Pergamon

Bioorganic & Medicinal Chemistry 10 (2002) 1381–1398

BIOORGANIC & MEDICINAL CHEMISTRY

Aryl Cyclopentadienyl Tricarbonyl Rhenium Complexes: Novel Ligands for the Estrogen Receptor with Potential Use as Estrogen Radiopharmaceuticals

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Received 20 August 2001; accepted 12 November 2001

Abstract—The need for imaging agents for estrogen receptor positive (ER+) tumors that are both cost effective and widely available, as well as the need for novel radiotherapeutic agents for the treatment of breast cancer, has prompted us to investigate cyclopentadienyl tricarbonyl metal [$CpMet(CO)_3$, Met = Re, Tc-99m] complexes that bind well to the ER. Thus, we have prepared a series of *p*-hydroxyphenyl-substituted $CpRe(CO)_3$ complexes and evaluated them (and, in some cases, their cyclopentadiene precursors) for binding to ER. These compounds constitute a new class of structurally integrated organometallic ligands for ER in which the $CpMet(CO)_3$ organometallic unit forms the very structural core of these molecules and thus is necessarily intimately involved in their interaction with the receptor. The $CpRe(CO)_3$ compounds were prepared by reaction of the lithium salt of the arene-substituted cyclopentadiene with a suitable $Re(CO)_3^+$ precursor, followed by deprotection of the methyl ether. The X-ray crystal structure of one of these analogues shows that it has the classical 'piano stool'-like geometry, with the alkyl groups directed upward, away from the tripodyl metal carbonyl base. The aryl-substituted $CpRe(CO)_3$ complexes that we have prepared all bind to the ER, some with affinity as great as 20% that of the native ligand, estradiol. In general, at least two *p*-hydroxyphenyl substituents and one to two alkyl groups attached to the organometallic cyclopentadienyl core are needed for high ER affinity. Where we have been able to make comparisons, the metal complexes bind to ER with an affinity greater than their cyclopentadiene precursors. The high affinity of some of these complexes indicates that the bulky $Re(CO)_3$ unit is able to exploit the considerable volume in the center of the ER ligand binding pocket that is not occupied by most ligands, a consideration that is supported by molecular modeling. The preparation of the best of these agents in technetium-99m labeled form is currently being investigated.

Introduction

The need for diagnostic imaging agents for estrogen receptor positive (ER+) tumors that are both cost effective and widely available has prompted us to search for methods to label ER ligands with the radiometal, technetium-99m. The radionuclide Tc-99m is known for its convenient 6-h half-life and bench-top generation, which makes it an ideal nuclide for imaging agents.[1–3] Because all isotopes of technetium are radioactive, most studies of technetium-labeled compounds begin with preparation of the corresponding rhenium analogues, which typically have very similar chemical and physical properties.[1–3] Beyond being a surrogate for technetium, rhenium-containing compounds prepared with the radionuclides Re-186 and Re-188 also have promise as radiotherapeutic agents.[1–3] Regardless of the element, however, the attachment of metals such as rhenium and technetium to small, lipophilic molecules, such as a hormonal steroid, presents a significant chemical challenge.[4]

In general, two complementary strategies have been used for attaching a metal radionuclide to a small molecule receptor ligand, the 'pendant' design in which a radiometal complex is linked to the receptor ligand, and the 'integrated' design in which the radiometal nuclide forms part of the core structure of the receptor ligand.[4] To date, both *pendant* and *integrated* mimics of estrogens and other steroids have been prepared having *inorganic* metal chelates as the core structure.[5–18] However, these systems have all exhibited either low receptor binding affinity, high non-specific binding, and/or low

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0968-0896/02/$ - see front matter
PII: S0968-0896(01)00406-0

complex stability, and thus have not proved useful in imaging. An alternate approach is *pendant* steroid radiopharmaceuticals that have the radiometal tethered through an *organometallic* link. This has also been investigated, but again, these agents have not proved to be satisfactory.[5] Estrogen radiopharmaceuticals having integrated organometallic core have not, thus far, been investigated.

We have recently conceived of a simple pharmacophore for the estrogen receptor on the basis of which we have developed a number of high-affinity ER ligands (Fig. 1).[19] The basic pharmacophore design consists of a central core structure, which may in some cases be a five-membered heterocycle or carbocycle, onto which are attached a phenol, a second aromatic group, and one or two other substituents, typically aliphatic chains. Of particular interest for receptor imaging purposes would be molecules in which the core unit was a cyclopentadienyl anion, because cyclopentadienyl anions (Cp−) are known to be good acceptors of metal tricarbonyl cations [$Met(CO)_3^+$]. Therefore, we thought that by associating the cyclopentadiene—which conforms to the core element of the pharmacophore—with a $Met(CO)_3^+$ (Met = Re, Tc-99m), we might be able to develop a new class of '*integrated organometallic*' ER imaging agents (Fig. 1).

Concern that the added bulk of the metal tricarbonyl would make the core of the ligand too large to bind well to the ER should be ameliorated by recent studies indicating that the ER is quite tolerant of ligands having bulky cores. For example, a phenolic 1,12-decacarborane was found to have affinity for the ER comparable to that of estradiol,[20] and some other phenols with bulky substituents at the *para* position are also known to be good ER ligands.[20] Also, X-ray crystal structures of the ER have shown that the ligand-binding pocket has a large amount of space (200 $Å^3$) that is not occupied by a typical ligand.[21]

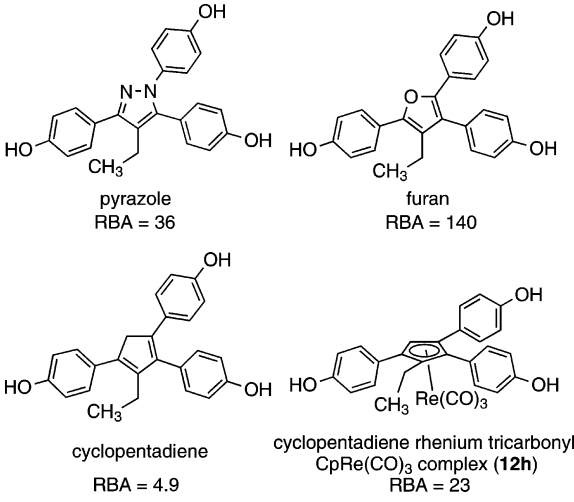
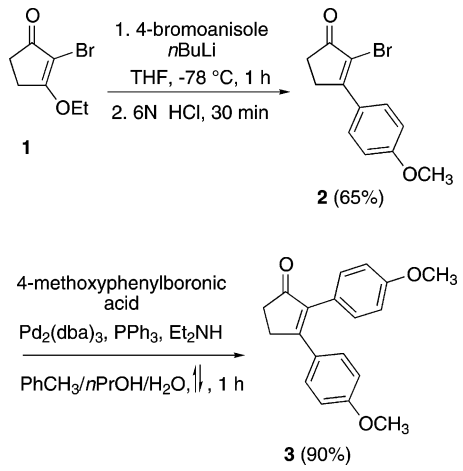


Figure 1. New steroidal heterocyclic (pyrazole and furan) ligands for the estrogen receptor (ER) and their cyclopentadiene and cyclopentadienyl rhenium tricarbonyl [$CpRe(CO)_3$] analogues. RBA is relative binding affinity to ERα, where estradiol = 100.



Scheme 1.

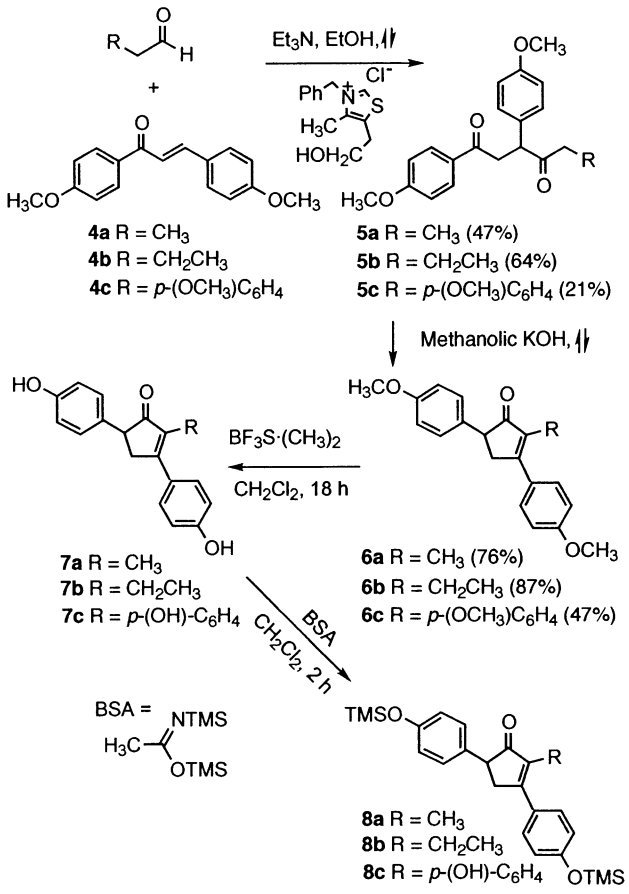
We are pleased to describe the first members of a novel class of integrated organometallic ER ligands that have significant affinity for the ER. Herein, we report the synthesis of highly substituted cyclopentadienes, as well as the rapid synthesis of highly substituted $CpRe(CO)_3$ complexes via the reaction of CpLi derivatives with a suitable $Re(CO)_3^+$ donor. The crystal structure of one of the highly substituted $CpRe(CO)_3$ complexes has also been determined. We have investigated the structure–affinity relationships of various aryl-substituted cyclopentadienyltricarbonyl rhenium [$CpRe(CO)_3$] complexes, as well as their corresponding phenolic cyclopentadiene precursors, and we find some complexes that bind to ER with high affinity. These results attest to the capacity of the ER ligand binding pocket to reshape itself to accommodate bulky substituents, a feature that is supported by molecular modeling. Further studies on labeling these compounds with the rhenium metal congener, the radionuclide technetium-99m, will be described elsewhere.

Results and Discussion

The general approach to the synthesis of highly substituted cyclopentadienes

All cyclopentadienes were prepared from common precursors, namely, the corresponding cyclopentenones. These cyclopentenone precursors were synthesized, in turn, by either cyclization of a 1,4-diketone or by a palladium-catalyzed Suzuki-type coupling. The synthesis of the cyclopentadienes for the binding affinity studies differed from the synthesis of cyclopentadienes for conversion to the $CpRe(CO)_3$ complexes only by the stage at which the phenols were deprotected.

A single set of letters are used to designate the sets of one to four substituents that are present in the two series of cyclopentadienes (**9a**–**h** and **10c**–**h**) and the corresponding $CpRe(CO)_3$ complexes (**11a**–**h** and **12a**–**h**). This substituted designation scheme is readily evident from Scheme 5 and Table 1.



Scheme 2.

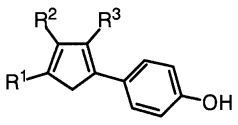
Synthesis of cyclopentenone 3 utilizing a palladium-catalyzed Suzuki coupling

The synthesis of 2,3-substituted cyclopentenone **3** was adapted from a recent synthesis of 2,3-substituted cyclopentenones (Scheme 1).[22] Treatment of 4-bromoanisole with *n*-butyllithium formed the aryl-lithium reagent, which when added to cyclopentenone **1** gave the 1,2-addition product. Treatment of this alcohol with 6 N HCl effected dehydration, as well as enol ether hydrolysis, to form the 3-aryl substituted cyclopentenone **2**. Substitution of the vinyl bromide in cyclopentenone **2** with 4-methoxyphenylboronic acid was effected under palladium-catalyzed Suzuki-type conditions, affording cyclopentenone **3**. The author noted that the cyclopentenone group was sensitive to the normal bases used in Suzuki reactions (e.g., Na_2CO_3), but that the organic base diethylamine was a suitable substitute.[22] The reactions in this sequence are rapid, and the intermediates are crystalline. In addition, there is literature precedent to suggest that this approach could be expanded to introduce additional substituents at the C-1 and C-5 positions.[23–27]

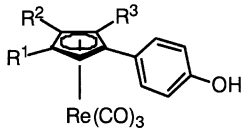
Synthesis of cyclopentenones 6a–c via 1,4-diketones 5a–c

A convenient alternative approach, particularly well suited to more highly substituted cyclopentenones, involves an intramolecular aldol condensation of 1,4-diketones (Scheme 2). The 1,4-diketones that we required were prepared by the well-known Stetter method, in which the reaction of 4,4′-dimethoxychalcone and aldehydes **4a–c** in the presence of a thiazolium catalyst gives the corresponding 1,4-diketones **5a–c**.[28,29] Aldehydes **4a**

Table 1. Relative binding affinity data for substituted CpRe complexes as well as their corresponding phenolic cyclopentadienes[a]



Cyclopentadiene I (10c-h)



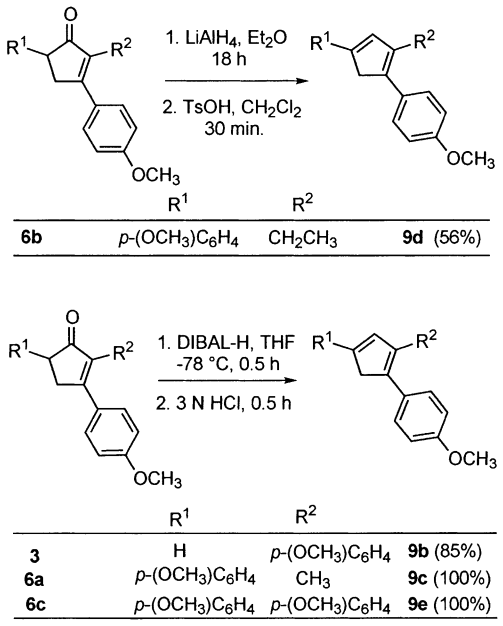
CpTMet II (12a-h)

Compd I	Compd II	R_1	R_2	R_3	RBA[b] (Cytosol 0 °C)	RBA ERα[b]	RBA ERβ[b]
—	**12a**	H	H	H	0.049±0.008	0.020±0.001	0.049±0.02
—	**12b**	H	H	Ar′	1.5±0.2	2.4±0.1	1.3±0.4
10c	—	Ar′	H	Me	0.064±0.004	1.2±0.2	0.37±0.07
—	**12c**	Ar′	H	Me	0.83±0.18	1.8±0.4	1.9±0.04
10d	—	Ar′	H	Et	0.31±0.1	0.37±0.06	0.50±0.1
—	**12d**	Ar′	H	Et	1.1±0.1	2.5±0.07	4.3±1.0
10e	—	Ar′	H	Ar′	0.11±0.0	3.8±1.7	0.23±0.15
—	**12e**	Ar′	H	Ar′	1.8±0.2	10.5±0.0	3.6±0.1
10f	—	Ar′	Me	Me	0.025±0.004	0.12±0.02	0.26±0.02
—	**12f**	Ar′	Me	Me	1.3±0.1	3.6±0.9	4.2±1.1
10g	—	Ar′	Et	Et	0.99±0.09	8.6±0.4	6.1±2.0
—	**12g**	Ar′	Et	Et	1.8±0.5	4.3±1.1	7.1±1.2
10 h	—	Ar′	Ar′	Et	1.0±0.2	4.9±0.6	1.5±0.2
—	**12 h**	Ar′	Ar′	Et	1.9±0.2	23±6	13±0

(Ar′ = *p*-(OH)–C_6H_4, Me = CH_3, Et = CH_2CH_3)

[a]Relative binding affinity (RBA), where estradiol is 100%. Values are the mean of at least 2 independent determinations (±SD).

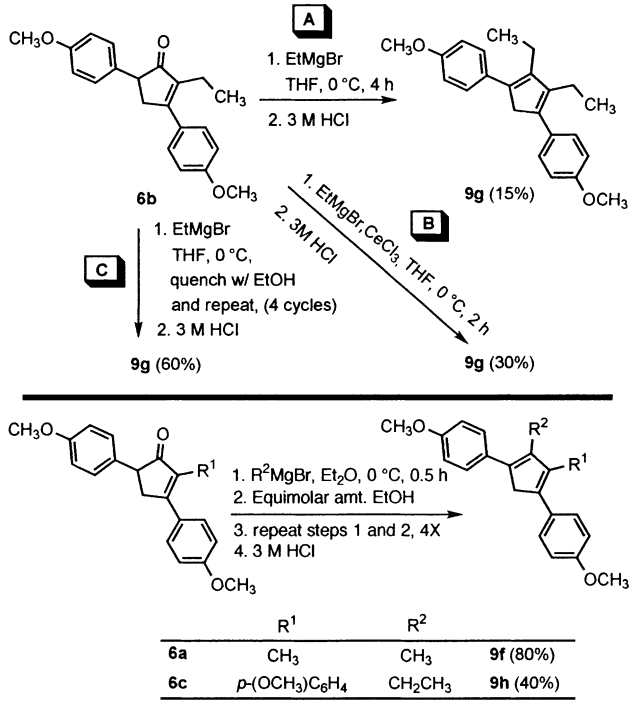
[b]Competitive radiometric binding assays were done with lamb uterine cytosol or with purified full-length human ER and ER (PanVera Inc.), using 10 nM [3H]-estradiol as tracer.



	R^1	R^2	
6b	*p*-$(OCH_3)C_6H_4$	CH_2CH_3	**9d** (56%)

	R^1	R^2	
3	H	*p*-$(OCH_3)C_6H_4$	**9b** (85%)
6a	*p*-$(OCH_3)C_6H_4$	CH_3	**9c** (100%)
6c	*p*-$(OCH_3)C_6H_4$	*p*-$(OCH_3)C_6H_4$	**9e** (100%)

Scheme 3.

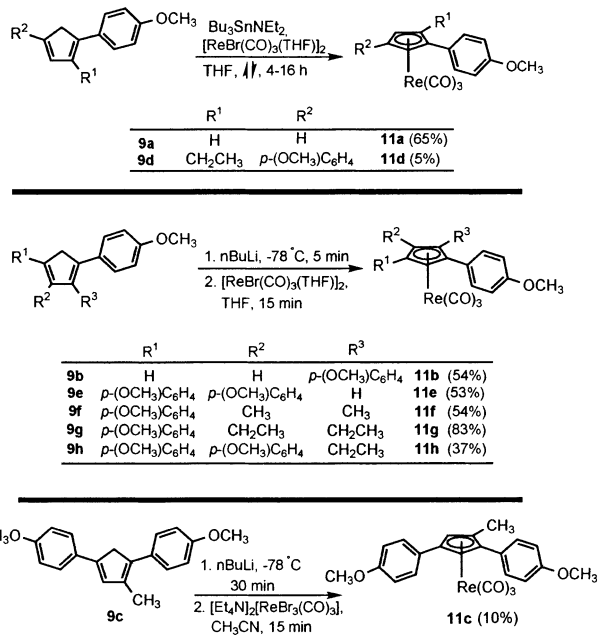


	R^1	R^2	
6a	CH_3	CH_3	**9f** (80%)
6c	*p*-$(OCH_3)C_6H_4$	CH_2CH_3	**9h** (40%)

Scheme 4.

and **4b** gave reasonable yields in this reaction (47 and 60%, respectively), whereas aldehyde **4c** reacted quite slowly and gave a poorer yield (21%).

The intramolecular aldol cyclization of the 1,4-diketones **5a–c**, using dilute methanolic KOH, gave the corresponding cyclopentenones **6a–c**, but reaction times varied significantly: The tri-aryl 1,4-diketone **5c** cyclized in 15 min at rt, whereas the di-aryl 1,4-diketones **5a** and **5b** required 24 h at reflux. These rate differences are presumed to be due to differences in the ease with which



	R^1	R^2	
9a	H	H	**11a** (65%)
9d	CH_2CH_3	*p*-$(OCH_3)C_6H_4$	**11d** (5%)

	R^1	R^2	R^3	
9b	H	H	*p*-$(OCH_3)C_6H_4$	**11b** (54%)
9e	*p*-$(OCH_3)C_6H_4$	*p*-$(OCH_3)C_6H_4$	H	**11e** (53%)
9f	*p*-$(OCH_3)C_6H_4$	CH_3	CH_3	**11f** (54%)
9g	*p*-$(OCH_3)C_6H_4$	CH_2CH_3	CH_2CH_3	**11g** (83%)
9h	*p*-$(OCH_3)C_6H_4$	*p*-$(OCH_3)C_6H_4$	CH_2CH_3	**11h** (37%)

Scheme 5.

the enolate required for the cyclization is able to form; in the case of diketone **5c**, this enolate has aryl stabilization, whereas it lacks such stabilization in the other two cases.

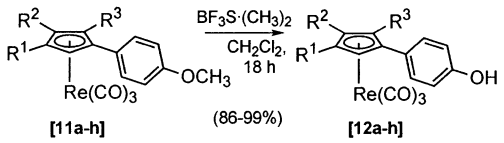
Tri-substituted cyclopentadiene (9b–e) synthesis

Tri-substituted cyclopentadienes (**9b–e**) were synthesized by hydride reduction of the cyclopentenones, followed by acid-catalyzed dehydration (Scheme 3). Although we initially used lithium aluminum hydride to reduce cyclopentenone **6b**, producing cyclopentadiene **9d** in 56% yield after acid-catalyzed dehydration with TsOH, the low yield that we obtained in this case suggested that this reagent was also reducing the double bond in cyclopentenone **6b**. Therefore, we used the milder diisobutylaluminum hydride for the reduction of cyclopentenones **3**, **6a**, and **6c**, and following acid-catalyzed dehydration, we obtained cyclopentadienes **9b, c** and **e** in good to excellent yields.

Tetra-substituted cyclopentadiene (9f–h) synthesis: overcoming competitive enolization

It proved to be more of a challenge to synthesize the tetra-substituted cyclopentadienes **9f–h**. Scheme 4 (top) shows three different conditions that we tried to effect the 1,2-addition of an ethyl group to the C-1 carbonyl group of the cyclopentenone. Typical conditions (**A**) for the addition of ethyl magnesium bromide to cyclopentenone **6b** and dehydration afforded cyclopentadiene **9g** in only 15% yield. Because starting material was recovered, it appeared that enolization was competing with 1,2-addition. Cyclopentenones are known to enolize readily, and the C-5 aromatic group in cyclopentenone **6b**, which would stabilize this enolate, appears to further exacerbate this problem. The typical solution of using $CeCl_3$ (**B**) to reduce the basicity of the Grignard reagent gave only a modest increase in yield.[30,31]

A more effective solution proved to be a reiterative cycle of Grignard addition-enolate protonation, all of which could be done in one pot (Scheme 4, top **C** and bottom). As the first stage, the Grignard reagent (1 equiv) is reacted with cyclopentenone **6b** (1 equiv) in Et_2O at 0 °C. This reaction is complete in a matter of minutes; some 1,2-addition takes place, but the major product is the enolate, which is unreactive towards further addition. As the second stage, EtOH (1 equiv) is added to the reaction mixture; this quenches any additional Grignard reagent and protonates the enolate, restoring the ketone so as to be reactive towards another cycle of addition. This cycle is then repeated by the addition to the same flask of a second portion of Grignard reagent (1.1 equiv), followed a few minute later by a second portion of EtOH (1.1 equiv). This process was repeated a third time, using 1.2 equiv of Grignard and 1.2 equiv of EtOH. Finally, 1.3 equiv of Grignard was added to the flask and allowed to react with cyclopentenone **6b**. After 30 min, 3 M HCl was added to the flask to dehydrate the tertiary alcohol, forming cyclopentadiene **9g** in 60% yield. This reiterative addition-enolate protonation approach proved to be effective in converting cyclopentenones **6a** and **6c** to the corresponding cyclopentadienes **9f** and **9 h** in good to reasonable yields (Scheme 4, bottom).



	R^1	R^2	R^3	
11a	H	H	H	**12a**
11b	H	H	Ar	**12b**
11c	Ar	H	Me	**12c**
11d	Ar	H	Et	**12d**
11e	Ar	H	Ar	**12e**
11f	Ar	Me	Me	**12f**
11g	Ar	Et	Et	**12g**
11h	Ar	Ar	Et	**12h**

Ar = *p*-$(OCH_3)C_6H_4$

Scheme 6.

Synthesis of cyclopentadienes (10c–h) for binding affinity studies

Deprotection of the phenolic methyl ethers of cyclopentadienes **9b**,**f**,**g** using varying reagents [BBr_3, $BF_3S(CH_3)_2$, TMSI, MeSNa, etc.] resulted in product degradation. Hence, we deprotected the methyl ethers at the cyclopentenone stage, using $BF_3S(CH_3)_2$ (Scheme 2). To avoid solubility problems that would arise during the hydride reduction (Scheme 3) or Grignard reaction (Scheme 4, bottom) on the free phenols, we temporarily reprotected the phenolic cyclopentenones **7a**–**c** as their trimethylsilyl (TMS) **8a**–**c** ethers using bis-(trimethylsilyl)acetamide (BSA) (Scheme 2).[32] Following this reprotection, tri- and tetra-substituted cyclopentadiene phenols (**10c**–**h**) were synthesized under the same conditions as their counterpart cyclopentadiene methyl ethers (**9c**–**h**) (not shown, but see Experimental). Yields were lower for the phenolic cyclopentadienes, because these phenols proved to be difficult to handle. Those with increasing number of phenolic groups or decreasing overall number of substituents were found to be particularly sensitive to heat, air and possibly also to acidic impurities in the solvents. Thus, we were unable to prepare the mono and disubstituted cyclopentadiene phenols **10a** and **10b** (not shown) that would have corresponded to the complexes **12a** and **12b** (cf., Table 1).

Synthesis of $CpRe(CO)_3$ complexes (11a–h and 12a–h)

There are a number of methods for synthesizing unsubstituted or monosubstituted $CpRe(CO)_3$ complexes,[33–35] but few of these have been used for preparing highly substituted $CpRe(CO)_3$ complexes.[36,37] We explored several methods to find one that afforded the highly substituted $CpRe(CO)_3$ complexes in good yield and with short reaction times, as would be needed for tracer-level synthesis with technetium-99m.

Attempts to synthesize a $CpRe(CO)_3$ complex **11a** by forming a lithium cyclopentadienide (CpLi) from 2-(4-methoxyphenyl)-1-3-cyclopentadiene **9a**,[38] followed by the addition to a solution of commercially available $Re(CO)_5Br$ in THF, failed (not shown). We presume this failure to be due to the unreactivity of this metal pentacarbonyl; for complexation to occur, this rhenium precursor must lose two molecules of carbon monoxide, and these are strongly coordinated. Heating the reaction to reflux for 18 h still did not effect the desired complexation reaction.

A recent publication from our laboratory of a one-pot synthesis of $CpRe(CO)_3$ complexes via a $CpSnBu_3$ species and a more reactive pre-reduced, aprotic rhenium tricarbonyl precursor ($[ReBr(CO)_3(THF)]_2$) gave us hope that this method would be effective for the synthesis of more complex tri- and tetra-substituted $CpRe(CO)_3$ complexes.[35] In this earlier work, mono-aryl complex **11a** was formed in 65% yield in 2 h (Scheme 5, top).[35] Unfortunately, we found that with more highly substituted cyclopentadienes, such as the tri-substituted cyclopentadiene **9d,** the yield after refluxing for 16 h was only 5% (Scheme 5, top), and no reaction occurred with the tetra-substituted cyclopentadiene **9g** (not shown). We were pleased to find, however, that the direct reaction of the more reactive corresponding lithium cyclopentadienyl anion derivatives (prepared by reacting the cyclopentadienes with *n*-BuLi) with $[ReBr(CO)_3(THF)]_2$ allowed us to synthesize highly substituted $CpRe(CO)_3$ complexes **11b**,**e**–**h** rapidly and in good yields (Scheme 5, middle).

Because we will eventually use these methods to prepare radiolabeled analogues of the $CpRe(CO)_3$ and $CpTc(CO)_3$ complexes at the tracer level, in one case we optimized conditions for the efficient use of the organometallic precursor by using an excess of the lithium cyclopentadienide component. Thus, eight equiv of *n*-BuLi were added to eight equiv of the cyclopentadiene **9f** in THF, and after 5 min at −78 °C this reaction mixture was allowed to react with one equiv of

$[ReBr(CO)_3(THF)]_2$. This gave complete consumption of $[ReBr(CO)_3(THF)]_2$ and a good yield of the $CpRe(CO)_3$ complex **11f**, based on the limiting organometallic precursor.

We also investigated whether another pre-reduced rhenium precursor, $[Et_4N]_2[ReBr_3(CO)_3]$, could be used, because it may be easier to prepare as the Tc-99m version of this species, since it has been prepared as the Tc-99g version.[39] Because of solubility considerations, reaction with this precursor was done in a mixture of CH_3CN and THF, but, unfortunately, this approach gave lower yields of complex **11c** than did $[ReBr(CO)_3(THF)]_2$ (Scheme 5, bottom). This reaction might work better at the tracer-level using Tc-99m, because the lithium cyclopentadienide will be in large excess, and at the tracer level, the $[Et_4N]_2[^{99m}TcCl_3(CO)_3]$ species may be soluble in THF alone.

Deprotection of the aryl-methyl ethers was accomplished using $BF_3S(CH_3)_2$ (Scheme 6). The phenolic $CpRe(CO)_3$ complexes are much more stable than their phenolic cyclopentadiene counterparts; they are still slightly sensitive to light in solution, but they can be stored indefinitely if they are kept cold (−20 °C) and in the dark.

Crystal structure of a highly substituted $CpRe(CO)_3$ complex (11g)

The crystal used for determining the crystal structure of complex **11g** was grown by slow evaporation of an ethyl acetate/hexanes solution. The crystal structure confirms that the $CpRe(CO)_3$ complex **11g** shows the typical 'piano stool' topology (Fig. 2). Details on the crystallographic data can be obtained from the author. In the crystal structure, the organic portion of the complex is not planar. The phenyl groups are closer to being planar with each other, whereas both phenyl rings are quite out of plane with the Cp ring, having torsional angles of 41 and 47°. Another interesting characteristic of the highly substituted $CpRe(CO)_3$ complex **11g** is that both ethyl groups are pointed above the Cp ring plane. Also, the carbonyls groups are not symmetrically placed below the Cp ring, as can be seen from the torsional angle of C(1)–C(5)–Re(1)–C(25) being 156° and C(4)–C(5)–Re(1)–C(24) being 180°.

Binding affinities of $CpRe(CO)_3$ complexes (12a–h) and their corresponding cyclopentadienes (10c–h) for the estrogen receptor

The binding affinities of phenolic cyclopentadienes **10c–h** and the $CpRe(CO)_3$ complexes **12a–h** for the estrogen receptor (ER) are shown in Table 1. The binding values were obtained from a competitive radiometric binding assay, using [^{3}H]-estradiol as the tracer, and the values are expressed as relative binding affinities (RBA), in percent, with estradiol having an affinity of 100%. ER preparations used in these experiments were lamb uterine cytosol[40] (considered to be almost all ERα)[41] or purified full-length human ERα and ERβ (PanVera Inc.).[42,43]

Looking at the RBA values for compounds **12a–h** in the uterine cytosol preparation of the estrogen receptor (ER), one can see that all of the $CpRe(CO)_3$ complexes have significant affinity, except for the mono-phenolic $CpRe(CO)_3$ complex **12a**, which has very low affinity (Table 1). One common attribute of $CpRe(CO)_3$ complexes **12b–h** that have good affinity is that they contain at least two phenolic groups, whereas complex **12a** has only one; the addition of the second phenolic group in $CpRe(CO)_3$ complex **12b** increases binding affinity for the ER by 30-fold. Further addition of phenolic or alkyl substituents do not seem to have any great effect on the RBA values in the uterine cytosol ER preparation. It is not certain what is responsible for this leveling off of binding affinities.

To investigate structure–binding affinity relationships in this series further, we measured the binding of the $CpRe(CO)_3$ complexes to purified human ERα and ERβ. What was first notable with these purified ER preparations is that in nearly all cases, the RBA values for the binding of the $CpRe(CO)_3$ complexes with purified human ERα are greater than for the ER from lamb uterus (Table 1). As we have speculated in the past,[44–46] these differences could be due to a reduced level of nonspecific binding in the purified human ER preparations or to the absence of specific coregulator proteins.[42] Therefore, correlations relating structure to binding affinity were drawn from binding data obtained with the purified ERα and ERβ preparations.

Looking at ERα values, one can see that the monophenolic complex **12a** still has very low affinity for ER. However, addition of a second phenol in complex **12b** increases binding affinity by 120-fold, and addition of a third phenolic group, as in complex **12e**, increases binding by an additional 4.4-fold. Adding one or two alkyl groups to the di-phenolic complexes (to give **12c**, **d**, **f**, **g**) does not significantly change ERα RBA values, but in the tri-phenolic complex **12 h**, the additional ethyl group increases binding by 2.2-fold over complex **12e**. Remarkably, complex **12 h** has an affinity for ERα that is greater than 20% that of estradiol, indicating that our presumption that the ER ligand binding pocket has sufficient space to accommodate a bulky $CpRe(CO)_3$ unit is, in fact, correct.

When comparing ERα and ERβ affinities, one can see that the complexes have only modest ER subtype selectivity, with ERα/ERβ RBA ratios rising to 2.9 in complex **12 h**. However, both the symmetrical diphenolic,

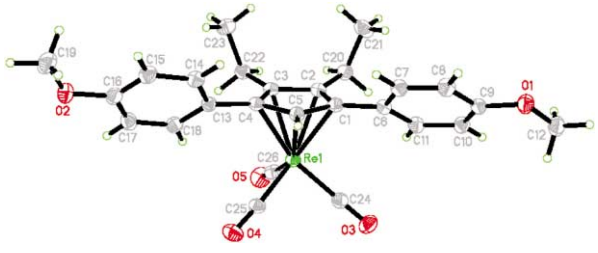


Figure 2. ORTEP view CpRe $(CO)_3$ complex **11g**.

diethyl complex **12g** and the diphenolic, monoethyl complex **12d** are slightly (1.7-fold) ERβ selective.

We were also interested in how the binding affinity of the eight $CpRe(CO)_3$ complexes compared to that of their corresponding phenolic cyclopentadienes, of which we could prepare and isolate only five, **10c–h**. Table 1 shows the uterine cytosol RBA values as well as those for the purified ERα and ERβ. In general, the cyclopentadiene precursors (**10c–h**) had somewhat lower binding to the ER in all receptor preparations than did their corresponding $CpRe(CO)_3$ complexes (**12c–h**). We are not certain whether the increase in affinity that occurs with complete formation is due to the added three-dimensionality that the $Re(CO)_3$ unit provides to the planar cyclopentadienide core of the ligand, which may result in a more complete filling of the ligand binding pocket in the ER, or whether it is due to the added stability that the $CpRe(CO)_3$ complexes has compared to the corresponding phenolic cyclopentadienes.

As was the case with the $CpRe(CO)_3$ complexes, the phenolic cyclopentadienes also show significantly greater affinity for purified human ERα than for the lamb uterine ER preparation. Again, this could be due to reduced non-specific binding in the purified ER preparation, which would be accentuated by the fact that the phenolic cyclopentadienes are less polar (in terms of their chromatographic properties) than their corresponding $Re(CO)_3$ complexes. Three of the phenolic cyclopentadienes, the tri-phenolic cyclopentadienes **10e** and **10 h**, and di-phenolic cyclopentadiene **10g**, exhibited human ERα RBA values that are significantly greater than 1%. The best of these, cyclopentadiene **10g**, has an ERα RBA value of 8.6. This is the only case where the phenolic cyclopentadiene (**10g**) was found to bind better to ER than did its corresponding $Re(CO)_3$ complex (**12g**).

Modeling of a cyclopentadienyl ligand (10h) and its corresponding $CpRe(CO)_3^+$ complex (12h) in the ligand binding pocket of the estrogen receptor

Although it is evident that the $CpRe(CO)_3$ complexes bind to the ER rather well, it is unclear, at this point, in what manner they are oriented or how they are accommodated within the ER ligand binding pocket. Thus, we have investigated some aspects of their potential binding modes by molecular modeling. To do this, we selected the organometallic complex **12h** and its cyclopentadiene precursor **10h**. Both of these systems have very good ERα binding affinity. They also have three *p*-hydroxyphenyl and one ethyl substituent on the Cp ring; this pattern of substitution has proved to be optimal or nearly optimal in two related heterocyclic systems that we have studied recently as novel ligands for the ER, pyrazoles and furans.[42,47] Thus, we have based our modeling here on the modeling work that we did on these other systems, in particular, the furans.[47]

We began with a well refined model that we had previously developed for the congeneric ethyl triphenolic furan in the ligand binding pocket of ERα,[47] as illustrated in Figure 3A. We then changed the furan core ring to generate cyclopentadiene **10h**. This ligand–receptor complex was docked and minimized using Flexidock process within the molecular modeling program SYBYL, by the same routine that we have used previously,[42,47] and the structure that we obtained is shown in Figure 3B. Not surprisingly, the ERα complexes with the furan and the structurally congruent cyclopentadienyl system **10h** are nearly identical (cf. Fig. 3A and B).

We also used the minimized furan structure to prepare starting structures of the $CpRe(CO)_3$ complex **12h** with the ERα ligand binding pocket. Starting with the X-ray crystal structure of the related complex **11g** (cf., Fig. 2), we built the organometallic complex **12h** by replacing one of the ethyl groups with a *p*-hydroxyphenyl group. It is of note that the addition of the metal tricarbonyl to the cyclopentadienide, which is a meso compound, to produce the complex, creates a molecule which is chiral. Because we do not know which enantiomer might be the preferred ligand, we prepared both of them, by generating structures that have the $Re(CO)_3$ unit both above or below the Cp ring. The two enantiomeric **12h** complexes were then inserted into the ERα ligand binding pocket by manually aligning their putative A-rings with that of the furan system.

Not surprisingly, these initial structures had severe steric clashes with certain residues in the ligand binding pocket, because of the major steric extension of the ligand that results from the attachment of the metal tricarbonyl unit either above or below the cyclopentadiene ring. However, when both of these structures were minimized using the Tripos force field, these steric clashes were removed by relatively small changes in torsional angles of some of the residues that surround the ligand, and structures having reasonable internal energies of the overall ligand–receptor complex were obtained. The minimized structures for the two **12h** enantiomers in the ERα ligand binding pocket are shown in Figure 3C and D.

It is of note that the ER ligand binding pocket is considered to have a volume of ca. 450 $Å^3$, of which estradiol, with a molecular volume of 250 $Å^3$, occupies only somewhat more than half.[21] The cyclopentadiene precursor **10h** has a molecular volume of 315 $Å^3$, and the $Re(CO)_3$ unit adds another 59 $Å^3$, giving a total molecular volume for each **12h** complex of 374 $Å^3$. Thus, even the apparently 'bulky' organometallic system **12h** does not have an overall volume that exceeds that of the ligand binding pocket, although the pocket needs to reshape itself substantially to achieve a reasonable fit with these ligands of unusual shape.

Clearly, because we have used a relatively simple molecular modeling approach, we have no assurance that the structures shown in Figure 3C and D correspond to the ligand–receptor complexes that form naturally with the enantiomeric organometallic systems **12h**. Nevertheless, our modeling work does indicate that the estrogen receptor is sufficiently flexible that the metal tricarbonyl

unit can be accommodated comfortably within the internal confines of its ligand binding pocket.

Based on this modeling, the enantiomer shown in Figure 3C, with the metal tricarbonyl unit above the cyclopentadiene ring appears to have fewer steric clashes than the enantiomer shown in Figure 3D; these clashes are indicated by the purple dotted surface of the protein interpenetrating the solid green surface of the ligand. Thus, we tentatively predict that the higher affinity enantiomer and the predominant binding mode are similar to that shown in Figure 3C. In this regard, it is of note that in the ERα-estradiol structure, there is more unoccupied space 'above' the ligand (i.e., ligand beta face) than 'below' the ligand (i.e., ligand alpha face),[21] a characteristic that had actually been predicted earlier from an analysis of ligand binding.[48] Also, it is in the beta face direction that the receptor opens up (by displacement of helix-12) to allow the bulky basic side chains of raloxifene and other antiestrogens to bind.[21,49]

Conclusion

Of the $CpRe(CO)_3$ complexes that we have prepared, complex **12h** has the best affinity for the estrogen receptor, equivalent to 23% that of estradiol (Table 1). This compound, as well as others that also have high affinity for ER, indicate that it is possible to accommodate the bulky $Re(CO)_3$ unit in the interior of the ligand binding pocket in ER, where there is known to be at least 200 $Å^3$ of space that is not occupied in the ER complex with estradiol.[21] This accommodation is supported by molecular modeling.

It is difficult to predict what this favorable binding affinity means in terms of how the Tc-99m analogue of this $CpRe(CO)_3$ complex will behave in vivo. In spite of the fact that $CpRe(CO)_3$ complexes seem to exhibit some non-specific binding, it is hoped that the Tc-99m complex will provide adequate levels of target tissue uptake and favorable target to background activity ratios that will enable it to be used to image ER+

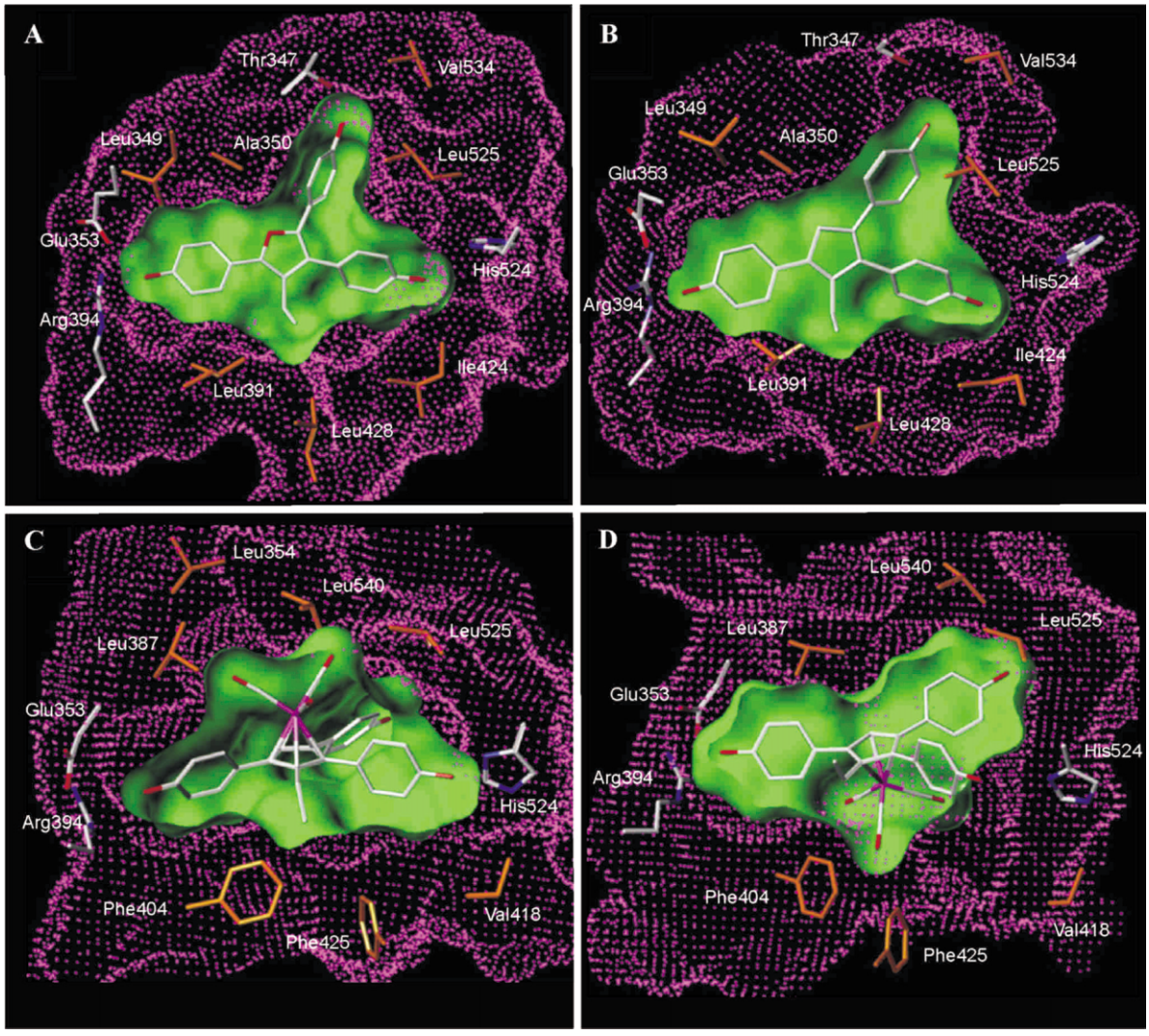


Figure 3. (A) Model of furan (cf., Fig. 1) in ERα ligand binding pocket. The surface of the ligand is shown as a continuous green shape; the surface of the ERα pocket is shown as purple dots. (B) Cyclopentadiene **10 h** in ERα ligand binding pocket. (C) and (D) enatiomers of CpRe(CO)3 complex **12 h** in the ERα ligand binding pocket. For details, see text and Experimental.

breast tumors. Similar considerations will apply to the potential use of the Re-186 and Re-188 analogues of the compounds we have prepared for radiotherapeutic applications in breast cancer. It might be possible to reduce the non-specific binding of the $CpRe(CO)_3$ complexes by the addition of more polar functionality to the complex itself, but this would need to be done in a manner that maintains acceptable binding affinity for the ER, and thus would require further investigation.

Nevertheless, from the results that we have obtained with this preliminary set of highly-substituted $CpRe(CO)_3$ complexes, it evident that organometallic complexes in this series can be high binding affinity ligands for the estrogen receptor and thereby, that radiolabeled analogues of these compounds continue to hold promise for the development of organometallic ER-based imaging and radiotherapeutic agents.

Experimental

General

All reagents and solvents were obtained from Aldrich (Milwaukee, WI), Fisher (Pittsburgh, PA), or Strem (Newburyport, NH). Tetrahydrofuran, acetonitrile, diethylether, and dichloromethane were dried by a Solvent Delivery System (SDS) (neutral alumina columns) designed by J. C. Meyer (Irvine, CA). Diethylamine was distilled from and stored over potassium hydroxide pellets. Xylenes were distilled from and stored over calcium hydride. Butyllithium was titrated using *N*-pivaloyl-*o*-toluidine, according to a literature method.[50] All reactions were performed under a dry (Drierite) nitrogen atmosphere unless otherwise stated.

Reaction progress was monitored using analytical thin-layer chromatography (TLC) on 0.25 mm Merck F-254 silica gel glass plates. Visualization was achieved by either UV light (254 nm), or phosphomolybdic acid indicator. Flash chromatography was performed according to the literature method[51] with Woelm silica gel (0.040–0.063 mm) packing.

In most cases, product isolation consisted of removing the solvent from the reaction mixture, extracting with an organic solvent, washing with saturated bicarbonate solution, and brine, drying with anhydrous. magnesium sulfate, and filtering. The use of such a workup will be indicated by the phrase 'product isolation' (which is followed, in parenthesis, by the extracting solvent). Purification in most cases was achieved by flash chromatography and is signified by the term 'purification' (which is followed, in parenthesis, by the elution solvent used in the flash chromatography, and the term 'Method A'). In the case of the deprotection of the aryl methyl ethers to form complexes **12a**–**h**, purification was accomplished by dissolving the crude product in 40% ethyl acetate/hexanes (0.5 mL), applying it to a 'plug' of silica gel (a Pasteur pipet with 1 cm silica gel atop a cotton plug), and eluting with 40% ethyl acetate/hexanes into a 4 mL amber vial. In this case, purification will be signified by the term 'purification' (followed, in parentheses, by the elution solvent, and the term 'Method B').

^1H and ^{13}C spectra were recorded on a U400 or U500 Varian FT-NMR spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) downfield from internal tetramethylsilane or by reference to proton resonances resulting from incomplete deuteration of the NMR solvent. Low resolution electron impact (EI) mass spectra were obtained on a Finnigan MAT CH5 or VG Instruments 70-VSE spectrometer. High resolution EI mass spectra were obtained on a Finnigan MAT 731 spectrometer. Elemental analyses were performed by the Microanalytical Service Laboratory of the University of Illinois. Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. Estrogen receptor binding affinity (RBA) assays were performed according to literature methods.[40,42,43] ER preparations used in these experiments were lamb uterine cytosol or purified full-length human ERα and ERβ (PanVera Inc., Madison, WI).[40,42,43] The synthesis of compounds **9a** and **11a** has been described elsewhere.[35,38]

2-Bromo-3-(4′-methoxyphenyl)-cyclopent-2-enone (2). To a stirring solution of 4-bromoanisole (1.25 mL, 9.97 mmol) in THF (40 mL) at −78 °C was added *n*-butyllithium (1.37 M in hexanes) (7.3 mL, 9.97 mmol) dropwise. After the reaction was stirred for 1 h, a solution of bromocyclopentenone **1**[22] (1.93 g, 9.41 mmol) in THF (8 mL) was added dropwise; stirring was continued for 1 h, and the reaction was warmed to rt over an additional 1 h. Product isolation (Et_2O) and purification by recrystallization from EtOH afforded light yellow needles (1.26 mg, 71% yield): mp 98–100 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 2.66 (m, 2H), 3.08 (m, 2H), 3.88 (s, 3H), 7.00 (AA′XX′, $J_{AX}=9.0$ Hz, 2H), 7.99 (AA′XX′, $J_{AX}=9.0$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.29, 32.26, 55.42, 113.97, 119.49, 126.26, 129.82, 161.88, 166.35, 201.70. MS (EI) 268 ($M^+ + H$, 96), 266 ($M^+ - H$, 100). HRMS calcd for $C_{12}H_{11}O_2Br$ 265.9942, found 265.9945.

2,3-Bis-(4-methoxyphenyl)-cyclopent-2-enone (3). A mixture of bromocyclopentenone **2** (500 mg, 1.87 mmol), 4-methoxyphenylboronic acid (347 mg, 2.28 mmol), tris(-dibenzylideneacetone)dipalladium(0) (38 mg, 0.041 mmol), and triphenylphosphine (21 mg, 0.081 mmol) was dissolved in toluene (10 mL) and nPrOH (3 mL), and then degassed by evacuation. After stirring for 10 min, diethylamine (237 μL, 2.29 mmol) and H_2O (3 mL) were added. The mixture was degassed a second time, refluxed for 1 h, then cooled to rt and poured into ethyl acetate (180 mL). The aqueous layer was removed, and the remaining organic layer was washed with 0.2 N NaOH, 0.05 N HCl, and brine, dried over anhyd $MgSO_4$, and filtered. The solvent was removed, and the product was purified by recrystallization from ethyl acetate/hexanes to afford brown needles (492 mg, 90% yield): ^1H NMR (500 MHz, $CDCl_3$) δ 2.67 (m, 2H), 3.02 (m, 2H), 3.81 (s, 3H), 3.82 (s, 3H), 6.80 (AA′XX′, $J_{AX}=9.0$ Hz, 2H), 6.89 (AA′XX′, $J_{AX}=8.9$ Hz, 2H), 7.17 (AA′XX′, $J_{AX}=8.9$ Hz, 2H), 7.34 (AA′XX′,

J_{AX} = 9.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.11, 34.54, 55.16, 55.22, 113.72, 114.05, 124.99, 128.09, 129.76, 130.65, 137.95, 159.10, 160.79, 166.58, 207.93. MS (EI) 294 (M^+, 100), 279 (8), 266 (15), 251 (27). HRMS calcd for $C_{19}H_{18}O_3$ 294.1256, found 294.1254.

(4-Methoxyphenyl)-acetaldehyde (4c). Pyridinium chlorochromate (PCC) (31 g, 140 mmol) was adsorbed onto an equal wt of silica gel (31 g) in CH_2Cl_2 (500 mL). The solvent was removed by filtration, and the PCC on silica was added to a stirring solution of 2-(4-methoxyphenyl)-ethanol (16 g, 110 mmol) in CH_2Cl_2 (800 mL). The mixture was stirred at rt for 2 h, at which time the mixture was passed through a plug of silica gel and eluted with CH_2Cl_2 to remove chromium waste. Purification (15% ethyl acetate/hexanes, Method A) afforded the acetaldehyde **4c** as a near colorless oil (7.9 g, 50% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.62 (d, J = 2.5 Hz, 2H), 3.80 (s, 3H), 6.90 (AA′XX′, J_{AX} = 8.7 Hz, 2H), 7.13 (AA′XX′, J_{AX} = 8.7 Hz, 2H), 9.71 (t, J = 2.5 Hz, 1H).

1,3-Di-(4′-methoxyphenyl)hexa-1,4-dione (5a). To a stirring solution of 4,4′-dimethoxychalcone (3.00 g, 11.2 mmol), *n*-propionaldehyde (**4a**) (2.13 g, 33.6 mmol), and 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (910 mg, 3.36 mmol) in EtOH, was added triethylamine (4.53 g, 44.8 mmol). The solution was refluxed for 48 h, at which time the reaction mixture was cooled, diluted with chloroform, and washed with 1% dilute HCl. Product isolation (chloroform) and purification (15% acetone/hexanes, Method A) afforded the corresponding 1,4-diketone **5a** as a light yellow oil (1.70 g, 47% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00 (t, J = 7.3 Hz, 3H), 2.57 (m, 2H), 3.06 (dd, J = 17.9, 3.8 Hz, 1H), 3.79 (s, 3H), 3.85 (s, 3H), 3.95 (dd, J = 17.9, 10.2 Hz, 1H), 4.35 (dd, J = 10.1, 3.7 Hz, 1H), 6.87 (AA′XX′, J_{AX} = 8.9 Hz, 2H), 6.90 (AA′XX′, J_{AX} = 9.0 Hz, 2H), 7.19 (AA′XX′, J_{AX} = 8.7 Hz, 2H), 7.93 (AA′XX′, J_{AX} = 9.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.08, 35.10, 42.43, 52.33, 55.50, 55.68, 113.91, 114.66, 129.57, 129.88, 130.58, 130.63, 159.18, 163.78, 197.16, 210.66. MS (EI) 326 (M^+, 14), 270 (4), 135 (100). HRMS calcd for $C_{20}H_{22}O_4$ 326.1518, found 326.1524.

1,3-Di-(4′ - methoxyphenyl)hepta - 1,4 - dione (5b). To a stirring solution of 4,4′-dimethoxychalcone (3.00 g, 11.2 mmol), *n*-butyraldehyde (**4b**) (2.42 g, 33.6 mmol), and 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (910 mg, 3.36 mmol) in EtOH, was added triethylamine (4.53 g, 44.8 mmol). The solution was refluxed for 72 h, at which time the reaction mixture was cooled, diluted with chloroform, and washed with 1% dilute HCl. Product isolation (chloroform) and purification (20% ethyl acetate/hexanes, Method A) afforded the corresponding 1,4-diketone **5b** as a light yellow solid (2.29 g, 60% yield): mp 79–81 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (t, J = 7.4 Hz, 3H), 1.5–1.7 (m, 2H), 2.48 (ddd, J = 10.3, 8.3, 1.5 Hz, 1H), 2.61 (ddd, J = 10.9, 8.3, 2.2 Hz, 1H), 3.05 (dd, J = 17.9, 3.8 Hz, 1H), 3.80 (s, 3H), 3.85 (s, 3H), 3.94 (dd, J = 17.8, 10.1 Hz, 1H), 4.34 (dd, J = 10.1, 3.7, 1H), 6.87(AA′XX′, J_{AX} = 8.8 Hz, 2H), 6.90 (AA′XX′, J_{AX} = 8.8 Hz, 2H), 7.19 (AA′XX′, J_{AX} = 9.0 Hz, 2H), 7.93 (AA′XX′, J_{AX} = 9.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.57, 17.08, 42.06, 43.63, 52.38, 55.25, 55.43, 113.65, 114.40, 129.38, 129.69, 130.26, 130.33, 158.93, 196.91, 209.75. MS (EI) 340 (M^+, 21), 135 (100). HRMS calcd for $C_{21}H_{24}O_4$: 340.1675, found: 340.1668.

1,3,5-Tri-(4′-methoxyphenyl)penta-1,4-dione (5c). To a stirring solution of 4,4′-dimethoxychalcone (2.00 g, 8.4 mmol), (4′-methoxyphenyl)acetaldehyde **4c** (3.10 g, 20.67 mmol), and 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (550 mg, 2.04 mmol) in EtOH, was added triethylamine (3.01 g, 33.6 mmol). The solution was refluxed for 120 h, at which time the reaction mixture was cooled, diluted with chloroform, and washed with 1% dilute HCl. Product isolation (chloroform) and purification (30% ethyl acetate/hexanes, Method A) afforded the corresponding 1,4-diketone **5c** as a light yellow oil (720 mg, 21% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.9 (dd, J = 17.8, 3.9 Hz, 1H), 3.77 (s, 3H), 3.79 (ABq, J = 5.1 Hz, 2H), 3.85 (s, 3H), 3.91 (dd, J = 18.1, 10.0 Hz, 1H), 4.40 (dd, J = 10.0, 3.9 Hz, 1H), 6.80 (AA′XX′, J_{AX} = 8.6 Hz, 2H), 6.87 (AA′XX′, J_{AX} = 8.6 Hz, 2H), 6.98 (AA′XX′, J_{AX} = 8.8 Hz, 2H), 6.90 (AA′XX′, J_{AX} = 8.8 Hz, 2H), 6.98 (AA′XX′, J_{AX} = 8.6 Hz, 2H), 7.15 (AA′XX′, J_{AX} = 8.8 Hz, 2H), 7.92 (AA′XX′, J_{AX} = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.34, 47.55, 51.77, 55.18, 55.26, 55.41, 113.60, 113.75, 114.38, 126.32, 129.32, 129.51, 129.55, 129.77, 130.30, 130.77, 158.35, 158.92, 163.46, 196.72, 207.57. MS (EI) 418 (M^+, 12), 400 (4), 297 (13), 135 (100). HRMS calcd for $C_{26}H_{26}O_5$ 418.1780, found 418.1782.

3,5-Di-(4′-methoxyphenyl)-2-methylcyclopent-2-en-1-one (6a). To a solution of the 1,4-diketone **5a** (1.70 g, 5.22 mmol) in methanol (160 mL) was added 1.8 M methanolic KOH (4.35 mL, 7.83 mmol). The stirring solution was heated to reflux for 48 h, at which time the reaction mixture was cooled to rt, and 1M dilute HCl (8 mL) was added to neutralize excess base. Product isolation (Et_2O) and purification (20% ethyl acetate/hexanes, Method A) afforded the corresponding cyclopentenone **6a** as a white solid (1.20 g, 76% yield): mp 90–92 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.06 (t, J = 2.0 Hz, 3H), 2.99 (ddq, J = 17.7, 2.8, 2.0 Hz, 1H), 3.40 (ddq, J = 17.7, 7.3, 2.0 Hz, 1H), 3.67 (dd, J = 7.4, 2.8 Hz, 1H), 6.86 (AA′XX′, J_{AX} = 8.8 Hz, 2H), 7.01 (AA′XX′, J_{AX} = 9.0 Hz, 2H), 7.11 (AA′XX′, J_{AX} = 8.7 Hz, 2H), 7.60 (AA′XX′, J_{AX} = 9.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.58, 39.00, 49.93, 55.29, 55.40, 114.09, 114.23, 128.53, 128.65, 129.51, 132.35, 133.74, 158.49, 160.82, 164.62, 209.00. MS (EI) 308 (M^+, 100), 293 (10), 279 (13), 265 (22). HRMS calcd for $C_{20}H_{20}O_3$ 308.1413, found 308.1414.

3,5-Di-(4′-methoxyphenyl)-2-ethylcyclopent-2-en-1-one (6b). To a solution of the 1,4-diketone **5b** (1.74 g, 5.13 mmol) in methanol (120 mL) was added 1.8 M methanolic KOH (4.27 mL, 7.69 mmol). The stirring solution was heated to reflux for 48 h, at which time the reaction mixture was cooled to rt, and 1 M dilute HCl (8 mL) was added to neutralize excess base. Product isolation (Et_2O) and purification (20% ethyl acetate/hexanes, Method A) afforded the corresponding cyclopentenone

6b as a light yellow solid (1.34 g, 81% yield): mp 58–61 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (t, J = 7.5 Hz, 3H), 2.51 (q, J = 7.5 Hz, 2H), 2.95 (m, 1H), 3.64 (dd, J = 7.3 2.6 Hz, 1H), 3.79 (s, 3H), 3.88 (s, 3H), 6.87 (AA′XX′, J_{AX} = 8.8 Hz, 2H), 7.00 (AA′XX′, J_{AX} = 9.0 Hz, 2H), 7.10 (AA′XX′, J_{AX} = 8.8 Hz, 2H), 7.55 (AA′XX′, J_{AX} = 9.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.75, 17.65, 39.39, 50.00, 55.22, 55.34, 114.07, 114.16, 128.44, 128.52, 129.07, 132.38, 139.77, 158.35, 160.70, 164.55, 208.72. MS EI 322 (M^+, 100), 291, (94), 265 (32). HRMS calcd for $C_{21}H_{22}O_3$ 322.1569, found 322.1568.

2,3,5-Tri-(4′-methoxyphenyl)cyclopent-2-en-1-one (6c). To a solution of the 1,4-diketone **5c** (899 mg, 2.15 mmol) in 1:1 methanol/THF (25 mL) was added 1.8 M methanolic KOH (1.79 mL, 3.23 mmol). The solution was stirred at rt for 20 min, at which time 1M dilute HCl (3.5 mL) was added to neutralize excess base. Product isolation (Et_2O) was followed by purification by recrystallization from CH_2Cl_2 to afford fine light yellow needles (408 mg, 47% yield): mp: 92–93 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.11 (dd, J = 18.1, 2.8 Hz, 1H), 3.57 (dd, J = 18.0, 7.3 Hz, 1H), 3.83 (dd, J = 7.3, 2.8 Hz, 1H), 3.82 (s, 3H), 3.84 (s, 3H), 3.84 (s, 3H), 6.86 (AA′XX′, J_{AX} = 8.6 Hz, 2H), 6.92 (AA′XX′, J_{AX} = 8.6 Hz, 2H), 6.93 (AA′XX′, J_{AX} = 8.6 Hz, 2H), 7.23 (AA′XX′, J_{AX} = 8.6 Hz, 2H), 7.27 (AA′XX′, J_{AX} = 8.6 Hz, 2H), 7.44 (AA′XX′, J_{AX} = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 39.09, 50.44, 55.07, 55.17, 113.73, 113.92, 114.12, 124.88, 127.76, 128.58, 129.85, 130.74, 132.22, 136.61, 158.41, 159.11, 160.90, 165.17, 206.95. MS (EI) 400 (M^+, 55), 251 (21), 135 (100), 121 (81). HRMS calcd for $C_{26}H_{24}O_4$ 400.1675, found 400.1672.

3,5-Di-(4′-hydroxyphenyl)-2-methylcyclopent-2-en-1-one (7a). To a stirring solution of cyclopentenone **6a** (400 mg, 1.3 mmol) in methylene chloride (65 mL) was added BF_3•$S(CH_3)_2$ (5.5 mL, 52 mmol) at rt. The solution was stirred for 18 h, until complete conversion to the diphenol, at which time the reaction was quenched with MeOH and the solvent removed under a stream of N_2. The brown residue was partitioned between ethyl acetate and H_2O, and the mixture was stirred for 15 min. Product isolation (ethyl acetate) and purification (40% ethyl acetate/hexanes, Method A) afforded the corresponding cyclopentenone as a brown solid (320 mg, 88% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.97 (t, J = 2.0 Hz, 3H), 2.93 (ddq, J = 17.7, 2.6, 2.0 Hz, 1H), 3.41 (ddq, J = 17.9, 7.4, 2.0 Hz, 1H), 3.59 (dd, J = 7.4, 2.8 Hz, 1H), 6.75 (AA′XX′, J_{AX} = 8.7 Hz, 2H), 6.98 (AA′XX′, J_{AX} = 8.9 Hz, 2H), 7.00 (AA′XX′, J_{AX} = 8.5 Hz, 2H), 7.61 (AA′XX′, J_{AX} = 8.8 Hz, 2H), 8.28 (br s, 1H), 8.99 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.06, 38.86, 49.91, 115.53, 115.77, 128.94, 130.08, 130.16 131.94, 132.50, 156.27, 159.28, 165.01, 208.40. MS (EI) 280 (M^+, 100). HRMS calcd for $C_{18}H_{16}O_3$ 280.1099, found 280.1102.

3,5-Di-(4′-hydroxyphenyl)-2-ethylcyclopent-2-en-1-one (7b). To a stirring solution of cyclopentenone **6b** (1.4 g, 4.4 mmol) in methylene chloride (70 mL) was added BF_3•$S(CH_3)_2$ (19 mL, 176 mmol) at rt. The solution was stirred for 18 h until complete conversion to the diphenol, at which time the reaction was quenched with MeOH and the solvent removed under a stream of N_2. The brown residue was partitioned between ethyl acetate and H_2O, and the mixture was stirred for 15 min. Product isolation (ethyl acetate) and purification (40% ethyl acetate/hexanes, Method A) afforded the corresponding cyclopentenone as a brown solid (1.6 g, 91% yield): mp 98–100 °C; ^{1}H NMR (400 MHz, $CDCl_3$ + acetone-d_6) δ 1.14 (t, J = 7.3 Hz, 3H), 2.50(q, J = 7.3 Hz, 2H), 2.94 (dd, J = 18.1, 2.4 Hz, 1H), 3.39 (dd, J = 18.1, 7.3 Hz, 1H), 3.63 (dd, J = 7.3 2.4 Hz, 1H), 6.74 (AA′XX′, J_{AX} = 8.5 Hz, 2H), 6.93 (AA′XX′, J_{AX} = 8.8 Hz, 2H), 7.02 (AA′XX′, J_{AX} = 8.5 Hz, 2H), 7.50 (AA′XX′, J_{AX} = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$ + acetone-d_6) δ 12.10, 17.09, 39.00, 49.55, 115.11, 115.20, 126.83, 128.03, 128.55, 128.81, 130.94, 138.40, 155.19, 158.27, 165.20, 208.93. MS EI 295 (M + 1, 20), 294 (M^+, 100). HRMS calcd for $C_{19}H_{18}O_3$ 294.1243, found 294.1249.

2,3,5-Tri-(4′-hydroxyphenyl)cyclopent-2-en-1-one (7c). To a stirring solution of cyclopentenone **6c** (200 mg, 0.5 mmol) in methylene chloride (25 mL) was added BF_3•$S(CH_3)_2$ (3.2 mL, 30 mmol) at rt. The solution was stirred for 18 h, until complete conversion to the triphenol, at which time the reaction was quenched with MeOH and the solvent removed under a stream of N_2. The brown residue was partitioned between ethyl acetate and H_2O, and the mixture was stirred for 15 min. Product isolation (ethyl acetate) and purification (40% ethyl acetate/hexanes, Method A) afforded the corresponding cyclopentenone as a brown solid (110 mg, 61% yield): mp 145 °C; ^{1}H NMR (400 MHz, $CDCl_3$ + acetone-d_6) δ 2.98 (dd, J = 18.1, 2.7 Hz, 1H), 3.43 (dd, J = 18.1, 7.3 Hz, 1H), 3.69 (dd, J = 7.3, 2.7 Hz, 1H), 6.75 (AA′XX′, J_{AX} = 8.6 Hz, 2H), 6.78 (AA′XX′, J_{AX} = 8.6 Hz, 2H), 6.79 (AA′XX′, J_{AX} = 8.6 Hz, 2H), 7.04 (AA′XX′, J_{AX} = 8.6 Hz, 2H), 7.10 (AA′XX′, J_{AX} = 8.6 Hz, 2H), 7.30 (AA′XX′, J_{AX} = 8.6 Hz, 2H), 7.57 (br s, 1H), 7.78 (br s, 1H), 8.35 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$ + acetone-d_6) δ 39.82, 51.24, 116.01, 116.05, 116.17, 125.46, 128.34, 129.59, 130.96, 131.73, 132.79, 156.95, 157.73, 159.93, 165.81, 206.13. MS (EI) 358 (M^+, 7), 107 (100). HRMS calcd for $C_{23}H_{18}O_4$ 358.1205, found 358.1205.

1,2-Di-(4′-methoxyphenyl)cyclopenta-1,3-diene (9b). To a stirring solution of cyclopentenone **3** (56 mg, 0.19 mmol) in THF (5 mL) at −78 °C was added diisobutylaluminum hydride (1 M soln in hexanes) (38 μL, 0.38 mmol). The reaction mixture was slowly warmed to rt, and a small portion of H_2O was added dropwise to quench excess DIBAL-H. HCl (3 M) was then added to the solution to dehydrate the secondary alcohol. Product isolation (Et_2O) gave 48 mg (85% yield) of a white solid, which was a 2:1 mixture of isomers, the major isomer being the 1,2-substituted cyclopentadiene and the minor isomer being the 2,3-substituted cyclopentadiene. The product was used without further purification: ^{1}H NMR (500 MHz, $CDCl_3$) (both isomers) δ 3.19 (m, 1H), 3.50 (m, 2H), 3.79 (s, 3H), 3.80 (s, 3H), 3.81 (s,

3H), 6.45 (m, 1H), 6.46 (m, 1H), 6.67 (m, 1H), 6.77 (AA′XX′, J_{AX} = 8.7 Hz, 2H), 6.79 (AA′XX′, J_{AX} = 8.7 Hz, 2H), 6.84 (AA′XX′, J_{AX} = 8.7 Hz, 2H), 7.10 (AA′XX′, J_{AX} = 8.7 Hz, 2H), 7.21 (AA′XX′, J_{AX} = 8.7 Hz, 2H), 7.28 (AA′XX′, J_{AX} = 8.7 Hz, 2H). MS (EI) 278 (M^+, 100), 263 (42).

2-Methyl-1,4-di-(4′-methoxyphenyl)cyclopenta-1,3-diene (9c). To a stirring solution of cyclopentenone **6a** (210 mg, 0.68 mmol) in THF (20 mL) at −78 °C was added diisobutylaluminum hydride (1 M soln in hexanes) (1.00 mL, 1.02 mmol). The reaction mixture was slowly warmed to rt, and a small portion of H_2O was added dropwise to quench excess DIBAL-H. HCl (3 M) was then added to the solution to dehydrate the secondary alcohol. Product isolation (Et_2O) gave 195 mg (100% yield) of **9c** as a white solid which was used without further purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.18 (t, J = 1.9 Hz, 3H), 3.70 (m, 2H), 3.83 (s, 3H), 3.84 (s, H), 6.66 (s, 1H), 6.88 (AA′XX′, J_{AX} = 8.9 Hz, 2H), 6.93 (AA′XX′, J_{AX} = 8.9 Hz, 2H), 7.37 (AA′XX′, J_{AX} = 8.9 Hz, 2H), 7.46 (AA′XX′, J_{AX} = 8.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.19, 43.88, 55.53, 114.07, 114.28, 126.17, 128.59, 129.33, 130.60, 131.68, 137.06, 137.25, 143.58, 157.99, 158.70. MS (EI) 292 (M^+, 100), 277 (30), 262 (4). HRMS calcd for $C_{20}H_{20}O_2$ 292.1463, found 292.1469.

2-Ethyl-1,4-di-(4′-methoxyphenyl)cyclopenta-1,3-diene (9d). To a stirring solution of cyclopentenone **6b** (236 mg, 0.73 mmol) in Et_2O (15 mL) at 0 °C was added lithium aluminum hydride (1M soln in Et_2O) (3.67 mL, 3.67 mmol). The reaction mixture was slowly warmed to rt and stirred for 12 h, at which time 3 M HCl was added to dehydrate the secondary alcohol. Product isolation (Et_2O) and purification (5% ethyl acetate/hexanes, Method A) afforded the corresponding cyclopentadiene **9d** as a white solid (126 mg, 56% yield): mp 93–95 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (t, J = 7.6 Hz, 3H), 2.56 (q, J = 7.6 Hz, 2H), 3.69 (s, 2H), 3.83 (s, 3H), 6.76 (s, 1H), 6.87 (AA′XX′, J_{AX} = 8.9 Hz, 2H), 6.92 (AA′XX′, J_{AX} = 9.0 Hz, 2H), 7.32 (AA′XX′, J_{AX} = 8.9 Hz, 2H), 7.47 (AA′XX′, J_{AX} = 9.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.13, 21.81, 44.18, 55.52, 114.07, 114.26, 126.15, 128.80, 129.24, 129.36, 129.41, 130.57, 136.79, 143.45, 143.97, 158.13, 158.68. MS (EI) 306 (M^+, 100), 291 (47), 277 (27). HRMS calcd for $C_{21}H_{22}O_2$ 306.1620, found 306.1615.

1,2,4-Tri-(4′-methoxyphenyl)cyclopenta-1,3-diene (9e). To a stirring solution of cyclopentenone **6c** (15 mg, 0.038 mmol) in THF (2 mL) at −78 °C was added diisobutylaluminum hydride (1 M soln in hexanes) (75 μL, 0.075 mmol). The reaction mixture was slowly warmed to rt, and a small portion of H_2O was added dropwise to quench excess DIBAL-H. HCl (3 M) was then added to the solution to dehydrate the secondary alcohol. Product isolation (Et_2O) 14 mg (100% yield) gave a light yellow solid, which was used without further purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.82 (s, 3H), 3.85 (s, 6H), 3.87 (br s, 2H), 6.80 (AA′XX′, J_{AX} = 9.0 Hz, 2H), 6.89 (AA′XX′, J_{AX} = 8.8 Hz, 2H), 6.89 (br s, 1H), 6.91 (AA′XX′, J_{AX} = 8.9 Hz, 2H), 7.27 (AA′XX′, J_{AX} = 9.0 Hz, 2H), 7.35 (AA′XX′, J_{AX} = 8.8 Hz, 2H), 7.52 (AA′XX′, J_{AX} = 8.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 45.15, 55.43, 55.45, 55.53, 113.91, 114.08, 114.31, 126.26, 129.02, 129.22, 129.77, 130.10, 130.13, 130.42, 137.26, 140.54, 144.08, 158.33, 158.83, 158.84. MS (EI) 384 (M^+, 100), 369 (13), 220 (12). HRMS calcd for $C_{26}H_{24}O_3$ 384.1726, found 384.1727.

2,3-Di-methyl-1,4-di-(4′-methoxyphenyl)cyclopenta-1,3-diene (9f). To a stirring solution of cyclopentenone **6a** (100 mg, 0.32 mmol) in Et_2O (7 mL) at 0 °C was added methylmagnesium bromide (3 M soln in THF; 106 μL, 0.32 mmol) dropwise. Stirring was continued for 0.5 h, at which point EtOH (19 μL, 0.32 mmol) was added dropwise to quench the enolate and any remaining methylmagnesium bromide. A second portion of methylmagnesium bromide (3 M soln in THF; 116 μL, 0.35 mmol) was added dropwise, followed by addition of EtOH (20 μL, 0.35 mmol) after 0.5 h. A third portion of methylmagnesium bromide (3 M soln in THF; 127 μL, 0.38 mmol) was added dropwise, followed by addition of EtOH (22 μL, 0.38 mmol) after 0.5 h. A fourth portion of methylmagnesium bromide (3 M soln in THF; 133 μL, 0.40 mmol) was added dropwise, followed by addition of 3 M HCl, after 0.5 h, to dehydrate the tertiary alcohol. Product isolation (Et_2O) and purification (5% ethyl acetate/hexanes, Method A) afforded the corresponding cyclopentadiene **9f** as a white crystalline solid (78 mg, 80% yield): mp 187–189 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.13 (t, J = 1.9 Hz, 6H), 3.59 (m, 2H), 3.84 (s, 6H), 6.94 (AA′XX′, J_{AX} = 9.1 Hz, 4H), 7.35 (AA′XX′, J_{AX} = 8.9 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.97, 45.34, 55.25, 113.77, 128.73, 130.49, 137.29, 138.51, 157.80. MS (EI) 306 (M^+, 100), 291 (23), 268 (21), 253 (23). HRMS calcd for $C_{21}H_{22}O_2$ 306.1620, found 306.1621.

2,3-Diethyl-1,4-di-(4′-methoxyphenyl)cyclopenta-1,3-diene (9g). To a stirring solution of cyclopentenone **6b** (532 mg, 1.65 mmol) in Et_2O (35 mL) at 0 °C was added ethylmagnesium bromide (1 M soln in THF; 2.10 mL, 2.10 mmol) dropwise. Stirring was continued for 0.5 h, at which point, EtOH (122 μL, 2.10 mmol) was added dropwise to quench the enolate and any remaining ethylmagnesium bromide. A second portion of ethylmagnesium bromide (1 M soln in THF; 2.25 mL, 2.25 mmol) was added dropwise, followed by addition of EtOH (131 μL, 2.25 mmol) after 0.5 h. A third portion of ethylmagnesium bromide (1 M soln in THF; 2.50 mL, 2.50 mmol) was added dropwise, followed by addition of EtOH (145 μL, 2.50 mmol) after 0.5 h. A fourth portion of ethylmagnesium bromide (1 M soln in THF; 2.75 mL, 2.75 mmol) was added dropwise, followed by addition of 3 M HCl, after 0.5 h, to dehydrate the tertiary alcohol. Product isolation (Et_2O) and purification (5% ethyl acetate/hexanes, Method A) afforded the corresponding cyclopentadiene **9g** as a light yellow solid (331 mg, 60% yield): mp 105–106 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (t, J = 7.6 Hz, 6H), 2.5 (q, J = 7.6 Hz, 4H), 3.58 (s, 2H), 3.83 (s, 6H), 6.92 (AA′XX′, J_{AX} = 9.0 Hz, 4H), 7.35 (AA′XX′, J_{AX} = 9.0 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.90, 19.78, 46.30, 55.48, 114.03, 128.74, 130.79, 137.79, 144.45,

158.12. MS (EI) 334 (M^+, 100), 319 (37), 305 (26). HRMS calcd for $C_{23}H_{26}O_2$ 334.1933, found 334.1934.

2-Ethyl-1,3,4-tri-(4′-methoxyphenyl)cyclopenta-1,3-diene (9 h). To a stirring solution of cyclopentenone **6c** (148 mg, 0.37mmol) in Et_2O (8 mL) at 0 °C was added ethylmagnesium bromide (1 M soln in THF; 440 μL, 0.44 mmol) dropwise. Stirring was continued for 0.5 h, at which point, EtOH (26 μL, 0.44 mmol) was added dropwise to quench the enolate and any remaining ethylmagnesium bromide. A second portion of ethylmagnesium bromide (1 M soln in THF; 480 μL, 0.48 mmol) was added dropwise, followed by addition of EtOH (28 μL, 0.48 mmol) after 0.5 h. A third portion of ethylmagnesium bromide (1 M soln in THF; 530 μL, 0.53 mmol) was added dropwise, followed by addition of EtOH (34 μL, 0.53 mmol) after 0.5 h. A fourth portion of ethylmagnesium bromide (1 M soln in THF; 580 μL, 0.58 mmol) was added dropwise, followed by addition of 3 M HCl, after 0.5 h, to dehydrate the tertiary alcohol. Product isolation (Et_2O) and purification (5% ethyl acetate/hexanes, Method A) afforded the corresponding cyclopentadiene **9h** as a light yellow solid (61 mg, 40% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, J = 7.5 Hz, 3H), 2.44 (q, J = 7.5 Hz, 2H), 3.77 (s, 3H), 3.79 (s, 2H), 3.87 (s, 3H), 3.88 (s, 3H), 6.71 (AA′XX′, J_{AX} = 9.0 Hz, 2H), 6.96 (AA′XX′, J_{AX} = 8.9 Hz, 2H), 6.97 (AA′XX′, J_{AX} = 8.8 Hz, 2H), 7.11 (AA′XX′, J_{AX} = 9.0 Hz, 2H), 7.21 (AA′XX′, J_{AX} = 8.7 Hz, 2H), 7.42 (AA′XX′, J_{AX} = 9.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.19, 20.05, 45.59, 55.35, 55.40, 55.51, 113.75, 114.10, 114.33, 128.64, 128.89, 129.76, 130.59, 130.63, 130.76, 137.13, 138.75, 143.49, 145.02, 158.01, 158.26, 158.75. MS (EI) 412 (M^+, 100), 397 (16), 383 (22). HRMS calcd for $C_{28}H_{28}O_3$ 412.2039, found 412.2048.

2-Methyl-1,4-di-(4′-hydroxyphenyl)cyclopenta-1,3-diene (10c). To a stirring suspension of cyclopentenone **7a** (84 mg, 0.3 mmol) in CH_2Cl_2 (5 mL) was added bis(trimethylsilyl)acetamide (730 μL, 3.0 mmol). The suspension quickly turned to a yellow solution, which was stirred an additional 2 h. The solvent and volatile by-products were removed under vacuum, and the crude TMS-protected cyclopentenone **8a** was redissolved in THF (5 mL) and cooled to −78 °C, at which time diisobutylaluminum hydride (1 M soln in hexanes) (1.5 mL, 1.5 mmol) was added. The reaction mixture was slowly warmed to rt, and a small portion of H_2O was added dropwise to quench excess DIBAL-H. HCl (3 M) was then added to the solution to dehydrate the secondary alcohol. Product isolation (ethyl acetate) and purification (40% ethyl acetate/hexanes, Method A) afforded cyclopentadiene **10c** as a white/red solid 46 mg (60% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.12 (t, J = 1.9 Hz, 3H), 3.69 (m, 2H), 6.65 (br s, 1H), 6.80 (AA′XX′, J_{AX} = 8.9 Hz, 2H), 6.85 (AA′XX′, J_{AX} = 8.9 Hz, 2H), 7.32 (AA′XX′, J_{AX} = 8.9 Hz, 2H), 7.44 (AA′XX′, J_{AX} = 8.9 Hz, 2H), 8.29 (s, 1H), 8.32 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.40, 43.51, 115.38, 115.59, 128.28, 128.56, 129.45, 130.72, 135.88, 137.21, 143.66, 155.83, 156.57. MS (EI) 264 (M^+, 100), 249 (30). HRMS calcd for $C_{18}H_{16}O_2$ 264.1150, found 264.1145.

2-Ethyl-1,4-di-(4′-hydroxyphenyl)cyclopenta-1,3-diene (10d). To a stirring suspension of cyclopentenone **7b** (63 mg, 0.21 mmol) in CH_2Cl_2 (4 mL) was added bis(trimethylsilyl)acetamide (511 μL, 2.1 mmol). The suspension quickly turned to a yellow solution, which was stirred an additional 2 h. The solvent and volatile by-products were removed under vacuum, and the crude TMS-protected cyclopentenone **8b** was redissolved in THF (4 mL) and cooled to −78 °C, at which time diisobutylaluminum hydride (1 M soln in hexanes) (1.1 mL, 1.1 mmol) was added. The reaction mixture was slowly warmed to rt, and a small portion of H_2O was added dropwise to quench excess DIBAL-H. HCl (3 M) was then added to the solution to dehydrate the secondary alcohol. Product isolation (ethyl acetate) and purification (40% ethyl acetate/hexanes, Method A) afforded cyclopentadiene **10d** as a red oil 21 mg (36% yield): ^{1}H NMR (500 MHz, acetone-d_6) δ 1.19 (t, J = 7.6 Hz, 3H), 2.52 (qt, J = 7.6, 1.0 Hz, 2H), 3.68 (m, 2H), 6.78 (m, 1H), 6.80 (AA′XX′, J_{AX} = 8.9 Hz, 2H), 6.85 (AA′XX′, J_{AX} = 9.0 Hz, 2H), 7.28 (AA′XX′, J_{AX} = 8.9 Hz, 2H), 7.45 (AA′XX′, J_{AX} = 9.0 Hz, 2H), 8.35 (br s, 2H); ^{13}C NMR (125 MHz, acetone-d_6) δ 13.52, 21.52, 43.80, 115.41, 115.56, 126.20, 128.37, 128.46, 128.75, 129.38, 136.76, 142.42, 144.06, 155.99, 156.54. MS (EI) 278 (M^+, 100), 63 (47). HRMS calcd for $C_{19}H_{18}O_2$ 278.1307, found 278.1304.

1,2,4-Tri-(4′-hydroxyphenyl)cyclopenta-1,3-diene (10e). To a stirring suspension of cyclopentenone **7c** (15 mg, 0.042 mmol) in CH_2Cl_2 (1 mL) was added bis(trimethylsilyl)acetamide (102 μL, 0.42 mmol). The suspension quickly turned to a yellow solution, which was stirred an additional 2 h. The solvent and volatile by-products were removed under vacuum, and the crude TMS-protected cyclopentenone **8c** was redissolved in THF (1 mL) and cooled to −78 °C, at which time diisobutylaluminum hydride (1 M soln in hexanes) (210 μL, 0.21 mmol) was added. The reaction mixture was slowly warmed to rt, and a small portion of H_2O was added dropwise to quench excess DIBAL-H. HCl (3 M) was then added to the solution to dehydrate the secondary alcohol. Product isolation (ethyl acetate) and purification (40% ethyl acetate/hexanes, Method A) afforded cyclopentadiene **10e** as a red solid 5 mg (35% yield): ^{1}H NMR (500 MHz, acetone-d_6) δ 3.84 (m, 2H), 6.71 (AA′XX′, J_{AX} = 8.9 Hz, 2H), 6.80 (AA′XX′, J_{AX} = 8.8 Hz, 2H), 6.82 (AA′XX′, J_{AX} = 8.8 Hz, 2H), 6.87 (br s, 1H), 7.20 (AA′XX′, J_{AX} = 8.9 Hz, 2H), 7.23 (AA′XX′, J_{AX} = 8.8 Hz, 2H), 7.49 (AA′XX′, J_{AX} = 8.8 Hz, 2H). MS (EI) 342 (M^+, 100). HRMS calcd for $C_{23}H_{18}O_3$ 342.1256, found 342.1262.

2,3-Di-methyl-1,4-di-(4′-hydroxyphenyl)cyclopenta-1,3-diene (10f). To a stirring suspension of cyclopentenone **7a** (84 mg, 0.3 mmol) in CH_2Cl_2 (5 mL) was added bis(trimethylsilyl)acetamide (730 μL, 3.0 mmol). The suspension quickly turned to a yellow solution, which was stirred an additional 2 h. The solvent and volatile by-products were removed under vacuum and the crude TMS-protected cyclopentenone **8a** was redissolved in Et_2O and cooled to 0 °C. Methylmagnesium bromide (3 M soln in THF; 110 μL, 0.33 mmol) was added dropwise to the stirring solution. Stirring was continued

for 0.5 h, at which point EtOH (19 μL, 0.33 mmol) was added dropwise to quench the enolate and any remaining methylmagnesium bromide. A second portion of methylmagnesium bromide (3 M soln in THF; 120 μL, 0.36 mmol) was added dropwise, followed by addition of EtOH (21 μL, 0.36 mmol) after 0.5 h. A third portion of methylmagnesium bromide (3 M soln in THF; 130 μL, 0.39 mmol) was added dropwise, followed by addition of EtOH (23 μL, 0.39 mmol) after 0.5 h. A fourth portion of methylmagnesium bromide (3 M soln in THF; 143 μL, 0.42 mmol) was added dropwise, followed by addition of 3 M HCl, after 0.5 h, to dehydrate the tertiary alcohol. Product isolation (ethyl acetate) and purification (40% ethyl acetate/hexanes, Method A) afforded the corresponding cyclopentadiene **10f** as a white/red solid (26 mg, 31% yield): ^{1}H NMR (500 MHz, CD_3OD) δ 2.06 (t, $J=1.7$ Hz, 6H), 3.49 (m, 2H), 6.77 (AA′XX′, $J_{AX}=8.8$ Hz, 4H), 7.23 (AA′XX′, $J_{AX}=8.8$ Hz, 4H); ^{13}C NMR (125 MHz, CD_3OD) δ 11.91, 29.45, 44.98, 114.88, 128.63, 129.63, 137.40, 155.49. MS (EI) 278 (M^+, 100), 263 (22). HRMS calcd for $C_{19}H_{18}O_2$ 278.1307, found 278.1309.

2,3-Diethyl-1,4-di-(4′-hydroxyphenyl)cyclopenta-1,3-diene (10g). To a stirring suspension of cyclopentenone **7b** (60 mg, 0.20 mmol) in CH_2Cl_2 (5 mL) was added bis(trimethylsilyl)acetamide (490 μL, 2.0 mmol). The suspension quickly turned to a yellow solution, which was stirred an additional 2 h. The solvent and volatile by-products were removed under vacuum, and the crude TMS-protected cyclopentenone **8b** was redissolved in Et_2O and cooled to 0 °C. Ethylmagnesium bromide (1 M soln in THF; 220 μL, 0.22 mmol) was added to the stirring solution dropwise. Stirring was continued for 0.5 h, at which point EtOH (13 μL, 0.22 mmol) was added dropwise to quench the enolate and any remaining ethylmagnesium bromide. A second portion of ethylmagnesium bromide (1 M soln in THF; 240 μL, 0.24 mmol) was added dropwise, followed by addition of EtOH (14 μL, 0.24 mmol) after 0.5 h. A third portion of ethylmagnesium bromide (1 M soln in THF; 260 μL, 0.26 mmol) was added dropwise, followed by addition of EtOH (15 μL, 0.26 mmol) after 0.5 h. A fourth portion of ethylmagnesium bromide (1 M soln in THF; 280 μL, 0.28 mmol) was added dropwise, followed by addition of 3 M HCl, after 0.5 h, to dehydrate the tertiary alcohol. Product isolation (ethyl acetate) and purification (40% ethyl acetate/hexanes, Method A) afforded the corresponding cyclopentadiene **10e** as a reddish oily solid (21 mg, 35% yield): ^{1}H NMR (500 MHz, acetone-d_6) δ 1.16 (t, $J=7.5$ Hz, 6H), 2.53 (q, $J=7.5$ Hz, 4H), 3.55 (s, 2H), 6.85 (AA′XX′, $J_{AX}=8.8$ Hz, 4H), 7.30 (AA′XX′, $J_{AX}=8.8$ Hz, 4H), 8.32 (br s, 2H); ^{13}C NMR (125 MHz, acetone-d_6) δ 14.96, 20.07, 46.46, 116.07, 129.34, 130.19, 138.49, 143.97, 156.65. MS (EI) 307 (M+1, 25), 306 (M^+, 82), 58 (100). HRMS calcd for $C_{21}H_{22}O_2$ 306.1620, found 306.1621.

2-Ethyl-1,3,4-tri-(4′-hydroxyphenyl)cyclopenta-1,3-diene (10 h). To a stirring suspension of cyclopentenone **7c** (40 mg, 0.11 mmol) in CH_2Cl_2 (4 mL) was added bis(trimethylsilyl)acetamide (270 μL, 1.1 mmol). The suspension quickly turned to a yellow solution, which was stirred an additional 2 h. The solvent and volatile by-products were removed under vacuum, and the crude TMS-protected cyclopentenone **8c** was redissolved in Et_2O and cooled to 0 °C. Ethylmagnesium bromide (1 M soln in THF; 120 μL, 0.12 mmol) was added to the stirring solution dropwise. Stirring was continued for 0.5 h, at which point EtOH (7 μL, 0.12 mmol) was added dropwise to quench the enolate and any remaining ethylmagnesium bromide. A second portion of ethylmagnesium bromide (1 M soln in THF; 130 μL, 0.13 mmol) was added dropwise, followed by addition of EtOH (8 μL, 0.13 mmol) after 0.5 h. A third portion of ethylmagnesium bromide (1 M soln in THF; 140 μL, 0.14 mmol) was added dropwise, followed by addition of EtOH (9 μL, 0.14 mmol) after 0.5 h. A fourth portion of ethylmagnesium bromide (1 M soln in THF; 150 μL, 0.15 mmol) was added dropwise, followed by addition of 3 M HCl, after 0.5 h, to dehydrate the tertiary alcohol. Product isolation (ethyl acetate) and purification (40% ethyl acetate/hexanes, Method A) afforded the corresponding cyclopentadiene **10 h** as a red solid (9 mg, 23% yield): ^{1}H NMR (500 MHz, $CDCl_3$ + acetone-d_6) δ 0.85 (t, $J=7.3$ Hz, 3H), 2.39 (q, $J=7.3$ Hz, 2H), 3.72 (s, 2H), 6.61 (AA′XX′, $J_{AX}=8.8$ Hz, 2H), 6.86 (AA′XX′, $J_{AX}=8.5$ Hz, 2H), 6.88 (AA′XX′, $J_{AX}=8.5$ Hz, 2H), 7.02 (AA′XX′, $J_{AX}=8.8$ Hz, 2H), 7.11 (AA′XX′, $J_{AX}=8.5$ Hz, 2H), 7.31 (AA′XX′, $J_{AX}=8.5$ Hz, 2H). MS (EI) 371 (M+1, 13), 370 (M^+, 17), 344 (100). HRMS calcd for $C_{25}H_{22}O_3$ 370.1569, found 370.1449.

1,2-Di-(4′-methoxyphenyl)cyclopentadienyltricarbonyl rhenium(I) (11b). To a stirring solution of cyclopentadiene **9b** (45 mg, 0.15 mmol) in THF (7 mL) at −78 °C was added *n*-butyllithium (1.55 M in hexanes) (200 μL, 0.31 mmol). The yellow solution was stirred for 5 min, at which time it was added via a cannulus to a flask containing a stirring solution of $[ReBr(CO)_3(THF)]_2$ in THF (7 mL) at rt. The resulting brown solution was stirred for 15 min and then quenched with MeOH. Purification (10% ethyl acetate/hexanes, Method A) afforded the corresponding $CpRe(CO)_3$ complex **11b** as a light yellow solid (44 mg, 54% yield): mp 88–89 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.81 (s, 6H), 5.35 (t, $J=2.7$ Hz, 1H), 5.56 (d, $J=2.7$ Hz, 2H), 6.79 (AA′XX′, $J_{AX}=8.9$ Hz, Hz, 4H), 7.18 (AA′XX′, $J_{AX}=8.9$ Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.47, 81.80, 108.35, 113.92, 124.24, 131.56, 159.63, 195.05. MS (EI) 548 (M^{+Re187}, 8), 546 (M^{+Re185}, 4), 520 (4), 518 (3), 492 (<2), 490 (<2), 464 (5), 462 (3), 205 (100). HRMS calcd for $C_{22}H_{17}O_5^{187}Re$ 546.0606, found 546.0610.

2-Methyl-1,4-di-(4′-methoxyphenyl)cyclopentadienyltricarbonyl rhenium(I) (11c). To a stirring solution of cyclopentadiene **9c** (36 mg, 0.12 mmol) in THF (6 mL) at −78 °C was added *n*-butyllithium (1.55 M in hexanes) (161 μL, 0.25 mmol). The yellow solution was stirred for 5 min, at which time it was added via a cannulus to a flask containing a stirring solution of $[Et_4N]_2[ReBr_3(CO)_3]$ in acetonitrile (6 mL) at rt. The resulting brown solution was stirred for 15 min and then quenched with MeOH. Purification (10% ethyl acetate/hexanes, Method A) afforded the corresponding $CpRe(CO)_3$ complex **11c** as a light yellow solid (7 mg, 10% yield): mp

133–135 °C. ^{1}H NMR (500 MHz, acetone-d_6) δ 2.44 (s, 3H), 3.81 (s, 3H), 3.83 (s, 3H), 6.06 (d, J = 2.3 Hz, 1H), 6.35 (d, J = 2.3 Hz, 1H), 6.92 (AA′XX′, J_{AX} = 8.6 Hz, 2H), 6.97 (AA′XX′, J_{AX} = 8.7 Hz, 2H), 7.48 (AA′XX′, J_{AX} = 8.7 Hz, 2H), 7.55 (AA′XX′, J_{AX} = 8.7 Hz, 2H); ^{13}C NMR (125 MHz, acetone-d_6) δ 12.93, 54.94, 80.68, 81.36, 104.11, 106.87, 106.99, 114.01, 114.18, 124.13, 124.74, 127.44, 131.06, 159.80, 160.16, 196.29. MS (EI) 562 (M^{+Re187}, 86), (M^{+Re185}, 56), 534 (50), 532 (31), 504 (55), 502 (35), 474 (44), 472 (28). HRMS calcd for $C_{23}H_{19}O_5^{187}Re$ 560.0762, found 560.0772.

2-Ethyl-1,4-di-(4′-methoxyphenyl)cyclopentadienyltricarbonyl rhenium(I) (11d). To a stirring solution of cyclopentadiene **9d** (50 mg, 0.16 mmol) and $[ReBr(CO)_3(THF)]_2$ (64 mg, 0.07 mmol) in THF (7 mL) at rt was added Bu_3SnNEt_2 (88 mg, 0.25 mmol). The solution was warmed to reflux and stirred for 16 h, at which time the solvent was removed under vacuum. Product isolation (Et_2O) and purification (5% ethyl acetate/hexanes, Method A) furnished complex **11d** as a light yellow oil (5 mg, 5% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.17 (t, J = 7.5 Hz, 3H), 2.61 (qABq, J_{AB} = 15.0 Hz, ν_{AB} 58.0 Hz, J = 7.5 Hz, 2H), 3.82 (s, 3H), 3.84 (s, 3H), 5.62 (d, J = 2.2 Hz, 1H), 5.84 (d, J = 2.2 Hz, 1H), 6.86 (AA′XX′, J_{AX} = 8.8 Hz, 2H), 6.89 (AA′XX′, J_{AX} = 8.8 Hz, 2H), 7.32 (AA′XX′, J_{AX} = 8.8 Hz, 2H), 7.34 (AA′XX′, J_{AX} = 8.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.54, 20.24, 55.31, 78.46, 81.74, 105.80, 106.90, 110.44, 113.86, 114.10, 124.18, 124.45, 127.35, 131.51, 159.38, 159.67, 195.47; MS (EI) 576 (M^{+Re187}, 100), 574 (M^{+Re185}, 61), 546 (53), 544 (24), 516 (57), 514 (21), 486 (33), 484(14). HRMS calcd for $C_{24}H_{21}O_5^{187}Re$ 576.0947, found 576.0940.

1,2,4-Tri-(4′-methoxyphenyl)cyclopentadienyltricarbonyl rhenium(I) (11e). To a stirring solution of cyclopentadiene **9e** (15 mg, 0.039 mmol) in THF (2 mL) at −78 °C was added *n*-butyllithium (1.55 M in hexanes) (50 μL, 0.078 mmol). The yellow solution was stirred for 5 min, at which time it was added via a cannulus to a flask containing a stirring solution of $[ReBr(CO)_3(THF)]_2$ in THF (2 mL) at rt. The resulting brown solution was stirred for 15 min and then quenched with MeOH. Purification (15% ethyl acetate/hexanes, Method A) afforded the corresponding CpRe complex **11e** as a light yellow solid (13 mg, 55% yield): mp 168–170 °C. ^{1}H NMR (500 MHz, acetone-d_6) δ 3.80 (s, 6H), 3.82 (s, 3H), 6.42 (s, 2H), 6.87 (AA′XX′, J_{AX} = 8.9 Hz, 4H), 6.95 (AA′XX′, J_{AX} = 8.9 Hz, 2H), 7.30 (AA′XX′, J_{AX} = 8.9 Hz, 4H), 7.64 (AA′XX′, J_{AX} = 8.9 Hz, 2H); ^{13}C NMR (125 MHz, acetone-d_6) δ 54.91, 81.70, 106.52, 107.76, 113.79, 114.22, 124.06, 124.34, 127.50, 131.60, 159.92, 160.24, 195.99. MS (EI) 654 (M^{+Re187}, 100), 652 (M^{+Re185}, 59), 626 (41), 624 (25), 596 (17), 594 (10), 570 (38), 568 (25). HRMS calcd for $C_{29}H_{23}O_6^{187}Re$ 652.1024, found 652.1031.

2,3-Dimethyl-1,4-di-(4′-methoxyphenyl)cyclopentadienyltricarbonyl rhenium(I) (11f). To a stirring solution of cyclopentadiene **9f** (70 mg, 0.23 mmol) in THF (5 mL) at −78 °C was added *n*-butyllithium (1.55 M in hexanes) (148 μL, 0.23 mmol). The yellow solution was stirred for 5 min, at which time it was added via a cannulus to a flask containing a stirring solution of $[ReBr(CO)_3(THF)]_2$ (32 mg, 0.038 mmol) in THF (5 mL) at rt. The resulting brown solution was stirred for 15 min and then quenched with MeOH. Purification (10% ethyl acetate/hexanes, Method A) afforded the corresponding CpRe complex **11f** as a light yellow solid (23 mg, 54% yield): mp 140–141 °C. ^{1}H NMR (500 MHz, acetone-d_6) δ 2.42 (s, 6H), 3.82 (s, 6H), 5.97 (s, 1H), 6.96 (AA′XX′, J_{AX} = 9.0 Hz, 4H), 7.45 (AA′XX′, J_{AX} = 9.0 Hz, 4H); ^{13}C NMR (125 MHz, acetone-d_6) δ 11.33, 54.95, 83.88, 101.10, 106.30, 113.99, 124.76, 131.34, 159.81, 197.03. MS (EI) 576 (M^{+Re187}, 100), 574 (M^{+Re185}, 56), 548 (53), 546 (38), 518 (64), 516 (59), 488 (41), 486 (38). HRMS calcd for $C_{24}H_{21}O_5^{187}Re$ 576.0947, found 576.0953.

2,3-Diethyl-1,4-di-(4′-methoxyphenyl)cyclopentadienyltricarbonyl rhenium(I) (11g). To a stirring solution of cyclopentadiene **9g** (95 mg, 0.28 mmol) in THF (15 mL) at −78 °C was added *n*-butyllithium (1.40 M in hexanes) (304 μL, 0.43 mmol). The solution was stirred for 5 min, at which time it was added via a cannulus to a flask containing a stirring solution of $[ReBr(CO)_3(THF)]_2$ in THF (10 mL) at rt. The resulting brown solution was stirred for 15 min and then quenched with MeOH. Purification (10% ethyl acetate/hexanes, Method A) afforded the corresponding $CpRe(CO)_3$ complex **11g** as a light yellow solid (133 mg, 82% yield): mp 119–121 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (t, J = 7.6 Hz, 6H), 2.59 (qABq, J_{AB} = 15.0 Hz, ν_{AB} 48.0 Hz, J = 7.5 Hz, 4H), 3.84 (s, 6H), 5.58 (s, 1H), 6.98 (AA′XX′, J_{AX} = 8.8 Hz, 4H), 7.35 (AA′XX′, J_{AX} = 8.8 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.41, 18.66, 55.30, 84.37, 106.16, 106.53, 113.81, 124.72, 131.57, 159.35, 196.24. MS (EI) 604 (M^{+Re187}, 100), 602 (M^{+Re185}, 60), 576 (38), 574 (46), 544 (34), 542 (27), 514 (17), 512 (25). HRMS calcd for $C_{26}H_{25}O_5^{187}Re$ 602.1232, found 602.1237.

3-Ethyl-1,2,4-tri-(4′-methoxyphenyl)cyclopentadienyltricarbonyl rhenium(I) (11 h). To a stirring solution of cyclopentadiene **9 h** (52 mg, 0.13 mmol) in THF (6.5 mL) at −78 °C was added *n*-butyllithium (1.55 M in hexanes) (168 μL, 0.26 mmol). The yellow solution was stirred for 5 min, at which time it was added via a cannulus to a flask containing a stirring solution of $[ReBr(CO)_3(THF)]_2$ in THF (6.5 mL) at rt. The resulting brown solution was stirred for 15 min and then quenched with MeOH. Purification (15% ethyl acetate/hexanes, Method A) afforded the corresponding CpRe complex **11 h** as a yellow oil (32 mg, 37% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.76 (t, J = 7.5 Hz, 3H), 2.53 (qABq, J_{AB} = 15.0 Hz, ν_{AB} 56.0 Hz, J = 7.5 Hz, 2H), 3.77 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 5.80 (s, 1H), 6.72 (AA′XX′, J_{AX} = 9.0 Hz, 2H), 6.88 (AA′XX′, J_{AX} = 8.8 Hz, 2H), 6.93 (AA′XX′, J_{AX} = 8.9 Hz, 2H), 7.11 (AA′XX′, J_{AX} = 9.0 Hz, 2H), 7.25 (AA′XX′, J_{AX} = 8.9 Hz, 2H), 7.41 (AA′XX′, J_{AX} = 8.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.99, 19.08, 82.28, 104.03, 104.47, 108.86, 111.16, 113.74, 114.12, 114.14, 124.03, 124.06, 124.89, 130.50, 132.50, 134.55, 159.44, 159.50, 159.61, 196.15. MS (EI) 682 (M^{+Re187}, 100), 680 (M^{+Re185}, 58), 654 (27), 652 (28), 622 (33), 620 (19), 594 (21), 592 (22). HRMS calcd for $C_{31}H_{27}O_6^{187}Re$ 680.1337, found 680.1348.

4′-Hydoxyphenylcyclopendadienyltricarbonyl rhenium(I) (12a). To a stirring solution of $CpRe(CO)_3$ **11a**[35] (100 mg, 0.22 mmol) in methylene chloride (5 mL) was added $BF_3S(CH_3)_2$ (230 μL, 2.2 mmol) at rt. The solution was stirred for 18 h, at which time the reaction was quenched with MeOH and the solvent removed under a stream of N_2. The grey solid was partitioned between ethyl acetate and H_2O, and the mixture was stirred for 15 min. Product isolation (ethyl acetate) and purification (20% ethyl acetate/hexanes, Method A) afforded the corresponding phenolic $CpRe(CO)_3$ complex as a white solid (85 mg, 87% yield): mp 118 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.39 (t, J = 2.1 Hz, 2H), 5.70 (t, J = 2.1 Hz, 2H), 6.81 (AA′XX′, J_{AX} = 8.8 Hz, 2H), 7.30 (AA′XX′, J_{AX} = 8.8 Hz, Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 80.92, 84.15, 109.50, 115.64, 124.24, 127.92, 155.78, 164.50, 168.96, 194.21. ν_{CO} (cm^{-1}) 2016, 1908. MS (EI) 428 (M^{+Re187}, 100), 426 (M^{+Re185}, 58), 400 (47), 398 (27), 372 (96), 370 (59), 344 (20), 342 (20). Anal. calcd for $C_{14}H_8O_4Re$: C, 39.43; H, 1.89. Found: C, 39.74; H, 2.22.

1,2-di-(4′ - hydroxyphenyl)cyclopentadienyltricarbonyl rhenium(I) (12b). To a stirring solution of $CpRe(CO)_3$ **11b** (19 mg, 0.035 mmol) in methylene chloride (3.5 mL) was added $BF_3S(CH_3)_2$ (146 μL, 1.39 mmol) at rt. The solution was stirred for 18 h, until complete conversion to the di-phenol, at which time the reaction was quenched with MeOH and the solvent removed under a stream of N_2. The green/grey residue was partitioned between ethyl acetate and H_2O, and the mixture was stirred for 15 min. Product isolation (ethyl acetate) and purification (40% ethyl acetate/hexanes, Method B) afforded the corresponding phenolic $CpRe(CO)_3$ complex **12b** as a brown/white semi-solid (19 mg, 100% yield): ^{1}H NMR (500 MHz, acetone-d_6) δ 5.61(t, J = 2.7 Hz, 1H), 5.83 (d, J = 2.7 Hz, 2H), 6.74 (AA′XX′, J_{AX} = 8.8 Hz, 4H), 7.14 (AA′XX′, J_{AX} = 8.8 Hz, 4H), 8.57 (s, 2H); ^{13}C NMR (125 MHz, acetone-d_6) δ 82.60, 85.22, 108.92, 115.22, 123.17, 131.63, 157.66, 195.69. ν_{CO} (cm^{-1}) 2019, 1926. MS (EI) 520 (M^{+Re187}, 33), 518 (M^{+Re185}, 19), 492 (15), 490 (9), 462 (8), 460 (5), 436 (26), 434 (21), 83 (100). HRMS calcd for $C_{20}H_{13}O_5^{187}Re$ 520.0321, found 520.0315.

2-Methyl-1,4-di - (4′ - hydroxyphenyl)cyclopentadienyltricarbonyl rhenium(I) (12c). To a stirring solution of $CpRe(CO)_3$ complex **11c** (5 mg, 0.01 mmol) in methylene chloride (1 mL) was added $BF_3S(CH_3)_2$ (38 μL, 0.36 mmol) at rt. The solution was stirred for 18 h until complete conversion to the di-phenol, at which time the reaction was quenched with MeOH and the solvent removed under a stream of N_2. The red residue was partitioned between ethyl acetate and H_2O, and the mixture was stirred for 15 min. Product isolation (ethyl acetate) and purification (40% ethyl acetate/hexanes, Method B) afforded the corresponding phenolic $CpRe(CO)_3$ complex as a white/red solid (4.5 mg, 94% yield): mp 242 °C (dec). ^{1}H NMR (500 MHz, acetone-d_6) δ 2.42 (s, 3H), 6.00 (d, J = 2.2 Hz, 1H), 6.26 (d, J = 2.2 Hz, 1H), 6.82 (AA′XX′, J_{AX} = 8.8 Hz, 2H), 6.87 (AA′XX′, J_{AX} = 8.7 Hz, 2H), 7.38 (AA′XX′, J_{AX} = 8.8 Hz, 2H), 7.45 (AA′XX′, J_{AX} = 8.8 Hz, 2H), 8.56 (s, 1H), 8.59 (s, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 12.92, 80.31, 80.93, 103.76, 107.45, 107.52, 115.42, 115.62, 123.03, 123.63, 127.56, 131.17, 157.58, 157.96, 196.42. ν_{CO} (cm^{-1}) 2014, 1917. MS (EI) 534 (M^{+Re187}, 100), 532 (M^{+Re185}, 59), 506 (60), 504 (39), 476 (75), 474 (48), 446 (65), 444 (41). HRMS calcd for $C_{21}H_{15}O_5^{187}Re$ 534.0477, found 534.0483.

2-Ethyl-1,4-di-(4′-hydroxyphenyl)cyclopentadienyltricarbonyl rhenium(I) (12d). To a stirring solution of $CpRe(CO)_3$ **11d** (14 mg, 0.024 mmol) in methylene chloride (2.5 mL) was added $BF_3S(CH_3)_2$ (102 μL, 0.64 mmol) at rt. The solution was stirred for 18 h until complete conversion to the di-phenol, at which time the reaction was quenched with MeOH and the solvent removed under a stream of N_2. The red residue was partitioned between ethyl acetate and H_2O, and the mixture was stirred for 15 min. Product isolation (ethyl acetate) and purification (40% ethyl acetate/hexanes, Method B) afforded the corresponding phenolic $CpRe(CO)_3$ **12d** complex as a white/red solid (11 mg, 88% yield): mp 200–201 °C. ^{1}H NMR (500 MHz, acetone-d_6) δ 1.19 (t, J = 7.5 Hz, 3H), 2.67 (qABq, J_{AB} = 15.0 Hz, ν_{AB} 77.0 Hz, J = 7.5 Hz, 2H), 6.07 (d, J = 2.3, 1H), 6.26 (d, J = 2.3 Hz, 1H), 6.82 (AA′XX′, J_{AX} = 8.8 Hz, 2H), 6.86 (AA′XX′, J_{AX} = 8.8 Hz, 2H), 7.35 (AA′XX′, J_{AX} = 8.8 Hz, 2H), 7.47 (AA′XX′, J_{AX} = 8.8 Hz, 2H), 8.56 (s, 1H), 8.59 (s, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 15.20, 20.32, 79.03, 81.56, 106.73, 107.74, 110.36, 115.42, 115.61, 123.15, 123.51, 127.55, 131.59, 157.62, 157.91, 196.35. ν_{CO} (cm^{-1}) 2011, 1918. MS (EI) 548 (M^{+Re187}, 56), 546 (M^{+Re185}, 33), 518 (38), 516 (14), 488 (34), 486 (10), 460 (21) 458 (22). HRMS calcd for $C_{22}H_{17}O_5^{187}Re$ 546.0606, found 546.0599.

1,2,4-Tri-(4′ - hydroxyphenyl)cyclopentadienyltricarbonyl rhenium(I) (12e). To a stirring solution of $CpRe(CO)_3$ **11e** (5.0 mg, 0.0077 mmol) in methylene chloride (1.5 mL) was added $BF_3S(CH_3)_2$ (48 μL, 0.46 mmol) at rt. The solution was stirred for 24 h until complete conversion to the tri-phenol, at which time the reaction was quenched with MeOH and the solvent removed under a stream of N_2. The red residue was partitioned between ethyl acetate and H_2O, and the mixture was stirred for 15 min. Product isolation (ethyl acetate) and purification (40% ethyl acetate/hexanes, Method B) afforded the corresponding phenolic $CpRe(CO)_3$ complex **12e** as a white/red solid (4.4 mg, 94% yield): ^{1}H NMR (500 MHz, acetone-d_6) δ 6.32 (s, 2H), 6.76 (AA′XX′, J_{AX} = 8.8 Hz, 4H), 6.85 (AA′XX′, J_{AX} = 8.8 Hz, 2H), 7.21 (AA′XX′, J_{AX} = 8.8 Hz, 4H), 7.54 (AA′XX′, J_{AX} = 8.8 Hz, 2H), 8.58 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 81.18, 107.08, 107.95, 115.12, 115.20, 115.65, 123.01, 123.33, 127.62, 131.67, 157.67, 158.03, 196.19. ν_{CO} (cm^{-1}) 2014, 1917. MS (EI) 612 (M^{+Re187}, 100), 610 (M^{+Re185}, 60), 584 (48), 582 (27), 554 (26), 552 (14), 528 (43), 526 (33). HRMS calcd for $C_{26}H_{17}O_6^{187}Re$ 610.0555, found 610.0548.

2,3-Dimethyl-1,4-di-(4′-hydroxyphenyl)cyclopentadienyltricarbonyl rhenium(I) (12f). To a stirring solution of $CpRe(CO)_3$ complex **11f** (15 mg, 0.026 mmol) in methylene chloride (2.5 mL) was added $BF_3S(CH_3)_2$ (109 μL, 1.04 mmol) at rt. The solution was stirred for 18 h, until

complete conversion to the di-phenol, at which time the reaction was quenched with MeOH and the solvent removed under a stream of N_2. The red residue was partitioned between ethyl acetate and H_2O, and the mixture was stirred for 15 min. Product isolation (ethyl acetate) and purification (40% ethyl acetate/hexanes, Method B) afforded the corresponding phenolic $CpRe(CO)_3$ complex **12f** as a white/red solid (14 mg, 99% yield): mp 255 °C (dec). ^{1}H NMR (500 MHz, acetone-d_6) δ 2.40 (s, 6H), 5.90 (s, 1H), 6.86 (AA′XX′, J_{AX} = 9.0 Hz, 4H), 7.35 (AA′XX′, J_{AX} = 9.0 Hz, 4H), 8.60 (s, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 11.97, 84.19, 101.49, 107.39, 116.03, 124.28, 132.06, 158.20, 197.81. ν_{CO} (cm^{-1}) 2005, 1920. MS (EI) 548 (M^{+Re187}, 77), 546 (M^{+Re185}, 45), 520 (47), 518 (32), 490 (63), 488 (53), 458 (37), 456 (18). HRMS calcd for $C_{22}H_{17}O_5^{187}Re$ 548.0634, found 548.0628.

2,3-Diethyl-1,4-di-(4′-hydroxyphenyl)cyclopentadienyltricarbonyl rhenium(I) (12g). To a stirring solution of $CpRe(CO)_3$ complex **11g** (30 mg, 0.05 mmol) in methylene chloride (5 mL) was added $BF_3S(CH_3)_2$ (210 μL, 2.0 mmol) at RT. The solution was stirred for 18 h until complete conversion to the di-phenol, at which time the reaction was quenched with MeOH and the solvent removed under a stream of N_2. The red residue was partitioned between ethyl acetate and H_2O, and the mixture was stirred for 15 min. Product isolation (ethyl acetate) and purification (40% ethyl acetate/hexanes, Method B) afforded the corresponding phenolic $CpRe(CO)_3$ complex **12g** as a white/red solid (27 mg, 93% yield): mp 147–149 °C. ^{1}H NMR (500 MHz, acetone-d_6) δ 1.06 (t, J = 7.6 Hz, 6H), 2.66 54 (qABq, J_{AB} = 15.2 Hz, ν_{AB} 45.0 Hz, J = 7.6 Hz, 2H), 5.88 (s, 1H), 6.87 (AA′XX′, J_{AX} = 8.8 Hz, 4H), 7.37 (AA′XX′, J_{AX} = 8.8 Hz, 4H), 8.62 (s, 2H); ^{13}C NMR (125 MHz, acetone-d_6) δ 17.09, 18.54, 84.08, 106.54, 107.13, 115.46, 123.59, 131.66, 157.66, 196.88. ν_{CO} (cm^{-1}) 2016, 1913. MS (EI) 576 (M^{+Re187}, 100), 574 (M^{+Re185}, 58), 546 (50), 544 (21), 516 (42), 514 (31), 484 (35), 482 (27). HRMS calcd for $C_{24}H_{21}O_5^{187}Re$ 574.0919, found 574.0923.

3-Ethyl-1,2,4-tri-(4′-hydroxyphenyl)cyclopentadienyltricarbonyl rhenium(I) (12 h). To a stirring solution of $CpRe(CO)_3$ complex **11 h** (27 mg, 0.04 mmol) in methylene chloride (4 mL) was added $BF_3S(CH_3)_2$ (250 μL, 2.38 mmol) at rt. The solution was stirred for 24 h until complete conversion to the tri-phenol, at which time the reaction was quenched with MeOH and the solvent removed under a stream of N_2. The red residue was partitioned between ethyl acetate and H_2O, and the mixture was stirred for 15 min. Product isolation (ethyl acetate) and purification (40% ethyl acetate/hexanes, Method B) afforded the corresponding phenolic $CpRe(CO)_3$ complex **12h** as a white/red semi-solid (22 mg, 86% yield): ^{1}H NMR (500 MHz, acetone-d_6) δ 0.75 (t, J = 7.6 Hz, 3H), 2.54 (qABq, J_{AB} = 15.2 Hz, ν_{AB} 78.0 Hz, J = 7.6 Hz, 2H), 6.15 (s, 1H), 6.66 (AA′XX′, J_{AX} = 8.9 Hz, 2H), 6.87 (AA′XX′, J_{AX} = 8.8 Hz, 2H), 6.89 (AA′XX′, J_{AX} = 8.8 Hz, 2H), 7.13 (AA′XX′, J_{AX} = 8.8 Hz, 2H), 7.19 (AA′XX′, J_{AX} = 8.6 Hz, 2H), 7.40 (AA′XX′, J_{AX} = 8.7 Hz, 2H), 8.52 (s, 1H), 8.62 (s, 1H), 8.64 (s, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 15.28, 18.91, 82.06, 104.53, 105.00, 109.72, 110.56, 114.99, 115.49, 115.62, 122.79, 122.84, 123.60, 130.60, 131.88, 134.65, 157.60, 157.66, 196.64. ν_{CO} (cm^{-1}) 2013, 1923. MS (EI) 640 (M^{+Re187}, 9), 638 (M^{+Re185}, 6), 612 (3), 610 (2), 578 (< 2), 552 (3), 550 (3), 71 (100). HRMS calcd for $C_{28}H_{21}O_6^{187}Re$ 640.0896, found 640.0890.

Molecular modeling

The protein structure used in the docking simulations was based on the X-ray crystallographic structure of the human estrogen receptor ligand binding domain bound to estradiol (1ere). Minimization was done as previously described with the program SYBYL 6.6 and the MMFF94 force field (Tripos, St. Louis, MO).[47] Cyclopentadiene **10 h** was overlayed onto the related furan and docked into the minimized receptor using the FlexiDock routine, and the receptor-ligand complex put through a minimization protocol as previously described.[47] $CpRe(CO)_3$ **12h** was constructed from the crystal structure of related structure **11g** (cf., Fig. 2). A single ethyl substituent was replaced by a *p*-hydroxyphenyl substituent and the structure minimized using the Tripos force field holding the CpRe core as an aggregate. The second enantiomer was built by reflecting the complex over a plane defined by the Cp ring. Both enantiomers were inserted into the minimized receptor by overlaying the A-ring of the CpRe complex onto that of the furan. The structures were minimized with the SYBYL anneal function holding the ligands as aggregates.

Acknowledgements

We are grateful for support of this research through research grants from the Department of Energy (DE FG02 86ER60401 and DE FG02 84ER60218). We thank Kathryn Carlson for assistance in binding assays and Scott ® Wilson for X-ray crystallography. NMR spectra were obtained in the Varian Oxford Instrument Center for Excellence in NMR Laboratory. Funding for this instrumentation was provided in part from the W. M. Keck Foundation, the National Institutes of Health (PHS 1 S10 RR104444-01), and the National Science Foundation (NSF CHE 96-10502). Mass spectra were obtained on instruments supported by grants from the National Institute of General Medical Sciences (GM 27029), the National Institutes of Health (RR 01575), and the National Science Foundation (PCM 8121494).

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