mL). The combined ethereal fraction was washed with saturated aqueous brine (3 × 20 mL) and dried with magnesium sulfate for 30 min. After the solvent was removed in vacuo, the dark red oil was purified by flash column chromatography to yield a white solid. Yield: 0.488 g (79.2%). R_f: 0.50 (ether/pentane; 1/5 v/v). ^{1}H NMR: δ 7.94 (d, 2H, C_6H_4, $^3J = 8.70$ Hz), 7.63 (d, 2H, C_6H_4, $^3J = 9.00$ Hz), 7.10 (s, 1H, C═C—*H*), 6.91 (d, 4H, C_6H_4), 3.85 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.52 (s, 1H, C≡C—*H*). ^{13}C NMR: δ 159.6, 159.3, 130.4, 129.3, 127.4, 117.7, 113.8, 113.7 (aromatic); 132.0 (*C*═CH); 134.3 (═*C*H); 84.7 (H*C*≡); 82.9 (C—*C*≡); 55.4, 55.3 (*Me*O). EI-MS (*m*/*z*, rel. abundance, ion): 264.1 (100, M^+), 249.1 (91, $M^+ - Me$). HR-EI: Calc. for $C_{18}H_{16}O_2$: 264.1150. Found: 264.1152.

4.7. Synthesis of **11**

To **10** (0.207 g, 0.783 mmol) in diethylether (5 mL) was added dicobalt octacarbonyl (0.268 g, 0.783 mmol), resulting in the colour of the solution to change from colourless to dark red immediately. The mixture was then allowed to stir at ambient temperature for 30 min. After the reaction, the suspension was filtered through a sintered glass frit and the dark red filtrate was concentrated in vacuo to a viscous solution. Pentane (1 mL) was added to dilute the solution, after which it was sealed under argon and cooled to 4 °C. **11** was isolated as a dark red oil. IR (ether, ν_{CO}, cm^{-1}): 2092 (s), 2051 (vs), 2028 (vs). ^{1}H NMR: δ 7.34 (d, 2H, C_6H_4, $^3J = 7.16$ Hz), 7.24 (d, 2H, C_6H_4, $^3J = 7.35$ Hz), 6.93 (d, 2H, C_6H_4), 6.89 (d, 2H, C_6H_4), 6.81 (s, 1H, C═C—*H*), 5.95 (s, 1H, C≡C—*H*), 3.85 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3). EI-MS (*m*/*z*): 522 ($M^+ - CO$), 466 ($M^+ - 3CO$), 438 ($M^+ - 4CO$), 410 ($M^+ - 5CO$), 382 ($M^+ - 6CO$), 323 ($M^+ - 6CO - Co$), 264 ($M^+ - 6CO - 2Co$).

4.8. Synthesis of 1-phenyl-1-pentyn-3-one

To phenylacetylene (2.131 g, 20.9 mmol) in THF (30 mL) was injected *n*-butyllithium (14.3 mL, 23.0 mmol; 1.6 M) dropwise at −78 °C, after which the solution was allowed to warm up to room temperature with stirring. The freshly generated phenylacetylide lithium reagent was then injected dropwise into a solution of propionyl chloride (7.736 g, 83.6 mmol) in THF (30 mL) at −78 °C. After stirring at −78 °C for 2 h, the reaction was quenched slowly with water (20 mL). The aqueous fraction was extracted with diethylether (3 × 20 mL). The combined ethereal fraction was then washed with saturated aqueous brine (3 × 20 mL) and dried with magnesium sulfate for 30 min. After the solvent was removed in vacuo, the light yellow oil was purified by flash column chromatography to yield a colourless liquid. Yield: 3.023 g (91.4%). R_f: 0.57 (ether/pentane; 1/5 v/v). ^{1}H NMR: δ 7.57 (dd, 2H, *o*-C_6H_5, $^3J = 8.14$ Hz, $^4J = 1.57$ Hz), 7.46–7.35 (m, 3H, *m*,*p*-C_6H_5), 2.70 (q, 2H, CH_3CH_2, $^3J = 7.35$ Hz), 1.22 (t, 3H, CH_3CH_2).^{13}C NMR: δ 188.5 (CO); 133.0, 130.6, 128.6, 120.0 (aromatic); 90.6 (≡*C*CO); 87.6 (*C*≡CCO); 38.8 (CH_2); 8.1 (CH_3).

4.9. Synthesis of **12**

To a suspension of Zn powder (25.5 mg, 0.392 mmol) in THF (20 mL) was injected $TiCl_4$ (35 mg, 0.182 mmol) dropwise at 0 °C, after which the mixture was refluxed for 2 h to a black suspension. A solution of **5c** (24.0 mg, 25.6 μmol) in THF (10 mL) was then injected into the freshly generated McMurry reagent at 0 °C. After refluxing the mixture for 2 h, the reaction was quenched with saturated aqueous sodium carbonate (100 mL). The aqueous fraction was extracted with ethyl acetate (3 × 50 mL). The combined yellowish ethereal fraction was washed with saturated aqueous brine (3 × 30 mL) and dried with sodium sulfate for 30 min. After the solvent was removed in vacuo, the yellow oil was purified by TLC. Yield: 1.987 g (71.7%). R_f: 0.42 (ether/pentane; 2/1 v/v). ^{1}H NMR (CD_3OD): δ 7.27 (d, 2H, C_6H_4, $^3J = 8.67$ Hz), 7.27–7.23 (m, 5H, C_6H_5), 6.95 (d, 2H, C_6H_4, $^3J = 8.58$ Hz), 6.77 (d, 2H, C_6H_4), 6.72 (d, 2H, C_6H_4), 2.32 (q, $2H_b$,CH_2CH_3, $^3J = 7.46$ Hz), 1.20 (t, 3H, CH_2CH_3). ^{13}C NMR (CD_3OD): δ 157.9, 148.7, 135.4, 134.2, 132.6, 132.1, 131.9, 129.3, 125.5, 115.8, 115.1; 128.7 (EtC═*C*); 121.4 (Et*C*═); 93.2 (Ph*C*≡C); 92.8 (PhC≡*C*); 28.7 (CH_2); 14.2 (CH_3). Calc. for $C_{24}H_{20}O_2$ (%): C, 84.68; H, 5.92. Found: C, 84.31; H, 5.87.

4.10. Synthesis of **13**

To **12** (0.338 g, 0.993 mmol) in diethylether (5 mL) was added $Co_2(CO)_8$ (0.335 g, 0.993 mmol), resulting in the colour of the solution to change from colourless to dark green immediately. The mixture was then allowed to stir at ambient temperature for 30 min. After the reaction, the suspension was filtered through a sintered glass frit and the dark green filtrate was concentrated in vacuo to a viscous solution. Pentane (1 mL) was added to dilute the solution, after which it was sealed under argon and recrystallized in the fridge. Yield: 0.366 g (58.8%). IR (ether, ν_{CO}, cm^{-1}): 2085 (m), 2048 (vs), 2024 (s), 2015 (sh, m). ^{1}H NMR (CD_3OD): δ 7.13–7.05 (m, 3H, *m*,*p*-C_6H_5), 6.96 (d, 4H, $^3J = 7.32$ Hz), 6.73 (d, 2H, $^3J = 8.63$ Hz), 6.72 (d, 2H, $^3J = 8.63$ Hz), 6.27 (d, 2H, $^3J = 8.62$ Hz), 2.58 (q, 2H, CH_2CH_3, $^3J = 7.45$ Hz), 0.95 (t, 3H, CH_2CH_3). Calc. for $C_{30}H_{20}O_8Co_2$ (%): C, 57.53; H, 3.22. Found: C, 57.78; H, 3.83.

5. Crystal structure determinations

Crystals were grown from dichloromethane/hexane solutions and mounted on quartz fibres. X-ray data were collected on a Bruker AXS APEX system, using Mo Kα radiation, at 223 K with the SMART suite of programs [26]. Data were processed and corrected for Lorentz and polarization effects with SAINT [27], and for absorption

effects with SADABS [28]. Structural solution and refinement were carried out with the SHELXTL suite of programs [29]. Crystallographic and refinement data are given in Table 3.

The structures were solved by either direct methods or Patterson maps to locate the heavy atoms, followed by difference maps for the light, non-hydrogen atoms. There were two crystallographically independent molecules each in the asymmetric units for **6** and **13**. There was a partial water molecule in **13**, which was modeled as disordered over three sites of equal occupancies. All non-hydrogen atoms were generally given anisotropic displacement parameters in the final model, except for the partial water molecule in **13**, for which the O atoms were given equivalent isotropic thermal parameters.

6. Biochemical experiments

6.1. Materials

17β-Estradiol and OH-Tam ($Z + E$) were obtained from Sigma–Aldrich (France). Stock solutions (1×10^{-3} M) of the compounds to be tested were prepared in DMSO and were kept at −20°C in the dark.

6.2. Animal tissues

Sheep uteri weighing approximately 7 g were obtained from the slaughterhouse at Mantes-la-Jolie, France. They were immediately frozen and kept in liquid nitrogen prior to use.

6.3. Determination of the relative binding affinity of the compounds for the estrogen receptor

RBA values were measured on ERα from lamb uterine cytosol. Sheep uterine cytosol were prepared in buffer A (0.05 M Tris–HCl, 0.25 M sucrose, 0.1% β-mercaptoethanol, pH 7.4 at 25 °C) as described earlier [30]. Aliquots (200 μl) of cytosol were incubated for 3 h at 0 °C with [6,7-^{3}H] estradiol (2×10^{-9} M, specific activity 1.62 TBq/mmol, NEN Life Science, Boston, MA) in the presence of nine concentrations of the hormones to be tested. At the end of the incubation period, the free and bound fractions of the tracer were separated by protamine sulfate precipitation. The percentage reduction in binding of [^{3}H] estradiol (Y) was calculated using the logit transformation of Y (logit Y: $\ln[y/1 - Y]$) vs. the log of the mass of the competing steroid. The concentration of unlabeled steroid required to displace 50% of the bound [^{3}H] estradiol was calculated for each steroid tested, and the results expressed as RBA. The RBA value of estradiol is by definition equal to 100%.

6.4. Measurement of octanol/water partition coefficient ($\log P_{o/w}$) of the compounds

The $\log P_{o/w}$ values of the compounds were determined by reversed-phase HPLC on a C-8 column (nucleosil 5.C8, from Macherey Nagel, France) according to the method previously described by Pomper [22]. Measurement of the chromatographic capacity factors (k') for each compounds was

Table 3
Crystal and refinement data for **5h**, **6** and **13**

Compound	**5h**	**6**	**13**
Empirical formula	$C_{18}H_6O_{13}Os_3$	$C_{10}HClO_{10}Os_3$	$C_{30}H_{20}Co_2O_8.0.19\ H_2O$
Formula weight	1000.83	887.16	629.70
Crystal system	Triclinic	Triclinic	Tetragonal
Space group	$P\bar{1}$	$P\bar{1}$	$P4/ncc$
a (Å)	9.6586(14)	9.1060(12)	25.6996(4)
b (Å)	12.8849(18)	14.0244(18)	25.6996(4)
c (Å)	18.699(3)	14.2271(18)	19.4047(6)
α (°)	83.516(3)	70.243(2)	90
β (°)	78.168(3)	89.376(3)	90
γ (°)	86.055(3)	76.668(2)	90
Volume (Å^3)	2260.6(6)	1659.4(4)	12816.2(5)
Z	4	4	16
Density (calculated) (Mg/m^3)	2.941	3.551	1.305
Absorption coefficient (mm^{-1})	16.886	23.121	1.079
F(000)	1784	1544	5118
Crystal size (mm^3)	$0.34 \times 0.28 \times 0.10$	$0.28 \times 0.18 \times 0.08$	$0.23 \times 0.06 \times 0.03$
Θ range for data collection (°)	2.04–30.01	2.30–30.04	2.06–26.37
Reflections collected	35247	25368	180992
Independent reflections [R(int)]	13113 [0.0395]	9424 [0.0444]	6564 [0.1383]
Max. and min. transmission	0.2830 and 0.0691	0.2592 and 0.0595	0.9683 and 0.7894
Data/restraints/parameters	13113/0/613	9424/0/439	6564/0/368
Goodness-of-fit on F^2	1.058	1.026	1.338
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0318$, $wR_2 = 0.0635$	$R_1 = 0.0315$, $wR_2 = 0.0670$	$R_1 = 0.1011$, $wR_2 = 0.2419$
R indices (all data)	$R_1 = 0.0406$, $wR_2 = 0.0664$	$R_1 = 0.0418$, $wR_2 = 0.0701$	$R_1 = 0.1191$, $wR_2 = 0.2534$
Largest diff. peak and hole (e Å^{-3})	2.005 and −1.793	1.654 and −1.854	0.973 and −0.697

done at various concentrations in the range 85–60% methanol (containing 0.25% octanol) and an aqueous phase consisting of 0.15% *n*-decylamine in 0.02 M MOPS (3-morpholinopropanesulfonic acid) buffer pH 7.4 (prepared in 1-octanol–saturated water). These capacity factors (k') were extrapolated to 100% of the aqueous component given the value of k'_w. $\log P_{o/w}$ (y) was then obtained by the formula: $\log P_{o/w} = 0.13418 + 0.98452 \log k'_w$.

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Appendix A. Supplementary data

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 280441–280443. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2005.08.041.

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