Synthesis and Screening of Mono- and Di-Aryl Technetium and Rhenium Metallocarboranes. A New Class of Probes for the Estrogen Receptor

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A series of mono and diaryl rhenium(I)-carborane derivatives were prepared using microwave heating and screened for their affinity for two isoforms of the estrogen receptor (ER). The rhenacarborane derivative $[(RR'C_2B_9H_9)Re(CO)_3]^-$ (R = p-PhOH, R′ = H), which was generated by taking advantage of a recently discovered cage isomerization process, and the neutral nitrosated analogue $[(RR'C_2B_9H_9)Re(CO)_2(NO)]$ (R = p-PhOH, R′ = H) showed the highest affinities of the compounds screened. As a result, the ^{99m}Tc analogue of one of the leads was produced in high yield (84%) and specific activity in a manner that is suitable for routine production in support of future preclinical and molecular imaging studies.

Introduction

The estrogen receptor (ER)[a] is an attractive target for molecular imaging and therapy due to its upregulation in osteoporosis, ovarian cancer, and breast cancer.[1] In the case of cancer, the ability to use molecular in vivo imaging to monitor the expression of the ER would offer a noninvasive means of classifying primary tumors, detecting metastases, guiding the optimal choice of therapy, and following the impact of novel interventions that are based on targeting the ER.[2]

To date, no ER targeted radiopharmaceuticals are in routine clinical use. Two compounds that have shown considerable promise are the positron emission tomography (PET) agent 16α-[^{18}F]-fluoro-17β-estradiol (FES) (Figure 1B), for which clinical trials have been reported, and the single photon emission computed tomography (SPECT) tracer, *cis*-methoxy-[^{123}I]-iodovinylestradiol (*cis*-MIVE) (Figure 1C), for which preclinical trials have been reported.[3] FES uptake in primary tumors is directly related to the level of ER expression and FES-PET scanning has shown a positive correlation between the presence of ER positive tumors and responses to hormonal therapy. *cis*-MIVE showed high affinity for the ER in human MCF-7 cells and rat uterus, as well as high target to nontarget tissue uptake in biodistribution studies. In spite of these results, the use of ^{18}F labeled compounds is limited to those centers located in close proximity to a cyclotron, while in the case of *cis*-MIVE, the radiopharmaceutical is not widely available, and because it is based on ^{123}I, it, like ^{18}F derivatives, is a costly agent to manufacture.

These limitations have spurred on a search for a suitable radiopharmaceutical derived from technetium-99m, the most widely used and cost-effective radionuclide in diagnostic medicine, that is capable of targeting the ER. To date, the majority of Tc-agents designed to target the ER have been prepared by derivatizing estradiol with a chelate designed to bind Tc(V) that is linked to either the 7α or 17α positions of the hormone.[4] As an alternative targeting strategy, Jaouen reported the inclusion of low oxidation state metal tricarbonyl fragments in the preparation of tamoxifen analogues and described their activity as selective estrogen receptor modulators.[5] Katzenellenbogen et al. synthesized and screened a series of $ArCpRe(CO)_3$ derivatives and identified potent binders of the ER (Figure 1D).[6] Unfortunately, the preparation of ^{99m}Tc analogues of these compounds under conditions suitable for routine clinical use is nontrivial. Issues in developing $CpTc(CO)_3$ derivatives of the type reported include the need to employ harsh reaction conditions, organic solvents, and HPLC to achieve high effective specific activity formulations. Furthermore, the fact that these complexes seem to exhibit notable nonspecific binding in vitro could affect possible target to nontarget ratios in vivo.

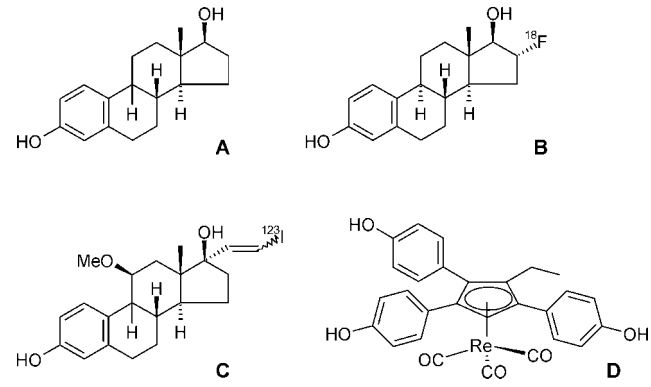

Figure 1. (A) Structure of 17β-estradiol (B) 16α-[^{18}F]-fluoro-17β-estradiol (FES) (C), *cis*-methoxy-[^{123}I]-iodovinylestradiol (*cis*-MIVE), and (D) an organometallic ER binding ligand.

Our group has shown that carboranes, which are carbon-containing polyhedral boron clusters, can be used as surrogates for cyclopentadienide derivatives. Technetium and rhenium metallocarboranes of the type $[(R_2C_2B_9H_9)M(CO)_3)]^-$ can be prepared in aqueous media in a single step in good yield.[7] Recently, we demonstrated that microwave-assisted heating can be used for rapid formation of rhena- and technacarboranes using clusters derivatized with a wide range of substituents.[8]

Carboranes can be considered as nonclassical bioisosteres for aryl rings. Endo et al. took advantage of this feature and recently

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[a] Abbreviations ER, estrogen receptor; PET, positron emission tomography; SPECT, single photon emission computed tomography; *cis*-MIVE, *cis*-methoxy-[^{123}I]-iodovinylestradiol; FES, 16a-[^{18}F]-fluoro-17β-estradiol; DCM, dichloromethane; RBA, relative binding affinity.

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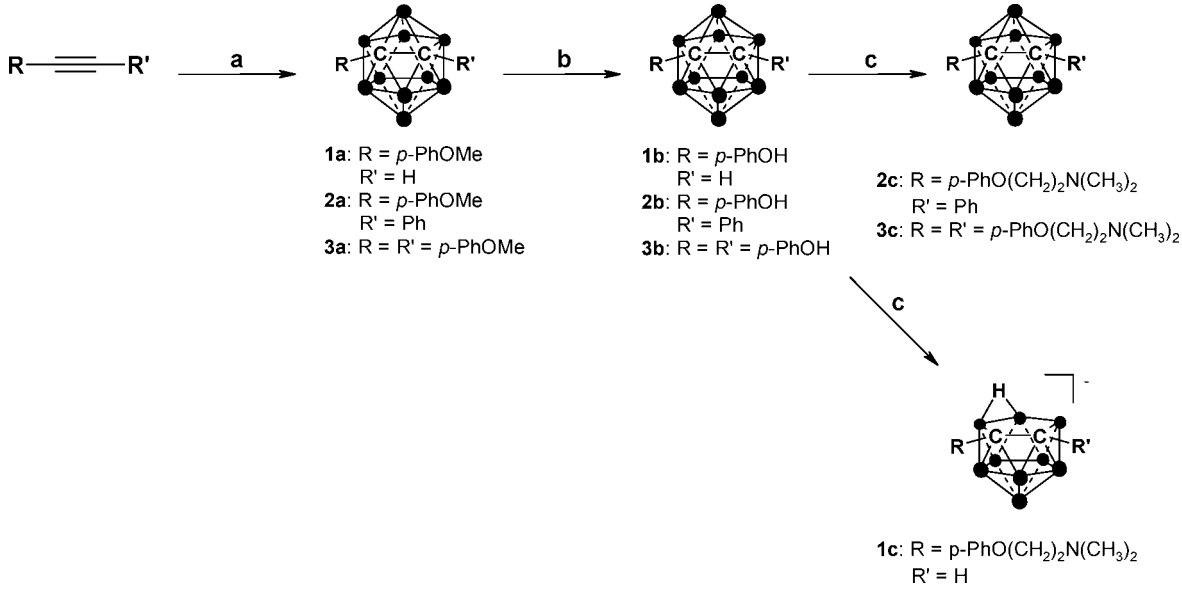
Scheme 1[a]



[a] (a) $B_{10}H_{14}$, MeCN, toluene, 110° C. (b) BBr_3, DCM, 25 °C. (c) NaOH, 2-chloro-*N*,*N*-dimethylethylamine hydrochloride, acetone 25 °C.

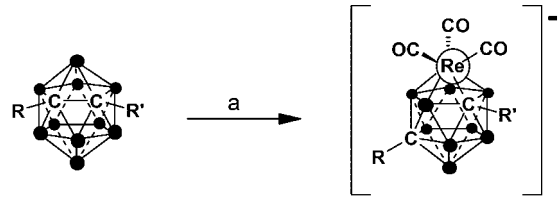
reported that certain aryl-substituted carboranes, like the Cp derivatives reported by Katzenellenbogen et al.,[6] are potent ligands for the ER.[9] Because the ER ligand binding domain has sufficient volume to accommodate the increased size that results when a boron vertex in a carborane is replaced with a $M(CO)_3$ (M = Tc, Re) moiety (approximately 70 Å^3), it should be feasible to develop ^{99m}Tc-based arylmetallocarboranes that can bind to the estrogen receptor with high affinity.[6] To test this hypothesis, a series of mono- and bis-arylated rhenacarboranes were synthesized, and their binding to both ERα and ERβ tested. Furthermore, the log *P* values for the target compounds were determined, and a method to produce the ^{99m}Tc analogue of one of the lead rhenacarborane complexes was developed.

Results and Discussion

Synthesis. The ability of a series of simple aryl-carborane derivatives to bind to the estrogen receptor was evaluated previously through the use of an ER-dependent luciferase reporter gene assay.[10] 1-Hydroxymethyl-12-(4-hydroxyphenyl)-1,12-dicarba-*closo*-dodecaborane elicited an ER-dependent transcriptional activity response greater than that of 17β-estradiol at subnanomolar ligand concentrations.[11] Through a structure–activity relationship (SAR) study, it was found that the 4-hydroxyphenyl substituent on the carborane cage was needed to achieve receptor binding, while the carborane cage mimicked the hydrophobic interactions that occurs between the C and D rings of estradiol and the ER ligand-binding domain. An analogous series of *ortho*-carborane ligands, which can form complexes with the $Re(CO)_3^+$ core, were synthesized according to the method shown in Scheme 1.

The 1,2-dicarba-*closo*-dodecaborane derivatives **1a**, **2a**, and **3a** were prepared using a conventional insertion reaction between decaborane and the corresponding alkyne. Consistent with literature reports, reactions proceeded in modest yield (30–44%) to generate air-stable white solids.[12] Subsequent demethylation of the methoxy groups with boron tribromide afforded the desired phenol-carboranes **1b**, **2b**, and **3b** in high yields. In an attempt to enhance receptor binding and to assess the importance of the free phenolic-OH moiety, conversion to the aminoalkylated analogues **1c**, **2c**, and **3c** was accomplished by combining the aryl-carboranes with 2-chloro-*N*,*N*-dimethylethylamine hydrochloride in the presence of a base. Because of the extended reaction time used to prepare **1c** (72 h), the *closo*-carborane product was converted by a base-mediated deboronation reaction to yield the corresponding *nido*-carborane, which was confirmed by ^{11}B NMR spectroscopy and high resolution mass spectrometry. No further attempts were made to produce the *closo*-carborane derivative due to the fact that the subsequent metalation with $Re(CO)_3$ proceeds equally well from both *closo*- and *nido*-carboranes.

Scheme 2[a]



1b: R = *p*-PhOH, R' = H
1c: R = *p*-PhO(CH$_2$)$_2$N(CH$_3$)$_2$, R' = H
2b: R = *p*-PhOH, R' = Ph
2c: R = *p*-PhO(CH$_2$)$_2$N(CH$_3$)$_2$, R' = Ph
3b: R = R' = *p*-PhOH
3c: R = R' = *p*-PhO(CH$_2$)$_2$N(CH$_3$)$_2$

1d: R = *p*-PhOH, R' = H
1e: R = *p*-PhO(CH$_2$)$_2$N(CH$_3$)$_2$, R' = H
2d: R = *p*-PhOH, R' = Ph
2e: R = *p*-PhO(CH$_2$)$_2$N(CH$_3$)$_2$, R' = Ph
3d: R = R' = *p*-PhOH
3e: R = R' = *p*-PhO(CH$_2$)$_2$N(CH$_3$)$_2$

[a] (a) $[Re(CO)_3(H_2O)_3]Br$, NaF, $EtOH_{(aq)}$, 15 min, 200 °C. Note that for the metal complexes, only the major structural isomer is shown.

We recently reported a new methodology to prepare η^5-carborane complexes of ^{99m}Tc(I) and Re(I) in aqueous media by employing microwave heating.[8] This direct synthetic approach allows for rapid conversion (<15 min) of a *closo*-carborane to the corresponding *closo*-rhenacarborane in good to excellent yields (Scheme 2). For the synthesis of the target rhenacarboranes, the corresponding *closo*-carboranes were combined with an excess of $[Re(CO)_3(H_2O)_3]Br$ in an aqueous ethanol solution and the mixtures heated to 200 °C for 15 min.

In the case of bulky groups or strong electron withdrawing functionalities directly linked or in conjugation to the bonding face of the carborane cage through one of the carbon atoms,

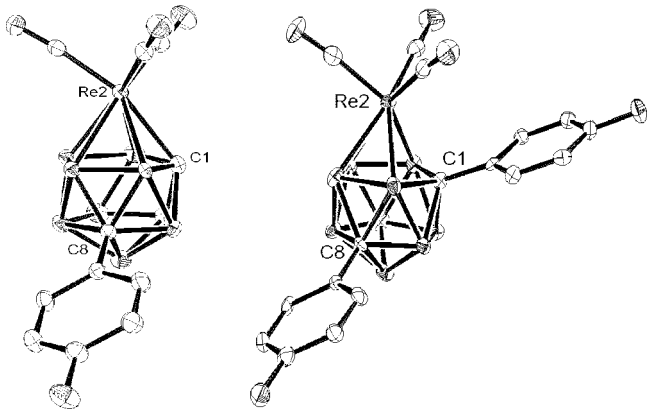


Figure 2. X-ray crystal structures of **1d** and **3d** showing 2,1,8-rhenacarboranes (50% thermal ellipsoids). The sodium counterions and hydrogen atoms were omitted for clarity.

we have shown that isomerization occurs in the microwave to give a 2,1,8-metallocarborane and not the 3,1,2-isomer.[13] The products **1d** and **3d** were recrystallized from methanol, and single crystals suitable for X-ray diffraction were obtained (Figure 2). The X-ray structure showed that the complexes obtained were the expected 2,1,8-isomers, where a cage carbon atom linked to an aryl group had migrated out of the bonding face of the η^5-carborane ligand. This is beneficial for the intended application of these compounds, as it reorients the hydroxyl groups in a more favorable relative orientation for binding to the ER according to the work of Endo et al.[9] It should be noted that this type of isomerization has been reported for other sterically hindered metallocarboranes[14] and has recently been reported for η^5-complexes of Re(I).[8]

To study the isomerization in bulk samples of **1d** and **3d** and for the remaining rhenacarboranes, NOE and 2-D NMR spectra were acquired. In the case of the monosubstituted aryl-rhenacarboranes **1d** and **1e**, there are two possible structural isomers; one in which the C-aryl group migrates and the other involves C−H migration. On the basis of integration of the crude ^{1}H NMR spectra, preferential migration of the C-substituted carbon atom out of the metal−carborane bonding face occurs in a 95:5 ratio in both examples (Figures 3 and 4). In the case of the homodisubstituted-*closo*-carboranes **3b** and **3c**, isomerization also occurred during the synthesis of the Re complexes, generating the corresponding rhenacarboranes **3d** and **3e**. Because both cage carbon atoms bear identical aryl substituents, enantiomeric 2,1,8 products are formed. The heterobis-substituted 2,1,8-*closo*-rhenacarboranes **2d** and **2e** were isolated as a mixture of 2,1,8-isomers due to the possibility of either cage carbon migrating out of the bonding face (Figure 5). Interestingly, despite the similarity in size between the two aryl groups, the structural isomers were not present in equal amounts. The substituted aryl group migrated preferentially (60:40, as determined by integration of signals in the ^{1}H NMR spectrum of the reaction mixture), suggesting that electronic effects also play a role in determining the preferred isomer. All reported isomeric ratios are based on NMR analysis of the crude reaction mixtures, as we observed that the amount of one isomer was often enhanced following purification due to fractionation during column chromatography. For the purpose of NMR characterization of the heterobis-substituted rhenacarboranes, isomer A refers to the cage carbon bearing the higher priority substituent migrating out of the rhenium−carborane bonding face, while isomer B corresponds to the carbon atom that bears the lower priority substituent migrating.

To determine if the mechanism of the rhenacarborane reaction involved stepwise formation of the 3,1,2 complex followed by isomerization or a concerted complexation/isomerization process, a NMR study of the conversion of monophenyl-*closo*-carborane to **1g** as a function of temperature was conducted (Scheme 3). A series of 15 min reactions were carried out at 10 °C increments between 100 and 200 °C using monophenyl-*closo*-carborane, $[Re(CO)_3(H_2O)_3]Br$ (1.5 equiv) and an excess of NaF in aqueous EtOH. The ^{1}H and ^{11}B NMR spectra of the reaction mixtures indicated that the initial step involves conversion of the *closo*-carborane to the corresponding *nido*-carborane with concomitant formation of BF_4^-. Conversion of the starting material to the *nido*-carborane is complete at 140 °C (Figure 6). There is no evidence of isomerization for either the *nido*-carborane ligand or the initial *closo*-complex prior to complexation. On the NMR time scale, it appears as though complexation and isomerization occur simultaneously to yield **1g**. For this ligand, complete consumption of the starting material is observed at temperatures above 190 °C.

The rhenacarborane complexes are anionic, which, despite the fact the negative charge is delocalized throughout the carborane cage, could have a detrimental influence on binding to the ER. To be able to probe the impact of the charge of the carborane complexes on ER binding, a neutral dicarbonylnitrosyl−rhenacarborane analogue of **1d** was prepared by replacing one CO ligand with an NO^+ ligand.[15]

The nitrosation reaction (Scheme 4) involved the addition of $NOBF_4$ to the tricarbonylrhenacarborane **1d** under inert atmosphere at −55 °C. The reaction mixture, which turned orange shortly after the addition of NO^+, was monitored carefully by TLC. Once the starting material had been consumed, the reaction was quenched by the addition of methanol. Purification by silica gel chromatography afforded a single 2,1,8 structural isomer **1f** in low yield (38% yield) but high purity. Subsequent recrystallization from dichloromethane produced single crystals suitable for X-ray analysis (Figure 7). The major byproduct was the result of nitration of the aromatic ring. Attempts to minimize this unwanted side product through the slow addition of a stoichiometric amount of $NOBF_4$ or decreased reaction temperature were unsuccessful. Use of alternative sources of NO^+, such as $NOHSO_4$ or $NaNO_2$, also did not improve the overall reaction yield. Absorbance spectra for **1f** recorded in water over the range 200–800 nm revealed an absorbance maximum at 228 nm, which has been ascribed to a metal-to-ligand charge transfer transition involving the $[NO^+]$ moiety.[16] Excitation at 300 nm resulted in a fluorescence emission maximum at 380 nm.

Screening. The X-ray data for **1b**, **1d**, **1f**, and **3d** can be used to determine the molecular volumes of the reported compounds to see whether or not the various carborane derivatives are of an appropriate size to fit in the ligand binding domain of the ER.[17] As expected, the monosubstituted *closo*-carborane **1b** was found to be the smallest ligand with a volume of 221.14 Å^3. Introduction of the $Re(CO)_3$ core (**1d**) resulted in an increase in size of the carborane moiety by approximately 70 Å^3 to 288.80 Å^3. Exchange of a carbonyl ligand with a nitrosyl ligand resulted in a very small (0.6%) increase in molecular volume to 290.57 Å^3. The ER ligand binding pocket has an accessible volume of approximately 450 Å^3, with the native substrate 17β-estradiol occupying somewhat more than half, at 245 Å^3.[18] The monosubstituted complexes are of comparable size and would therefore be expected to fit into the ER binding pocket. The larger, bis-substituted analogue **3d** has a volume of 367.69 Å^3, which is still well within the overall size limitations of the ligand binding domain.

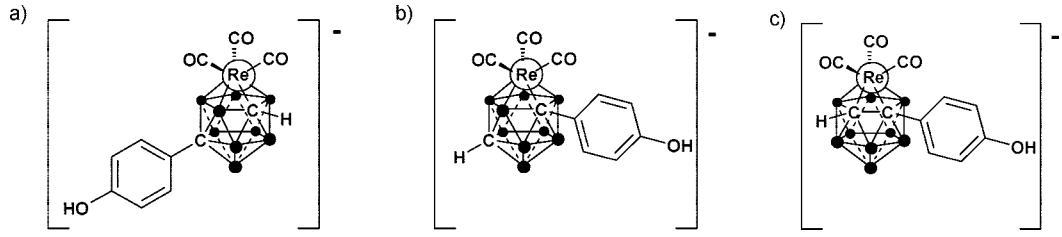


Figure 3. The major (a) and minor (b) structural 2,1,8-isomers of **1d**. The 3,1,2-isomer (c) was not detected.

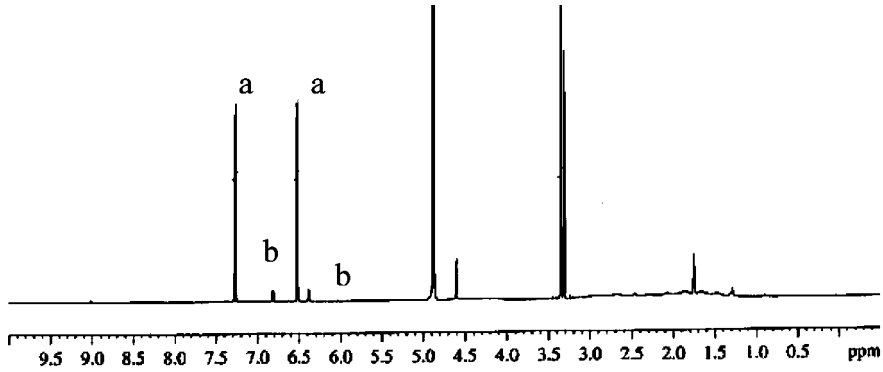


Figure 4. ^{1}H NMR of the reaction mixture containing **1d** (CD_3OD, 700 MHz). The labelled peaks correspond to the protons on the aryl groups of the major (a) and minor (b) 2,1,8-rhenacarborane isomers.

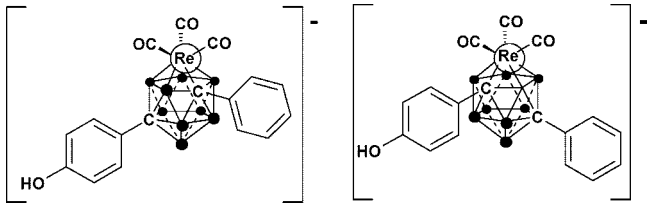


Figure 5. Two (2,1,8) isomers of **2d** (the corresponding enantiomers are not shown).

Determination of log *P* Values by HPLC. High binding affinity for ER requires the appropriate orientation and number of hydrogen bonding functionalities and a suitably hydrophobic group.[19] To get a sense of the change in lipophilicity upon substitution of a BH vertex with the $Re(CO)_3^+$ core, the log *P* values for all compounds reported were measured by HPLC.[20,29] The determination of partition coefficients by HPLC has the advantage of speed of determination and applicability to compounds having log *P* values above 4.

In the preliminary measurement and calculation, we found a linear correlation between the retention parameters and the methanol concentration in the mobile phase for both *closo*-carboranes and the rhenacarboranes. The capacity factor, log k'_w, at 100% water was estimated for each compound by extrapolation of the data generated by plotting log k' versus the percent methanol content. The log k'_w values were plotted in turn against the log *P* values of known standards. The retention data and calculated log *P* values of reference compounds, *closo*-carboranes and rhenacarboranes are given in Table 1.

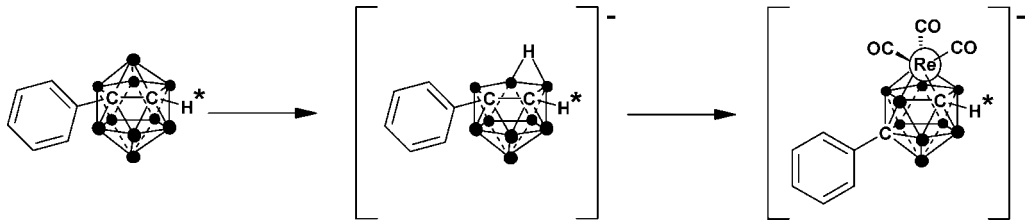
With the exception of the one *nido*-carborane, **1c**, all of the complexes are lipophilic, having log *P* values greater than 4.9. The log *P* measured for **1b** was 5.75, which is identical to the previously reported value.[19] These log *P* values are also similar to those reported by Katzenellenbogen for a series of cyclopentadienyl metal tricarbonyl substituted β-estradiol analogues that exhibited estrogen receptor binding affinity.[21] For the isomeric mixtures of the heterobisaryl substituted complexes **2d** and **2e**, the log *P* values for both structural isomers are reported. In all cases but one, the *closo*-carboranes exhibited higher log *P* values than that of the corresponding rhenacarborane analogues. Furthermore, aminoalkyl functionalization of the phenol OH moiety results in a lowering of the observed log *P* values for the monosubstituted compounds, whereas a small increase in lipophilicity is observed for the bis-substituted compounds **2e**, **3c**, and **3e**. Transformation of the anionic rhenacarboranes **1d** to the neutral analogue **1f** through the replacement of a CO ligand with an NO^+ ligand resulted in an increase in the log *P* value by 0.68 units.

ER Binding Affinity. The binding affinities of *closo*-carboranes and rhenacarboranes were determined using [^{3}H]-estradiol and a standard radiometric assay.[31] Initially, a prescreen was run to identify promising ligands for ERα and ERβ (Table 2). For these experiments, 1.13 nM [^{3}H]-estradiol was employed and the percentage of [^{3}H]-estradiol displaced for each compound at 1 μM concentration was determined and expressed relative to that of the positive and negative controls (estradiol and nicotine respectively).

The phenolic-*closo*-carboranes **1b**, **2b**, and **3b** caused pronounced displacement of [^{3}H]-estradiol from both forms of the estrogen receptor (765 to 100% displacement). It has been reported previously that **1b** showed high binding affinity toward the ER with a relative binding affinity (RBA) of 2.85%.[19] Interestingly, conversion of the monophenol-*closo*-carborane to the tricarbonylrhenacarborane (**1b** to **1d**) did not dramatically alter the binding affinity as determined during this prescreen (ERα; 84% to 78%, ERβ; 100% to 89%). However, for the larger bis-substituted analogues, **2b** and **3b**, metalation of the carborane with the $Re(CO)_3$ moiety significantly diminished the affinity.

On the basis of the results of the prescreening studies, select compounds were investigated in greater detail using competitive radiometric binding assays over a large range of ligand concentrations. The binding values were obtained from a

Scheme 3[a]



[a] Conversion of monophenyl-*closo*-carborane to sodium *rac*-8-phenyl-2,2,2-tricarbonyl-2-rhenium-2,1,8-dicarba-*closo*-dodecaborate **1g**.

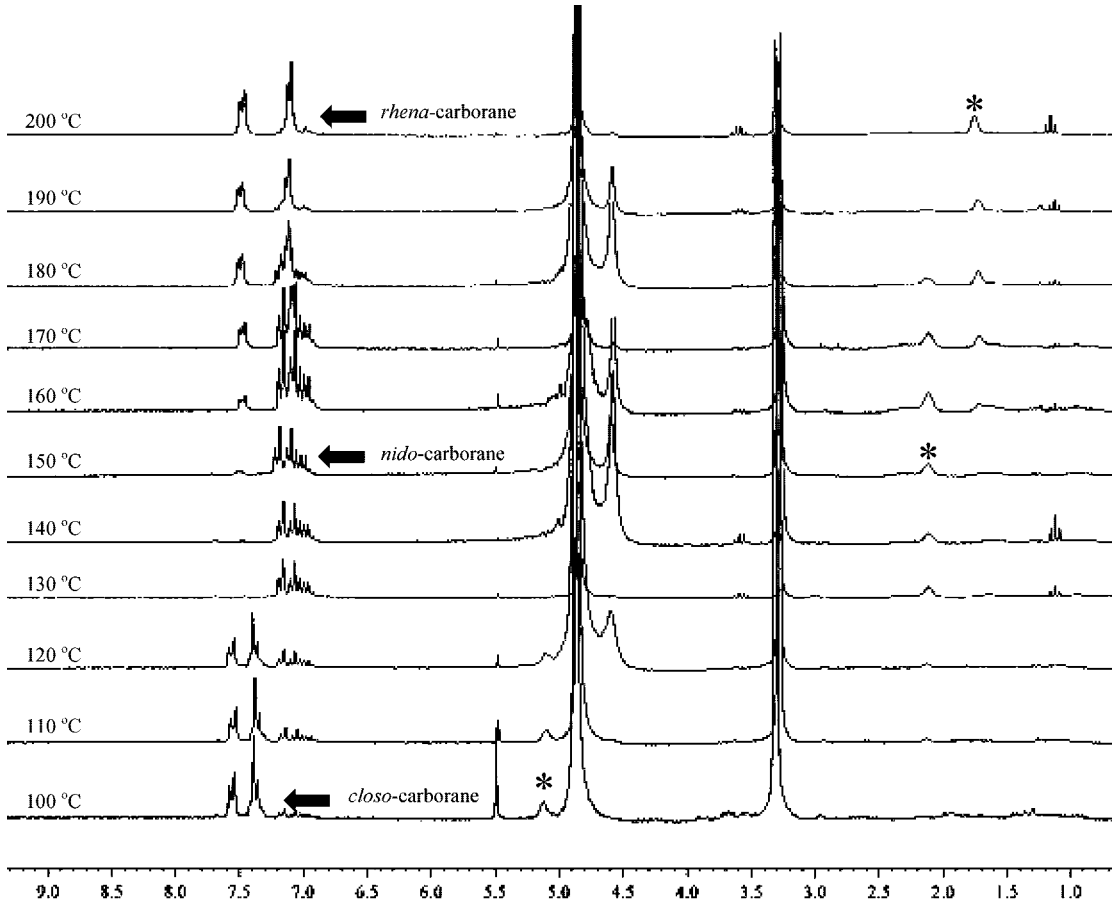
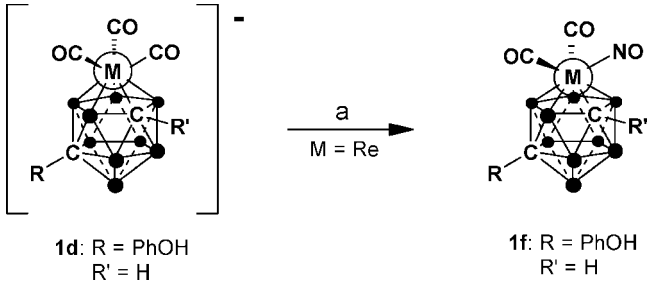


Figure 6. ^{1}H NMR spectra of samples taken from reactions of monophenyl-*closo*-carborane with $[Re(CO)_3(H_2O)_3]Br$ in a microwave reactor at different temperatures (increasing from bottom to top). A star (*) indicates carborane−CH proton resonances.

Scheme 4[a]



1d: R = PhOH
R' = H

1f: R = PhOH
R' = H

[a] (a) $NOBF_4$, THF, −55 °C.

competitive radiometric binding assay, using 1.13 nM [^{3}H]-estradiol as the tracer for both ERα and ERβ. The values are expressed as relative binding affinities (RBAs), in percent, with β-estradiol having an affinity of 100%, and are presented in Table 3. The monophenol-*closo*-carborane **1b** showed RBA values of 3.9% and 4.8% for ERα and ERβ respectively. The *closo*-bis-substituted phenol **3b** exhibited a greater potency (11.8% ERα; 12.3% ERβ) than the corresponding monosubstituted analogue, which is consistent with what has been reported previously.[22] A comparison of mono- and bis-phenol substituted rhenacarboranes **1d** and **3d** was inconclusive as neither complex exhibited significantly greater binding affinity.

The Re complex **1d** retained affinity for the ER however replacing a boron vertex with the $Re(CO)_3^+$ core resulted in a significant decrease in the relative binding affinities of roughly 25- and 10-fold for ERα and ERβ, respectively (RBA values of 0.16% and 0.55% for ERα and ERβ, respectively), as compared to the monophenol-*closo*-carborane analogue **1b**. Interestingly, replacement of a CO ligand with an NO^+ ligand, compound **1f**, exhibited a pronounced improvement in the RBA values for both ERα and ERβ (2.9% and 3.01%, respectively), as compared to the $Re(CO)_3$ compound **1d**. These values are similar to the RBA values observed for the neutral monophenol-*closo*-carborane **1b** (3.9%, 4.8%). When comparing ERα and

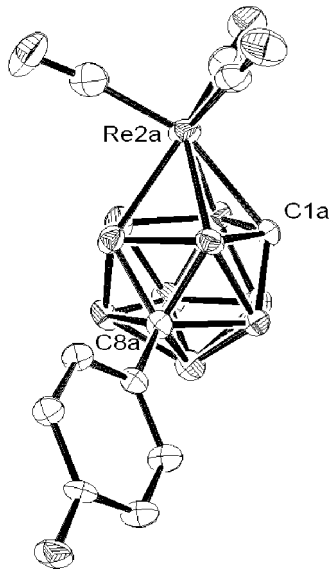


Figure 7. X-ray crystal structure of **1f** (50% thermal probability ellipsoids) with hydrogen atoms omitted for clarity. Because of 3-fold positional disorder, the nitrosyl and carbonyl ligands were not defined in the structure.

ERβ affinities for **1b**, **1d**, **1f**, and **3b**, modest selectivity for the β-receptor was observed, which is consistent with reports on $ArCpRe(CO)_3$ derivatives.[6]

Radiolabeling Arylcarboranes with Technetium-99m. A method to produce the ^{99m}Tc analogue of **1d**, which is the key precursor to the potent nitrosated product **1f**, was developed. A report detailing the synthesis of **1f**, including a description of the factors that impact the yield of the nitrosation reaction and the various reagents used to generate the product, will be reported elsewhere.

The preparation of ^{99m}Tc-**1d** was performed using microwave heating from the monophenol-*closo*-carborane **1b**. A modification to our reported procedure was used which involved the in situ formation of the *nido*-carborane by heating **1b** at 200 °C for 15 min in the presence of sodium fluoride prior to the addition of the metal. $[^{99m}Tc(CO)_3(H_2O)_3]^+$ was added and the reaction mixture heated in the microwave at 200 °C for 5 min.[23] The desired product ^{99m}Tc-**1d** was isolated using a reverse phase C18 Sep-Pak cartridge in greater than 80% radiochemical yield. The γ-HPLC of ^{99m}Tc-**1d** (Figure 8) was identical to that of the analogous rhenium complex including the presence of a peak corresponding to the minor structural isomer associated with migration of the carborane CH group. The excess starting material and small amount of residual $^{99m}TcO_4^-$ present in the reaction mixture was removed by solid phase extraction, giving the product in high effective specific activity.

In an effort to further examine the effect of temperature on the coordination/ isomerization of the metallocarboranes, we repeated the above experiment by decreasing the reaction temperature from 200 to 100 °C by 25 °C increments (Figure 9). As the reaction temperature is decreased, the peaks in the γ-HPLC around 12.5 min associated with the major and minor isomers diminish, while a new peak at 11.0 min appears. The structure of the compound giving rise to this peak, which is the major product at 100 °C, is unknown. One possibility is that it corresponds to 3,1,2-monophenol-*closo*-technacarborane. Efforts to confirm this hypothesis are ongoing through the synthesis and characterization of macroscopic amounts of authentic standards using the long-lived isotope, ^{99}Tc.

Conclusions

A series of arylcarboranes and the corresponding rhenacarboranes were prepared and their affinities for ERα and ERβ determined. In the case of monoarylated ligands, the corresponding rhenacarboranes retain the ability of the parent *closo*-carboranes to bind to the estrogen receptor. In the case of metallocarborane **1f**, conversion to the neutral complex by exchanging a CO ligand for a NO^+ ligand, produced a modestly potent substrate with relative binding affinities of 2.9% and 3.01% for ERα and ERβ, respectively. The ^{99m}Tc analogue of **1d** can be prepared in high radiochemical yield and effective specific activity from a readily accessible technetium starting material in a single step. On the basis of the promising in vitro binding affinities reported here, assessing the target to nontarget selectivity of these lead complexes for the ER and evaluating their distribution in animal models of breast cancer remains work in progress.

Experimental Section

General. Unless otherwise noted, all nonaqueous reactions were carried out using commercial grade solvents and reagents under nitrogen that had been passed through drierite. Acetone was dried over molecular sieves prior to use. Chemicals were purchased from Sigma-Aldrich and used without further purification. Reactions requiring microwave heating were performed using a Biotage Initiator Sixty instrument. $[Re(CO)_3(H_2O)_3]Br$ was prepared according to a literature procedure.[24] ^{1}H, ^{13}C, and ^{11}B NMR spectra were recorded on Bruker AV700, Bruker DRX500, or Bruker AV200 spectrometers. ^{1}H chemical shifts are reported in ppm relative to the residual proton signal of the NMR solvents. Coupling constants (J) are reported in Hertz (Hz). For the ^{1}H NMR assignments of aromatic groups, ortho and meta labels are with respect to the carbon atom attached to the carborane. ^{13}C chemical shifts are reported in ppm relative to the carbon signal of the solvents. ^{11}B chemical shifts are reported in ppm relative to an external standard of $BF_3 \cdot Et_2O$. Low resolution mass spectra were obtained on a Waters/Micromass GCT-ToF instrument using electron impact ionization or a Waters/Micromass Quattro Ultima spectrometer using electrospray type ionization. High resolution mass spectra were obtained on a Waters/Micromass Q-ToF ultimaglobal spectrometer. Infrared spectra were obtained on a Bruker Tensor 27 FTIR spectrometer. Purification of all products was achieved by flash chromatography or by using a Biotage SP1 automated purification system. Flash chromatography was performed using Ultrapure Silica Gel from Silicycle (70–230 mesh). Analytical HPLC was performed using a Varian Pro Star model 330 PDA detector, model 230 solvent delivery system, and a C-18 Nucleosil column (4.6 mm × 250 mm). The elution protocols used were as follows: HPLC method A: solvent A = methanol, solvent B = triethylammonium phosphate buffer (5.5 mL of conc o-H_3PO_4 + 7 mL of NEt_3 in 1 L of H_2O): Gradient elution 0–3 min, 0% A; 3–6 min 25% A; 6–9 min 33% A; 9–20 min 100% A; 20–22 min 100% A; 22–25 min 0% A; 25–30 min 0% A. HPLC method B: solvent A = acetonitrile (0.1% TFA), Solvent B = H_2O (0.1% TFA): Gradient elution starting at 50% A to 90% A over 30 min. All analytical HPLC experiments were monitored at 254 using a flow rate of 1.0 mL min^{-1}.

Crystallographic Details. X-ray crystallographic data for **1b**, **1d**, **1f**, and **3d** were collected from single crystals mounted on glass fibers, or in paratone oil in a cryoloop. Data was collected at 173 K in all cases on a Bruker P4 diffractometer equipped with a Bruker SMART 1K CCD area detector (using the program SMART[25]) and a rotating anode utilizing graphite-monochromated Mo Kα radiation (λ = 0.710 73Å). Data processing was carried out by use of the program SAINT,[26] while the program SADABS[27] was utilized for

Table 1. Retention Data and Calculated log *P* Values for the Reference Compounds, *closo*-Carboranes and Rhenacarboranes[a]

compound	log P[b]	% organic modifier: log k'[c] 80	75	70	65	60	log k'_w 0	R^2	log *P* calcd
phenol	1.46	−0.720	−0.636	−0.533	−0.417	−0.302	0.955	0.990[f]	1.33
2-cresol	1.95	−0.554	−0.410	−0.292	−0.163	−0.034	1.510		2.02
4-cresol	1.94	−0.573	−0.451	−0.316	−0.192	−0.054	1.500		2.01
4-chlorophenol	2.39	−0.469	−0.335	−0.186	−0.047	0.096	1.797		2.38
4-phenylphenol	3.20	−0.211	−0.051	0.112	0.291	0.471	2.510		3.26
2,4,6-trichlornol	3.69	0.043	0.207	0.383	0.562	0.717	2.765		3.58
diphenyl ether	4.20	0.209	0.401	0.602	0.816	1.009	3.431		4.41
pentachlorophenol	5.12	0.521	0.723	0.940	1.151	1.353	3.870		4.95
1b		0.176	0.428	0.716	0.985	1.313	4.514	0.999	5.75
1c[d]		−1.423	−1.104	−0.849	−0.599	−0.359	2.819	0.997	3.65
1d		−0.609	−0.321	0.031	0.315	0.664	4.383	0.998	5.59
1e		−0.427	−0.206	0.093	0.373	0.688	3.872	0.996	4.96
1f		0.307	0.575	0.871	1.173	1.497	4.928	0.999	6.27
2b		0.534	0.885	1.220	1.577	−0.359	6.074	1.000	7.69
2c		0.137	0.540	0.809	1.148	1.920	5.447	0.994	6.91
2d[e]		−0.449	−0.138	0.166	0.526	0.834	4.711	0.998	6.00
		−0.473	−0.255	0.163	0.505	0.820	4.848	0.987	6.17
2e[e]		−0.359	−0.008	0.275	0.633	0.950	4.863	0.998	6.19
		−0.350	−0.001	0.287	0.649	0.966	4.913	0.998	6.25
3b		0.329	0.602	0.922	1.245	1.541	5.221	0.999	6.63
3c		0.174	0.462	0.785	1.151	1.457	5.361	0.997	6.81
3d		−1.141	−0.724	−0.442	−0.092	0.257	4.370	0.995	5.57
3e		−1.356	−1.122	−0.670	−0.143	0.201	5.113	0.974	6.50

[a] Compound numbering is given in schemes 2 and 4. [b] Values cited in the OECD guidelines.[20,30] [c] The capacity factor k is given by $k = (t_R - t_o)/t_o$ [d] **1c** is a *nido*-carborane [e] Log P determinations for both 2,1,8-rhenacarborane isomers are given [f] R^2 value for the calibration curve

Table 2. Percent [^{3}H]-Estradiol Displaced in the Prescreen Assays for *closo*-Carboranes (**1b**, **1c**, **2b**, **2c**, **3b**, **3c**) and Rhenacarboranes (**1d**, **1e**, **1f**, **2d**, **2e**, **3d**, **3e**) to ERα and ERβ[a]

compound	% [^{3}H]-estradiol displaced: ERα	ERβ
estradiol	±>100	100
1b	84 ± 1.6	100 ± 6.6
1c	3 ± 4.3	24 ± 5.0
1d	78 ± 3.5	89 ± 7.4
1e	47 ± 8.1	13 ± 5.2
1f		90 ± 7.6
2b	76 ± 5.2	79 ± 2.5
2c	24 ± 11.8	85 ± 3.2
2d	29 ± 2.6	43 ± 1.4
2e	31 ± 1.4	10 ± 2.8
3b	90 ± 9.8	84 ± 3.5
3c	32 ± 9.1	88 ± 6.1
3d	68 ± 4.5	38 ± 6.7
3e	21 ± 8.6	29 ± 3.9

[a] Compound numbering is given in Schemes 2 and 4.

Table 3. Relative Binding Affinities (RBA β-estradiol = 100%) for Select *closo*-Carboranes and Rhenacarboranes[d]

compound	RBA ERα[a]	K_i (nM)	RBA ERβ[a]	K_i (nM)
1b	3.93 ± 0.06	8.82	4.84 ± 0.18	10.2
1c	*b*		0.79 ± 0.03	131
1d	0.16 ± 0.01	215	0.55 ± 0.02	109
1f	2.94 ± 0.07	11.30	3.01 ± 0.13	16.9
3b	11.83 ± 0.06	4.65	12.30 ± 0.16	4.9
3d	0.11 ± 0.01	1003	*c*	

[a] Competitive radiometric binding assays were done in triplicate with purified full-length human ERα and ERβ (Pan Vera Inc.), using hydroxyapatite and 1.13 nM [^{3}H]estradiol. Compound numbering is given in Schemes 2 and 4. [b] Not done due to an initial screen [^{3}H]-estradiol displacement of 3% at 10^{-6} M. [c] Not done due to an initial screen [^{3}H]-estradiol displacement of 38% at 10^{-6} M. [d] K_d for ERα was determined to be 1.10 nM; K_d for ERβ was determined to be 1.04 nM.

the scaling of diffraction data, the application of a decay correction, and an empirical absorption correction based on redundant reflections. The structures were solved by using the direct methods or Patterson heavy-atom methods procedure in the Bruker SHELXTL[28] program library and refined by full-matrix least-squares methods on F^2. All nonhydrogen atoms were refined using anisotropic thermal parameters and hydrogen atoms were determined using the difference map and refined using isotropic thermal parameters.

1-(4-Methoxyphenyl)-1,2-dicarba-*closo*-dodecaborane (1a). Acetonitrile (10 mL) was added to a stirred solution of decaborane (0.507 g, 4.12 mmol) in toluene (40 mL) and the mixture was heated to reflux under nitrogen for 3 h. The orange solution was cooled to room temperature and ethynylanisole (0.55 mL, 6.23 mmol) was added. The reaction mixture was heated to reflux overnight producing a deep-orange colored solution. The solution was cooled and the solvent removed under reduced pressure to give an orange solid. The desired product was isolated by silica gel column chromatography (66% ethyl acetate:33% hexanes) to afford **1a** (0.46 g, 44% yield) as an off-white solid; mp 105–107 °C; TLC R_f 0.48 (hexanes:ethyl acetate; 4:1); FTIR (KBr, cm^{-1}): ν 2594, 2573. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.42 (d, ^3J = 8.6 Hz, 2 H, C_{meta}-*H*), 6.82 (d, ^3J = 8.6 Hz, 2 H, C_{ortho}-*H*), 3.86 (br s, 1 H, $C_{carborane}$-*H*), 3.81 (s, 3 H, OCH_3), 3.65–0.80 (br m, B-*H*). ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ: 160.89, 129.40, 125.68, 114.14, 61.12, 55.59. ^{11}B{^{1}H} (160 MHz, $CDCl_3$) δ: −2.30, −5.13, −9.50, −11.02, −11.85, −13.10. HRMS (EI) calcd for $C_9H_{18}B_{10}O$, 252.2288 (M^+); found, 252.2281.

1-(4-Hydroxyphenyl)-1,2-dicarba-*closo*-dodecaborane (1b). Compound **1a** (0.438 g, 1.75 mmol) in DCM (15 mL) was cooled to −78 °C under nitrogen. BBr_3 (7 mmol, 1 M in DCM) was added dropwise and the reaction mixture allowed to warm slowly to room temperature overnight. The solvent was subsequently removed by passing a flow of nitrogen gas over the solution. The flask was cooled in an ice bath and THF (12 mL) was added. The solution was warmed to room temperature over 30 min before the solvent was again removed by passing nitrogen gas over the top of the sample. The flask was cooled in an ice bath, and 12 mL of methanol was added. The mixture was warmed to room temperature over 30 min before the solvent was removed under reduced pressure, yielding an off-white solid. The desired product was isolated by silica gel chromatography (10% ethyl acetate: 90% hexanes to 20% ethyl acetate:80% hexanes) as a white solid (0.37 g, 90%); mp 104–107 °C; TLC R_f 0.64 (hexanes:ethyl acetate; 1:1); FTIR (KBr, cm^{-1}): ν 3218, 2597, 2580. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.39 (d, ^3J = 8.0 Hz, 2 H, C_{meta}-*H*), 6.77 (d, ^3J = 8.0 Hz, 2 H, C_{ortho}-

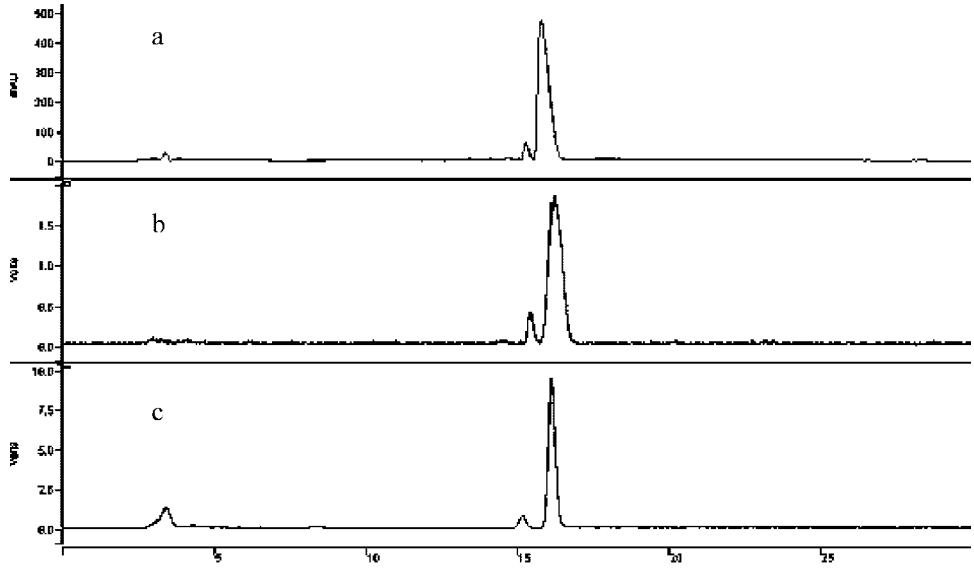


Figure 8. (a) UV-HPLC trace of Re-**1d** (b) γ-HPLC trace of purified ^{99m}Tc-**1d** (c) γ-HPLC trace of the crude reaction mixture containing ^{99m}Tc-**1d**. The two peaks in the purified product correspond to the two isomers (HPLC method A).

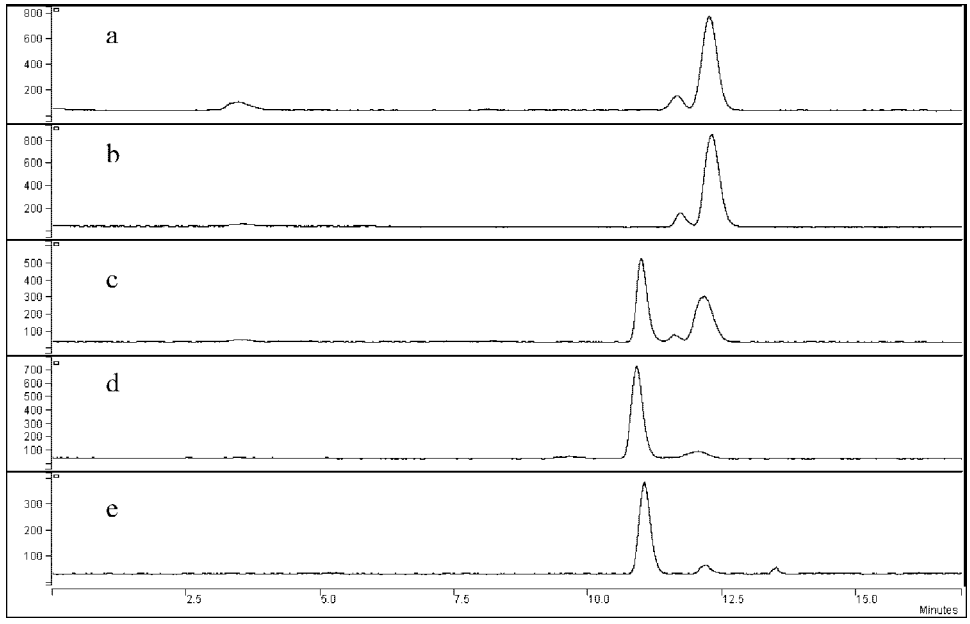


Figure 9. γ-HPLC traces of the products formed when **1b** was heated in a microwave with $[^{99m}Tc(CO)_3(OH_2)_3]^+$ at: (a) 200 °C, (b) 175 °C, (c) 150 °C, (d) 125 °C, and (e) 100 °C (HPLC method B).

H), 5.18 (br s, 1 H, O*H*), 3.88 (br s, 1 H, $C_{carborane}$-*H*), 3.65–0.80 (br m, B-*H*). $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$) δ: 156.89, 129.68, 126.02, 115.64, 76.80, 61.11. ^{11}B $\{^1H\}$ (160 MHz, $CDCl_3$) δ: −2.41, −5.19, −9.58, −11.14, −11.96, −13.19. HRMS (EI) calcd for $C_8H_{16}B_{10}O$, 238.2132 (M^+); found, 238.2128.

Sodium 7-(4-(*N,N*-Dimethylamino)ethoxyphenyl)-1,2-dicarba-*nido*-undecaborate (1c). Compound **1b** (0.233 g, 0.99 mmol) in acetone (20 mL), sodium hydroxide (0.2g, 5 mmol), and 2-chloro-*N,N*-dimethylethylamine hydrochloride (0.165 g, 1.05 mmol) were dissolved in acetone (20 mL). The solution was heated to reflux for 72 h before allowing the mixture to cool to room temperature. The solvent was removed under reduced pressure, yielding an off-white solid. The desired product was isolated by silica gel chromatography (20% methanol:80% dichloromethane) as a white solid (0.28 g, 93%); mp 210–212 °C; TLC R_f 0.32 (dichloromethane:methanol; 9:1); FTIR (thin film, cm^{-1}) ν: 3447, 2518. ^1H NMR (200 MHz, CD_3OD) δ: 7.11 (d, ^3J = 8.2 Hz, 2 H, C_{meta}-*H*), 6.70 (d, ^3J = 8.2 Hz, 2 H, C_{ortho}-*H*), 4.11 (t, ^3J = 5.1 Hz, 2 H, OCH_2), 3.02 (t, ^3J = 5.1 Hz, 2 H, NCH_2), 2.55 (s, 6 H, CH_3), 2.10 (br s, 1 H, $C_{carborane}$-*H*), 3.6–0.8 (br m, B-*H*). $^{13}C\{^1H\}$ NMR (50 MHz, acetone-d_6) δ: 155.92, 141.05, 128.77, 114.48, 63.10, 57.60, 44.20. $^{11}B\{^1H\}$ (160 MHz, acetone-d_6) δ: −8.60, −10.16, −13.46, −16.76, −17.48, −19.32, −22.15, −32.48, −35.67. HRMS (ES^-) calcd for $C_{12}H_{25}B_9ON$, 298.2897 (M^-); found, 298.2948.

Sodium *rac*-8-(4-Hydroxyphenyl)-2,2,2-tricarbonyl-2-rhenium-2,1,8-dicarba-*closo*-dodecaborate (Isomer A) (1d). Compound **1b** (85.2 mg, 0.36 mmol) was combined with sodium fluoride (155 mg, 3.6 mmol) and $[Re(CO)_3(H_2O)_3]Br$ (298 mg, 0.72 mmol) as a dry solid mixture in a 5 mL Emry's microwave vial. Aqueous ethanol (12% v/v, 4 mL) was added and the reaction vessel crimp-sealed. The reaction mixture was heated at 200 °C for 15 min with stirring. After cooling to room temperature, the solvent was removed by passing air over the aqueous mixture, producing an amber-colored oil. The oil was dissolved in a minimum of methanol and the desired product isolated by silica gel column chromatography (4% methanol:96% dichloromethane to 32% methanol:68% dichlo-

romethane) as an amber-colored oil (129 mg, 72% yield). The oil solidified upon standing under ambient laboratory conditions, resulting in crystals that were suitable for X-ray diffraction studies; mp (decomposed >240 °C); TLC R_f 0.28 (16% methanol:84% dichloromethane); FTIR (KBr, cm^{-1}) ν: H 2598, 2570, 2543, 2520, 1995, 1883. ^{1}H NMR (700 MHz, CD_3OD) δ: 7.27 (d, ^3J = 8.4 MHz, 2 H, C_{meta}-*H*), 6.52 (d, ^3J = 8.4 MHz, 2 H, C_{ortho}-*H*), 1.75 (s, 1 H, $C_{carborane}$-*H*), 3.4–1.0 (br m, B-*H*). ^{13}C{^{1}H} NMR (176 MHz, CD_3OD) δ: 200.65, 156.74, 135.53, 130.63, 114.76, 57.47, 29.08. ^{11}B{^{1}H} NMR (160 MHz, CD_3OD) δ: −4.90, −7.22, −7.95, −9.31, −11.95, −18.45, −19.92. HRMS (ES^-) calcd for $C_{11}H_{15}B_9O_4Re$, 495.1422 (M^-); found, 495.1458.

Sodium *rac*-8-(4-(*N*,*N*-Dimethylamino)ethoxyphenyl)-2,2,2-tricarbonyl-2-rhenium-2,1,8-dicarba-*closo*-dodecaborate (Isomer A) (1e). Compound **1c** (99.7 mg, 0.32 mmol) was combined with sodium fluoride (163 mg, 3.8 mmol) and $[Re(CO)_3(H_2O)_3]Br$ (195 mg, 0.48 mmol) as a dry solid mixture in a 5 mL Emry's microwave vial. Aqueous ethanol (12% v/v, 4 mL) was added and the reaction vessel was crimp-sealed. The reaction mixture was heated at 200 °C for 15 min with stirring. The solvent was then removed by passing air over the aqueous mixture, yielding an amber colored oil. The oil was dissolved in a minimum of methanol and the desired product isolated by silica gel column chromatography (4% methanol: 96% dichloromethane to 32% methanol: 68% dichloromethane) as an amber-colored oil, (102 mg, 54% yield). The oil solidified upon standing under ambient laboratory conditions; mp (decomposed >240 °C); TLC R_f 0.26 (dichloromethane:methanol; 6:1); FTIR (KBr, cm^{-1}) ν: H 2536, 1997, 1890. ^{1}H NMR (700 MHz, CD_3OD) δ: 7.43 (d, ^3J = 8.9 MHz, 2 H, C_{meta}-*H*), 6.77 (d, ^3J = 8.9 MHz, 2 H, C_{ortho}-*H*), 4.27 (t, ^3J = 4.9 Hz, 2 H, OCH_2), 3.52 (t, ^3J = 4.9 Hz, 2 H, NCH_2), 2.93 (s, 6H, CH_3), 1.77 (s, 1 H, $C_{carborane}$-*H*), 3.4–1.0 (br m, B-*H*). ^{13}C{^{1}H} NMR (176 MHz, CD_3OD) δ: 200.51, 157.53, 138.26, 130.98, 114.33, 63.14, 57.84, 43.92, 29.08. ^{11}B{^{1}H} NMR (160 MHz, CD_3OD) δ: −4.87, −7.81, −11.70, −18.31, −19.85. HRMS (ES^-) calcd for $C_{15}H_{24}B_9O_4NRe$, 567.2147 (M^-); found, 567.2142.

***Rac*-8-(4-Hydroxyphenyl)-2,2-dicarbonyl-2-nitrosyl-2-rhenium-2,1,8-dicarba-*closo*-dodecaborate (1f).** Compound **1d** (0.26 g, 0.48 mmol) in THF (30 mL) was cooled to −55 °C under argon. $NOBF_4$ (60 mg, 0.52 mmol) was added to the reaction flask and the mixture was stirred for 1 h, during which time the reaction mixture turned orange. The solvent was removed under reduced pressure, leaving a yellow solid that was dissolved in a minimum of methanol, and the desired product was isolated by silica gel column chromatography (4% methanol:96% dichloromethane to 32% methanol:68% dichloromethane) as a yellow solid (91 mg, 38%). Single crystals suitable for X-ray diffraction were obtained by slow evaporation of a concentrated dichloromethane solution; mp (140 °C); TLC R_f 0.30 (dichloromethane); FTIR (KBr, cm^{-1}) ν: H 3364, 2585, 2083, 2027, 1990, 1774. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.35 (d, ^3J = 8.6 MHz, 2 H, C_{meta}-*H*), 6.68 (d, ^3J = 8.8 MHz, 2 H, C_{ortho}-*H*), 4.82 (br s, 1 H, Ar−O*H*), 2.67 (s, 1 H, $C_{carborane}$-*H*) 3.4–0.9 (br m, B-*H*). ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ: 188.66, 188.22, 155.51, 131.89, 129.60, 114.92, 67.01, 41.62. ^{11}B{^{1}H} NMR (160 MHz, $CDCl_3$) δ: 2.50, −3.26, −6.02, −6.61, −10.06, −10.69, −15.24. HRMS (EI) calcd for $C_{10}H_{15}B_9NO_4Re$, 499.1396 (M^+); found, 499.1397.

Sodium *rac*-8-phenyl-2,2,2-tricarbonyl-2-rhenium-2,1,8-dicarba-*closo*-dodecaborate (1g). 1-Phenyl-1,2-dicarbo-*closo*-dodecaborane (85.2 mg, 0.36 mmol) was combined with sodium fluoride (155 mg, 3.6 mmol) and $[Re(CO)_3(H_2O)_3]Br$ (298 mg, 0.72 mmol) as a dry solid mixture in a 5 mL Emry's microwave vial. Aqueous ethanol (12% v/v, 4 mL) was added and the reaction vessel was crimp-sealed. The reaction mixture was heated at 200 °C for 15 min with stirring. The solvent was then removed by passing air over the aqueous mixture producing an amber-colored oil. The oil was dissolved in a minimum of methanol, and the desired product was isolated by silica gel column chromatography (4% methanol: 96% dichloromethane to 32% methanol:68% dichloromethane) as an amber-colored oil (129 mg, 70% yield). The oil solidified upon standing under ambient laboratory conditions; mp (decomposed >240 °C); TLC R_f 0.42 (dichloromethane:methanol; 8:1); FTIR (KBr, cm^{-1}) ν: H 2554, 2000, 1880. ^{1}H NMR (500 MHz, CD_3OD) δ: 7.45 (m, 2 H, Ar-*H*), 7.09 (m, 3 H, Ar-*H*), 1.75 (s, 1 H, $C_{carborane}$-*H*), 3.4–1.0 (br m, B-*H*). ^{13}C{^{1}H} NMR (125 MHz, CD_3OD) δ: 198.59, 142.94, 127.78, 126.20, 125.19, 56.15, 27.67. ^{11}B{^{1}H} NMR (160 MHz, CD_3OD) δ: −4.92, −6.97, −7.90, −8.88, −11.69, −12.56, −18.30, −19.69. HRMS (ES^-) calcd for $C_{11}H_{15}B_9O_3Re$, 479.1472 (M^-); found, 479.1474.

1-(4-Methoxyphenyl)-2-phenyl-1,2-dicarba-*closo*-dodecaborane (2a). Acetonitrile (10 mL) was added to a stirred solution of decaborane (1.16 g, 9.6 mmol) in toluene (50 mL), and the mixture was heated to reflux under nitrogen for 3 h. The orange solution was then cooled to room temperature, and 1-(4-methoxyphenyl)-2-phenylacetylene (1.96 g, 9.42 mmol) was added. The reaction mixture was heated to reflux for 16 h, producing a clear deep-orange-colored solution. The solution was cooled and the solvent removed under reduced pressure to give an orange solid. The desired product was isolated by silica gel column chromatography (20% ethyl acetate:80% hexanes) as an off-white solid (1.35 g, 43% yield); mp 85 – 87 °C; TLC R_f 0.51 (hexanes:ethyl acetate; 9:1); FTIR (KBr, cm^{-1}) ν: 2584, 2575. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.49 (m, Ar-*H*), 7.39 (m, Ar-*H*), 7.23 (m, Ar-*H*), 6.68 (d, ^3J = 9.0 Hz, 2 H, C_{ortho}-*H*, phenol ring), 3.74 (s, 3 H, OCH_3), 3.65–0.80 (br m, B-*H*). ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ: 160.94, 132.16, 130.76, 130.22, 128.38, 123.04, 113.60, 85.86, 85.55, 55.36. ^{11}B{^{1}H} (160 MHz, $CDCl_3$) δ: −2.84, −9.51, −10.96, −11.82. HRMS (EI) calcd for $C_{15}H_{22}B_{10}O$, 327.2523 (M^+); found, 327.2542.

1-(4-Hydroxyphenyl)-2-phenyl-1,2-dicarba-*closo*-dodecaborane (2b). Compound **2a** (0.35 g, 1.07 mmol) in DCM (15 mL) was cooled to −78 °C under nitrogen. BBr_3 (4.57 mmol, 1 M in DCM) was added dropwise and the reaction mixture warmed to room temperature overnight. The solvent was subsequently removed by passing a flow of nitrogen gas over the solution. The flask was cooled in an ice bath and THF (12 mL) was added. The solution was warmed to room temperature over 30 min and the solvent removed by passing nitrogen gas over the top of the sample. The flask was cooled in an ice bath and 12 mL of methanol added. The mixture was warmed to room temperature over 30 min before the solvent was removed under reduced pressure, yielding an off-white solid. The desired product was isolated by silica gel chromatography (8% ethyl acetate:92% hexanes to 66% ethyl acetate:34% hexanes) as a white solid (0.26 g, 78%); mp 129 − 131 °C; TLC R_f 0.53 (hexanes:ethyl acetate; 1:1); FTIR (KBr, cm^{-1}) ν: 3489, 3259, 2592. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.55 (m, 2 H, Ar-*H*), 7.42 (d, ^3J = 8.5 Hz, C_{meta}-*H*, phenol ring), 7.32 (m, Ar-*H*), 6.68 (d, ^3J = 8.5 Hz, 2 H, C_{ortho}-*H*, phenol ring), 3.70–0.80 (m, B-*H*). ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ: 157.15, 132.45, 130.79, 130.25, 128.40, 123.38, 115.18, 85.68, 85.52. ^{11}B{^{1}H} ($CDCl_3$, 160 MHz) δ: −1.80, −8.47, −9.89, −10.77. HRMS (EI) calcd for $C_{14}H_{19}B_{10}O$, 313.2366 (M^+); found, 313.2367.

1-(4-(*N*,*N*-Dimethylamino)ethoxyphenyl)-2-phenyl-1,2-dicarba-*closo*-dodecaborane (2c). Compound **2b** (0.113 g, 0.36 mmol), sodium hydroxide (0.16 g, 4 mmol), and 2-chloro-*N*,*N*-dimethylethylamine hydrochloride (0.078 g, 0.4 mmol) were dissolved in acetone (20 mL). The mixture was heated to reflux for 4 h before allowing the mixture to cool to room temperature. The solvent was removed under reduced pressure, yielding an off-white solid. The desired product was isolated by silica gel chromatography (2% methanol:98% dichloromethane to 18% methanol:82% dichloromethane) as a white solid (47 mg, 34% yield); mp 121–123 °C; TLC R_f 0.36 (dichloromethane:methanol; 9.1); FTIR (KBr, cm^{-1}) ν: 3448, 2599. ^{1}H NMR (200 MHz, CD_3OD) δ: 7.50 (m, 2 H, Ar-*H*), 7.42 (d, ^3J = 8.6 Hz, C_{meta}-*H*, phenol ring), 7.20 (m, 3 H, Ar-*H*), 6.72 (d, ^3J = 8.6 Hz, 2 H, C_{ortho}-*H*, phenol ring), 3.99 (t, ^3J = 5.3 Hz, 2 H, OCH_2), 2.71 (t, ^3J = 5.3 Hz, 2 H, NCH_2), 2.29 (s, 6 H, CH_3), 0.80 – 3.6 (br m, B-*H*). ^{13}C{^{1}H} NMR (50 MHz, CD_3OD) δ: 161.62, 133.48, 131.97, 131.44, 129.45, 124.20, 115.97, 115.15, 87.45, 87.14, 66.54, 58.79, 45.71. ^{11}B{^{1}H} (160 MHz, CD_3OD) δ: −2.27, −8.61, −10.36. HRMS (ES^+) calcd for $C_{18}H_{29}B_{10}NO$, 384.3340 (M^+); found, 384.3321.

Sodium *rac*-8-(4-Hydroxyphenyl)-1-phenyl-2,2,2-tricarbonyl-2-rhenium-2,1,8-dicarba-*closo*-dodecaborate (Isomer A) and Sodium *rac*-1-(4-Hydroxyphenyl)-8-phenyl-2,2,2-tricarbonyl-2-rhenium-2,1,8-dicarba-*closo*-dodecaborate (Isomer B) (2d). Compound **2b** (86.6 mg, 0.28 mmol) was combined with sodium fluoride (160 mg, 3.8 mmol) and $[Re(CO)_3(H_2O)_3]Br$ (197 mg, 0.44 mmol) as a dry solid mixture in a 5 mL Emry's microwave vial. Aqueous ethanol (12% v/v, 4 mL) was added and the reaction vessel crimp-sealed and heated at 200 °C for 15 min with stirring. The solvent was then removed by passing air over the aqueous mixture. The desired product was isolated by silica gel column chromatography (16% methanol:84% dichloromethane) as a viscous amber oil (123 mg, 74% yield), which solidified upon standing; mp (decomposed >240 °C); TLC R_f 0.70 (dichloromethane:methanol; 4:1); FTIR (KBr, cm^{-1}): ν H 2544, 2524, 2515, 1995, 1865; ^{1}H NMR (700 MHz, CD_3OD) δ: 7.56 (d, ^3J = 8.75 MHz, 2 H, C_{ortho}-*H*, phenyl ring, isomer B), 7.37 (d, ^3J = 8.8 MHz, 2 H, C_{meta}-*H*, phenol ring, isomer A), 7.15 (m, 2H, C_{meta}-*H*, phenyl ring, isomer B), 7.11 (m, 1 H, C_{para}-*H*, phenyl ring, isomer B), 7.05 (d, ^3J = 8.5 MHz, 2 H, C_{ortho}-*H*, phenyl ring, isomer A), 6.96 (m, 2 H, C_{meta}-*H*, phenyl ring, isomer A), 6.89 (d, ^3J = 8.8 MHz, 2 H, C_{meta}-*H*, phenol ring, isomer B), 6.82 (m, 1 H, C_{para}-*H*, phenyl ring, isomer A), 6.58 (d, ^3J = 8.7 MHz, 2 H, C_{ortho}-*H*, phenol ring, isomer A), 6.42 (d, ^3J = 8.8 MHz, 2 H, C_{ortho}-*H*, phenol ring, isomer B), 3.5–1.0 (br m, B-*H*, both isomers). $^{13}C\{^1H\}$ NMR (176 MHz, CD_3OD) δ: 201.10, 200.97, 156.86, 154.73, 149.25, 144.43, 140.90, 135.57, 130.67, 129.72, 128.21, 127.82, 127.22, 126.58, 125.72, 124.88, 114.85, 114.57, 58.54, 58.37, 57.10, 56.82. $^{11}B\{^1H\}$ NMR (160 MHz, CD_3OD) δ: −4.89, −7.58, −8.25, −11.61, −16.26, −17.75. HRMS (ES^-) calcd for $C_{17}H_{19}B_9O_4Re$, 572.1726 (M^-); found, 572.1714.

Sodium *rac*-8-(4-(*N*,*N*-Dimethylamino)ethoxyphenyl)-1-phenyl-2,2,2-tricarbonyl-2-rhenium-2,1,8-dicarba-*closo*-dodecaborate (Isomer A) and Sodium *rac*-1-(4-(*N*,*N*-Dimethylamino)ethoxyphenyl)-8-phenyl-2,2,2-tricarbonyl-2-rhenium-2,1,8-dicarba-*closo*-dodecaborate (Isomer B) (2e). Compound **2c** (40.9 mg, 0.11 mmol) was combined with sodium fluoride (50 mg, 1.1 mmol) and $[Re(CO)_3(H_2O)_3]Br$ (67.5 mg, 0.15 mmol) as a dry solid mixture in a 5 mL Emry's microwave vial. Aqueous ethanol (12% v/v, 4 mL) was added and the reaction vessel crimp-sealed and heated at 200 °C for 15 min with stirring. The solvent was then removed by passing air over the aqueous mixture, leaving an amber-colored oil. The desired product was isolated by silica gel column chromatography (4% methanol:96% dichloromethane to 32% methanol:68% dichloromethane) as a viscous amber oil (52 mg, 71% yield), which solidified upon standing; mp (decomposed >240 °C); TLC R_f 0.62 (dichloromethane:methanol; 10:1); FTIR (KBr, cm^{-1}) ν: H 2539, 1993, 1876. ^{1}H NMR (700 MHz, CD_3OD) δ: 7.55 (d, ^3J = 7.5 MHz, 2 H, C_{ortho}-*H*, phenyl ring, isomer B), 7.52 (d, ^3J = 8.9 MHz, 2 H, C_{meta}-*H*, aryl ring, isomer A), 7.16 (m, 2 H, C_{meta}-*H*, phenyl ring, isomer B), 7.13 (m, 1 H, C_{para}-*H*, phenyl ring, isomer B), 7.04 (d, ^3J = 7.4 MHz, 2 H, C_{ortho}-*H*, phenyl ring, isomer A), 7.04 (d, ^3J = 9.0 MHz, 2 H, C_{meta}-*H*, aryl ring, isomer B), 6.96 (m, 2 H, C_{meta}-*H*, phenyl ring, isomer A), 6.84 (m, 1H, C_{para}-*H*, phenyl ring, isomer A), 6.81 (d, ^3J = 8.9 MHz, 2 H, C_{ortho}-*H*, aryl ring, isomer A), 6.66 (d, ^3J = 9.0 MHz, 2 H, C_{ortho}-*H*, aryl ring, isomer B), 4.27 (t, ^3J = 5.0 MHz, 2 H, OCH_2, isomer A), 4.21 (t, ^3J = 5.0 MHz, 2 H, OCH_2, isomer B), 3.42 (m, 4 H, NCH_2, both isomers), 2.87 (s, 6 H, CH_3, isomer B), 2.86 (s, 6 H, CH_3, isomer A), 3.5–1.0 (br m, B-*H*, both isomers). $^{13}C\{^1H\}$ NMR (176 MHz, CD_3OD) δ: 200.98, 200.87, 157.79, 156.02, 149.16, 144.33, 143.31, 138.09, 130.99, 130.72, 129.75, 128.29, 127.90, 127.33, 126.85, 126.63, 125.74, 125.00, 114.42, 114.19, 63.63, 63.38, 58.03, 58.01, 57.84, 57.60, 57.16, 56.34, 44.20, 44.08. $^{11}B\{^1H\}$ NMR (160 MHz, CD_3OD) δ: −4.34, −6.63, −10.78, −14.77, −15.81, −16.99. HRMS (ES^-) calcd for $C_{21}H_{28}B_9NO_4Re$, 643.2463 (M^-); found, 643.2446.

1,2-bis-(4-Methoxyphenyl)-1,2-dicarba-*closo*-dodecaborane (3a). Acetonitrile (10 mL) was added to a stirred solution of decaborane (0.56 g, 4.6 mmol) in toluene (50 mL), and the mixture was heated to reflux under nitrogen for 3 h. The orange solution was then cooled to room temperature and 1,2-(4-methoxyphenyl)-acetylene (0.63 g, 2.6 mmol) added. The reaction mixture was heated to reflux for 16 h, producing a clear deep-orange-colored solution. The solution was cooled and the solvent removed under reduced pressure to give an orange solid. The desired product was isolated by silica gel column chromatography (20% ethyl acetate:80% hexanes) as an off-white solid (0.28 g, 30% yield); mp 140–142 °C; TLC R_f 0.47 (hexanes:ethyl acetate; 4:1); FTIR (KBr, cm^{-1}) ν: 2640, 2591, 2564. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.47 (d, ^3J = 9.0 Hz, 4 H, C_{meta}-*H*), 6.76 (d, ^3J = 9.0 Hz, 4 H, C_{ortho}-*H*), 3.84 (s, 6 H, OCH_3), 3.6–0.80 (br m, B-*H*). $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$) δ: 160.92, 132.24, 123.29, 113.62, 86.08, 55.40. $^{11}B\{^1H\}$ (160 MHz, $CDCl_3$) δ: −3.22, −9.52, −11.20. HRMS (EI) calcd for $C_{16}H_{24}B_{10}O_2$, 358.2707 (M^+); found, 358.2725.

1,2-bis-(4-Hydroxyphenyl)-1,2-dicarba-*closo*-dodecaborane (3b). Compound **3a** (0.22 g, 0.61 mmol) in DCM (10 mL) was cooled to −78 °C under nitrogen. BBr_3 (2.5 mmol, 1 M in DCM) was added dropwise and the reaction mixture warmed to room temperature overnight. The solvent was removed by passing a flow of nitrogen gas over the solution. The flask was cooled in an ice bath and THF (12 mL) was added. The solution was warmed to room temperature over 30 min, and the solvent was removed by passing nitrogen over the sample. The flask was cooled in an ice bath and 12 mL of methanol was added. The mixture was again warmed to room temperature over 30 min before the solvent was removed under reduced pressure, yielding an off-white solid. The desired product was isolated by silica gel chromatography (3:1 hexanes: ethyl acetate) as a white solid (0.16 g, 80% yield); mp 123–125 °C; TLC R_f 0.46 (hexanes:ethyl acetate; 1:1); FTIR (KBr, cm^{-1}) ν: 2567, 2501. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 7.31 (d, ^3J = 8.8 Hz, 4 H, C_{meta}-*H*), 6.57 (d, ^3J = 8.8 Hz, 4 H, C_{ortho}-*H*) 3.89 (br s, 1 H, OH), 3.68–3.38 (m, B-*H*), 1.90–1.49 (m, B-*H*). $^{13}C\{^1H\}$ NMR (50 MHz, DMSO-d_6) δ: 159.28, 132.28, 120.50, 115.11, 87.34. $^{11}B\{^1H\}$ (160 MHz, DMSO-d_6) δ: −3.38, −9.47, −11.35. HRMS (EI) calcd for $C_{14}H_{20}B_{10}O_2$, 330.2394 (M^+); found, 330.2379.

1,2-bis-(4-(*N*,*N*-Dimethylamino)ethoxyphenyl)-1,2-dicarba-*closo*-dodecaborane (3c). Compound **3b** (0.256 g, 0.78 mmol), sodium hydroxide (0.32 g, 7.8 mmol), and 2-chloro-*N*,*N*-dimethylethylamine hydrochloride (0.28 g, 1.95 mmol) were dissolved in acetone (20 mL) and the mixture heated to reflux for 4 h. The reaction was monitored by TLC and additional 2-chloro-*N*,*N*-dimethylethylamine hydrochloride (0.24 g, 1.67 mmol) added, and the mixture was stirred at reflux for 3 h in order to drive the reaction to completion. The solvent was removed under reduced pressure, yielding an yellow-white solid. The product was isolated by silica gel chromatography (5% methanol:95% dichloromethane to 40% methanol: 60% dichloromethane) as an off-white solid (152 mg, 41% yield); mp 92 – 94 °C; TLC R_f 0.32 (dichloromethane:methanol; 4.1); FTIR (KBr, cm^{-1}) ν: 3447, 2588. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 7.42 (d, ^3J = 8.8 Hz, 4 H, C_{meta}-*H*), 6.79 (d, ^3J = 8.8 Hz, 4 H, C_{ortho}-*H*), 3.99 (t, ^3J = 6.0 Hz, 2 H, OCH_2), 2.61 (t, ^3J = 5.8 Hz, 4 H, NCH_2), 2.21 (s, 12 H, CH_3), 3.4–1.0 (br m, B-*H*). $^{13}C\{^1H\}$ NMR (50 MHz, DMSO-d_6) δ: 159.92, 132.24, 122.07, 114.36, 86.65, 65.51, 57.18, 45.16. $^{11}B\{^1H\}$ (160 MHz, DMSO-d_6) δ: −3.22, −9.36, −11.20. HRMS (EI) calcd for $C_{22}H_{38}B_{10}N_2O_2$, 472.3864 (M^+); found, 472.3854.

Sodium *rac*-1,8-bis-(4-Hydroxyphenyl)-2,2,2-tricarbonyl-2-rhenium-2,1,8-dicarba-*closo*-dodecaborate (3d). Compound **3b** (93 mg, 0.29 mmol) was combined with sodium fluoride (162 mg, 3.8 mmol) and $[Re(CO)_3(H_2O)_3]Br$ (172 mg, 0.43 mmol) as a dry solid mixture in a 5 mL Emry's microwave vial. Aqueous ethanol (12% v/v, 5 mL) was added and the reaction vessel crimp-sealed and heated at 200 °C for 15 min with stirring. Additional $[Re(CO)_3(H_2O)_3]Br$ (52 mg, 0.13 mmol) was added as a solid and the reaction was heated in the microwave at 200 °C for 15 min with stirring. The solvent was removed by passing air over the mixture, producing an off-white solid. The product was isolated by silica gel column chromatography (5% methanol:95% dichloromethane to 40% methanol:60% dichloromethane) as an off-white solid (110 mg, 62% yield); mp (decomposed >240 °C); TLC R_f 0.32 (dichloromethane: methanol; 5:1); FTIR (KBr, cm^{-1}) ν: H 3552, 2556, 2000, 1903. ^{1}H NMR (500 MHz, CD_3OD) δ: 7.37 (d, ^3J = 8.8 MHz, 2 H,

C_{meta}-*H*, ring B), 6.88 (d, ^3J = 8.8 MHz, 2 H, C_{meta}-*H*, ring A), 6.58 (d, ^3J = 8.8 MHz, 2 H, C_{ortho}-*H*, ring B), 6.41 (d, ^3J = 8.8 MHz, 2 H, C_{ortho}-*H*, ring A), 3.4–1.0 (br m, B-*H*). $^{13}C\{^1H\}$ NMR (176 MHz, CD_3OD) δ: 201.27, 156.86, 154.72, 141.06, 135.72, 130.71, 126.62, 114.85, 114.56, 58.54, 56.93. $^{11}B\{^1H\}$ NMR (160 MHz, CD_3OD) δ: −4.59, −7.36, −11.52, −15.07, −17.56. HRMS (ES^-) calcd for $C_{17}H_{19}B_9O_5Re$, 588.1675 (M^-); found, 588.1678.

Sodium *rac*-1,8-bis-(4-(*N*,*N*-Dimethylamino)ethoxyphenyl)-2,2,2-tricarbonyl-2-rhenium-2,1,8-dicarba-*closo*-dodecaborate (3e). Compound **3c** (81.2 mg, 0.18 mmol) was combined with sodium fluoride (90 mg, 2.2 mmol) and $[Re(CO)_3(H_2O)_3]Br$ (112 mg, 0.27 mmol) as a dry solid mixture in a 5 mL Emry's microwave vial. Aqueous ethanol (12% v/v, 4 mL) was added and the reaction vessel crimp-sealed and heated at 200 °C for 15 min with stirring. The solvent was then removed by passing air over the aqueous mixture, producing an off-white solid. The product was isolated by silica gel column chromatography (6% methanol:94% dichloromethane to 50% methanol:50% dichloromethane) as an off-white solid (103 mg, 76% yield); mp (decomposed >240 °C); TLC R_f 0.19 (dichloromethane:methanol; 5:1); FTIR (KBr, cm^{-1}) ν: H 2583, 2555, 2533, 1994, 1869. ^1H NMR (700 MHz, CD_3OD) δ: 7.47 (d, ^3J = 8.9 MHz, 2 H, C_{meta}-*H*, ring B), 6.97 (d, ^3J = 8.9 MHz, 2 H, C_{meta}-*H*, ring A), 6.74 (d, ^3J = 8.9 MHz, 2 H, C_{ortho}-*H*, ring B), 6.56 (d, ^3J = 8.9 MHz, 2 H, C_{ortho}-*H*, ring A), 4.07 (t, ^3J = 5.6 Hz, 2 H, OCH_2, ring B), 4.01 (t, ^3J = 5.6 Hz, 2 H, OCH_2, ring A), 2.76 (t, ^3J = 5.6 Hz, 2 H, CH_2N, ring B), 2.73 (t, ^3J = 5.6 Hz, 2 H, CH_2N, ring A), 2.34 (s, 6 H, CH_3, ring B), 2.32 (s, 6 H, CH_3, ring A). $^{13}C\{^1H\}$ NMR (176 MHz, CD_3OD) δ: 201.10, 158.67, 156.92, 142.27, 137.05, 130.77, 126.63, 114.18, 113.96, 66.50, 66.44, 59.16, 59.10, 58.25, 56.62, 45.80, 45.77. $^{11}B\{^1H\}$ (160 MHz, CD_3OD) δ: −4.76, −7.49, −11.62, −15.16, −17.61. HRMS (ES^-) calcd for $C_{25}H_{37}B_9N_2O_5Re$, 730.3150 (M^-); found, 730.3170.

Radiochemistry. *Caution*. ^{99m}Tc is a γ-emitter (E_γ = 140 KeV, $t_{1/2}$ = 6 h) and can only be used in a licensed facility. Sodium pertechnetate was obtained from a commercial ^{99}Mo/^{99m}Tc generator (Bristol-Myers Squibb).

$[^{99m}Tc(CO)_3(H_2O)_3]^+$. $^{99m}TcO_4^-$ (2.5 mL) from a ^{99}Mo/^{99m}Tc generator (5.5 GBq, 150 mCi) was added to a sealed Emry vial containing sodium tartrate (17 mg), sodium tetraborate (3.5 mg), sodium carbonate (3.2 mg), and sodium boranocarbonate (8.1 mg) under nitrogen. The reaction mixture was heated in a microwave reactor at 130 °C for 3 min with stirring. γ-HPLC (method A): t_R = 4 min. Yield > 95%.

Sodium *rac*-8-(4-Hydroxyphenyl)-2,2,2-tricarbonyl-2-^{99m}technetium-2,1,8-dicarba-*closo*-dodecaborate (Isomer A) and Sodium *rac*-1-(4-Hydroxyphenyl)-2,2,2-tricarbonyl-2-^{99m}technetium-2,1,8-dicarba-*closo*-dedecaborate (Isomer B) ^{99m}Tc-1d. Compound **1b** (8.5 mg, 0.04 mmol) was combined with sodium fluoride (15 mg, 0.4 mmol) as a dry solid mixture in a 5 mL Emry's microwave vial. Aqueous ethanol (12% v/v, 4 mL) was added and the reaction vessel crimp-sealed. The reaction mixture was then heated in a microwave reactor at 200 °C for 15 min to generate the *nido*-carborane in situ. To the reaction mixture was added the solution containing $[^{99m}Tc(CO)_3(H_2O)_3]^+$ (1.05 GBq, 28.3 mCi) and the reaction mixture heated in a microwave reactor at 200 °C for 5 min with stirring. After cooling, the solution was loaded onto a C18 SPE cartridge (the C18 SPE cartridge was activated prior to use by washing with 10 mL of ethanol, followed by 10 mL of 10 mM HCl), which was subsequently washed with 10 mM HCl (5 mL), 80:20 10 mM HCl−acetonitrile (5 mL), followed by 50:50 10 mM HCl−acetonitrile (2 mL). The desired product was then eluted with 20:80 10 mM HCl−acetonitrile (5 mL) in 1 mL fractions. The nature of the product was verified by comparison of the γ-HPLC trace with the UV-HPLC trace of the rhenium standard, **1d**. γ-HPLC (method A): t_R = 15.2 min (isomer B), 16.0 min (isomer A); UV-HPLC t_R = 15.1 min (isomer B), 15.9 min (isomer A). Yield: 0.70 GBq (18.96 mCi, 84%, decay-corrected).

Determination of log *P* Values. Log *P* values were determined as described in the literature,[29] employing the reference compounds described by Endo et al.[30] The samples were prepared as solutions of 0.1–0.5 mg/ mL in methanol. The measurements were performed on a Nucleosil 100-5 C_{18} column, 250 mm × 4.6 mm (Varian), on a Varian Prostar HPLC using Star Chromatography workstation software. The injection volume was 20 μL in all cases. The void volume was measured with dithiourea as an unretained compound. The flow-rate was 1 mL/ min in all cases, and detection was by UV absorption at 240 nm. The measurements were performed in methanol–water (containing 0.1% TFA) as the mobile phases starting with 80% (v/v) organic modifier decreasing in 5% (v/v) increments of organic modifier to 60% (v/v). The retention times were determined for seven reference phenols in the range of log *P* between 1.46 and 5.12. The capacity factor, log k'_w, with 100% aqueous eluent, was estimated by extrapolation of the measured log k' values. The log k'_w values were plotted as a function of log *P*.

Estrogen Receptor Binding Affinities. All compounds were initially screened at a concentration of 1 μM and the results compared with the binding affinity of estradiol. For promising compounds, relative binding affinities were determined by a competitive radiometric binding assay, using 1.13 nM [6,7-^{3}H]estra-1,3,5(10)-triene-3,17-β-diol ([^{3}H]-estradiol, Amersham BioSciences, Piscataway, NJ) and purified full-length human ERα and ERβ (PanVera/Invitrogen, Carlsbad, CA) following a previously described procedure.[31] Incubations were for 18–24 h at 4 °C. Hydroxyapatite (BioRad, Hercules, CA) was used to isolate the receptor–ligand complexes, and unbound ^{3}H-estradiol was removed by repeated washing and centrifugation at 4 °C. The binding affinities are expressed relative to estradiol according to eq 1 with nontritiated estradiol set to a RBA of 100%. The values given are the average ± standard deviations (s.d.) of three independent determinations. All statistical analyses were performed using GraphPad Prism v4.0.

$$\mathrm{RBA} = \frac{\mathrm{IC}_{50}^{^3\text{H-estradiol}}}{\mathrm{IC}_{50}^{\text{compound}}} \times 100\% \quad (1)$$

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Supporting Information Available: Complete spectral data for all novel compounds and X-ray data for compounds **1b**, **1d**, **1f**, and **3d** are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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